PASS information

Title	An observational, retrospective database post-authorisation safety study (PASS) to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced *Cervarix* in their National Immunisation Programmes (NIP)
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Procedure number	To be allocated
Marketing Authorisation Holder (MAH)	GlaxoSmithKline Biologicals SA Rue de l'Institut, 89 1330 Rixensart, Belgium
Joint PASS	No
Research question and objectives	To assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal cancer in females and males.
Countries of study	Finland, the Netherlands, England, Denmark, and Norway
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1. ABSTRACT

Title

An observational, retrospective database post-authorisation safety study (PASS) to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced *Cervarix* in their National Immunisation Programmes (NIP).

Date: Interim Report Final, 09 June 2022.

Author: PPD, Epidemiology Lead, GlaxoSmithKline Biologicals SA.

Keywords

Post-authorisation safety study, database, anal cancer, European countries.

Rationale and background

Anal cancer is an uncommon type of cancer, representing around 0.3% of all incident cancers diagnosed in 2020 worldwide. Squamous cell carcinoma (SCC) is the most frequent histopathological type of anal cancer. There is evidence to suggest that human papillomavirus (HPV) infection is associated with anal cancer, particularly with SCC. Moreover, in a recent worldwide study, HPV deoxyribonucleic acid (DNA) was detected in more than 88% of anal cancers and more than 95% of anal intraepithelial neoplasia (AIN) grades 2/3. The most frequently detected virus type, detected in over 80.7% of invasive anal cancer cases was HPV-16, followed by HPV-18 (3.6% of cases). Over the last 4 decades, anal cancer incidence has been gradually increasing and is more common in women than in men, except for certain high-risk groups such as human immunodeficiency virus (HIV)-infected people, and this raise is more relevant in high-income countries. Risk factors for anal cancer are HPV infection, including a former HPV-related malignancy, HIV infection, more than 10 lifetime sexual partners, ano-receptive intercourse, chronic immunosuppression, cigarette smoking, a history of gynaecological or haematologic malignancy, and age. Hence, HIV and immunocompromised patients, and men who have sex with men (MSM) are particularly vulnerable populations.

GlaxoSmithKline Biologicals SA (GSK) has developed a prophylactic HPV vaccine, *Cervarix*, based on L1 proteins of HPV-16 and HPV-18 formulated with AS04 (comprising of aluminium hydroxide [$Al(OH)_3$] and 3-*O*-desacyl-4'-monophosphoryl lipid A).

Cervarix is a vaccine for use from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal, and anal) and cervical and anal cancers causally related to certain oncogenic HPV types.

In the context of the European Union Risk Management Plan (EU-RMP) for *Cervarix*, a safety concern was raised linked to missing information on the impact and effectiveness of the vaccine against anal lesions and cancer, since it was not prospectively evaluated in clinical trials.

The interim analysis assessed the data on anal cancer in countries where *Cervarix* vaccination has been introduced in the NIP. Five European countries were initially selected to perform a trend analysis and to assess feasibility for a case-control study: Finland, the Netherlands, England, Denmark, and Norway.

Research question and objectives

The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal cancer in females and males.

Primary objectives:

- To assess trends and changes over time in the age-standardised incidence of anal cancer by sex, HPV type, and histological classification for each country* separately.
- To assess trends and changes over time in the crude incidence of anal cancer by age category, sex, HPV type, and histological classification for each country* separately.

Secondary objective:

- To conduct a feasibility assessment for a case-control study to determine the impact and effectiveness of *Cervarix* against anal cancer.

**Five European countries are considered for this study, and each country was selected based on a set of criteria.*

Study design

- **Type of study and design**: This is a Targeted Safety Study (TSS) and a PASS. The study is designed as an observational, retrospective database study.
- **Study population**: Females and males of all age groups in the 5 selected European countries.
- **Data collection**: Retrospective data collection from national cancer registries.
- **Study period**:
  - Pre-*Cervarix* launch period (i.e., before *Cervarix* introduction in the NIP): The start and end calendar year for each country was considered based on the data availability in their respective cancer registries.
  - Post-*Cervarix* launch period (i.e., after *Cervarix* introduction in the NIP): The start calendar year for each country was the date when *Cervarix* was introduced in their NIP. An interim analysis was performed in 2022. For the analysis, data up to the most recent and complete available calendar year in each cancer registry was considered.
- This study is a trend analysis of incidence of anal cancer in 5 selected European countries. However, the interim analysis was performed for 3 European countries: England, the Netherlands, and Finland. It was not performed for Denmark and

Norway. In Denmark, *Cervarix* was only introduced in the NIP from February 2016 until November 2017 and the doses applied thereafter have been reported mainly from the private market. The vast majority of females vaccinated against HPV in Denmark have received the quadrivalent HPV vaccine. In Norway, *Cervarix* was only introduced in the NIP in September 2017. Hence, a decision was made to focus the study on those countries that administered *Cervarix* for at least 5 birth cohorts (either routine or catch-up campaign cohorts), or that have implemented *Cervarix* in their NIPs in a continuous manner since the introduction in their NIP. The analysis for Denmark and Norway may be performed during the final analysis, planned in 2026, depending on the data availability during that time.

- The feasibility assessment for a case-control study was conducted considering the 3 selected European countries that were approached for the trend analysis. The interaction with the national cancer registries was to provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise was intended to facilitate the understanding whether this case-control study to determine vaccine effectiveness against anal cancer can be performed.
- Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting system, data of small intestine cancer in the same population was analysed. Small intestine cancer is relatively rare, with an occurrence of similar magnitude to anal cancer. Small intestine cancer also has a similar mean age of diagnosis as anal cancer, and there is no screening programme for it. It is not associated with HPV infection. This analysis may allow to control for potential changes in cancer surveillance and reporting system over time.

Setting

The following country eligibility criteria were checked in order to perform analysis:

- Should have a stable, consolidated and validated cancer registry.
- The cancer registry should preferably be population-based and nationwide.
- Administration of *Cervarix* for at least 5 birth cohorts (either routine or catch-up campaign cohorts) within the NIP.

Subjects and study size (including dropouts)

Sample size computation was not applicable, as there was no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 3 European countries were collected within the established timeframe.

Note: National cancer registries are nationwide and thus this interim analysis was population-based.

Endpoints

Primary endpoint

- Occurrence and age-standardised incidence of anal cancer during the study period (i.e., pre- and post- *Cervarix* launch period) by sex, HPV type and histological classification for each country* separately.
- Occurrence and crude incidence of anal cancer during the study period (i.e., pre- and post-*Cervarix* launch period) by age category, sex, HPV type, and histological classification for each country* separately.

Note: Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting system, data of small intestine cancer in the same population was analysed by age category and sex for each country* separately.

Secondary endpoint

- Expected number of anal cancer cases needed to conduct the case-control study based on the vaccine coverage rate and the expected VE and other factors for each country* separately.

Note: Other feasibility assessment checks with findings for the conduct of a case-control study will be further described in the study report.

**Five European countries are considered for this study and each country was selected based on a set of criteria.*

Data sources

- This interim analysis collected anal cancer data from the following national cancer registries:
  - The Finnish Cancer Registry (FCR)
  - The Netherlands Cancer Registry (NCR)
  - National Cancer Registration and Analysis Service (NCRAS)
  - The Danish Cancer Registry
  - The Cancer Registry of Norway (CRN)
- Eurostat was the source for data on the European Standard Population for age distribution used to estimate the age-standardised incidence rates. It was also the source for the population data and birth cohort data, except for England, for which the source for population data was the UK Health Security Agency and for birth cohort data it was Office of National Statistics.
- Vaccine coverage data was retrieved from the respective websites of national public health institutes.

- Vaccination registries:
  - Finnish National Vaccination Registry since 2009
  - Dutch vaccination registry (Præventis) since 2005
  - Immunisations are registered in Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002) (UK)
  - Danish vaccination registry since 2009, although compulsory as of 15 November 2015
  - Norwegian vaccination registry since 1995.

Results

The interim analysis was performed for 3 European countries: England, the Netherlands, and Finland. It was not performed for Denmark and Norway. In Denmark, *Cervarix* was only introduced in the NIP from February 2016 until November 2017 and the doses applied thereafter have been reported mainly from the private market. The vast majority of females vaccinated against HPV in Denmark have received the quadrivalent HPV vaccine. In Norway, *Cervarix* was only introduced in the NIP in September 2017. Hence, a decision was made to focus the study on those countries that administered *Cervarix* for at least 5 birth cohorts (either routine or catch-up campaign cohorts), or that have implemented *Cervarix* in their NIPs in a continuous manner since the introduction in their NIP. The analysis for Denmark and Norway may be performed during the final analysis, planned in 2026, depending on the data availability during that time.

Primary and secondary objective results for England

Primary objective results for England

In England, between 1995 and 2018:

- An increasing trend in the age-standardised incidence and crude incidence of anal cancer was observed over time.
- Overall, the age-standardised incidence rates were higher than the crude incidence rates.

Similar results were observed for small intestine cancer.

- An increasing trend in the age-standardised incidence and crude incidence of anal cancer was observed over time both in females and males. Females presented higher incidence rates than males, throughout the study period. There was either 1 case or no case of anal cancer reported below 20 years of age. Both in females and males, the crude incidence of anal cancer was similar and almost null for age categories 0-9, and 10-19 years. In females, the age category above 80 years showed the highest crude incidence of anal cancer throughout the year categories considered.

Similar results were observed for small intestine cancer, except that males presented higher age-standardised incidence rate or crude incidence rate, or both than females, throughout the study period: the incidence was highest among the age category above 80 years throughout the year categories considered, although the highest number of cases were presented by age category 70-79 years.

- Concerning the histological classification of the tumours, SCCs were the most frequently occurring tumours, followed by adenocarcinomas or other tumours, throughout the study period. Number of cases and thus incidence of SCC, both age-standardised and crude incidence, increased over time.
- A univariate Poisson regression model showed a significantly increasing trend in the incidence of anal cancer. A 3.29% annual increase (Annual Percentage Change [APC]) in the incidence of anal cancer was observed. In a separate univariate analysis of the pre-*Cervarix* and the post-*Cervarix* launch periods, an increasing trend in the incidence rate of anal cancer was observed in both periods. The APC for the pre-*Cervarix* and the post-*Cervarix* launch periods are very similar in magnitude and sign (both had positive sign) at 2.44% and 3.46%, respectively.

Similar results were observed for small intestine cancer.

Note: The overall population at risk (i.e., N) is the sum of the population for every calendar year during the study period.

- A multivariate Poisson regression model was fitted considering the following risk factors: calendar year, age category (by 10-year age group), *Cervarix* introduction period in the NIP (pre- and post-*Cervarix* introduction periods), and sex. After adjusting for the rest of the variables, the incidence rates of anal cancer increased over time and with age, and there was also strong evidence that the incidence rates of anal cancer were higher in females compared to males. And when comparing the incidence rates between the pre- and post-introduction periods of the *Cervarix* in the NIP, there was no difference observed in the incidence rates.
- In a multivariate Poisson regression model, on stratification by age, the incidence rates of anal cancer were observed to be significantly higher in females when compared to males for all age categories except for the 0-29 age category where there was no difference in the incidence rate of anal cancer observed between females and males. Similarly, there seemed to be no statistically significant difference in the incidence rates of anal cancer over time for the 0-29 age category. However, in all other age categories, incidence rates of anal cancer significatively increased over time. Conversely, there was no difference in the evolution of the incidence rate of anal cancer when comparing the pre- and post-*Cervarix* introduction periods in the NIP for any of the age categories.
- In a multivariate Poisson regression model, on stratification by sex, the incidence rates of anal cancer significatively increased by age and over time in both sexes. There was no difference observed in the incidence rate of anal cancer when comparing the pre- to the post-*Cervarix* introduction periods in the NIP either for females or males.

- The multivariate Poisson regression model for incidence of anal cancer by histological classification showed that the incidence rate of anal cancer increased with age for SCC, adenocarcinoma and Other (i.e., other specified carcinoma and unspecified carcinoma, melanoma, other specified malignant neoplasm and unspecified malignant neoplasm) cancers. The incidence rates of anal cancer were higher in females when compared to males for SCC and Other cancers. The incidence rates of anal cancer were highest in males for adenocarcinoma cancer. When comparing the incidence rates between the pre- and post-introduction periods in the NIP for the different type of cancers, there was no difference observed in the incidence rates for anal cancer among SCC and adenocarcinoma cancers whereas there was some evidence that in the post-*Cervarix* launch period the incidence rates was higher among the "Others" cancer category.
- Since 1995 and until the year of introduction of *Cervarix* in the NIP (2008), the observed number of anal cancer cases was close to the predicted anal cancer cases. Following the introduction of *Cervarix* in the NIP, the observed number of cases depart from the predicted line, indicating an acceleration of the increase in anal cancer incidence. However, this change is to be considered cautiously since confounding by age may have occurred as the population considered for the post-*Cervarix* introduction period may be older.

Secondary objective results for England

Number of expected anal cancer cases with 80% power to demonstrate VE with assumed vaccine coverage with the estimated timeframe for conducting the matched case-control study

- Considering 60% vaccine coverage and 60% VE, the required sample size would be 126 cases that, in a case to control ratio 1:1 scenario, would be reached in 2038. In a case to control ratio 1:4 scenario, 70 cases would be required, and the sample size reached in 2035.
- Considering 60% vaccine coverage and 90% VE, the required sample size would be 25 cases that, in a case to control ratio 1:1 scenario, would be reached in 2031. In a case to control ratio 1:4 scenario, 14 cases would be required, and the sample size reached in 2029.
- Considering 80% vaccine coverage and 60% VE, the required sample size would be 160 cases that, in a case to control ratio 1:1 scenario, would be reached in 2040. In a case to control ratio 1:4 scenario, 86 cases would be required, and the sample size reached in 2037.
- Considering 80% vaccine coverage and 90% VE, the required sample size would be 25 cases that, in a case to control ratio 1:1 scenario, would be reached in 2034. In a case to control ratio 1:4 scenario, 13 cases would be required, and the sample size reached in 2031.

Assessment of the individual vaccination status

In England, HPV vaccination is school-based but there are provisions to administer the vaccine in certain healthcare facilities. Immunisations are registered in the Child Health Information Systems. However, there are limitations in providing data on vaccines given outside of the school setting. At the time of the data request for this interim analysis, PHE, the institution dealing with data requests for NCRAS (PHE Office for Data Release [ODR]) was under a reorganisation and transition to the current United Kingdom Health Security Agency (UKHSA), and there was no clarity concerning future accountability for the management of the data. Therefore, it was not possible to obtain information about the possibility of linkage between the cancer and the vaccination registries to assess individual vaccination status. For the same reason, it was not possible to assess whether the vaccination registry could provide data about the specific HPV vaccine brand.

Availability on the covariates of interest in the database

The availability of data on other covariates of interest (apart form age, sex, and HPV type) was not assessed at the time of this interim analysis. Relevant enquiries to the cancer registry will be made to retrieve this information.

HPV genotyping data (or information on at least whether the anal cancer case was HPV-related) was not available at the time of data extraction.

Primary and secondary objective results for the Netherlands

Primary objective results for the Netherlands

In the Netherlands, between 1992 and 2020:

- An increasing trend in the age-standardised incidence and crude incidence of anal cancer was observed over time.

Similar results were observed for small intestine cancer.

- An increasing trend in the age-standardised incidence and crude incidence of anal cancer was observed over time both in females and males. Females presented higher incidence rates than males, throughout the study period. There was no case of anal cancer reported below 20 years of age. Both in males and females, the crude incidence of anal cancer was similar and null for age categories 0-9, and 10-19 years. In females, the age category above 80 years showed the highest crude incidence of anal cancer throughout the year categories considered, except for the year category 2014-2018 when the crude incidence was higher at the 70-79 age category.

Similar results were observed for small intestine cancer, except that males presented higher age-standardised incidence rate or crude incidence rate, or both than females, throughout the study period: the overall crude incidence was highest among the age category above 80 years throughout the year categories considered, although the highest number of cases were presented by age category 70-79 years.

- A univariate Poisson regression model showed a significantly increasing trend in the incidence of anal cancer. A 5.09% annual increase (APC) in the incidence of anal cancer was observed. In a separate univariate analysis of the pre-*Cervarix* and the post-*Cervarix* launch periods, an increasing trend in the incidence rate of anal cancer was observed in both periods (i.e., pre- and post-*Cervarix* launch periods). The APC for the pre-*Cervarix* and the post-*Cervarix* launch periods are very similar in magnitude and sign (both had positive sign) at 4.90% and 5.00%, respectively.

Note: The overall population at risk (i.e., N) is the sum of the population for every calendar year during the study period.

Similar results were observed for small intestine cancer.

- A multivariate Poisson regression model was fitted considering the following risk factors: calendar year, age category (by 10-year age groups), *Cervarix* introduction period in the NIP (pre- and post-*Cervarix* introduction periods), and sex. After adjusting for the rest of the variables, the incidence rates of anal cancer increased over time and with age, and there was also strong evidence that the incidence rates of anal cancer were higher in females compared to males. And when comparing the incidence rates between the pre- and post-introduction periods of the *Cervarix* in the NIP, there was no difference observed in the incidence rates.
- In a multivariate Poisson regression model, on stratification by age, the incidence rates of anal cancer were observed to be significatively higher in females when compared to males for all age categories except for the 0-29 age category where there was no difference in the incidence rate of anal cancer observed between females and males. Similarly, there seemed to be no statistically significant difference in the incidence rates of anal cancer over time for the 0-29 age category. However, in all other age categories, incidence rates of anal cancer significatively increased over time. Conversely, there was no difference in the evolution of the incidence rate of anal cancer when comparing the pre- and post-*Cervarix* introduction periods in the NIP for any of the age categories.
- In a multivariate Poisson regression model, on stratification by sex, the incidence rates of anal cancer significatively increased by age and over time in both sexes. There was no difference observed in the incidence rate of anal cancer when comparing the pre- to the post-*Cervarix* introduction periods in the NIP either for females or males.
- Since 1992 and until the year of introduction of *Cervarix* in the NIP (2009), the observed number of anal cancer cases were close to the predicted anal cancer cases for most age categories. However, following the introduction of *Cervarix* in the NIP, the observed number of cases depart from the predicted line, indicating an acceleration of the increase in anal cancer incidence for the age categories 60-69 and 70-79 years, whereas the observed number of cases declines compared to the predicted line for the 30-39, 40-49, and 50-59 age categories.

Secondary objective results for the Netherlands

Number of expected anal cancer cases with 80% power to demonstrate VE with assumed vaccine coverage with the estimated timeframe for conducting the matched case-control study

- Considering 60% vaccine coverage and 60% VE, the required sample size would be 126 cases that, in a case to control ratio 1:1 scenario, would be reached in 2052. In a case to control ratio 1:4 scenario, 70 cases would be required, and the sample size reached in 2047.
- Considering 60% vaccine coverage and 90% VE, the required sample size would be 25 cases that, in a case to control ratio 1:1 scenario, would be reached in 2042. In a case to control ratio 1:4 scenario, 14 cases would be required, and the sample size reached in 2039.
- Considering 80% vaccine coverage and 60% VE, the required sample size would be 160 cases that, in a case to control ratio 1:1 scenario, would be reached in 2055. In a case to control ratio 1:4 scenario, 86 cases would be required, and the sample size reached in 2050.
- Considering 80% vaccine coverage and 90% VE, the required sample size would be 25 cases that, in a case to control ratio 1:1 scenario, would be reached in 2046. In a case to control ratio 1:4 scenario, 13 cases would be required, and the sample size reached in 2041.

Assessment of the individual vaccination status

For the Netherlands, at the time of the data extraction, the Dutch Cancer Registry confirmed that they had no possibility of linkage to retrieve information on the individual vaccination status of cases and controls. However, the Dutch immunisation registry Præventis supports linkage to disease registers to address VE studies via a trusted third party. Whether they have developed this functionality to link with the cancer registry is to be assessed for the final analysis.

Availability on the covariates of interest in the database

The availability of data on other covariates of interest (apart form age, sex, and HPV type) was not assessed at the time of this interim analysis. Relevant enquiries to the cancer registry will be made to retrieve this information.

HPV genotyping data (or information on at least whether the anal cancer case was HPV-related) was not available at the time of data extraction.

Primary and secondary objective results for Finland

Primary objective results for Finland

In Finland, between 1992 and 2019:

- An increasing trend in the age-standardised incidence and crude incidence of anal cancer was observed over time.

Similar results were observed for small intestine cancer.

- An increasing trend in the age-standardised incidence and crude incidence of anal cancer was observed over time both in females and males. There was no case of anal cancer reported below 20 years of age. Both in females and males, the crude incidence of anal cancer was null for age categories 0-9, and 10-19 years. In females, the age category above 80 years showed the highest crude incidence of anal cancer throughout the year categories considered.

Similar results were observed for small intestine cancer, except that males presented higher age-standardised incidence rate or crude incidence rate, or both than females: the incidence was highest among the age category above 80 years throughout the year categories considered, although the highest number of cases were presented by age category 70-79 years, except for the year category 2003-2007, 2008-2012, and 2013-2017 where the highest number of cases corresponds to the 60-69 years age group.

- A univariate Poisson regression model showed a significantly increasing trend in the incidence of anal cancer. A 2.91% annual increase (APC) in the incidence of anal cancer was observed. In a separate univariate analysis of the pre-*Cervarix* and the post-*Cervarix* launch periods, an increasing trend in the incidence rate of anal cancer was observed in the pre-*Cervarix* launch period. However, a decreasing trend in the incidence rate of anal cancer was noted in the post-*Cervarix* launch period. The APC for the pre-*Cervarix* and the post-*Cervarix* launch periods are opposite in sign at 2.99% and - 1.09%, respectively.

A univariate Poisson regression model showed a significantly increasing trend in the incidence of small intestine cancer. A 4.16% annual increase (APC) in the incidence of small intestine cancer was observed. In a separate univariate analysis of the pre-*Cervarix* and the post-*Cervarix* launch periods, an increasing trend in the incidence rate of small intestine cancer was observed in both periods. The APC for the pre-*Cervarix* and the post-*Cervarix* launch periods are very similar in magnitude and sign (both had positive sign) at 3.41% and 3.94%, respectively.

Note: The overall population at risk (i.e., N) is the sum of the population for every calendar year during the study period.

- A multivariate Poisson regression model was fitted considering the following risk factors: calendar year, age category (by 10-year age groups), *Cervarix* introduction period in the NIP (pre- and post-*Cervarix* introduction periods), and sex. After adjusting for the rest of the variables, the incidence rates of anal cancer increased

over time and with age, and there was also strong evidence that the incidence rates of anal cancer were higher in females compared to males. And when comparing the incidence rates between the pre- and post-introduction periods of the *Cervarix* in the NIP, there was no difference observed in the incidence rates.

- In a multivariate Poisson regression model, on stratification by age, the incidence rates of anal cancer were observed to be significatively higher in females when compared to males for age categories 40-49, 50-59, and 60-69 years. For the rest of the age categories, there was no difference in the incidence rate of anal cancer observed between females and males.
- In a multivariate Poisson regression model, on stratification by sex, the incidence rates of anal cancer significatively increased by age and over time in both sexes. There was no difference observed in the incidence rate of anal cancer when comparing the pre- to the post-*Cervarix* introduction periods in the NIP either for females or males.
- Due to the relatively low number of anal cancer cases overall and within each age category, it is inappropriate to make a visual interpretation of the figures corresponding to observed versus predicted number of cases, as indicated by the low precision (wide 95% CIs) of the estimates.

Secondary objective results for Finland

Number of expected anal cancer cases with 80% power to demonstrate VE with assumed vaccine coverage with the estimated timeframe for conducting the matched case-control study

- Considering 60% vaccine coverage and 60% VE, the required sample size would be 126 cases that, in a case to control ratio 1:1 scenario, would be reached in 2071. In a case to control ratio 1:4 scenario, 70 cases would be required, and the sample size reached in 2064.
- Considering 60% vaccine coverage and 90% VE, the required sample size would be 25 cases that, in a case to control ratio 1:1 scenario, would be reached in 2058. In a case to control ratio 1:4 scenario, 14 cases would be required, and the sample size reached in 2054.
- Considering 80% vaccine coverage and 60% VE, the required sample size would be 160 cases that, in a case to control ratio 1:1 scenario, would be reached in 2077. In a case to control ratio 1:4 scenario, 86 cases would be required, and the sample size reached in 2069.
- Considering 80% vaccine coverage and 90% VE, the required sample size would be 25 cases that, in a case to control ratio 1:1 scenario, would be reached in 2062. In a case to control ratio 1:4 scenario, 13 cases would be required, and the sample size reached in 2057.

Assessment of the individual vaccination status

For Finland, the Finnish Public Health Institute (THL) confirmed that they were able to provide combined data from the cancer registry and the vaccine registry.

Availability on the covariates of interest in the database

The availability of data on other covariates of interest (apart form age, sex, and HPV type) was not assessed at the time of this interim analysis. Relevant enquiries to the cancer registry will be made to retrieve this information.

HPV genotyping data (or information on at least whether the anal cancer case was HPV-related) was not available at the time of data extraction.

Discussion

- The trend analysis has shown that in the recent decades the incidence of anal cancer has been increasing in the study countries, aligned with reports from other parts of the world. The definite reason for this increase remains unknown. However, recent studies point to several factors that may result in the incidence and persistence of anal HPV infection, such as the main risk factors for anal cancer. Among them, changes in sexual behaviour and practices, including lower age of sexual debut, increased number of sexual partners, and anoreceptive intercourse both in heterosexual and homosexual relationships. Nevertheless, the correlation between anoreceptive intercourse and anal cancer seems to be less strong in women than in men, most likely because cervical HPV persistent infection has been characterised as the most relevant reason for the persistence of anal HPV infection in women. In this respect, autoinoculation and post-toilet wiping behaviours have been associated with the prevalence of anal HPV persistent infection in women. Immunosuppression is also an important risk factor for anal cancer. Anal HPV infection and cancer are found to be prevalent in HIV-infected patients, increasing the risk of anal cancer with the duration of HIV infection. At present and due to improved treatments, HIV patients' survival rates have improved, and this can partially explain an increase in anal cancer incidence.
    - Advancements in awareness of anal cancer may also have contributed to an increased diagnosis frequency. For instance, in England there is no anal cancer screening programme. However, in 2018, the UK introduced an HPV targeted vaccination programme for MSM (with a pilot started in 2016) and this may have contributed to increased screening and anal cancer detection. Furthermore, an additional reason for the increase of incidence of anal cancer might have been the implementation of colorectal cancer screening programmes since the anus is also investigated during colonoscopy. England, Finland, and the Netherlands have a nationwide colorectal cancer screening programme in place.
- This database analysis has revealed that the incidence of anal cancer has been increasing in both men and women for several decades, with higher incidence rates in women than in men. This is probably due to sex differences in risk factors as described above, including smoking as anal cancer trends among women in some

European countries correlate with increasing trends in smoking prevalence among them. Smoking appears to delay the clearance of anal HPV infection, leading to an increased risk of anal cancer.

- In this study, age-specific incidence of anal cancer has shown to be greater in the older age categories, peaking among the 80+ years of age population. Age is one of the main risk factors of cancer due to a number of interrelated biological phenomena (i.e., long-life accumulative oxidative stress and DNA damage, cellular senescence, immunosenescence, inflammageing, etc.). Underpinning this argument, we have found almost no anal cancer cases among the age category 0-19 years of age in all 3 study countries.
  - Because the number of people reaching older ages is increasing rapidly, a raise in the incidence rates for many types of cancer, including anal cancer, is likely to occur.
  - *Cervarix* has proven protection against HPV-16/18 anal infection and this depends on vaccination policies, vaccine coverage, and the degree of herd immunity achieved, but as anal cancer may take several decades to develop and HPV vaccines (including *Cervarix*) were only implemented about 10-15 years ago, it is too early to detect the impact of the vaccine on anal cancer incidence at a population level, in addition only few age classes were targeted for vaccination. Despite HPV vaccination, it is unlikely that drastic reductions in anal cancer will be observed in the very next decades as anal cancer will occur more frequently among the older age categories, both in men and women, who have not been exposed to the vaccine. Moreover, among men, the highest risk lies with the MSM community that have been shown to benefit less from herd immunity of females-only HPV vaccination policy, than heterosexual men. All 3 countries, England, Finland, and most recently the Netherlands, have introduced a gender-neutral HPV vaccination approach in their NIPs. However, these programmes started later than the routine females-only vaccination schedules and thus, impact of this new approach will take some more time to manifest. Therefore, even if a decreasing trend in the incidence of anal cancer was observed for Finland in the post-*Cervarix* launch period (ACP - 1.09%) vs. the pre-*Cervarix* launch period (ACP 2.99%), prudence mandates caution in the interpretation and invites to reassess this trend in the final report (2026). As a reflection, this study has not found statistically significant differences in incidence rates increase between the pre-, and post-*Cervarix* launch periods in the different multivariate analyses for any of the study countries.
- The only country providing information on histological classification of anal cancer was England. The study has shown increasing trends in incidence rates of SCC over time, with age, and as the most predominant type of anal tumour among both sexes. Anal SCCs are mainly HPV-related. At present, 88% of all anal SCC tumours are usually HPV positive with geographical variations. HPV 16 is the most frequently identified type, present in 86% of the cases, although co-infection with different HPV types may occur. Therefore, in the absence of causal HPV type information, it can be inferred that most anal cancer cases from England in this study were HPV-related. Little is known about risk factors for adenocarcinoma. Considering that histologically the rectum mainly consists of glandular cells instead of squamous

cells, it has been hypothesised that adenocarcinoma cases may have originated in the rectum and have been miscoded to anal cancer. Assessing if this has occurred in this study and to which extent it may have occurred is beyond the scope of this analysis.

- Changes in trends may occur over time for reasons other than HPV vaccination (i.e., changes in the surveillance and reporting system, increment of anal cancer diagnosis due to increased awareness among physicians, implementation of an anal cancer screening programme). In order to control for potential changes in the surveillance and reporting of anal cancer over time, we proposed to describe trends of another cancer that shares similar characteristics (similar incidence, similar mean age of diagnosis, absence of a screening programme) but is not HPV-related. Negative controls are often used in observational studies to allow detection of confounding and other sources of bias. In this study, we have included a negative control (small intestine cancer).
  - In this analysis we have not observed any particular array or disruption of the data that makes us think that there has been a surveillance artifact. Small intestine cancer also increased steadily over time and with age, although sex distribution is different to that of anal cancer as it is more prevalent in men than in women.
- Data from the national cancer registries have been accessed by directly downloading the data form the publicly available websites (the Netherlands, and Finland) or through request to the cancer registry in England. However, linkage to vaccination status of each case and control, and other information on risk factors and potential confounders might prove challenging since in some of these countries the different databases of interest are not directly linked and would require additional time and administrative efforts. Furthermore, this information might not be accessible at all.
- The exposure to *Cervarix* during the study period was reduced in England as they switched to the quadrivalent HPV vaccine in 2012, and subsequently to the nonavalent vaccine in 2019, making it difficult to assess the impact of *Cervarix* alone if brand information for every case and control is not available in the vaccine registry.
- Additionally, HPV typing of anal cancer samples is not systematically performed in all 3 European countries or this information is not available at the cancer registry. Therefore, a slight overestimation of the number of cases may occur if all cancer cases are considered as HPV-related (according to the scientific literature around 90% of all anal cancer cases are HPV-related).

Conclusion

The incidence of anal cancer in Finland, the Netherlands, and England increased over time throughout the study period. Anal cancer incidence increased with age and was higher in females compared to males. There was no difference in terms of evolution of incidence rates for anal cancer in the pre-*Cervarix* launch period compared to the post-*Cervarix* launch period in all 3 countries. However, since anal cancer may take decades to develop, it is possible that not enough time has passed from the introduction of *Cervarix* in the respective NIPs to detect a measurable impact of the vaccination on anal cancer at a population level. The use of small intestine cancer as a negative control was

subject to the same potential sources of bias as anal cancer but not to the exposure (HPV), demonstrated a similar trend, suggesting that the anal cancer data were not likely to have been affected by surveillance artifacts.

A feasibility assessment was performed to calculate the required sample size for a case-control study (i.e., with several scenarios for combinations of different vaccine coverage and VE estimates, and case to control ratios). The overall assessment showed that the estimated sample size, would demand a considerable amount of time in all the selected countries, making it difficult to achieve it within a reasonable time frame, in light of the current interim analysis. Moreover, if countries switch to another vaccine brand or the vaccine coverage drops drastically during the conduct of the study, it will jeopardise the study's ability to provide the planned results. This has already occurred in England where *Cervarix* was replaced by *Gardasil* in 2012 making it difficult to disentangle specific VE attributable to *Cervarix* alone. Additionally, the inaccessibility to individual vaccination status of subjects identified through the cancer registry in some countries (i.e., the Netherlands) is a major drawback since it precludes the conduct of the study. The likely unavailability of information in the cancer registries on vaccine uptake determinants, risk factors, and potential confounders will limit the information derived from the analysis.

In conclusion, as population-based registries are constantly evolving and establishing links with other national healthcare and demographic databases, we will reassess the feasibility for a case-control study prior to the final report in 2026 as we consider that a robust and statistically powered case-control study to determine the VE of *Cervarix* against anal cancer cannot be proposed at this stage.

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Not applicable as this is a retrospective database study.

2. LIST OF ABBREVIATIONS

AIN	Anal intraepithelial neoplasia
APC	Annual Percentage Change
CI	Confidence interval
CRN	Cancer Registry of Norway
DNA	Deoxyribonucleic acid
EU-RMP	European Union Risk Management Plan
FCR	Finnish Cancer Registry
GPP	Good Pharmaco-epidemiology Practices
GSK	GlaxoSmithKline Biologicals SA
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IR	Incidence ratio
MAH	Marketing Authorisation Holder
MSM	Men who have sex with men
NCR	Netherlands Cancer Registry
NCRAS	National Cancer Registration and Analysis Service
NIP	National Immunisation Programme
PASS	Post-authorisation safety study
PHE	Public Health England
SAP	Statistical analysis plan
SCC	Squamous cell carcinoma
TSS	Targeted safety study
UK	United Kingdom
VE	Vaccine effectiveness
VLP	Virus-like particle
WHO	World Health Organisation

3. ETHICS

Not applicable, as this study is an observational, retrospective PASS, based on data extracted from the national cancer registry databases.

3.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Not applicable.

3.2. Ethical conduct of the study

Not applicable.

3.3. Subject information and consent

Not applicable.

4. INVESTIGATORS

Not applicable as this is a retrospective database study.

5. OTHER RESPONSIBLE PARTIES

GlaxoSmithKline Biologicals SA has the overall responsibility for the conduct of the study.

PPD, MD, Clinical & Epidemiology Project Lead, GlaxoSmithKline Biologicals SA.

6. MILESTONES

Milestone	Planned date	Actual date
Start of first round data collection	Quarter 3, 2021	12 August 2021
End of first round data collection	Quarter 4, 2021	25 January 2022
Interim report of study results	Quarter 1, 2022	To be updated later
Start of second round data collection	Quarter 3, 2026	-
End of second round data collection	Quarter 4, 2026	-
Registration in the EU PAS register	To be determined	-
Final report of study results	Quarter 1, 2027	-

7. RATIONALE AND BACKGROUND

Cervarix is a prophylactic HPV vaccine developed by GSK. It is based on the L1 proteins of HPV-16 and HPV-18 formulated with AS04 (comprising of aluminium hydroxide [$Al(OH)_3$] and 3-*O*-desacyl-4'-monophosphoryl lipid A), and is indicated for use from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal, and anal); and cervical and anal cancers causally related to certain oncogenic HPV types [*Cervarix* Summary of Product Characteristics, 2021].

In the context of the European Union Risk Management Plan (EU-RMP) for *Cervarix*, a safety concern was raised linked to missing information on the impact and effectiveness of the vaccine against anal lesions and cancer, since it was not prospectively evaluated in clinical trials.

Anal cancer is an uncommon type of cancer, representing around 0.3% of all incident cancers diagnosed in 2020 worldwide [Sung, 2021]. SCC is the most frequent histopathological type of anal cancer [Hoff, 2017]. There is evidence to suggest that HPV infection is associated with anal cancer, particularly with SCC [Hoff, 2017; De Martel, 2020]. Moreover, in a recent worldwide study, HPV DNA was detected in more than 88% of anal cancers and more than 95% of AIN grades 2/3. HPV-16 was the most frequently detected virus type, detected in over 80.7% of invasive anal cancer cases, followed by HPV-18 (3.6% of cases) [Alemany, 2015; Clifford, 2019]. Over the last 4 decades, anal cancer incidence has been gradually increasing and is more common in women than in men, except for certain high-risk groups such as HIV-infected people, and this raise is more relevant in high - income countries [Lum, 2020]. Risk factors for anal cancer are HPV infection, including a former HPV-related malignancy, HIV infection, more than 10 lifetime sexual partners, ano-receptive intercourse, chronic immunosuppression, cigarette smoking, a history of gynaecological or haematologic malignancy, and age. Hence, HIV and immunocompromised patients, and MSM are particularly vulnerable populations [Nelson, 2017; Van der Zee, 2013; Clifford, 2021].

An observational study of effectiveness of *Cervarix* against HPV anal positivity in Dutch women showed a pooled VE of approximately 90% for HPV - 16/18 [Woestenberg, 2020], with adjusted VEs of 88.2% (95% confidence interval [CI], 41.3% – 97.6%) against anal HPV-16 and 91.9% (95% CI, 30.5% – 99.1%) against anal HPV-18 [Woestenberg, 2020]. The results also demonstrated cross-protection against anal HPV-45 and HPV-31 and a high correlation between anal and cervicovaginal VE. The results support the notion that *Cervarix* may offer protection against HPV-related anal cancer (including cross-protection against HPV-31/33/45) [Clifford, 2019].

Furthermore, a recent study using a quadrivalent HPV vaccine (types 6, 11, 16, and 18) among young MSM aged 16-20 years provides evidence of reduction in the prevalence of HPV, including a reduction in anal HPV-16 prevalence, which could lead to a decrease in anal cancer incidence, since HPV-16 is the HPV type most frequently associated to anal cancer. The study demonstrated a 69% reduction in the prevalence of anal HPV-16/18 and a 70% reduction in the prevalence of anal HPV-16 following HPV vaccination [Chow, 2021].

Population-based cancer registries are platforms that collect, store, validate, and analyse data on incidence and survival of the most relevant types of cancer and are crucial for the planning and evaluation of prevention activities. For instance, the World Health Organisation (WHO) global initiative to eliminate cervical cancer points to sound surveillance and monitoring systems as crucial to monitor the evolution of cervical cancer incidence and the impact of interventions over time [WHO, 2020; Piñeros, 2021].

This study assessed the data on anal cancer in countries where *Cervarix* vaccination has been introduced in the NIP. Five European countries were initially selected to perform a trend analysis and to assess feasibility for a case-control study: Finland, the Netherlands, England, Denmark, and Norway.

Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting system, data of small intestine cancer in the same population was analysed. Small intestine cancer is relatively rare, with an occurrence of similar magnitude to anal cancer. Small intestine cancer also has a similar mean age of diagnosis as anal cancer, and there is no screening programme for it. It is not associated with HPV infection. This analysis may allow to control for potential changes in cancer surveillance systems and reporting over time.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries aiming to determine the impact and effectiveness of *Cervarix* against anal cancer in females and males.

Please refer to Section 6 for details on study milestones.

8.1. Primary objectives

- To assess trends and changes over time in the age-standardised incidence of anal cancer by sex, HPV type, and histological classification for each country* separately.
- To assess trends and changes over time in the crude incidence of anal cancer by age category, sex, HPV type, and histological classification for each country* separately.

8.2. Secondary objective

- To conduct a feasibility assessment for a case-control study to determine the impact and effectiveness of *Cervarix* against anal cancer.

**Five European countries are considered for this study, and each country was selected based on a set of criteria (please refer to Section 9.2 of the protocol [Appendix 17.1.1] for country eligibility criteria).*

9. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	31 March 2022	Section 4 Abstract, Section 8 Primary objective and Section 9.3.1.1 Primary endpoint	Primary objective and its corresponding endpoint updated	For clarity: The primary objective and its corresponding endpoint has been split into 2 independent objectives and endpoints, respectively (i.e., for age-standardised incidence and for crude incidence)
		Section 4 Abstract and Section 9.1.1 Discussion of study design	Study population updated	For better interpretation of the study results so it can be comparable with publications across countries and to align with the age definition as per the European standardised population, the entire age group from 0 – 80+ population will be considered instead of the adult population (>18 years of age)
		Section 4 Abstract and Section 9.1.1 Discussion of study design	Study population updated	Study period (i.e., pre- and post-*Cervarix* launch period) will be considered based on the *Cervarix* introduction in the National Immunisation Programme (NIP)
		Section 4 Abstract, Section 7 Rationale and background, Section 8 Research question and objectives, Section 9.4.3 Websites of national public health institutes and Section 9.9 Limitations of the research methods	County specified: Changed from United Kingdom (UK) to England	For the UK, all analyses will be based specifically on data from England, and not data from UK. The National Cancer Registration and Analysis Service (NCRAS) is the cancer registry in England. As the population of England comprises around 84% of the total UK population, the NCRAS is considered to be representative of the population in the UK
		Section 9.7.2.1 Primary analysis	Inclusion of Poisson / Negative binomial regression model for pre- and post-*Cervarix* launch periods	The trend in the incidence of anal cancer and small intestine cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer/small intestine cancer incidences as outcome variable and

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
				calendar year as the independent variables. The model will include the population followed up as the offset variable. APC will be estimated based on the parameter estimates of the regression model. The same model will be generated for the pre- and post-*Cervarix* launch periods separately
		Section 4 Abstract and Section 9.4.2 Eurostat	Data source updated	Eurostat will be the source for population data and birth cohort data, except for England, for which the source for population data will be UK Health Security Agency and for birth cohort data it will be Office for National Statistics
		Section 9.7.2 Statistical analysis	Updated to clarify HPV type and histological classification assessment	A sentence has been added to clarify HPV type and histological classification assessment
		Title page, Section 3 Responsible parties and Section 4 Abstract	Sponsor signatory updated	Change in the study team
2	25 May 2022	Section 4 Abstract, Section 8.2 Secondary objective and Section 9.3.1.2 Secondary endpoint	Secondary objective and its corresponding endpoint updated	• The feasibility assessment for a case-control study to determine the effectiveness of *Cervarix* will be conducted only against anal cancer. The data for anal lesions is not available in the cancer registries • Expected number of anal cancer cases is the endpoint which can be used to estimate the time frame by when the estimated sample size for a case-control study would be reached
		Section 9.1.2 Feasibility assessment	Feasibility assessment updated	Additional information added for clarity
		Section 4 Abstract, Section 9.4 Data sources	Data sources updated	Vaccination registry for each of the 5 selected European countries was added
		Section 9.7.2.2 Secondary analysis	Secondary analysis updated	Additional information added for clarity

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
		Section 9.9 Strengths and limitations of the research methods	Updated to add the strengths of the study	Additional points on strengths of the study included
		Title page and Section 3 Responsible parties	Marketing Authorisation Holder (MAH) contact person updated	The sponsor signatory should be the MAH contact person

10. RESEARCH METHODS

10.1. Study design

10.1.1. Discussion of study design

- **Type of study and design**: A TSS and a PASS. An observational, retrospective database study.
- **Study population**: Females and males of all age groups in the 5 selected European countries.

Please refer to Section 9.2 of the protocol (Appendix 17.1.1) for country eligibility criteria.

- **Data collection**: Retrospective data collection from national cancer registries.
- **Study period**:
  - Pre-*Cervarix* launch period (i.e., before *Cervarix* introduction in the NIP): The start and end calendar year for each country was considered based on the data availability in their respective cancer registries.
  - Post-*Cervarix* launch period (i.e., after *Cervarix* introduction in the NIP): The start calendar year for each country was the date when *Cervarix* was introduced in their NIP. An interim analysis was performed in 2022. For the analysis, data up to the most recent and complete available calendar year in each cancer registry was considered.
- This study is a trend analysis of incidence of anal cancer in 5 selected European countries. The study assessed data on anal cancer in countries where *Cervarix* vaccination has been introduced in the NIP. Five European countries were initially selected to perform a trend analysis and to assess feasibility for a case-control study: Finland, the Netherlands, England, Denmark, and Norway. However, the interim analysis was performed for 3 European countries: England, the Netherlands, and Finland. It was not performed for Denmark and Norway. In Denmark, *Cervarix* was only introduced in the NIP from February 2016 until November 2017 and the doses applied thereafter have been reported mainly from the private market (refer to Annex 5). The vast majority of females vaccinated against HPV in Denmark have received the quadrivalent HPV vaccine (refer to Annex 5). In Norway, *Cervarix* was only introduced in the NIP in September 2017 (refer to Annex 5). Hence, a decision was

made to focus the study on those countries that administered *Cervarix* for at least 5 birth cohorts (either routine or catch-up campaign cohorts), or that have implemented *Cervarix* in their NIPs in a continuous manner since the introduction in their NIP (refer to Section 9.2 of the protocol [Appendix 17.1.1] for details on country eligibility criteria). The analysis for Denmark and Norway maybe performed during the final analysis, planned in 2026, depending on the data availability during that time.

- Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population was analysed. Small intestine cancer is relatively rare, with an occurrence of similar magnitude to anal cancer. Small intestine cancer also has a similar mean age of diagnosis as anal cancer, and there is no screening programme for it. It is not associated with HPV infection. This analysis may allow to control for potential changes in cancer surveillance systems and reporting over time.

10.1.2. Feasibility assessment

As mentioned above, the objectives of the feasibility assessment are:

- To describe the main requirements for the conduct of an additional study assessing the effectiveness of *Cervarix* in the prevention of anal cancer
- To assess a case-control study design and the data sources that would meet those requirements

Apart from the background and rationale, the interim report includes an overview on the main methodological requirements, sample size estimations, data sources needed to perform this case-control study and the time frame when the case control study could be conducted.

10.1.2.1. Context and rationale

After the inclusion of the indication of anal cancer in the EU label of *Cervarix* (29 July 2016), there is a need to assess the impact and effectiveness of *Cervarix* against anal cancer.

Monitoring trends of anal cancers to reveal the impact of vaccination can be challenging due to the need of robust baseline data before the implementation of vaccination, hurdles in the interpretation of year-to-year variations in natural trends and changes for reasons other than HPV vaccination. Moreover, a significantly high vaccine coverage might be needed to demonstrate the impact of the vaccine by ecological methods such as a trend analysis.

Therefore, the impact in the real world or effectiveness of the vaccine might be better assessed by the conduct of epidemiological studies such as case-control studies. Using a case-control design, VE can be estimated comparing the proportion of vaccination exposure among anal cancer cases with the proportion of vaccine recipients among control patients who are free of an HPV-related cancer.

A case-control study represents a classical approach to determine VE (in a real world setting) and it also offers an opportunity to investigate other aspects such as assessing VE in incomplete vaccination (i.e., not a full vaccination schedule).

However, generating evidence in a real world setting is challenging. Establishing the association between vaccine exposure and rare outcomes such as anal cancer may require a large sample size. Feasibility assessments are helpful in planning and designing optimal studies by providing information on the scientific and operational feasibility of the study.

The feasibility assessment for a case-control study was conducted considering the 3 European countries that were approached for the trend analysis. The interaction with the national cancer registries was to provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). A feasibility assessment requires consideration of several other important factors apart from sample size calculation, such as use of a standard case definition for anal cancer (i.e., WHO International Classification of Diseases [ICD]-10 classification), possibility to determine HPV vaccination status through linkage to vaccine registries in the relevant countries, allowing an adjustment for potential confounders (e.g., age, sex, socioeconomic status, health seeking behaviour, access to medical care etc.) for cases and controls, choice of controls and ratio of cases to controls. Since the sample size is determinant and a limiting factor for the conduct of the study, we have attempted to estimate the sample size in this interim analysis. This exercise was intended to facilitate the understanding whether this case-control study to determine vaccine effectiveness against anal cancer can be performed.

10.1.2.2. Main feasibility requirements

10.1.2.2.1. Outcome assessment

Background on anal cancer

Refer to Section 7 for details on the rationale and background.

Case definition for the purpose of the case-control study

A case definition needs to be established to accurately identify anal cancer cases and mitigate the risk of misclassification in the analyses. This is key and requires tailoring depending on the type and format of available information recorded in the data source (e.g., medical records or claims data, prescription data, laboratory data, imaging data). The existence of a validated case definition is an important criterion to consider when selecting a data source. Ideally the WHO ICD-10 classification should be used (preferably ICD-10 code C21 for anal cancer). In addition, information on HPV typing for every anal cancer case is required.

Exposure

The HPV vaccine brand and the date of administration of the different doses to the study subject must be recorded and be reliable. In countries where different brands of HPV vaccine are/have been used (in particular when the 2 brands [i.e., *Cervarix*, *Gardasil* or *Gardasil 9*] were used during the same period), availability of the vaccine brand data is a key factor to consider in the feasibility assessment.

Information on the exposure (i.e., *Cervarix* vaccination) for every case or control is needed for the study. All 3 European countries have vaccine registries (see Section 9.4 of the protocol [Appendix 17.1.1] for details on study data sources).

Please see Annex 5 for details on the vaccine schemes and policies in the selected European countries.

Covariates of interest/Confounders

The determinants of HPV vaccine uptake and risk factors for anal cancer to identify potential confounders were reviewed.

Determinants of HPV vaccine uptake:

Different studies have pointed to several predictors of HPV vaccination, including race or ethnicity, age, health insurance status, health care utilisation, previous vaccination history and knowledge about HPV, cervical cancer and the HPV vaccine. Deprivation has also been shown to predict the uptake of vaccination [Kessels, 2012; Rockliffe, 2017].

Other studies have found that the proportion of immigrants and foreigners was associated with lower vaccination coverage. At the individual level, the use of medical services (number of reimbursed pharmaceutical and medical procedures) was associated with vaccine-seeking behaviour [Héquet, 2017].

Risk factors for anal cancer:

Risk factors for anal cancer are HPV infection, including a former HPV-related malignancy, HIV infection, more than 10 lifetime sexual partners, anoreceptive intercourse, chronic immunosuppression, cigarette smoking, a history of gynaecological or haematologic malignancy, and age [Nelson, 2017; Van der Zee, 2013; Clifford, 2021].

Additionally, and in relation to HPV infection, the various HPV genotypes have different oncogenic potential. HPV-16 is the most common type detected (73% of all HPV-positive anal tumours) followed by HPV-18 (approximately 5% of cases) [De Martel, 2020; De Vuyst, 2009; Bruni, 2021]. Therefore, HPV type can be also considered as a risk factor for anal cancer.

Co-variates to consider:

Based on the determinants of HPV vaccination and risk factors for anal cancer mentioned above, the following variables are worth considering in the analysis, whenever available:

- Sex (even if in some countries male vaccination is recommended, females have predominantly been exposed to HPV vaccination and are the main population of interest). Furthermore, women show higher incidence of anal cancer, particularly in high-income countries
- Age
- HPV type
- Race and ethnicity
- Region of residency (or any other proxy variable for socioeconomic status)
- Sexual behaviour and practices
- Other vaccinations
- Use of healthcare resources
- Smoking
- Concomitant condition (i.e., HIV, other cancer, immunosuppression)

However, we expect that complete and accurate or any information on some of these covariates may not be available in the databases that we are accessing for the conduct of this study.

10.1.2.3. Study design and sample size estimation

This section presents a potential study design for the conduct of a case-control study assessing the Vaccine Effectiveness (VE) of *Cervarix* against anal cancer, as well as the sample size estimations and other factors. For this analysis, a prospective database matched case-control study is proposed, having as main data source the national cancer registry in every selected country to retrieve the cases and controls. VE will be calculated as follows: VE=(1-OR)*100. Matched OR for vaccination will be estimated via conditional logistic regression analysis.

10.1.2.3.1. Matched case-control study

Case: Female who has been or is eligible for HPV vaccination (according to the routine HPV NIP) with a diagnosis of HPV-related anal cancer.

Control: Female who has been or is eligible for HPV vaccination (according to the routine HPV NIP) with a diagnosis of a non-HPV-related cancer (e.g., colon cancer, an aetiology mainly related to genetic and dietary factors, or any other type of cancer that is not HPV-related) and retrieved from the same cancer registry to ensure that the comparison group is representative of the source population that produced the cases.

Matching factor: Age.

Vaccination status: Cases and controls will be exposed to HPV vaccination if they had received at least 1 dose of *Cervarix*.

Method and software: Prospective-database matched case-control analysis.

Sample size estimation:

The following parameters have been considered for the sample size calculation:

- Two-sided CI (1-alpha): 95%
- Power: 80%
- Ratio of cases to controls: Several scenarios have been contemplated: case to control ratio 1:1, 1:2, 1:3, and 1:4 (Table 14.2.1.17, Table 14.2.2.15, and Table 14.2.3.15).
- Hypothetical proportion of controls with exposure: Different scenarios of 90%, 80%, 60%, 40%, and 30% of vaccine coverage have been considered for the sample size calculation.
- VE: Different scenarios of 90%, 80%, 70%, 60%, 50%, 40%, and 30% of vaccines effectiveness have been considered for the sample size calculation.
- Allowance for a dropout rate of 30%

For the estimation of the required number of cases to conduct a case-control study and the year when the required sample size would be reached, the following parameters were considered or calculated:

- Year of introduction of *Cervarix* in the NIP (2008 for England, 2009 for the Netherlands, and 2013 for Finland) (see Annex 5).
- Starting point (year) for the case -control study including cases aged 25 years (i.e., when the first ever vaccinated birth cohort turns 25 years of age: 2020 for England, 2021 for the Netherlands, 2025 for Finland [see Annex 5]).
- Average female birth cohort size: Rounded up average from the latest 10 years for each country from the respective data source (Eurostat for Finland and the Netherlands, and Office for National Statistics for England) (Table 14.2.1.16, Table 14.2.2.14, and Table14.2.3.14).
- Average crude incidence (per 100000) by age category: Calculated as the average of the estimated crude incidence of anal cancer for every age category from 2014 to 2018 for England, from 2016 to 2020 for the Netherlands and from 2015 to 2019 in Finland (the respective national cancer registries are the data source for the estimated crude incidence).

The number of cases is calculated by incrementing year (adding a new birth cohort) and adjusting for the incidence rate in that age category. For example, for the Netherlands, in 2021, there would be 1 cohort. In 2022, there would be 2 cohorts, and in 2023 there would be 5 cohorts of ≤ 29 years of age. In 2024, there would be 5 cohorts of ≤29 years of age and 1 cohort of 30 years of age. Therefore, the incidence rate of every included birth cohort is considered accordingly in computing the total number of cases and the cumulative number of cases for every calendar year. For this analysis, only female

cohorts vaccinated within the routine NIP have been considered, and not those vaccinated under catch-up campaigns.

To facilitate the interpretation of the results of the required sample size estimation we have focused on the following combined scenarios for every selected country:

- *Cervarix* vaccine coverage estimates of 60% and 80% that represent a moderate and an optimistic vaccine coverage scenario (Table 14.2.1.15, Table 14.2.2.13, and Table 14.2.3.13).
- *Cervarix* effectiveness estimates of 60% and 90% (based on results from the Costa Rica vaccine Trial [Kreimer, 2011], and data from the Netherlands on vaccine effectiveness of *Cervarix* on anal HPV 16/18 infection) [Woestenberg, 2020].
- Case-control ratio of 1:1 and 1:4.

10.1.2.4. Data sources in selected countries

10.1.2.4.1. Exposure to Cervarix by country

Date of introduction of *Cervarix* in the NIP of the selected countries, as well as the different schemes and vaccination policies are displayed in Annex 5.

10.1.2.4.2. Datasources

Existing databases in selected countries

- National cancer registries

An exhaustive description of the national cancer registries has been included in Section 9.4 of the protocol (Appendix 17.1.1) and Section 2.3 of the SAP (Appendix 17.1.4).

- Vaccination registries

All the selected countries have a vaccination registry in place:

Country	Vaccination registry
Finland	Finnish National Vaccination Registry since 2009
The Netherlands	Dutch vaccination registry (Præventis) since 2005
UK/England	Immunisations are registered in the Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002).

10.1.3. Case definition

In this study, for case identification of anal cancer and small intestine cancer, [ICD-10] codes were used (i.e., C21 for anal cancer and C17 for small intestine cancer).

For histological classification of anal cancer, the WHO ICD-O-2 (or) 3 was used based on the coding version of the cancer registries in the selected countries.

10.2. Setting

Refer to Section 9.2 of the protocol (Appendix 17.1.1) for details on country eligibility criteria.

10.3. Subjects

Refer to Section 9.2 of the protocol (Appendix 17.1.1) for details on country eligibility criteria.

10.4. Variables

Refer to Section 9.3 of the protocol (Appendix 17.1.1) for details on study variables.

10.5. Data sources and measurement

Refer to Section 9.4 of the protocol (Appendix 17.1.1) for details on study data sources.

10.6. Bias

Epidemiological studies are subject to bias. However, this study has controlled for the most important biases affecting ecological studies. Data were obtained from national cancer registries that have a quality assurance system in place, ensuring the validity and completeness of the data. Additionally, the cancer registries in the 3 European countries are nationwide and population-based, which ensures representativeness in a real world setup, gathering a large sample size followed for decades, and informing of a rare outcome such as anal cancer for the whole population. The completeness of the data has minimised a potential selection bias. The use of a harmonised, standardised, and universal case definition (i.e., ICD-10 classification) guarantees accuracy in the outcome measurement and comparability across the 3 European countries.

The approach to the statistical analysis (i.e., multivariate models) has allowed to control for potential known confounders (i.e., age and sex).

10.7. Study size

Sample size computation for the primary objective is not applicable, as there is no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 3 European countries were collected within the established timeframe.

Note: National cancer registries are nationwide and thus this study is population-based.

10.8. Data transformation

10.8.1. Data collection

Refer to the protocol (Appendix 17.1.1) Section 9.3 for details on study variables and Section 9.4 for details on study data sources.

10.9. Statistical methods

10.9.1. Main summary measures

- All primary and secondary endpoint analyses were performed for each country separately.
- Exact Poisson 95% CI was presented for incidences [Ulm, 1990].
- Normal approximation of the log transformed Maximum Likelihood Estimate method was used to derive the 95% CI of age-standardised incidences [Ng, 2008].
- The Wald's 95% CI was presented for the Poisson / negative binomial regression estimates and for the percentage reduction of the anal cancer cases in the observed counts compared to the predicted counts.

10.9.2. Main statistical methods

10.9.2.1. Analysis for primary endpoints

Refer to Section 5.2 of the statistical analysis plan (SAP) (Appendix 17.1.4) for the primary endpoint analysis planned to be performed in the study.

10.9.2.2. Analysis for secondary endpoint

Refer to Section 5.3 of the SAP (Appendix 17.1.4) for the secondary endpoint analysis planned to be performed in the study.

10.9.3. Missing values

Number of cancer cases are provided by calendar year, sex and age category. The cancer registry of Finland does not provide this data when there are less than 5 cases reported in a given year, by sex and age category, due to potential risk of patient identification. However, in those instances, the number of cancer cases were back-computed using the provided crude incidence and population data. This did not have an impact on the total number of cases.

10.9.4. Sensitivity analyses

Not applicable for this study.

10.9.5. Amendments to the statistical analysis plan

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
Amendment 1	2 June 2022	Amendment 1 (25 May 2022)	Primary objective updated for more clarity	Primary objective, study period (based on the introduction of *Cervarix* in NIP) and data source (European standard population) aligned to the update in the protocol amendment
			Study population updated	For better interpretation of the study results so it can be comparable with publications across countries and to align with the age definition as per the European standard population, inclusion of all age groups instead of adult population (>18 years of age)
			County specified: Changed from United Kingdom (UK) to England	For the UK, all analyses will be based specifically on data from England, and not data from UK. The National Cancer Registration and Analysis Service (NCRAS) is the cancer registry in England
			Inclusion of Poisson / Negative binomial regression model for pre- and post-*Cervarix* launch periods	To see the change in trends pre and post *Cervarix* launch periods; to have more clarity and to compare the trend
			Inclusion of year variable in multivariate Poisson / Negative binomial regression model.	To adjust the segmented effect of the model, the year variable is added in the multivariate Poisson / Negative binomial regression model
			Secondary endpoint updated	More appropriate is to mention the number of anal cancer cases as the endpoint to evaluate the time frame to conduct a case control study, based on the vaccine coverage rate, expected vaccine effectiveness and other factors like crude incidence and birth cohort

10.10. Quality control

To ensure compliance with Good Pharmaco-epidemiology Practices or other applicable guidelines and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study.

Note: For the interim analysis, there was no quality assurance audit conducted by GSK. There was also no regulatory inspection conducted by a regulatory agency.

11. RESULTS

The interim analysis was performed for 3 countries: England, the Netherlands, and Finland. It was not performed for Denmark and Norway. In Denmark, *Cervarix* was only introduced in the NIP from February 2016 until November 2017 and the doses applied thereafter have been reported mainly from the private market (refer to Annex 5). The vast majority of females vaccinated against HPV in Denmark have received the quadrivalent HPV vaccine (refer to Annex 5). In Norway, *Cervarix* was only introduced in the NIP in September 2017 (refer to Annex 5). Hence, a decision was made to focus the study on those countries that administered *Cervarix* for at least 5 birth cohorts (either routine or catch-up campaign cohorts), or that have implemented *Cervarix* in their NIPs in a continuous manner since the introduction in their NIP (refer to Section 9.2 of the protocol [Appendix 17.1.1] for details on country eligibility criteria). The analysis for Denmark and Norway maybe performed during the final analysis, planned in 2026, depending on the data availability during that time.

11.1. Participants

- For **England**, population data was available from 1995 to 2019 inclusive. Data was available for both females and males of all age categories (for the purpose of the analysis, age categorisation was done by 10 years).
- For the **Netherlands**, population data was available from 1992 to 2020 inclusive. Data was available for both females and males of all age categories (for the purpose of the analysis, age categorisation was done by 10 years).
- For **Finland**, population data was available from 1992 to 2020 inclusive. Data was available for both females and males of all age categories (for the analysis, data by 10 years age categorisation was considered).

Note: The population data are not shown in this report for 2019 (i.e., for England) and for 2020 (i.e., for Finland), because cancer data were not available for these years.

Refer to Table 14.1.1 for more details.

11.2. Descriptive data

The study population data was available by calendar year and sex (female and male). For the purpose of the analysis, the population data was categorised by 10 years for age (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79 and 80+).

Note: The age categorisation by 10 years was to follow the age categorisation of cancer data in the FCR.

Refer to Table 14.1.1 for more details.

11.3. Outcome data

All analyses were performed for each country separately. The analysis planned by histological classification was only performed for England and the analysis planned by HPV type was not performed for any of the 3 selected European countries. This is because histological classification (i.e., for the Netherlands and Finland) and the HPV type data were not yet available during the time of data extraction for the interim analysis. These analyses maybe performed during the final analysis, planned in 2026, depending on the data availability during that time.

11.4. Main results

11.4.1. Primary and secondary objective results for England

11.4.1.1. Primary objective results for England

In England, between 1995 and 2018:

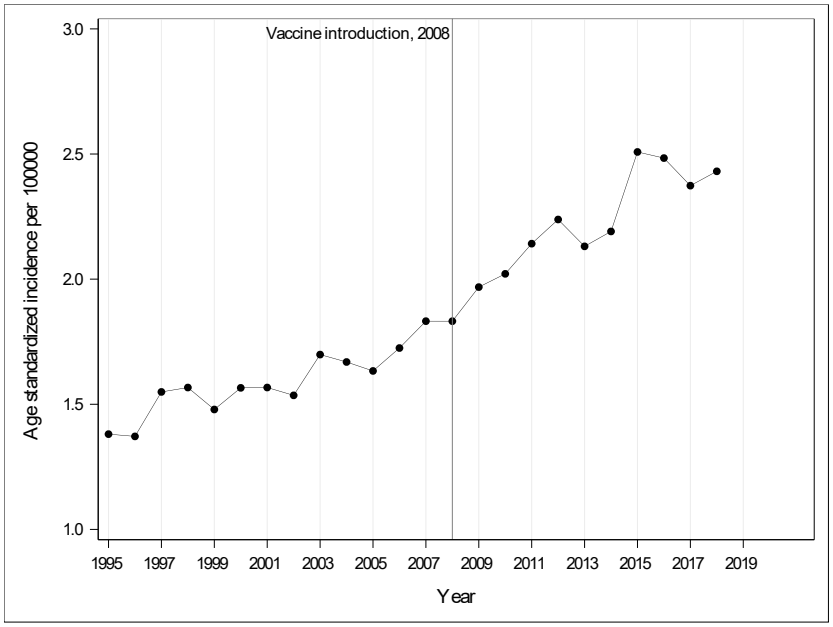
- An increasing trend in the age-standardised incidence and crude incidence of anal cancer was observed over time (Table 11.1, Figure 11.1, and Figure 11.2).
- Overall, the age-standardised incidence rates were higher than the crude incidence rates (Table 11.1).

Table 11.1 Incidence of anal cancer by calendar year – England

			Age-standardised Incidence per 100000			Crude Incidence per 100000		
				95% CI			95% CI	
Calendar Year	N	n	Value	LL	UL	Value	LL	UL
1995	48384614	556	1.381	0.813	2.343	1.149	1.056	1.249
1996	48521172	554	1.372	0.809	2.326	1.142	1.049	1.241
1997	48666657	634	1.549	0.940	2.552	1.303	1.203	1.408
1998	48822555	644	1.567	0.958	2.564	1.319	1.219	1.425
1999	49034531	616	1.479	0.882	2.481	1.256	1.159	1.360
2000	49234229	654	1.566	0.957	2.562	1.328	1.228	1.434
2001	49449746	664	1.567	0.951	2.582	1.343	1.243	1.449
2002	49679267	658	1.536	0.927	2.545	1.324	1.225	1.430
2003	49925517	736	1.699	1.048	2.752	1.474	1.370	1.585
2004	50194600	726	1.669	1.033	2.697	1.446	1.343	1.556
2005	50606034	722	1.633	1.002	2.661	1.427	1.325	1.535
2006	50965186	767	1.725	1.068	2.785	1.505	1.400	1.615
2007	51381093	831	1.832	1.149	2.921	1.617	1.509	1.731
2008	51815853	836	1.832	1.147	2.927	1.613	1.506	1.727
2009	52196381	916	1.968	1.249	3.102	1.755	1.643	1.872
2010	52642452	951	2.021	1.294	3.157	1.807	1.694	1.925
2011	53107169	1022	2.142	1.385	3.313	1.924	1.808	2.046
2012	53493729	1075	2.238	1.466	3.417	2.010	1.891	2.133
2013	53865817	1049	2.131	1.380	3.291	1.947	1.831	2.069
2014	54316618	1098	2.191	1.422	3.374	2.021	1.904	2.145
2015	54786327	1274	2.508	1.675	3.756	2.325	2.199	2.457
2016	55268067	1274	2.484	1.654	3.730	2.305	2.180	2.435
2017	55619430	1238	2.374	1.563	3.605	2.226	2.104	2.353
2018	55977178	1282	2.431	1.616	3.656	2.290	2.167	2.419

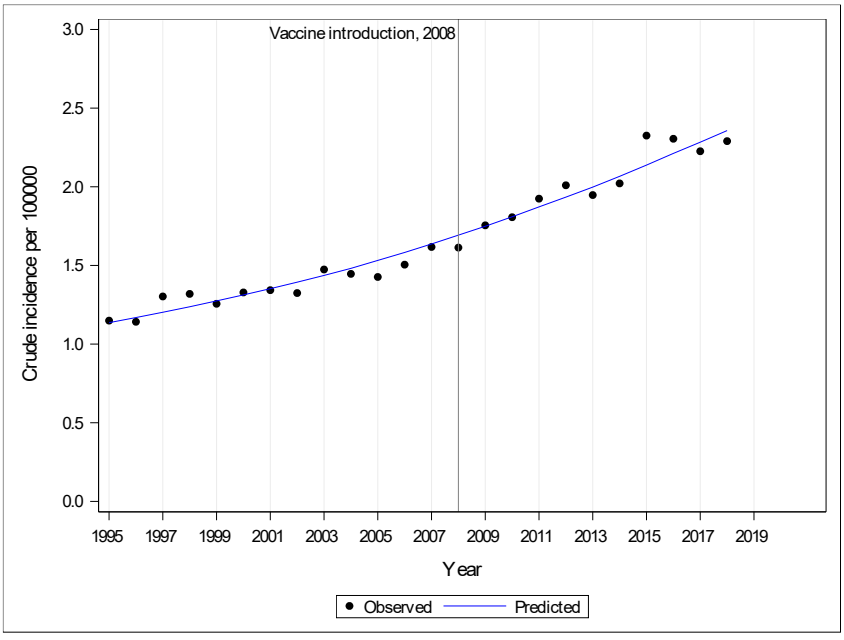
N = population in each category
n = number of anal cancer cases reported
Study period: Pre-*Cervarix* launch (Year 1995 – Year 2007), Post-*Cervarix* launch (Year 2008 – Year 2018)
Age-standardised Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))CI=confidence interval; LL=lower limit; UL=upper limit
Age-standardised Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact Poisson confidence interval
Source : Table 14.2.1.1

Figure 11.1 Trend over time in the age standardised incidence of anal cancer – England



Note: The vaccine introduction year is considered as the year *Cervarix* was introduced in the NIP
Source: Figure 14.2.1.1.1

Figure 11.2 Trend over time in the crude incidence of anal cancer – England



Note: The vaccine introduction year is considered as the year *Cervarix* was introduced in the NIP
Line - Represents the predicted incidence, Period - Represents the observed Incidence
Source: Figure 14.2.1.1.2

Similar results were observed for small intestine cancer (Table 14.2.1.5 till Figure 14.2.1.5.2).

- An increasing trend in the age-standardised incidence and crude incidence of anal cancer was observed over time both in females and males. Females presented higher incidence rates than males, throughout the study period. There was either 1 case or no case of anal cancer reported below 20 years of age. Both in females and males, the crude incidence of anal cancer was similar and almost null for age categories 0-9, and 10-19 years. In females, the age category above 80 years showed the highest crude incidence of anal cancer throughout the year categories considered. Refer to Table 14.2.1.2 till Figure 14.2.1.3.3.

Similar results were observed for small intestine cancer, except that males presented higher age-standardised incidence rate or crude incidence rate, or both than females, throughout the study period: the incidence was highest among the age category above 80 years throughout the year categories considered, although the highest number of cases were presented by age category 70-79 years (Table 14.2.1.6 till Figure 14.2.1.7.3).

- Concerning the histological classification of the tumours, SCCs were the most frequently occurring tumours, followed by adenocarcinomas or other tumours, throughout the study period. Number of cases and thus incidence of SCC, both age-standardised and crude incidence, increased over time. Refer to Table 14.2.1.4 till Figure 14.2.1.4.2.
- A univariate Poisson regression model showed a significantly increasing trend in the incidence of anal cancer. A 3.29% annual increase (APC) in the incidence of anal cancer was observed (Table 11.2). In a separate univariate analysis of the pre-*Cervarix* and the post-*Cervarix* launch periods, an increasing trend in the incidence rate of anal cancer was observed in both periods. The APC for the pre-*Cervarix* and the post-*Cervarix* launch periods are very similar in magnitude and sign (both had positive sign) at 2.44% and 3.46%, respectively (Table 11.3 and Table 11.4).

Table 11.2 Univariate Poisson regression model for incidence of anal cancer – England

			Incidence ratio (e(β))				
				95% CI			
Characteristics	N	n	Value	LL	UL	p-value	Annual Percentage Change (%)
Calendar year	1237954222	20777	1.033	1.030	1.036	<.0001	3.29

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Source: Table 14.2.1.8

Table 11.3 Univariate Poisson regression model for incidence of anal cancer for Pre-*Cervarix* launch (Year 1995 – Year 2007) - England

			Incidence ratio (e(β))				
				95% CI			
Characteristics	N	n	Value	LL	UL	p-value	Annual Percentage Change (%)
Calendar year	644865201	8762	1.024	1.019	1.030	<.0001	2.44

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Source: Table 14.2.1.8.1

Table 11.4 Univariate Poisson regression model for incidence of anal cancer for Post-*Cervarix* launch (Year 2008 – Year 2018)- England

			Incidence ratio (e(β))				
				95% CI			
Characteristics	N	n	Value	LL	UL	p-value	Annual Percentage Change (%)
Calendar year	593089021	12015	1.035	1.026	1.043	<.0001	3.46

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Source: Table 14.2.1.8.2

A univariate Poisson regression model showed a significantly increasing trend in the incidence of small intestine cancer. A 4.82% annual increase (APC) in the incidence of small intestine cancer was observed (Table 14.2.1.10). In a separate univariate analysis of the pre-*Cervarix* and the post-*Cervarix* launch periods, an increasing trend in the incidence rate of small intestine cancer was observed in both periods. The APC for the pre-*Cervarix* and the post-*Cervarix* launch periods are very similar in magnitude and sign (both had positive sign) at 3.75% and 4.61%, respectively (Table 14.2.1.10.1 and Table 14.2.1.10.2).

Note: The overall population at risk (i.e., N) is the sum of the population for every calendar year during the study period.

- A multivariate Poisson regression model was fitted considering the following risk factors: calendar year, age category (by 10-year age groups), *Cervarix* introduction period in the NIP (pre- and post-*Cervarix* introduction periods), and sex. After adjusting for the rest of the variables, the incidence rates of anal cancer increased over time and with age, and there was also strong evidence that the incidence rates of anal cancer were higher in females compared to males. And when comparing the incidence rates between the pre- and post-introduction periods of the *Cervarix* in the NIP, there was no difference observed in the incidence rates (Table 11.5).

Table 11.5 Multivariate Poisson regression model for incidence of anal cancer – England

				Adjusted incidence ratio (e(β))				
					95% CI			
Characteristics	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
Calendar year		1237954222	20777	1.024	1.018	1.030	<.0001	-
Age category (in years)	0-29	467161578	64	Reference	-	-	-	<.0001
	30-39	177023115	571	23.683	16.334	34.339	<.0001	-
	40-49	171763931	2192	92.334	64.587	132.000	<.0001	-
	50-59	152797459	4248	200.108	140.320	285.370	<.0001	-
	60-69	123957930	5175	297.967	209.039	424.724	<.0001	-
	70-79	90195502	4825	380.777	267.092	542.849	<.0001	-
	80+	55054707	3702	458.258	321.203	653.795	<.0001	-
Study period	Pre-*Cervarix* launch	644865201	8762	Reference	-	-	-	0.1699
	Post-*Cervarix* launch	593089021	12015	1.057	0.977	1.144	0.1699	-
Gender	Female	630699438	13080	Reference	-	-	-	<.0001
	Male	607254784	7697	0.688	0.660	0.716	<.0001	-

N = population at risk in each category
n = number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk)+ intercept + (β1 × calendar year) +(β2 × age category) + (β3 × study period) + (β4 × gender)
Adjusted incidence ratio (e(β)) = change in incidence of anal cancer compared to the reference category of each independent variable adjusted for other covariates (Exponentiated regression coefficient – β)
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Study period: Pre-*Cervarix* launch (Year 1995 – Year 2007), Post-*Cervarix* launch (Year 2008 – Year 2018)
Source: Table 14.2.1.9

- In a multivariate Poisson regression model, on stratification by age, the incidence rates of anal cancer were observed to be significatively higher in females when compared to males for all age categories except for the 0-29 age category where there was no difference in the incidence rate of anal cancer observed between females and males. Similarly, there seemed to be no statistically significant difference in the incidence rates of anal cancer over time for the 0-29 age category. However, in all other age categories, incidence rates of anal cancer significatively increased over time. Conversely, there was no difference in the evolution of the incidence rate of anal cancer when comparing the pre- and post-*Cervarix* introduction periods in the NIP for any of the age categories (Table 14.2.1.9.1).
- In a multivariate Poisson regression model, on stratification by sex, the incidence rates of anal cancer significatively increased by age and over time in both sexes. There was no difference observed in the incidence rate of anal cancer when comparing the pre- to the post-*Cervarix* introduction periods in the NIP either for females or males (Table 14.2.1.9.2).
- The multivariate Poisson regression model for incidence of anal cancer by histological classification showed that the incidence rate of anal cancer increased with age for SCC, adenocarcinoma and Other (i.e., other specified carcinoma and unspecified carcinoma, melanoma, other specified malignant neoplasm and

unspecified malignant neoplasm) cancers. The incidence rates of anal cancer were higher in females when compared to males for SCC and Other cancers. The incidence rates of anal cancer were highest in males for adenocarcinoma cancer. When comparing the incidence rates between the pre- and post-introduction periods in the NIP for the different type of cancers, there was no difference observed in the incidence rates for anal cancer among SCC and adenocarcinoma cancers whereas there was some evidence that in the post-*Cervarix* launch period the incidence rates was higher among the "Others" cancer category (Table 14.2.1.9.3).

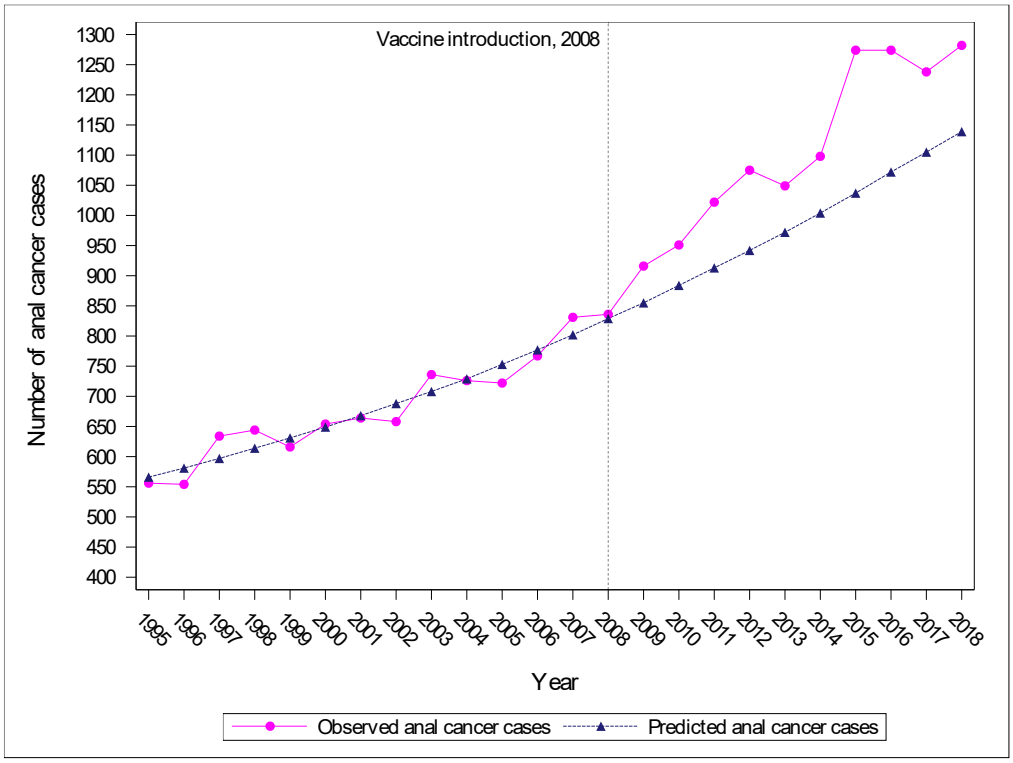
- Since 1995 and until the year of introduction of *Cervarix* in the NIP (2008), the observed number of anal cancer cases were close to the predicted anal cancer cases. Following the introduction of *Cervarix* in the NIP, the observed number of cases depart from the predicted line, indicating an acceleration of the increase in anal cancer incidence. However, this change is to be considered cautiously since confounding by age may have occurred as the population considered for the post-*Cervarix* introduction period may be older (Table 11.6 and Figure 11.3).

Table 11.6 Trend overtime of anal cancer cases by observed counts versus predicted counts – England

					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1995	556	566	10	1.77	-10.43	12.62
1996	554	581	27	4.65	-7.12	15.12
1997	634	597	-37	-6.2	-18.76	5.03
1998	644	614	-30	-4.89	-17.15	6.09
1999	616	631	15	2.38	-9.08	12.63
2000	654	649	-5	-0.77	-12.33	9.6
2001	664	668	4	0.6	-10.67	10.72
2002	658	688	30	4.36	-6.43	14.05
2003	736	708	-28	-3.95	-15.25	6.24
2004	726	729	3	0.41	-10.37	10.14
2005	722	753	31	4.12	-6.19	13.42
2006	767	777	10	1.29	-9.07	10.66
2007	831	802	-29	-3.62	-14.17	5.96
2008	836	829	-7	-0.84	-11.01	8.39
2009	916	855	-61	-7.13	-17.6	2.4
2010	951	884	-67	-7.58	-17.9	1.83
2011	1022	913	-109	-11.94	-22.39	-2.38
2012	1075	942	-133	-14.12	-24.55	-4.56
2013	1049	972	-77	-7.92	-17.76	1.1
2014	1098	1004	-94	-9.36	-19.13	-0.39
2015	1274	1037	-237	-22.85	-33.35	-13.19
2016	1274	1072	-202	-18.84	-28.9	-9.57
2017	1238	1105	-133	-12.04	-21.5	-3.31
2018	1282	1139	-143	-12.55	-21.91	-3.92

Note: Poisson model has been used to predict the counts using the pre-vaccination period from 1995-Most recent available year's data
Model is calculated by, log(No. of anal cancer cases) = log (Population at risk) + intercept + (β × calendar year)
%Reduction = ((predicted counts –observed counts)/ predicted counts)×100
Wald's 95% CI and %reduction was estimated using Poisson model for non-zero observed counts
*Positive sign indicates the reduction and negative sign indicates the increase in observed counts
Source: Table 14.2.1.11

Figure 11.3 Predicted and observed counts of anal cancer cases – England



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP
Source: Figure 14.2.1.11.1

- Refer to Table 14.2.1.12 for the trend overtime of anal cancer cases by observed counts versus predicted counts, by age category (20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and 80+ years).
  - Refer to Figure 14.2.1.12.1 till Figure 14.2.1.12.9 for the predicted and observed counts of anal cancer cases, for each age category. Note that the predicted counts were not estimated for age category 0-9 years (Figure 14.2.1.12.1) and 10-19 years (Figure 14.2.1.12.2), because the number of observed counts for the pre-*Cervarix* period was less than 5.
- Refer to Table 14.2.1.13 for the trend overtime of anal cancer cases by observed counts versus predicted counts, by gender.
  - Refer to Figure 14.2.1.13.1 for the trend overtime of anal cancer cases by observed counts versus predicted counts, by male.
  - Refer to Figure 14.2.1.13.2 for the trend overtime of anal cancer cases by observed counts versus predicted counts, by female.
- Refer to Table 14.2.1.14 for the trend overtime of anal cancer cases by observed counts versus predicted counts, by histological classification.
- Refer to Table 14.2.1.15 for the summary of HPV vaccine coverage in females by year.
- Refer to Table 14.2.1.16 for the summary of birth cohort by year and sex.

11.4.1.2. Secondary objective results for England

11.4.1.2.1. Number of expected anal cancer cases with 80% power to demonstrate VE with assumed vaccine coverage with the estimated timeframe for conducting the matched case-control study

Refer to Table 14.2.1.17:

- Considering 60% vaccine coverage and 60% VE, the required sample size would be 126 cases that, in a case to control ratio 1:1 scenario, would be reached in 2038. In a case to control ratio 1:4 scenario, 70 cases would be required, and the sample size reached in 2035.
- Considering 60% vaccine coverage and 90% VE, the required sample size would be 25 cases that, in a case to control ratio 1:1 scenario, would be reached in 2031. In a case to control ratio 1:4 scenario, 14 cases would be required, and the sample size reached in 2029.
- Considering 80% vaccine coverage and 60% VE, the required sample size would be 160 cases that, in a case to control ratio 1:1 scenario, would be reached in 2040. In a case to control ratio 1:4 scenario, 86 cases would be required, and the sample size reached in 2037.
- Considering 80% vaccine coverage and 90% VE, the required sample size would be 25 cases that, in a case to control ratio 1:1 scenario, would be reached in 2034. In a case to control ratio 1:4 scenario, 13 cases would be required, and the sample size reached in 2031.

11.4.1.2.2. Assessment of the individual vaccination status

In England, HPV vaccination is school-based but there are provisions to administer the vaccine in certain healthcare facilities. Immunisations are registered in the Child Health Information Systems. However, there are limitations in providing data on vaccines given outside of the school setting. At the time of the data request for this interim analysis, PHE, the institution dealing with data requests for NCRAS (PHE ODR) was under a reorganisation and transition to the current UKHSA, and there was no clarity concerning future accountability for the management of the data. Therefore, it was not possible to obtain information about the possibility of linkage between the cancer and the vaccination registries to assess individual vaccination status. For the same reason, it was not possible to assess whether the vaccination registry could provide data about the specific HPV vaccine brand.

11.4.1.2.3. Availability on the covariates of interest in the database

The availability of data on other covariates of interest (apart form age, sex, and HPV type) was not assessed at the time of this interim analysis. Relevant enquiries to the cancer registry will be made to retrieve this information.

HPV genotyping data (or information on at least whether the anal cancer case was HPV-related) was not available at the time of data extraction.

11.4.2. Primary and secondary objective results for the Netherlands

11.4.2.1. Primary objective results for the Netherlands

In the Netherlands, between 1992 and 2020:

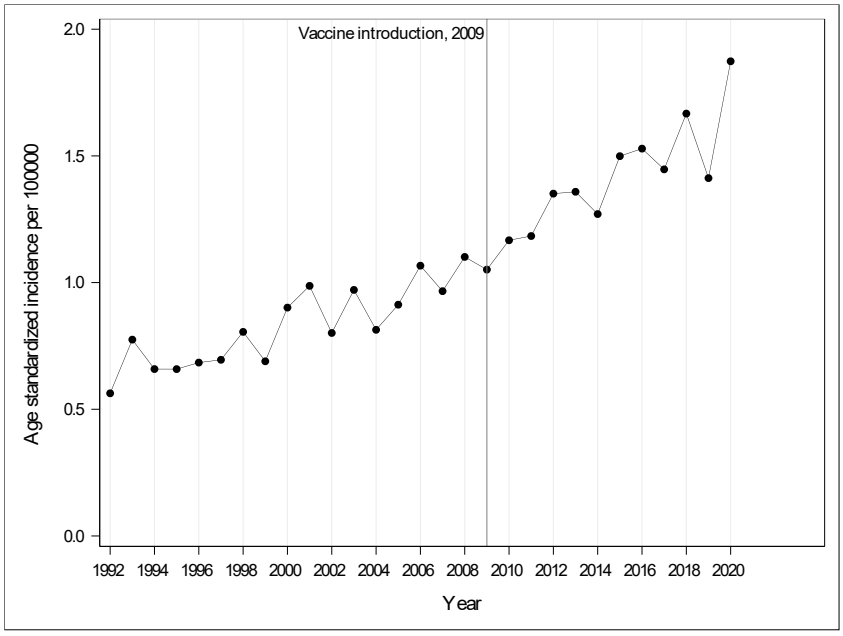
- An increasing trend in the age-standardised incidence and crude incidence of anal cancer was observed over time (Table 11.7, Figure 11.4, and Figure 11.5).

Table 11.7 Incidence of anal cancer by calendar year – Netherlands

			Age-standardised Incidence per 100000			Crude Incidence per 100000		
				95% CI			95% CI	
Calendar Year	N	n	Value	LL	UL	Value	LL	UL
1992	15129150	60	0.563	0.253	1.255	0.397	0.303	0.510
1993	15239182	85	0.775	0.385	1.558	0.558	0.446	0.690
1994	15341553	74	0.659	0.316	1.375	0.482	0.379	0.606
1995	15424122	74	0.659	0.312	1.391	0.480	0.377	0.602
1996	15493889	80	0.684	0.322	1.452	0.516	0.409	0.643
1997	15567107	84	0.695	0.329	1.469	0.540	0.430	0.668
1998	15654192	98	0.805	0.401	1.618	0.626	0.508	0.763
1999	15760225	85	0.689	0.327	1.454	0.539	0.431	0.667
2000	15863950	112	0.901	0.469	1.731	0.706	0.581	0.850
2001	15987075	125	0.987	0.528	1.846	0.782	0.651	0.932
2002	16105285	109	0.801	0.390	1.647	0.677	0.556	0.816
2003	16192572	130	0.971	0.509	1.852	0.803	0.671	0.953
2004	16258032	109	0.814	0.405	1.636	0.670	0.550	0.809
2005	16305526	129	0.913	0.464	1.796	0.791	0.661	0.940
2006	16334210	152	1.067	0.574	1.982	0.931	0.789	1.091
2007	16357992	142	0.966	0.503	1.857	0.868	0.731	1.023
2008	16405399	162	1.101	0.598	2.027	0.987	0.841	1.152
2009	16485787	161	1.051	0.554	1.996	0.977	0.832	1.140
2010	16574989	176	1.167	0.646	2.109	1.062	0.911	1.231
2011	16655799	184	1.184	0.655	2.140	1.105	0.951	1.276
2012	16730348	214	1.351	0.776	2.353	1.279	1.113	1.462
2013	16779575	217	1.358	0.779	2.368	1.293	1.127	1.477
2014	16829289	205	1.270	0.718	2.247	1.218	1.057	1.397
2015	16900726	248	1.499	0.881	2.550	1.467	1.290	1.662
2016	16979120	257	1.529	0.900	2.598	1.514	1.334	1.710
2017	17081507	243	1.447	0.854	2.452	1.423	1.249	1.613
2018	17181084	287	1.667	1.012	2.746	1.670	1.483	1.875
2019	17282163	245	1.412	0.831	2.399	1.418	1.246	1.607
2020	17407585	330	1.873	1.183	2.965	1.896	1.697	2.112

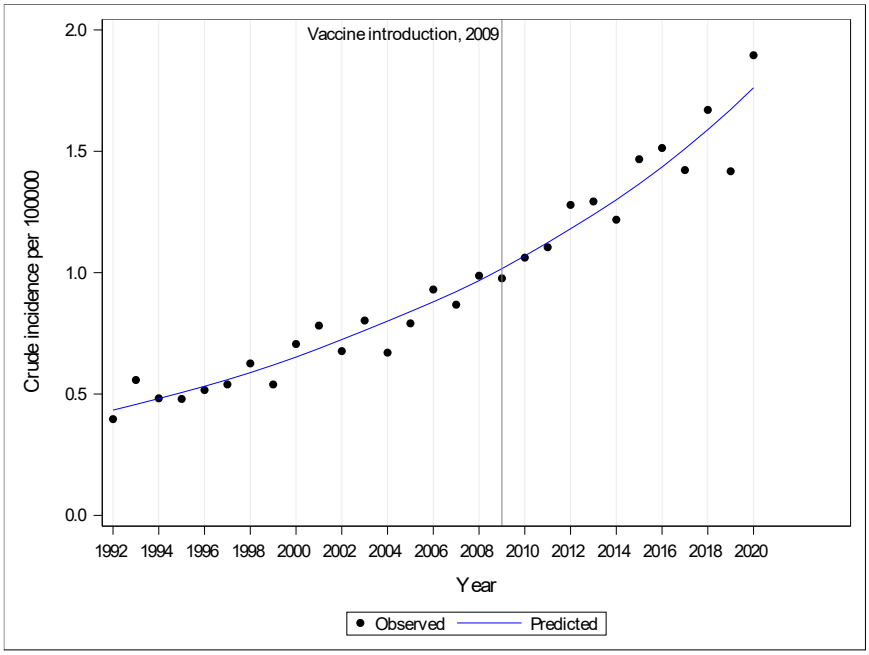
N = population in each category
n = number of anal cancer cases reported
Study period: Pre-*Cervarix* launch (Year 1992 – Year 2008), Post-*Cervarix* launch (Year 2009 – Year 2020)
Age-standardised Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))
CI=confidence interval; LL=lower limit; UL=upper limit
Age-standardised Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact Poisson confidence interval
Source: Table 14.2.2.1

Figure 11.4 Trend over time in the age standardised incidence of anal cancer – Netherlands



Note: The vaccine introduction year is considered as the year *Cervarix* was introduced in the NIP
Source: Figure 14.2.2.1.1

Figure 11.5 Trend over time in the crude incidence of anal cancer – Netherlands



Note: The vaccine introduction year is considered as the year *Cervarix* was introduced in the NIP
Line - Represents the predicted incidence , Period - Represents the observed Incidence
Source: Figure 14.2.2.1.2

Similar results were observed for small intestine cancer (Table 14.2.2.4 till Figure 14.2.2.4.2).

- An increasing trend in the age-standardised incidence and crude incidence of anal cancer was observed over time both in females and males. Females presented higher incidence rates than males, throughout the study period. There was no case of anal cancer reported below 20 years of age. Both in males and females, the crude incidence of anal cancer was similar and null for age categories 0-9, and 10-19 years. In females, the age category above 80 years showed the highest crude incidence of anal cancer throughout the year categories considered, except for the year category 2014-2018 when the crude incidence was higher at the 70-79 age category. Refer to Table 14.2.2.2 till Figure 14.2.2.3.3.

Similar results were observed for small intestine cancer, except that males presented higher age-standardised incidence rate or crude incidence rate, or both than females, throughout the study period: the overall crude incidence was highest among the age category above 80 years throughout the year categories considered, although the highest number of cases were presented by age category 70-79 years (Table 14.2.2.5 till Figure 14.2.2.6.3).

- A univariate Poisson regression model showed a significantly increasing trend in the incidence of anal cancer. A 5.09% annual increase (APC) in the incidence of anal cancer was observed (Table 11.8). In a separate univariate analysis of the pre-*Cervarix* and the post-*Cervarix* launch periods, an increasing trend in the incidence rate of anal cancer was observed in both periods (i.e., pre- and post-*Cervarix* launch periods). The APC for the pre-*Cervarix* and the post-*Cervarix* launch periods are very similar in magnitude and sign (both had positive sign) at 4.90% and 5.00%, respectively (Table 11.9 and Table 11.10).

Table 11.8 Univariate Poisson regression model for incidence of anal cancer – Netherlands

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	472307433	4577	1.051	1.047	1.055	<.0001	5.09

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Source: Table 14.2.2.7

Table 11.9 Univariate Poisson regression model for incidence of anal cancer for Pre-*Cervarix* launch (Year 1992 – Year 2008) - Netherlands

			Incidence ratio (e(β))				
				95% CI			
Characteristics	N	n	Value	LL	UL	p-value	Annual Percentage Change (%)
Calendar year	269419461	1810	1.049	1.039	1.059	<.0001	4.90

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Source: Table 14.2.2.7.1

Table 11.10 Univariate Poisson regression model for incidence of anal cancer for Post-*Cervarix* launch (Year 2009 – Year 2020) - Netherlands

			Incidence ratio (e(β))				
				95% CI			
Characteristics	N	n	Value	LL	UL	p-value	Annual Percentage Change (%)
Calendar year	202887972	2767	1.050	1.036	1.064	<.0001	5.00

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Source: Table 14.2.2.7.2

A univariate Poisson regression model showed a significantly increasing trend in the incidence of small intestine cancer. A 4.60% annual increase (APC) in the incidence of small intestine cancer was observed (Table 14.2.2.9). In a separate univariate analysis of the pre-*Cervarix* and the post-*Cervarix* launch periods, an increasing trend in the incidence rate of small intestine cancer was observed in both periods. The APC for the pre-*Cervarix* and the post-*Cervarix* launch periods are very similar in magnitude and sign (both had positive sign) at 3.89% and 3.60%, respectively (Table 14.2.2.9.1 and Table 14.2.2.9.2).

Note: The overall population at risk (i.e., N) is the sum of the population for every calendar year during the study period.

- A multivariate Poisson regression model was fitted considering the following risk factors: calendar year, age category (by 10-year age groups), *Cervarix* introduction period in the NIP (pre- and post-*Cervarix* introduction periods), and sex. After adjusting for the rest of the variables, the incidence rates of anal cancer increased over time and with age and, there was also strong evidence that the incidence rates of anal cancer were higher in females compared to males. And when comparing the

incidence rates between the pre- and post-introduction periods of the *Cervarix* in the NIP, there was no difference observed in the incidence rates (Table 11.11).

Table 11.11 Multivariate Poisson regression model for incidence of anal cancer – Netherlands

				Adjusted incidence ratio (e(β))				
					95% CI			
Characteristics	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
Calendar year		472307433	4577	1.038	1.030	1.047	<.0001	-
Age category (in years)	0-29	174616131	10	Reference	-	-	-	<.0001
	30-39	68084726	132	34.639	16.857	71.180	<.0001	-
	40-49	69975252	543	134.470	66.724	271.000	<.0001	-
	50-59	61827352	1062	286.881	142.791	576.372	<.0001	-
	60-69	48032015	1236	422.739	210.506	848.948	<.0001	-
	70-79	32244722	958	490.653	244.125	986.135	<.0001	-
	80+	17527235	636	588.367	292.186	1184.778	<.0001	-
Study period	Pre-*Cervarix* launch	269419461	1810	Reference	-	-	-	0.9082
	Post-*Cervarix* launch	202887972	2767	1.008	0.885	1.148	0.9082	-
Gender	Female	238503238	2518	Reference	-	-	-	0.0241
	Male	233804195	2059	0.927	0.868	0.990	0.0241	-

N = population at risk in each category
n = number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk)+ intercept + (β1 × calendar year) +(β2 × age category) + (β3 × study period) + (β4 × gender)
Adjusted incidence ratio (e(β)) = change in incidence of anal cancer compared to the reference category of each independent variable adjusted for other covariates (Exponentiated regression coefficient – β)
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Study period: Pre-*Cervarix* launch (Year 1992 – Year 2008), Post-*Cervarix* launch (Year 2009 – Year 2020)
Source: Table 14.2.2.8

- In a multivariate Poisson regression model, on stratification by age, the incidence rates of anal cancer were observed to be significatively higher in females when compared to males for all age categories except for the 0-29 age category where there was no difference in the incidence rate of anal cancer observed between females and males. Similarly, there seemed to be no statistically significant difference in the incidence rates of anal cancer over time for the 0-29 age category. However, in all other age category, incidence rates of anal cancer significatively increased over time. Conversely, there was no difference in the evolution of the incidence rate of anal cancer when comparing the pre- and post-*Cervarix* introduction periods in the NIP for any of the age categories (Table 14.2.2.8.1).
- In a multivariate Poisson regression model, on stratification by sex, the incidence rates of anal cancer significatively increased by age and over time in both sexes. There was no difference observed in the incidence rate of anal cancer when comparing the pre- to the post-*Cervarix* introduction periods in the NIP either for females or males (Table 14.2.2.8.2).

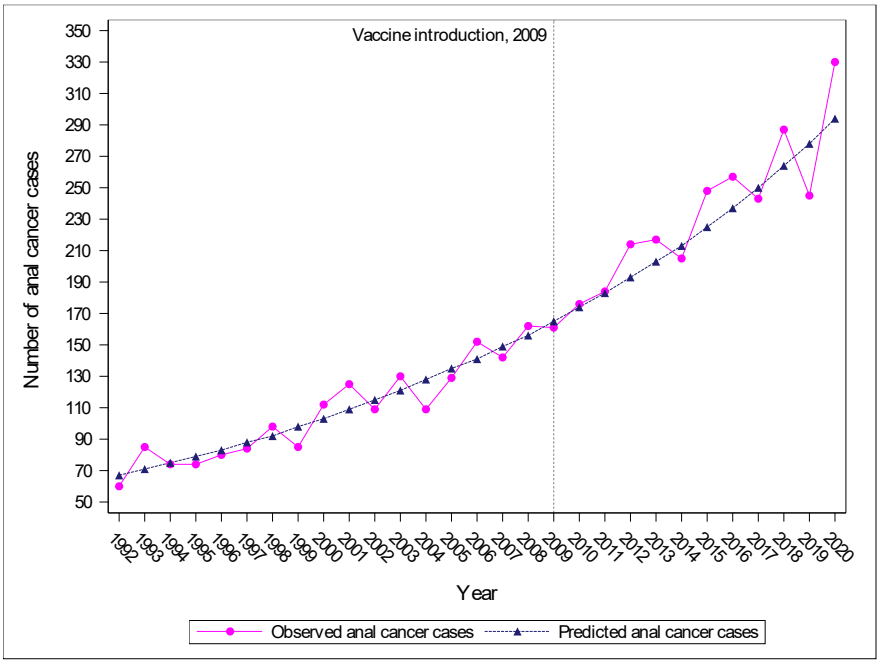
Since 1992 and until the year of introduction of *Cervarix* in the NIP (2009), the observed number of anal cancer cases were close to the predicted anal cancer cases for most age categories. However, following the introduction of *Cervarix* in the NIP, the observed number of cases depart from the predicted line, indicating an acceleration of the increase in anal cancer incidence for the age categories 60-69 and 70-79 years, whereas the observed number of cases declines compared to the predicted line for the 30-39, 40-49, and 50-59 age categories (Table 11.12 and Table 11.6).

Table 11.12 Trend overtime of anal cancer cases by observed counts versus predicted counts – Netherlands

					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	60	67	7	10.45	-26.87	36.79
1993	85	71	-14	-19.72	-64.06	12.64
1994	74	75	1	1.33	-36.03	28.43
1995	74	79	5	6.33	-28.62	31.78
1996	80	83	3	3.61	-31.03	29.1
1997	84	88	4	4.55	-28.72	29.21
1998	98	92	-6	-6.52	-41.58	19.86
1999	85	98	13	13.27	-15.97	35.13
2000	112	103	-9	-8.74	-42.1	16.79
2001	125	109	-16	-14.68	-48.26	11.3
2002	109	115	6	5.22	-23.17	27.06
2003	130	121	-9	-7.44	-37.62	16.12
2004	109	128	19	14.84	-9.94	34.04
2005	129	135	6	4.44	-21.64	24.93
2006	152	141	-11	-7.8	-35.57	14.28
2007	142	149	7	4.7	-19.93	24.27
2008	162	156	-6	-3.85	-29.38	16.65
2009	161	165	4	2.42	-21.24	21.47
2010	176	174	-2	-1.15	-24.73	17.97
2011	184	183	-1	-0.55	-23.38	18.06
2012	214	193	-21	-10.88	-34.7	8.72
2013	217	203	-14	-6.9	-29.44	11.72
2014	205	213	8	3.76	-16.59	20.55
2015	248	225	-23	-10.22	-32.02	7.98
2016	257	237	-20	-8.44	-29.37	9.11
2017	243	250	7	2.8	-15.97	18.53
2018	287	264	-23	-8.71	-28.49	8.02
2019	245	278	33	11.87	-4.64	25.78
2020	330	294	-36	-12.24	-31.35	4.08

Note: Poisson model has been used to predict the counts using the pre-vaccination period from 1992-Most recent available year's data
Model is calculated by, log(No. of anal cancer cases) = log (Population at risk) + intercept + (β × calendar year)
%Reduction = ((predicted counts –observed counts)/ predicted counts)×100
Wald's 95% CI and %reduction was estimated using Poisson model for non-zero observed counts
*Positive sign indicates the reduction and negative sign indicates the increase in observed counts
Source: Table 14.2.2.10

Figure 11.6 Predicted and observed counts of anal cancer cases – Netherlands



Note: The vaccine introduction year is considered as the year when *Cervarix* was introduced in the NIP
Source: Figure 14.2.2.10.1

- Refer to Table 14.2.2.11 for the trend overtime of anal cancer cases by observed counts versus predicted counts, by age category (30-39, 40-49, 50-59, 60-69, 70-79, and 80+ years). Note that the predicted counts were not estimated for age category 0-9 years (Figure 14.2.2.11.1) and 10-19 years (Figure 14.2.2.11.2), because the number of observed counts for the pre-*Cervarix* period was less than 5.
  - Refer to Figure 14.2.2.11.1 till Figure 14.2.2.11.9 for the predicted and observed counts of anal cancer cases, for each age category.
- Refer to Table 14.2.2.12 for the trend overtime of anal cancer cases by observed counts versus predicted counts, by gender.
  - Refer to Figure 14.2.2.12.1 for the trend overtime of anal cancer cases by observed counts versus predicted counts, by male.
  - Refer to Figure 14.2.2.12.2 for the trend overtime of anal cancer cases by observed counts versus predicted counts, by female.
- Refer to Table 14.2.2.13 for the summary of HPV vaccine coverage in females by year.
- Refer to Table 14.2.2.14 for the summary of birth cohort by year and sex.

11.4.2.2. Secondary objective results for the Netherlands

11.4.2.2.1. Number of expected anal cancer cases with 80% power to demonstrate VE with assumed vaccine coverage with the estimated timeframe for conducting the matched case-control study

Refer to Table 14.2.2.15:

- Considering 60% vaccine coverage and 60% VE, the required sample size would be 126 cases that, in a case to control ratio 1:1 scenario, would be reached in 2052. In a case to control ratio 1:4 scenario, 70 cases would be required, and the sample size reached in 2047.
- Considering 60% vaccine coverage and 90% VE, the required sample size would be 25 cases that, in a case to control ratio 1:1 scenario, would be reached in 2042. In a case to control ratio 1:4 scenario, 14 cases would be required, and the sample size reached in 2039.
- Considering 80% vaccine coverage and 60% VE, the required sample size would be 160 cases that, in a case to control ratio 1:1 scenario, would be reached in 2055. In a case to control ratio 1:4 scenario, 86 cases would be required, and the sample size reached in 2050.
- Considering 80% vaccine coverage and 90% VE, the required sample size would be 25 cases that, in a case to control ratio 1:1 scenario, would be reached in 2046. In a case to control ratio 1:4 scenario, 13 cases would be required, and the sample size reached in 2041.

11.4.2.2.2. Assessment of the individual vaccination status

For the Netherlands, at the time of the data extraction, the Dutch Cancer Registry confirmed that they had no possibility of linkage to retrieve information on the individual vaccination status of cases and controls. However, the Dutch immunisation registry Præventis supports linkage to disease registers to address VE studies via a trusted third party. Whether they have developed this functionality to link with the cancer registry is to be assessed for the final analysis.

11.4.2.2.3. Availability on the covariates of interest in the database

The availability of data on other covariates of interest (apart form age, sex, and HPV type) was not assessed at the time of this interim analysis. Relevant enquiries to the cancer registry will be made to retrieve this information.HPV genotyping data (or information on at least whether the anal cancer case was HPV-related) was not available at the time of data extraction.

11.4.3. Primary and secondary objective results for Finland

11.4.3.1. Primary objective results for Finland

In Finland, between 1992 and 2019:

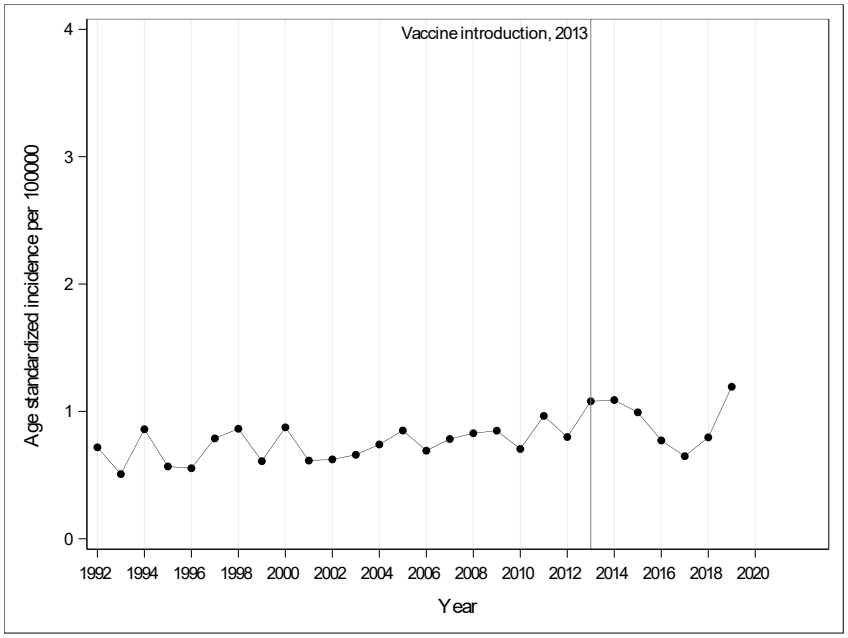
- An increasing trend in the age-standardised incidence and crude incidence of anal cancer was observed over time (Table 11.13, Figure 11.7 and Figure 11.8).

Table 11.13 Incidence of anal cancer by calendar year – Finland

			Age-standardised Incidence per 100000			Crude Incidence per 100000		
				95% CI			95% CI	
Calendar Year	N	n	Value	LL	UL	Value	LL	UL
1992	5029002	26	0.718	0.362	1.422	0.517	0.338	0.758
1993	5054982	20	0.508	0.215	1.200	0.396	0.242	0.611
1994	5077912	31	0.860	0.472	1.567	0.610	0.415	0.867
1995	5098754	23	0.568	0.248	1.300	0.451	0.286	0.677
1996	5116826	22	0.554	0.247	1.240	0.430	0.269	0.651
1997	5132320	33	0.788	0.391	1.587	0.643	0.443	0.903
1998	5147349	35	0.864	0.454	1.645	0.680	0.474	0.946
1999	5159646	26	0.609	0.280	1.328	0.504	0.329	0.738
2000	5171302	38	0.875	0.457	1.676	0.735	0.520	1.009
2001	5181115	28	0.614	0.278	1.355	0.540	0.359	0.781
2002	5194901	28	0.623	0.296	1.314	0.539	0.358	0.779
2003	5206295	30	0.659	0.308	1.410	0.576	0.389	0.823
2004	5219732	35	0.740	0.354	1.548	0.671	0.467	0.933
2005	5236611	42	0.850	0.424	1.703	0.802	0.578	1.084
2006	5255580	34	0.692	0.326	1.469	0.647	0.448	0.904
2007	5276955	40	0.783	0.377	1.626	0.758	0.542	1.032
2008	5300484	43	0.829	0.406	1.692	0.811	0.587	1.093
2009	5326314	44	0.849	0.426	1.689	0.826	0.600	1.109
2010	5351427	37	0.705	0.335	1.485	0.691	0.487	0.953
2011	5375276	52	0.965	0.507	1.834	0.967	0.722	1.269
2012	5401267	42	0.799	0.385	1.660	0.778	0.560	1.051
2013	5426674	59	1.080	0.587	1.986	1.087	0.828	1.402
2014	5451270	59	1.089	0.591	2.007	1.082	0.824	1.396
2015	5471753	56	0.993	0.535	1.840	1.023	0.773	1.329
2016	5487308	43	0.772	0.382	1.558	0.784	0.567	1.056
2017	5503297	37	0.649	0.301	1.397	0.672	0.473	0.927
2018	5513130	46	0.796	0.383	1.656	0.834	0.611	1.113
2019	5517919	70	1.194	0.661	2.156	1.269	0.989	1.603

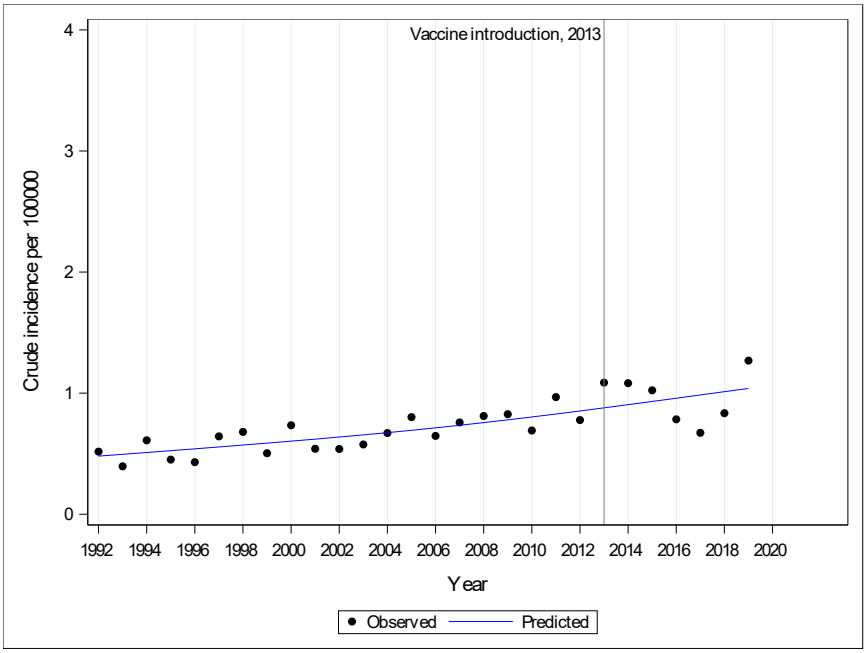
N = population in each category
n = number of anal cancer cases reported
Study period: Pre-*Cervarix* launch (Year 1992 – Year 2012), Post-*Cervarix* launch (Year 2013 – Year 2019)
Age-standardised Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))
CI=confidence interval; LL=lower limit; UL=upper limit
Age-standardised Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact Poisson confidence interval
Source: Table 14.2.3.1

Figure 11.7 Trend over time in the age standardised incidence of anal cancer – Finland



Note: The vaccine introduction year is considered as the year *Cervarix* was introduced in the NIP
Source: Figure 14.2.3.1.1

Figure 11.8 Trend over time in the crude incidence of anal cancer – Finland



Note: The vaccine introduction year is considered as the year *Cervarix* was introduced in the NIP
Line - Represents the predicted incidence , Period - Represents the observed Incidence
Source: Figure 14.2.3.1.2

Similar results were observed for small intestine cancer (Table 14.2.3.4 till Figure 14.2.3.4.2).

- An increasing trend in the age-standardised incidence and crude incidence of anal cancer was observed over time both in females and males. There was no case of anal cancer reported below 20 years of age. Both in females and males, the crude incidence of anal cancer was null for age categories 0-9, and 10-19 years. In females, the age category above 80 years showed the highest crude incidence of anal cancer throughout the year categories considered. Refer to Table 14.2.3.2 till Figure 14.2.3.3.3.

Similar results were observed for small intestine cancer, except that males presented higher age-standardised incidence rate or crude incidence rate, or both than females: the incidence was highest among the age category above 80 years throughout the year categories considered, although the highest number of cases were presented by age category 70-79 years, except for the year category 2003-2007, 2008-2012, and 2013-2017 where the highest number of cases corresponds to the 60-69 years age group (Table 14.2.3.5 till Figure 14.2.3.6.3).

- A univariate Poisson regression model showed a significantly increasing trend in the incidence of anal cancer. A 2.91% annual increase (APC) in the incidence of anal cancer was observed (Table 11.14). In a separate univariate analysis of the pre-*Cervarix* and the post-*Cervarix* launch periods, an increasing trend in the incidence rate of anal cancer was observed in the pre-*Cervarix* launch period. However, a decreasing trend in the incidence rate of anal cancer was noted in the post-*Cervarix* launch period. The APC for the pre-*Cervarix* and the post-*Cervarix* launch periods are opposite in sign at 2.99% and - 1.09%, respectively (Table 11.15 and Table 11.16).

Table 11.14 Univariate Poisson regression model for incidence of anal cancer – Finland

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	147685401	1079	1.029	1.021	1.038	<.0001	2.91

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Source: Table 14.2.3.7

Table 11.15 Univariate Poisson regression model for incidence of anal cancer for Pre-*Cervarix* launch (Year 1992 – Year 2012) - Finland

			Incidence ratio (e(β))				
				95% CI			
Characteristics	N	n	Value	LL	UL	p-value	Annual Percentage Change (%)
Calendar year	109314050	709	1.030	1.019	1.041	<.0001	2.99

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Source: Table 14.2.3.7.1

Table 11.16 Univariate Poisson regression model for incidence of anal cancer for Post-*Cervarix* launch (Year 2013 – Year 2019) - Finland

			Incidence ratio (e(β))				
				95% CI			
Characteristics	N	n	Value	LL	UL	p-value	Annual Percentage Change (%)
Calendar year	38371351	370	0.989	0.906	1.080	0.8076	-1.09

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Source: Table 14.2.3.7.2

A univariate Poisson regression model showed a significantly increasing trend in the incidence of small intestine cancer. A 4.16% annual increase (APC) in the incidence of small intestine cancer was observed (Table 14.2.3.9). In a separate univariate analysis of the pre-*Cervarix* and the post-*Cervarix* launch periods, an increasing trend in the incidence rate of small intestine cancer was observed in both periods. The APC for the pre-*Cervarix* and the post-*Cervarix* launch periods are very similar in magnitude and sign (both had positive sign) at 3.41% and 3.94%, respectively (Table 14.2.3.9.1 and Table 14.2.3.9.2).

Note: The overall population at risk (i.e., N) is the sum of the population for every calendar year during the study period.

- A multivariate Poisson regression model was fitted considering the following risk factors: calendar year, age category (by 10-year age groups), *Cervarix* introduction period in the NIP (pre- and post-*Cervarix* introduction periods), and sex. After adjusting for the rest of the variables, the incidence rates of anal cancer increased over time and with age, and there was also strong evidence that the incidence rates of anal cancer were higher in females compared to males. And when comparing the

incidence rates between the pre- and post-introduction periods of the *Cervarix* in the NIP, there was no difference observed in the incidence rates (Table 11.17).

Table 11.17 Multivariate Poisson regression model for incidence of anal cancer – Finland

				Adjusted incidence ratio (e(β))				
					95% CI			
Characteristics	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
Calendar year		147685401	1079	1.015	1.002	1.028	0.0200	-
Age category (in years)	0-29	53414167	6	Reference	-	-	-	<.0001
	30-39	19791287	24	10.833	4.222	27.795	<.0001	-
	40-49	21084704	101	42.947	18.038	102.256	<.0001	-
	50-59	19972250	236	103.556	44.107	243.134	<.0001	-
	60-69	16366462	270	141.523	60.354	331.853	<.0001	-
	70-79	10988423	250	192.931	82.214	452.749	<.0001	-
	80+	6068108	192	256.890	109.101	604.877	<.0001	-
Study period	Pre-*Cervarix* launch	109314050	709	Reference	-	-	-	0.6372
	Post-*Cervarix* launch	38371351	370	1.052	0.852	1.298	0.6372	-
Gender	Female	75390276	679	Reference	-	-	-	<.0001
	Male	72295125	400	0.738	0.647	0.842	<.0001	-

N = population at risk in each category
n = number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk)+ intercept + (β1 × calendar year) +(β2 × age category) + (β3 × study period) + (β4 × gender)
Adjusted incidence ratio (e(β)) = change in incidence of anal cancer compared to the reference category of each independent variable adjusted for other covariates (Exponentiated regression coefficient – β)
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Study period: Pre-*Cervarix* launch (Year 1992 – Year 2012), Post-*Cervarix* launch (Year 2013 – Year 2019)
Source: Table 14.2.3.8

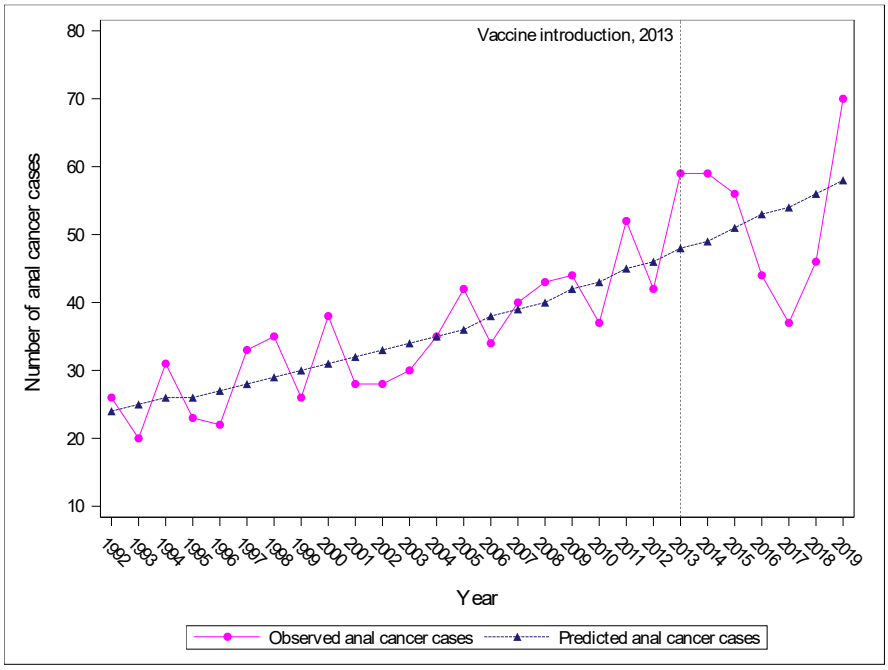
- In a multivariate Poisson regression model, on stratification by age, the incidence rates of anal cancer were observed to be significatively higher in females when compared to males for age categories 40-49, 50-59, and 60-69 years. For the rest of the age categories, there was no difference in the incidence rate of anal cancer observed between females and males (Table 14.2.3.8.1).
- In a multivariate Poisson regression model, on stratification by sex, the incidence rates of anal cancer significatively increased by age and over time in both sexes. There was no difference observed in the incidence rate of anal cancer when comparing the pre- to the post-*Cervarix* introduction periods in the NIP either for females or males (Table 14.2.3.8.2).
- Due to the relatively low number of anal cancer cases overall and within each age category, it is inappropriate to make a visual interpretation of the figures corresponding to observed versus predicted number of cases, as indicated by the low precision (wide 95% CIs) of the estimates (Table 11.18 and Figure 11.9).

Table 11.18 Trend overtime of anal cancer cases by observed counts versus predicted counts – Finland

					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	26	24	-2	-8.33	-88.67	37.8
1993	20	25	5	20	-44.03	55.56
1994	31	26	-5	-19.23	-100.79	29.2
1995	23	26	3	11.54	-55.03	49.52
1996	22	27	5	18.52	-43.07	53.59
1997	33	28	-5	-17.86	-95.01	28.77
1998	35	29	-6	-20.69	-97.43	26.22
1999	26	30	4	13.33	-46.53	48.74
2000	38	31	-7	-22.58	-96.98	23.72
2001	28	32	4	12.5	-45.3	47.31
2002	28	33	5	15.15	-40.39	48.72
2003	30	34	4	11.76	-44.16	46
2004	35	35	0	0	-59.76	37.41
2005	42	36	-6	-16.67	-82.09	25.25
2006	34	38	4	10.53	-42.11	43.67
2007	40	39	-1	-2.56	-59.42	34.02
2008	43	40	-3	-7.5	-65.35	30.11
2009	44	42	-2	-4.76	-59.89	31.36
2010	37	43	6	13.95	-33.54	44.56
2011	52	45	-7	-15.56	-72.22	22.47
2012	42	46	4	8.7	-38.73	39.91
2013	59	48	-11	-22.92	-79.91	16.02
2014	59	49	-10	-20.41	-75.86	17.56
2015	56	51	-5	-9.8	-60.46	24.86
2016	44	53	9	16.98	-23.82	44.34
2017	37	54	17	31.48	-4.1	54.9
2018	46	56	10	17.86	-21.32	44.39
2019	70	58	-12	-20.69	-70.93	14.78

Note: Poisson model has been used to predict the counts using the pre-vaccination period from 1992-Most recent available year's data
Model is calculated by, log(No. of anal cancer cases) = log (Population at risk) + intercept + (β × calendar year)
%Reduction = ((predicted counts –observed counts)/ predicted counts)×100
Wald's 95% CI and %reduction was estimated using Poisson model for non-zero observed counts
*Positive sign indicates the reduction and negative sign indicates the increase in observed counts
Source: Table 14.2.3.10

Figure 11.9 Predicted and observed counts of anal cancer cases – Finland



Note: The vaccine introduction year is considered as the year when *Cervarix* was introduced in the NIP
Source: Figure 14.2.3.10.1

- Refer to Table 14.2.3.11 for the trend overtime of anal cancer cases by observed counts versus predicted counts, by age category (30-39, 40-49, 50-59, 60-69, 70-79, and 80+ years). Note that the predicted counts were not estimated for age category 0- 9 years (Figure 14.2.3.11.1) and 10-19 years (Figure 14.2.3.11.2), because the number of observed counts for the pre-*Cervarix* period was less than 5.
  - Refer to Figure 14.2.3.11.1 till Figure 14.2.3.11.9 for the predicted and observed counts of anal cancer cases, for each age category.
- Refer to Table 14.2.3.12 for the trend overtime of anal cancer cases by observed counts versus predicted counts, by gender.
  - Refer to Figure 14.2.3.12.1 for the trend overtime of anal cancer cases by observed counts versus predicted counts, by male.
  - Refer to Figure 14.2.3.12.2 for the trend overtime of anal cancer cases by observed counts versus predicted counts, by female.
- Refer to Table 14.2.3.13 for the summary of HPV vaccine coverage in females by year.
- Refer to Table 14.2.3.14 for the summary of birth cohort by year and sex.

11.4.3.2. Secondary objective results for Finland

11.4.3.2.1. Number of expected anal cancer cases with 80% power to demonstrate VE with assumed vaccine coverage with the estimated timeframe for conducting the matched case-control study

Refer to Table 14.2.3.15:

- Considering 60% vaccine coverage and 60% VE, the required sample size would be 126 cases that, in a case to control ratio 1:1 scenario, would be reached in 2071. In a case to control ratio 1:4 scenario, 70 cases would be required, and the sample size reached in 2064.
- Considering 60% vaccine coverage and 90% VE, the required sample size would be 25 cases that, in a case to control ratio 1:1 scenario, would be reached in 2058. In a case to control ratio 1:4 scenario, 14 cases would be required, and the sample size reached in 2054.
- Considering 80% vaccine coverage and 60% VE, the required sample size would be 160 cases that, in a case to control ratio 1:1 scenario, would be reached in 2077. In a case to control ratio 1:4 scenario, 86 cases would be required, and the sample size reached in 2069.
- Considering 80% vaccine coverage and 90% VE, the required sample size would be 25 cases that, in a case to control ratio 1:1 scenario, would be reached in 2062. In a case to control ratio 1:4 scenario, 13 cases would be required, and the sample size reached in 2057.

11.4.3.2.2. Assessment of the individual vaccination status

For Finland, the Finnish Public Health Institute (THL) confirmed that they were able to provide combined data from the cancer registry and the vaccine registry.

11.4.3.2.3. Availability on the covariates of interest in the database

The availability of data on other covariates of interest (apart form age, sex, and HPV type) was not assessed at the time of this interim analysis. Relevant enquiries to the cancer registry will be made to retrieve this information.

HPV genotyping data (or information on at least whether the anal cancer case was HPV-related) was not available at the time of data extraction.

11.5. Other analyses

Not applicable.

11.6. Adverse events/adverse reactions

Not applicable.

12. DISCUSSION

12.1. Key results

- The trend analysis has shown that in the recent decades the incidence of anal cancer has been increasing in the study countries, aligned with reports from other parts of the world [Islami, 2017; Kang, 2018; Heer, 2020]. The definite reason for this increase remains unknown. However, recent studies point to several factors that may result in the incidence and persistence of anal HPV infection, such as the main risk factors for anal cancer. Among them, changes in sexual behaviour and practices, including lower age of sexual debut, increased number of sexual partners, and anoreceptive intercourse both in heterosexual and homosexual relationships. Nevertheless, the correlation between anoreceptive intercourse and anal cancer seems to be less strong in women than in men, most likely because cervical HPV persistent infection has been characterised as the most relevant reason for the persistence of anal HPV infection in women [Moscicki, 2014]. In this respect, autoinoculation and post-toilet wiping behaviours have been associated with the prevalence of anal HPV persistent infection in women [Kang, 2018]. Immunosuppression is also an important risk factor for anal cancer. Anal HPV infection and cancer are found to be prevalent in HIV-infected patients, increasing the risk of anal cancer with the duration of HIV infection. At present and due to improved treatments, HIV patients' survival rates have improved, and this can partially explain an increase in anal cancer incidence.

  Advancements in awareness of anal cancer may also have contributed to an increased diagnosis frequency. For instance, in England there is no anal cancer screening programme. However, in 2018, the UK introduced an HPV targeted vaccination programme for MSM (with a pilot started in 2016) and this may have contributed to increased screening and anal cancer detection [UK Health Security Agency, 2022]. Furthermore, an additional reason for the increase of incidence of anal cancer might have been the implementation of colorectal cancer screening programmes since the anus is also investigated during colonoscopy [Heer, 2020]. England, Finland, and the Netherlands have a nationwide colorectal cancer screening programme in place.

- This database analysis has revealed that the incidence of anal cancer has been increasing in both men and women for several decades, with higher incidence rates in women than in men. This is probably due to sex differences in risk factors as described above, including smoking, as anal cancer trends among women in some European countries correlate with increasing trends in smoking prevalence among them [Islami, 2017]. Smoking appears to delay the clearance of anal HPV infection [Shvetsov, 2009], leading to an increased risk of anal cancer.

- In this study, age-specific incidence of anal cancer has shown to be greater in the older age categories, peaking among the 80+ years of age population. Age is one of the main risk factors of cancer due to a number of interrelated biological phenomena (i.e., long-life accumulative oxidative stress and DNA damage, cellular senescence, immunosenescence, inflammageing, etc.) [Berben, 2021]. Underpinning this

argument, we have found almost no anal cancer cases among the age category 0-19 years of age in all 3 study countries.

  - Because the number of people reaching older ages is increasing rapidly, a raise in the incidence rates for many types of cancer, including anal cancer, is likely to occur.
  - *Cervarix* has proven protection against HPV-16/18 anal infection [Kreimer, 2011; Woestenberg, 2020] and this depends on vaccination policies, vaccine coverage, and the degree of herd immunity achieved, but as anal cancer may take several decades to develop and HPV vaccines (including *Cervarix*) were only implemented about 10-15 years ago, it is too early to detect the impact of the vaccine on anal cancer incidence at a population level, in addition only few age classes were targeted for vaccination. Despite HPV vaccination, it is unlikely that drastic reductions in anal cancer will be observed in the very next decades as anal cancer will occur more frequently among the older age categories, both in men and women, who have not been exposed to the vaccine. Moreover, among men, the highest risk lies with the MSM community that have been shown to benefit less from herd immunity of females-only HPV vaccination policy, than heterosexual men. All 3 countries, England, Finland, and most recently the Netherlands, have introduced a gender-neutral HPV vaccination approach in their NIPs [Annex 5]. However, these programmes started later than the routine females-only vaccination schedules and thus, impact of this new approach will take some more time to manifest. Therefore, even if a decreasing trend in the incidence of anal cancer was observed for Finland in the post-*Cervarix* launch period (ACP - 1.09%) vs. the pre-*Cervarix* launch period (ACP 2.99%), prudence mandates caution in the interpretation and invites to reassess this trend in the final report (2026). As a reflection, this study has not found statistically significant differences in incidence rates increase between the pre-, and post-*Cervarix* launch periods in the different multivariate analyses for any of the study countries.

- The only country providing information on histological classification of anal cancer was England. The study has shown increasing trends in incidence rates of SCC over time, with age, and as the most predominant type of anal tumour among both sexes. Anal SCCs are mainly HPV-related. At present, 88% of all anal SCC tumours are usually HPV positive with geographical variations. HPV 16 is the most frequently identified type, present in 86% of the cases, although co-infection with different HPV types may occur [Hoff, 2017]. Therefore, in the absence of causal HPV type information, it can be inferred that most anal cancer cases from England in this study were HPV-related. Little is known about risk factors for adenocarcinoma. Considering that histologically the rectum mainly consists of glandular cells instead of squamous cells, it has been hypothesised that adenocarcinoma cases may have originated in the rectum and have been miscoded to anal cancer. Assessing if this has occurred in this study and to which extent it may have occurred is beyond the scope of this analysis.
- Changes in trends may occur over time for reasons other than HPV vaccination (i.e., changes in the surveillance and reporting system, increment of anal cancer diagnosis due to increased awareness among physicians, implementation of an anal cancer

screening programme). In order to control for potential changes in the surveillance and reporting of anal cancer over time, we proposed to describe trends of another cancer that shares similar characteristics (similar incidence, similar mean age of diagnosis, absence of a screening programme) but is not HPV-related. Negative controls are often used in observational studies to allow detection of confounding and other sources of bias. In this study, we have included a negative control (small intestine cancer).

  - In this analysis we have not observed any particular array or disruption of the data that makes us think that there has been a surveillance artifact. Small intestine cancer also increased steadily over time and with age, although sex distribution is different to that of anal cancer as it is more prevalent in men than in women.

- Data from the national cancer registries have been accessed by directly downloading the data form the publicly available websites (the Netherlands, and Finland) or through request to the cancer registry in England. However, linkage to vaccination status of each case and control, and other information on risk factors and potential confounders might prove challenging since in some of these countries the different databases of interest are not directly linked and would require additional time and administrative efforts. Furthermore, this information might not be accessible at all.
- The exposure to *Cervarix* during the study period was reduced in England as they switched to the quadrivalent HPV vaccine in 2012, and subsequently to the nonavalent vaccine in 2019, making it difficult to assess the impact of *Cervarix* alone if brand information for every case and control is not available in the vaccine registry.
- Additionally, HPV typing of anal cancer samples is not systematically performed in all 3 European countries or this information is not available at the cancer registry. Therefore, a slight overestimation of the number of cases may occur if all cancer cases are considered as HPV-related (according to the scientific literature around 90% of all anal cancer cases are HPV-related).

12.2. Strengths and limitations

The primary analysis had the following strengths and limitations:

Strengths

- Use of nationwide longitudinal data from national cancer registries using the same case definition (aligned with ICD-10 codes).
- A harmonised and coordinated approach in the analysis allowing comparisons across countries and with external similar studies.
- Use of an HPV negative control (i.e., small intestine cancer) has permitted to assess for potential bias owed to changes in the surveillance and reporting system of anal cancer over time.

Limitations

- At the time of data extraction during the interim analysis, for the Netherlands the cancer data for 2019 and 2020 were provisional.
- The cancer registry of Finland does not provide the number of cancer cases when less than 5 cases are reported in a given year, by sex and age category, due to potential risk of patient identification. Therefore, in those instances, the number of cancer cases were back-computed using the provided crude incidence and population data. This may have introduced some bias by round-offs and back-calculation.
- Limitations in the cancer registry data such as accuracy in the cancer diagnosis methods, case ascertainment, misclassification of primary location (e.g., misclassification as rectal cancer).
- Lack of/limited information on the existence of targeted anal cancer screening programmes (i.e., directed towards at-risk groups such as MSM, HIV-positive patients, or subjects previously diagnosed of an HPV-related cancer), that could have led to overdiagnosis and may also have an impact on temporal incidence trends.
- Lack of information of the aetiology of the anal cancer cases (i.e., whether HPV-related) could have introduced some bias and limited the interpretation. Additionally, if no causative HPV type could be provided, further sub-analysis of the incidence by HPV type will be limited by this constraint.
- Percentage of anal cancers with unspecified histology (unspecified carcinomas or unspecified morphology).
- Variations in registry practices in diagnosis and information collection could have introduced some bias in international comparisons (i.e., consistency of histological classifications).
- Changes in trends may occur over time for reasons other than HPV vaccination (i.e., changes in the surveillance and reporting system, increment of anal cancer diagnosis due to increased awareness among physicians, implementation of an anal cancer screening programme).

12.3. Interpretation

In this study, we explored trends in anal cancer incidence by sex, age category, and histological classification (when available) across 3 European countries using data from consolidated and validated national cancer registries. Consistently with relevant scientific literature [Islami, 2017; Kang, 2018], it was observed that the incidence of anal cancer has increased both in females and males with age and over time in the 3 selected European countries. Despite *Cervarix* having shown protection against anal HPV-16/18 infection [Kreimer, 2011; Woestenberg, 2020], further increases in anal cancer incidence rates are expected due to demographic changes, including ageing, and also because the most affected population groups (i.e., older age groups) include for some time population cohorts that will not have had access to HPV vaccination.

With respect to the feasibility assessment for a case-control study and notwithstanding considerations of other relevant parameters for the study, the estimation of the sample size required for the completion of the study under different scenarios has revealed that it may be unachievable within a reasonable time frame.

12.4. Generalisability

Building on the strengths of this study, the primary analysis results are consistent among the 3 European countries. The results are aligned with reports from other parts of the world as well as with the International Agency for Research on Cancer [Islami, 2017].

13. CONCLUSION

The incidence of anal cancer in Finland, the Netherlands, and England increased over time throughout the study period. Anal cancer incidence increased with age and was higher in females compared to males. There was no difference in terms of evolution of incidence rates for anal cancer in the pre-*Cervarix* launch period compared to the post-*Cervarix* launch period in all 3 countries. However, since anal cancer may take decades to develop, it is possible that not enough time has passed from the introduction of *Cervarix* in the respective NIPs to detect a measurable impact of the vaccination on anal cancer at a population level. The use of small intestine cancer as a negative control was subject to the same potential sources of bias as anal cancer but not to the exposure (HPV), demonstrated a similar trend, suggesting that the anal cancer data were not likely to have been affected by surveillance artifacts.

A feasibility assessment was performed to calculate the required sample size for a case-control study (i.e., with several scenarios for combinations of different vaccine coverage and VE estimates, and case to control ratios). The overall assessment showed that the estimated sample size, would demand a considerable amount of time in all the selected countries, making it difficult to achieve it within a reasonable time frame, in light of the current interim analysis. Moreover, if countries switch to another vaccine brand or the vaccine coverage drops drastically during the conduct of the study, it will jeopardise the study's ability to provide the planned results. This has already occurred in England where *Cervarix* was replaced by *Gardasil* in 2012 making it difficult to disentangle specific VE attributable to *Cervarix* alone. Additionally, the inaccessibility to individual vaccination status of subjects identified through the cancer registry in some countries (i.e., the Netherlands) is a major drawback since it precludes the conduct of the study. The likely unavailability of information in the cancer registries on vaccine uptake determinants, risk factors, and potential confounders will limit the information derived from the analysis.

In conclusion, as population-based registries are constantly evolving and establishing links with other national healthcare and demographic databases, we will reassess the feasibility for a case-control study prior to the final report in 2026 as we consider that a robust and statistically powered case-control study to determine the VE of *Cervarix* against anal cancer cannot be proposed at this stage.

14. TABLES, FIGURES AND GRAPHS

Demographic data	Table 14.1.1
14.2 Trends over time and Feasibility assessment	
14.2.1 England	
England data	Table 14.2.1.1 till Table 14.2.1.17
14.2.2 The Netherlands	
The Netherlands data	Table 14.2.2.1 till Table 14.2.2.15
14.2.3 Finland	
Finland data	Table 14.2.3.1 till Table 14.2.3.15

14.1 Demographic data

Table 14.1.1 Demographic characteristics for the study population by calendar year, gender and by age category

			England			Netherlands			Finland		
Year	Gender	Age Category (in years)	n	N	%	n	N	%	n	N	%
1992	Male	0-9	-	-	-	949760	15129150	6.3	328285	5029002	6.5
		10-19	-	-	-	972378	15129150	6.4	323857	5029002	6.4
		20-29	-	-	-	1316049	15129150	8.7	361930	5029002	7.2
		30-39	-	-	-	1237655	15129150	8.2	400971	5029002	8.0
		40-49	-	-	-	1119559	15129150	7.4	395967	5029002	7.9
		50-59	-	-	-	775335	15129150	5.1	268188	5029002	5.3
		60-69	-	-	-	611323	15129150	4.0	213093	5029002	4.2
		70-79	-	-	-	363411	15129150	2.4	109704	5029002	2.2
		80+	-	-	-	134952	15129150	0.9	41047	5029002	0.8
	Female	0-9	-	-	-	908614	15129150	6.0	313982	5029002	6.2
		10-19	-	-	-	931487	15129150	6.2	309154	5029002	6.1
		20-29	-	-	-	1255574	15129150	8.3	347331	5029002	6.9
		30-39	-	-	-	1189285	15129150	7.9	384193	5029002	7.6
		40-49	-	-	-	1066216	15129150	7.0	379385	5029002	7.5
		50-59	-	-	-	764269	15129150	5.1	276455	5029002	5.5
		60-69	-	-	-	694916	15129150	4.6	266659	5029002	5.3
		70-79	-	-	-	529031	15129150	3.5	200601	5029002	4.0
		80+	-	-	-	309336	15129150	2.0	108200	5029002	2.2
1993	Male	0-9	-	-	-	963404	15239182	6.3	328605	5054982	6.5
		10-19	-	-	-	951118	15239182	6.2	328471	5054982	6.5
		20-29	-	-	-	1306404	15239182	8.6	354163	5054982	7.0
		30-39	-	-	-	1254086	15239182	8.2	397283	5054982	7.9
		40-49	-	-	-	1146489	15239182	7.5	412841	5054982	8.2
		50-59	-	-	-	787349	15239182	5.2	266740	5054982	5.3
		60-69	-	-	-	617005	15239182	4.0	215979	5054982	4.3
		70-79	-	-	-	371046	15239182	2.4	110746	5054982	2.2
		80+	-	-	-	138367	15239182	0.9	42454	5054982	0.8
	Female	0-9	-	-	-	921409	15239182	6.0	314641	5054982	6.2
		10-19	-	-	-	910539	15239182	6.0	313638	5054982	6.2
		20-29	-	-	-	1248386	15239182	8.2	339504	5054982	6.7
		30-39	-	-	-	1205786	15239182	7.9	381139	5054982	7.5
		40-49	-	-	-	1094832	15239182	7.2	395454	5054982	7.8
		50-59	-	-	-	772076	15239182	5.1	274091	5054982	5.4
		60-69	-	-	-	695765	15239182	4.6	265209	5054982	5.2
		70-79	-	-	-	537097	15239182	3.5	201906	5054982	4.0
		80+	-	-	-	318024	15239182	2.1	112118	5054982	2.2
1994	Male	0-9	-	-	-	977687	15341553	6.4	327806	5077912	6.5
		10-19	-	-	-	939589	15341553	6.1	334460	5077912	6.6
		20-29	-	-	-	1283290	15341553	8.4	344688	5077912	6.8
		30-39	-	-	-	1273941	15341553	8.3	395849	5077912	7.8
		40-49	-	-	-	1165238	15341553	7.6	421660	5077912	8.3
		50-59	-	-	-	808077	15341553	5.3	272515	5077912	5.4
		60-69	-	-	-	618994	15341553	4.0	216322	5077912	4.3
		70-79	-	-	-	378733	15341553	2.5	113806	5077912	2.2
		80+	-	-	-	140338	15341553	0.9	43090	5077912	0.8
	Female	0-9	-	-	-	934834	15341553	6.1	314256	5077912	6.2
		10-19	-	-	-	899044	15341553	5.9	319802	5077912	6.3
		20-29	-	-	-	1229634	15341553	8.0	330197	5077912	6.5
		30-39	-	-	-	1224565	15341553	8.0	379886	5077912	7.5
		40-49	-	-	-	1116595	15341553	7.3	404512	5077912	8.0
		50-59	-	-	-	789106	15341553	5.1	279028	5077912	5.5

			England			Netherlands			Finland		
Year	**Gender**	**Age Category (in years)**	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
		60-69	-	-	-	692387	15341553	4.5	261087	5077912	5.1
		70-79	-	-	-	545544	15341553	3.6	204806	5077912	4.0
		80+	-	-	-	323957	15341553	2.1	114142	5077912	2.2
1995	Male	0-9	3256128	48384614	6.7	988568	15424122	6.4	327477	5098754	6.4
		10-19	2970121	48384614	6.1	933547	15424122	6.1	336721	5098754	6.6
		20-29	3536763	48384614	7.3	1248156	15424122	8.1	337325	5098754	6.6
		30-39	3613088	48384614	7.5	1292387	15424122	8.4	393618	5098754	7.7
		40-49	3265121	48384614	6.7	1180127	15424122	7.7	428461	5098754	8.4
		50-59	2632009	48384614	5.4	831791	15424122	5.4	278765	5098754	5.5
		60-69	2174033	48384614	4.5	623960	15424122	4.0	217745	5098754	4.3
		70-79	1494886	48384614	3.1	385291	15424122	2.5	117121	5098754	2.3
		80+	604796	48384614	1.2	143655	15424122	0.9	44416	5098754	0.9
	Female	0-9	3109573	48384614	6.4	945429	15424122	6.1	314168	5098754	6.2
		10-19	2860753	48384614	5.9	892611	15424122	5.8	321780	5098754	6.3
		20-29	3525289	48384614	7.3	1198967	15424122	7.8	323595	5098754	6.3
		30-39	3650828	48384614	7.5	1241643	15424122	8.1	377101	5098754	7.4
		40-49	3293527	48384614	6.8	1133276	15424122	7.3	412604	5098754	8.1
		50-59	2655955	48384614	5.5	809597	15424122	5.2	284138	5098754	5.6
		60-69	2353728	48384614	4.9	691014	15424122	4.5	259277	5098754	5.1
		70-79	2032468	48384614	4.2	552001	15424122	3.6	207101	5098754	4.1
		80+	1355548	48384614	2.8	332102	15424122	2.2	117341	5098754	2.3
1996	Male	0-9	3250814	48521172	6.7	994406	15493889	6.4	327437	5116826	6.4
		10-19	3005651	48521172	6.2	934437	15493889	6.0	335878	5116826	6.6
		20-29	3438980	48521172	7.1	1210622	15493889	7.8	333054	5116826	6.5
		30-39	3684675	48521172	7.6	1306835	15493889	8.4	390332	5116826	7.6
		40-49	3271096	48521172	6.7	1199569	15493889	7.7	427691	5116826	8.4
		50-59	2683076	48521172	5.5	849782	15493889	5.5	291594	5116826	5.7
		60-69	2171707	48521172	4.5	629437	15493889	4.1	219089	5116826	4.3
		70-79	1512415	48521172	3.1	392129	15493889	2.5	121542	5116826	2.4
		80+	611451	48521172	1.3	145072	15493889	0.9	45084	5116826	0.9
	Female	0-9	3099340	48521172	6.4	950287	15493889	6.1	314076	5116826	6.1
		10-19	2895205	48521172	6.0	892479	15493889	5.8	321497	5116826	6.3
		20-29	3425703	48521172	7.1	1166987	15493889	7.5	319128	5116826	6.2
		30-39	3723998	48521172	7.7	1253595	15493889	8.1	374397	5116826	7.3
		40-49	3302793	48521172	6.8	1156249	15493889	7.5	412990	5116826	8.1
		50-59	2710067	48521172	5.6	825558	15493889	5.3	295384	5116826	5.8
		60-69	2341469	48521172	4.8	690689	15493889	4.5	257732	5116826	5.0
		70-79	2035088	48521172	4.2	559352	15493889	3.6	210636	5116826	4.1
		80+	1357644	48521172	2.8	336404	15493889	2.2	119285	5116826	2.3
1997	Male	0-9	3243190	48666657	6.7	998010	15567107	6.4	327261	5132320	6.4
		10-19	3056720	48666657	6.3	938992	15567107	6.0	333581	5132320	6.5
		20-29	3328485	48666657	6.8	1177446	15567107	7.6	329596	5132320	6.4
		30-39	3742356	48666657	7.7	1314474	15567107	8.4	386457	5132320	7.5
		40-49	3209100	48666657	6.6	1184518	15567107	7.6	423022	5132320	8.2
		50-59	2804634	48666657	5.8	902233	15567107	5.8	308835	5132320	6.0
		60-69	2178262	48666657	4.5	635633	15567107	4.1	219956	5132320	4.3
		70-79	1535495	48666657	3.2	398900	15567107	2.6	126520	5132320	2.5
		80+	612602	48666657	1.3	146597	15567107	0.9	45368	5132320	0.9
	Female	0-9	3089105	48666657	6.3	951974	15567107	6.1	313886	5132320	6.1
		10-19	2944607	48666657	6.1	898388	15567107	5.8	319183	5132320	6.2
		20-29	3324736	48666657	6.8	1139042	15567107	7.3	315602	5132320	6.1
		30-39	3783748	48666657	7.8	1262233	15567107	8.1	371257	5132320	7.2
		40-49	3246731	48666657	6.7	1145806	15567107	7.4	408891	5132320	8.0
		50-59	2837157	48666657	5.8	875156	15567107	5.6	311589	5132320	6.1

			England			Netherlands			Finland		
Year	**Gender**	**Age Category (in years)**	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
		60-69	2336917	48666657	4.8	691778	15567107	4.4	256389	5132320	5.0
		70-79	2046244	48666657	4.2	565105	15567107	3.6	214152	5132320	4.2
		80+	1346568	48666657	2.8	340822	15567107	2.2	120775	5132320	2.4
1998	Male	0-9	3217923	48822555	6.6	1000287	15654192	6.4	326416	5147349	6.3
		10-19	3113114	48822555	6.4	947681	15654192	6.1	331323	5147349	6.4
		20-29	3238108	48822555	6.6	1145267	15654192	7.3	326228	5147349	6.3
		30-39	3777531	48822555	7.7	1322186	15654192	8.4	383870	5147349	7.5
		40-49	3187171	48822555	6.5	1177479	15654192	7.5	416178	5147349	8.1
		50-59	2893623	48822555	5.9	950202	15654192	6.1	325754	5147349	6.3
		60-69	2193336	48822555	4.5	642661	15654192	4.1	221987	5147349	4.3
		70-79	1567436	48822555	3.2	405736	15654192	2.6	131362	5147349	2.6
		80+	607066	48822555	1.2	148575	15654192	0.9	45980	5147349	0.9
	Female	0-9	3063816	48822555	6.3	955190	15654192	6.1	313670	5147349	6.1
		10-19	2996476	48822555	6.1	906012	15654192	5.8	316873	5147349	6.2
		20-29	3242433	48822555	6.6	1111760	15654192	7.1	312458	5147349	6.1
		30-39	3823934	48822555	7.8	1269412	15654192	8.1	369059	5147349	7.2
		40-49	3226919	48822555	6.6	1141630	15654192	7.3	402946	5147349	7.8
		50-59	2932830	48822555	6.0	921125	15654192	5.9	327254	5147349	6.4
		60-69	2342659	48822555	4.8	694159	15654192	4.4	256462	5147349	5.0
		70-79	2071113	48822555	4.2	570213	15654192	3.6	216758	5147349	4.2
		80+	1327067	48822555	2.7	344617	15654192	2.2	122771	5147349	2.4
1999	Male	0-9	3196668	49034531	6.5	1008076	15760225	6.4	322912	5159646	6.3
		10-19	3145993	49034531	6.4	955529	15760225	6.1	331267	5159646	6.4
		20-29	3192146	49034531	6.5	1115519	15760225	7.1	323707	5159646	6.3
		30-39	3815787	49034531	7.8	1330343	15760225	8.4	381961	5159646	7.4
		40-49	3200659	49034531	6.5	1179828	15760225	7.5	407592	5159646	7.9
		50-59	2959524	49034531	6.0	987245	15760225	6.3	340707	5159646	6.6
		60-69	2208744	49034531	4.5	652294	15760225	4.1	224567	5159646	4.4
		70-79	1588356	49034531	3.2	414971	15760225	2.6	136730	5159646	2.6
		80+	608956	49034531	1.2	149466	15760225	0.9	46632	5159646	0.9
	Female	0-9	3042515	49034531	6.2	962651	15760225	6.1	310335	5159646	6.0
		10-19	3025071	49034531	6.2	913586	15760225	5.8	316904	5159646	6.1
		20-29	3196026	49034531	6.5	1086150	15760225	6.9	309657	5159646	6.0
		30-39	3863340	49034531	7.9	1277632	15760225	8.1	367407	5159646	7.1
		40-49	3242024	49034531	6.6	1146761	15760225	7.3	395441	5159646	7.7
		50-59	3002663	49034531	6.1	956473	15760225	6.1	341511	5159646	6.6
		60-69	2348983	49034531	4.8	698352	15760225	4.4	257149	5159646	5.0
		70-79	2084433	49034531	4.3	578663	15760225	3.7	219904	5159646	4.3
		80+	1312643	49034531	2.7	346686	15760225	2.2	125263	5159646	2.4
2000	Male	0-9	3154707	49234229	6.4	1016040	15863950	6.4	319590	5171302	6.2
		10-19	3168195	49234229	6.4	965254	15863950	6.1	331548	5171302	6.4
		20-29	3172716	49234229	6.4	1078017	15863950	6.8	323196	5171302	6.2
		30-39	3844353	49234229	7.8	1341202	15863950	8.5	376521	5171302	7.3
		40-49	3233884	49234229	6.6	1189790	15863950	7.5	400855	5171302	7.8
		50-59	3016985	49234229	6.1	1018389	15863950	6.4	354432	5171302	6.9
		60-69	2217814	49234229	4.5	663272	15863950	4.2	227778	5171302	4.4
		70-79	1576976	49234229	3.2	422999	15863950	2.7	142741	5171302	2.8
		80+	645930	49234229	1.3	151354	15863950	1.0	46365	5171302	0.9
	Female	0-9	3002560	49234229	6.1	969121	15863950	6.1	307307	5171302	5.9
		10-19	3031981	49234229	6.2	922593	15863950	5.8	316762	5171302	6.1
		20-29	3177957	49234229	6.5	1054140	15863950	6.6	309318	5171302	6.0
		30-39	3891869	49234229	7.9	1288145	15863950	8.1	361983	5171302	7.0
		40-49	3278248	49234229	6.7	1158982	15863950	7.3	390076	5171302	7.5
		50-59	3067180	49234229	6.2	986383	15863950	6.2	353328	5171302	6.8

			England			Netherlands			Finland		
Year	**Gender**	**Age Category (in years)**	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
		60-69	2350919	49234229	4.8	704660	15863950	4.4	258603	5171302	5.0
		70-79	2048439	49234229	4.2	584624	15863950	3.7	226209	5171302	4.4
		80+	1353516	49234229	2.7	348985	15863950	2.2	124690	5171302	2.4
2001	Male	0-9	3095716	49449746	6.3	1021641	15987075	6.4	315082	5181115	6.1
		10-19	3216796	49449746	6.5	977888	15987075	6.1	332564	5181115	6.4
		20-29	3154663	49449746	6.4	1051043	15987075	6.6	323926	5181115	6.3
		30-39	3865277	49449746	7.8	1348842	15987075	8.4	369754	5181115	7.1
		40-49	3287696	49449746	6.6	1204040	15987075	7.5	395721	5181115	7.6
		50-59	3071462	49449746	6.2	1044404	15987075	6.5	370007	5181115	7.1
		60-69	2214669	49449746	4.5	675011	15987075	4.2	226895	5181115	4.4
		70-79	1577659	49449746	3.2	428927	15987075	2.7	147108	5181115	2.8
		80+	681649	49449746	1.4	158059	15987075	1.0	48284	5181115	0.9
	Female	0-9	2948911	49449746	6.0	975272	15987075	6.1	302617	5181115	5.8
		10-19	3066265	49449746	6.2	933252	15987075	5.8	317848	5181115	6.1
		20-29	3152389	49449746	6.4	1030469	15987075	6.4	309506	5181115	6.0
		30-39	3904257	49449746	7.9	1296750	15987075	8.1	355782	5181115	6.9
		40-49	3329184	49449746	6.7	1173955	15987075	7.3	385971	5181115	7.4
		50-59	3126145	49449746	6.3	1012467	15987075	6.3	368223	5181115	7.1
		60-69	2340886	49449746	4.7	711375	15987075	4.4	255545	5181115	4.9
		70-79	2019972	49449746	4.1	585102	15987075	3.7	227440	5181115	4.4
		80+	1396150	49449746	2.8	358578	15987075	2.2	128842	5181115	2.5
2002	Male	0-9	3060302	49679267	6.2	1025327	16105285	6.4	310551	5194901	6.0
		10-19	3260365	49679267	6.6	991753	16105285	6.2	333359	5194901	6.4
		20-29	3137187	49679267	6.3	1030440	16105285	6.4	326485	5194901	6.3
		30-39	3859766	49679267	7.8	1346820	16105285	8.4	362509	5194901	7.0
		40-49	3353458	49679267	6.8	1222094	16105285	7.6	392833	5194901	7.6
		50-59	3110310	49679267	6.3	1070889	16105285	6.6	374532	5194901	7.2
		60-69	2223492	49679267	4.5	685824	16105285	4.3	235819	5194901	4.5
		70-79	1579620	49679267	3.2	434637	16105285	2.7	151283	5194901	2.9
		80+	708259	49679267	1.4	164183	16105285	1.0	50226	5194901	1.0
	Female	0-9	2917558	49679267	5.9	978533	16105285	6.1	298018	5194901	5.7
		10-19	3101618	49679267	6.2	945023	16105285	5.9	318879	5194901	6.1
		20-29	3129215	49679267	6.3	1012010	16105285	6.3	311304	5194901	6.0
		30-39	3902973	49679267	7.9	1296457	16105285	8.0	349100	5194901	6.7
		40-49	3396272	49679267	6.8	1192848	16105285	7.4	383815	5194901	7.4
		50-59	3171542	49679267	6.4	1039694	16105285	6.5	372072	5194901	7.2
		60-69	2348387	49679267	4.7	716700	16105285	4.5	263477	5194901	5.1
		70-79	1995813	49679267	4.0	584629	16105285	3.6	227546	5194901	4.4
		80+	1423130	49679267	2.9	367424	16105285	2.3	133093	5194901	2.6
2003	Male	0-9	3046168	49925517	6.1	1026880	16192572	6.3	305147	5206295	5.9
		10-19	3287116	49925517	6.6	1004718	16192572	6.2	333302	5206295	6.4
		20-29	3137852	49925517	6.3	1010747	16192572	6.2	330956	5206295	6.4
		30-39	3833356	49925517	7.7	1332120	16192572	8.2	354310	5206295	6.8
		40-49	3428438	49925517	6.9	1235906	16192572	7.6	389193	5206295	7.5
		50-59	3123627	49925517	6.3	1095715	16192572	6.8	390373	5206295	7.5
		60-69	2259496	49925517	4.5	698537	16192572	4.3	235026	5206295	4.5
		70-79	1583281	49925517	3.2	441074	16192572	2.7	154538	5206295	3.0
		80+	728371	49925517	1.5	169774	16192572	1.0	52071	5206295	1.0
	Female	0-9	2901843	49925517	5.8	980451	16192572	6.1	292511	5206295	5.6
		10-19	3139054	49925517	6.3	956950	16192572	5.9	319179	5206295	6.1
		20-29	3131858	49925517	6.3	993260	16192572	6.1	315791	5206295	6.1
		30-39	3866646	49925517	7.7	1288043	16192572	8.0	340792	5206295	6.5
		40-49	3472223	49925517	7.0	1208033	16192572	7.5	380451	5206295	7.3
		50-59	3184239	49925517	6.4	1066486	16192572	6.6	387710	5206295	7.4

			England			Netherlands			Finland		
Year	**Gender**	**Age Category (in years)**	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
		60-69	2387008	49925517	4.8	724134	16192572	4.5	261169	5206295	5.0
		70-79	1977776	49925517	4.0	585548	16192572	3.6	227415	5206295	4.4
		80+	1437165	49925517	2.9	374196	16192572	2.3	136361	5206295	2.6
2004	Male	0-9	3041627	50194600	6.1	1027493	16258032	6.3	301243	5219732	5.8
		10-19	3297343	50194600	6.6	1013241	16258032	6.2	331834	5219732	6.4
		20-29	3186950	50194600	6.3	996883	16258032	6.1	336926	5219732	6.5
		30-39	3775410	50194600	7.5	1302846	16258032	8.0	344819	5219732	6.6
		40-49	3503730	50194600	7.0	1252219	16258032	7.7	387763	5219732	7.4
		50-59	3125608	50194600	6.2	1112518	16258032	6.8	398561	5219732	7.6
		60-69	2307949	50194600	4.6	718932	16258032	4.4	240655	5219732	4.6
		70-79	1588199	50194600	3.2	445901	16258032	2.7	156356	5219732	3.0
		80+	746718	50194600	1.5	175881	16258032	1.1	54736	5219732	1.0
	Female	0-9	2894229	50194600	5.8	980212	16258032	6.0	288609	5219732	5.5
		10-19	3160463	50194600	6.3	966611	16258032	5.9	318165	5219732	6.1
		20-29	3172983	50194600	6.3	981181	16258032	6.0	321918	5219732	6.2
		30-39	3808517	50194600	7.6	1267656	16258032	7.8	331211	5219732	6.3
		40-49	3550487	50194600	7.1	1224574	16258032	7.5	379001	5219732	7.3
		50-59	3189869	50194600	6.4	1085858	16258032	6.7	396594	5219732	7.6
		60-69	2436947	50194600	4.9	739862	16258032	4.6	265820	5219732	5.1
		70-79	1961604	50194600	3.9	583747	16258032	3.6	224838	5219732	4.3
		80+	1445967	50194600	2.9	382417	16258032	2.4	140683	5219732	2.7
2005	Male	0-9	3041169	50606034	6.0	1022549	16305526	6.3	297999	5236611	5.7
		10-19	3293596	50606034	6.5	1017110	16305526	6.2	331455	5236611	6.3
		20-29	3271880	50606034	6.5	988061	16305526	6.1	339788	5236611	6.5
		30-39	3728747	50606034	7.4	1266170	16305526	7.8	338396	5236611	6.5
		40-49	3595266	50606034	7.1	1268310	16305526	7.8	385853	5236611	7.4
		50-59	3132166	50606034	6.2	1125929	16305526	6.9	405168	5236611	7.7
		60-69	2355583	50606034	4.7	742047	16305526	4.6	246587	5236611	4.7
		70-79	1602055	50606034	3.2	453606	16305526	2.8	158858	5236611	3.0
		80+	766181	50606034	1.5	182197	16305526	1.1	57973	5236611	1.1
	Female	0-9	2897543	50606034	5.7	975993	16305526	6.0	285128	5236611	5.4
		10-19	3171706	50606034	6.3	972305	16305526	6.0	318083	5236611	6.1
		20-29	3270109	50606034	6.5	974218	16305526	6.0	324429	5236611	6.2
		30-39	3754468	50606034	7.4	1239334	16305526	7.6	325274	5236611	6.2
		40-49	3639846	50606034	7.2	1241134	16305526	7.6	376337	5236611	7.2
		50-59	3191765	50606034	6.3	1101650	16305526	6.8	404652	5236611	7.7
		60-69	2482692	50606034	4.9	759552	16305526	4.7	270711	5236611	5.2
		70-79	1955828	50606034	3.9	583985	16305526	3.6	224575	5236611	4.3
		80+	1455434	50606034	2.9	391376	16305526	2.4	145345	5236611	2.8
2006	Male	0-9	3045013	50965186	6.0	1016487	16334210	6.2	295490	5255580	5.6
		10-19	3304842	50965186	6.5	1016638	16334210	6.2	331445	5255580	6.3
		20-29	3345103	50965186	6.6	984702	16334210	6.0	340118	5255580	6.5
		30-39	3664285	50965186	7.2	1225645	16334210	7.5	335370	5255580	6.4
		40-49	3670558	50965186	7.2	1280423	16334210	7.8	383001	5255580	7.3
		50-59	3138059	50965186	6.2	1144051	16334210	7.0	404641	5255580	7.7
		60-69	2402003	50965186	4.7	759540	16334210	4.6	258721	5255580	4.9
		70-79	1619066	50965186	3.2	461898	16334210	2.8	161895	5255580	3.1
		80+	788761	50965186	1.5	188023	16334210	1.2	61669	5255580	1.2
	Female	0-9	2905205	50965186	5.7	970242	16334210	5.9	282875	5255580	5.4
		10-19	3168162	50965186	6.2	972259	16334210	6.0	318036	5255580	6.1
		20-29	3354769	50965186	6.6	971917	16334210	6.0	324992	5255580	6.2
		30-39	3695971	50965186	7.3	1207576	16334210	7.4	321374	5255580	6.1
		40-49	3715149	50965186	7.3	1252430	16334210	7.7	373876	5255580	7.1
		50-59	3201287	50965186	6.3	1123086	16334210	6.9	405220	5255580	7.7

			England			Netherlands			Finland		
Year	**Gender**	**Age Category (in years)**	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
		60-69	2525343	50965186	5.0	774701	16334210	4.7	281690	5255580	5.4
		70-79	1953345	50965186	3.8	585599	16334210	3.6	224389	5255580	4.3
		80+	1468265	50965186	2.9	398993	16334210	2.4	150778	5255580	2.9
2007	Male	0-9	3063967	51381093	6.0	1008972	16357992	6.2	294799	5276955	5.6
		10-19	3321063	51381093	6.5	1015181	16357992	6.2	331299	5276955	6.3
		20-29	3438318	51381093	6.7	983534	16357992	6.0	339054	5276955	6.4
		30-39	3599070	51381093	7.0	1187960	16357992	7.3	333429	5276955	6.3
		40-49	3729440	51381093	7.3	1286067	16357992	7.9	380065	5276955	7.2
		50-59	3081701	51381093	6.0	1130465	16357992	6.9	400700	5276955	7.6
		60-69	2513000	51381093	4.9	810127	16357992	5.0	274834	5276955	5.2
		70-79	1641924	51381093	3.2	471365	16357992	2.9	164251	5276955	3.1
		80+	812050	51381093	1.6	194843	16357992	1.2	65311	5276955	1.2
	Female	0-9	2922550	51381093	5.7	963906	16357992	5.9	282547	5276955	5.4
		10-19	3178971	51381093	6.2	969044	16357992	5.9	317883	5276955	6.0
		20-29	3439916	51381093	6.7	971978	16357992	5.9	323917	5276955	6.1
		30-39	3622842	51381093	7.1	1175664	16357992	7.2	318597	5276955	6.0
		40-49	3786602	51381093	7.4	1259526	16357992	7.7	371257	5276955	7.0
		50-59	3147571	51381093	6.1	1112805	16357992	6.8	401659	5276955	7.6
		60-69	2641335	51381093	5.1	821903	16357992	5.0	297295	5276955	5.6
		70-79	1958999	51381093	3.8	588653	16357992	3.6	224364	5276955	4.3
		80+	1481774	51381093	2.9	405999	16357992	2.5	155694	5276955	3.0
2008	Male	0-9	3098759	51815853	6.0	1000823	16405399	6.1	295390	5300484	5.6
		10-19	3313513	51815853	6.4	1014265	16405399	6.2	330744	5300484	6.2
		20-29	3513336	51815853	6.8	990318	16405399	6.0	338898	5300484	6.4
		30-39	3554750	51815853	6.9	1153602	16405399	7.0	331628	5300484	6.3
		40-49	3774583	51815853	7.3	1291237	16405399	7.9	378447	5300484	7.1
		50-59	3072649	51815853	5.9	1123529	16405399	6.8	394668	5300484	7.4
		60-69	2603238	51815853	5.0	855415	16405399	5.2	290648	5300484	5.5
		70-79	1670782	51815853	3.2	481089	16405399	2.9	167432	5300484	3.2
		80+	833316	51815853	1.6	201795	16405399	1.2	68932	5300484	1.3
	Female	0-9	2956000	51815853	5.7	956049	16405399	5.8	282487	5300484	5.3
		10-19	3174398	51815853	6.1	969313	16405399	5.9	317889	5300484	6.0
		20-29	3516115	51815853	6.8	977145	16405399	6.0	323050	5300484	6.1
		30-39	3574687	51815853	6.9	1145998	16405399	7.0	316405	5300484	6.0
		40-49	3831409	51815853	7.4	1264680	16405399	7.7	369516	5300484	7.0
		50-59	3130394	51815853	6.0	1108335	16405399	6.8	396261	5300484	7.5
		60-69	2733906	51815853	5.3	865323	16405399	5.3	312447	5300484	5.9
		70-79	1973403	51815853	3.8	592789	16405399	3.6	225574	5300484	4.3
		80+	1490615	51815853	2.9	413694	16405399	2.5	160068	5300484	3.0
2009	Male	0-9	3133145	52196381	6.0	993668	16485787	6.0	297521	5326314	5.6
		10-19	3313726	52196381	6.3	1018225	16485787	6.2	327615	5326314	6.2
		20-29	3519191	52196381	6.7	1002693	16485787	6.1	341203	5326314	6.4
		30-39	3533516	52196381	6.8	1125226	16485787	6.8	331110	5326314	6.2
		40-49	3818175	52196381	7.3	1296724	16485787	7.9	377671	5326314	7.1
		50-59	3092821	52196381	5.9	1125704	16485787	6.8	386983	5326314	7.3
		60-69	2670901	52196381	5.1	890371	16485787	5.4	304745	5326314	5.7
		70-79	1696801	52196381	3.3	493978	16485787	3.0	171389	5326314	3.2
		80+	855556	52196381	1.6	209807	16485787	1.3	73416	5326314	1.4
	Female	0-9	2990532	52196381	5.7	948522	16485787	5.8	284299	5326314	5.3
		10-19	3170128	52196381	6.1	973170	16485787	5.9	314904	5326314	5.9
		20-29	3542574	52196381	6.8	986139	16485787	6.0	324653	5326314	6.1
		30-39	3544922	52196381	6.8	1119803	16485787	6.8	314895	5326314	5.9
		40-49	3876697	52196381	7.4	1270393	16485787	7.7	368433	5326314	6.9
		50-59	3147862	52196381	6.0	1113108	16485787	6.8	389204	5326314	7.3

			England			Netherlands			Finland		
Year	**Gender**	**Age Category (in years)**	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
		60-69	2801162	52196381	5.4	897985	16485787	5.4	326283	5326314	6.1
		70-79	1986302	52196381	3.8	598870	16485787	3.6	227054	5326314	4.3
		80+	1502370	52196381	2.9	421401	16485787	2.6	164936	5326314	3.1
2010	Male	0-9	3179493	52642452	6.0	986182	16574989	5.9	299564	5351427	5.6
		10-19	3302338	52642452	6.3	1023448	16574989	6.2	324839	5351427	6.1
		20-29	3566316	52642452	6.8	1014928	16574989	6.1	343010	5351427	6.4
		30-39	3527351	52642452	6.7	1092119	16574989	6.6	332493	5351427	6.2
		40-49	3838029	52642452	7.3	1305878	16574989	7.9	373253	5351427	7.0
		50-59	3127838	52642452	5.9	1135362	16574989	6.8	381713	5351427	7.1
		60-69	2732779	52642452	5.2	919962	16574989	5.6	317435	5351427	5.9
		70-79	1718958	52642452	3.3	507341	16574989	3.1	175443	5351427	3.3
		80+	884142	52642452	1.7	218256	16574989	1.3	77317	5351427	1.4
	Female	0-9	3035352	52642452	5.8	941948	16574989	5.7	286336	5351427	5.4
		10-19	3150032	52642452	6.0	976756	16574989	5.9	312220	5351427	5.8
		20-29	3572826	52642452	6.8	997337	16574989	6.0	326096	5351427	6.1
		30-39	3543590	52642452	6.7	1088388	16574989	6.6	316245	5351427	5.9
		40-49	3903248	52642452	7.4	1279459	16574989	7.7	363842	5351427	6.8
		50-59	3180878	52642452	6.0	1124849	16574989	6.8	384489	5351427	7.2
		60-69	2861342	52642452	5.4	925994	16574989	5.6	337770	5351427	6.3
		70-79	1993679	52642452	3.8	607044	16574989	3.7	229271	5351427	4.3
		80+	1524261	52642452	2.9	429738	16574989	2.6	170091	5351427	3.2
2011	Male	0-9	3234217	53107169	6.1	976190	16655799	5.9	302067	5375276	5.6
		10-19	3271327	53107169	6.2	1025804	16655799	6.2	320802	5375276	6.0
		20-29	3641472	53107169	6.9	1026784	16655799	6.2	345527	5375276	6.4
		30-39	3520939	53107169	6.6	1063612	16655799	6.4	335335	5375276	6.2
		40-49	3848018	53107169	7.2	1308966	16655799	7.9	368162	5375276	6.8
		50-59	3183772	53107169	6.0	1147992	16655799	6.9	377765	5375276	7.0
		60-69	2794611	53107169	5.3	944171	16655799	5.7	331591	5375276	6.2
		70-79	1724705	53107169	3.2	521650	16655799	3.1	175962	5375276	3.3
		80+	914101	53107169	1.7	228313	16655799	1.4	81205	5375276	1.5
	Female	0-9	3084664	53107169	5.8	932145	16655799	5.6	288901	5375276	5.4
		10-19	3120354	53107169	5.9	979680	16655799	5.9	307991	5375276	5.7
		20-29	3612016	53107169	6.8	1009483	16655799	6.1	328316	5375276	6.1
		30-39	3530583	53107169	6.6	1062720	16655799	6.4	317859	5375276	5.9
		40-49	3925541	53107169	7.4	1285251	16655799	7.7	358598	5375276	6.7
		50-59	3242308	53107169	6.1	1138574	16655799	6.8	381200	5375276	7.1
		60-69	2925300	53107169	5.5	950041	16655799	5.7	352118	5375276	6.6
		70-79	1988177	53107169	3.7	615189	16655799	3.7	227170	5375276	4.2
		80+	1545064	53107169	2.9	439234	16655799	2.6	174707	5375276	3.3
2012	Male	0-9	3315406	53493729	6.2	965892	16730348	5.8	304603	5401267	5.6
		10-19	3225457	53493729	6.0	1026756	16730348	6.1	316800	5401267	5.9
		20-29	3658984	53493729	6.8	1040011	16730348	6.2	347797	5401267	6.4
		30-39	3505229	53493729	6.6	1040139	16730348	6.2	339765	5401267	6.3
		40-49	3840766	53493729	7.2	1303459	16730348	7.8	362194	5401267	6.7
		50-59	3258288	53493729	6.1	1164439	16730348	7.0	375750	5401267	7.0
		60-69	2834788	53493729	5.3	969318	16730348	5.8	335965	5401267	6.2
		70-79	1749576	53493729	3.3	534622	16730348	3.2	184527	5401267	3.4
		80+	944954	53493729	1.8	238235	16730348	1.4	85133	5401267	1.6
	Female	0-9	3161532	53493729	5.9	921536	16730348	5.5	291490	5401267	5.4
		10-19	3068720	53493729	5.7	980570	16730348	5.9	303855	5401267	5.6
		20-29	3622144	53493729	6.8	1020837	16730348	6.1	330522	5401267	6.1
		30-39	3525341	53493729	6.6	1040906	16730348	6.2	321399	5401267	6.0
		40-49	3923558	53493729	7.3	1282399	16730348	7.7	352557	5401267	6.5
		50-59	3318902	53493729	6.2	1156546	16730348	6.9	379672	5401267	7.0

			England			Netherlands			Finland		
Year	**Gender**	**Age Category (in years)**	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
		60-69	2970163	53493729	5.6	975228	16730348	5.8	355914	5401267	6.6
		70-79	2006947	53493729	3.8	621675	16730348	3.7	235234	5401267	4.4
		80+	1562974	53493729	2.9	447780	16730348	2.7	178090	5401267	3.3
2013	Male	0-9	3380804	53865817	6.3	953132	16779575	5.7	306987	5426674	5.7
		10-19	3194389	53865817	5.9	1027146	16779575	6.1	311990	5426674	5.7
		20-29	3669986	53865817	6.8	1049843	16779575	6.3	349001	5426674	6.4
		30-39	3513192	53865817	6.5	1019598	16779575	6.1	346956	5426674	6.4
		40-49	3817291	53865817	7.1	1289060	16779575	7.7	355356	5426674	6.5
		50-59	3332412	53865817	6.2	1178148	16779575	7.0	373341	5426674	6.9
		60-69	2859684	53865817	5.3	993467	16779575	5.9	350189	5426674	6.5
		70-79	1797852	53865817	3.3	549443	16779575	3.3	184707	5426674	3.4
		80+	968359	53865817	1.8	247502	16779575	1.5	88095	5426674	1.6
	Female	0-9	3221245	53865817	6.0	909056	16779575	5.4	294076	5426674	5.4
		10-19	3036756	53865817	5.6	981439	16779575	5.8	299052	5426674	5.5
		20-29	3619084	53865817	6.7	1030234	16779575	6.1	332052	5426674	6.1
		30-39	3538007	53865817	6.6	1020683	16779575	6.1	327645	5426674	6.0
		40-49	3898376	53865817	7.2	1273154	16779575	7.6	345412	5426674	6.4
		50-59	3399325	53865817	6.3	1171940	16779575	7.0	377025	5426674	6.9
		60-69	2997886	53865817	5.6	1000144	16779575	6.0	370927	5426674	6.8
		70-79	2051396	53865817	3.8	630268	16779575	3.8	233171	5426674	4.3
		80+	1569773	53865817	2.9	455318	16779575	2.7	180692	5426674	3.3
2014	Male	0-9	3432889	54316618	6.3	938929	16829289	5.6	308716	5451270	5.7
		10-19	3180262	54316618	5.9	1029195	16829289	6.1	308766	5451270	5.7
		20-29	3698559	54316618	6.8	1060199	16829289	6.3	348643	5451270	6.4
		30-39	3539084	54316618	6.5	1009484	16829289	6.0	355383	5451270	6.5
		40-49	3773649	54316618	6.9	1264256	16829289	7.5	347351	5451270	6.4
		50-59	3415987	54316618	6.3	1195096	16829289	7.1	372917	5451270	6.8
		60-69	2872678	54316618	5.3	1011034	16829289	6.0	357877	5451270	6.6
		70-79	1860944	54316618	3.4	570132	16829289	3.4	189963	5451270	3.5
		80+	999144	54316618	1.8	256060	16829289	1.5	90748	5451270	1.7
	Female	0-9	3270433	54316618	6.0	894902	16829289	5.3	295163	5451270	5.4
		10-19	3023747	54316618	5.6	983014	16829289	5.8	295922	5451270	5.4
		20-29	3626240	54316618	6.7	1038888	16829289	6.2	332162	5451270	6.1
		30-39	3564129	54316618	6.6	1009081	16829289	6.0	335523	5451270	6.2
		40-49	3852118	54316618	7.1	1253537	16829289	7.4	336755	5451270	6.2
		50-59	3487882	54316618	6.4	1189480	16829289	7.1	376254	5451270	6.9
		60-69	3016714	54316618	5.6	1018930	16829289	6.1	379527	5451270	7.0
		70-79	2111426	54316618	3.9	646043	16829289	3.8	237513	5451270	4.4
		80+	1590733	54316618	2.9	461029	16829289	2.7	182087	5451270	3.3
2015	Male	0-9	3479293	54786327	6.4	930776	16900726	5.5	308803	5471753	5.6
		10-19	3185751	54786327	5.8	1027958	16900726	6.1	306089	5471753	5.6
		20-29	3719848	54786327	6.8	1071722	16900726	6.3	348782	5471753	6.4
		30-39	3588525	54786327	6.6	1008646	16900726	6.0	360229	5471753	6.6
		40-49	3726947	54786327	6.8	1234136	16900726	7.3	342288	5471753	6.3
		50-59	3505039	54786327	6.4	1213715	16900726	7.2	372309	5471753	6.8
		60-69	2887466	54786327	5.3	1026035	16900726	6.1	364408	5471753	6.7
		70-79	1912128	54786327	3.5	593446	16900726	3.5	195270	5471753	3.6
		80+	1024289	54786327	1.9	266424	16900726	1.6	93685	5471753	1.7
	Female	0-9	3312850	54786327	6.0	887201	16900726	5.2	295506	5471753	5.4
		10-19	3027833	54786327	5.5	982124	16900726	5.8	292792	5471753	5.4
		20-29	3630377	54786327	6.6	1047984	16900726	6.2	332869	5471753	6.1
		30-39	3610421	54786327	6.6	1006095	16900726	6.0	339587	5471753	6.2
		40-49	3798867	54786327	6.9	1228645	16900726	7.3	331708	5471753	6.1
		50-59	3584283	54786327	6.5	1207855	16900726	7.1	374173	5471753	6.8

			England			Netherlands			Finland		
Year	**Gender**	**Age Category (in years)**	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
		60-69	3034390	54786327	5.5	1034581	16900726	6.1	387436	5471753	7.1
		70-79	2160720	54786327	3.9	664831	16900726	3.9	242027	5471753	4.4
		80+	1597300	54786327	2.9	468552	16900726	2.8	183792	5471753	3.4
2016	Male	0-9	3513322	55268067	6.4	925323	16979120	5.4	307984	5487308	5.6
		10-19	3204220	55268067	5.8	1029489	16979120	6.1	304115	5487308	5.5
		20-29	3748307	55268067	6.8	1081810	16979120	6.4	348900	5487308	6.4
		30-39	3648743	55268067	6.6	1015681	16979120	6.0	361726	5487308	6.6
		40-49	3676251	55268067	6.7	1203967	16979120	7.1	340102	5487308	6.2
		50-59	3582002	55268067	6.5	1229579	16979120	7.2	370591	5487308	6.8
		60-69	2907183	55268067	5.3	1044842	16979120	6.2	364669	5487308	6.6
		70-79	1965277	55268067	3.6	610817	16979120	3.6	206094	5487308	3.8
		80+	1055615	55268067	1.9	275627	16979120	1.6	97309	5487308	1.8
	Female	0-9	3343990	55268067	6.1	881569	16979120	5.2	294112	5487308	5.4
		10-19	3045444	55268067	5.5	982118	16979120	5.8	290983	5487308	5.3
		20-29	3623236	55268067	6.6	1055138	16979120	6.2	332844	5487308	6.1
		30-39	3657891	55268067	6.6	1011073	16979120	6.0	341022	5487308	6.2
		40-49	3742094	55268067	6.8	1202759	16979120	7.1	328146	5487308	6.0
		50-59	3668753	55268067	6.6	1221554	16979120	7.2	372020	5487308	6.8
		60-69	3055845	55268067	5.5	1055613	16979120	6.2	388254	5487308	7.1
		70-79	2212058	55268067	4.0	679040	16979120	4.0	252265	5487308	4.6
		80+	1617836	55268067	2.9	473121	16979120	2.8	186172	5487308	3.4
2017	Male	0-9	3525982	55619430	6.3	922745	17081507	5.4	304951	5503297	5.5
		10-19	3224051	55619430	5.8	1032133	17081507	6.0	305313	5503297	5.5
		20-29	3748745	55619430	6.7	1094427	17081507	6.4	350341	5503297	6.4
		30-39	3687356	55619430	6.6	1028329	17081507	6.0	362277	5503297	6.6
		40-49	3615190	55619430	6.5	1177652	17081507	6.9	338810	5503297	6.2
		50-59	3647368	55619430	6.6	1240975	17081507	7.3	368581	5503297	6.7
		60-69	2861994	55619430	5.1	1036122	17081507	6.1	361856	5503297	6.6
		70-79	2084005	55619430	3.7	657140	17081507	3.8	220036	5503297	4.0
		80+	1086362	55619430	2.0	285579	17081507	1.7	100162	5503297	1.8
	Female	0-9	3356345	55619430	6.0	878724	17081507	5.1	291483	5503297	5.3
		10-19	3062717	55619430	5.5	983571	17081507	5.8	291095	5503297	5.3
		20-29	3609020	55619430	6.5	1061903	17081507	6.2	332538	5503297	6.0
		30-39	3712687	55619430	6.7	1021980	17081507	6.0	340890	5503297	6.2
		40-49	3677676	55619430	6.6	1178819	17081507	6.9	325754	5503297	5.9
		50-59	3738862	55619430	6.7	1232247	17081507	7.2	369578	5503297	6.7
		60-69	3011572	55619430	5.4	1047861	17081507	6.1	385074	5503297	7.0
		70-79	2333950	55619430	4.2	722604	17081507	4.2	266621	5503297	4.8
		80+	1635548	55619430	2.9	478696	17081507	2.8	187937	5503297	3.4
2018	Male	0-9	3520187	55977178	6.3	920523	17181084	5.4	300802	5513130	5.5
		10-19	3267642	55977178	5.8	1031363	17181084	6.0	306445	5513130	5.6
		20-29	3741648	55977178	6.7	1103136	17181084	6.4	350237	5513130	6.4
		30-39	3735580	55977178	6.7	1043479	17181084	6.1	362437	5513130	6.6
		40-49	3566200	55977178	6.4	1150911	17181084	6.7	337202	5513130	6.1
		50-59	3694804	55977178	6.6	1250353	17181084	7.3	367103	5513130	6.7
		60-69	2859328	55977178	5.1	1033415	17181084	6.0	357302	5513130	6.5
		70-79	2166506	55977178	3.9	698388	17181084	4.1	233956	5513130	4.2
		80+	1116047	55977178	2.0	295473	17181084	1.7	103647	5513130	1.9
	Female	0-9	3350406	55977178	6.0	875642	17181084	5.1	287772	5513130	5.2
		10-19	3103052	55977178	5.5	983128	17181084	5.7	291460	5513130	5.3
		20-29	3586930	55977178	6.4	1071802	17181084	6.2	331840	5513130	6.0
		30-39	3769500	55977178	6.7	1034666	17181084	6.0	340330	5513130	6.2
		40-49	3623626	55977178	6.5	1156224	17181084	6.7	323501	5513130	5.9
		50-59	3793976	55977178	6.8	1241003	17181084	7.2	367451	5513130	6.7

			England			Netherlands			Finland		
Year	**Gender**	**Age Category (in years)**	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
		60-69	3007639	55977178	5.4	1045860	17181084	6.1	379931	5513130	6.9
		70-79	2421420	55977178	4.3	762277	17181084	4.4	280624	5513130	5.1
		80+	1652687	55977178	3.0	483441	17181084	2.8	191090	5513130	3.5
2019	Male	0-9	-	-	-	913891	17282163	5.3	295062	5517919	5.3
		10-19	-	-	-	1027835	17282163	5.9	308308	5517919	5.6
		20-29	-	-	-	1117353	17282163	6.5	347134	5517919	6.3
		30-39	-	-	-	1060110	17282163	6.1	364159	5517919	6.6
		40-49	-	-	-	1127000	17282163	6.5	336342	5517919	6.1
		50-59	-	-	-	1258588	17282163	7.3	366458	5517919	6.6
		60-69	-	-	-	1038005	17282163	6.0	351333	5517919	6.4
		70-79	-	-	-	730336	17282163	4.2	246439	5517919	4.5
		80+	-	-	-	307968	17282163	1.8	108055	5517919	2.0
	Female	0-9	-	-	-	869613	17282163	5.0	281634	5517919	5.1
		10-19	-	-	-	980499	17282163	5.7	293397	5517919	5.3
		20-29	-	-	-	1084435	17282163	6.3	328114	5517919	5.9
		30-39	-	-	-	1048089	17282163	6.1	341988	5517919	6.2
		40-49	-	-	-	1134107	17282163	6.6	321601	5517919	5.8
		50-59	-	-	-	1249800	17282163	7.2	366324	5517919	6.6
		60-69	-	-	-	1051908	17282163	6.1	373436	5517919	6.8
		70-79	-	-	-	791774	17282163	4.6	293480	5517919	5.3
		80+	-	-	-	490852	17282163	2.8	194655	5517919	3.5
2020	Male	0-9	-	-	-	908364	17407585	5.2	-	-	-
		10-19	-	-	-	1024578	17407585	5.9	-	-	-
		20-29	-	-	-	1134264	17407585	6.5	-	-	-
		30-39	-	-	-	1081863	17407585	6.2	-	-	-
		40-49	-	-	-	1099863	17407585	6.3	-	-	-
		50-59	-	-	-	1270737	17407585	7.3	-	-	-
		60-69	-	-	-	1049662	17407585	6.0	-	-	-
		70-79	-	-	-	757590	17407585	4.4	-	-	-
		80+	-	-	-	321110	17407585	1.8	-	-	-
	Female	0-9	-	-	-	864531	17407585	5.0	-	-	-
		10-19	-	-	-	977784	17407585	5.6	-	-	-
		20-29	-	-	-	1099286	17407585	6.3	-	-	-
		30-39	-	-	-	1066068	17407585	6.1	-	-	-
		40-49	-	-	-	1108213	17407585	6.4	-	-	-
		50-59	-	-	-	1261681	17407585	7.2	-	-	-
		60-69	-	-	-	1064184	17407585	6.1	-	-	-
		70-79	-	-	-	816829	17407585	4.7	-	-	-
		80+	-	-	-	500978	17407585	2.9	-	-	-

N = total population during the respective year
n = population in each category
% = (n/N)*100

14.2 Trend over time and Feasibility assessment

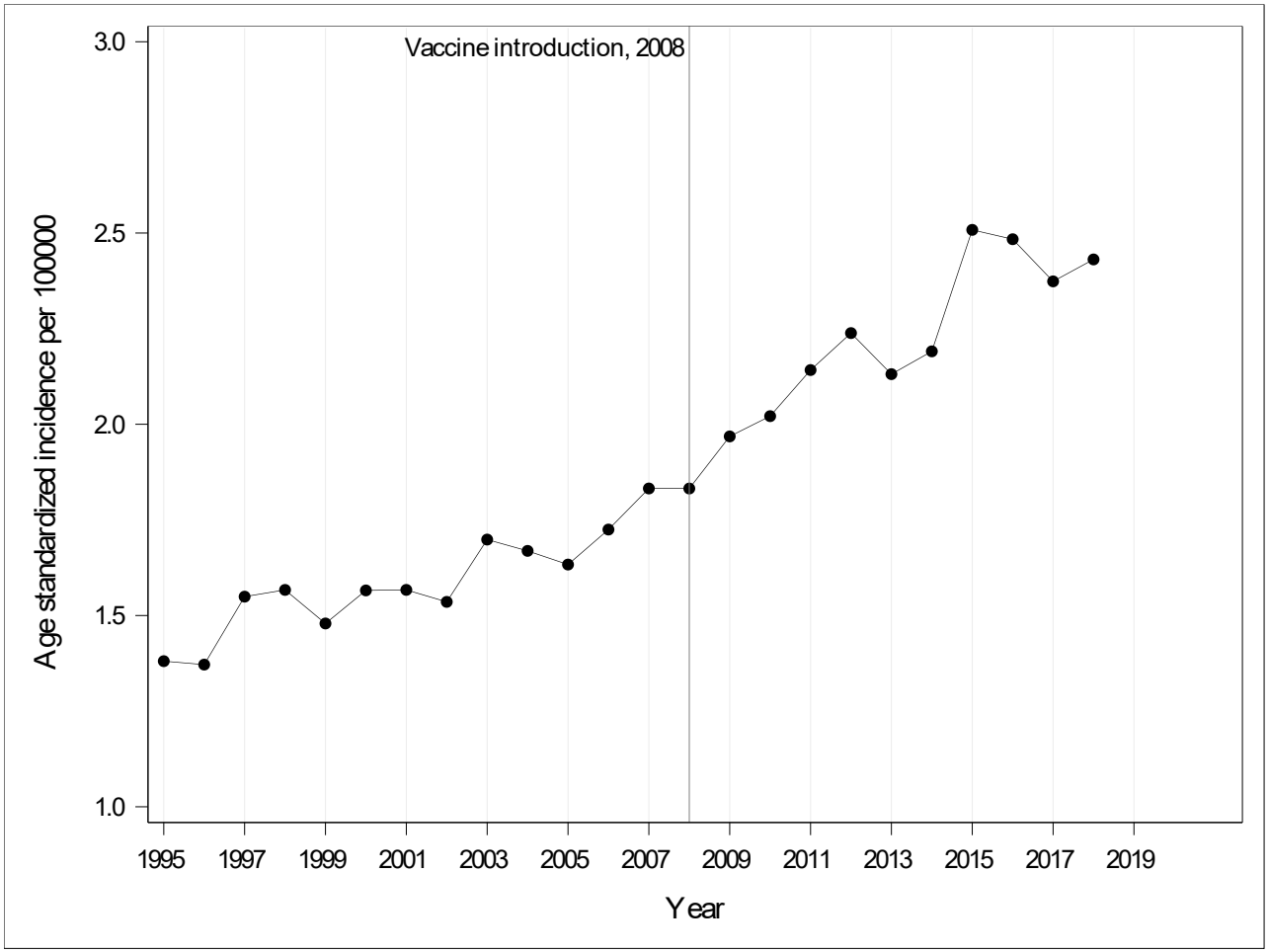
14.2.1 England

Table 14.2.1.1 Incidence of anal cancer by calendar year - England

			Age standardized Incidence per 100000			Crude Incidence per 100000		
				95% CI			95% CI	
Calendar Year	N	n	Value	LL	UL	Value	LL	UL
1995	48384614	556	1.381	0.813	2.343	1.149	1.056	1.249
1996	48521172	554	1.372	0.809	2.326	1.142	1.049	1.241
1997	48666657	634	1.549	0.940	2.552	1.303	1.203	1.408
1998	48822555	644	1.567	0.958	2.564	1.319	1.219	1.425
1999	49034531	616	1.479	0.882	2.481	1.256	1.159	1.360
2000	49234229	654	1.566	0.957	2.562	1.328	1.228	1.434
2001	49449746	664	1.567	0.951	2.582	1.343	1.243	1.449
2002	49679267	658	1.536	0.927	2.545	1.324	1.225	1.430
2003	49925517	736	1.699	1.048	2.752	1.474	1.370	1.585
2004	50194600	726	1.669	1.033	2.697	1.446	1.343	1.556
2005	50606034	722	1.633	1.002	2.661	1.427	1.325	1.535
2006	50965186	767	1.725	1.068	2.785	1.505	1.400	1.615
2007	51381093	831	1.832	1.149	2.921	1.617	1.509	1.731
2008	51815853	836	1.832	1.147	2.927	1.613	1.506	1.727
2009	52196381	916	1.968	1.249	3.102	1.755	1.643	1.872
2010	52642452	951	2.021	1.294	3.157	1.807	1.694	1.925
2011	53107169	1022	2.142	1.385	3.313	1.924	1.808	2.046
2012	53493729	1075	2.238	1.466	3.417	2.010	1.891	2.133
2013	53865817	1049	2.131	1.380	3.291	1.947	1.831	2.069
2014	54316618	1098	2.191	1.422	3.374	2.021	1.904	2.145
2015	54786327	1274	2.508	1.675	3.756	2.325	2.199	2.457
2016	55268067	1274	2.484	1.654	3.730	2.305	2.180	2.435
2017	55619430	1238	2.374	1.563	3.605	2.226	2.104	2.353
2018	55977178	1282	2.431	1.616	3.656	2.290	2.167	2.419

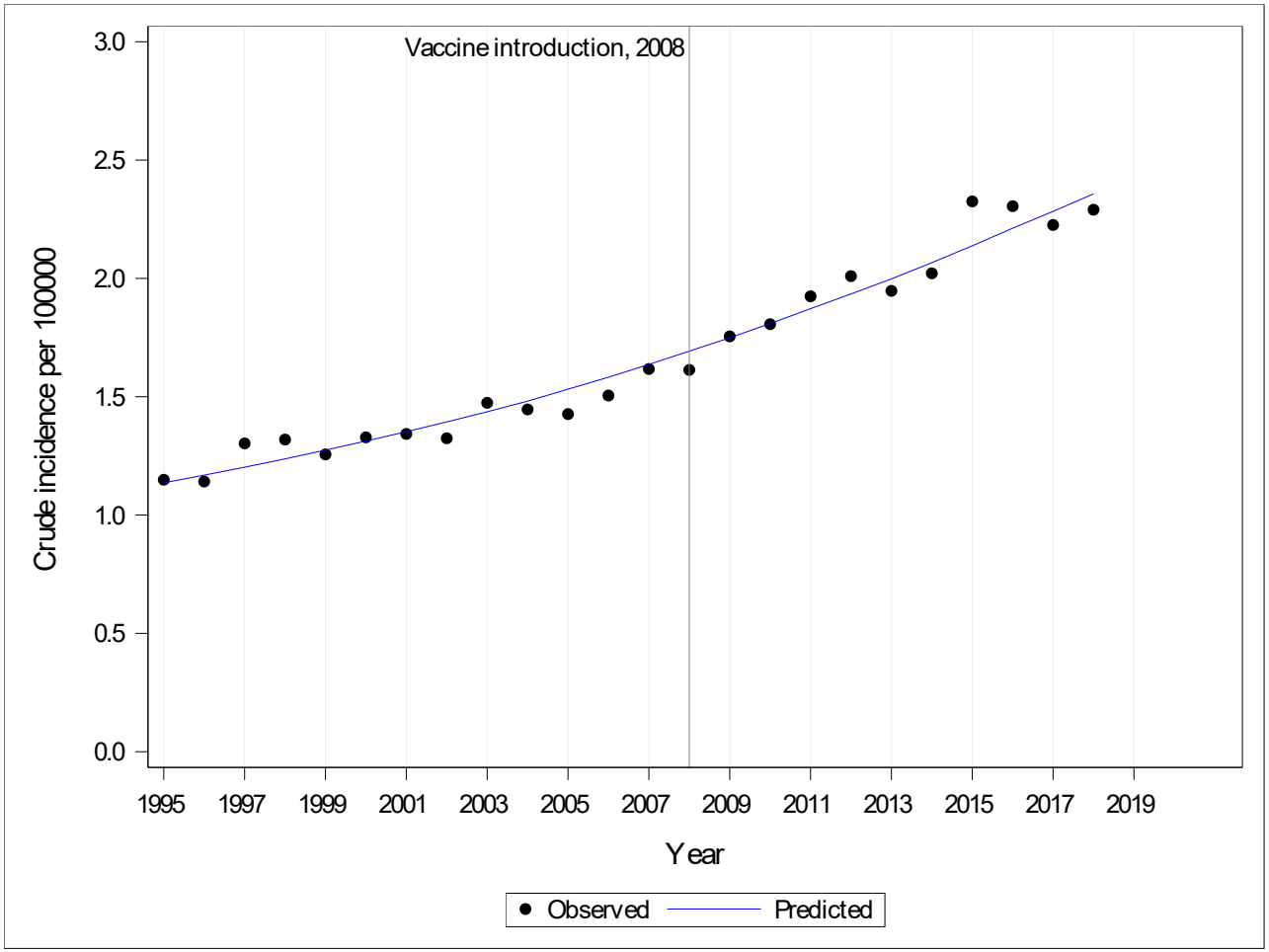
N = population in each category
n = number of anal cancer cases reported
Study period: Pre Cervarix launch (Year 1995 – Year 2007), Post Cervarix launch (Year 2008 – Year 2018)
Age standardized Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))
CI=confidence interval; LL=lower limit; UL=upper limit
Age standardized Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.1.1.1 Trend over time in the age standardized incidence of anal cancer - England



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.1.1.2 Trend over time in the crude incidence of anal cancer - England



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP
Line - Represents the predicted incidence , Period - Represents the observed Incidence

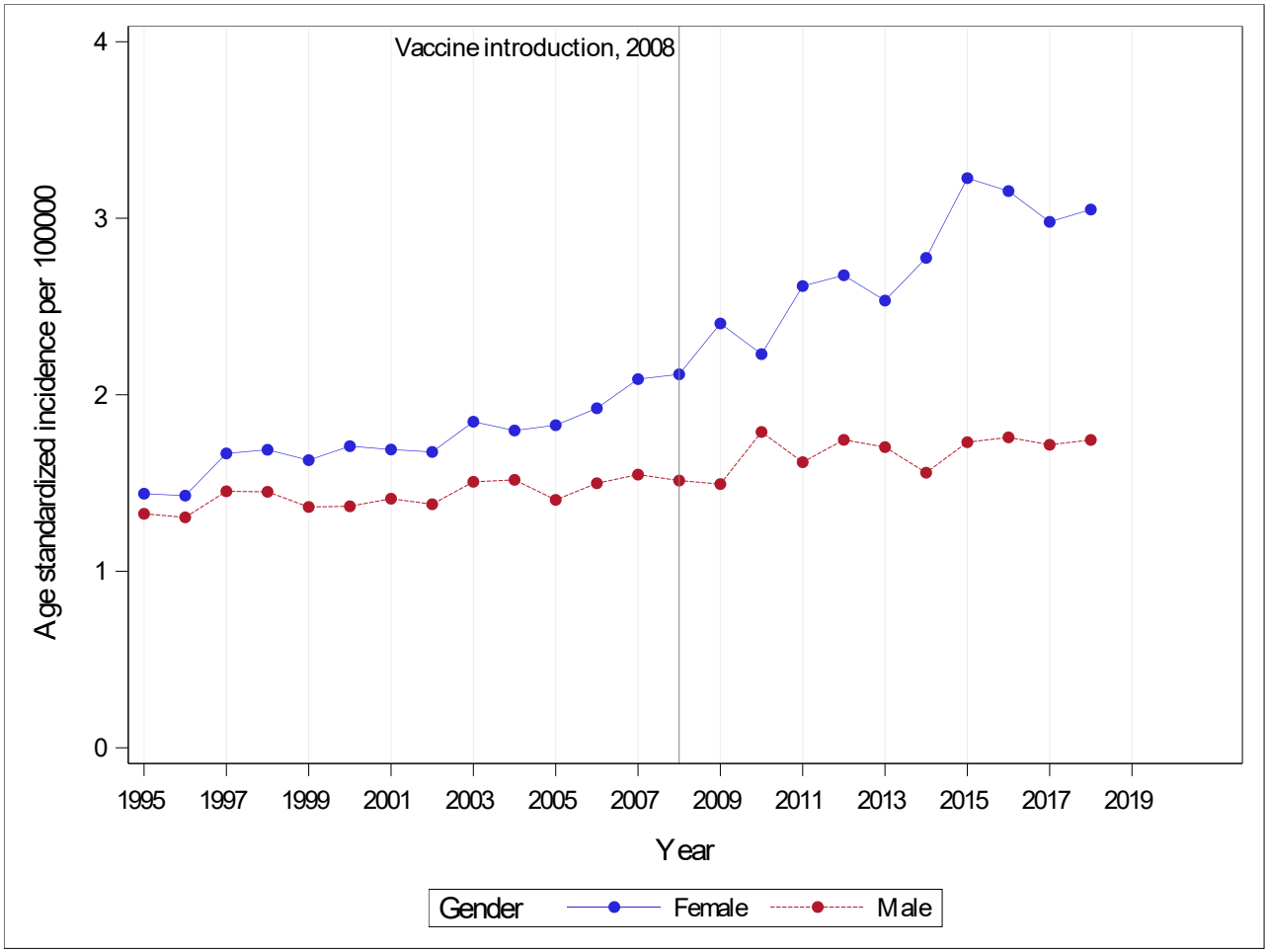
Table 14.2.1.2 Incidence of anal cancer by calendar year and gender - England

				Age standardized Incidence per 100000			Crude Incidence per 100000		
					95% CI			95% CI	
Calendar Year	Gender	N	n	Value	LL	UL	Value	LL	UL
1995	Male	23546945	229	1.326	0.776	2.263	0.973	0.851	1.107
	Female	24837669	327	1.439	0.855	2.424	1.317	1.178	1.467
1996	Male	23629865	228	1.305	0.762	2.238	0.965	0.844	1.099
	Female	24891307	326	1.428	0.849	2.402	1.310	1.171	1.460
1997	Male	23710844	252	1.453	0.878	2.403	1.063	0.936	1.202
	Female	24955813	382	1.668	1.023	2.718	1.531	1.381	1.692
1998	Male	23795308	254	1.450	0.877	2.399	1.067	0.940	1.207
	Female	25027247	390	1.688	1.045	2.727	1.558	1.407	1.721
1999	Male	23916833	242	1.364	0.810	2.297	1.012	0.888	1.148
	Female	25117698	374	1.630	0.986	2.692	1.489	1.342	1.648
2000	Male	24031560	253	1.368	0.805	2.326	1.053	0.927	1.191
	Female	25202669	401	1.709	1.066	2.739	1.591	1.439	1.755
2001	Male	24165587	267	1.411	0.833	2.391	1.105	0.976	1.246
	Female	25284159	397	1.690	1.044	2.736	1.570	1.419	1.732
2002	Male	24292759	263	1.380	0.813	2.341	1.083	0.956	1.222
	Female	25386508	395	1.676	1.030	2.727	1.556	1.406	1.717
2003	Male	24427705	294	1.507	0.901	2.519	1.204	1.070	1.349
	Female	25497812	442	1.847	1.161	2.938	1.733	1.576	1.903
2004	Male	24573534	296	1.518	0.918	2.509	1.205	1.071	1.350
	Female	25621066	430	1.798	1.131	2.856	1.678	1.523	1.845
2005	Male	24786643	279	1.404	0.831	2.374	1.126	0.997	1.266
	Female	25819391	443	1.828	1.149	2.907	1.716	1.560	1.883
2006	Male	24977690	304	1.499	0.897	2.503	1.217	1.084	1.362
	Female	25987496	463	1.923	1.220	3.033	1.782	1.623	1.952
2007	Male	25200533	317	1.548	0.936	2.558	1.258	1.123	1.404
	Female	26180560	514	2.089	1.344	3.245	1.963	1.797	2.141
2008	Male	25434926	318	1.514	0.907	2.527	1.250	1.117	1.395
	Female	26380927	518	2.116	1.364	3.281	1.964	1.798	2.140
2009	Male	25633832	320	1.494	0.892	2.502	1.248	1.115	1.393
	Female	26562549	596	2.404	1.586	3.643	2.244	2.067	2.431
2010	Male	25877244	391	1.789	1.116	2.870	1.511	1.365	1.668
	Female	26765208	560	2.230	1.456	3.416	2.092	1.923	2.273
2011	Male	26133162	359	1.618	0.984	2.660	1.374	1.235	1.523
	Female	26974007	663	2.616	1.757	3.894	2.458	2.274	2.652
2012	Male	26333448	388	1.745	1.084	2.807	1.473	1.330	1.628
	Female	27160281	687	2.677	1.812	3.954	2.529	2.344	2.726
2013	Male	26533969	386	1.703	1.056	2.747	1.455	1.313	1.607
	Female	27331848	663	2.534	1.693	3.792	2.426	2.245	2.618
2014	Male	26773196	365	1.558	0.939	2.587	1.363	1.227	1.511
	Female	27543422	733	2.775	1.885	4.085	2.661	2.472	2.861
2015	Male	27029286	410	1.731	1.073	2.794	1.517	1.374	1.671
	Female	27757041	864	3.227	2.253	4.623	3.113	2.909	3.327
2016	Male	27300920	425	1.759	1.089	2.839	1.557	1.412	1.712
	Female	27967147	849	3.154	2.193	4.536	3.036	2.835	3.247
2017	Male	27481053	422	1.717	1.055	2.794	1.536	1.393	1.689
	Female	28138377	816	2.979	2.047	4.337	2.900	2.704	3.106
2018	Male	27667942	435	1.744	1.078	2.822	1.572	1.428	1.727
	Female	28309236	847	3.049	2.116	4.396	2.992	2.794	3.200

N = population in each category
n = number of anal cancer cases reported

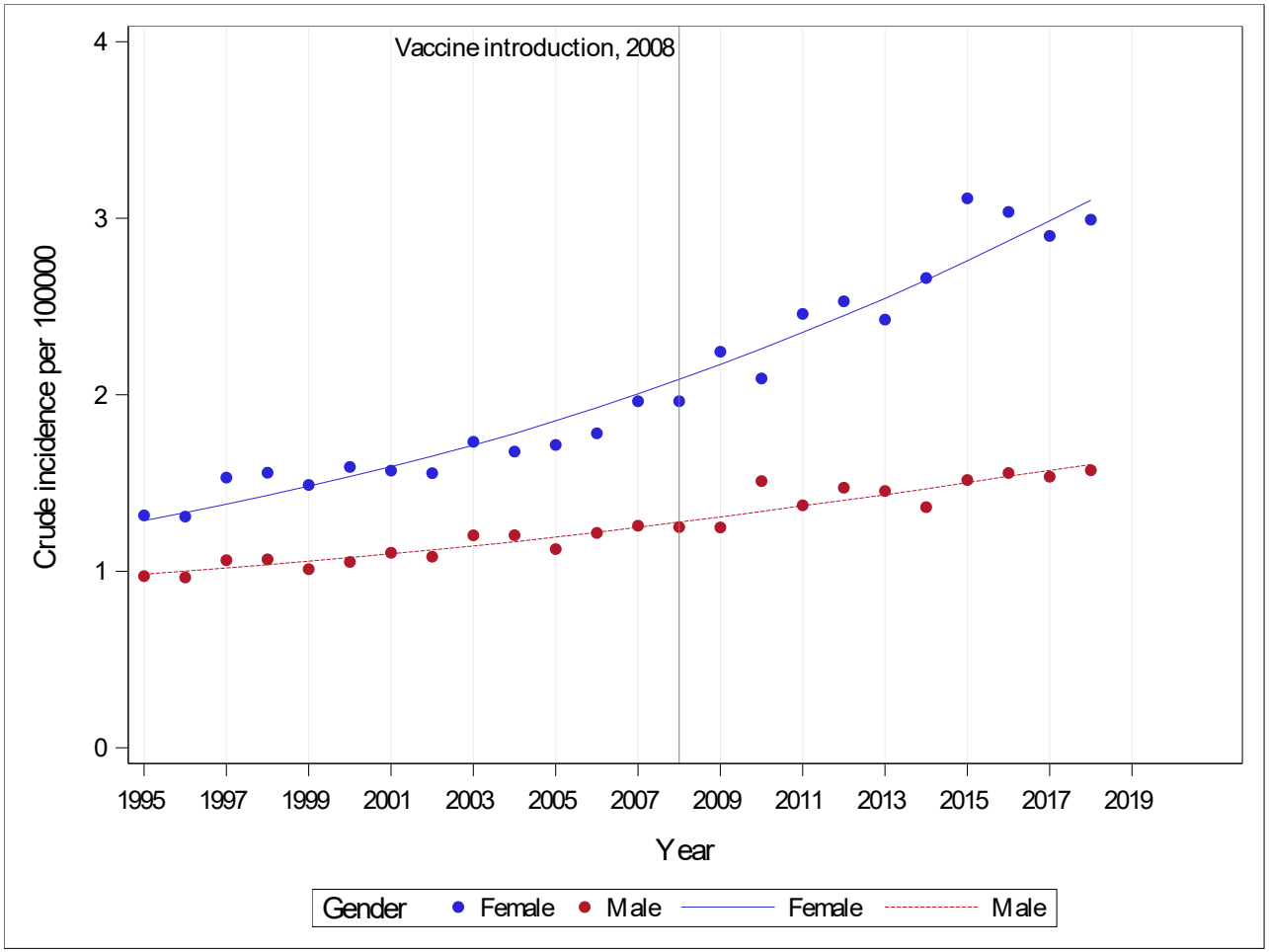
Study period: Pre Cervarix launch (Year 1995 – Year 2007), Post Cervarix launch (Year 2008 – Year 2018)
Age standardized Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))
CI=confidence interval; LL=lower limit; UL=upper limit
Age standardized Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.1.2.1 Trend over time in the age standardized incidence of anal cancer by gender - England



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.1.2.2 Trend over time in the crude incidence of anal cancer by gender - England



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP
Line - Represents the predicted incidence , Period - Represents the observed Incidence

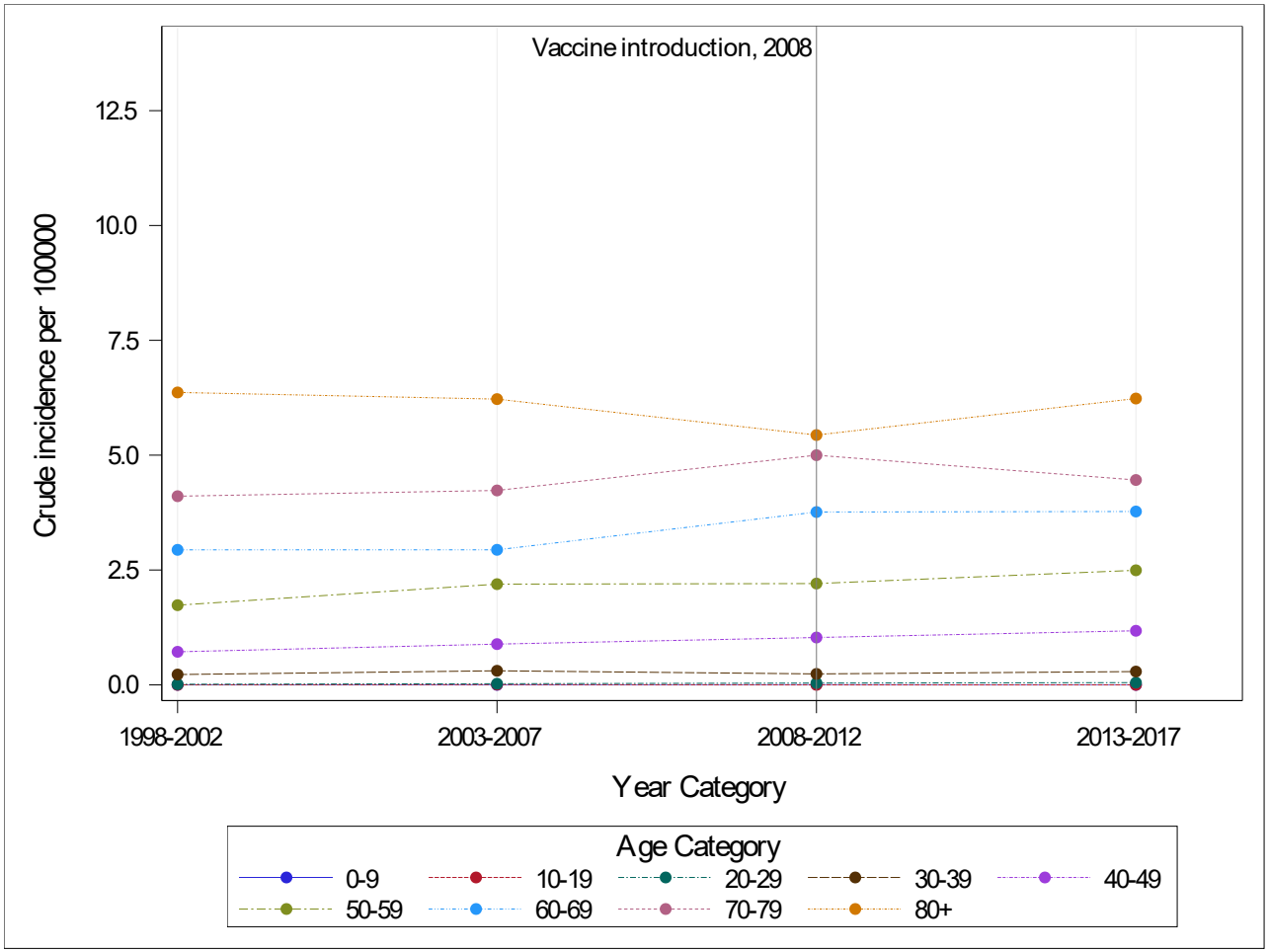
Table 14.2.1.3 Crude incidence of anal cancer for year and age category by gender - England

		Male					Female					Total				
					95% CI					95% CI					95% CI	
Year category	Age category (in years)	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL
1998-2002	0-9	15725316	0	0.000	0.000	0.023	14975360	0	0.000	0.000	0.025	30700676	0	0.000	0.000	0.012
	10-19	15904463	0	0.000	0.000	0.023	15221411	0	0.000	0.000	0.024	31125874	0	0.000	0.000	0.012
	20-29	15894820	2	0.013	0.002	0.045	15898020	7	0.044	0.018	0.091	31792840	9	0.028	0.013	0.054
	30-39	19162714	43	0.224	0.162	0.302	19386373	65	0.335	0.259	0.427	38549087	108	0.280	0.230	0.338
	40-49	16262868	117	0.719	0.595	0.862	16472647	226	1.372	1.199	1.563	32735515	343	1.048	0.940	1.165
	50-59	15051904	261	1.734	1.530	1.958	15300360	314	2.052	1.831	2.292	30352264	575	1.894	1.743	2.056
	60-69	11058055	325	2.939	2.628	3.277	11731834	379	3.231	2.913	3.573	22789889	704	3.089	2.865	3.326
	70-79	7890047	324	4.106	3.671	4.579	10219770	535	5.235	4.801	5.698	18109817	859	4.743	4.431	5.071
	80+	3251860	207	6.366	5.528	7.294	6812506	431	6.327	5.743	6.953	10064366	638	6.339	5.857	6.851
2003-2007	0-9	15237944	0	0.000	0.000	0.024	14521370	0	0.000	0.000	0.025	29759314	0	0.000	0.000	0.012
	10-19	16503960	1	0.006	0.000	0.034	15818356	1	0.006	0.000	0.035	32322316	2	0.006	0.001	0.022
	20-29	16380103	4	0.024	0.007	0.063	16369635	5	0.031	0.010	0.071	32749738	9	0.027	0.013	0.052
	30-39	18600868	57	0.306	0.232	0.397	18748444	62	0.331	0.254	0.424	37349312	119	0.319	0.264	0.381
	40-49	17927432	159	0.887	0.754	1.036	18164307	248	1.365	1.201	1.546	36091739	407	1.128	1.021	1.243
	50-59	15601161	342	2.192	1.966	2.437	15914731	450	2.828	2.572	3.101	31515892	792	2.513	2.341	2.694
	60-69	11838031	348	2.940	2.639	3.265	12473325	487	3.904	3.565	4.267	24311356	835	3.435	3.206	3.676
	70-79	8034525	340	4.232	3.794	4.706	9807552	494	5.037	4.602	5.501	17842077	834	4.674	4.362	5.003
	80+	3842081	239	6.221	5.457	7.061	7288605	545	7.477	6.863	8.132	11130686	784	7.044	6.559	7.554
2008-2012	0-9	15961020	1	0.006	0.000	0.035	15228080	0	0.000	0.000	0.024	31189100	1	0.003	0.000	0.018
	10-19	16426361	0	0.000	0.000	0.022	15683632	0	0.000	0.000	0.024	32109993	0	0.000	0.000	0.011
	20-29	17899299	7	0.039	0.016	0.081	17865675	8	0.045	0.019	0.088	35764974	15	0.042	0.023	0.069
	30-39	17641785	42	0.238	0.172	0.322	17719123	75	0.423	0.333	0.531	35360908	117	0.331	0.274	0.397
	40-49	19119571	197	1.030	0.891	1.185	19460453	330	1.696	1.518	1.889	38580024	527	1.366	1.252	1.488
	50-59	15735368	347	2.205	1.979	2.450	16020344	660	4.120	3.811	4.446	31755712	1007	3.171	2.978	3.373
	60-69	13636317	513	3.762	3.443	4.102	14291873	746	5.220	4.852	5.608	27928190	1259	4.508	4.262	4.764
	70-79	8560822	428	5.000	4.537	5.496	9948508	662	6.654	6.157	7.181	18509330	1090	5.889	5.544	6.249
	80+	4432069	241	5.438	4.773	6.169	7625284	543	7.121	6.535	7.746	12057353	784	6.502	6.055	6.974
2013-2017	0-9	17332290	0	0.000	0.000	0.021	16504863	0	0.000	0.000	0.022	33837153	0	0.000	0.000	0.011
	10-19	15988673	0	0.000	0.000	0.023	15196497	0	0.000	0.000	0.024	31185170	0	0.000	0.000	0.012

		Male					Female					Total				
					95% CI					95% CI					95% CI	
Year category	Age category (in years)	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL
	20-29	18585445	9	0.048	0.022	0.092	18107957	10	0.055	0.026	0.102	36693402	19	0.052	0.031	0.081
	30-39	17976900	52	0.289	0.216	0.379	18083135	96	0.531	0.430	0.648	36060035	148	0.410	0.347	0.482
	40-49	18609328	219	1.177	1.026	1.343	18969131	411	2.167	1.962	2.387	37578459	630	1.676	1.548	1.813
	50-59	17482808	436	2.494	2.265	2.739	17879105	890	4.978	4.656	5.316	35361913	1326	3.750	3.551	3.957
	60-69	14389005	543	3.774	3.463	4.105	15116407	1081	7.151	6.731	7.591	29505412	1624	5.504	5.240	5.778
	70-79	9620206	429	4.459	4.047	4.902	10869550	817	7.516	7.010	8.050	20489756	1246	6.081	5.748	6.428
	80+	5133769	320	6.233	5.569	6.955	8011190	620	7.739	7.142	8.373	13144959	940	7.151	6.701	7.623

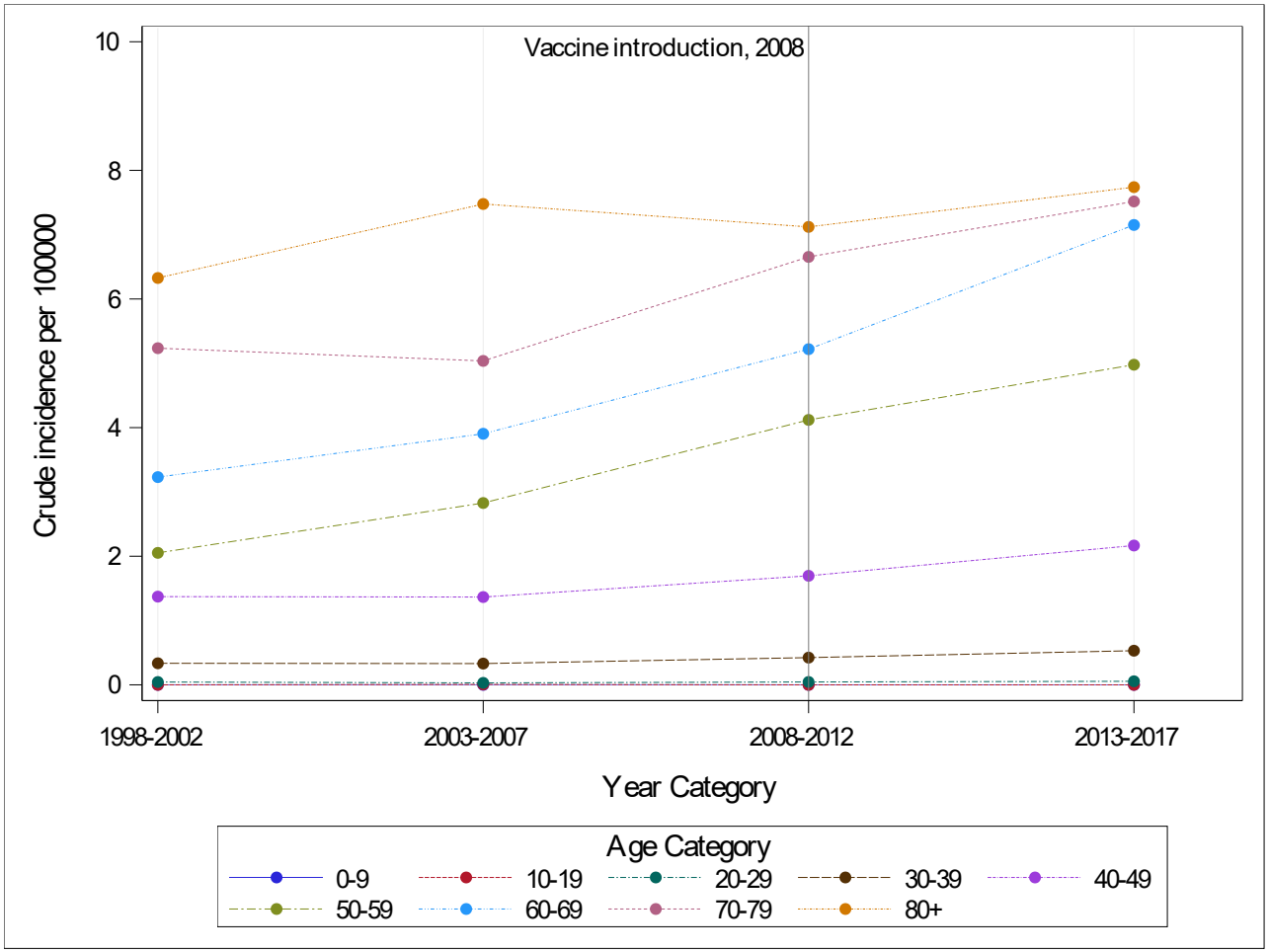
N = population in each category
n = number of anal cancer cases reported in each category
Study period: Pre Cervarix launch (Year 1995 – Year 2007), Post Cervarix launch (Year 2008 – Year 2018)
Crude Incidence per 100000 = (n/N)*100000
95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.1.3.1 Trend over time in the crude incidence of anal cancer by age category for Male - England



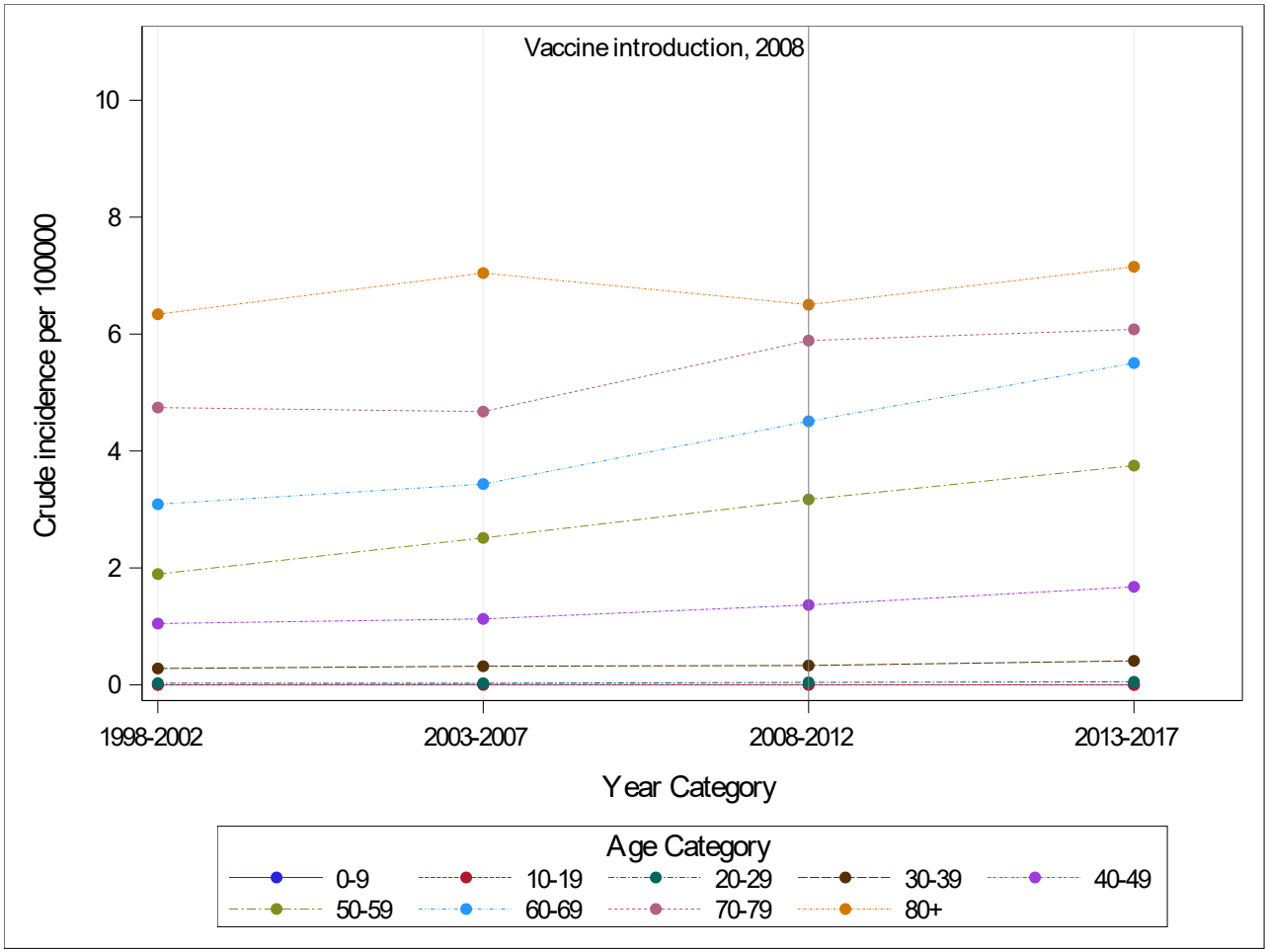
Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.1.3.2 Trend over time in the crude incidence of anal cancer by age category for Female - England



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.1.3.3 Trend over time in the crude incidence of anal cancer by age category - England



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

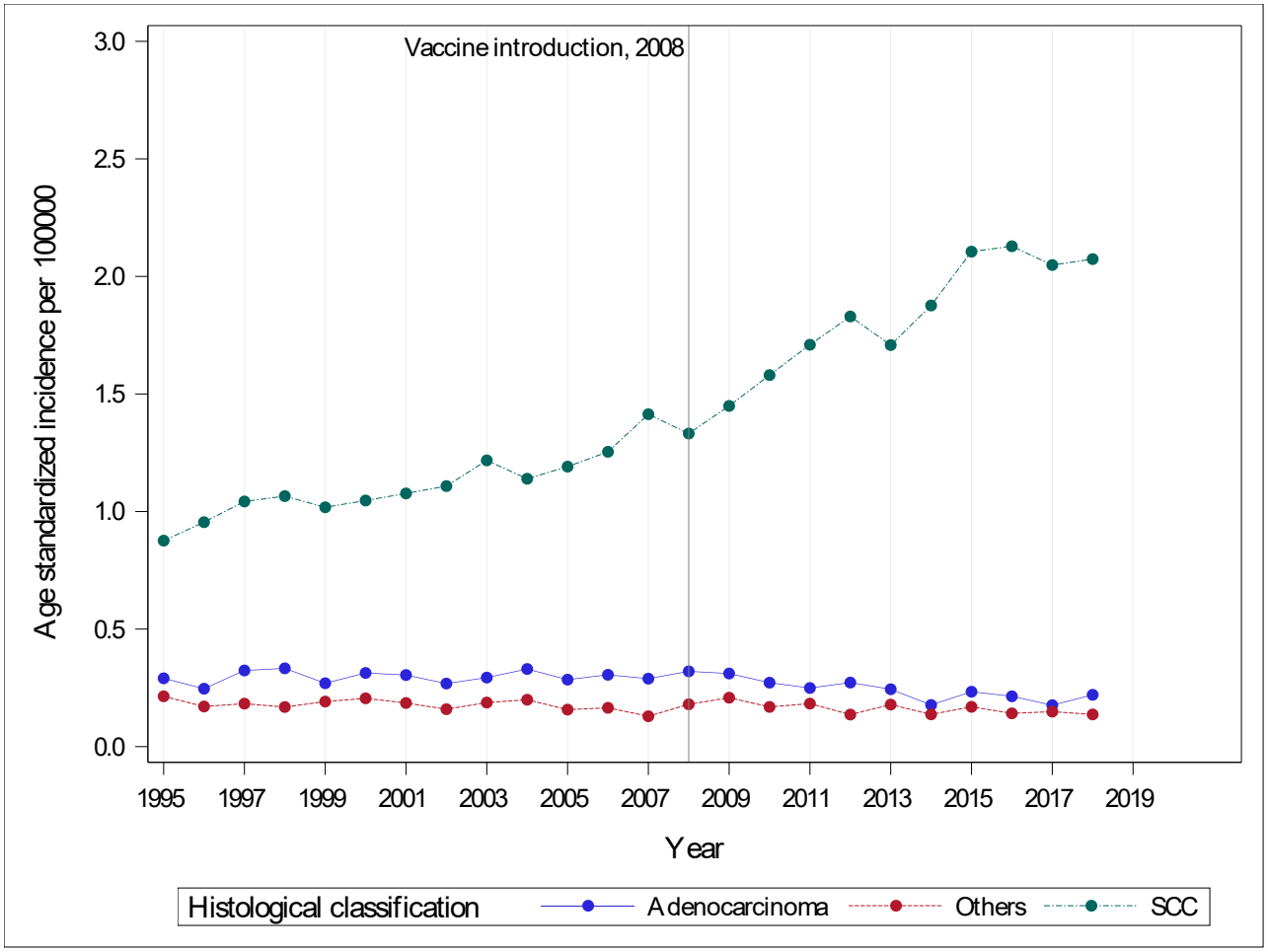
Table 14.2.1.4 Incidence of anal cancer by calendar year and histological classification - England

				Age standardized Incidence per 100000			Crude Incidence per 100000		
					95% CI			95% CI	
Calendar Year	Histological classification	N	n	Value	LL	UL	Value	LL	UL
1995	SCC	48384614	355	0.876	0.445	1.726	0.734	0.659	0.814
	Adenocarcinoma	48384614	115	0.291	0.096	0.881	0.238	0.196	0.285
	Others	48384614	86	0.214	0.059	0.782	0.178	0.142	0.220
1996	SCC	48521172	386	0.955	0.502	1.814	0.796	0.718	0.879
	Adenocarcinoma	48521172	98	0.246	0.075	0.805	0.202	0.164	0.246
	Others	48521172	70	0.171	0.039	0.749	0.144	0.112	0.182
1997	SCC	48666657	431	1.043	0.557	1.952	0.886	0.804	0.973
	Adenocarcinoma	48666657	130	0.324	0.115	0.915	0.267	0.223	0.317
	Others	48666657	73	0.183	0.049	0.682	0.150	0.118	0.189
1998	SCC	48822555	442	1.066	0.578	1.963	0.905	0.823	0.994
	Adenocarcinoma	48822555	134	0.333	0.120	0.927	0.274	0.230	0.325
	Others	48822555	68	0.168	0.042	0.679	0.139	0.108	0.177
1999	SCC	49034531	428	1.018	0.539	1.923	0.873	0.792	0.960
	Adenocarcinoma	49034531	110	0.270	0.083	0.875	0.224	0.184	0.270
	Others	49034531	78	0.192	0.050	0.729	0.159	0.126	0.199
2000	SCC	49234229	440	1.047	0.566	1.936	0.894	0.812	0.981
	Adenocarcinoma	49234229	129	0.313	0.108	0.910	0.262	0.219	0.311
	Others	49234229	85	0.205	0.057	0.737	0.173	0.138	0.213
2001	SCC	49449746	461	1.077	0.581	1.996	0.932	0.849	1.021
	Adenocarcinoma	49449746	126	0.305	0.103	0.900	0.255	0.212	0.303
	Others	49449746	77	0.186	0.048	0.712	0.156	0.123	0.195
2002	SCC	49679267	479	1.108	0.605	2.030	0.964	0.880	1.055
	Adenocarcinoma	49679267	112	0.268	0.084	0.854	0.225	0.186	0.271
	Others	49679267	67	0.159	0.036	0.701	0.135	0.105	0.171
2003	SCC	49925517	531	1.217	0.681	2.177	1.064	0.975	1.158
	Adenocarcinoma	49925517	125	0.294	0.098	0.884	0.250	0.208	0.298
	Others	49925517	80	0.187	0.047	0.741	0.160	0.127	0.199
2004	SCC	50194600	499	1.139	0.627	2.071	0.994	0.909	1.085
	Adenocarcinoma	50194600	141	0.330	0.123	0.886	0.281	0.236	0.331
	Others	50194600	86	0.199	0.052	0.761	0.171	0.137	0.212
2005	SCC	50606034	531	1.191	0.663	2.139	1.049	0.962	1.142
	Adenocarcinoma	50606034	123	0.285	0.097	0.840	0.243	0.202	0.290
	Others	50606034	68	0.157	0.036	0.694	0.134	0.104	0.170
2006	SCC	50965186	560	1.254	0.706	2.229	1.099	1.010	1.194
	Adenocarcinoma	50965186	134	0.306	0.104	0.899	0.263	0.220	0.311
	Others	50965186	73	0.165	0.040	0.676	0.143	0.112	0.180
2007	SCC	51381093	645	1.414	0.826	2.421	1.255	1.160	1.356
	Adenocarcinoma	51381093	128	0.289	0.094	0.892	0.249	0.208	0.296
	Others	51381093	58	0.129	0.025	0.673	0.113	0.086	0.146
2008	SCC	51815853	611	1.332	0.764	2.322	1.179	1.088	1.276
	Adenocarcinoma	51815853	143	0.320	0.110	0.929	0.276	0.233	0.325
	Others	51815853	82	0.180	0.040	0.800	0.158	0.126	0.196
2009	SCC	52196381	677	1.449	0.846	2.482	1.297	1.201	1.399
	Adenocarcinoma	52196381	144	0.311	0.104	0.934	0.276	0.233	0.325
	Others	52196381	95	0.208	0.055	0.792	0.182	0.147	0.222
2010	SCC	52642452	745	1.580	0.948	2.635	1.415	1.315	1.521
	Adenocarcinoma	52642452	127	0.272	0.086	0.857	0.241	0.201	0.287

				Age standardized Incidence per 100000			Crude Incidence per 100000		
					95% CI			95% CI	
Calendar Year	Histological classification	N	n	Value	LL	UL	Value	LL	UL
	Others	52642452	79	0.169	0.039	0.739	0.150	0.119	0.187
2011	SCC	53107169	817	1.709	1.042	2.804	1.538	1.435	1.648
	Adenocarcinoma	53107169	118	0.249	0.075	0.827	0.222	0.184	0.266
	Others	53107169	87	0.183	0.044	0.759	0.164	0.131	0.202
2012	SCC	53493729	883	1.830	1.138	2.942	1.651	1.544	1.763
	Adenocarcinoma	53493729	127	0.272	0.087	0.851	0.237	0.198	0.282
	Others	53493729	65	0.136	0.029	0.651	0.122	0.094	0.155
2013	SCC	53865817	843	1.708	1.041	2.802	1.565	1.461	1.674
	Adenocarcinoma	53865817	120	0.244	0.077	0.773	0.223	0.185	0.266
	Others	53865817	86	0.179	0.044	0.732	0.160	0.128	0.197
2014	SCC	54316618	941	1.876	1.168	3.014	1.732	1.623	1.847
	Adenocarcinoma	54316618	89	0.177	0.045	0.701	0.164	0.132	0.202
	Others	54316618	68	0.137	0.029	0.652	0.125	0.097	0.159
2015	SCC	54786327	1071	2.105	1.346	3.292	1.955	1.840	2.076
	Adenocarcinoma	54786327	118	0.234	0.068	0.802	0.215	0.178	0.258
	Others	54786327	85	0.169	0.042	0.684	0.155	0.124	0.192
2016	SCC	55268067	1093	2.128	1.364	3.321	1.978	1.862	2.098
	Adenocarcinoma	55268067	108	0.214	0.059	0.772	0.195	0.160	0.236
	Others	55268067	73	0.141	0.030	0.677	0.132	0.104	0.166
2017	SCC	55619430	1069	2.049	1.299	3.230	1.922	1.808	2.041
	Adenocarcinoma	55619430	91	0.176	0.042	0.741	0.164	0.132	0.201
	Others	55619430	78	0.149	0.033	0.661	0.140	0.111	0.175
2018	SCC	55977178	1092	2.074	1.326	3.244	1.951	1.837	2.070
	Adenocarcinoma	55977178	117	0.220	0.063	0.776	0.209	0.173	0.250
	Others	55977178	73	0.137	0.029	0.656	0.130	0.102	0.164

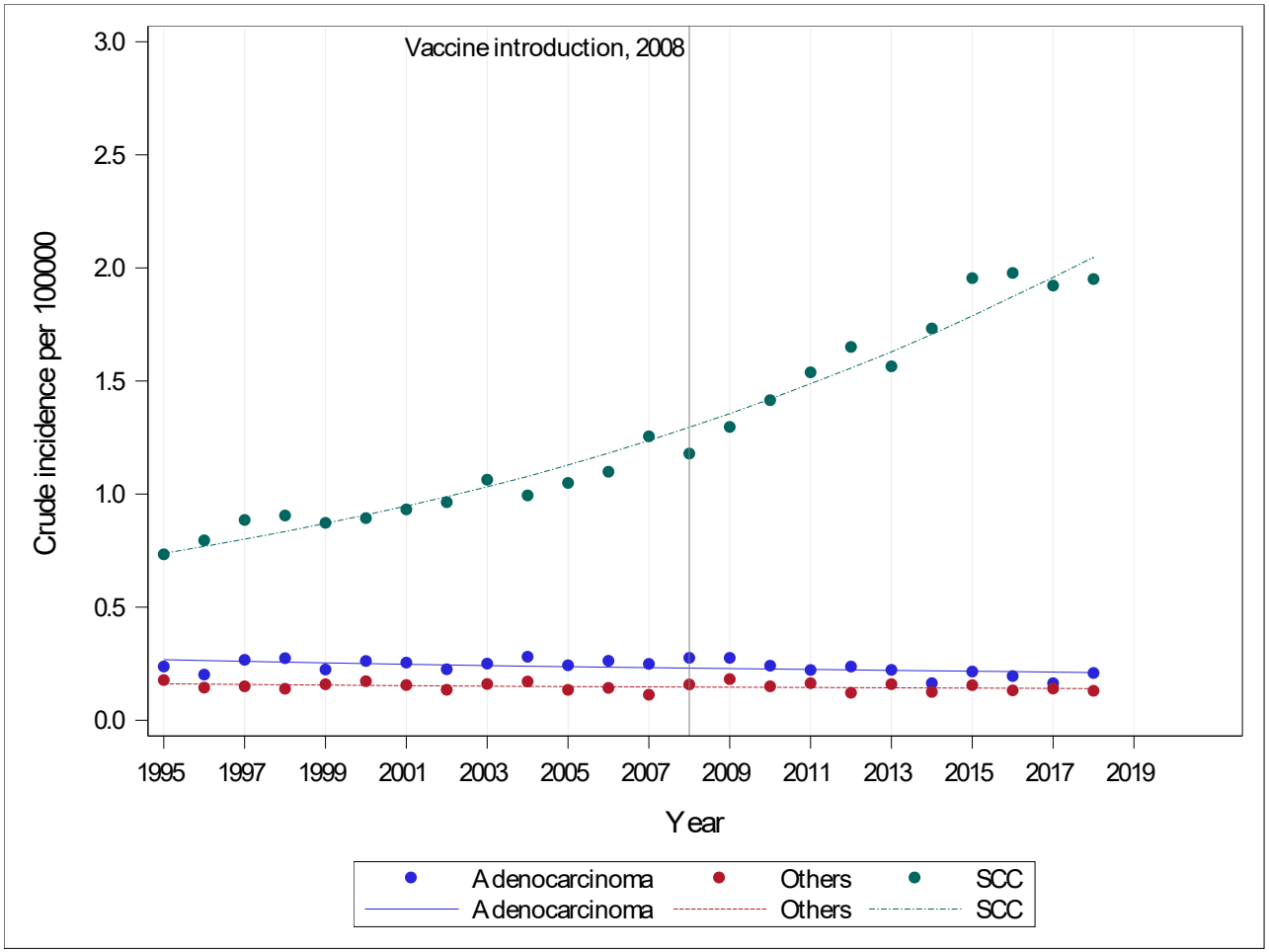
N = population in each category
n = number of anal cancer cases reported
Study period: Pre Cervarix launch (Year 1995 – Year 2007), Post Cervarix launch (Year 2008 – Year 2018)
Age standardized Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))
CI=confidence interval; LL=lower limit; UL=upper limit
Age standardized Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.1.4.1 Trend over time in the age standardized incidence of anal cancer by histological classification - England



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.1.4.2 Trend over time in the crude incidence of anal cancer by histological classification - England



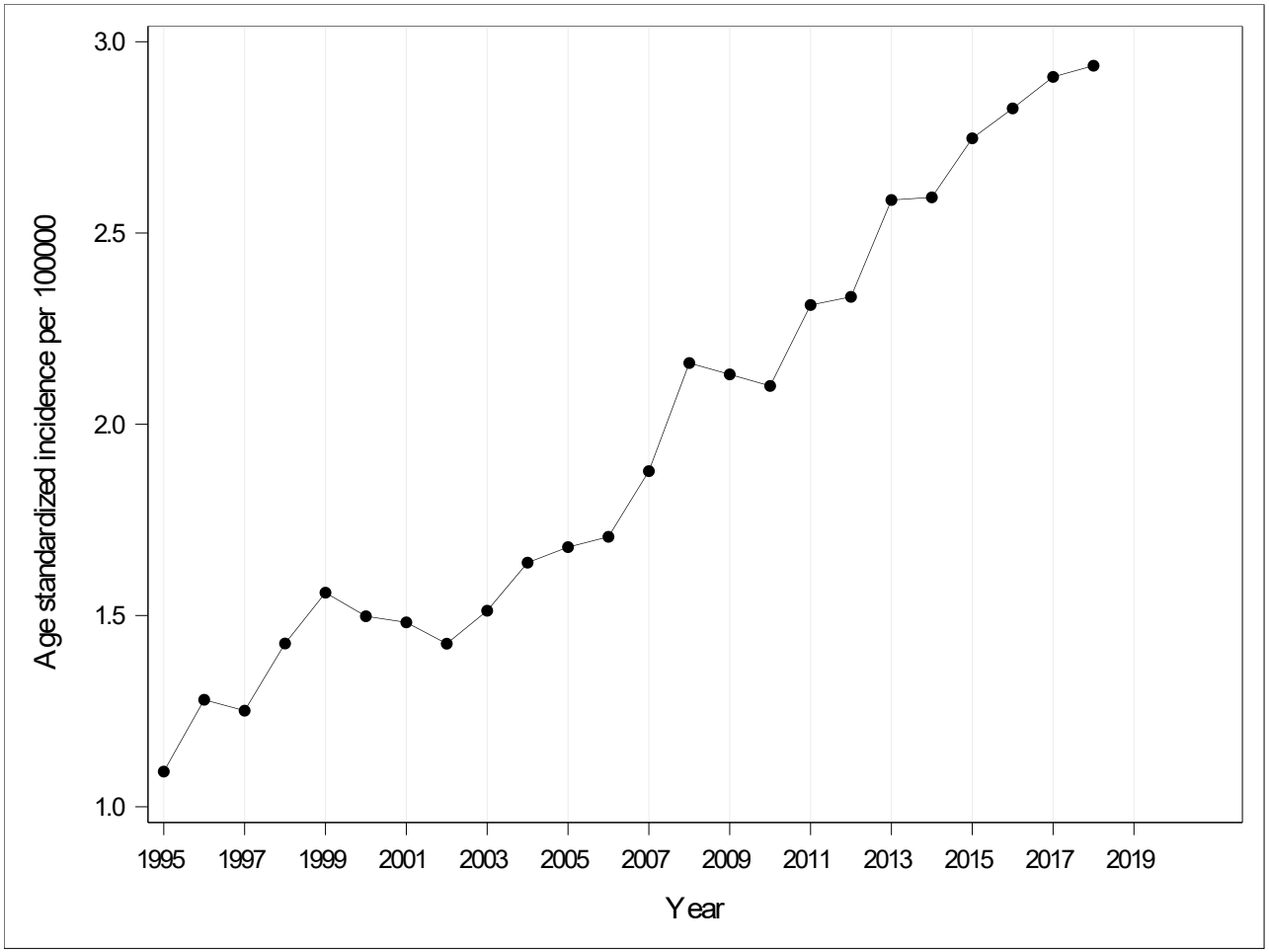
Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP
Line - Represents the predicted incidence , Period - Represents the observed Incidence

Table 14.2.1.5 Incidence of small intestine cancer by calendar year - England

			Age standardized Incidence per 100000			Crude Incidence per 100000		
				95% CI			95% CI	
Calendar Year	N	n	Value	LL	UL	Value	LL	UL
1995	48384614	439	1.092	0.607	1.966	0.907	0.824	0.996
1996	48521172	515	1.280	0.741	2.211	1.061	0.972	1.157
1997	48666657	509	1.251	0.720	2.173	1.046	0.957	1.141
1998	48822555	582	1.427	0.852	2.388	1.192	1.097	1.293
1999	49034531	643	1.560	0.954	2.550	1.311	1.212	1.417
2000	49234229	624	1.498	0.909	2.470	1.267	1.170	1.371
2001	49449746	620	1.482	0.894	2.458	1.254	1.157	1.356
2002	49679267	601	1.426	0.851	2.392	1.210	1.115	1.310
2003	49925517	647	1.513	0.921	2.485	1.296	1.198	1.400
2004	50194600	699	1.638	1.011	2.655	1.393	1.291	1.500
2005	50606034	729	1.679	1.050	2.685	1.441	1.338	1.549
2006	50965186	747	1.706	1.061	2.742	1.466	1.362	1.575
2007	51381093	838	1.877	1.198	2.943	1.631	1.522	1.745
2008	51815853	973	2.160	1.417	3.292	1.878	1.762	2.000
2009	52196381	973	2.130	1.398	3.247	1.864	1.749	1.985
2010	52642452	973	2.100	1.377	3.203	1.848	1.734	1.968
2011	53107169	1090	2.312	1.540	3.471	2.052	1.932	2.178
2012	53493729	1116	2.333	1.562	3.485	2.086	1.966	2.212
2013	53865817	1254	2.586	1.766	3.787	2.328	2.201	2.461
2014	54316618	1272	2.593	1.770	3.799	2.342	2.215	2.474
2015	54786327	1372	2.748	1.893	3.988	2.504	2.374	2.640
2016	55268067	1437	2.826	1.960	4.073	2.600	2.467	2.738
2017	55619430	1504	2.908	2.024	4.179	2.704	2.569	2.844
2018	55977178	1547	2.937	2.047	4.214	2.764	2.628	2.905

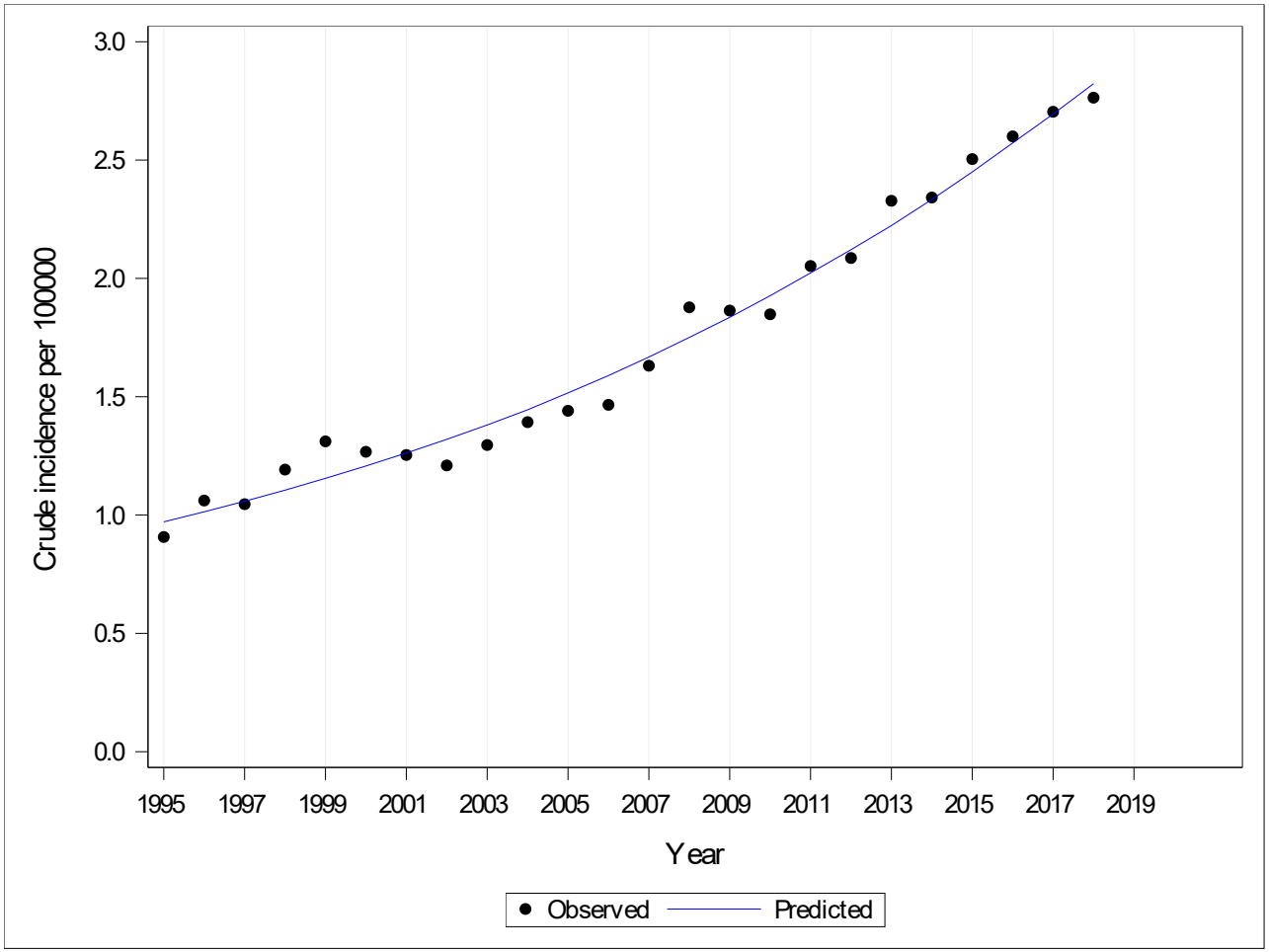
N = population in each category
n = number of small intestine cancer cases reported
Study period: Pre Cervarix launch (Year 1995 – Year 2007), Post Cervarix launch (Year 2008 – Year 2018)
Age standardized Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))
CI=confidence interval; LL=lower limit; UL=upper limit
Age standardized Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.1.5.1 Trend over time in the age standardized incidence of small intestine cancer - England



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.1.5.2 Trend over time in the crude incidence of small intestine cancer - England



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP
Line - Represents the predicted incidence , Period - Represents the observed Incidence

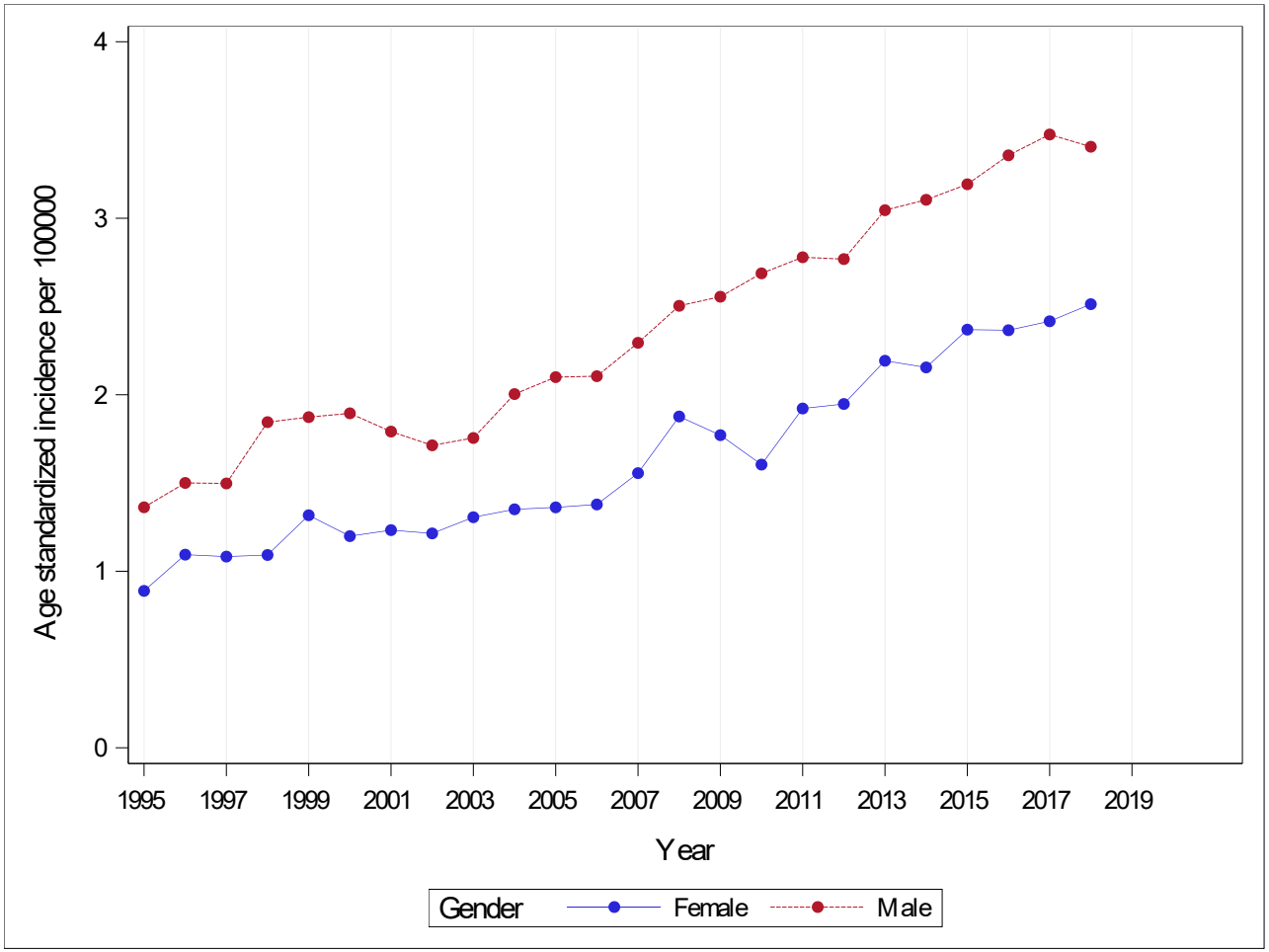
Table 14.2.1.6 Incidence of small intestine cancer by calendar year and gender - England

				Age standardized Incidence per 100000			Crude Incidence per 100000		
					95% CI			95% CI	
Calendar Year	Gender	N	n	Value	LL	UL	Value	LL	UL
1995	Male	23546945	235	1.362	0.807	2.299	0.998	0.874	1.134
	Female	24837669	204	0.889	0.464	1.702	0.821	0.712	0.942
1996	Male	23629865	265	1.501	0.903	2.493	1.121	0.990	1.265
	Female	24891307	250	1.094	0.610	1.963	1.004	0.884	1.137
1997	Male	23710844	261	1.497	0.911	2.461	1.101	0.971	1.243
	Female	24955813	248	1.083	0.595	1.970	0.994	0.874	1.125
1998	Male	23795308	330	1.845	1.173	2.902	1.387	1.241	1.545
	Female	25027247	252	1.092	0.609	1.958	1.007	0.886	1.139
1999	Male	23916833	337	1.873	1.198	2.929	1.409	1.263	1.568
	Female	25117698	306	1.317	0.772	2.247	1.218	1.086	1.363
2000	Male	24031560	343	1.895	1.218	2.947	1.427	1.280	1.587
	Female	25202669	281	1.199	0.687	2.092	1.115	0.988	1.253
2001	Male	24165587	331	1.791	1.132	2.836	1.370	1.226	1.526
	Female	25284159	289	1.233	0.709	2.143	1.143	1.015	1.283
2002	Male	24292759	317	1.714	1.076	2.730	1.305	1.165	1.457
	Female	25386508	284	1.215	0.691	2.136	1.119	0.992	1.257
2003	Male	24427705	334	1.755	1.103	2.792	1.367	1.225	1.522
	Female	25497812	313	1.306	0.771	2.212	1.228	1.095	1.371
2004	Male	24573534	382	2.004	1.299	3.091	1.555	1.403	1.718
	Female	25621066	317	1.351	0.793	2.300	1.237	1.105	1.381
2005	Male	24786643	398	2.100	1.388	3.177	1.606	1.452	1.771
	Female	25819391	331	1.362	0.805	2.304	1.282	1.148	1.428
2006	Male	24977690	415	2.105	1.376	3.221	1.661	1.505	1.829
	Female	25987496	332	1.378	0.813	2.337	1.278	1.144	1.423
2007	Male	25200533	460	2.294	1.535	3.429	1.825	1.662	2.000
	Female	26180560	378	1.556	0.947	2.555	1.444	1.302	1.597
2008	Male	25434926	515	2.504	1.694	3.700	2.025	1.854	2.207
	Female	26380927	458	1.877	1.196	2.944	1.736	1.581	1.903
2009	Male	25633832	531	2.555	1.740	3.753	2.071	1.899	2.255
	Female	26562549	442	1.771	1.118	2.807	1.664	1.512	1.827
2010	Male	25877244	566	2.688	1.852	3.901	2.187	2.011	2.375
	Female	26765208	407	1.604	0.992	2.594	1.521	1.376	1.676
2011	Male	26133162	599	2.779	1.922	4.017	2.292	2.112	2.483
	Female	26974007	491	1.922	1.230	3.004	1.820	1.663	1.989
2012	Male	26333448	609	2.769	1.914	4.004	2.313	2.133	2.504
	Female	27160281	507	1.948	1.258	3.015	1.867	1.708	2.036
2013	Male	26533969	681	3.046	2.144	4.327	2.567	2.377	2.767
	Female	27331848	573	2.193	1.452	3.312	2.096	1.928	2.275
2014	Male	26773196	702	3.105	2.193	4.395	2.622	2.432	2.823
	Female	27543422	570	2.155	1.417	3.277	2.069	1.903	2.247
2015	Male	27029286	740	3.192	2.263	4.504	2.738	2.544	2.942
	Female	27757041	632	2.369	1.586	3.539	2.277	2.103	2.462
2016	Male	27300920	792	3.357	2.402	4.691	2.901	2.702	3.110
	Female	27967147	645	2.366	1.587	3.526	2.306	2.132	2.491
2017	Male	27481053	838	3.475	2.498	4.834	3.049	2.846	3.263
	Female	28138377	666	2.416	1.622	3.600	2.367	2.191	2.554
2018	Male	27667942	839	3.405	2.431	4.770	3.032	2.831	3.245
	Female	28309236	708	2.513	1.707	3.700	2.501	2.320	2.692

N = population in each category

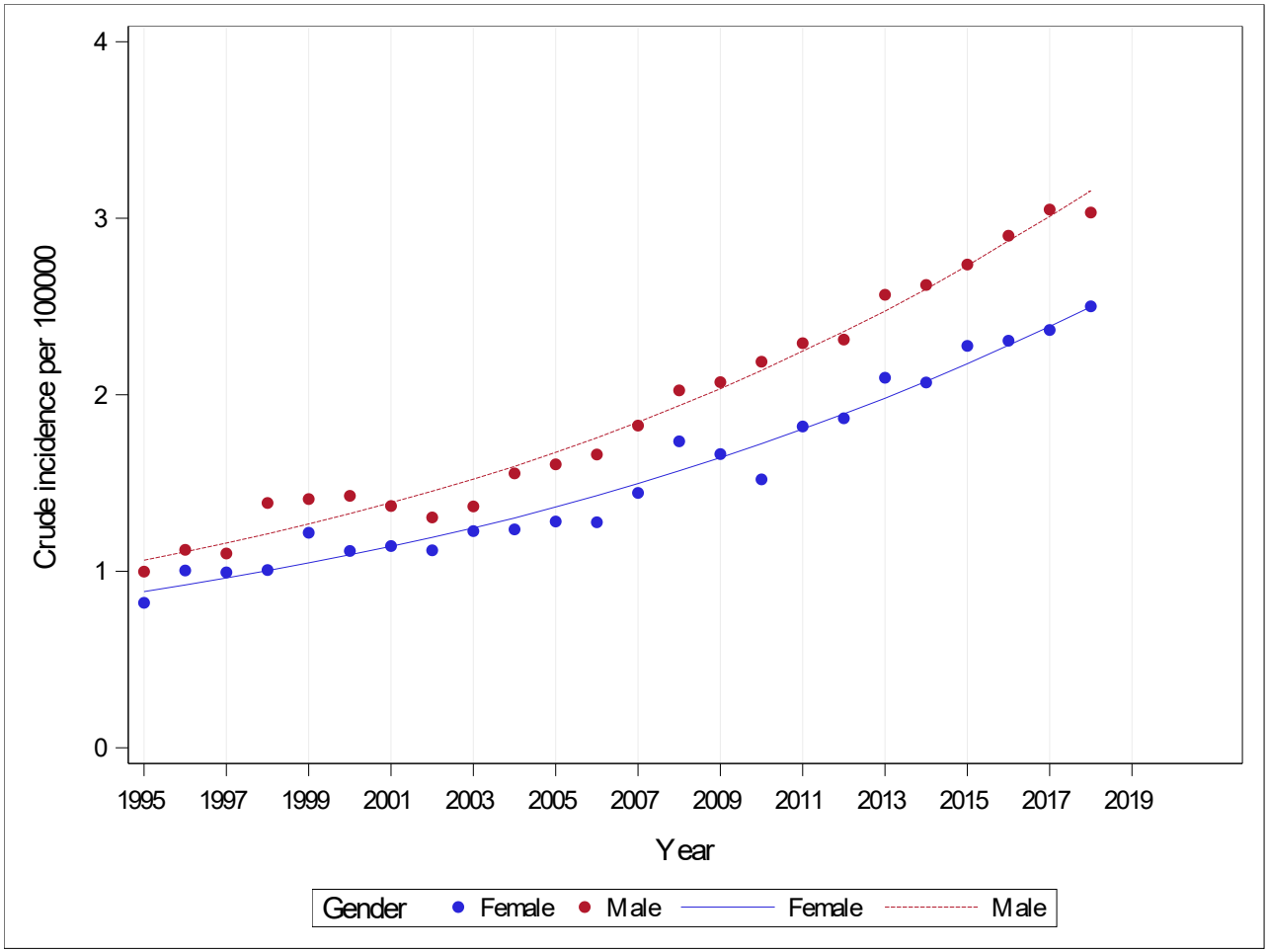
n = number of small intestine cancer cases reported
Study period: Pre Cervarix launch (Year 1995 – Year 2007), Post Cervarix launch (Year 2008 – Year 2018)
Age standardized Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))
CI=confidence interval; LL=lower limit; UL=upper limit
Age standardized Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.1.6.1 Trend over time in the age standardized incidence of small intestine cancer by gender - England



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.1.6.2 Trend over time in the crude incidence of small intestine cancer by gender - England



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP
Line - Represents the predicted incidence , Period - Represents the observed Incidence

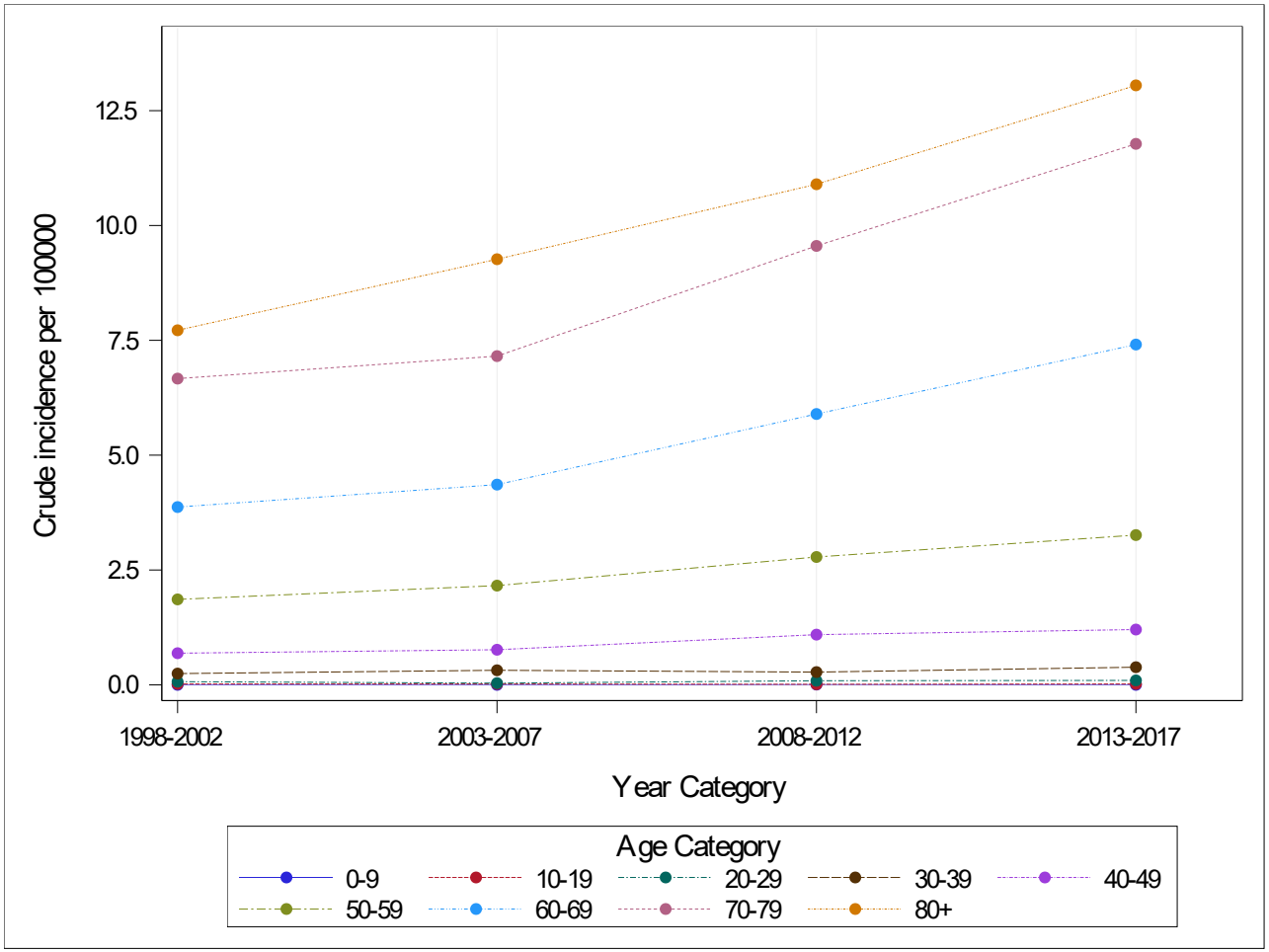
Table 14.2.1.7 Crude incidence of small intestine cancer for year and age category by gender - England

		Male					Female					Total				
					95% CI					95% CI					95% CI	
Year category	Age category (in years)	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL
1998-2002	0-9	15725316	0	0.000	0.000	0.023	14975360	0	0.000	0.000	0.025	30700676	0	0.000	0.000	0.012
	10-19	15904463	3	0.019	0.004	0.055	15221411	2	0.013	0.002	0.047	31125874	5	0.016	0.005	0.037
	20-29	15894820	11	0.069	0.035	0.124	15898020	3	0.019	0.004	0.055	31792840	14	0.044	0.024	0.074
	30-39	19162714	47	0.245	0.180	0.326	19386373	29	0.150	0.100	0.215	38549087	76	0.197	0.155	0.247
	40-49	16262868	112	0.689	0.567	0.829	16472647	98	0.595	0.483	0.725	32735515	210	0.642	0.558	0.734
	50-59	15051904	280	1.860	1.649	2.091	15300360	202	1.320	1.144	1.515	30352264	482	1.588	1.449	1.736
	60-69	11058055	428	3.870	3.512	4.255	11731834	289	2.463	2.188	2.764	22789889	717	3.146	2.920	3.385
	70-79	7890047	526	6.667	6.109	7.261	10219770	431	4.217	3.829	4.635	18109817	957	5.284	4.955	5.630
	80+	3251860	251	7.719	6.793	8.735	6812506	358	5.255	4.725	5.829	10064366	609	6.051	5.580	6.551
2003-2007	0-9	15237944	0	0.000	0.000	0.024	14521370	0	0.000	0.000	0.025	29759314	0	0.000	0.000	0.012
	10-19	16503960	3	0.018	0.004	0.053	15818356	1	0.006	0.000	0.035	32322316	4	0.012	0.003	0.032
	20-29	16380103	6	0.037	0.013	0.080	16369635	11	0.067	0.034	0.120	32749738	17	0.052	0.030	0.083
	30-39	18600868	59	0.317	0.241	0.409	18748444	36	0.192	0.134	0.266	37349312	95	0.254	0.206	0.311
	40-49	17927432	137	0.764	0.642	0.903	18164307	130	0.716	0.598	0.850	36091739	267	0.740	0.654	0.834
	50-59	15601161	337	2.160	1.936	2.403	15914731	228	1.433	1.253	1.631	31515892	565	1.793	1.648	1.947
	60-69	11838031	516	4.359	3.991	4.752	12473325	361	2.894	2.603	3.209	24311356	877	3.607	3.373	3.854
	70-79	8034525	575	7.157	6.584	7.766	9807552	477	4.864	4.437	5.320	17842077	1052	5.896	5.545	6.264
	80+	3842081	356	9.266	8.328	10.280	7288605	427	5.858	5.316	6.441	11130686	783	7.035	6.550	7.545
2008-2012	0-9	15961020	1	0.006	0.000	0.035	15228080	0	0.000	0.000	0.024	31189100	1	0.003	0.000	0.018
	10-19	16426361	2	0.012	0.001	0.044	15683632	1	0.006	0.000	0.036	32109993	3	0.009	0.002	0.027
	20-29	17899299	16	0.089	0.051	0.145	17865675	12	0.067	0.035	0.117	35764974	28	0.078	0.052	0.113
	30-39	17641785	49	0.278	0.205	0.367	17719123	40	0.226	0.161	0.307	35360908	89	0.252	0.202	0.310
	40-49	19119571	209	1.093	0.950	1.252	19460453	152	0.781	0.662	0.916	38580024	361	0.936	0.842	1.037
	50-59	15735368	438	2.784	2.529	3.057	16020344	310	1.935	1.726	2.163	31755712	748	2.355	2.190	2.531
	60-69	13636317	804	5.896	5.495	6.318	14291873	561	3.925	3.607	4.264	27928190	1365	4.888	4.632	5.154
	70-79	8560822	818	9.555	8.911	10.233	9948508	636	6.393	5.906	6.910	18509330	1454	7.855	7.457	8.270
	80+	4432069	483	10.898	9.948	11.914	7625284	593	7.777	7.163	8.429	12057353	1076	8.924	8.399	9.474
2013-2017	0-9	17332290	0	0.000	0.000	0.021	16504863	0	0.000	0.000	0.022	33837153	0	0.000	0.000	0.011
	10-19	15988673	3	0.019	0.004	0.055	15196497	3	0.020	0.004	0.058	31185170	6	0.019	0.007	0.042

		Male					Female					Total				
					95% CI					95% CI					95% CI	
Year category	Age category (in years)	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL
	20-29	18585445	18	0.097	0.057	0.153	18107957	12	0.066	0.034	0.116	36693402	30	0.082	0.055	0.117
	30-39	17976900	69	0.384	0.299	0.486	18083135	56	0.310	0.234	0.402	36060035	125	0.347	0.289	0.413
	40-49	18609328	224	1.204	1.051	1.372	18969131	204	1.075	0.933	1.234	37578459	428	1.139	1.034	1.252
	50-59	17482808	570	3.260	2.998	3.539	17879105	410	2.293	2.077	2.526	35361913	980	2.771	2.601	2.950
	60-69	14389005	1066	7.408	6.970	7.867	15116407	759	5.021	4.670	5.391	29505412	1825	6.185	5.905	6.476
	70-79	9620206	1133	11.777	11.101	12.484	10869550	917	8.436	7.899	9.001	20489756	2050	10.005	9.577	10.448
	80+	5133769	670	13.051	12.081	14.078	8011190	725	9.050	8.403	9.733	13144959	1395	10.612	10.063	11.184

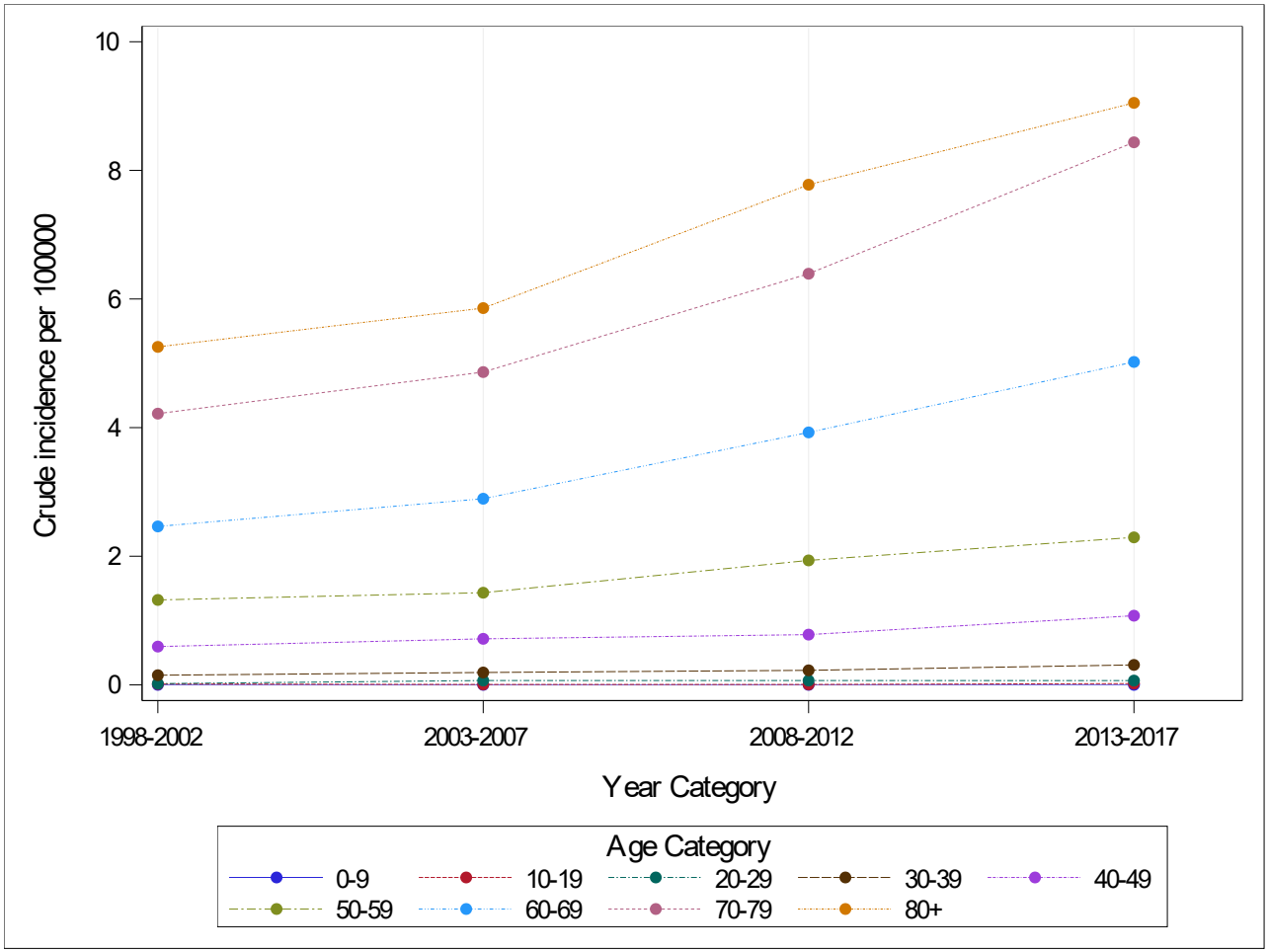
N = population in each category
n = number of small intestine cancer cases reported in each category
Study period: Pre Cervarix launch (Year 1995 – Year 2007), Post Cervarix launch (Year 2008 – Year 2018)
Crude Incidence per 100000 = (n/N)*100000
95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.1.7.1 Trend over time in the crude incidence of small intestine cancer by age category for Male - England



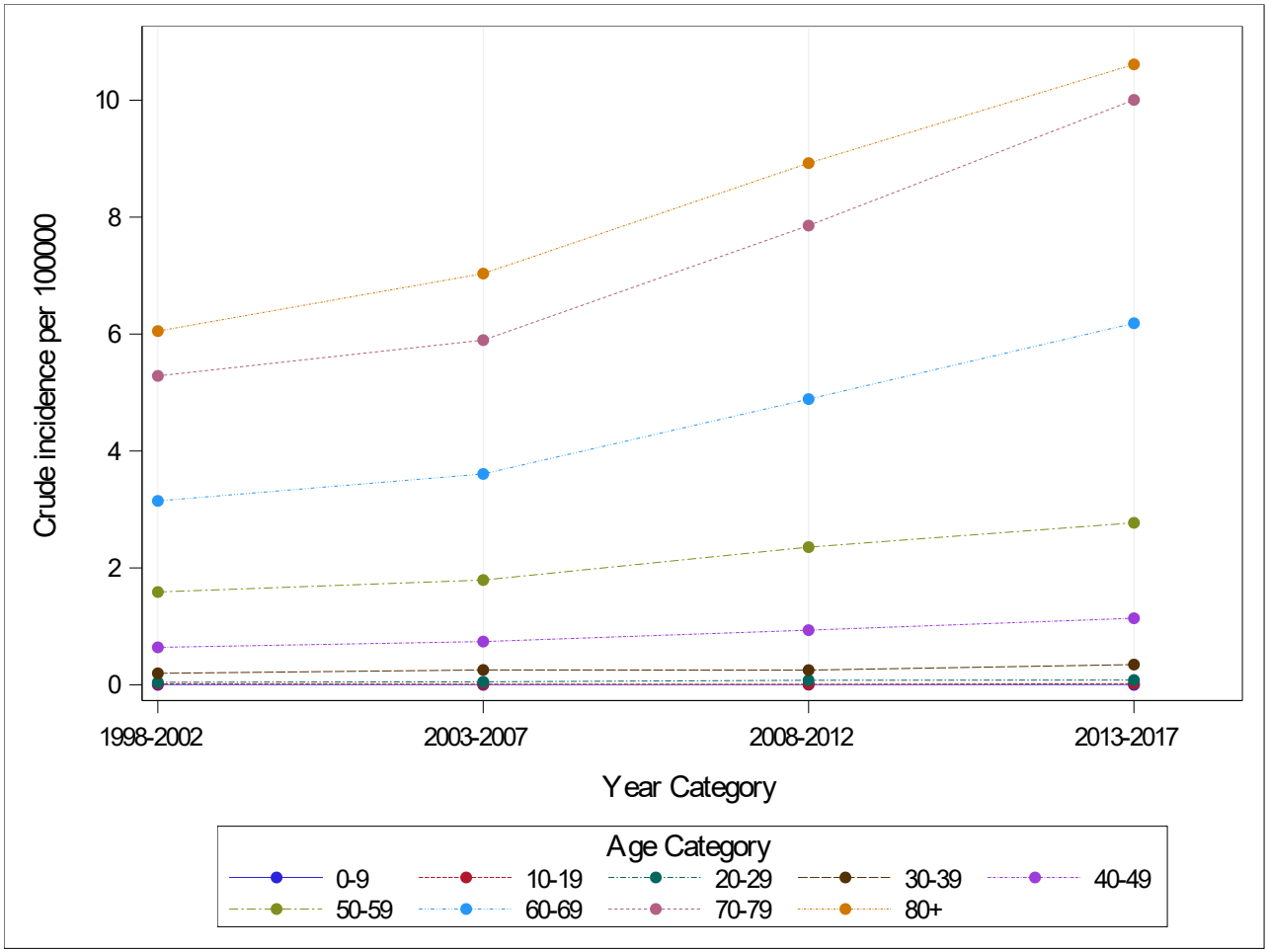
Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.1.7.2 Trend over time in the crude incidence of small intestine cancer by age category for Female - England



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.1.7.3 Trend over time in the crude incidence of small intestine cancer by age category - England



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Table 14.2.1.8 Univariate Poisson regression model for incidence of anal cancer - England

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	1237954222	20777	1.033	1.030	1.036	<.0001	3.29

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.1.8.1 Univariate Poisson regression model for incidence of anal cancer for Pre-Cervarix launch (Year 1995 – Year 2007) - England

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	644865201	8762	1.024	1.019	1.030	<.0001	2.44

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.1.8.2 Univariate Poisson regression model for incidence of anal cancer for Post-Cervarix launch (Year 2008 – Year 2018)- England

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	593089021	12015	1.035	1.026	1.043	<.0001	3.46

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.1.9 Multivariate Poisson regression model for incidence of anal cancer - England

				Adjusted incidence ratio (e(β))				
					95% CI			
Characteristics	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
Calendar year		1237954222	20777	1.024	1.018	1.030	<.0001	-
Age category (in years)	0-29	467161578	64	Reference	-	-	-	<.0001
	30-39	177023115	571	23.683	16.334	34.339	<.0001	-
	40-49	171763931	2192	92.334	64.587	132.000	<.0001	-
	50-59	152797459	4248	200.108	140.320	285.370	<.0001	-
	60-69	123957930	5175	297.967	209.039	424.724	<.0001	-
	70-79	90195502	4825	380.777	267.092	542.849	<.0001	-
	80+	55054707	3702	458.258	321.203	653.795	<.0001	-
Study period	Pre-Cervarix launch	644865201	8762	Reference	-	-	-	0.1699
	Post-Cervarix launch	593089021	12015	1.057	0.977	1.144	0.1699	-
Gender	Female	630699438	13080	Reference	-	-	-	<.0001
	Male	607254784	7697	0.688	0.660	0.716	<.0001	-

N = population at risk in each category
n = number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk)+ intercept + (β1 × calendar year) +(β2 × age category) + (β3 × study period) + (β4 × gender)
Adjusted incidence ratio (e(β)) = change in incidence of anal cancer compared to the reference category of each independent variable adjusted for other covariates (Exponentiated regression coefficient – β)
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Study period: Pre-Cervarix launch (Year 1995 – Year 2007), Post-Cervarix launch (Year 2008 – Year 2018)

Table 14.2.1.9.1 Multivariate Poisson regression model for incidence of anal cancer by age category - England

					Adjusted incidence ratio (e(β))				
						95% CI			
Age Category (in years)	**Characteristics**	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
0-29	Calendar year		467161578	64	1.051	0.992	1.115	0.0924	-
	Study period	Pre-Cervarix launch	245811921	25	Reference	-	-	-	0.9030
		Post-Cervarix launch	221349657	39	0.951	0.427	2.121	0.9030	-
	Gender	Female	229705555	34	Reference	-	-	-	0.4275
		Male	237456023	30	0.852	0.574	1.265	0.4275	-
30-39	Calendar year		177023115	571	1.034	1.009	1.059	0.0074	-
	Study period	Pre-Cervarix launch	98097092	278	Reference	-	-	-	0.4536
		Post-Cervarix launch	78926023	293	0.880	0.629	1.230	0.4536	-
	Gender	Female	88865149	347	Reference	-	-	-	<.0001
		Male	88157966	224	0.650	0.548	0.772	<.0001	-
40-49	Calendar year		171763931	2192	1.023	1.010	1.036	0.0006	-
	Study period	Pre-Cervarix launch	88415622	936	Reference	-	-	-	0.3420
		Post-Cervarix launch	83348309	1256	1.089	0.913	1.298	0.3420	-
	Gender	Female	86533215	1402	Reference	-	-	-	<.0001
		Male	85230716	790	0.572	0.522	0.628	<.0001	-
50-59	Calendar year		152797459	4248	1.040	1.027	1.054	<.0001	-
	Study period	Pre-Cervarix launch	78191054	1636	Reference	-	-	-	0.6493
		Post-Cervarix launch	74606405	2612	1.042	0.872	1.247	0.6493	-
	Gender	Female	77111695	2643	Reference	-	-	-	<.0001
		Male	75685764	1605	0.619	0.566	0.678	<.0001	-
60-69	Calendar year		123957930	5175	1.028	1.015	1.041	<.0001	-
	Study period	Pre-Cervarix launch	60657361	1938	Reference	-	-	-	0.1190
		Post-Cervarix launch	63300569	3237	1.151	0.964	1.374	0.1190	-
	Gender	Female	63653192	3130	Reference	-	-	-	<.0001
		Male	60304738	2045	0.689	0.630	0.753	<.0001	-
70-79	Calendar year		90195502	4825	1.012	1.002	1.022	0.0202	-
	Study period	Pre-Cervarix launch	46608490	2175	Reference	-	-	-	0.0691
		Post-Cervarix launch	43587012	2650	1.138	0.990	1.308	0.0691	-
	Gender	Female	49380600	3005	Reference	-	-	-	<.0001

					Adjusted incidence ratio (e(β))				
						95% CI			
Age Category (in years)	**Characteristics**	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
		Male	40814902	1820	0.726	0.677	0.780	<.0001	-
80+	Calendar year		55054707	3702	1.016	1.005	1.028	0.0051	-
	Study period	Pre-Cervarix launch	27083661	1774	Reference	-	-	-	0.0926
		Post-Cervarix launch	27971046	1928	0.874	0.747	1.023	0.0926	-
	Gender	Female	35450032	2519	Reference	-	-	-	<.0001
		Male	19604675	1183	0.843	0.775	0.918	<.0001	-

N = population at risk in each category
n = number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk)+ intercept + (β1 × calendar year) + (β2 × study period) + (β3 × gender)
Adjusted incidence ratio (e(β)) = change in incidence of anal cancer compared to the reference category of each independent variable adjusted for other covariates (Exponentiated regression coefficient – β)
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Study period: Pre-Cervarix launch (Year 1995 – Year 2007), Post-Cervarix launch (Year 2008 – Year 2018)

Table 14.2.1.9.2 Multivariate Poisson regression model for incidence of anal cancer by gender - England

					Adjusted incidence ratio (e(β))				
						95% CI			
Gender	**Characteristics**	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
Male	Calendar year		607254784	7697	1.012	1.005	1.019	0.0005	-
	Age category (in years)	0-29	237456023	30	Reference	-	-	-	<.0001
		30-39	88157966	224	20.216	13.502	30.268	<.0001	-
		40-49	85230716	790	73.222	49.766	107.733	<.0001	-
		50-59	75685764	1605	167.127	113.999	245.014	<.0001	-
		60-69	60304738	2045	266.363	181.826	390.205	<.0001	-
		70-79	40814902	1820	350.828	239.402	514.114	<.0001	-
		80+	19604675	1183	470.002	320.187	689.915	<.0001	-
	Study period	Pre-Cervarix launch	315055806	3478	Reference	-	-	-	0.5264
		Post-Cervarix launch	292198978	4219	1.031	0.938	1.134	0.5264	-
Female	Calendar year		630699438	13080	1.031	1.024	1.039	<.0001	-
	Age category (in years)	0-29	229705555	34	Reference	-	-	-	<.0001
		30-39	88865149	347	26.700	15.993	44.577	<.0001	-
		40-49	86533215	1402	108.795	66.316	178.485	<.0001	-
		50-59	77111695	2643	228.680	139.776	374.130	<.0001	-
		60-69	63653192	3130	326.249	199.510	533.498	<.0001	-
		70-79	49380600	3005	410.698	251.126	671.666	<.0001	-
		80+	35450032	2519	475.662	290.695	778.324	<.0001	-
	Study period	Pre-Cervarix launch	329809395	5284	Reference	-	-	-	0.1750
		Post-Cervarix launch	300890043	7796	1.073	0.969	1.187	0.1750	-

N = population at risk in each category
n = number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk)+ intercept + (β1 × calendar year) + (β2 × age category) + (β3 × study period)
Adjusted incidence ratio (e(β)) = change in incidence of anal cancer compared to the reference category of each independent variable adjusted for other covariates (Exponentiated regression coefficient – β)
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Study period: Pre-Cervarix launch (Year 1995 – Year 2007), Post-Cervarix launch (Year 2008 – Year 2018)

Table 14.2.1.9.3 Multivariate Poisson regression model for incidence of anal cancer by histological classification - England

					Adjusted incidence ratio (e(β))				
						95% CI			
Histological classification	**Characteristics**	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
SCC	Calendar year		1237954222	16030	1.038	1.032	1.045	<.0001	-
	Age category (in years)	0-29	467161578	49	Reference	-	-	-	<.0001
		30-39	177023115	484	26.297	17.670	39.137	<.0001	-
		40-49	171763931	1930	105.859	72.128	155.364	<.0001	-
		50-59	152797459	3660	223.814	152.842	327.743	<.0001	-
		60-69	123957930	4193	312.513	213.482	457.484	<.0001	-
		70-79	90195502	3481	355.624	242.822	520.829	<.0001	-
		80+	55054707	2233	352.766	240.506	517.427	<.0001	-
	Study period	Pre-Cervarix launch	644865201	6188	Reference	-	-	-	0.3061
		Post-Cervarix launch	593089021	9842	1.046	0.960	1.139	0.3061	-
	Gender	Female	630699438	10475	Reference	-	-	-	<.0001
		Male	607254784	5555	0.604	0.578	0.631	<.0001	-
Adenocarcinoma	Calendar year		1237954222	2907	0.983	0.972	0.995	0.0052	-
	Age category (in years)	0-29	467161578	9	Reference	-	-	-	<.0001
		30-39	177023115	50	14.612	6.536	32.666	<.0001	-
		40-49	171763931	133	40.425	18.807	86.894	<.0001	-
		50-59	152797459	350	119.944	56.654	253.935	<.0001	-
		60-69	123957930	646	274.252	130.101	578.124	<.0001	-
		70-79	90195502	867	506.988	240.819	1067.342	<.0001	-
		80+	55054707	852	840.134	398.992	1769.019	<.0001	-
	Study period	Pre-Cervarix launch	644865201	1605	Reference	-	-	-	0.9873
		Post-Cervarix launch	593089021	1302	1.001	0.849	1.181	0.9873	-
	Gender	Female	630699438	1474	Reference	-	-	-	<.0001
		Male	607254784	1433	1.250	1.150	1.358	<.0001	-

					Adjusted incidence ratio (e(β))				
						95% CI			
Histological classification	**Characteristics**	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
Others	Calendar year		1237954222	1840	0.977	0.963	0.991	0.0010	-
	Age category (in years)	0-29	467161578	6	Reference	-	-	-	<.0001
		30-39	177023115	37	16.199	6.480	40.498	<.0001	-
		40-49	171763931	129	58.450	24.500	139.445	<.0001	-
		50-59	152797459	238	121.626	51.436	287.597	<.0001	-
		60-69	123957930	336	211.212	89.599	497.891	<.0001	-
		70-79	90195502	477	408.067	173.492	959.808	<.0001	-
		80+	55054707	617	851.421	362.378	2000.442	<.0001	-
	Study period	Pre-Cervarix launch	644865201	969	Reference	-	-	-	0.0503
		Post-Cervarix launch	593089021	871	1.215	1.000	1.477	0.0503	-
	Gender	Female	630699438	1131	Reference	-	-	-	<.0001
		Male	607254784	709	0.812	0.734	0.898	<.0001	-

N = population at risk in each category
n = number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk)+ intercept + (β1 × calendar year) + (β2 × age category) + (β3 × study period) + (β4 × gender)
Adjusted incidence ratio (e(β)) = change in incidence of anal cancer compared to the reference category of each independent variable adjusted for other covariates (Exponentiated regression coefficient – β)
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Study period: Pre-Cervarix launch (Year 1995 – Year 2007), Post-Cervarix launch (Year 2008 – Year 2018)

Table 14.2.1.10 Univariate Poisson regression model for incidence of small intestine cancer - England

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	1237954222	21704	1.048	1.045	1.051	<.0001	4.82

N = overall population at risk
n = total number of small intestine cancer cases reported
Model is calculated by log(No. of small intestine cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of small intestine cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.1.10.1 Univariate Poisson regression model for incidence of small intestine cancer for Pre-Cervarix launch (Year 1995 – Year 2007) - England

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	644865201	8193	1.037	1.029	1.046	<.0001	3.75

N = overall population at risk
n = total number of small intestine cancer cases reported
Model is calculated by log(No. of small intestine cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of small intestine cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.1.10.2 Univariate Poisson regression model for incidence of small intestine cancer for Post-Cervarix launch (Year 2008 – Year 2018) - England

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	593089021	13511	1.046	1.040	1.052	<.0001	4.61

N = overall population at risk
n = total number of small intestine cancer cases reported
Model is calculated by log(No. of small intestine cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of small intestine cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.1.11 Trend overtime of anal cancer cases by observed counts versus predicted counts - England

					95% CI	
Year	**Observed counts**	**Predicted counts**	**Difference (Predicted-Observed)**	**%Reduction***	**LL**	**UL**
1995	556	566	10	1.77	-10.43	12.62
1996	554	581	27	4.65	-7.12	15.12
1997	634	597	-37	-6.2	-18.76	5.03
1998	644	614	-30	-4.89	-17.15	6.09
1999	616	631	15	2.38	-9.08	12.63
2000	654	649	-5	-0.77	-12.33	9.6
2001	664	668	4	0.6	-10.67	10.72
2002	658	688	30	4.36	-6.43	14.05
2003	736	708	-28	-3.95	-15.25	6.24
2004	726	729	3	0.41	-10.37	10.14
2005	722	753	31	4.12	-6.19	13.42
2006	767	777	10	1.29	-9.07	10.66
2007	831	802	-29	-3.62	-14.17	5.96
2008	836	829	-7	-0.84	-11.01	8.39
2009	916	855	-61	-7.13	-17.6	2.4
2010	951	884	-67	-7.58	-17.9	1.83
2011	1022	913	-109	-11.94	-22.39	-2.38
2012	1075	942	-133	-14.12	-24.55	-4.56
2013	1049	972	-77	-7.92	-17.76	1.1
2014	1098	1004	-94	-9.36	-19.13	-0.39
2015	1274	1037	-237	-22.85	-33.35	-13.19
2016	1274	1072	-202	-18.84	-28.9	-9.57
2017	1238	1105	-133	-12.04	-21.5	-3.31
2018	1282	1139	-143	-12.55	-21.91	-3.92

Note:Poisson model has been used to predict the counts using the pre-vaccination period from 1995-Most recent available year's data

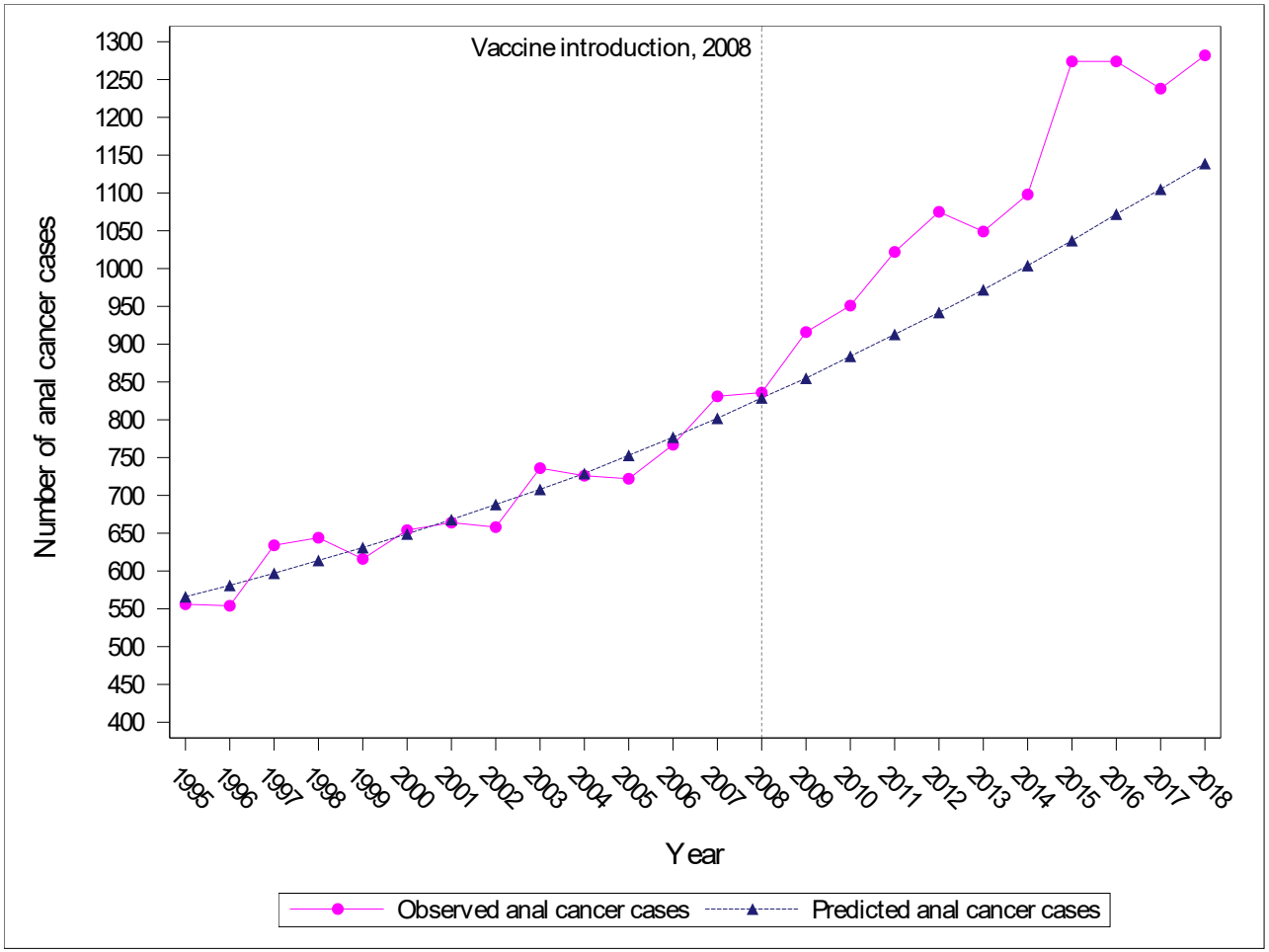
Model is calculated by, log(No. of anal cancer cases) = log (Population at risk) + intercept + (β × calendar year)

%Reduction = ((predicted counts –observed counts)/ predicted counts)×100

Wald's 95% CI and %reduction was estimated using Poisson model for non-zero observed counts

*Positive sign indicates the reduction and negative sign indicates the increase in observed counts

Figure 14.2.1.11.1 Predicted and observed counts of anal cancer cases - England



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Table 14.2.1.12 Trend overtime of anal cancer cases by observed counts versus predicted counts, by age category - England

20-29 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1995	1	2	1	50	-451.41	95.47
1996	2	2	0	0	-609.91	85.91
1997	2	2	0	0	-609.91	85.91
1998	1	2	1	50	-451.41	95.47
1999	2	2	0	0	-609.91	85.91
2000	0	2	2	-	-	-
2001	3	2	-1	-50	-797.69	74.94
2002	3	2	-1	-50	-797.69	74.94
2003	1	2	1	50	-451.41	95.47
2004	2	2	0	0	-609.91	85.91
2005	3	2	-1	-50	-797.69	74.94
2006	1	2	1	50	-451.41	95.47
2007	2	2	0	0	-609.91	85.91
2008	1	2	1	50	-451.41	95.47
2009	3	2	-1	-50	-797.69	74.94
2010	3	3	0	0	-395.45	79.82
2011	2	3	1	33.33	-298.98	88.86
2012	6	3	-3	-100	-699.69	49.98
2013	3	3	0	0	-395.45	79.82
2014	4	3	-1	-33.33	-495.74	70.16
2015	3	3	0	0	-395.45	79.82
2016	5	3	-2	-66.67	-597.39	60.17
2017	4	3	-1	-33.33	-495.74	70.16
2018	4	3	-1	-33.33	-495.74	70.16

30-39 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1995	20	17	-3	-17.65	-124.58	38.37
1996	11	18	7	38.89	-29.38	71.14
1997	20	19	-1	-5.26	-97.23	43.82
1998	24	19	-5	-26.32	-130.59	30.81
1999	21	20	-1	-5	-93.7	43.08
2000	16	21	5	23.81	-46	60.24
2001	18	22	4	18.18	-52.54	56.11
2002	29	23	-6	-26.09	-117.94	27.05
2003	24	23	-1	-4.35	-84.87	41.1
2004	20	24	4	16.67	-50.85	53.96
2005	30	24	-6	-25	-113.81	26.92
2006	17	24	7	29.17	-31.85	61.95
2007	28	25	-3	-12	-92.06	34.69
2008	25	25	0	0	-74.08	42.56
2009	27	26	-1	-3.85	-77.94	39.4
2010	18	27	9	33.33	-21.04	63.28
2011	31	28	-3	-10.71	-84.55	33.58
2012	16	29	13	44.83	-1.58	70.03
2013	26	30	4	13.33	-46.53	48.74
2014	18	31	13	41.94	-3.79	67.52
2015	31	32	1	3.13	-58.75	40.88
2016	34	34	0	0	-60.86	37.83
2017	39	36	-3	-8.33	-70.41	31.13
2018	28	37	9	24.32	-23.64	53.68

40-49 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1995	52	61	9	14.75	-23.4	41.11
1996	56	63	7	11.11	-27.4	37.98
1997	78	63	-15	-23.81	-72.56	11.17
1998	60	64	4	6.25	-33.33	34.08
1999	70	65	-5	-7.69	-50.94	23.16
2000	70	67	-3	-4.48	-46.05	25.26
2001	72	70	-2	-2.86	-42.93	25.98
2002	71	72	1	1.39	-36.86	28.95
2003	77	76	-1	-1.32	-39.09	26.2
2004	79	79	0	0	-36.6	26.79
2005	82	82	0	0	-35.81	26.37
2006	77	86	9	10.47	-21.77	34.17
2007	92	89	-3	-3.37	-38.34	22.76
2008	93	92	-1	-1.09	-34.85	24.22
2009	101	95	-6	-6.32	-40.69	19.66
2010	107	97	-10	-10.31	-45.19	16.19
2011	126	100	-26	-26	-63.82	3.09
2012	100	102	2	1.96	-29.18	25.59
2013	109	103	-6	-5.83	-38.53	19.16
2014	127	104	-23	-22.12	-58.25	5.77
2015	147	104	-43	-41.35	-81.7	-9.96
2016	119	105	-14	-13.33	-47.34	12.83
2017	128	105	-23	-21.9	-57.8	5.82
2018	99	106	7	6.6	-22.83	28.98

50-59 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1995	84	80	-4	-5	-42.61	22.69
1996	91	86	-5	-5.81	-42.09	21.2
1997	94	95	1	1.05	-31.59	25.6
1998	99	103	4	3.88	-26.65	27.06
1999	113	110	-3	-2.73	-33.57	20.99
2000	115	118	3	2.54	-25.99	24.62
2001	129	126	-3	-2.38	-30.87	19.91
2002	119	134	15	11.19	-13.67	30.62
2003	162	142	-20	-14.08	-42.92	8.93
2004	142	149	7	4.7	-19.93	24.27
2005	128	157	29	18.47	-2.96	35.44
2006	169	165	-4	-2.42	-26.93	17.35
2007	191	170	-21	-12.35	-38.15	8.62
2008	170	178	8	4.49	-17.85	22.6
2009	191	188	-3	-1.6	-24.26	16.93
2010	199	200	1	0.5	-21.07	18.23
2011	216	214	-2	-0.93	-21.94	16.45
2012	231	229	-2	-0.87	-21.1	15.98
2013	220	247	27	10.93	-6.82	25.73
2014	250	266	16	6.02	-11.7	20.92
2015	270	286	16	5.59	-11.49	20.06
2016	280	308	28	9.09	-6.88	22.67
2017	306	329	23	6.99	-8.67	20.4
2018	279	350	71	20.29	6.71	31.89

60-69 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1995	137	130	-7	-5.38	-33.97	17.1
1996	115	132	17	12.88	-11.87	32.15
1997	147	134	-13	-9.7	-38.64	13.19
1998	146	137	-9	-6.57	-34.55	15.59
1999	143	140	-3	-2.14	-28.95	19.09
2000	137	143	6	4.2	-21.1	24.21
2001	142	145	3	2.07	-23.43	22.3
2002	136	148	12	8.11	-15.98	27.19
2003	163	153	-10	-6.54	-32.83	14.56
2004	132	159	27	16.98	-4.57	34.09
2005	168	165	-3	-1.82	-26.22	17.86
2006	188	171	-17	-9.94	-35.24	10.63
2007	184	182	-2	-1.1	-24.09	17.63
2008	209	192	-17	-8.85	-32.41	10.51
2009	262	200	-62	-31	-57.47	-8.98
2010	251	208	-43	-20.67	-45.02	-0.41
2011	257	216	-41	-18.98	-42.58	0.71
2012	280	223	-57	-25.56	-49.71	-5.31
2013	290	229	-61	-26.64	-50.6	-6.49
2014	302	235	-67	-28.51	-52.4	-8.37
2015	363	240	-123	-51.25	-78.04	-28.49
2016	369	246	-123	-50	-76.26	-27.65
2017	300	247	-53	-21.46	-43.73	-2.63
2018	354	251	-103	-41.04	-65.79	-19.98

70-79 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1995	154	163	9	5.52	-17.76	24.2
1996	166	164	-2	-1.22	-25.6	18.43
1997	162	166	4	2.41	-21.18	21.4
1998	177	169	-8	-4.73	-29.31	15.17
1999	165	171	6	3.51	-19.5	22.09
2000	167	169	2	1.18	-22.38	20.21
2001	171	168	-3	-1.79	-25.94	17.73
2002	179	167	-12	-7.19	-32.35	13.19
2003	162	167	5	2.99	-20.41	21.85
2004	192	167	-25	-14.97	-41.47	6.56
2005	152	167	15	8.98	-13.38	26.94
2006	164	168	4	2.38	-21.05	21.28
2007	164	170	6	3.53	-19.55	22.16
2008	202	173	-29	-16.76	-43.05	4.69
2009	186	175	-11	-6.29	-30.65	13.54
2010	207	177	-30	-16.95	-42.94	4.31
2011	228	177	-51	-28.81	-56.76	-5.85
2012	267	179	-88	-49.16	-80.25	-23.43
2013	212	184	-28	-15.22	-40.37	5.43
2014	214	190	-24	-12.63	-36.93	7.36
2015	249	196	-53	-27.04	-53.19	-5.36
2016	288	201	-87	-43.28	-71.57	-19.66
2017	283	213	-70	-32.86	-58.72	-11.22
2018	314	222	-92	-41.44	-67.96	-19.11

80+ years						
					95% CI	
Year	**Observed counts**	**Predicted counts**	**Difference (Predicted-Observed)**	**%Reduction***	**LL**	**UL**
1995	108	116	8	6.9	-21	28.36
1996	113	118	5	4.24	-23.95	26.01
1997	131	120	-11	-9.17	-39.85	14.78
1998	137	120	-17	-14.17	-45.87	10.65
1999	102	121	19	15.7	-9.71	35.23
2000	149	128	-21	-16.41	-47.42	8.08
2001	129	135	6	4.44	-21.64	24.93
2002	121	141	20	14.18	-9.41	32.69
2003	146	146	0	0	-25.78	20.5
2004	159	150	-9	-6	-32.49	15.2
2005	159	155	-4	-2.58	-27.98	17.78
2006	150	160	10	6.25	-17.14	24.97
2007	170	165	-5	-3.03	-27.64	16.83
2008	136	170	34	20	-0.23	36.15
2009	146	175	29	16.57	-3.93	33.03
2010	166	182	16	8.79	-12.56	26.09
2011	161	189	28	14.81	-5.11	30.96
2012	175	196	21	10.71	-9.47	27.18
2013	189	201	12	5.97	-14.69	22.91
2014	183	209	26	12.44	-6.78	28.2
2015	211	215	4	1.86	-18.67	18.84
2016	179	223	44	19.73	2.28	34.06
2017	178	230	52	22.61	5.88	36.36
2018	204	238	34	14.29	-3.34	28.91

Note:Poisson model has been used to predict the counts using the pre-vaccination period from 1995-Most recent available year‘s data

Model is calculated by, log(No. of anal cancer cases) = log (Population at risk) + intercept + (β × calendar year)

%Reduction = ((predicted counts –observed counts)/ predicted counts)×100

Wald’s 95% CI and %reduction was estimated using Poisson model for non-zero observed counts

*Positive sign indicates the reduction and negative sign indicates the increase in observed counts

The predicted counts are not estimated for 0-9, 10-19 age groups because the number of observed counts for the pre vaccination period is less than 5

Figure 14.2.1.12.1 Predicted and observed counts of anal cancer cases, by 0-9 years - England

The predicted counts are not estimated for 0-9 age groups because the number of observed counts for the pre vaccination

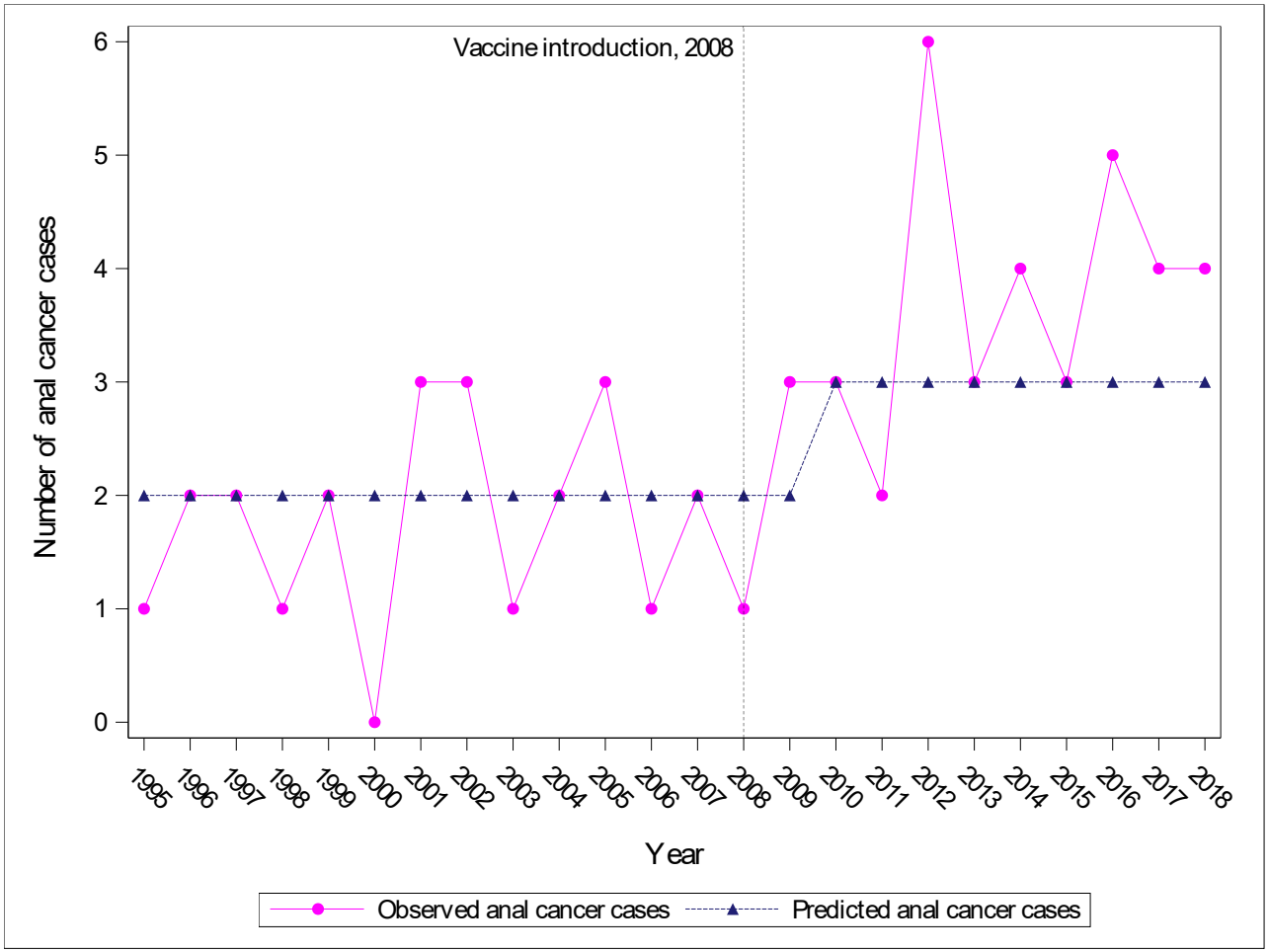
period is less than 5

Figure 14.2.1.12.2 Predicted and observed counts of anal cancer cases, by10-19 years England

The predicted counts are not estimated for 10-19 age groups because the number of observed counts for the pre vaccination

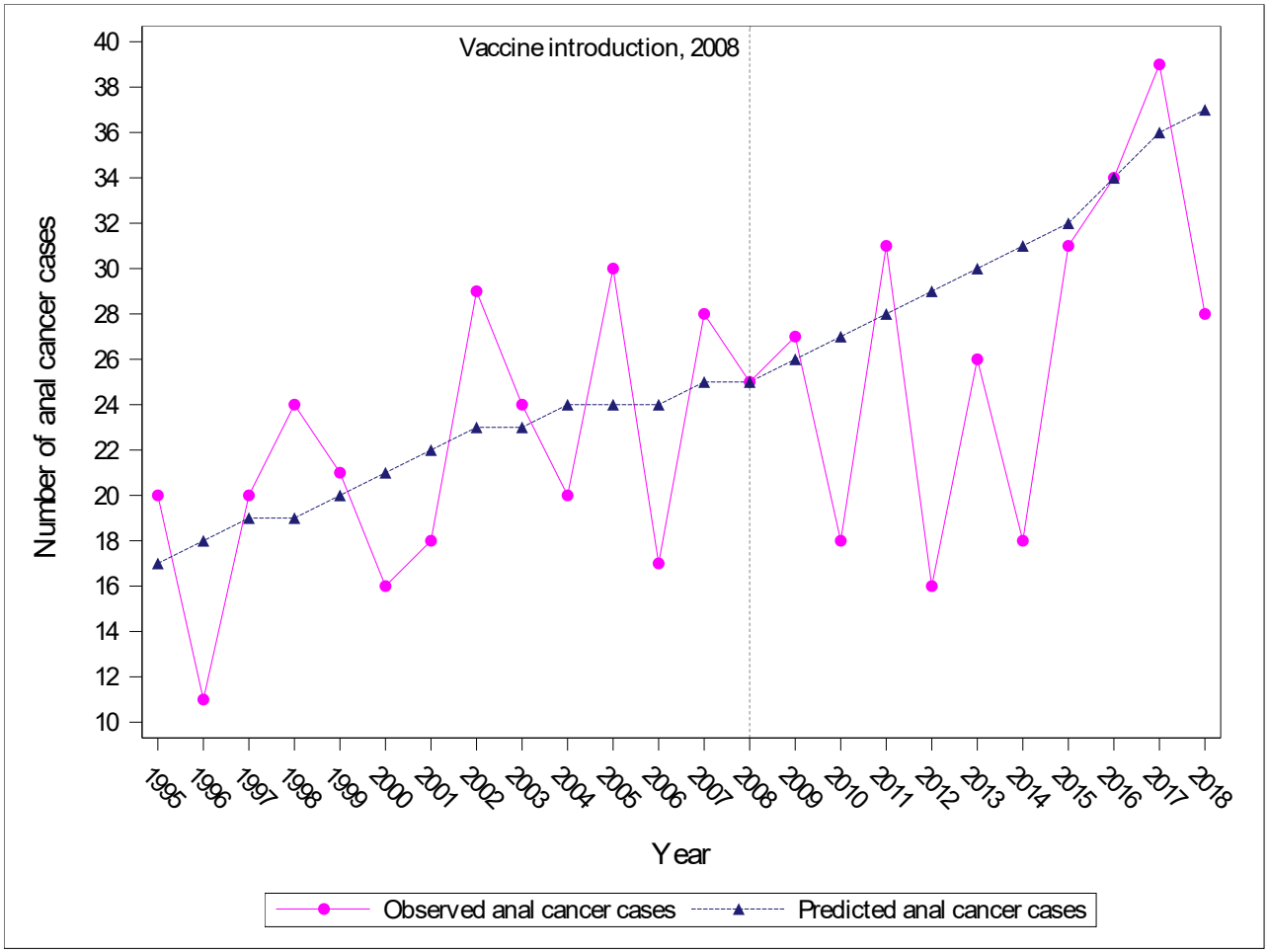
period is less than 5

Figure 14.2.1.12.3 Predicted and observed counts of anal cancer cases, by 20-29 years - England



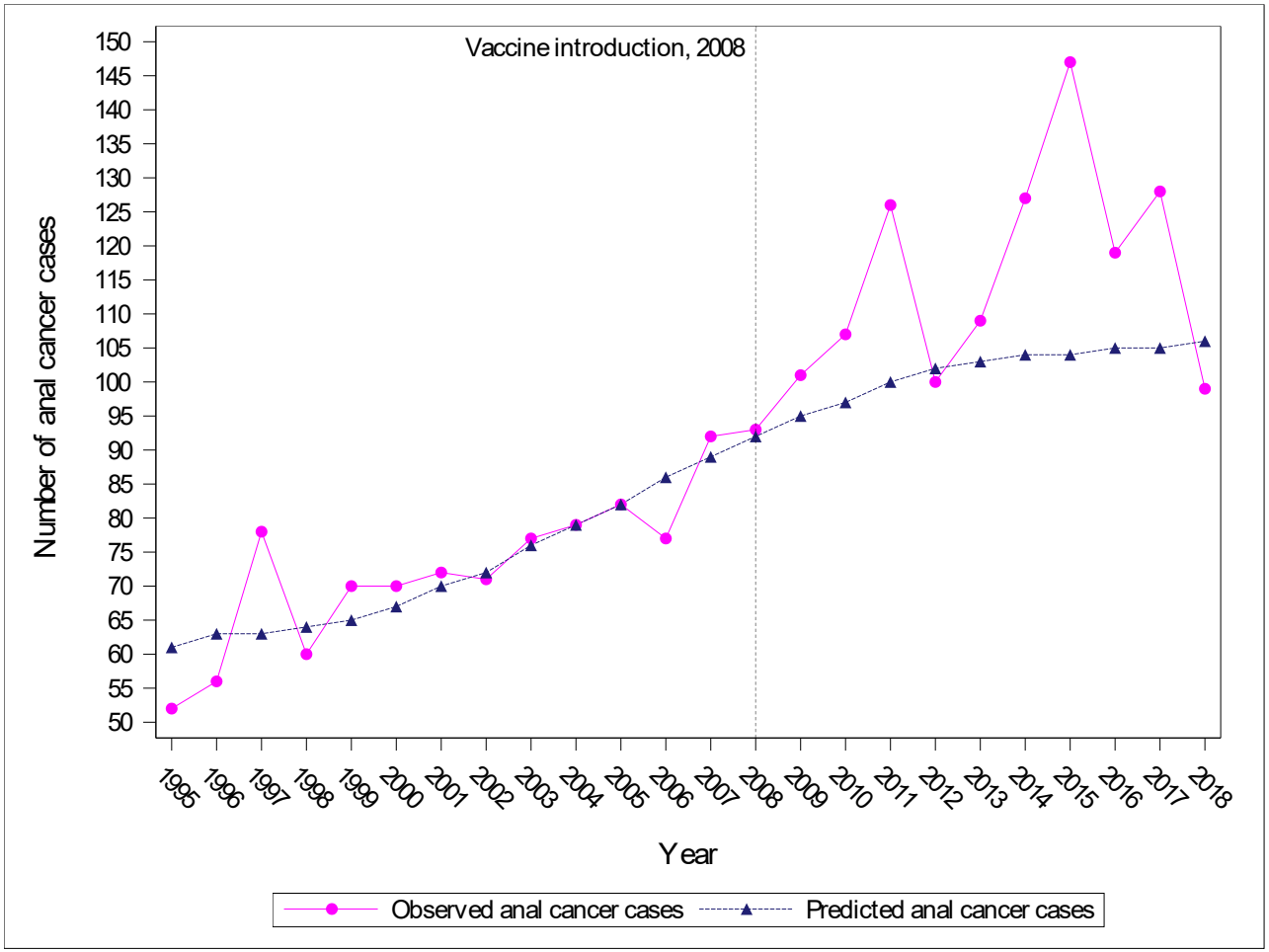
Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.1.12.4 Predicted and observed counts of anal cancer cases, by 30-39 years - England



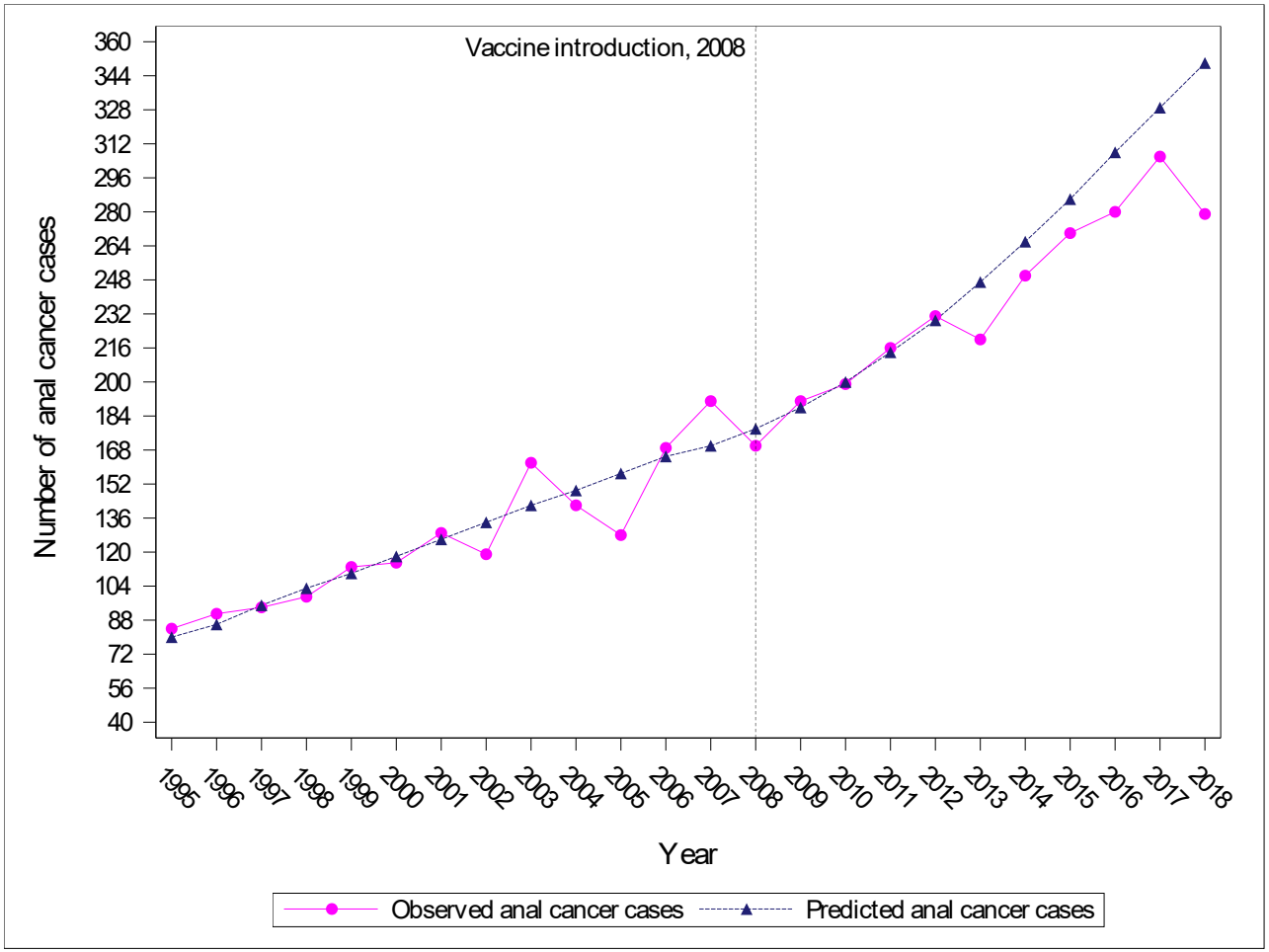
Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.1.12.5 Predicted and observed counts of anal cancer cases, by 40-49 years - England



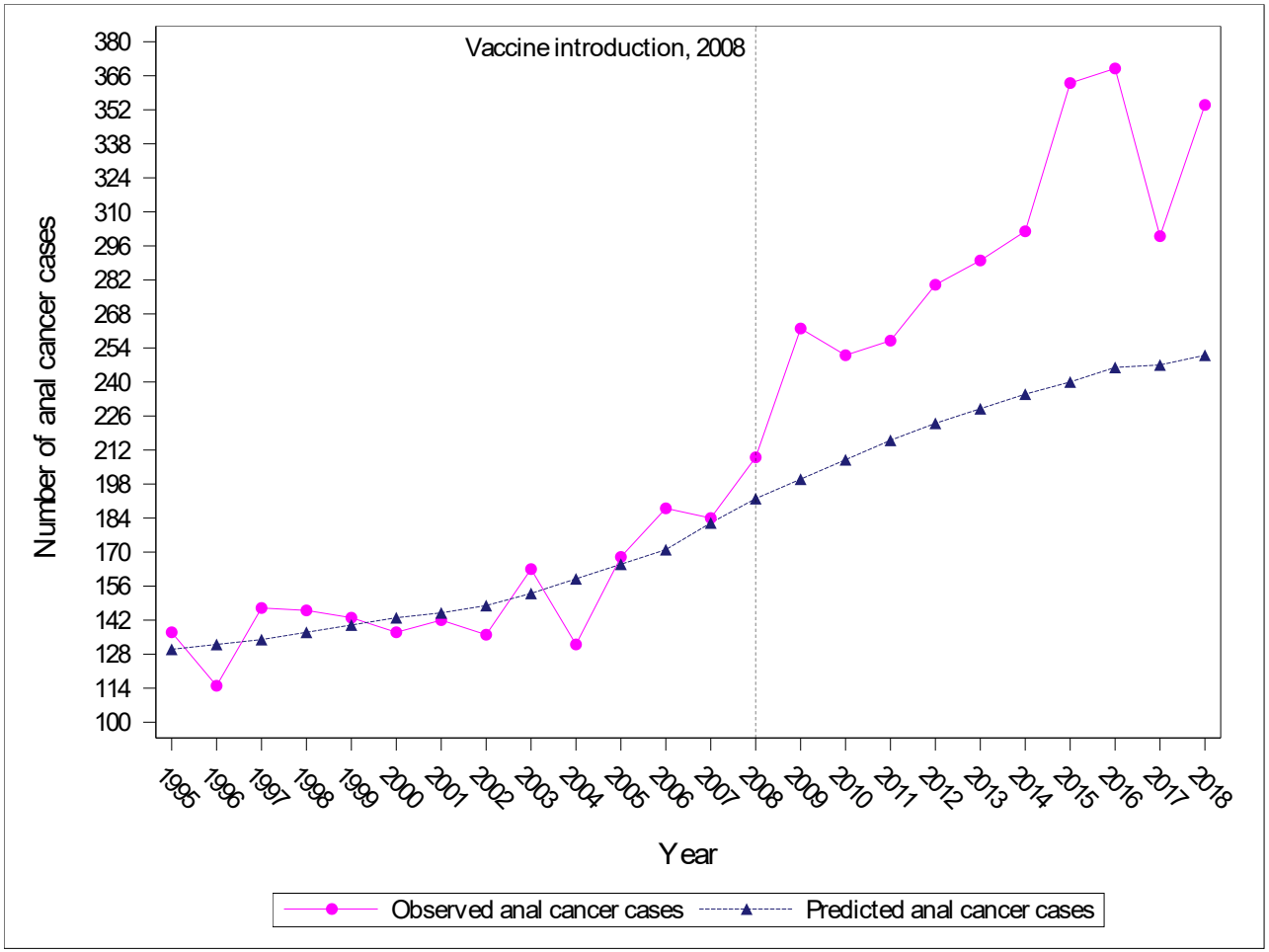
Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.1.12.6 Predicted and observed counts of anal cancer cases, by 50-59 years - England



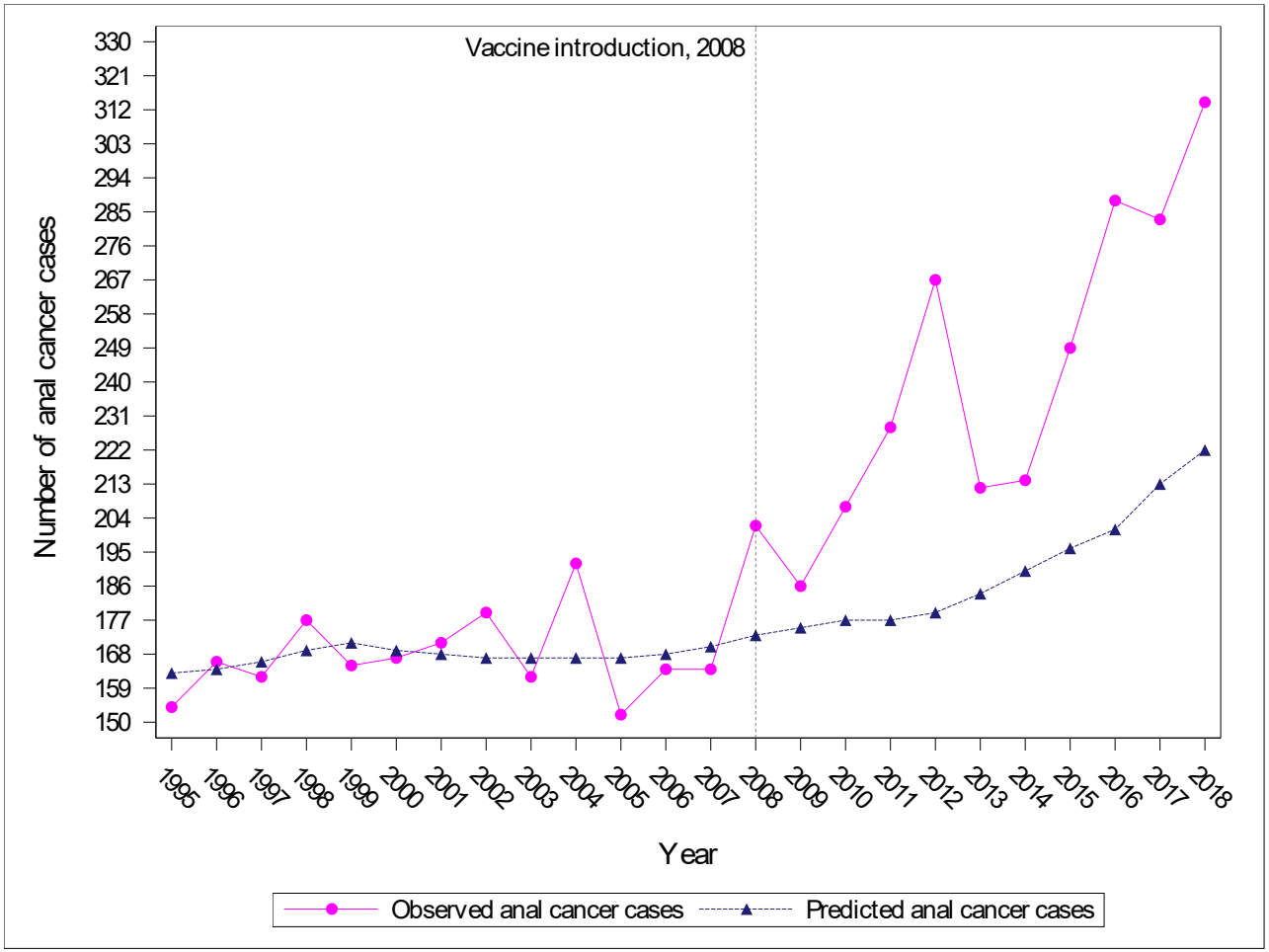
Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.1.12.7 Predicted and observed counts of anal cancer cases, by 60-69 years - England



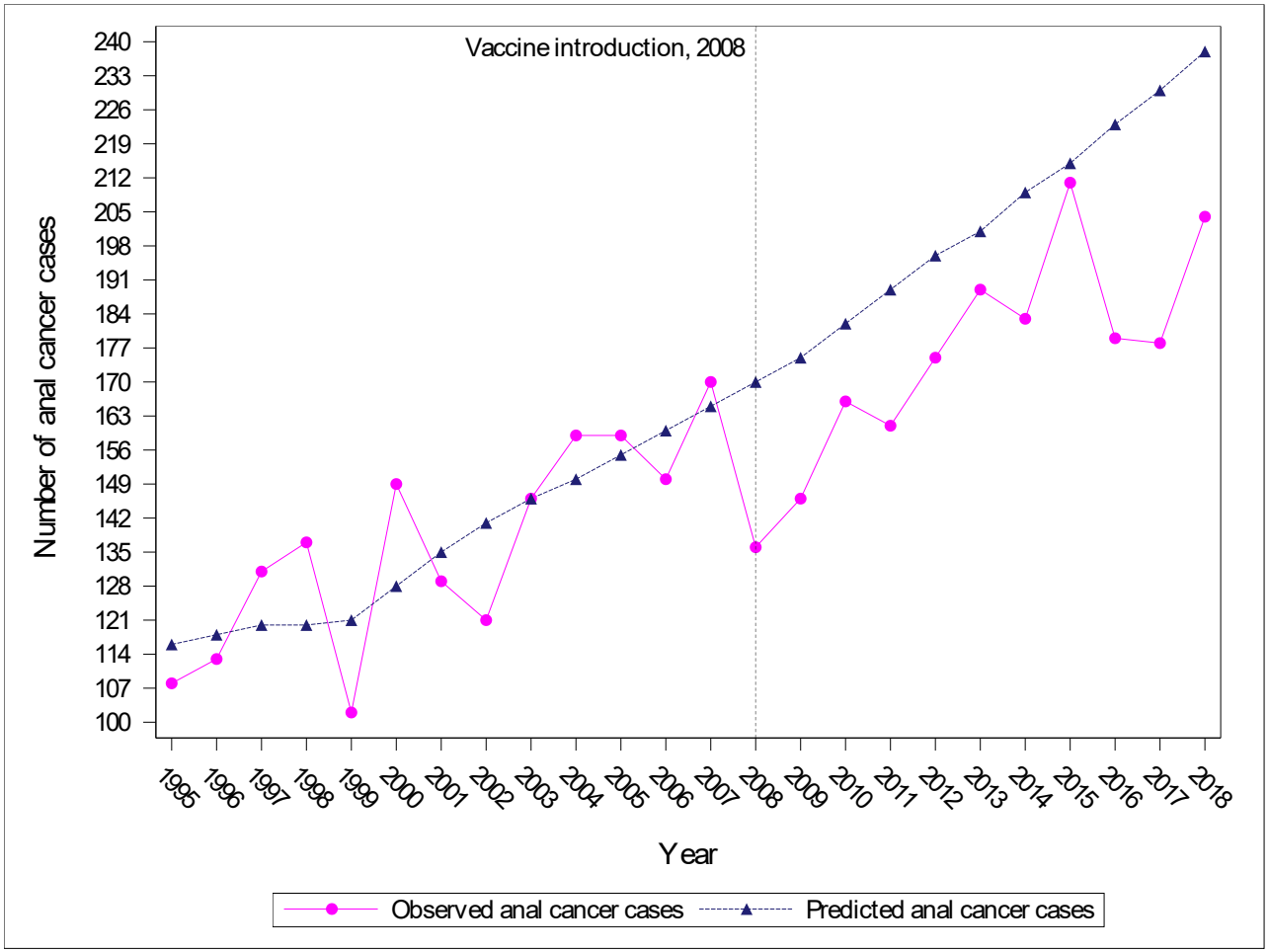
Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.1.12.8 Predicted and observed counts of anal cancer cases, by 70-79 years - England



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.1.12.9 Predicted and observed counts of anal cancer cases, by 80 years and above - England



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Table 14.2.1.13 Trend overtime of anal cancer cases by observed counts versus predicted counts, by gender - England

Male						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1995	229	229	0	0	-20.1	16.74
1996	228	235	7	2.98	-16.41	19.14
1997	252	240	-12	-5	-25.3	12.01
1998	254	246	-8	-3.25	-23.04	13.35
1999	242	252	10	3.97	-14.56	19.5
2000	253	259	6	2.32	-16.16	17.86
2001	267	266	-1	-0.38	-18.95	15.3
2002	263	272	9	3.31	-14.55	18.38
2003	294	280	-14	-5	-23.67	10.85
2004	296	287	-9	-3.14	-21.32	12.32
2005	279	295	16	5.42	-11.4	19.7
2006	304	304	0	0	-17.23	14.7
2007	317	313	-4	-1.28	-18.4	13.37
2008	318	322	4	1.24	-15.31	15.42
2009	320	331	11	3.32	-12.73	17.09
2010	391	341	-50	-14.66	-32.58	0.84
2011	359	351	-8	-2.28	-18.49	11.71
2012	388	361	-27	-7.48	-24.04	6.87
2013	386	372	-14	-3.76	-19.64	10.01
2014	365	383	18	4.7	-9.99	17.43
2015	410	394	-16	-4.06	-19.49	9.38
2016	425	406	-19	-4.68	-19.93	8.63
2017	422	417	-5	-1.2	-15.86	11.61
2018	435	429	-6	-1.4	-15.86	11.26

Female						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1995	327	336	9	2.68	-13.33	16.42
1996	326	346	20	5.78	-9.61	19.01
1997	382	357	-25	-7	-23.61	7.37
1998	390	367	-23	-6.27	-22.55	7.85
1999	374	379	5	1.32	-13.83	14.46
2000	401	390	-11	-2.82	-18.2	10.56
2001	397	402	5	1.24	-13.45	14.03
2002	395	415	20	4.82	-9.24	17.07
2003	442	428	-14	-3.27	-17.95	9.58
2004	430	442	12	2.71	-11.1	14.81
2005	443	457	14	3.06	-10.47	14.94
2006	463	473	10	2.11	-11.27	13.89
2007	514	489	-25	-5.11	-18.97	7.13
2008	518	507	-11	-2.17	-15.48	9.6
2009	596	524	-72	-13.74	-27.91	-1.14
2010	560	543	-17	-3.13	-16.05	8.35
2011	663	562	-101	-17.97	-32	-5.43
2012	687	581	-106	-18.24	-32.06	-5.88
2013	663	601	-62	-10.32	-23.19	1.21
2014	733	622	-111	-17.85	-31.13	-5.9
2015	864	644	-220	-34.16	-48.57	-21.15
2016	849	667	-182	-27.29	-40.87	-15.01
2017	816	689	-127	-18.43	-31.07	-7.01
2018	847	712	-135	-18.96	-31.43	-7.68

Note: Poisson model has been used to predict the counts using the pre-vaccination period from 1995-Most recent available year‘s data

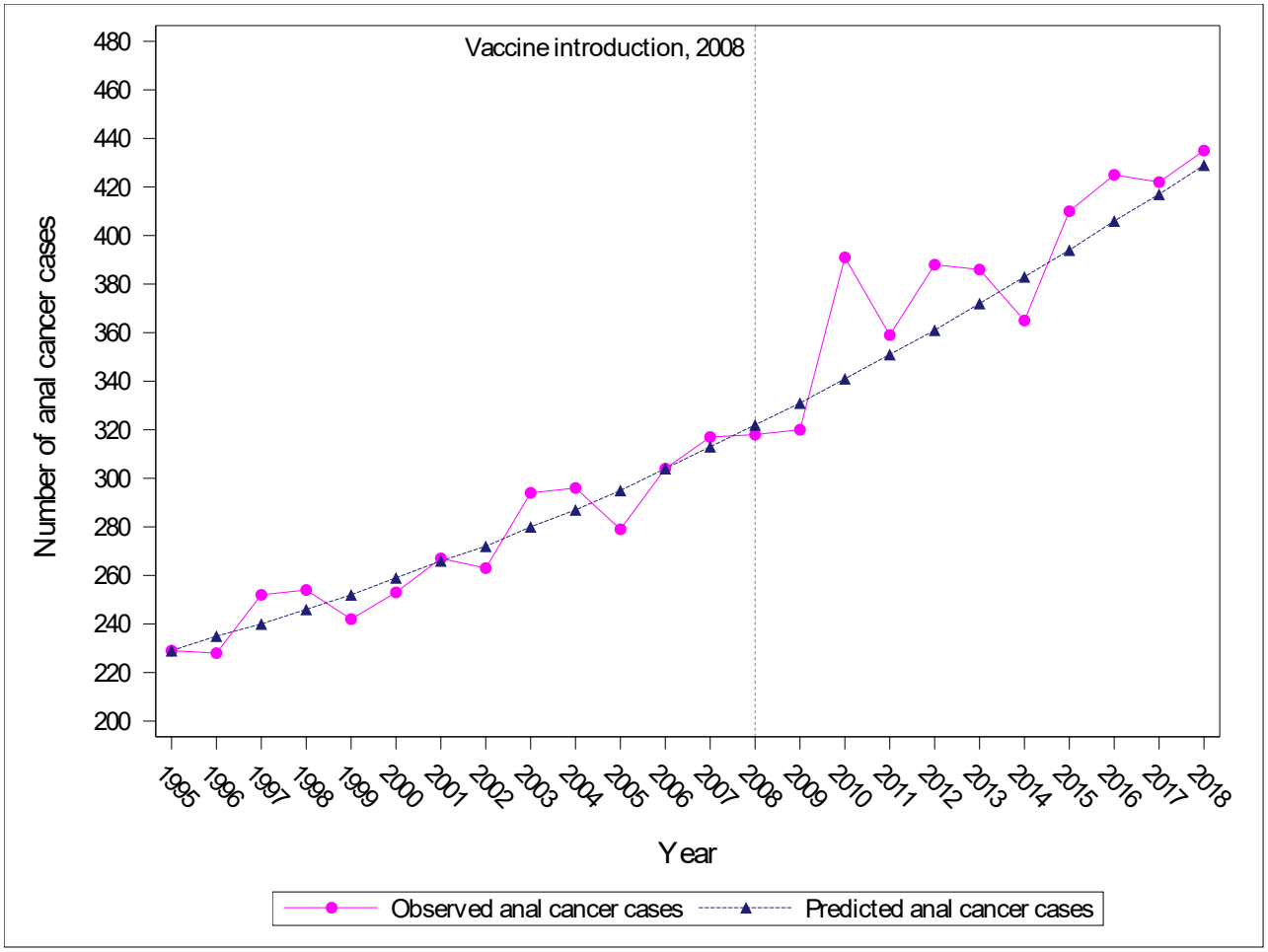
Model is calculated by, log (No. of anal cancer cases) = log (Population at risk) + intercept + (β × calendar year)

%Reduction = ((predicted counts –observed counts)/ predicted counts) ×100

Wald’s 95% CI and %reduction was estimated using Poisson model for non-zero observed counts

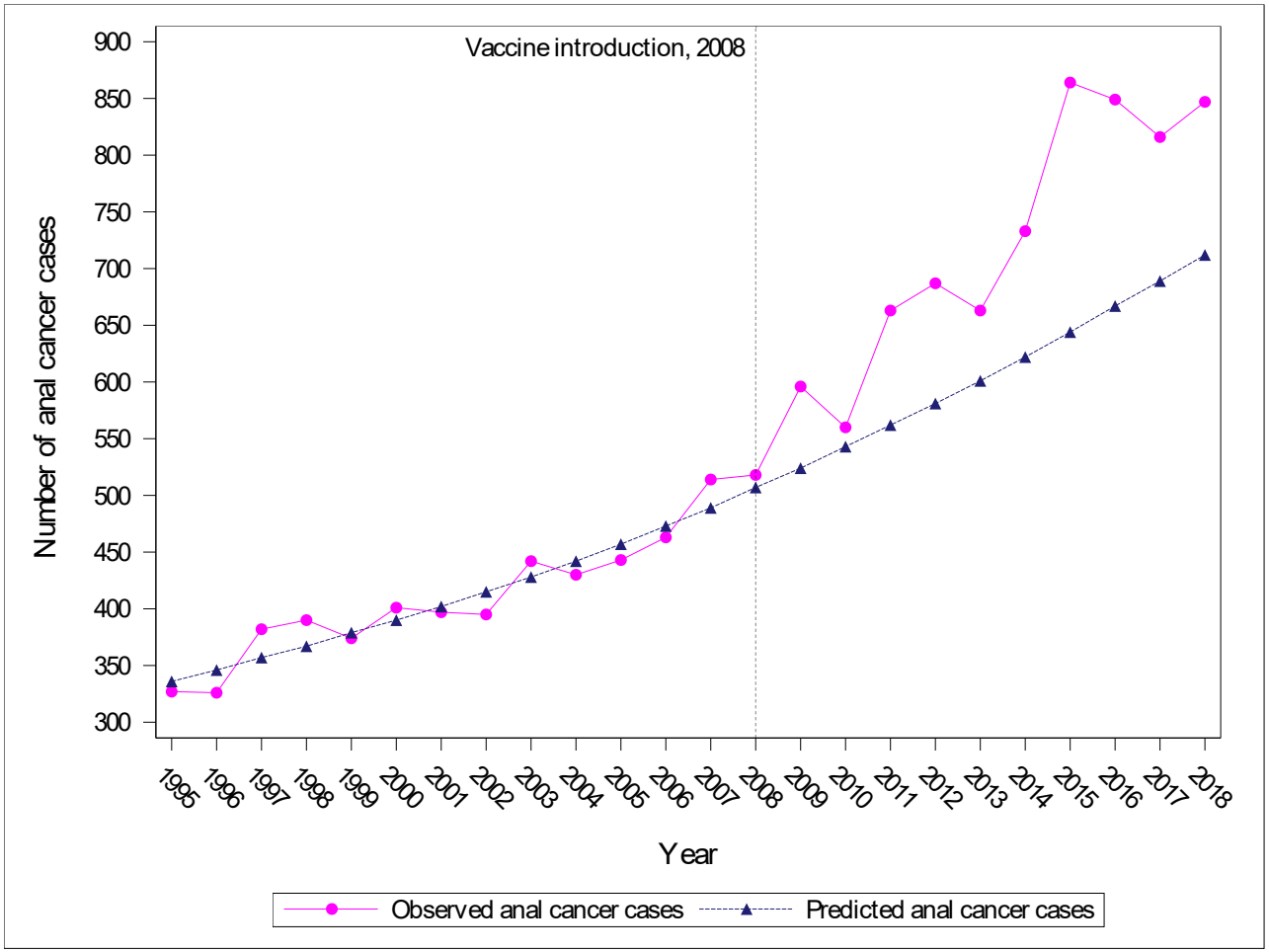
*Positive sign indicates the reduction and negative sign indicates the increase in observed counts

Figure 14.2.1.13.1 Predicted and observed counts of anal cancer cases, by Male - England



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.1.13.2 Predicted and observed counts of anal cancer cases, by Female - England



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Table 14.2.1.14 Trend overtime of anal cancer cases by observed counts versus predicted counts, by histological classification - England

Adenocarcinoma						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1995	115	116	1	0.86	-28.31	23.4
1996	98	117	19	16.24	-9.55	35.96
1997	130	118	-12	-10.17	-41.35	14.13
1998	134	119	-15	-12.61	-44.14	12.03
1999	110	120	10	8.33	-18.73	29.23
2000	129	122	-7	-5.74	-35.43	17.45
2001	126	123	-3	-2.44	-31.33	20.1
2002	112	124	12	9.68	-16.62	30.04
2003	125	126	1	0.79	-27.06	22.54
2004	141	127	-14	-11.02	-41.11	12.65
2005	123	129	6	4.65	-22.06	25.52
2006	134	131	-3	-2.29	-30.14	19.6
2007	128	133	5	3.76	-22.67	24.5
2008	143	135	-8	-5.93	-34.01	16.27
2009	144	137	-7	-5.11	-32.81	16.81
2010	127	139	12	8.63	-16.22	28.17
2011	118	141	23	16.31	-6.87	34.47
2012	127	143	16	11.19	-12.79	30.07
2013	120	145	25	17.24	-5.4	35.02
2014	89	148	59	39.86	21.78	53.77
2015	118	150	32	21.33	-0.12	38.19
2016	108	152	44	28.95	9.07	44.48
2017	91	154	63	40.91	23.43	54.4
2018	117	156	39	25	4.68	40.99

SCC						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1995	355	373	18	4.83	-10.06	17.7
1996	386	387	1	0.26	-14.84	13.37
1997	431	402	-29	-7.21	-22.82	6.41
1998	442	418	-24	-5.74	-20.87	7.49
1999	428	434	6	1.38	-12.7	13.71
2000	440	451	11	2.44	-11.25	14.45
2001	461	469	8	1.71	-11.78	13.56
2002	479	488	9	1.84	-11.34	13.47
2003	531	508	-23	-4.53	-18.05	7.44
2004	499	529	30	5.67	-6.6	16.53
2005	531	552	21	3.8	-8.37	14.61
2006	560	576	16	2.78	-9.21	13.45
2007	645	601	-44	-7.32	-19.93	3.97
2008	611	627	16	2.55	-8.93	12.83
2009	677	654	-23	-3.52	-15.26	7.03
2010	745	683	-62	-9.08	-21.01	1.68
2011	817	713	-104	-14.59	-26.69	-3.64
2012	883	744	-139	-18.68	-30.84	-7.65
2013	843	775	-68	-8.77	-19.92	1.33
2014	941	809	-132	-16.32	-27.78	-5.88
2015	1071	845	-226	-26.75	-38.71	-15.82
2016	1093	883	-210	-23.78	-35.26	-13.28
2017	1069	920	-149	-16.2	-26.9	-6.39
2018	1092	958	-134	-13.99	-24.32	-4.51

Others						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1995	86	79	-7	-8.86	-47.75	19.79
1996	70	78	8	10.26	-23.92	35.01
1997	73	78	5	6.41	-28.78	31.98
1998	68	77	9	11.69	-22.37	36.27
1999	78	76	-2	-2.63	-40.76	25.17
2000	85	75	-10	-13.33	-54.6	16.92
2001	77	74	-3	-4.05	-43.16	24.37
2002	67	74	7	9.46	-26.01	34.94
2003	80	73	-7	-9.59	-50.5	20.2
2004	86	72	-14	-19.44	-63.36	12.66
2005	68	72	4	5.56	-31.56	32.2
2006	73	71	-2	-2.82	-42.54	25.84
2007	58	71	13	18.31	-15.56	42.25
2008	82	70	-12	-17.14	-61.15	14.85
2009	95	70	-25	-35.71	-84.8	0.33
2010	79	69	-10	-14.49	-58.14	17.11
2011	87	69	-18	-26.09	-72.94	8.07
2012	65	68	3	4.41	-34.29	31.96
2013	86	68	-18	-26.47	-73.83	7.98
2014	68	67	-1	-1.49	-42.22	27.57
2015	85	67	-18	-26.87	-74.75	7.9
2016	73	67	-6	-8.96	-51.8	21.79
2017	78	66	-12	-18.18	-64.03	14.85
2018	73	65	-8	-12.31	-56.88	19.6

Note: Poisson model has been used to predict the counts using the pre-vaccination period from 1995-Most recent available year‘s data
Model is calculated by, log (No. of anal cancer cases) = log (Population at risk) + intercept + (β × calendar year)
%Reduction = ((predicted counts –observed counts)/ predicted counts) ×100
Wald’s 95% CI and %reduction was estimated using Poisson model for non-zero observed counts
*Positive sign indicates the reduction and negative sign indicates the increase in observed counts

Table 14.2.1.15 Summary of HPV vaccine coverage in Females by year - England

Year	HPV vaccine coverage (%)
2008	80.10
2009	76.40
2010	84.20
2011	86.80
2012	86.10
2013	86.70
2014	89.40
2015	85.10
2016	83.10
2017	83.80
2018	83.90
2019	64.70

Table 14.2.1.16 Summary of birth cohort by year and gender - England

Year	Gender	Birth cohort
2013	Male	340856
	Female	323661
	Total	664517
2014	Male	339383
	Female	322116
	Total	661499
2015	Male	341098
	Female	323301
	Total	664399
2016	Male	340159
	Female	322998
	Total	663157
2017	Male	331544
	Female	315250
	Total	646794
2018	Male	321513
	Female	304138
	Total	625651
2019	Male	313832
	Female	296673
	Total	610505

Table 14.2.1.17 Feasibility assessment: Number of anal cancer cases and time frame predicted for the Vaccine effectiveness - England

		Case-Control Ratio 1:1		Case-Control Ratio 1:2		Case-Control Ratio 1:3		Case-Control Ratio 1:4	
Vaccine Coverage	Vaccine Effectiveness	Number of cases required	Year	Number of cases required	Year	Number of cases required	Year	Number of cases required	Year
30	30	1019	2048	720	2046	624	2045	577	2044
	40	514	2044	364	2041	317	2041	294	2040
	50	290	2040	208	2039	181	2038	168	2038
	60	176	2038	126	2036	111	2036	103	2036
	70	109	2036	81	2035	70	2034	66	2033
	80	69	2034	52	2032	46	2032	43	2032
	90	42	2032	33	2031	29	2030	27	2030
40	30	867	2047	612	2045	529	2044	489	2043
	40	433	2043	307	2041	265	2040	244	2040
	50	242	2040	173	2038	150	2037	138	2037
	60	144	2037	104	2036	90	2035	83	2035
	70	88	2035	65	2034	56	2033	52	2033
	80	55	2033	40	2032	35	2031	33	2031
	90	33	2031	25	2030	22	2030	21	2030
60	30	820	2047	577	2045	497	2044	456	2043
	40	399	2043	281	2041	242	2040	222	2040
	50	217	2040	153	2038	131	2037	121	2037
	60	126	2038	90	2036	77	2035	70	2035
	70	74	2036	53	2034	46	2033	42	2033
	80	44	2034	31	2032	27	2031	25	2031
	90	25	2031	18	2030	16	2030	14	2029
80	30	1158	2051	811	2048	694	2047	636	2046
	40	549	2046	384	2043	328	2042	299	2042
	50	289	2042	202	2040	172	2039	156	2039
	60	160	2040	112	2038	95	2037	86	2037
	70	90	2038	64	2036	53	2035	48	2035
	80	49	2036	35	2034	30	2033	26	2033
	90	25	2034	17	2032	14	2031	13	2031
90	30	1994	2056	1395	2052	1191	2051	1087	2050
	40	930	2050	649	2048	551	2046	502	2046

		Case-Control Ratio 1:1		Case-Control Ratio 1:2		Case-Control Ratio 1:3		Case-Control Ratio 1:4	
Vaccine Coverage	**Vaccine Effectiveness**	**Number of cases required**	**Year**	**Number of cases required**	**Year**	**Number of cases required**	**Year**	**Number of cases required**	**Year**
	50	480	2047	334	2044	283	2043	257	2042
	60	259	2043	181	2041	152	2040	138	2040
	70	140	2041	98	2039	82	2038	74	2038
	80	73	2039	51	2037	42	2036	38	2036
	90	34	2037	22	2035	18	2034	17	2034

Average female birth cohort for the last 7 years (2013-2019) available data = 315448.14286
Average incidence (per 100000) available from latest 5 years period (2014-2018):
20-29: 0.0553345005
30-39: 0.5183767774
40-49: 2.1743764329
50-59: 5.100881869
60-69: 7.4284639929
70-79: 7.9223749962
80+: 8.0033948941
Year = Year to reach the number of cases required for the completion of case-control study
Life Expectancy of 83 years in England has been considered as the upper limit of age for the feasibility assessment

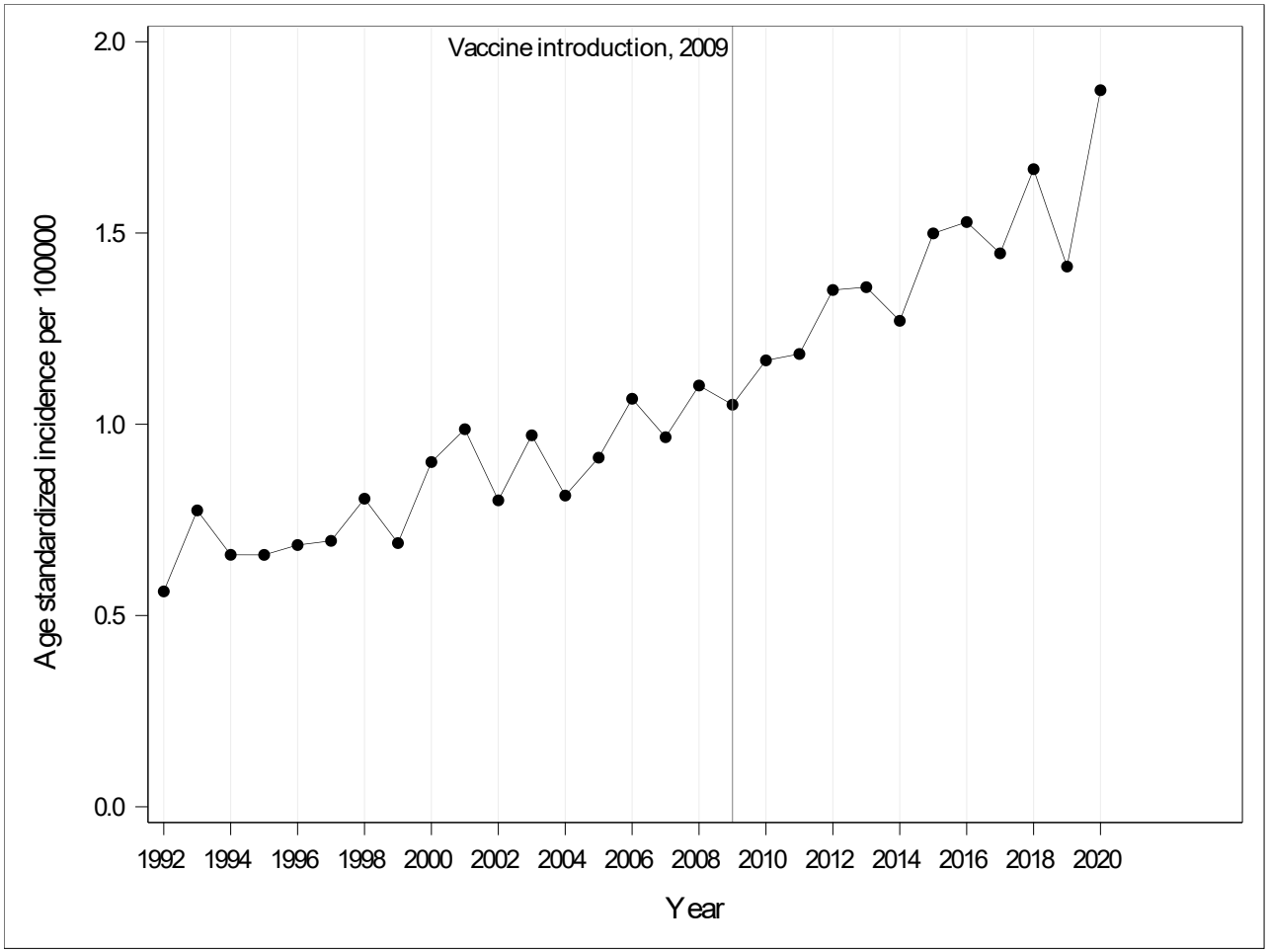
14.2.2 Netherlands

Table 14.2.2.1 Incidence of anal cancer by calendar year - Netherlands

			Age standardized Incidence per 100000			Crude Incidence per 100000		
				95% CI			95% CI	
Calendar Year	N	n	Value	LL	UL	Value	LL	UL
1992	15129150	60	0.563	0.253	1.255	0.397	0.303	0.510
1993	15239182	85	0.775	0.385	1.558	0.558	0.446	0.690
1994	15341553	74	0.659	0.316	1.375	0.482	0.379	0.606
1995	15424122	74	0.659	0.312	1.391	0.480	0.377	0.602
1996	15493889	80	0.684	0.322	1.452	0.516	0.409	0.643
1997	15567107	84	0.695	0.329	1.469	0.540	0.430	0.668
1998	15654192	98	0.805	0.401	1.618	0.626	0.508	0.763
1999	15760225	85	0.689	0.327	1.454	0.539	0.431	0.667
2000	15863950	112	0.901	0.469	1.731	0.706	0.581	0.850
2001	15987075	125	0.987	0.528	1.846	0.782	0.651	0.932
2002	16105285	109	0.801	0.390	1.647	0.677	0.556	0.816
2003	16192572	130	0.971	0.509	1.852	0.803	0.671	0.953
2004	16258032	109	0.814	0.405	1.636	0.670	0.550	0.809
2005	16305526	129	0.913	0.464	1.796	0.791	0.661	0.940
2006	16334210	152	1.067	0.574	1.982	0.931	0.789	1.091
2007	16357992	142	0.966	0.503	1.857	0.868	0.731	1.023
2008	16405399	162	1.101	0.598	2.027	0.987	0.841	1.152
2009	16485787	161	1.051	0.554	1.996	0.977	0.832	1.140
2010	16574989	176	1.167	0.646	2.109	1.062	0.911	1.231
2011	16655799	184	1.184	0.655	2.140	1.105	0.951	1.276
2012	16730348	214	1.351	0.776	2.353	1.279	1.113	1.462
2013	16779575	217	1.358	0.779	2.368	1.293	1.127	1.477
2014	16829289	205	1.270	0.718	2.247	1.218	1.057	1.397
2015	16900726	248	1.499	0.881	2.550	1.467	1.290	1.662
2016	16979120	257	1.529	0.900	2.598	1.514	1.334	1.710
2017	17081507	243	1.447	0.854	2.452	1.423	1.249	1.613
2018	17181084	287	1.667	1.012	2.746	1.670	1.483	1.875
2019	17282163	245	1.412	0.831	2.399	1.418	1.246	1.607
2020	17407585	330	1.873	1.183	2.965	1.896	1.697	2.112

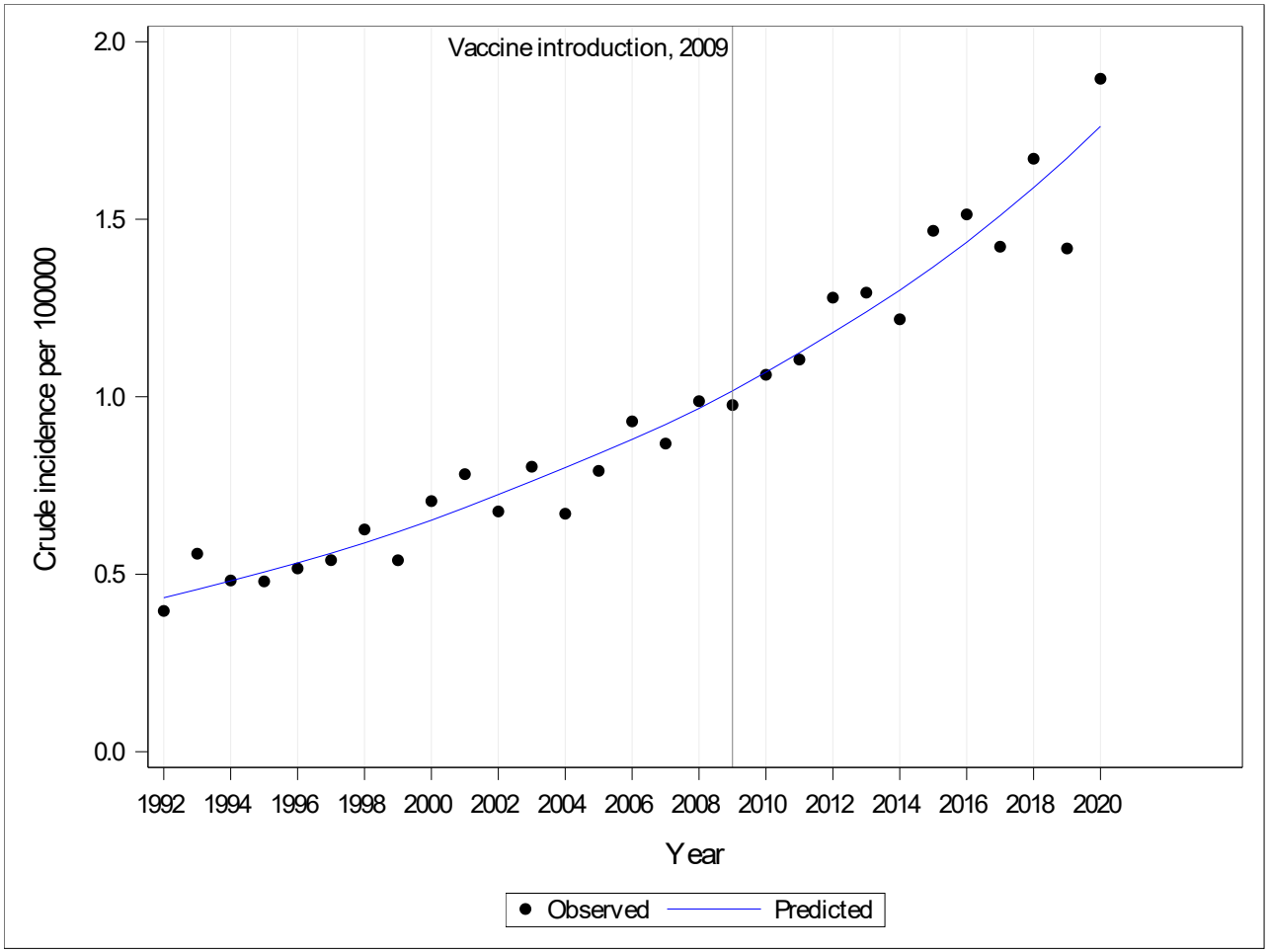
N = population in each category
n = number of anal cancer cases reported
Study period: Pre Cervarix launch (Year 1992 – Year 2008), Post Cervarix launch (Year 2009 – Year 2020)
Age standardized Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))
CI=confidence interval; LL=lower limit; UL=upper limit
Age standardized Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.2.1.1 Trend over time in the age standardized incidence of anal cancer - Netherlands



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.2.1.2 Trend over time in the crude incidence of anal cancer - Netherlands



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP
Line - Represents the predicted incidence , Period - Represents the observed Incidence

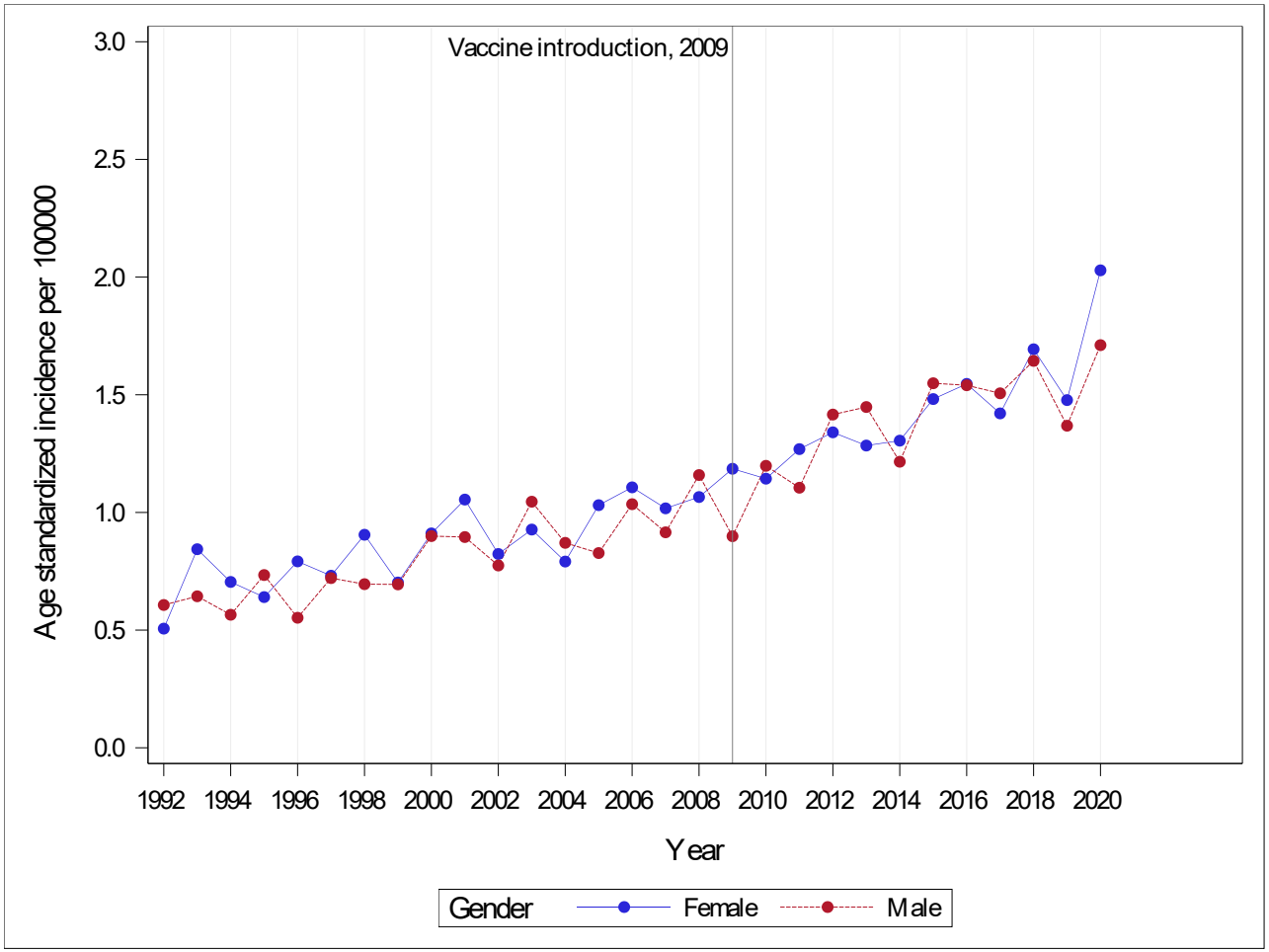
Table 14.2.2.2 Incidence of anal cancer by calendar year and gender - Netherlands

				Age standardized Incidence per 100000			Crude Incidence per 100000		
					95% CI			95% CI	
Calendar Year	Gender	N	n	Value	LL	UL	Value	LL	UL
1992	Male	7480422	29	0.607	0.274	1.344	0.388	0.260	0.557
	Female	7648728	31	0.506	0.224	1.144	0.405	0.275	0.575
1993	Male	7535268	32	0.644	0.291	1.424	0.425	0.290	0.600
	Female	7703914	53	0.844	0.435	1.638	0.688	0.515	0.900
1994	Male	7585887	27	0.565	0.249	1.283	0.356	0.235	0.518
	Female	7755666	47	0.705	0.348	1.428	0.606	0.445	0.806
1995	Male	7627482	33	0.734	0.372	1.449	0.433	0.298	0.608
	Female	7796640	41	0.640	0.295	1.389	0.526	0.377	0.713
1996	Male	7662289	28	0.552	0.240	1.270	0.365	0.243	0.528
	Female	7831600	52	0.792	0.391	1.604	0.664	0.496	0.871
1997	Male	7696803	35	0.721	0.360	1.444	0.455	0.317	0.632
	Female	7870304	49	0.731	0.345	1.551	0.623	0.461	0.823
1998	Male	7740074	37	0.695	0.331	1.458	0.478	0.337	0.659
	Female	7914118	61	0.905	0.467	1.756	0.771	0.590	0.990
1999	Male	7793271	36	0.694	0.335	1.440	0.462	0.324	0.640
	Female	7966954	49	0.702	0.332	1.487	0.615	0.455	0.813
2000	Male	7846317	50	0.899	0.469	1.724	0.637	0.473	0.840
	Female	8017633	62	0.911	0.477	1.741	0.773	0.593	0.991
2001	Male	7909855	50	0.895	0.464	1.730	0.632	0.469	0.833
	Female	8077220	75	1.055	0.574	1.938	0.929	0.730	1.164
2002	Male	7971967	49	0.775	0.372	1.611	0.615	0.455	0.813
	Female	8133318	60	0.823	0.404	1.679	0.738	0.563	0.950
2003	Male	8015471	62	1.046	0.567	1.928	0.774	0.593	0.992
	Female	8177101	68	0.927	0.475	1.808	0.832	0.646	1.054
2004	Male	8045914	52	0.871	0.449	1.688	0.646	0.483	0.848
	Female	8212118	57	0.791	0.388	1.614	0.694	0.526	0.899
2005	Male	8065979	51	0.827	0.417	1.640	0.632	0.471	0.831
	Female	8239547	78	1.031	0.538	1.976	0.947	0.748	1.181
2006	Male	8077407	67	1.035	0.555	1.929	0.829	0.643	1.053
	Female	8256803	85	1.107	0.599	2.044	1.029	0.822	1.273
2007	Male	8088514	61	0.916	0.472	1.777	0.754	0.577	0.969
	Female	8269478	81	1.017	0.534	1.939	0.980	0.778	1.217
2008	Male	8112073	78	1.159	0.644	2.085	0.962	0.760	1.200
	Female	8293326	84	1.065	0.570	1.992	1.013	0.808	1.254
2009	Male	8156396	66	0.899	0.449	1.800	0.809	0.626	1.029
	Female	8329391	95	1.186	0.647	2.172	1.141	0.923	1.394
2010	Male	8203476	83	1.198	0.673	2.131	1.012	0.806	1.254
	Female	8371513	93	1.143	0.623	2.099	1.111	0.897	1.361
2011	Male	8243482	80	1.105	0.602	2.029	0.970	0.770	1.208
	Female	8412317	104	1.269	0.714	2.256	1.236	1.010	1.498
2012	Male	8282871	101	1.416	0.839	2.391	1.219	0.993	1.482
	Female	8447477	113	1.340	0.757	2.374	1.338	1.102	1.608
2013	Male	8307339	109	1.448	0.847	2.475	1.312	1.077	1.583
	Female	8472236	108	1.284	0.724	2.277	1.275	1.046	1.539
2014	Male	8334385	94	1.215	0.674	2.191	1.128	0.911	1.380
	Female	8494904	111	1.305	0.746	2.284	1.307	1.075	1.574
2015	Male	8372858	120	1.549	0.927	2.589	1.433	1.188	1.714
	Female	8527868	128	1.482	0.862	2.547	1.501	1.252	1.785
2016	Male	8417135	122	1.540	0.917	2.587	1.449	1.204	1.731
	Female	8561985	135	1.546	0.906	2.638	1.577	1.322	1.866

				Age standardized Incidence per 100000			Crude Incidence per 100000		
					95% CI			95% CI	
Calendar Year	**Gender**	**N**	**n**	**Value**	**LL**	**UL**	**Value**	**LL**	**UL**
2017	Male	8475102	118	1.506	0.906	2.503	1.392	1.152	1.667
	Female	8606405	125	1.421	0.828	2.437	1.452	1.209	1.730
2018	Male	8527041	136	1.644	0.997	2.712	1.595	1.338	1.887
	Female	8654043	151	1.693	1.030	2.783	1.745	1.478	2.046
2019	Male	8581086	111	1.368	0.804	2.328	1.294	1.064	1.558
	Female	8701077	134	1.477	0.876	2.490	1.540	1.290	1.824
2020	Male	8648031	142	1.711	1.064	2.750	1.642	1.383	1.935
	Female	8759554	188	2.029	1.298	3.171	2.146	1.850	2.476

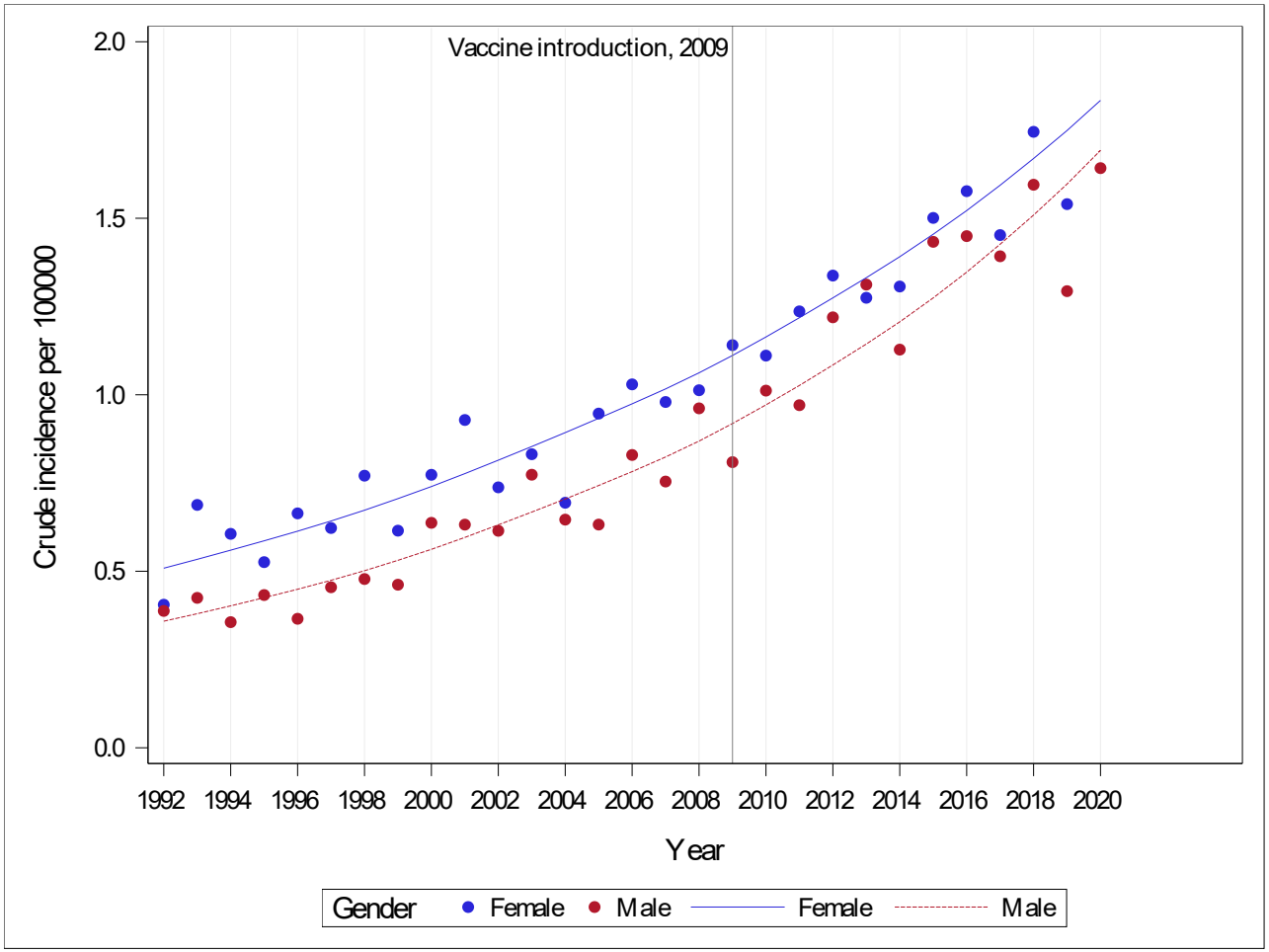
N = population in each category
n = number of anal cancer cases reported
Study period: Pre Cervarix launch (Year 1992 – Year 2008), Post Cervarix launch (Year 2009 – Year 2020)
Age standardized Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))
CI=confidence interval; LL=lower limit; UL=upper limit
Age standardized Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.2.2.1 Trend over time in the age standardized incidence of anal cancer by gender - Netherlands



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.2.2.2 Trend over time in the crude incidence of anal cancer by gender - Netherlands



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP
Line - Represents the predicted incidence , Period - Represents the observed Incidence

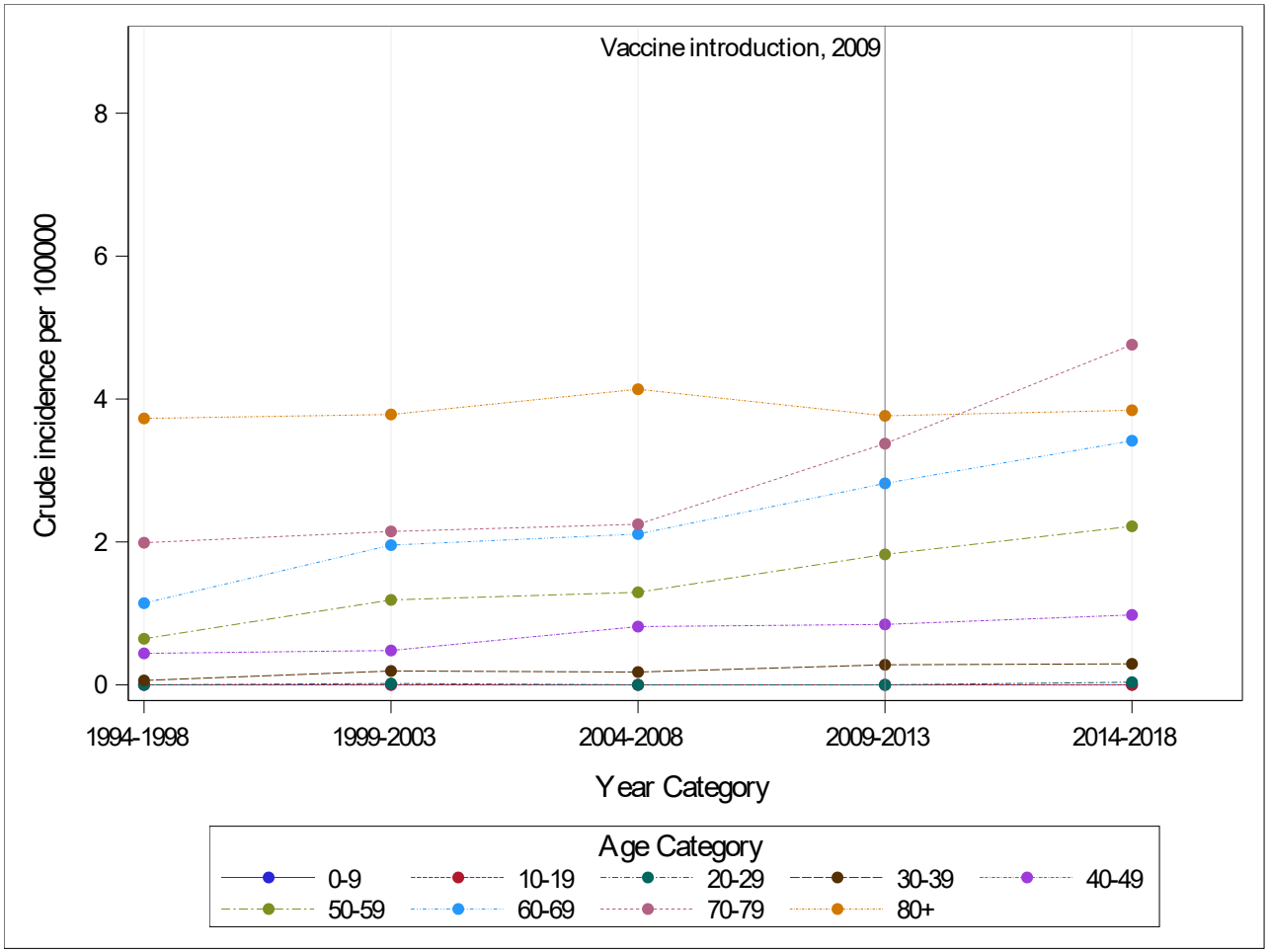
Table 14.2.2.3 Crude incidence of anal cancer for year and age category by gender - Netherlands

		Male					Female					Total				
					95% CI					95% CI					95% CI	
Year category	Age category (in years)	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL
1994-1998	0-9	4958958	0	0.000	0.000	0.074	4737714	0	0.000	0.000	0.078	9696672	0	0.000	0.000	0.038
	10-19	4694246	0	0.000	0.000	0.079	4488534	0	0.000	0.000	0.082	9182780	0	0.000	0.000	0.040
	20-29	6064781	0	0.000	0.000	0.061	5846390	2	0.034	0.004	0.124	11911171	2	0.017	0.002	0.061
	30-39	6509823	4	0.061	0.017	0.157	6251448	9	0.144	0.066	0.273	12761271	13	0.102	0.054	0.174
	40-49	5906931	26	0.440	0.288	0.645	5693556	38	0.667	0.472	0.916	11600487	64	0.552	0.425	0.705
	50-59	4342085	28	0.645	0.428	0.932	4220542	36	0.853	0.597	1.181	8562627	64	0.747	0.576	0.954
	60-69	3150685	36	1.143	0.800	1.582	3460027	44	1.272	0.924	1.707	6610712	80	1.210	0.960	1.506
	70-79	1960789	39	1.989	1.414	2.719	2792215	72	2.579	2.018	3.247	4753004	111	2.335	1.921	2.812
	80+	724237	27	3.728	2.457	5.424	1677902	49	2.920	2.160	3.861	2402139	76	3.164	2.493	3.960
1999-2003	0-9	5097964	0	0.000	0.000	0.072	4866028	0	0.000	0.000	0.076	9963992	0	0.000	0.000	0.037
	10-19	4895142	0	0.000	0.000	0.075	4671404	0	0.000	0.000	0.079	9566546	0	0.000	0.000	0.039
	20-29	5285766	1	0.019	0.000	0.105	5176029	1	0.019	0.000	0.108	10461795	2	0.019	0.002	0.069
	30-39	6699327	13	0.194	0.103	0.332	6447027	14	0.217	0.119	0.364	13146354	27	0.205	0.135	0.299
	40-49	6031658	29	0.481	0.322	0.691	5880579	49	0.833	0.616	1.102	11912237	78	0.655	0.518	0.817
	50-59	5216642	62	1.189	0.911	1.524	5061503	60	1.185	0.905	1.526	10278145	122	1.187	0.986	1.417
	60-69	3374938	66	1.956	1.512	2.488	3555221	58	1.631	1.239	2.109	6930159	124	1.789	1.488	2.133
	70-79	2142608	46	2.147	1.572	2.864	2918566	72	2.467	1.930	3.107	5061174	118	2.331	1.930	2.792
	80+	792836	30	3.784	2.553	5.402	1795869	60	3.341	2.550	4.301	2588705	90	3.477	2.796	4.273
2004-2008	0-9	5076324	0	0.000	0.000	0.073	4846402	0	0.000	0.000	0.076	9922726	0	0.000	0.000	0.037
	10-19	5076435	0	0.000	0.000	0.073	4849532	0	0.000	0.000	0.076	9925967	0	0.000	0.000	0.037
	20-29	4943498	0	0.000	0.000	0.075	4876439	0	0.000	0.000	0.076	9819937	0	0.000	0.000	0.038
	30-39	6136223	11	0.179	0.089	0.321	6036228	12	0.199	0.103	0.347	12172451	23	0.189	0.120	0.284
	40-49	6378256	52	0.815	0.609	1.069	6242344	57	0.913	0.692	1.183	12620600	109	0.864	0.709	1.042
	50-59	5636492	73	1.295	1.015	1.628	5531734	115	2.079	1.716	2.495	11168226	188	1.683	1.451	1.942
	60-69	3886061	82	2.110	1.678	2.619	3961341	76	1.919	1.512	2.401	7847402	158	2.013	1.712	2.353
	70-79	2313859	52	2.247	1.678	2.947	2934773	61	2.079	1.590	2.670	5248632	113	2.153	1.774	2.588
	80+	942739	39	4.137	2.942	5.655	1992479	64	3.212	2.474	4.102	2935218	103	3.509	2.864	4.256
2009-2013	0-9	4875064	0	0.000	0.000	0.076	4653207	0	0.000	0.000	0.079	9528271	0	0.000	0.000	0.039
	10-19	5121379	0	0.000	0.000	0.072	4891615	0	0.000	0.000	0.075	10012994	0	0.000	0.000	0.037

		Male					Female					Total				
					95% CI					95% CI					95% CI	
Year category	Age category (in years)	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL
	20-29	5134259	0	0.000	0.000	0.072	5044030	1	0.020	0.001	0.110	10178289	1	0.010	0.000	0.055
	30-39	5340694	15	0.281	0.157	0.463	5332500	9	0.169	0.077	0.320	10673194	24	0.225	0.144	0.335
	40-49	6504087	55	0.846	0.637	1.101	6390656	71	1.111	0.868	1.401	12894743	126	0.977	0.814	1.163
	50-59	5751645	105	1.826	1.493	2.210	5705017	151	2.647	2.241	3.104	11456662	256	2.235	1.969	2.526
	60-69	4717289	133	2.819	2.361	3.341	4749392	133	2.800	2.345	3.319	9466681	266	2.810	2.482	3.169
	70-79	2607034	88	3.375	2.707	4.159	3073046	76	2.473	1.949	3.095	5680080	164	2.887	2.462	3.365
	80+	1142113	43	3.765	2.725	5.071	2193471	72	3.282	2.568	4.134	3335584	115	3.448	2.846	4.138
2014-2018	0-9	4638296	0	0.000	0.000	0.080	4418038	0	0.000	0.000	0.083	9056334	0	0.000	0.000	0.041
	10-19	5150138	0	0.000	0.000	0.072	4913955	0	0.000	0.000	0.075	10064093	0	0.000	0.000	0.037
	20-29	5411294	2	0.037	0.004	0.134	5275715	3	0.057	0.012	0.166	10687009	5	0.047	0.015	0.109
	30-39	5105619	15	0.294	0.164	0.485	5082895	16	0.315	0.180	0.511	10188514	31	0.304	0.207	0.432
	40-49	6030922	59	0.978	0.745	1.262	6019984	54	0.897	0.674	1.170	12050906	113	0.938	0.773	1.127
	50-59	6129718	136	2.219	1.861	2.624	6092139	156	2.561	2.175	2.996	12221857	292	2.389	2.123	2.680
	60-69	5151448	176	3.417	2.930	3.960	5202845	222	4.267	3.724	4.867	10354293	398	3.844	3.475	4.241
	70-79	3129923	149	4.761	4.027	5.589	3474795	129	3.712	3.099	4.411	6604718	278	4.209	3.729	4.734
	80+	1379163	53	3.843	2.879	5.027	2364839	70	2.960	2.307	3.740	3744002	123	3.285	2.730	3.920

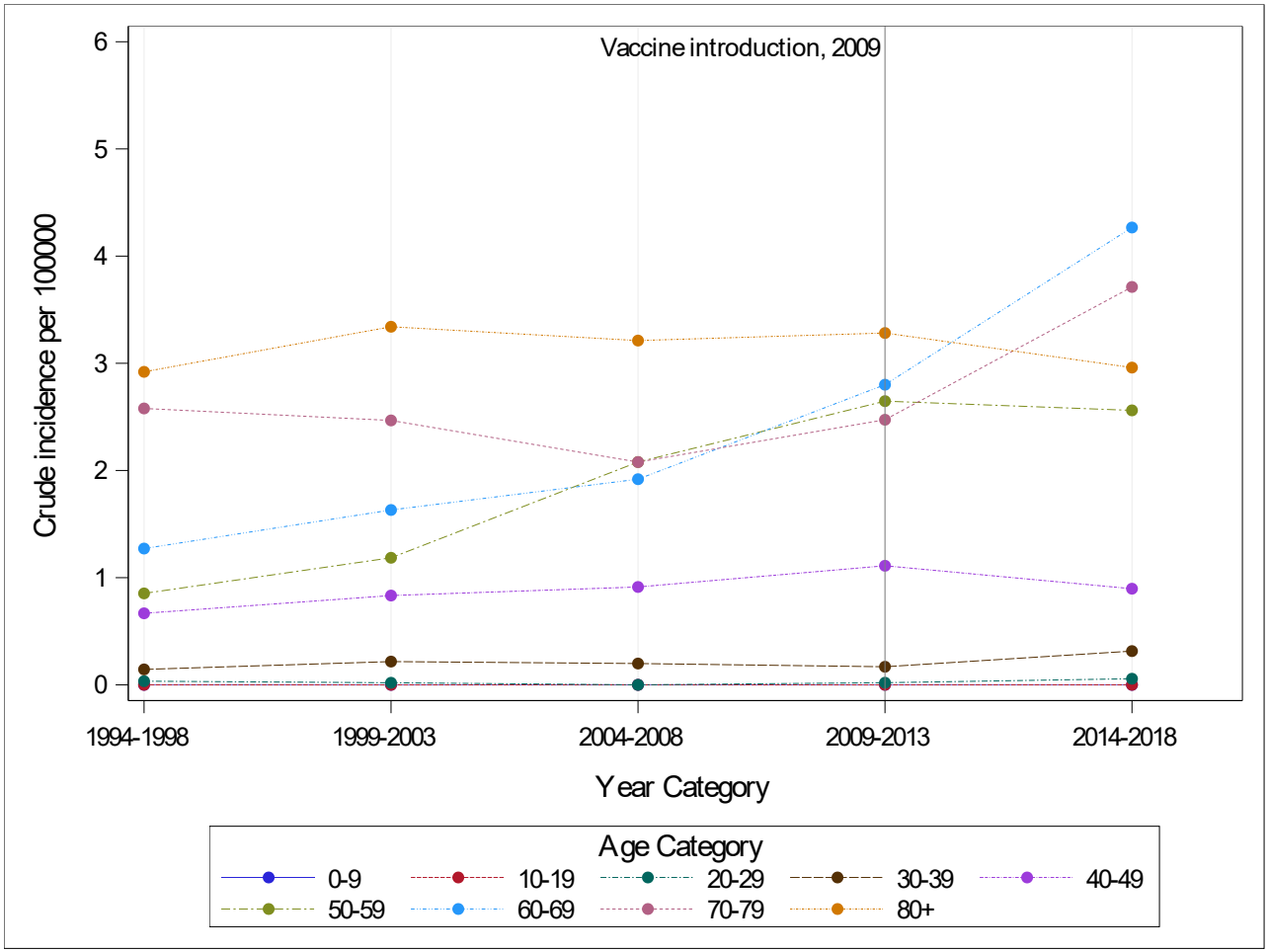
N = population in each category
n = number of anal cancer cases reported in each category
Study period: Pre Cervarix launch (Year 1992 – Year 2008), Post Cervarix launch (Year 2009 – Year 2020)
Crude Incidence per 100000 = (n/N)*100000
95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.2.3.1 Trend over time in the crude incidence of anal cancer by age category for Male - Netherlands



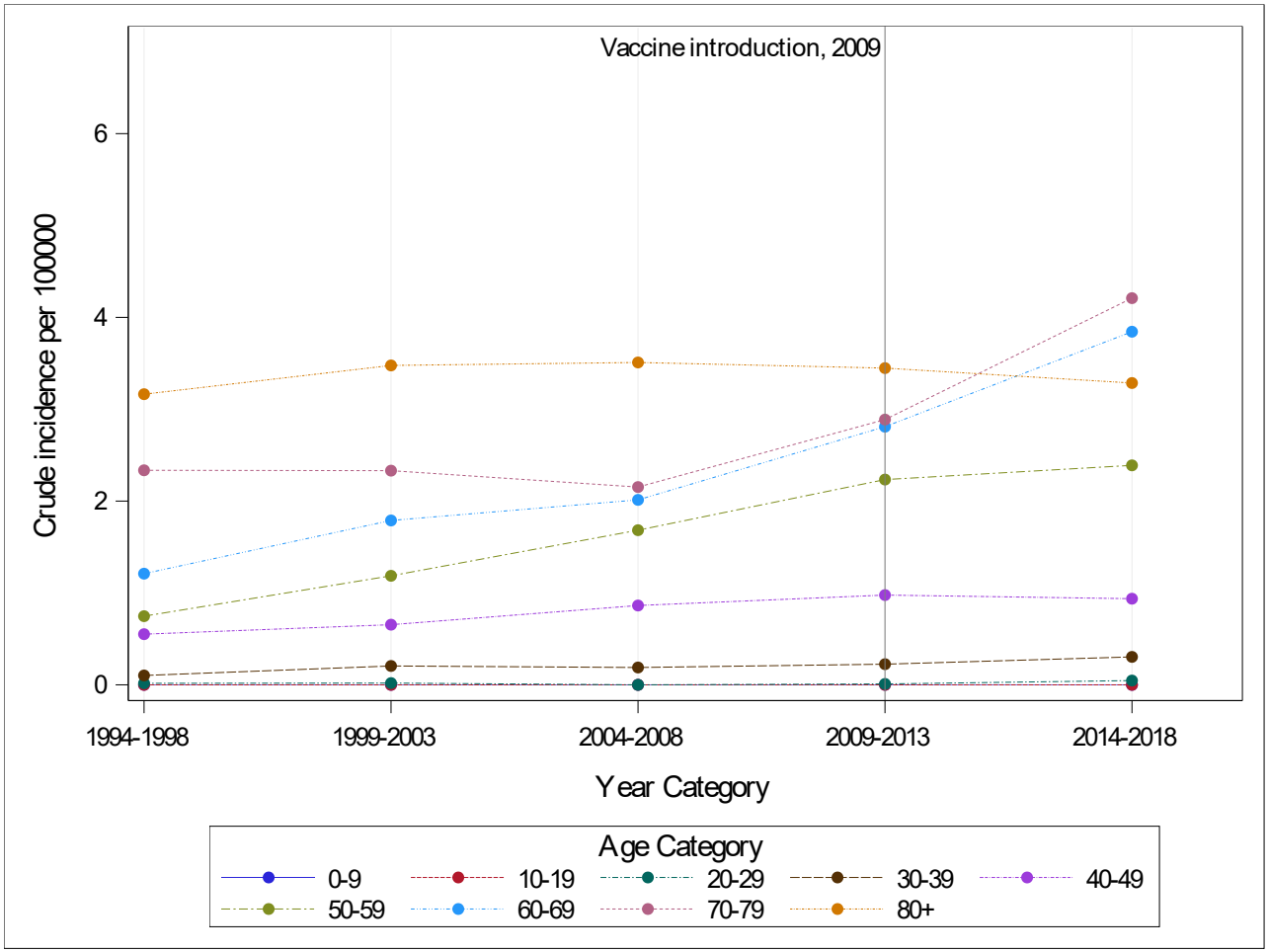
Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.2.3.2 Trend over time in the crude incidence of anal cancer by age category for Female - Netherlands



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.2.3.3 Trend over time in the crude incidence of anal cancer by age category - Netherlands



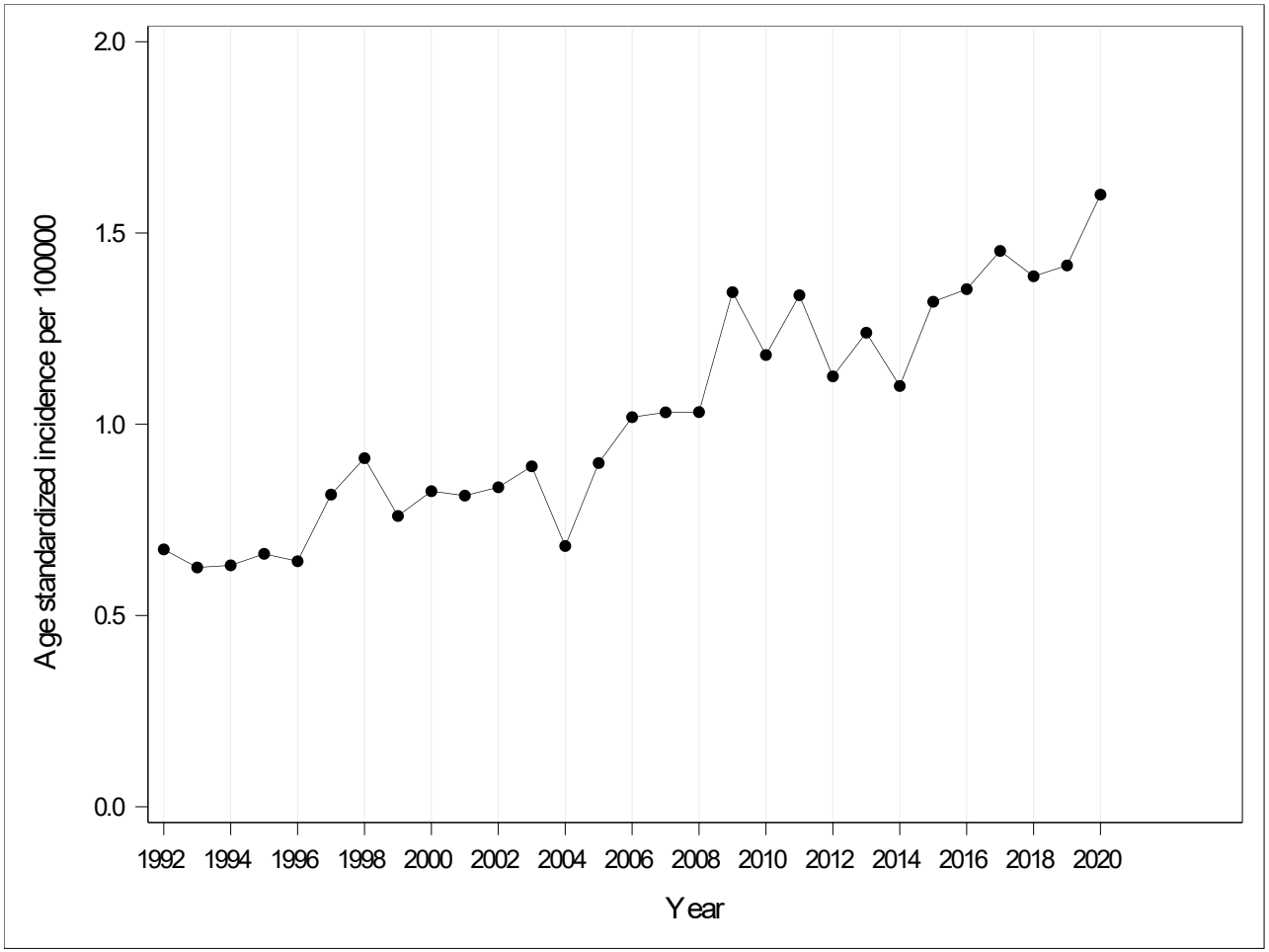
Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Table 14.2.2.4 Incidence of small intestine cancer by calendar year - Netherlands

			Age standardized Incidence per 100000			Crude Incidence per 100000		
				95% CI			95% CI	
Calendar Year	N	n	Value	LL	UL	Value	LL	UL
1992	15129150	74	0.673	0.316	1.431	0.489	0.384	0.614
1993	15239182	70	0.626	0.282	1.388	0.459	0.358	0.580
1994	15341553	70	0.631	0.290	1.374	0.456	0.356	0.576
1995	15424122	74	0.661	0.314	1.392	0.480	0.377	0.602
1996	15493889	74	0.642	0.295	1.397	0.478	0.375	0.600
1997	15567107	96	0.816	0.408	1.631	0.617	0.500	0.753
1998	15654192	106	0.911	0.478	1.736	0.677	0.554	0.819
1999	15760225	90	0.760	0.383	1.508	0.571	0.459	0.702
2000	15863950	98	0.825	0.426	1.600	0.618	0.502	0.753
2001	15987075	100	0.813	0.417	1.587	0.626	0.509	0.761
2002	16105285	102	0.835	0.434	1.609	0.633	0.516	0.769
2003	16192572	109	0.890	0.469	1.688	0.673	0.553	0.812
2004	16258032	90	0.682	0.318	1.463	0.554	0.445	0.680
2005	16305526	119	0.899	0.470	1.717	0.730	0.605	0.873
2006	16334210	134	1.019	0.557	1.862	0.820	0.687	0.972
2007	16357992	138	1.031	0.571	1.862	0.844	0.709	0.997
2008	16405399	143	1.032	0.568	1.874	0.872	0.735	1.027
2009	16485787	190	1.345	0.797	2.272	1.153	0.994	1.329
2010	16574989	166	1.181	0.685	2.038	1.002	0.855	1.166
2011	16655799	199	1.337	0.789	2.268	1.195	1.035	1.373
2012	16730348	169	1.125	0.632	2.004	1.010	0.864	1.174
2013	16779575	185	1.239	0.727	2.112	1.103	0.949	1.273
2014	16829289	173	1.100	0.611	1.980	1.028	0.880	1.193
2015	16900726	209	1.320	0.773	2.254	1.237	1.075	1.416
2016	16979120	216	1.353	0.803	2.280	1.272	1.108	1.454
2017	17081507	237	1.453	0.884	2.388	1.387	1.216	1.576
2018	17181084	231	1.387	0.840	2.289	1.345	1.177	1.530
2019	17282163	243	1.415	0.847	2.364	1.406	1.235	1.594
2020	17407585	280	1.600	0.991	2.585	1.608	1.426	1.808

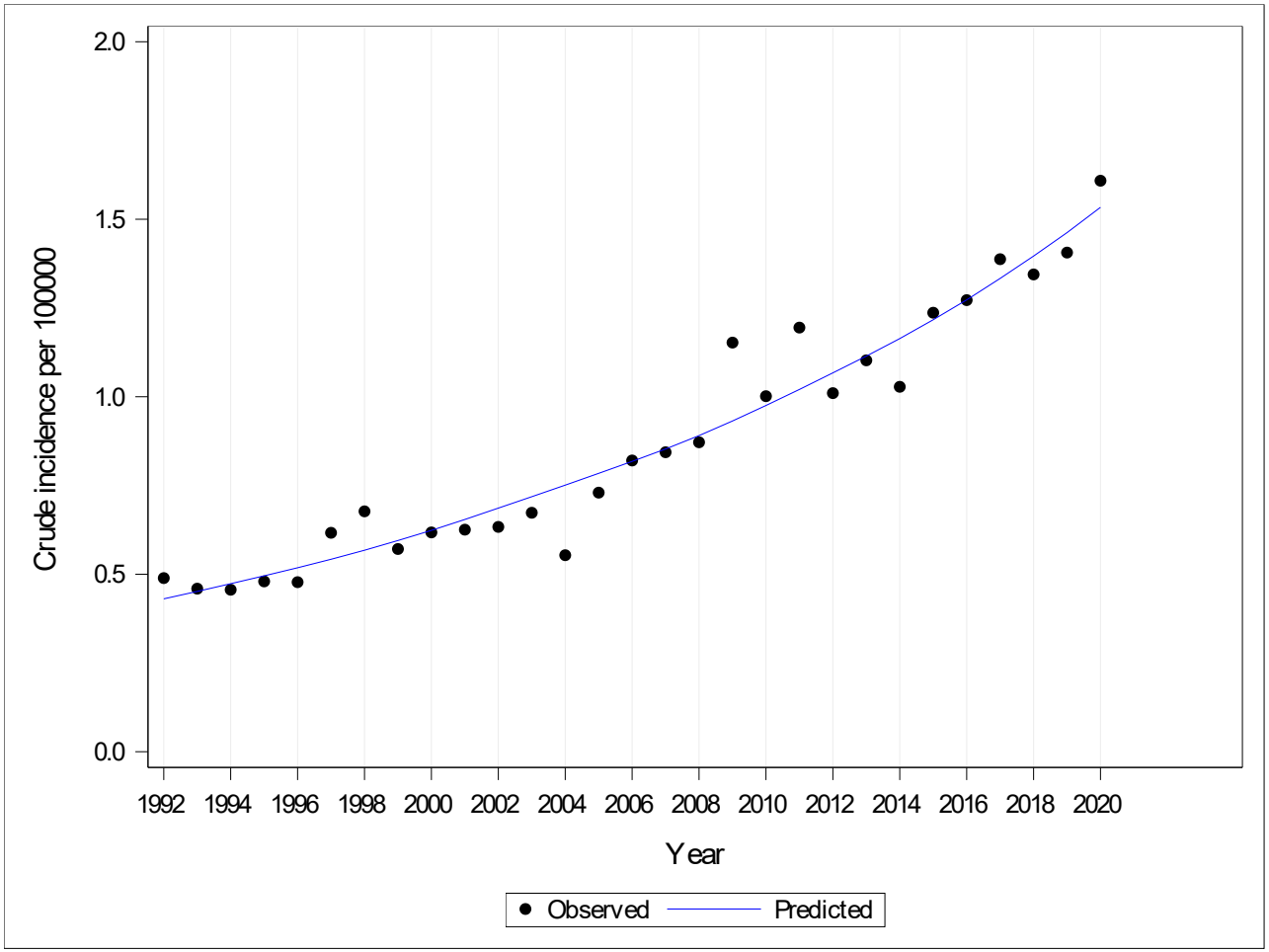
N = population in each category
n = number of small intestine cancer cases reported
Study period: Pre Cervarix launch (Year 1992 – Year 2008), Post Cervarix launch (Year 2009 – Year 2020)
Age standardized Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))
CI=confidence interval; LL=lower limit; UL=upper limit
Age standardized Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.2.4.1 Trend over time in the age standardized incidence of small intestine cancer - Netherlands



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.2.4.2 Trend over time in the crude incidence of small intestine cancer - Netherlands



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP
Line - Represents the predicted incidence , Period - Represents the observed Incidence

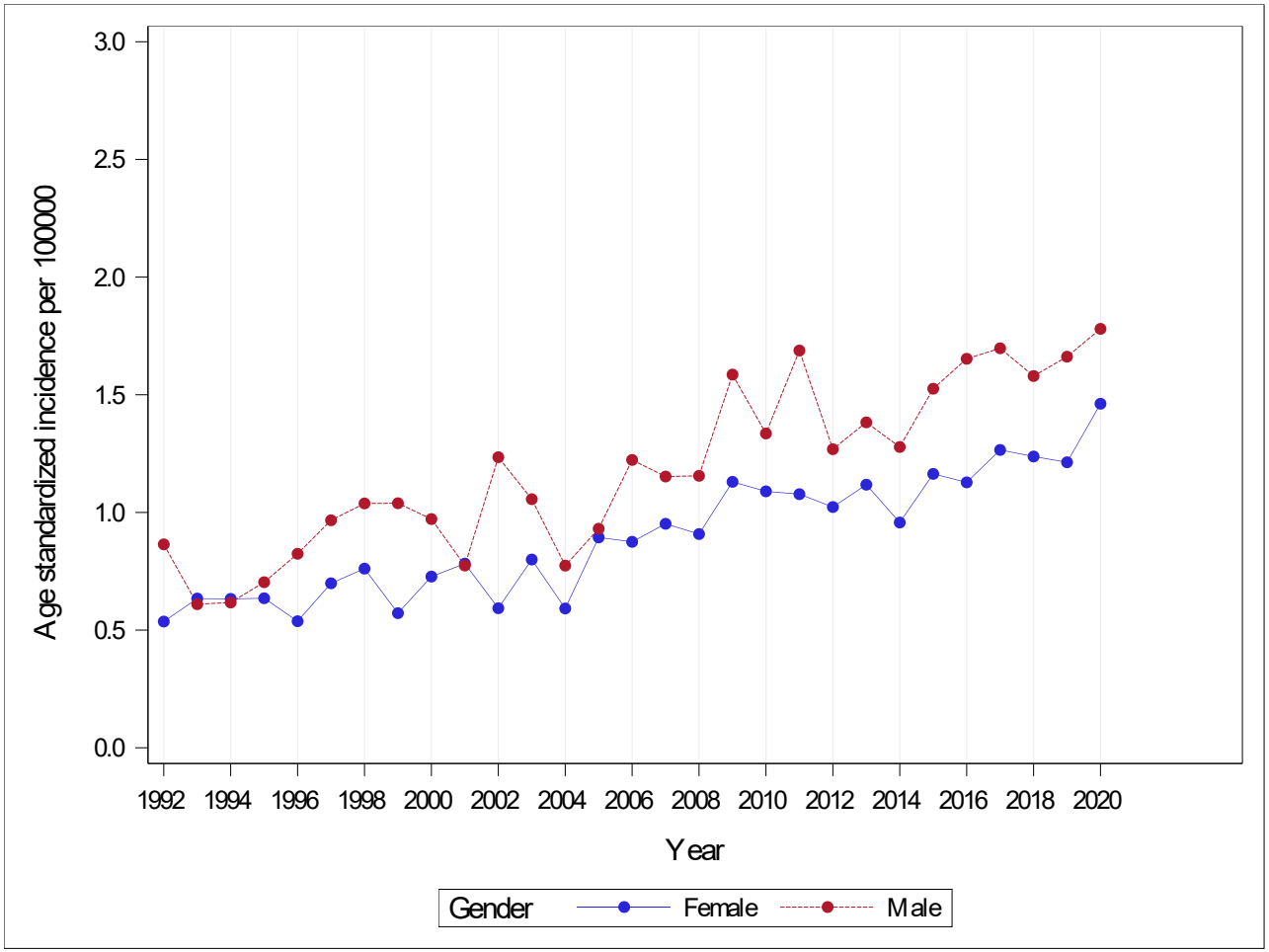
Table 14.2.2.5 Incidence of small intestine cancer by calendar year and gender - Netherlands

				Age standardized Incidence per 100000			Crude Incidence per 100000		
					95% CI			95% CI	
Calendar Year	Gender	N	n	Value	LL	UL	Value	LL	UL
1992	Male	7480422	41	0.864	0.447	1.671	0.548	0.393	0.744
	Female	7648728	33	0.536	0.232	1.240	0.431	0.297	0.606
1993	Male	7535268	31	0.610	0.271	1.372	0.411	0.280	0.584
	Female	7703914	39	0.634	0.288	1.397	0.506	0.360	0.692
1994	Male	7585887	31	0.617	0.279	1.365	0.409	0.278	0.580
	Female	7755666	39	0.633	0.293	1.367	0.503	0.358	0.687
1995	Male	7627482	33	0.703	0.343	1.442	0.433	0.298	0.608
	Female	7796640	41	0.635	0.296	1.365	0.526	0.377	0.713
1996	Male	7662289	39	0.824	0.425	1.599	0.509	0.362	0.696
	Female	7831600	35	0.538	0.225	1.285	0.447	0.311	0.622
1997	Male	7696803	51	0.967	0.512	1.826	0.663	0.493	0.871
	Female	7870304	45	0.699	0.333	1.466	0.572	0.417	0.765
1998	Male	7740074	56	1.038	0.557	1.936	0.724	0.547	0.940
	Female	7914118	50	0.761	0.385	1.505	0.632	0.469	0.833
1999	Male	7793271	51	1.039	0.583	1.851	0.654	0.487	0.860
	Female	7966954	39	0.572	0.259	1.262	0.490	0.348	0.669
2000	Male	7846317	49	0.972	0.531	1.779	0.624	0.462	0.826
	Female	8017633	49	0.727	0.360	1.472	0.611	0.452	0.808
2001	Male	7909855	45	0.774	0.376	1.595	0.569	0.415	0.761
	Female	8077220	55	0.782	0.405	1.513	0.681	0.513	0.886
2002	Male	7971967	61	1.235	0.735	2.074	0.765	0.585	0.983
	Female	8133318	41	0.593	0.266	1.321	0.504	0.362	0.684
2003	Male	8015471	54	1.056	0.597	1.870	0.674	0.506	0.879
	Female	8177101	55	0.800	0.402	1.593	0.673	0.507	0.875
2004	Male	8045914	47	0.774	0.376	1.592	0.584	0.429	0.777
	Female	8212118	43	0.592	0.262	1.336	0.524	0.379	0.705
2005	Male	8065979	54	0.931	0.498	1.739	0.669	0.503	0.874
	Female	8239547	65	0.894	0.465	1.720	0.789	0.609	1.005
2006	Male	8077407	70	1.223	0.712	2.102	0.867	0.676	1.095
	Female	8256803	64	0.875	0.454	1.686	0.775	0.597	0.990
2007	Male	8088514	67	1.153	0.663	2.004	0.828	0.642	1.052
	Female	8269478	71	0.952	0.513	1.766	0.859	0.671	1.083
2008	Male	8112073	73	1.156	0.653	2.046	0.900	0.705	1.131
	Female	8293326	70	0.908	0.485	1.699	0.844	0.658	1.066
2009	Male	8156396	102	1.586	0.975	2.579	1.251	1.020	1.518
	Female	8329391	88	1.130	0.642	1.988	1.056	0.847	1.302
2010	Male	8203476	81	1.335	0.808	2.208	0.987	0.784	1.227
	Female	8371513	85	1.090	0.613	1.937	1.015	0.811	1.255
2011	Male	8243482	112	1.688	1.064	2.677	1.359	1.119	1.635
	Female	8412317	87	1.078	0.595	1.952	1.034	0.828	1.276
2012	Male	8282871	86	1.269	0.743	2.168	1.038	0.830	1.282
	Female	8447477	83	1.023	0.556	1.884	0.983	0.783	1.218
2013	Male	8307339	93	1.383	0.836	2.287	1.119	0.904	1.371
	Female	8472236	92	1.118	0.637	1.960	1.086	0.875	1.332
2014	Male	8334385	92	1.278	0.744	2.195	1.104	0.890	1.354
	Female	8494904	81	0.957	0.509	1.801	0.954	0.757	1.185
2015	Male	8372858	112	1.526	0.936	2.488	1.338	1.101	1.610
	Female	8527868	97	1.164	0.653	2.073	1.137	0.922	1.388
2016	Male	8417135	121	1.653	1.038	2.631	1.438	1.193	1.718

				Age standardized Incidence per 100000			Crude Incidence per 100000		
					95% CI			95% CI	
Calendar Year	**Gender**	**N**	**n**	**Value**	**LL**	**UL**	**Value**	**LL**	**UL**
	Female	8561985	95	1.128	0.634	2.006	1.110	0.898	1.356
2017	Male	8475102	126	1.697	1.079	2.671	1.487	1.238	1.770
	Female	8606405	111	1.266	0.740	2.164	1.290	1.061	1.553
2018	Male	8527041	120	1.580	0.990	2.521	1.407	1.167	1.683
	Female	8654043	111	1.238	0.729	2.100	1.283	1.055	1.545
2019	Male	8581086	133	1.662	1.041	2.652	1.550	1.298	1.837
	Female	8701077	110	1.213	0.693	2.122	1.264	1.039	1.524
2020	Male	8648031	145	1.780	1.135	2.792	1.677	1.415	1.973
	Female	8759554	135	1.462	0.882	2.422	1.541	1.292	1.824

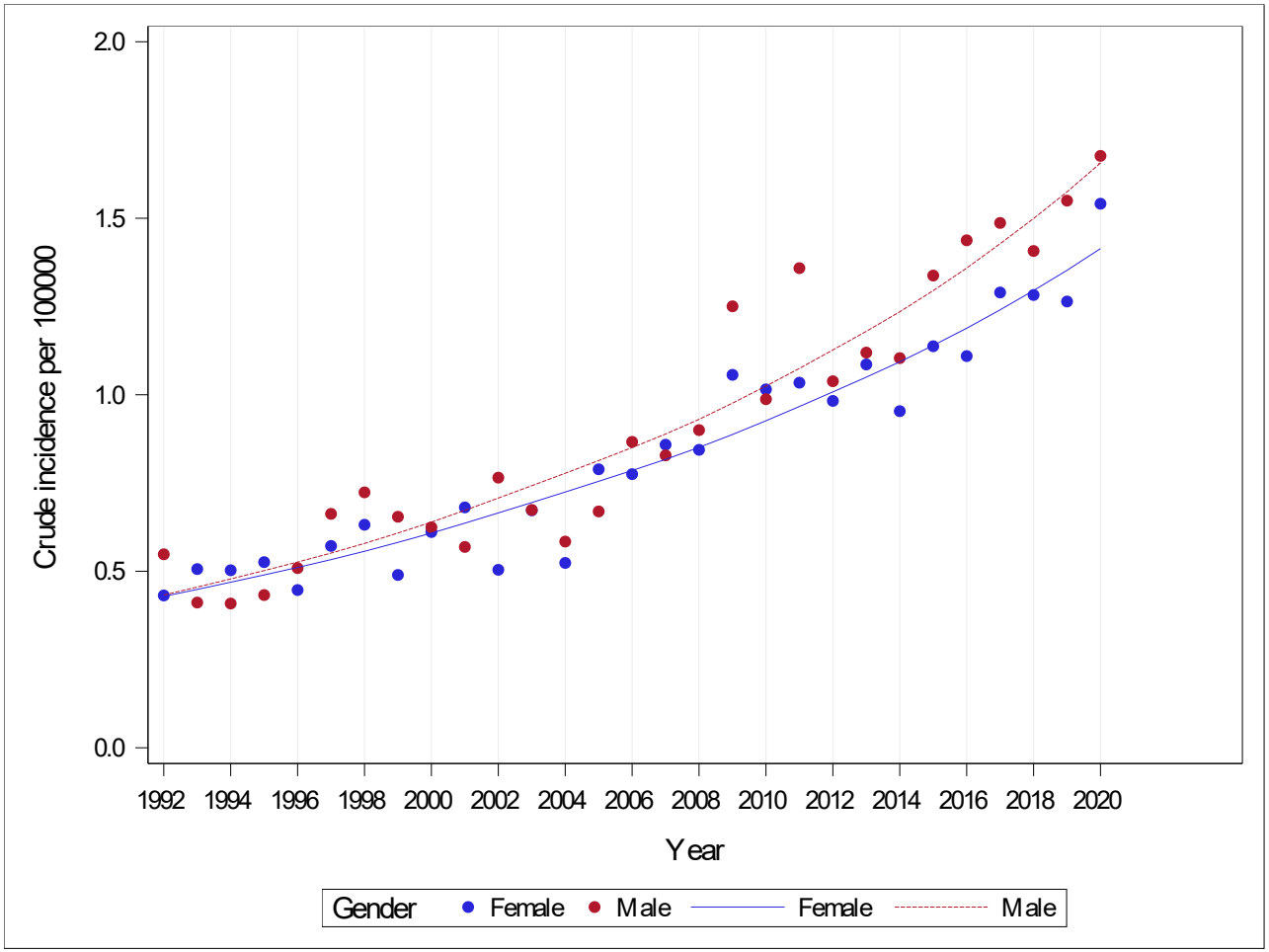
N = population in each category
n = number of small intestine cancer cases reported
Study period: Pre Cervarix launch (Year 1992 – Year 2008), Post Cervarix launch (Year 2009 – Year 2020)
Age standardized Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))
CI=confidence interval; LL=lower limit; UL=upper limit
Age standardized Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.2.5.1 Trend over time in the age standardized incidence of small intestine cancer by gender - Netherlands



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.2.5.2 Trend over time in the crude incidence of small intestine cancer by gender - Netherlands



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP
Line - Represents the predicted incidence , Period - Represents the observed Incidence

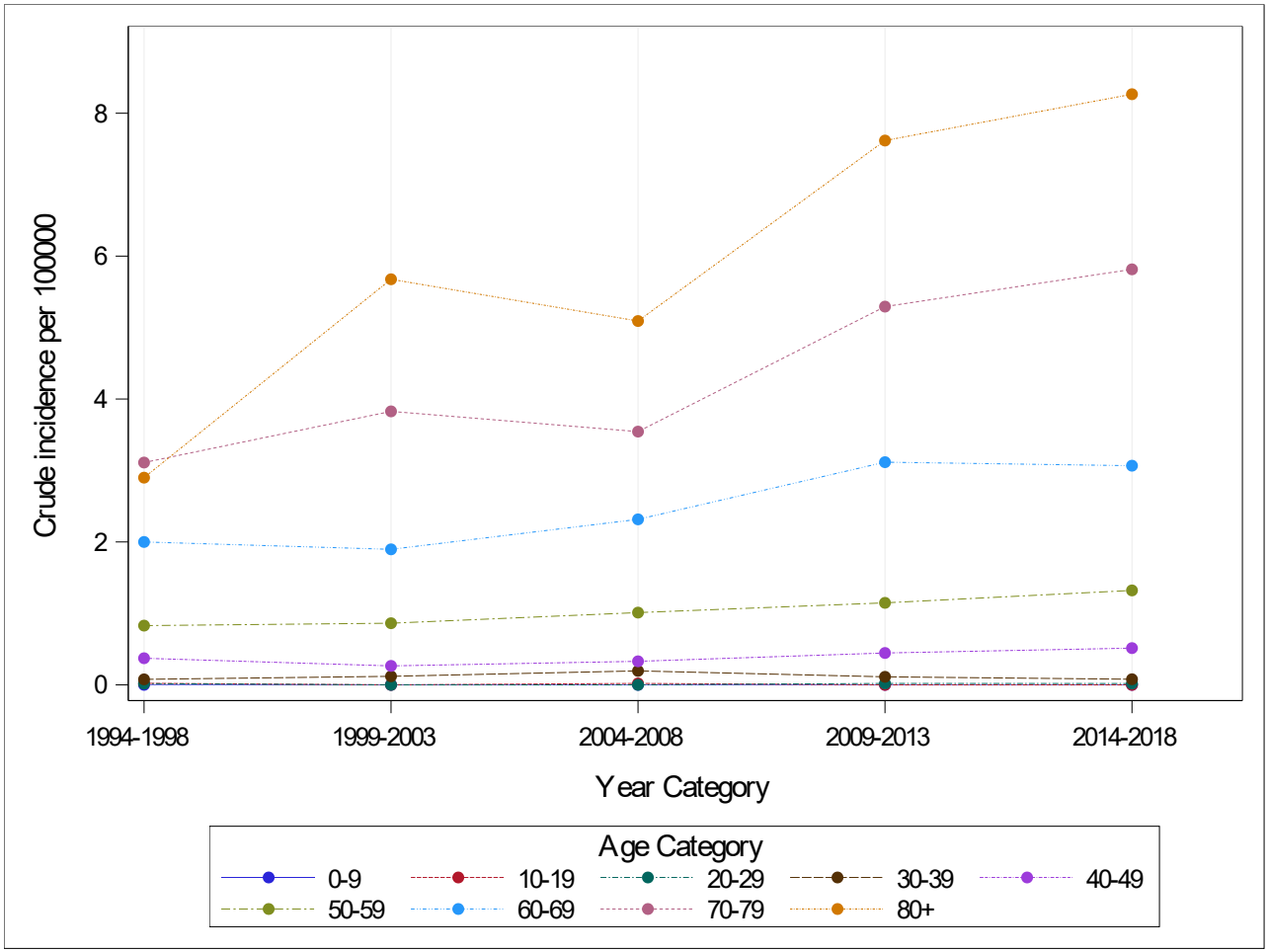
Table 14.2.2.6 Crude incidence of small intestine cancer for year and age category by gender - Netherlands

		Male					Female					Total				
					95% CI					95% CI					95% CI	
Year category	Age category (in years)	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL
1994-1998	0-9	4958958	0	0.000	0.000	0.074	4737714	0	0.000	0.000	0.078	9696672	0	0.000	0.000	0.038
	10-19	4694246	1	0.021	0.001	0.119	4488534	0	0.000	0.000	0.082	9182780	1	0.011	0.000	0.061
	20-29	6064781	1	0.016	0.000	0.092	5846390	1	0.017	0.000	0.095	11911171	2	0.017	0.002	0.061
	30-39	6509823	5	0.077	0.025	0.179	6251448	3	0.048	0.010	0.140	12761271	8	0.063	0.027	0.124
	40-49	5906931	22	0.372	0.233	0.564	5693556	19	0.334	0.201	0.521	11600487	41	0.353	0.254	0.479
	50-59	4342085	36	0.829	0.581	1.148	4220542	21	0.498	0.308	0.761	8562627	57	0.666	0.504	0.862
	60-69	3150685	63	2.000	1.537	2.558	3460027	57	1.647	1.248	2.134	6610712	120	1.815	1.505	2.171
	70-79	1960789	61	3.111	2.380	3.996	2792215	65	2.328	1.797	2.967	4753004	126	2.651	2.208	3.156
	80+	724237	21	2.900	1.795	4.432	1677902	44	2.622	1.905	3.520	2402139	65	2.706	2.088	3.449
1999-2003	0-9	5097964	0	0.000	0.000	0.072	4866028	0	0.000	0.000	0.076	9963992	0	0.000	0.000	0.037
	10-19	4895142	0	0.000	0.000	0.075	4671404	0	0.000	0.000	0.079	9566546	0	0.000	0.000	0.039
	20-29	5285766	0	0.000	0.000	0.070	5176029	2	0.039	0.005	0.140	10461795	2	0.019	0.002	0.069
	30-39	6699327	8	0.119	0.052	0.235	6447027	5	0.078	0.025	0.181	13146354	13	0.099	0.053	0.169
	40-49	6031658	16	0.265	0.152	0.431	5880579	19	0.323	0.195	0.505	11912237	35	0.294	0.205	0.409
	50-59	5216642	45	0.863	0.629	1.154	5061503	27	0.533	0.352	0.776	10278145	72	0.701	0.548	0.882
	60-69	3374938	64	1.896	1.460	2.422	3555221	57	1.603	1.214	2.077	6930159	121	1.746	1.449	2.086
	70-79	2142608	82	3.827	3.044	4.750	2918566	62	2.124	1.629	2.723	5061174	144	2.845	2.399	3.350
	80+	792836	45	5.676	4.140	7.595	1795869	67	3.731	2.891	4.738	2588705	112	4.326	3.562	5.206
2004-2008	0-9	5076324	0	0.000	0.000	0.073	4846402	0	0.000	0.000	0.076	9922726	0	0.000	0.000	0.037
	10-19	5076435	1	0.020	0.000	0.110	4849532	0	0.000	0.000	0.076	9925967	1	0.010	0.000	0.056
	20-29	4943498	0	0.000	0.000	0.075	4876439	0	0.000	0.000	0.076	9819937	0	0.000	0.000	0.038
	30-39	6136223	12	0.196	0.101	0.342	6036228	8	0.133	0.057	0.261	12172451	20	0.164	0.100	0.254
	40-49	6378256	21	0.329	0.204	0.503	6242344	23	0.368	0.234	0.553	12620600	44	0.349	0.253	0.468
	50-59	5636492	57	1.011	0.766	1.310	5531734	56	1.012	0.765	1.315	11168226	113	1.012	0.834	1.216
	60-69	3886061	90	2.316	1.862	2.847	3961341	57	1.439	1.090	1.864	7847402	147	1.873	1.583	2.202
	70-79	2313859	82	3.544	2.819	4.399	2934773	92	3.135	2.527	3.845	5248632	174	3.315	2.841	3.846
	80+	942739	48	5.092	3.754	6.751	1992479	77	3.865	3.050	4.830	2935218	125	4.259	3.545	5.074
2009-2013	0-9	4875064	0	0.000	0.000	0.076	4653207	0	0.000	0.000	0.079	9528271	0	0.000	0.000	0.039
	10-19	5121379	0	0.000	0.000	0.072	4891615	0	0.000	0.000	0.075	10012994	0	0.000	0.000	0.037

		Male					Female					Total				
					95% CI					95% CI					95% CI	
Year category	Age category (in years)	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL
	20-29	5134259	1	0.019	0.000	0.109	5044030	1	0.020	0.001	0.110	10178289	2	0.020	0.002	0.071
	30-39	5340694	6	0.112	0.041	0.245	5332500	7	0.131	0.053	0.270	10673194	13	0.122	0.065	0.208
	40-49	6504087	29	0.446	0.299	0.640	6390656	31	0.485	0.330	0.689	12894743	60	0.465	0.355	0.599
	50-59	5751645	66	1.147	0.887	1.460	5705017	52	0.911	0.681	1.195	11456662	118	1.030	0.853	1.233
	60-69	4717289	147	3.116	2.633	3.663	4749392	111	2.337	1.923	2.815	9466681	258	2.725	2.403	3.079
	70-79	2607034	138	5.293	4.447	6.254	3073046	117	3.807	3.149	4.563	5680080	255	4.489	3.955	5.076
	80+	1142113	87	7.617	6.101	9.396	2193471	116	5.288	4.370	6.343	3335584	203	6.086	5.277	6.983
2014-2018	0-9	4638296	0	0.000	0.000	0.080	4418038	0	0.000	0.000	0.083	9056334	0	0.000	0.000	0.041
	10-19	5150138	0	0.000	0.000	0.072	4913955	0	0.000	0.000	0.075	10064093	0	0.000	0.000	0.037
	20-29	5411294	1	0.018	0.000	0.103	5275715	2	0.038	0.005	0.137	10687009	3	0.028	0.006	0.082
	30-39	5105619	4	0.078	0.021	0.201	5082895	6	0.118	0.043	0.257	10188514	10	0.098	0.047	0.181
	40-49	6030922	31	0.514	0.349	0.730	6019984	23	0.382	0.242	0.573	12050906	54	0.448	0.337	0.585
	50-59	6129718	81	1.321	1.049	1.642	6092139	62	1.018	0.780	1.305	12221857	143	1.170	0.986	1.378
	60-69	5151448	158	3.067	2.608	3.584	5202845	122	2.345	1.947	2.800	10354293	280	2.704	2.397	3.040
	70-79	3129923	182	5.815	5.001	6.724	3474795	171	4.921	4.211	5.717	6604718	353	5.345	4.802	5.932
	80+	1379163	114	8.266	6.818	9.930	2364839	109	4.609	3.785	5.560	3744002	223	5.956	5.200	6.791

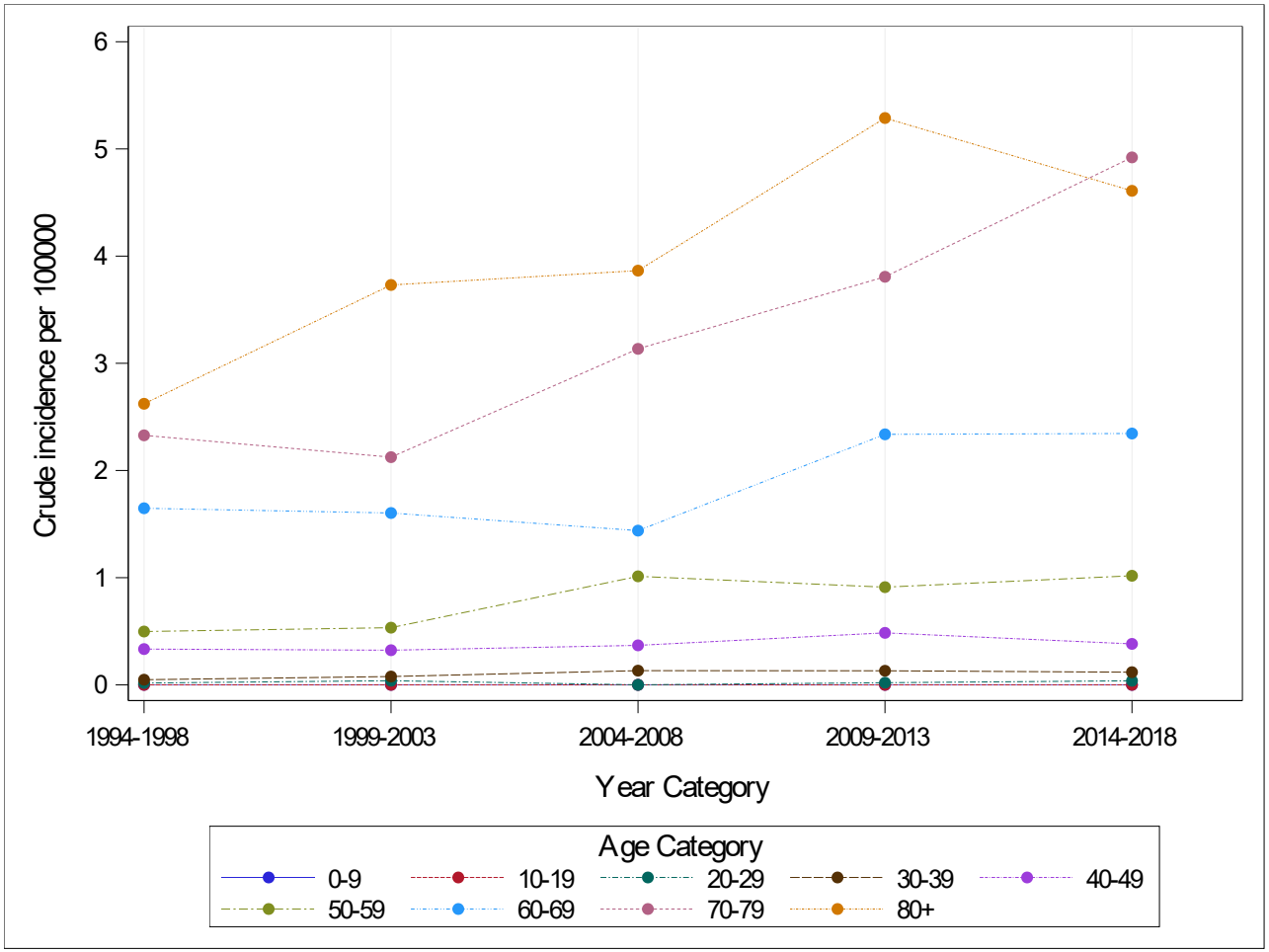
N = population in each category
n = number of small intestine cancer cases reported in each category
Study period: Pre Cervarix launch (Year 1992 – Year 2008), Post Cervarix launch (Year 2009 – Year 2020)
Crude Incidence per 100000 = (n/N)*100000
95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.2.6.1 Trend over time in the crude incidence of small intestine cancer by age category for Male - Netherlands



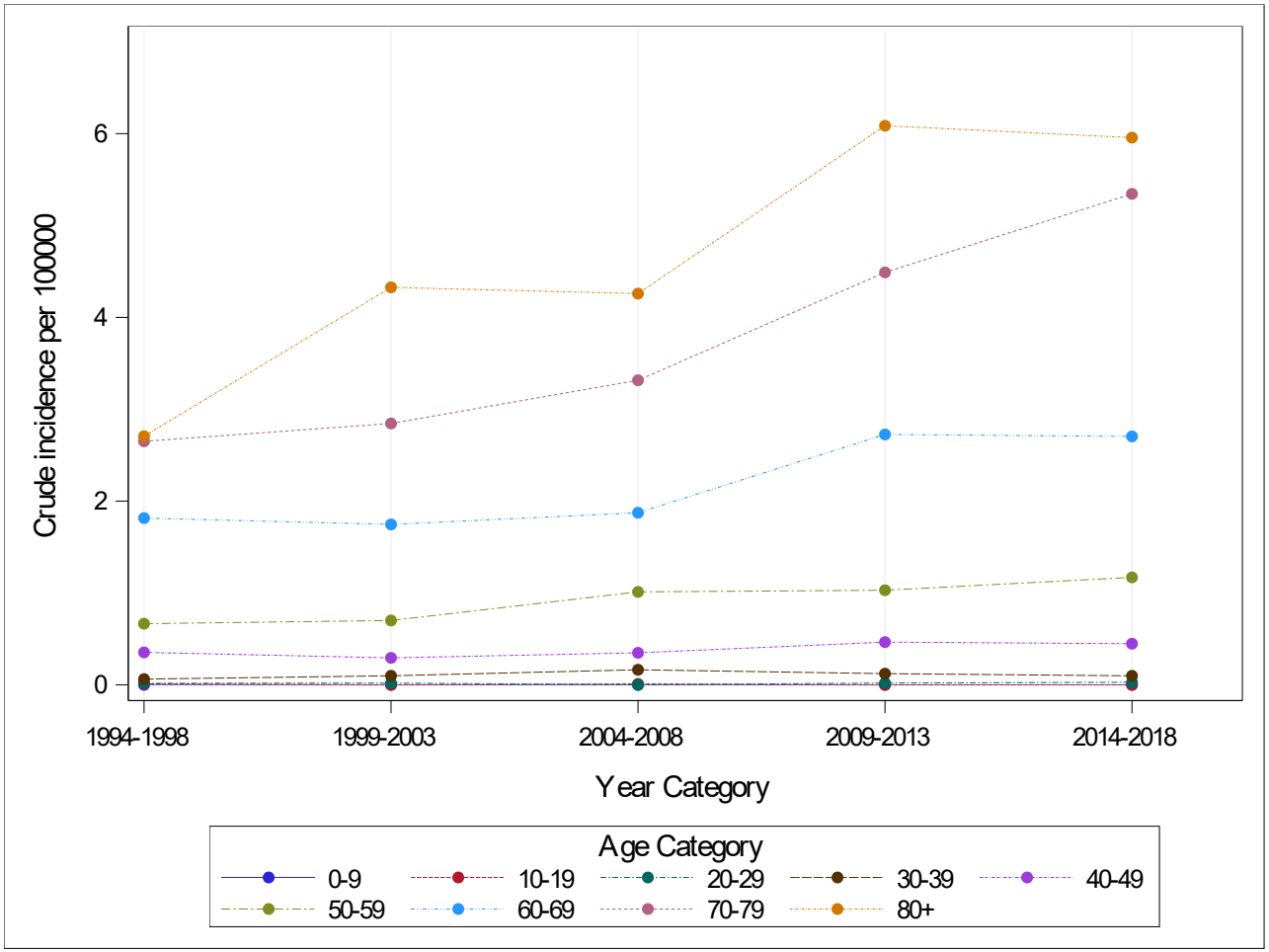
Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.2.6.2 Trend over time in the crude incidence of small intestine cancer by age category for Female - Netherlands



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.2.6.3 Trend over time in the crude incidence of small intestine cancer by age category - Netherlands



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Table 14.2.2.7 Univariate Poisson regression model for incidence of anal cancer - Netherlands

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	472307433	4577	1.051	1.047	1.055	<.0001	5.09

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.2.7.1 Univariate Poisson regression model for incidence of anal cancer for Pre-Cervarix launch (Year 1992 – Year 2008) - Netherlands

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	269419461	1810	1.049	1.039	1.059	<.0001	4.90

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.2.7.2 Univariate Poisson regression model for incidence of anal cancer for Post-Cervarix launch (Year 2009 – Year 2020) - Netherlands

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	202887972	2767	1.050	1.036	1.064	<.0001	5.00

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.2.8 Multivariate Poisson regression model for incidence of anal cancer - Netherlands

				Adjusted incidence ratio (e(β))				
					95% CI			
Characteristics	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
Calendar year		472307433	4577	1.038	1.030	1.047	<.0001	-
Age category (in years)	0-29	174616131	10	Reference	-	-	-	<.0001
	30-39	68084726	132	34.639	16.857	71.180	<.0001	-
	40-49	69975252	543	134.470	66.724	271.000	<.0001	-
	50-59	61827352	1062	286.881	142.791	576.372	<.0001	-
	60-69	48032015	1236	422.739	210.506	848.948	<.0001	-
	70-79	32244722	958	490.653	244.125	986.135	<.0001	-
	80+	17527235	636	588.367	292.186	1184.778	<.0001	-
Study period	Pre-Cervarix launch	269419461	1810	Reference	-	-	-	0.9082
	Post-Cervarix launch	202887972	2767	1.008	0.885	1.148	0.9082	-
Gender	Female	238503238	2518	Reference	-	-	-	0.0241
	Male	233804195	2059	0.927	0.868	0.990	0.0241	-

N = population at risk in each category
n = number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk)+ intercept + (β1 × calendar year) +(β2 × age category) + (β3 × study period) + (β4 × gender)
Adjusted incidence ratio (e(β)) = change in incidence of anal cancer compared to the reference category of each independent variable adjusted for other covariates (Exponentiated regression coefficient – β)
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Study period: Pre-Cervarix launch (Year 1992 – Year 2008), Post-Cervarix launch (Year 2009 – Year 2020)

Table 14.2.2.8.1 Multivariate Poisson regression model for incidence of anal cancer by age category - Netherlands

					Adjusted incidence ratio (e(β))				
						95% CI			
Age Category (in years)	Characteristics	Categories	N	n	Value	LL	UL	P-value for the category of the variable	P-value for the variable
0-29	Calendar year		174616131	10	0.955	0.841	1.085	0.4783	-
	Study period	Pre-Cervarix launch	103086708	4	Reference	-	-	-	0.1938
		Post-Cervarix launch	71529423	6	4.290	0.477	38.587	0.1938	-
	Gender	Female	85607189	7	Reference	-	-	-	0.1219
		Male	89008942	3	0.412	0.134	1.267	0.1219	-
30-39	Calendar year		68084726	132	1.058	1.017	1.100	0.0047	-
	Study period	Pre-Cervarix launch	42966888	68	Reference	-	-	-	0.3193
		Post-Cervarix launch	25117838	64	0.726	0.387	1.363	0.3193	-
	Gender	Female	33659326	67	Reference	-	-	-	0.7685
		Male	34425400	65	0.953	0.690	1.316	0.7685	-
40-49	Calendar year		69975252	543	1.035	1.014	1.057	0.0012	-
	Study period	Pre-Cervarix launch	40560420	263	Reference	-	-	-	0.5749
		Post-Cervarix launch	29414832	280	0.909	0.652	1.268	0.5749	-
	Gender	Female	34630487	295	Reference	-	-	-	0.0315
		Male	35344765	248	0.827	0.695	0.983	0.0315	-
50-59	Calendar year		61827352	1062	1.049	1.027	1.070	<.0001	-
	Study period	Pre-Cervarix launch	33108027	396	Reference	-	-	-	0.9554
		Post-Cervarix launch	28719325	666	1.009	0.730	1.395	0.9554	-
	Gender	Female	30658761	597	Reference	-	-	-	0.0015
		Male	31168591	465	0.769	0.653	0.904	0.0015	-
60-69	Calendar year		48032015	1236	1.047	1.032	1.062	<.0001	-
	Study period	Pre-Cervarix launch	24007282	403	Reference	-	-	-	0.4524
		Post-Cervarix launch	24024733	833	1.093	0.867	1.376	0.4524	-
	Gender	Female	24435599	654	Reference	-	-	-	0.1058
		Male	23596416	582	0.911	0.814	1.020	0.1058	-
70-79	Calendar year		32244722	958	1.027	1.010	1.044	0.0021	-
	Study period	Pre-Cervarix launch	16863395	376	Reference	-	-	-	0.3182
		Post-Cervarix launch	15381327	582	1.152	0.872	1.522	0.3182	-
	Gender	Female	17868126	500	Reference	-	-	-	0.1452

					Adjusted incidence ratio (e(β))				
						95% CI			
Age Category (in years)	**Characteristics**	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
		Male	14376596	458	1.106	0.966	1.268	0.1452	-
80+	Calendar year		17527235	636	1.024	1.004	1.045	0.0175	-
	Study period	Pre-Cervarix launch	8826741	300	Reference	-	-	-	0.1803
		Post-Cervarix launch	8700494	336	0.802	0.580	1.108	0.1803	-
	Gender	Female	11643750	398	Reference	-	-	-	0.0736
		Male	5883485	238	1.169	0.985	1.386	0.0736	-

N = population at risk in each category
n = number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk)+ intercept + (β1 × calendar year) + (β2 × study period) + (β3 × gender)
Adjusted incidence ratio (e(β)) = change in incidence of anal cancer compared to the reference category of each independent variable adjusted for other covariates (Exponentiated regression coefficient – β)
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Study period: Pre-Cervarix launch (Year 1992 – Year 2008), Post-Cervarix launch (Year 2009 – Year 2020)

Table 14.2.2.8.2 Multivariate Poisson regression model for incidence of anal cancer by gender - Netherlands

					Adjusted incidence ratio (e(β))				
						95% CI			
Gender	**Characteristics**	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
Male	Calendar year		233804195	2059	1.041	1.029	1.052	<.0001	-
	Age category (in years)	0-29	89008942	3	Reference	-	-	-	<.0001
		30-39	34425400	65	57.560	18.168	182.366	<.0001	-
		40-49	35344765	248	207.083	66.611	643.785	<.0001	-
		50-59	31168591	465	423.014	136.498	1310.939	<.0001	-
		60-69	23596416	582	683.431	220.686	2116.481	<.0001	-
		70-79	14376596	458	878.402	283.420	2722.430	<.0001	-
		80+	5883485	238	1093.175	351.513	3399.682	<.0001	-
	Study period	Pre-Cervarix launch	133254993	777	Reference	-	-	-	0.8971
		Post-Cervarix launch	100549202	1282	1.012	0.850	1.203	0.8971	-
Female	Calendar year		238503238	2518	1.036	1.024	1.048	<.0001	-
	Age category (in years)	0-29	85607189	7	Reference	-	-	-	<.0001
		30-39	33659326	67	24.830	9.796	62.938	<.0001	-
		40-49	34630487	295	103.256	42.172	252.817	<.0001	-
		50-59	30658761	597	228.193	93.689	555.797	<.0001	-
		60-69	24435599	654	310.742	127.637	756.528	<.0001	-
		70-79	17868126	500	330.456	135.540	805.675	<.0001	-
		80+	11643750	398	399.519	163.607	975.598	<.0001	-
	Study period	Pre-Cervarix launch	136164468	1033	Reference	-	-	-	0.9705
		Post-Cervarix launch	102338770	1485	1.004	0.833	1.209	0.9705	-

N = population at risk in each category
n = number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk)+ intercept + (β1 × calendar year) + (β2 × age category) + (β3 × study period)
Adjusted Incidence ratio (e(β)) = change in incidence of anal cancer compared to the reference category of each independent variable adjusted for other covariates (Exponentiated regression coefficient – β)
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Study period: Pre-Cervarix launch (Year 1992 – Year 2008), Post-Cervarix launch (Year 2009 – Year 2020)

Table 14.2.2.9 Univariate Poisson regression model for incidence of small intestine cancer - Netherlands

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	472307433	4185	1.046	1.041	1.051	<.0001	4.60

N = overall population at risk
n = total number of small intestine cancer cases reported
Model is calculated by log(No. of small intestine cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of small intestine cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.2.9.1 Univariate Poisson regression model for incidence of small intestine cancer for Pre-Cervarix launch (Year 1992 – Year 2008) - Netherlands

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	269419461	1687	1.039	1.029	1.049	<.0001	3.89

N = overall population at risk
n = total number of small intestine cancer cases reported
Model is calculated by log(No. of small intestine cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of small intestine cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.2.9.2 Univariate Poisson regression model for incidence of small intestine cancer for Post-Cervarix launch (Year 2009 – Year 2020) - Netherlands

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	202887972	2498	1.036	1.022	1.050	<.0001	3.60

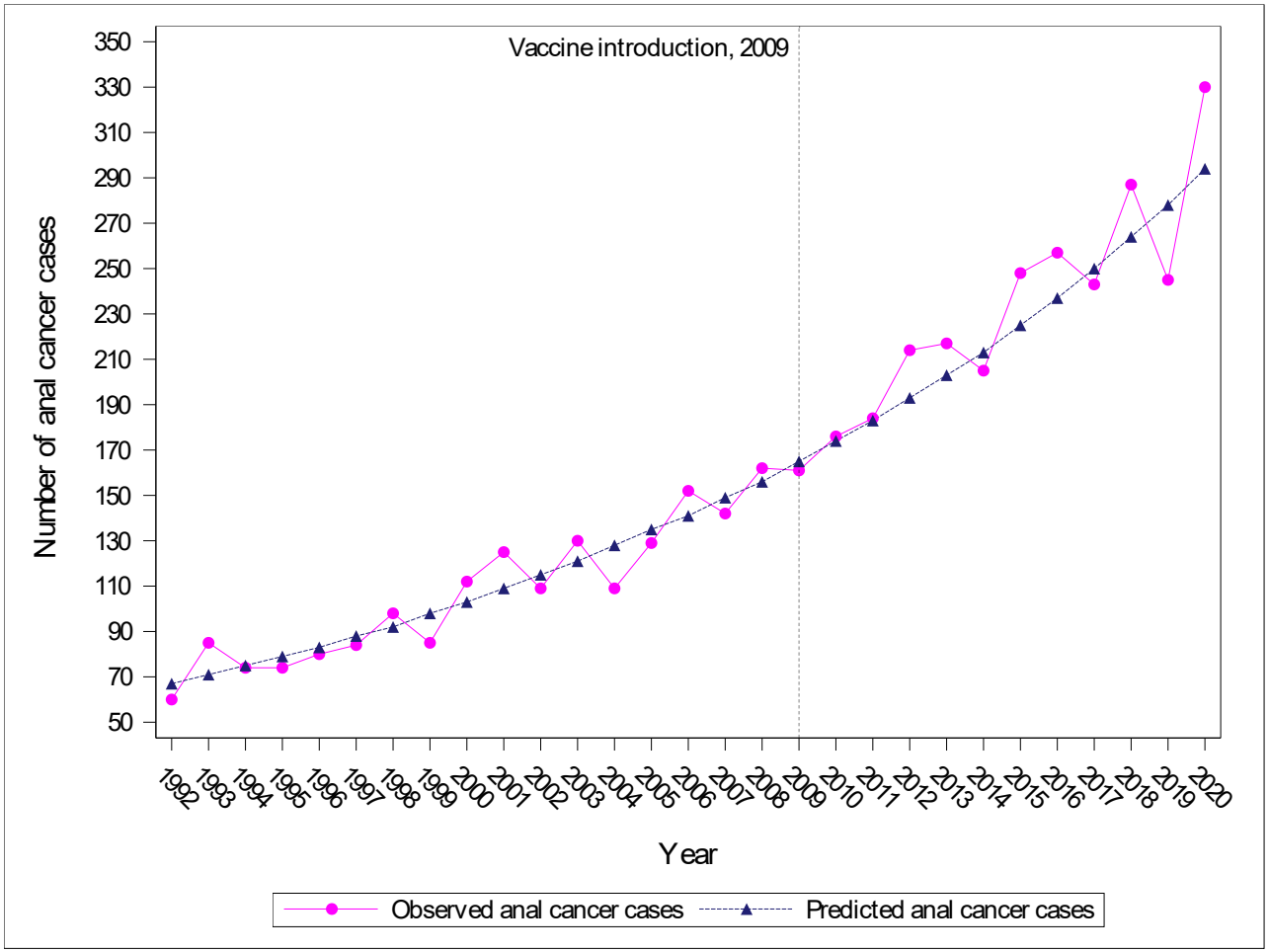
N = overall population at risk
n = total number of small intestine cancer cases reported
Model is calculated by log(No. of small intestine cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of small intestine cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.2.10 Trend overtime of anal cancer cases by observed counts versus predicted counts - Netherlands

					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	60	67	7	10.45	-26.87	36.79
1993	85	71	-14	-19.72	-64.06	12.64
1994	74	75	1	1.33	-36.03	28.43
1995	74	79	5	6.33	-28.62	31.78
1996	80	83	3	3.61	-31.03	29.1
1997	84	88	4	4.55	-28.72	29.21
1998	98	92	-6	-6.52	-41.58	19.86
1999	85	98	13	13.27	-15.97	35.13
2000	112	103	-9	-8.74	-42.1	16.79
2001	125	109	-16	-14.68	-48.26	11.3
2002	109	115	6	5.22	-23.17	27.06
2003	130	121	-9	-7.44	-37.62	16.12
2004	109	128	19	14.84	-9.94	34.04
2005	129	135	6	4.44	-21.64	24.93
2006	152	141	-11	-7.8	-35.57	14.28
2007	142	149	7	4.7	-19.93	24.27
2008	162	156	-6	-3.85	-29.38	16.65
2009	161	165	4	2.42	-21.24	21.47
2010	176	174	-2	-1.15	-24.73	17.97
2011	184	183	-1	-0.55	-23.38	18.06
2012	214	193	-21	-10.88	-34.7	8.72
2013	217	203	-14	-6.9	-29.44	11.72
2014	205	213	8	3.76	-16.59	20.55
2015	248	225	-23	-10.22	-32.02	7.98
2016	257	237	-20	-8.44	-29.37	9.11
2017	243	250	7	2.8	-15.97	18.53
2018	287	264	-23	-8.71	-28.49	8.02
2019	245	278	33	11.87	-4.64	25.78
2020	330	294	-36	-12.24	-31.35	4.08

Note:Poisson model has been used to predict the counts using the pre-vaccination period from 1992-Most recent available year's data
Model is calculated by, log(No. of anal cancer cases) = log (Population at risk) + intercept + (β × calendar year)
%Reduction = ((predicted counts –observed counts)/ predicted counts)×100
Wald's 95% CI and %reduction was estimated using Poisson model for non-zero observed counts
*Positive sign indicates the reduction and negative sign indicates the increase in observed counts

Figure 14.2.2.10.1 Predicted and observed counts of anal cancer cases - Netherlands



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Table 14.2.2.11 Trend overtime of anal cancer cases by observed counts versus predicted counts, by age category - Netherlands

30-39 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	2	2	0	0	-609.91	85.91
1993	3	2	-1	-50	-797.69	74.94
1994	3	2	-1	-50	-797.69	74.94
1995	2	3	1	33.33	-298.98	88.86
1996	2	3	1	33.33	-298.98	88.86
1997	3	3	0	0	-395.45	79.82
1998	3	3	0	0	-395.45	79.82
1999	0	4	4	-	-	-
2000	5	4	-1	-25	-365.49	66.43
2001	5	4	-1	-25	-365.49	66.43
2002	8	5	-3	-60	-389.08	47.66
2003	9	5	-4	-80	-437.09	39.68
2004	3	5	2	40	-151.06	85.66
2005	4	5	1	20	-197.92	78.52
2006	6	6	0	0	-210.06	67.75
2007	5	6	1	16.67	-173.05	74.57
2008	5	6	1	16.67	-173.05	74.57
2009	6	6	0	0	-210.06	67.75
2010	2	7	5	71.43	-37.53	94.06
2011	4	7	3	42.86	-95.2	83.27
2012	5	7	2	28.57	-125.05	77.33
2013	7	7	0	0	-185.09	64.92
2014	4	8	4	50	-66.04	84.94
2015	4	8	4	50	-66.04	84.94
2016	9	9	0	0	-151.92	60.3
2017	6	10	4	40	-65.09	78.19
2018	8	11	3	27.27	-80.81	70.75
2019	5	12	7	58.33	-18.27	85.32
2020	4	13	9	69.23	5.64	89.97

40-49 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	5	8	3	37.5	-91.05	79.55
1993	7	9	2	22.22	-108.84	71.03
1994	10	10	0	0	-140.25	58.38
1995	9	11	2	18.18	-97.44	66.1
1996	12	11	-1	-9.09	-147.23	51.86
1997	18	12	-6	-50	-211.4	27.75
1998	15	13	-2	-15.38	-142.49	45.1
1999	21	13	-8	-61.54	-222.6	19.11
2000	11	14	3	21.43	-73.07	64.33
2001	14	16	2	12.5	-79.27	57.29
2002	19	17	-2	-11.76	-115.02	41.91
2003	13	18	5	27.78	-47.4	64.61
2004	19	19	0	0	-88.87	47.05
2005	21	21	0	0	-83.1	45.38
2006	16	22	6	27.27	-38.48	61.8
2007	29	24	-5	-20.83	-107.53	29.64
2008	24	25	1	4	-68.08	45.17
2009	27	27	0	0	-70.48	41.34
2010	22	28	6	21.43	-37.33	55.05
2011	23	30	7	23.33	-31.98	55.47
2012	31	32	1	3.13	-58.75	40.88
2013	23	34	11	32.35	-14.83	60.15
2014	25	35	10	28.57	-19.34	57.25
2015	29	36	7	19.44	-31.37	50.6
2016	21	38	17	44.74	5.84	67.57
2017	17	39	22	56.41	22.95	75.34
2018	21	41	20	48.78	13.33	69.73
2019	16	42	26	61.9	32.25	78.58
2020	25	44	19	43.18	7.17	65.22

50-59 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	7	9	2	22.22	-108.84	71.03
1993	15	9	-6	-66.67	-280.84	27.06
1994	10	10	0	0	-140.25	58.38
1995	7	12	5	41.67	-48.16	77.03
1996	17	13	-4	-30.77	-169.23	36.48
1997	10	15	5	33.33	-48.39	70.05
1998	20	17	-3	-17.65	-124.58	38.37
1999	9	19	10	52.63	-4.7	78.57
2000	26	21	-5	-23.81	-120.04	30.33
2001	26	24	-2	-8.33	-88.67	37.8
2002	28	26	-2	-7.69	-83.66	36.85
2003	33	29	-4	-13.79	-87.4	30.9
2004	20	32	12	37.5	-9.27	64.25
2005	38	35	-3	-8.57	-71.84	31.4
2006	50	39	-11	-28.21	-94.87	15.66
2007	40	42	2	4.76	-46.85	38.23
2008	40	45	5	11.11	-36.09	41.94
2009	47	49	2	4.08	-43.12	35.71
2010	47	53	6	11.32	-31.33	40.12
2011	49	59	10	16.95	-21.3	43.14
2012	55	64	9	14.06	-23.22	40.07
2013	58	71	13	18.31	-15.56	42.25
2014	49	78	29	37.18	10.2	56.05
2015	58	85	27	31.76	4.73	51.13
2016	75	94	19	20.21	-8.07	41.1
2017	47	103	56	54.37	35.57	67.68
2018	63	112	49	43.75	23.41	58.69
2019	46	122	76	62.3	47.07	73.14
2020	72	134	62	46.27	28.45	59.65

60-69 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	17	16	-1	-6.25	-110.29	46.32
1993	24	16	-8	-50	-182.37	20.32
1994	10	17	7	41.18	-28.46	73.06
1995	16	18	2	11.11	-74.31	54.67
1996	16	18	2	11.11	-74.31	54.67
1997	17	19	2	10.53	-72.13	53.49
1998	21	20	-1	-5	-93.7	43.08
1999	21	21	0	0	-83.1	45.38
2000	26	22	-4	-18.18	-108.51	33.02
2001	25	23	-2	-8.7	-91.49	38.3
2002	22	25	3	12	-56.07	50.38
2003	30	26	-4	-15.38	-95.08	31.75
2004	25	28	3	10.71	-53.11	47.93
2005	29	30	1	3.33	-61.04	41.98
2006	35	31	-4	-12.9	-83.08	30.37
2007	25	35	10	28.57	-19.34	57.25
2008	44	38	-6	-15.79	-78.72	24.98
2009	43	41	-2	-4.88	-60.87	31.63
2010	46	44	-2	-4.55	-58.05	30.85
2011	53	47	-6	-12.77	-67	23.86
2012	60	50	-10	-20	-74.65	17.55
2013	64	53	-11	-20.75	-73.78	16.09
2014	58	56	-2	-3.57	-49.52	28.26
2015	84	59	-25	-42.37	-98.62	-2.06
2016	79	63	-16	-25.4	-74.61	9.94
2017	77	65	-12	-18.46	-64.8	14.85
2018	100	67	-33	-49.25	-103.38	-9.53
2019	78	70	-8	-11.43	-53.86	19.3
2020	91	74	-17	-22.97	-67.13	9.52

70-79 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	15	20	5	25	-46.49	61.6
1993	19	20	1	5	-78	49.3
1994	20	20	0	0	-85.85	46.19
1995	27	21	-6	-28.57	-127.41	27.31
1996	18	21	3	14.29	-60.87	54.33
1997	23	21	-2	-9.52	-97.89	39.38
1998	23	22	-1	-4.55	-87.56	41.73
1999	16	22	6	27.27	-38.48	61.8
2000	22	22	0	0	-80.57	44.62
2001	34	23	-11	-47.83	-150.93	12.92
2002	18	23	5	21.74	-45.02	57.76
2003	28	23	-5	-21.74	-111.33	29.87
2004	26	23	-3	-13.04	-98.11	35.5
2005	21	23	2	8.7	-64.97	49.47
2006	21	24	3	12.5	-57.16	51.28
2007	20	24	4	16.67	-50.85	53.96
2008	25	24	-1	-4.17	-82.38	40.51
2009	22	25	3	12	-56.07	50.38
2010	36	25	-11	-44	-139.86	13.55
2011	30	26	-4	-15.38	-95.08	31.75
2012	34	26	-8	-30.77	-117.9	21.52
2013	42	27	-15	-55.56	-152.26	4.08
2014	44	28	-16	-57.14	-152.39	2.16
2015	53	29	-24	-82.76	-187.4	-16.22
2016	52	30	-22	-73.33	-171.67	-10.59
2017	64	32	-32	-100	-205.72	-30.84
2018	65	34	-31	-91.18	-189.46	-26.26
2019	62	35	-27	-77.14	-168.1	-17.05
2020	78	37	-41	-110.81	-211.75	-42.55

80+ years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	14	14	0	0	-109.76	52.33
1993	17	15	-2	-13.33	-126.93	43.4
1994	19	15	-4	-26.67	-149.27	35.63
1995	13	16	3	18.75	-68.91	60.92
1996	15	16	1	6.25	-89.62	53.65
1997	13	16	3	18.75	-68.91	60.92
1998	16	17	1	5.88	-86.28	52.45
1999	17	17	0	0	-95.87	48.94
2000	22	17	-5	-29.41	-143.69	31.28
2001	20	18	-2	-11.11	-110.04	41.22
2002	14	18	4	22.22	-56.38	61.32
2003	17	19	2	10.53	-72.13	53.49
2004	16	19	3	15.79	-63.75	56.69
2005	16	20	4	20	-54.38	58.54
2006	24	21	-3	-14.29	-105.28	36.37
2007	23	21	-2	-9.52	-97.89	39.38
2008	24	22	-2	-9.09	-94.55	38.83
2009	16	22	6	27.27	-38.48	61.8
2010	23	23	0	0	-78.24	43.9
2011	24	24	0	0	-76.08	43.21
2012	29	25	-4	-16	-98.05	32.06
2013	23	26	3	11.54	-55.03	49.52
2014	24	26	2	7.69	-60.76	47
2015	20	27	7	25.93	-32.07	58.45
2016	19	28	9	32.14	-21.51	62.1
2017	30	28	-2	-7.14	-79.32	35.98
2018	30	29	-1	-3.45	-72.34	37.9
2019	38	30	-8	-26.67	-104.43	21.52
2020	60	31	-29	-93.55	-198.58	-25.46

Note:Poisson model has been used to predict the counts using the pre-vaccination period from 1992-Most recent available year‘s data
Model is calculated by, log(No. of anal cancer cases) = log (Population at risk) + intercept + (β × calendar year)
%Reduction = ((predicted counts –observed counts)/ predicted counts)×100
Wald’s 95% CI and %reduction was estimated using Poisson model for non-zero observed counts
*Positive sign indicates the reduction and negative sign indicates the increase in observed counts
The predicted counts are not estimated for 0-9, 10-19, 20-29 age groups because the number of observed counts for the pre vaccination period is less than 5

Figure 14.2.2.11.1 Predicted and observed counts of anal cancer cases, by 0-9 years - Netherlands

The predicted counts are not estimated for 0-9 age groups because the number of observed counts for the pre vaccination

period is less than 5

Figure 14.2.2.11.2 Predicted and observed counts of anal cancer cases, by 10-19 years - Netherlands

The predicted counts are not estimated for 10-19 age groups because the number of observed counts for the pre vaccination

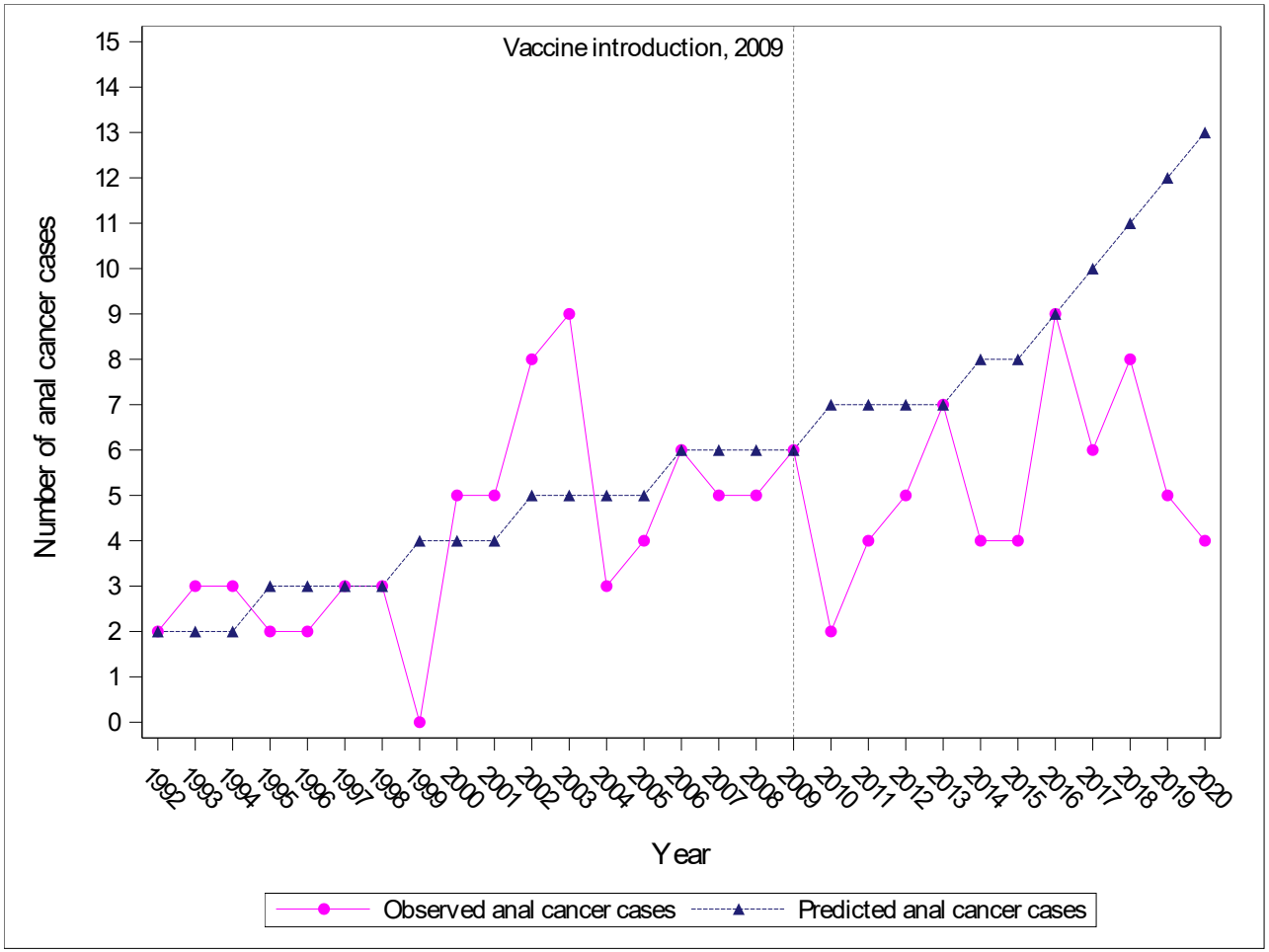
period is less than 5

Figure 14.2.2.11.3 Predicted and observed counts of anal cancer cases, by 20-29 years - Netherlands

The predicted counts are not estimated for 20-29 age groups because the number of observed counts for the pre vaccination

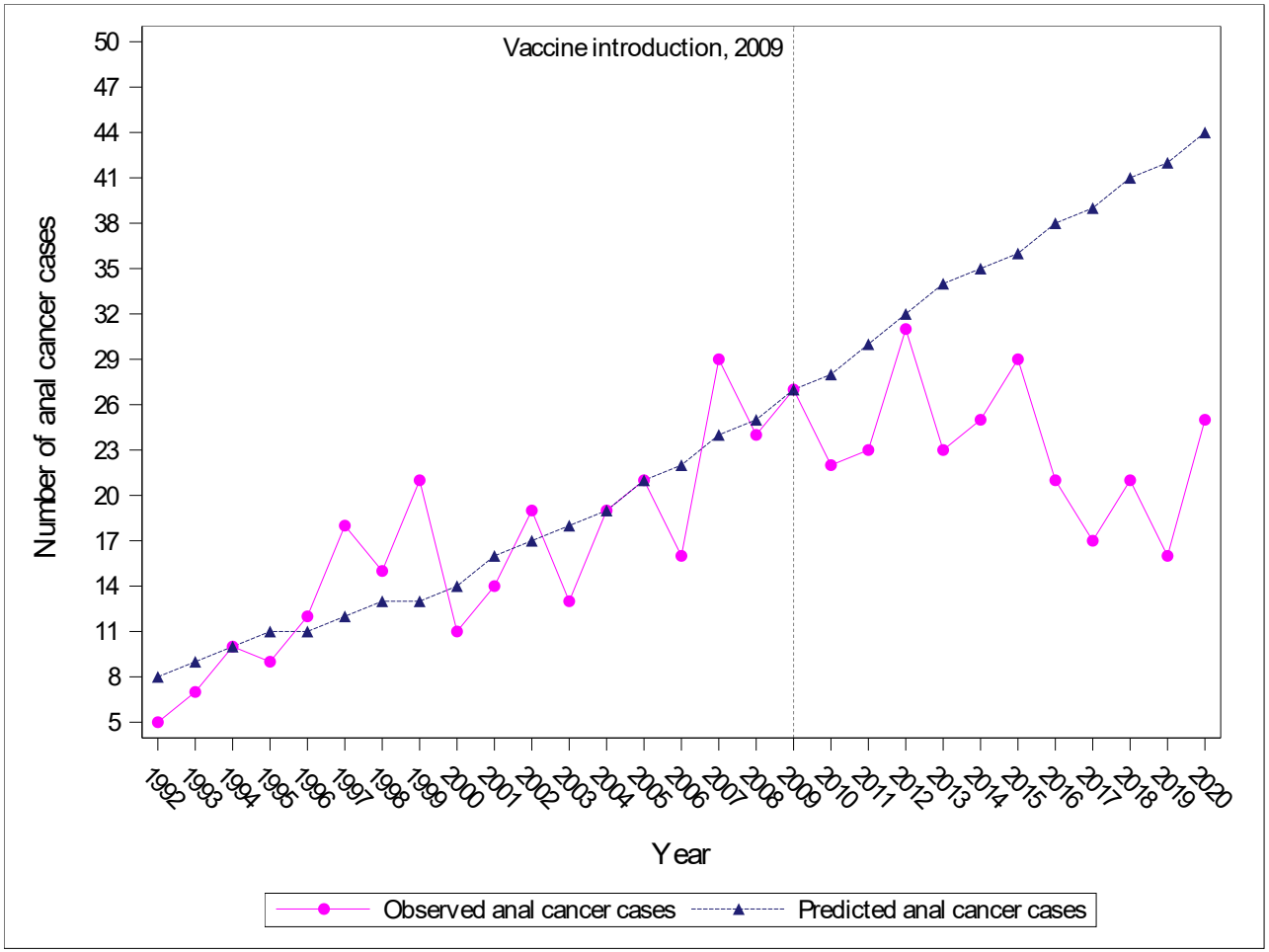
period is less than 5

Figure 14.2.2.11.4 Predicted and observed counts of anal cancer cases, by 30-39 years - Netherlands



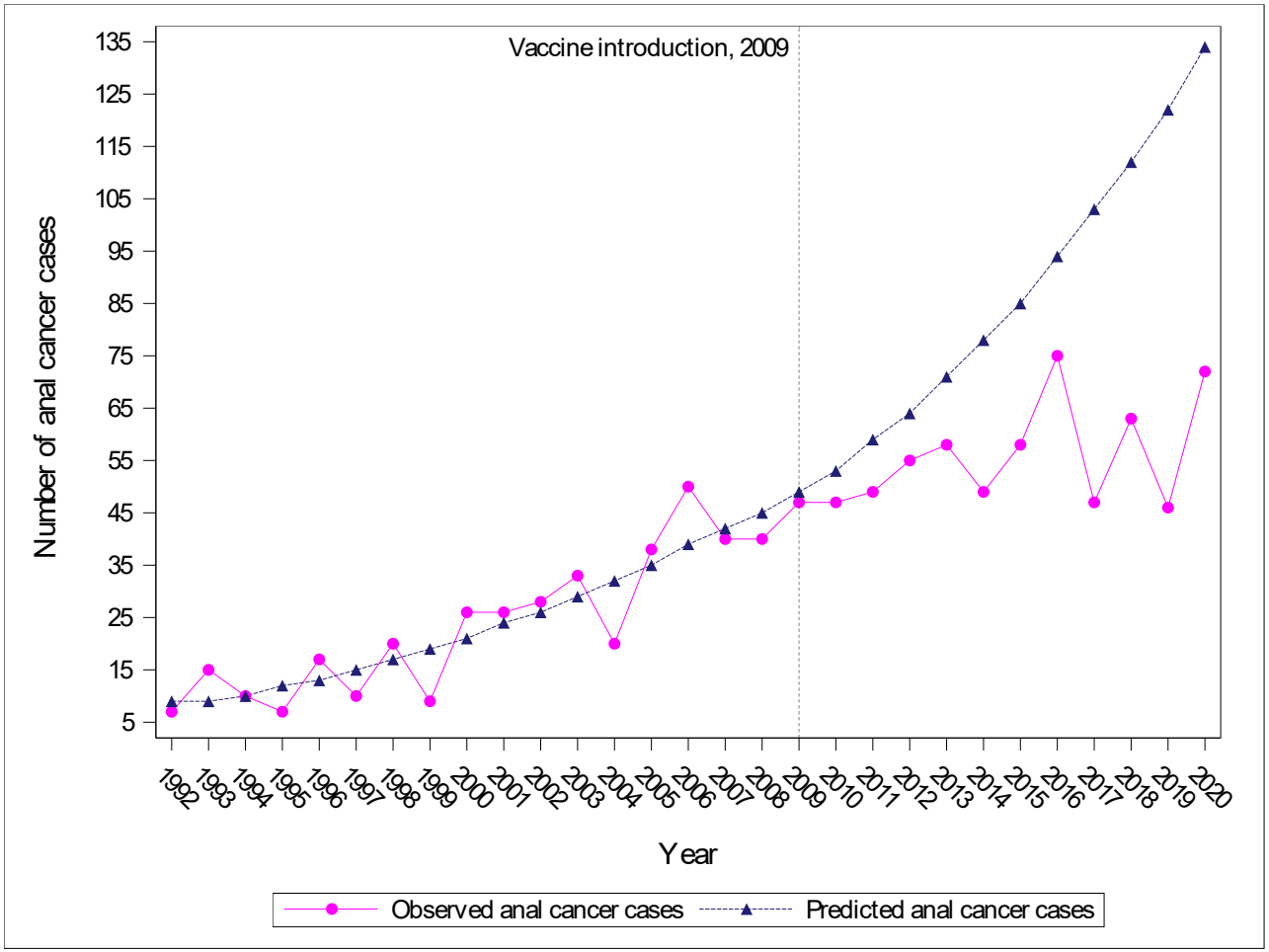
Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.2.11.5 Predicted and observed counts of anal cancer cases, by 40-49 years - Netherlands



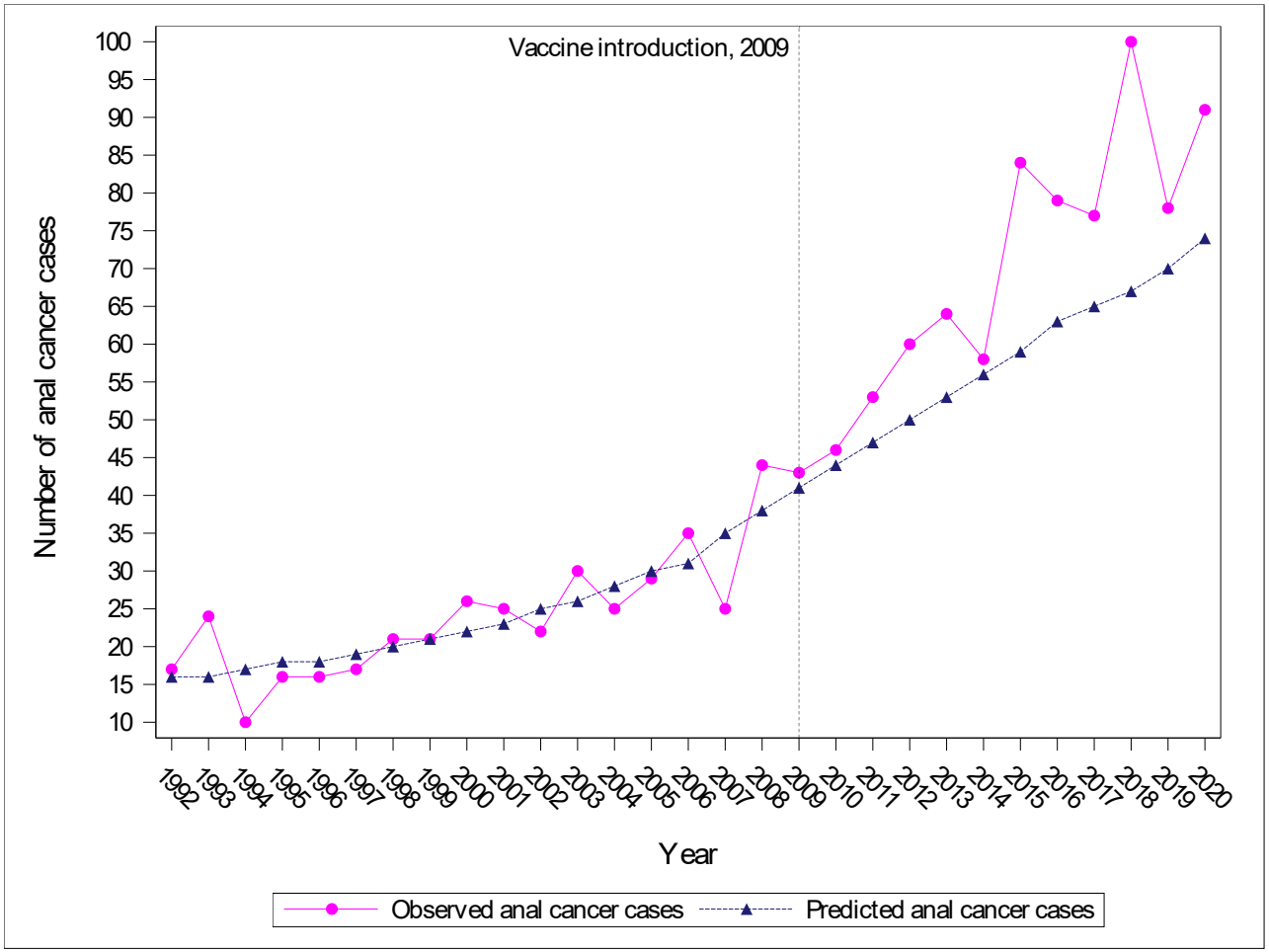
Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.2.11.6 Predicted and observed counts of anal cancer cases, by 50-59 years - Netherlands



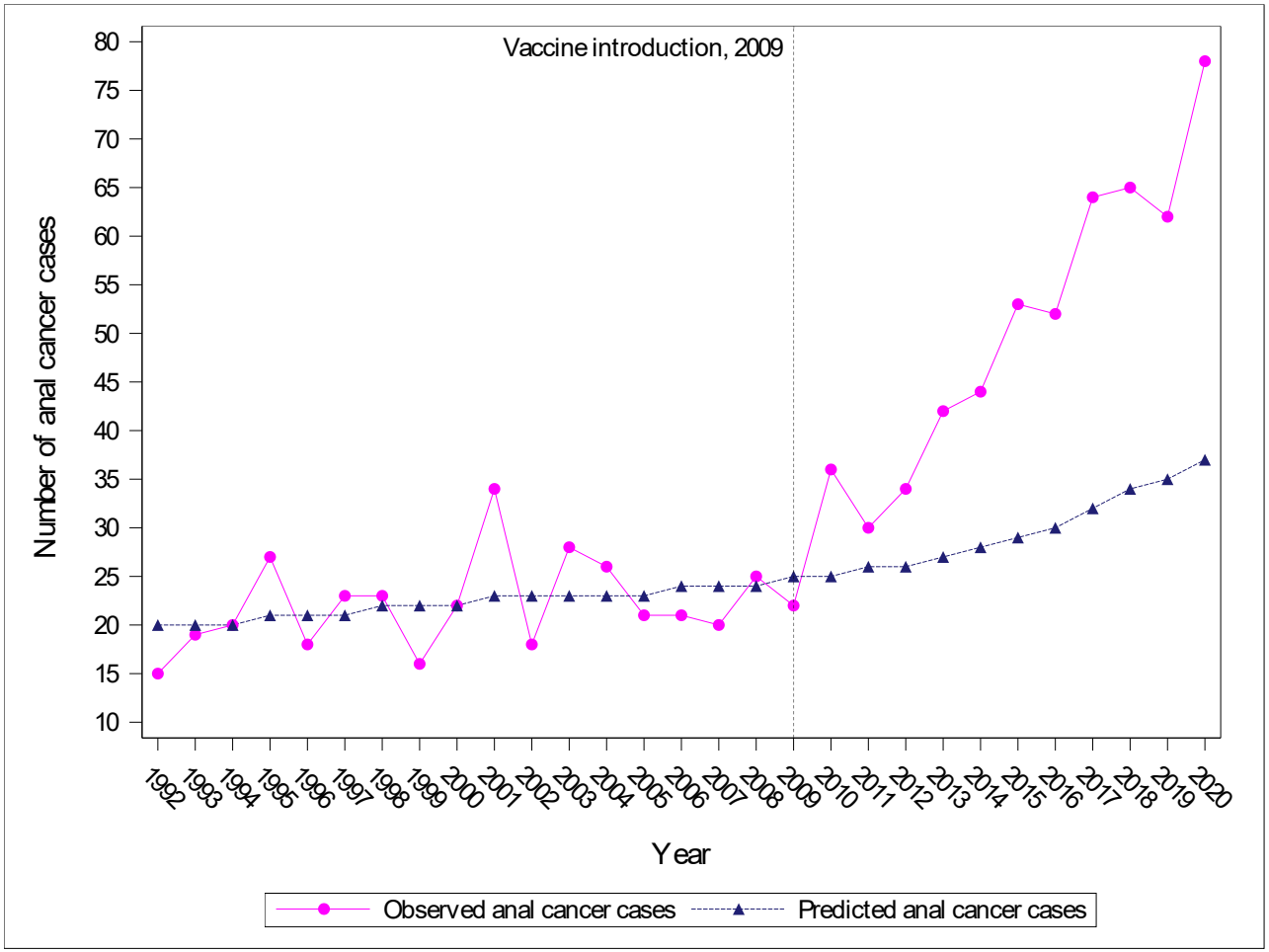
Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.2.11.7 Predicted and observed counts of anal cancer cases, by 60-69 years - Netherlands



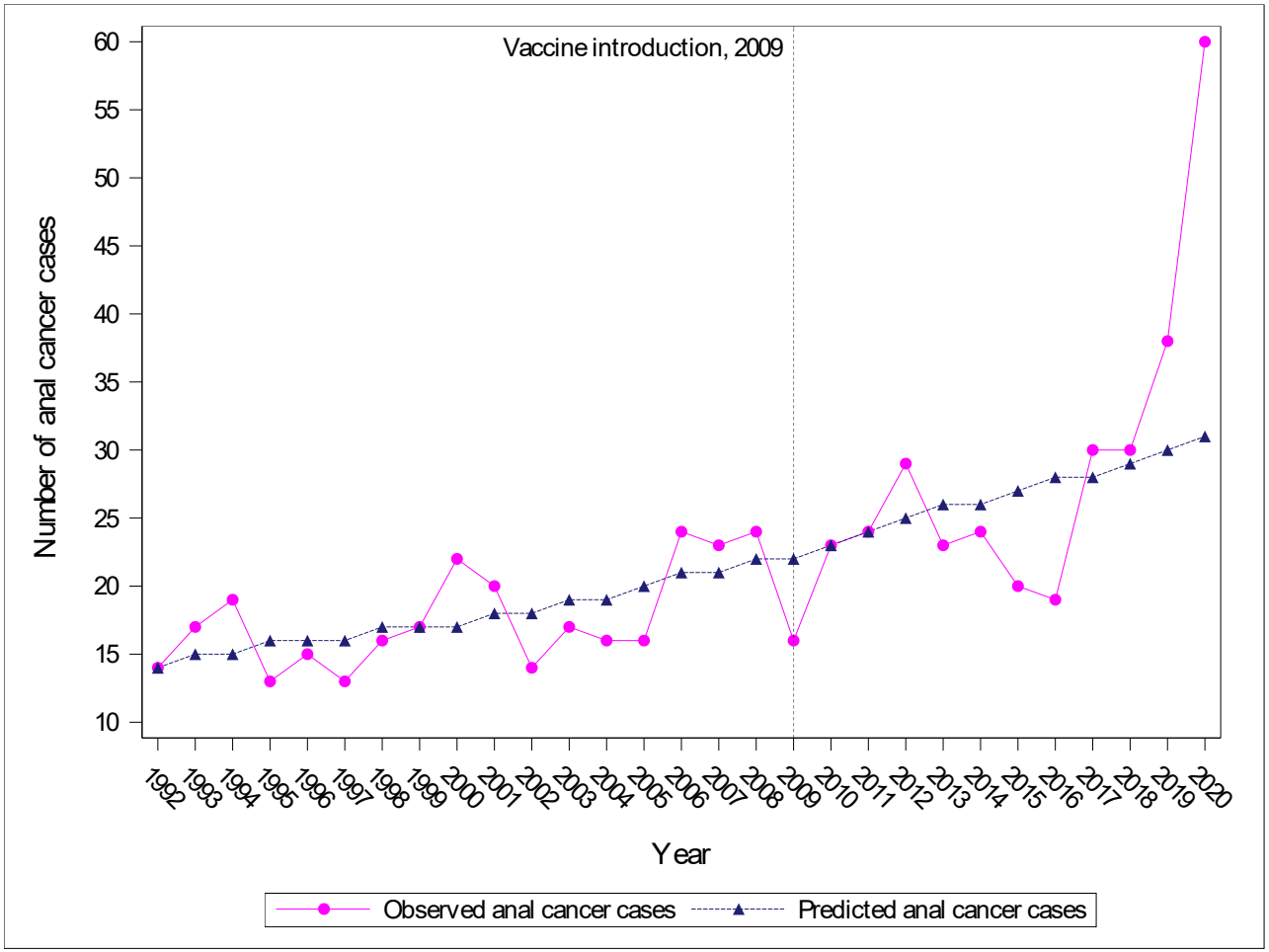
Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.2.11.8 Predicted and observed counts of anal cancer cases, by 70-79 years - Netherlands



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.2.11.9 Predicted and observed counts of anal cancer cases, by 80 years and above - Netherlands



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Table 14.2.2.12 Trend overtime of anal cancer cases by observed counts versus predicted counts, by gender - Netherlands

Male						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	29	26	-3	-11.54	-89.37	34.31
1993	32	28	-4	-14.29	-89.78	31.18
1994	27	30	3	10	-51.37	46.49
1995	33	32	-1	-3.13	-67.71	36.59
1996	28	34	6	17.65	-35.8	50.06
1997	35	36	1	2.78	-54.82	38.95
1998	37	38	1	2.63	-53.11	38.08
1999	36	41	5	12.2	-37.38	43.88
2000	50	44	-6	-13.64	-70.4	24.22
2001	50	47	-3	-6.38	-58.42	28.56
2002	49	50	1	2	-45.32	33.91
2003	62	53	-9	-16.98	-68.79	18.93
2004	52	56	4	7.14	-35.44	36.34
2005	51	60	9	15	-23.46	41.48
2006	67	63	-4	-6.35	-50.01	24.6
2007	61	67	6	8.96	-28.79	35.64
2008	78	71	-7	-9.86	-51.52	20.34
2009	66	76	10	13.16	-20.77	37.55
2010	83	81	-2	-2.47	-39.17	24.55
2011	80	86	6	6.98	-26.13	31.39
2012	101	92	-9	-9.78	-45.62	17.23
2013	109	97	-12	-12.37	-47.73	14.52
2014	94	103	9	8.74	-20.7	31
2015	120	110	-10	-9.09	-41.3	15.78
2016	122	117	-5	-4.27	-34.37	19.08
2017	118	125	7	5.6	-21.4	26.6
2018	136	133	-3	-2.26	-29.86	19.48
2019	111	141	30	21.28	-0.95	38.61
2020	142	151	9	5.96	-18.25	25.22

Female						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	31	41	10	24.39	-20.55	52.58
1993	53	43	-10	-23.26	-84.29	17.57
1994	47	45	-2	-4.44	-57.19	30.6
1995	41	47	6	12.77	-32.61	42.62
1996	52	49	-3	-6.12	-56.78	28.16
1997	49	51	2	3.92	-42.2	35.08
1998	61	54	-7	-12.96	-62.92	21.68
1999	49	57	8	14.04	-25.93	41.32
2000	62	59	-3	-5.08	-50.09	26.43
2001	75	62	-13	-20.97	-69.35	13.59
2002	60	65	5	7.69	-31.11	35.01
2003	68	68	0	0	-39.95	28.55
2004	57	72	15	20.83	-12.06	44.07
2005	78	75	-3	-4	-42.79	24.25
2006	85	78	-7	-8.97	-48.18	19.86
2007	81	82	1	1.22	-34.28	27.33
2008	84	85	1	1.18	-33.6	26.9
2009	95	89	-6	-6.74	-42.53	20.06
2010	93	93	0	0	-33.3	24.98
2011	104	98	-6	-6.12	-39.84	19.47
2012	113	102	-11	-10.78	-44.79	15.23
2013	108	107	-1	-0.93	-31.87	22.74
2014	111	112	1	0.89	-28.86	23.77
2015	128	117	-11	-9.4	-40.57	14.86
2016	135	122	-13	-10.66	-41.35	13.37
2017	125	128	3	2.34	-24.95	23.68
2018	151	134	-17	-12.69	-42.2	10.7
2019	134	140	6	4.29	-21.3	24.47
2020	188	147	-41	-27.89	-58.69	-3.07

Note:Poisson model has been used to predict the counts using the pre-vaccination period from 1992-Most recent available year‘s data

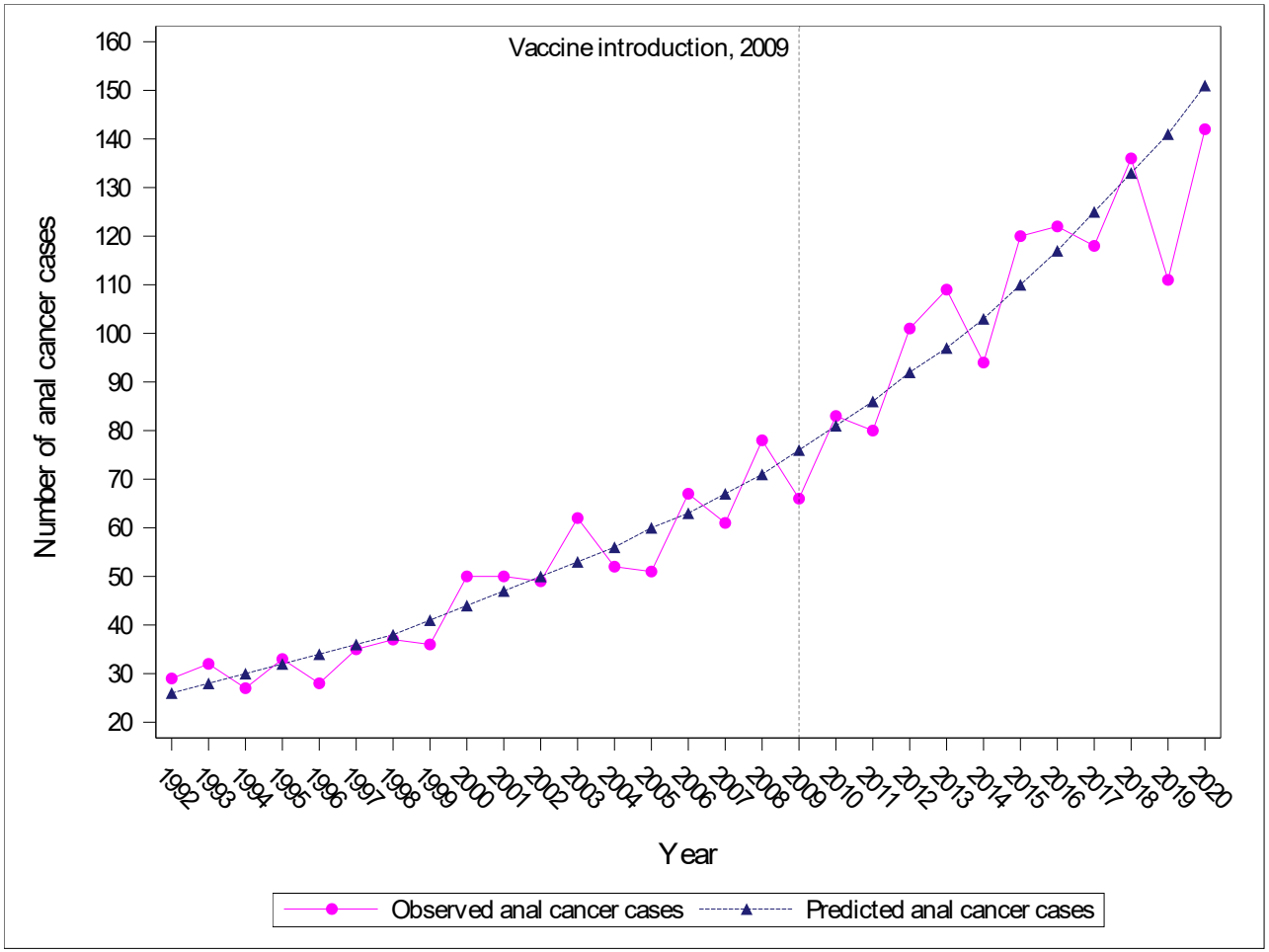
Model is calculated by, log(No. of anal cancer cases) = log (Population at risk) + intercept + (β × calendar year)

%Reduction = ((predicted counts –observed counts)/ predicted counts)×100

Wald’s 95% CI and %reduction was estimated using Poisson model for non-zero observed counts

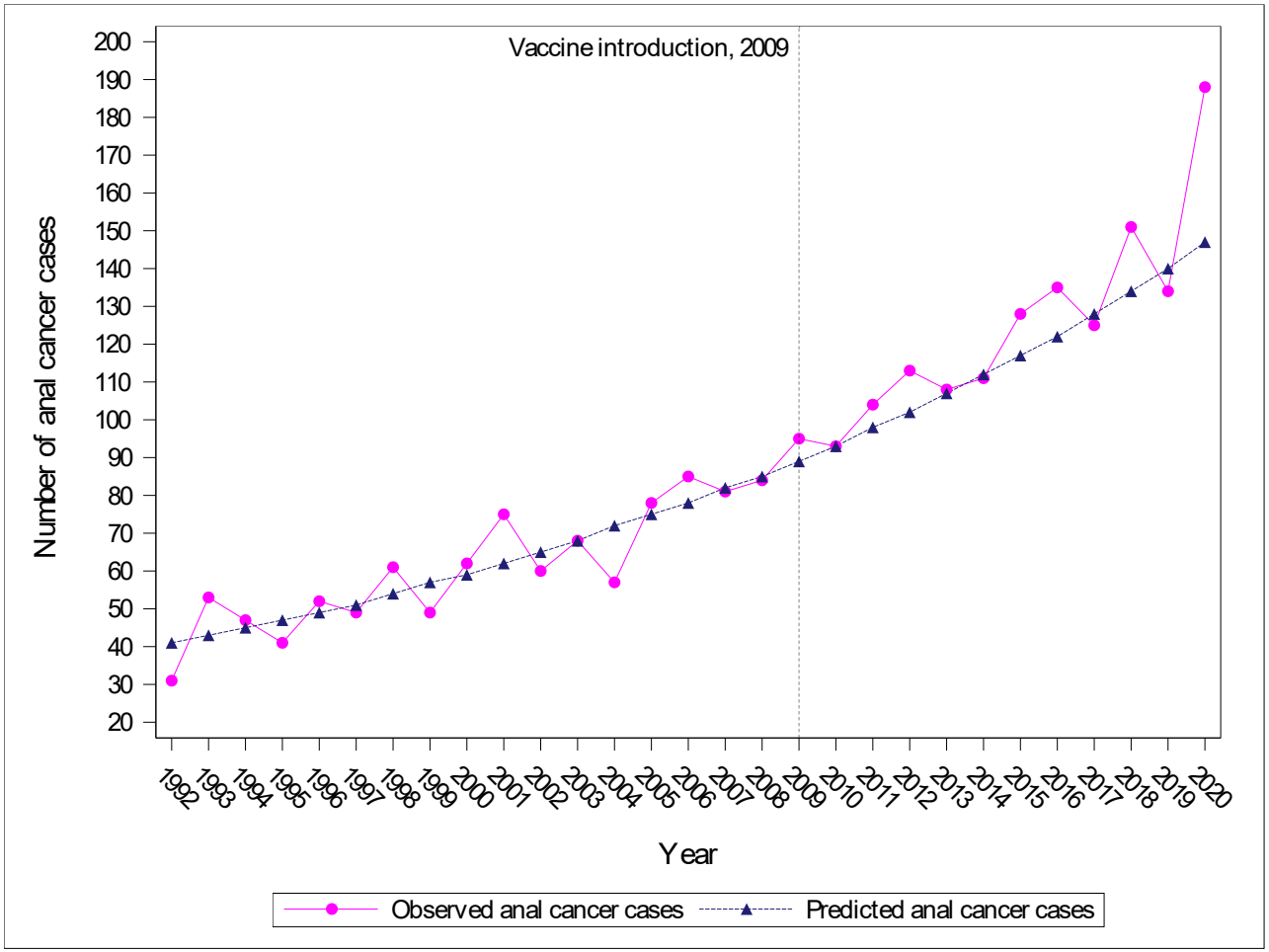
*Positive sign indicates the reduction and negative sign indicates the increase in observed counts

Figure 14.2.2.12.1 Predicted and observed counts of anal cancer cases, by Male - Netherlands



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.2.12.2 Predicted and observed counts of anal cancer cases, by Female - Netherlands



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Table 14.2.2.13 Summary of HPV vaccine coverage in Females by year - Netherlands

Year	HPV vaccine coverage (%)
2009	-
2010	-
2011	-
2012	56.00
2013	58.10
2014	58.90
2015	61.00
2016	61.00
2017	53.40
2018	45.50
2019	45.50
2020	53.00

Note : Vaccine coverage data from 2009 to 2011 is not available as per the Dutch government publication

Table 14.2.2.14 Summary of birth cohort by year and gender - Netherlands

Year	Gender	Birth cohort
2007	Male	92560
	Female	88776
	Total	181336
2008	Male	94838
	Female	89796
	Total	184634
2009	Male	94619
	Female	90296
	Total	184915
2010	Male	94129
	Female	90268
	Total	184397
2011	Male	92353
	Female	87707
	Total	180060
2012	Male	90180
	Female	85779
	Total	175959
2013	Male	87957
	Female	83384
	Total	171341
2014	Male	89510
	Female	85671
	Total	175181
2015	Male	87427
	Female	83083
	Total	170510
2016	Male	88587
	Female	83933
	Total	172520
2017	Male	87159
	Female	82677
	Total	169836
2018	Male	86204
	Female	82321
	Total	168525
2019	Male	86893
	Female	82787
	Total	169680

Table 14.2.2.15 Feasibility assessment: Number of anal cancer cases and time frame predicted for the Vaccine effectiveness - Netherlands

		Case-Control Ratio 1:1		Case-Control Ratio 1:2		Case-Control Ratio 1:3		Case-Control Ratio 1:4	
Vaccine Coverage	Vaccine Effectiveness	Number of cases required	Year	Number of cases required	Year	Number of cases required	Year	Number of cases required	Year
30	30	1019	2069	720	2065	624	2063	577	2062
	40	514	2061	364	2058	317	2057	294	2056
	50	290	2056	208	2053	181	2052	168	2052
	60	176	2052	126	2050	111	2049	103	2048
	70	109	2049	81	2047	70	2046	66	2045
	80	69	2046	52	2044	46	2043	43	2042
	90	42	2043	33	2041	29	2040	27	2040
40	30	867	2067	612	2063	529	2062	489	2061
	40	433	2060	307	2057	265	2056	244	2055
	50	242	2055	173	2052	150	2051	138	2051
	60	144	2051	104	2049	90	2048	83	2047
	70	88	2048	65	2046	56	2045	52	2044
	80	55	2045	40	2043	35	2042	33	2041
	90	33	2042	25	2040	22	2039	21	2039
60	30	820	2067	577	2063	497	2062	456	2061
	40	399	2060	281	2057	242	2056	222	2055
	50	217	2055	153	2052	131	2051	121	2051
	60	126	2052	90	2049	77	2048	70	2047
	70	74	2048	53	2046	46	2045	42	2044
	80	44	2046	31	2043	27	2042	25	2041
	90	25	2042	18	2040	16	2039	14	2039
80	30	1158	2073	811	2068	694	2066	636	2065
	40	549	2065	384	2061	328	2059	299	2059
	50	289	2059	202	2056	172	2055	156	2054
	60	160	2055	112	2052	95	2051	86	2050
	70	90	2052	64	2049	53	2048	48	2047
	80	49	2049	35	2047	30	2045	26	2044
	90	25	2046	17	2043	14	2042	13	2041
90	30	1994	2084	1395	2077	1191	2074	1087	2073

		Case-Control Ratio 1:1		Case-Control Ratio 1:2		Case-Control Ratio 1:3		Case-Control Ratio 1:4	
Vaccine Coverage	**Vaccine Effectiveness**	**Number of cases required**	**Year**	**Number of cases required**	**Year**	**Number of cases required**	**Year**	**Number of cases required**	**Year**
	40	930	2072	649	2067	551	2066	502	2064
	50	480	2066	334	2062	283	2060	257	2059
	60	259	2061	181	2058	152	2056	138	2055
	70	140	2057	98	2054	82	2053	74	2052
	80	73	2054	51	2051	42	2050	38	2049
	90	34	2051	22	2048	18	2046	17	2046

Average female birth cohort for the last 10 years (2010-2019) available data = 84761
Average incidence (per 100000) available from latest 5 years period (2016-2020):
20-29: 0.0566230905
30-39: 0.3104086739
40-49: 0.816750477
50-59: 2.8196085313
60-69: 4.4994609072
70-79: 4.0888311137
80+: 4.0829353095
Year = Year to reach the number of cases required for the completion of case-control study
Life Expectancy of 84 years in Netherlands has been considered as the upper limit of age for the feasibility assessment

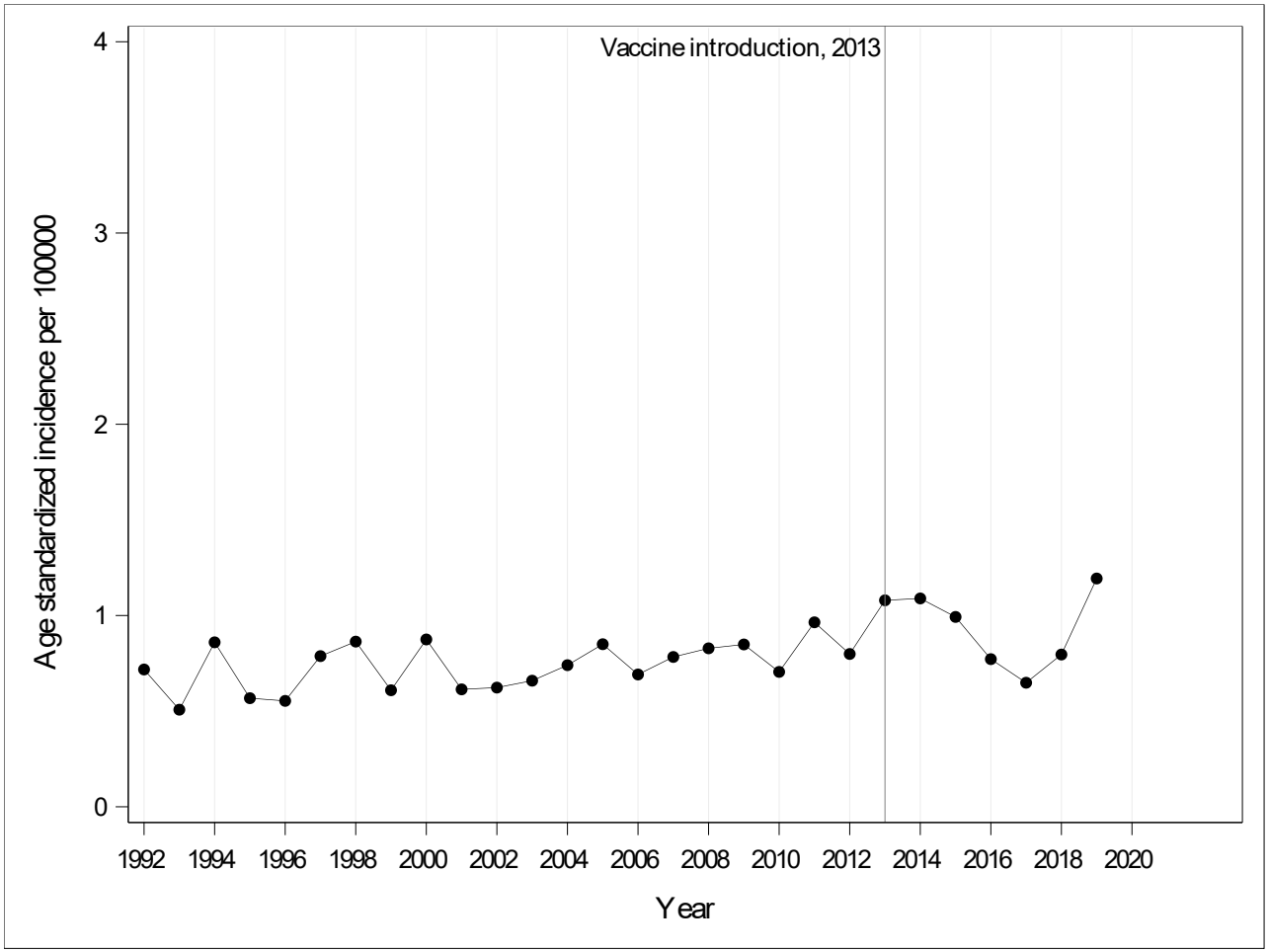
14.2.3 Finland

Table 14.2.3.1 Incidence of anal cancer by calendar year - Finland

			Age standardized Incidence per 100000			Crude Incidence per 100000		
				95% CI			95% CI	
Calendar Year	N	n	Value	LL	UL	Value	LL	UL
1992	5029002	26	0.718	0.362	1.422	0.517	0.338	0.758
1993	5054982	20	0.508	0.215	1.200	0.396	0.242	0.611
1994	5077912	31	0.860	0.472	1.567	0.610	0.415	0.867
1995	5098754	23	0.568	0.248	1.300	0.451	0.286	0.677
1996	5116826	22	0.554	0.247	1.240	0.430	0.269	0.651
1997	5132320	33	0.788	0.391	1.587	0.643	0.443	0.903
1998	5147349	35	0.864	0.454	1.645	0.680	0.474	0.946
1999	5159646	26	0.609	0.280	1.328	0.504	0.329	0.738
2000	5171302	38	0.875	0.457	1.676	0.735	0.520	1.009
2001	5181115	28	0.614	0.278	1.355	0.540	0.359	0.781
2002	5194901	28	0.623	0.296	1.314	0.539	0.358	0.779
2003	5206295	30	0.659	0.308	1.410	0.576	0.389	0.823
2004	5219732	35	0.740	0.354	1.548	0.671	0.467	0.933
2005	5236611	42	0.850	0.424	1.703	0.802	0.578	1.084
2006	5255580	34	0.692	0.326	1.469	0.647	0.448	0.904
2007	5276955	40	0.783	0.377	1.626	0.758	0.542	1.032
2008	5300484	43	0.829	0.406	1.692	0.811	0.587	1.093
2009	5326314	44	0.849	0.426	1.689	0.826	0.600	1.109
2010	5351427	37	0.705	0.335	1.485	0.691	0.487	0.953
2011	5375276	52	0.965	0.507	1.834	0.967	0.722	1.269
2012	5401267	42	0.799	0.385	1.660	0.778	0.560	1.051
2013	5426674	59	1.080	0.587	1.986	1.087	0.828	1.402
2014	5451270	59	1.089	0.591	2.007	1.082	0.824	1.396
2015	5471753	56	0.993	0.535	1.840	1.023	0.773	1.329
2016	5487308	43	0.772	0.382	1.558	0.784	0.567	1.056
2017	5503297	37	0.649	0.301	1.397	0.672	0.473	0.927
2018	5513130	46	0.796	0.383	1.656	0.834	0.611	1.113
2019	5517919	70	1.194	0.661	2.156	1.269	0.989	1.603

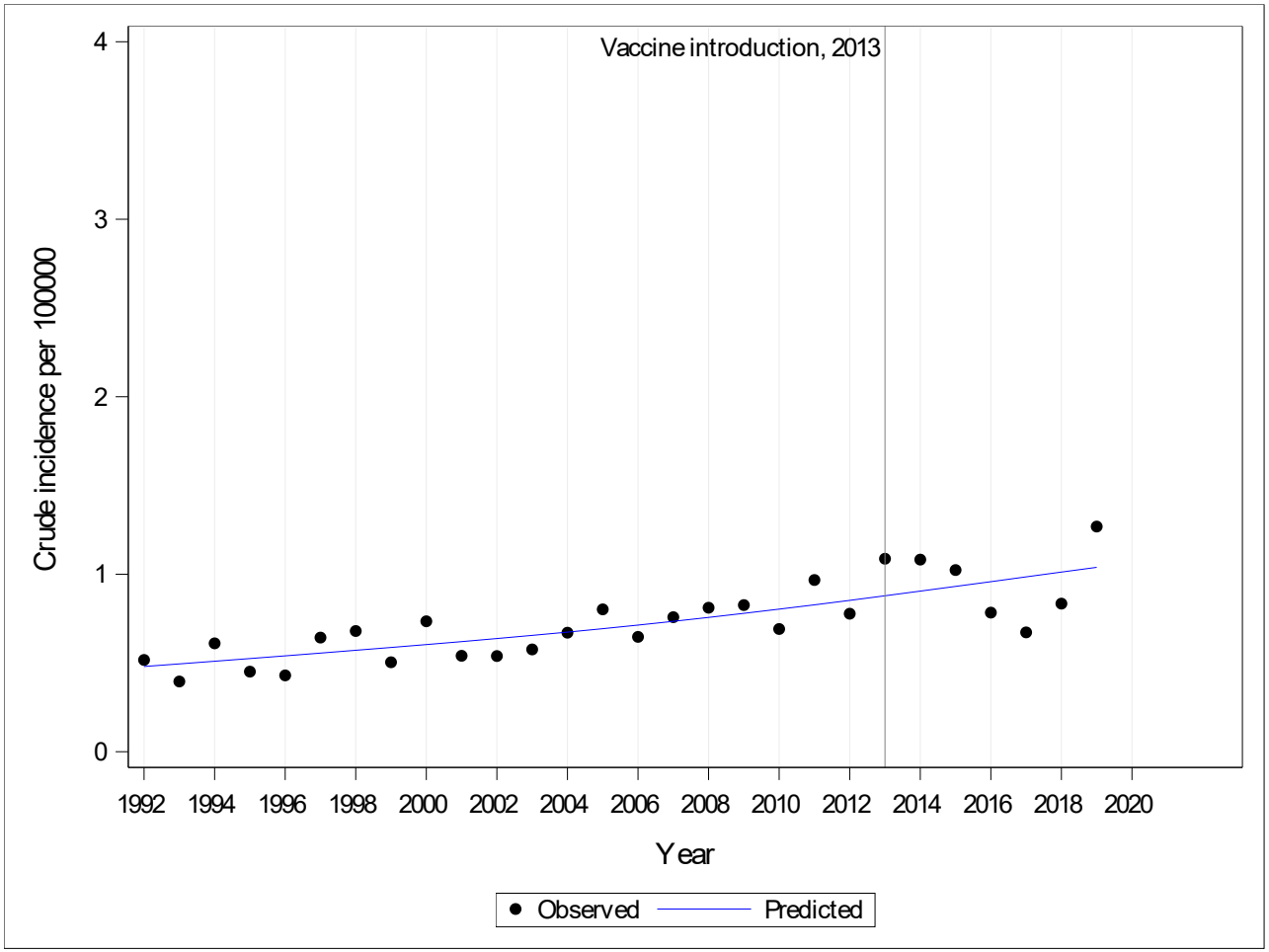
N = population in each category
n = number of anal cancer cases reported
Study period: Pre Cervarix launch (Year 1992 – Year 2012), Post Cervarix launch (Year 2013 – Year 2019)
Age standardized Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))
CI=confidence interval; LL=lower limit; UL=upper limit
Age standardized Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.3.1.1 Trend over time in the age standardized incidence of anal cancer - Finland



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.3.1.2 Trend over time in the crude incidence of anal cancer - Finland



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP
Line - Represents the predicted incidence , Period - Represents the observed Incidence

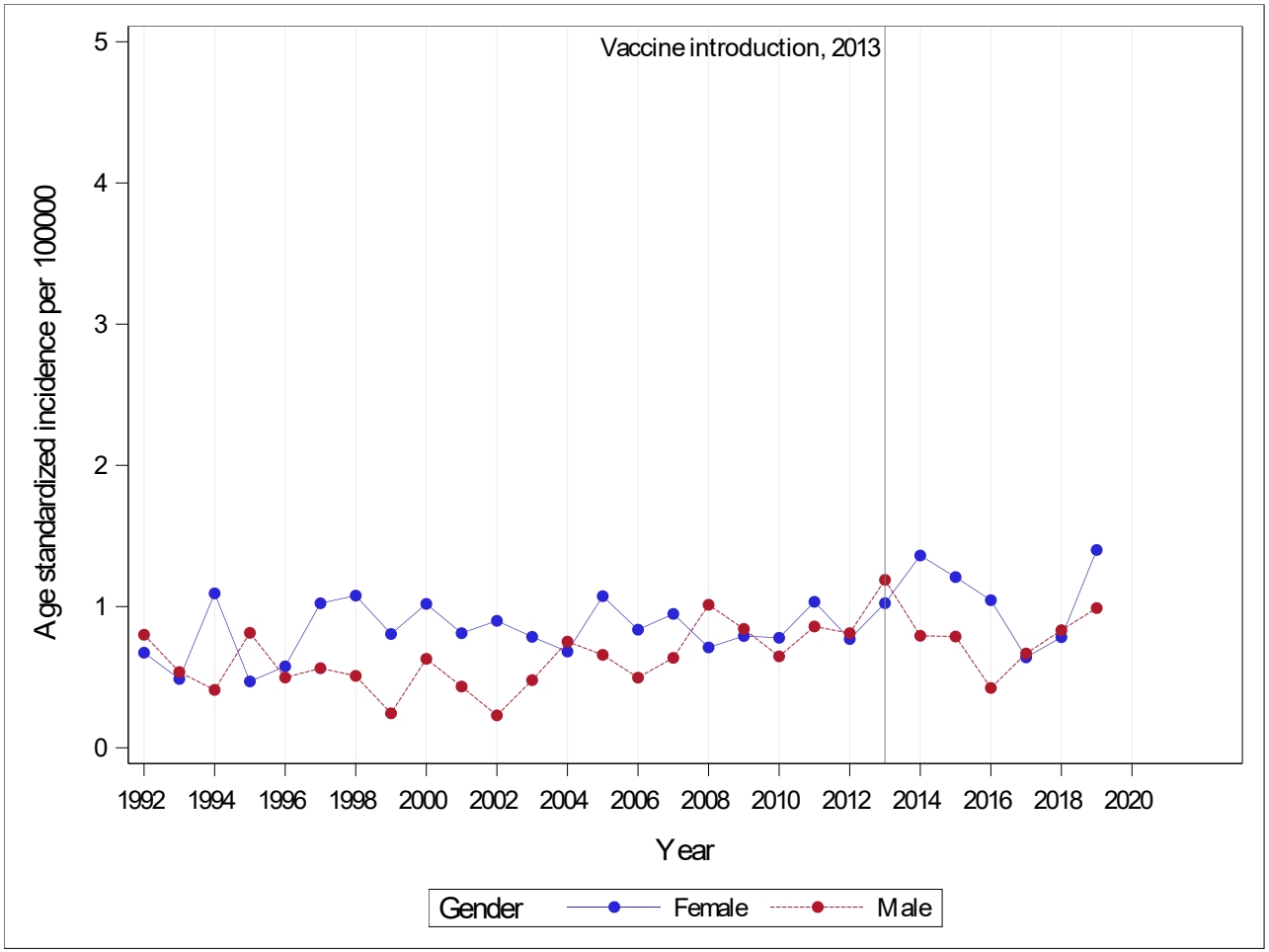
Table 14.2.3.2 Incidence of anal cancer by calendar year and gender - Finland

				Age standardized Incidence per 100000			Crude Incidence per 100000		
					95% CI			95% CI	
Calendar Year	Gender	N	n	Value	LL	UL	Value	LL	UL
1992	Male	2443042	11	0.800	0.421	1.522	0.450	0.225	0.806
	Female	2585960	15	0.673	0.333	1.360	0.580	0.325	0.957
1993	Male	2457282	9	0.536	0.232	1.240	0.366	0.167	0.695
	Female	2597700	11	0.487	0.203	1.168	0.423	0.211	0.758
1994	Male	2470196	6	0.410	0.165	1.016	0.243	0.089	0.529
	Female	2607716	25	1.093	0.639	1.870	0.959	0.620	1.415
1995	Male	2481649	12	0.814	0.426	1.555	0.484	0.250	0.845
	Female	2617105	11	0.470	0.181	1.217	0.420	0.210	0.752
1996	Male	2491701	8	0.497	0.210	1.179	0.321	0.139	0.633
	Female	2625125	14	0.576	0.261	1.271	0.533	0.292	0.895
1997	Male	2500596	8	0.563	0.262	1.210	0.320	0.138	0.630
	Female	2631724	25	1.023	0.541	1.937	0.950	0.615	1.402
1998	Male	2509098	9	0.509	0.212	1.222	0.359	0.164	0.681
	Female	2638251	26	1.078	0.603	1.925	0.986	0.644	1.444
1999	Male	2516075	6	0.244	0.059	1.004	0.238	0.088	0.519
	Female	2643571	20	0.806	0.413	1.571	0.757	0.462	1.168
2000	Male	2523026	12	0.630	0.287	1.382	0.476	0.246	0.831
	Female	2648276	26	1.019	0.559	1.859	0.982	0.641	1.439
2001	Male	2529341	7	0.434	0.187	1.007	0.277	0.111	0.570
	Female	2651774	21	0.812	0.396	1.662	0.792	0.490	1.211
2002	Male	2537597	4	0.229	0.069	0.761	0.158	0.043	0.404
	Female	2657304	24	0.899	0.475	1.703	0.903	0.579	1.344
2003	Male	2544916	10	0.479	0.193	1.186	0.393	0.188	0.723
	Female	2661379	20	0.786	0.391	1.578	0.751	0.459	1.161
2004	Male	2552893	17	0.752	0.351	1.608	0.666	0.388	1.066
	Female	2666839	18	0.681	0.321	1.447	0.675	0.400	1.067
2005	Male	2562077	13	0.658	0.317	1.366	0.507	0.270	0.868
	Female	2674534	29	1.074	0.568	2.030	1.084	0.726	1.557
2006	Male	2572350	11	0.497	0.202	1.224	0.428	0.213	0.765
	Female	2683230	23	0.836	0.421	1.663	0.857	0.543	1.286
2007	Male	2583742	14	0.637	0.293	1.384	0.542	0.296	0.909
	Female	2693213	26	0.948	0.482	1.865	0.965	0.631	1.415
2008	Male	2596787	23	1.013	0.543	1.890	0.886	0.561	1.329
	Female	2703697	20	0.711	0.321	1.571	0.740	0.452	1.142
2009	Male	2611653	21	0.842	0.407	1.738	0.804	0.498	1.229
	Female	2714661	23	0.791	0.396	1.582	0.847	0.537	1.271
2010	Male	2625067	15	0.647	0.302	1.385	0.571	0.320	0.942
	Female	2726360	22	0.779	0.383	1.585	0.807	0.506	1.222
2011	Male	2638416	21	0.859	0.430	1.715	0.796	0.493	1.217
	Female	2736860	31	1.034	0.557	1.919	1.133	0.770	1.608
2012	Male	2652534	20	0.812	0.391	1.685	0.754	0.461	1.164
	Female	2748733	22	0.770	0.366	1.619	0.800	0.502	1.212
2013	Male	2666622	28	1.189	0.675	2.095	1.050	0.698	1.518
	Female	2760052	31	1.024	0.543	1.930	1.123	0.763	1.594
2014	Male	2680364	19	0.793	0.393	1.599	0.709	0.427	1.107
	Female	2770906	40	1.362	0.782	2.370	1.444	1.031	1.966
2015	Male	2691863	19	0.788	0.410	1.514	0.706	0.425	1.102
	Female	2779890	37	1.209	0.679	2.152	1.331	0.937	1.835
2016	Male	2701490	11	0.424	0.169	1.058	0.407	0.203	0.729
	Female	2785818	32	1.045	0.561	1.947	1.149	0.786	1.622

				Age standardized Incidence per 100000			Crude Incidence per 100000		
					95% CI			95% CI	
Calendar Year	**Gender**	**N**	**n**	**Value**	**LL**	**UL**	**Value**	**LL**	**UL**
2017	Male	2712327	17	0.668	0.318	1.400	0.627	0.365	1.004
	Female	2790970	20	0.640	0.292	1.403	0.717	0.438	1.107
2018	Male	2719131	22	0.833	0.415	1.672	0.809	0.507	1.225
	Female	2793999	24	0.783	0.370	1.656	0.859	0.550	1.278
2019	Male	2723290	27	0.989	0.524	1.868	0.991	0.653	1.443
	Female	2794629	43	1.401	0.805	2.437	1.539	1.114	2.073

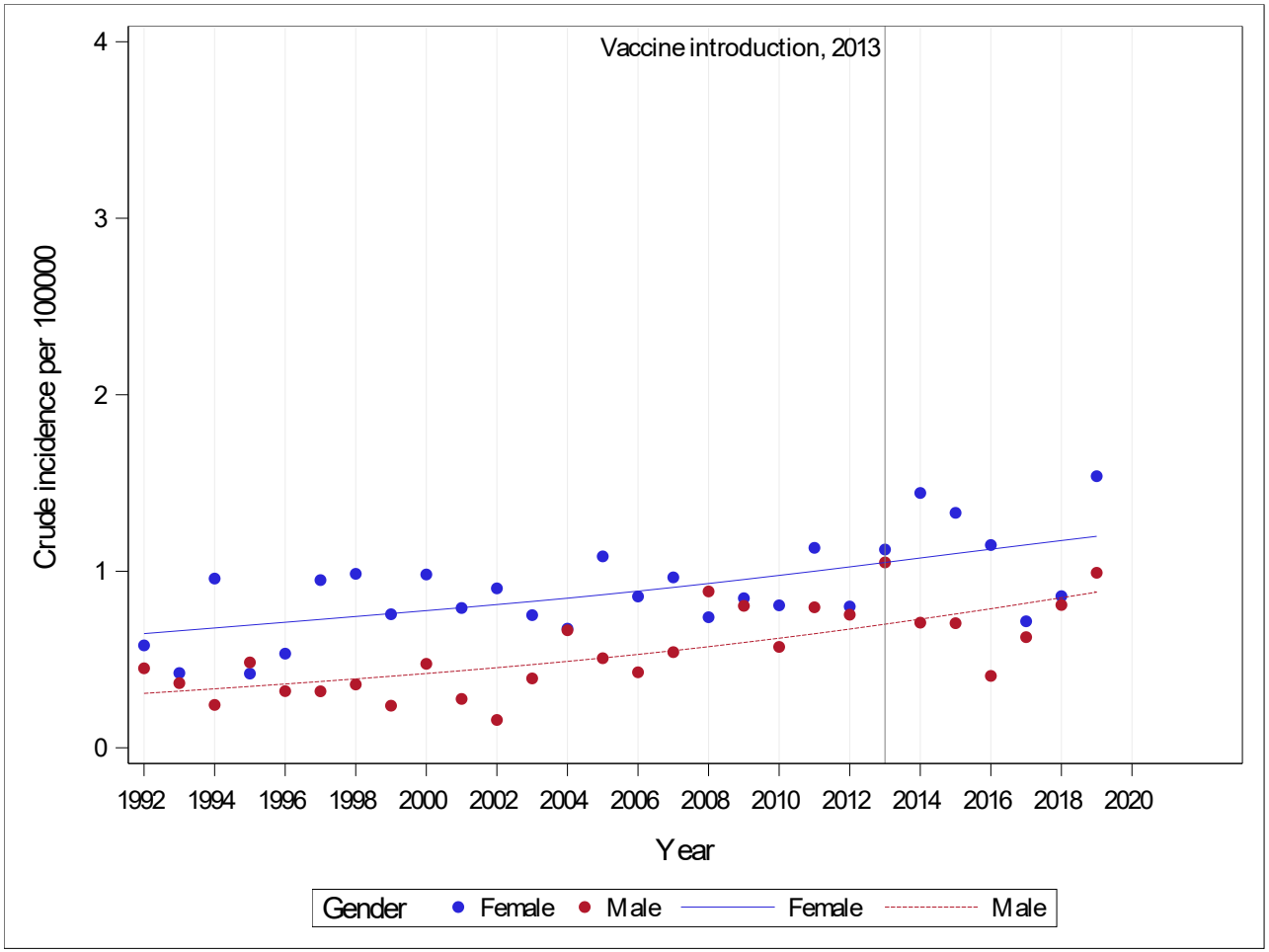
N = population in each category
n = number of anal cancer cases reported
Study period: Pre Cervarix launch (Year 1992 – Year 2012), Post Cervarix launch (Year 2013 – Year 2019)
Age standardized Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))
CI=confidence interval; LL=lower limit; UL=upper limit
Age standardized Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.3.2.1 Trend over time in the age standardized incidence of anal cancer by gender - Finland



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.3.2.2 Trend over time in the crude incidence of anal cancer by gender - Finland



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP
Line - Represents the predicted incidence , Period - Represents the observed Incidence

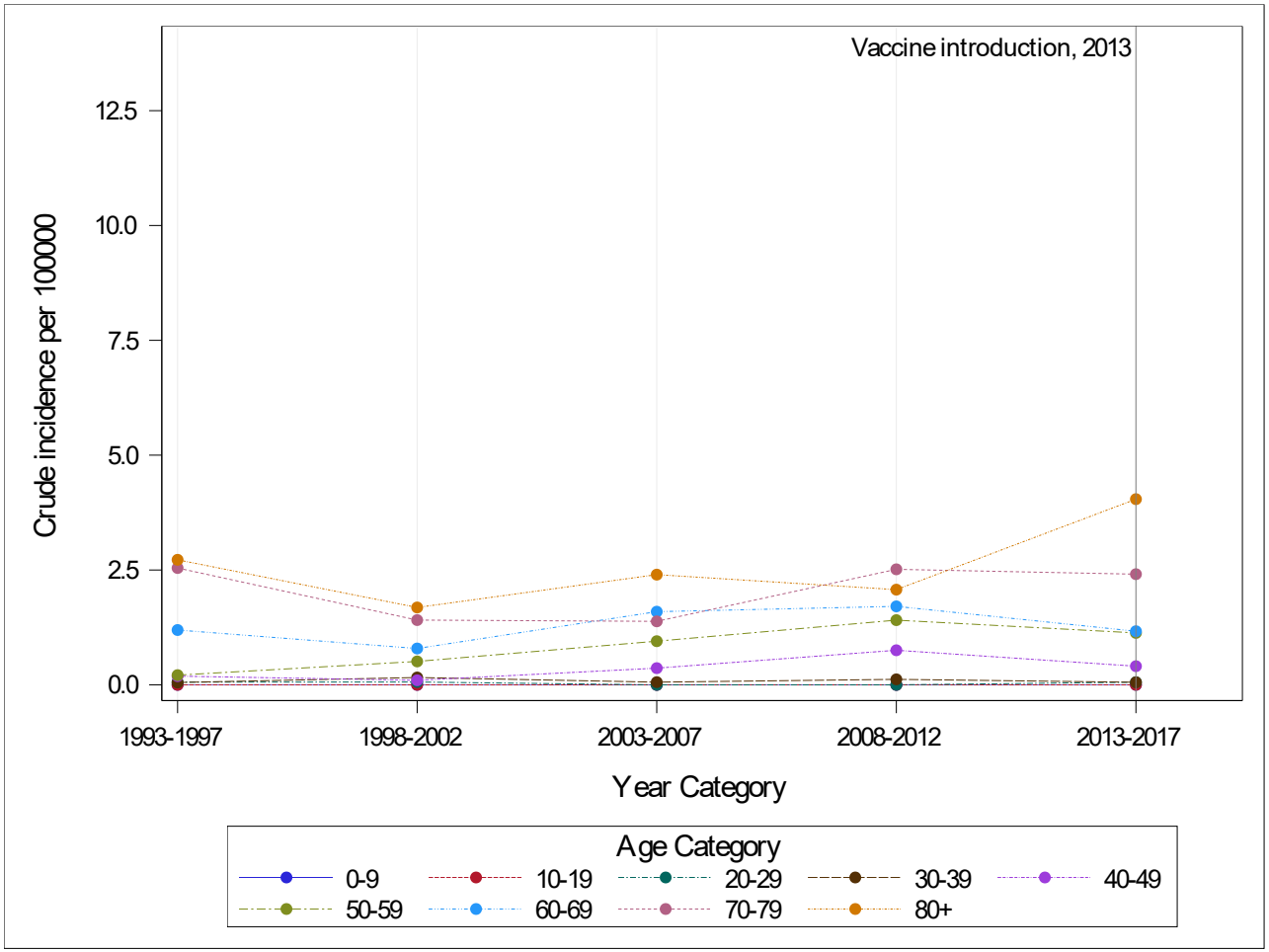
Table 14.2.3.3 Crude incidence of anal cancer for year and age category by gender - Finland

		Male					Female					Total				
					95% CI					95% CI					95% CI	
Year category	Age category (in years)	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL
1993-1997	0-9	1638586	0	0.000	0.000	0.225	1571027	0	0.000	0.000	0.235	3209613	0	0.000	0.000	0.115
	10-19	1669111	0	0.000	0.000	0.221	1595900	0	0.000	0.000	0.231	3265011	0	0.000	0.000	0.113
	20-29	1698826	1	0.059	0.001	0.328	1628026	0	0.000	0.000	0.227	3326852	1	0.030	0.001	0.167
	30-39	1963539	1	0.051	0.001	0.284	1883780	6	0.319	0.117	0.693	3847319	7	0.182	0.073	0.375
	40-49	2113675	4	0.189	0.052	0.485	2034451	6	0.295	0.108	0.642	4148126	10	0.241	0.116	0.443
	50-59	1418449	3	0.211	0.044	0.618	1444230	10	0.692	0.332	1.273	2862679	13	0.454	0.242	0.777
	60-69	1089091	13	1.194	0.636	2.041	1299694	19	1.462	0.880	2.283	2388785	32	1.340	0.916	1.891
	70-79	589735	15	2.544	1.424	4.195	1038601	25	2.407	1.558	3.553	1628336	40	2.456	1.755	3.345
	80+	220412	6	2.722	0.999	5.925	583661	20	3.427	2.093	5.292	804073	26	3.234	2.112	4.738
1998-2002	0-9	1594551	0	0.000	0.000	0.231	1531947	0	0.000	0.000	0.241	3126498	0	0.000	0.000	0.118
	10-19	1660061	0	0.000	0.000	0.222	1587266	0	0.000	0.000	0.232	3247327	0	0.000	0.000	0.114
	20-29	1623542	1	0.062	0.002	0.343	1552243	0	0.000	0.000	0.238	3175785	1	0.031	0.001	0.175
	30-39	1874615	3	0.160	0.033	0.468	1803331	4	0.222	0.060	0.568	3677946	7	0.190	0.077	0.392
	40-49	2013179	2	0.099	0.012	0.359	1958249	12	0.613	0.317	1.070	3971428	14	0.353	0.193	0.591
	50-59	1765432	9	0.510	0.233	0.968	1762388	21	1.192	0.738	1.821	3527820	30	0.850	0.574	1.214
	60-69	1137046	9	0.792	0.362	1.503	1291236	18	1.394	0.826	2.203	2428282	27	1.112	0.733	1.618
	70-79	709224	10	1.410	0.676	2.593	1117857	32	2.863	1.958	4.041	1827081	42	2.299	1.657	3.107
	80+	237487	4	1.684	0.459	4.312	634659	30	4.727	3.189	6.748	872146	34	3.898	2.700	5.448
2003-2007	0-9	1494678	0	0.000	0.000	0.247	1431670	0	0.000	0.000	0.258	2926348	0	0.000	0.000	0.126
	10-19	1659335	0	0.000	0.000	0.222	1591346	0	0.000	0.000	0.232	3250681	0	0.000	0.000	0.113
	20-29	1686842	0	0.000	0.000	0.219	1611047	2	0.124	0.015	0.448	3297889	2	0.061	0.007	0.219
	30-39	1706324	1	0.059	0.001	0.327	1637248	2	0.122	0.015	0.441	3343572	3	0.090	0.019	0.262
	40-49	1925875	7	0.363	0.146	0.749	1880922	14	0.744	0.407	1.249	3806797	21	0.552	0.341	0.843
	50-59	1999443	19	0.950	0.572	1.484	1995835	30	1.503	1.014	2.146	3995278	49	1.226	0.907	1.621
	60-69	1255823	20	1.593	0.973	2.460	1376685	23	1.671	1.059	2.507	2632508	43	1.633	1.182	2.200
	70-79	795898	11	1.382	0.690	2.473	1125581	26	2.310	1.509	3.385	1921479	37	1.926	1.356	2.654
	80+	291760	7	2.399	0.965	4.943	728861	19	2.607	1.569	4.071	1020621	26	2.547	1.664	3.733
2008-2012	0-9	1499145	0	0.000	0.000	0.246	1433513	0	0.000	0.000	0.257	2932658	0	0.000	0.000	0.126
	10-19	1620800	0	0.000	0.000	0.228	1556859	0	0.000	0.000	0.237	3177659	0	0.000	0.000	0.116

		Male					Female					Total				
					95% CI					95% CI					95% CI	
Year category	Age category (in years)	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL
	20-29	1716435	0	0.000	0.000	0.215	1632637	1	0.061	0.002	0.341	3349072	1	0.030	0.001	0.166
	30-39	1670331	2	0.120	0.015	0.433	1586803	1	0.063	0.002	0.351	3257134	3	0.092	0.019	0.269
	40-49	1859727	14	0.753	0.412	1.263	1812946	10	0.552	0.265	1.014	3672673	24	0.653	0.419	0.972
	50-59	1916879	27	1.409	0.928	2.049	1930826	30	1.554	1.048	2.218	3847705	57	1.481	1.122	1.919
	60-69	1580384	27	1.708	1.126	2.486	1684532	30	1.781	1.202	2.542	3264916	57	1.746	1.322	2.262
	70-79	874753	22	2.515	1.576	3.808	1144303	22	1.923	1.205	2.911	2019056	44	2.179	1.583	2.926
	80+	386003	8	2.073	0.895	4.084	847892	24	2.831	1.814	4.212	1233895	32	2.593	1.774	3.661
2013-2017	0-9	1537441	0	0.000	0.000	0.240	1470340	0	0.000	0.000	0.251	3007781	0	0.000	0.000	0.123
	10-19	1536273	0	0.000	0.000	0.240	1469844	0	0.000	0.000	0.251	3006117	0	0.000	0.000	0.123
	20-29	1745667	1	0.057	0.001	0.319	1662465	0	0.000	0.000	0.222	3408132	1	0.029	0.001	0.163
	30-39	1786571	1	0.056	0.001	0.312	1684667	1	0.059	0.002	0.331	3471238	2	0.058	0.007	0.208
	40-49	1723907	7	0.406	0.163	0.837	1667775	16	0.959	0.548	1.558	3391682	23	0.678	0.430	1.018
	50-59	1857739	21	1.130	0.700	1.728	1869050	32	1.712	1.171	2.417	3726789	53	1.422	1.065	1.860
	60-69	1798999	21	1.167	0.723	1.784	1911218	49	2.564	1.897	3.389	3710217	70	1.887	1.471	2.384
	70-79	996070	24	2.409	1.544	3.585	1231597	28	2.273	1.511	3.286	2227667	52	2.334	1.743	3.061
	80+	469999	19	4.043	2.434	6.313	920680	34	3.693	2.557	5.160	1390679	54	3.883	2.917	5.066

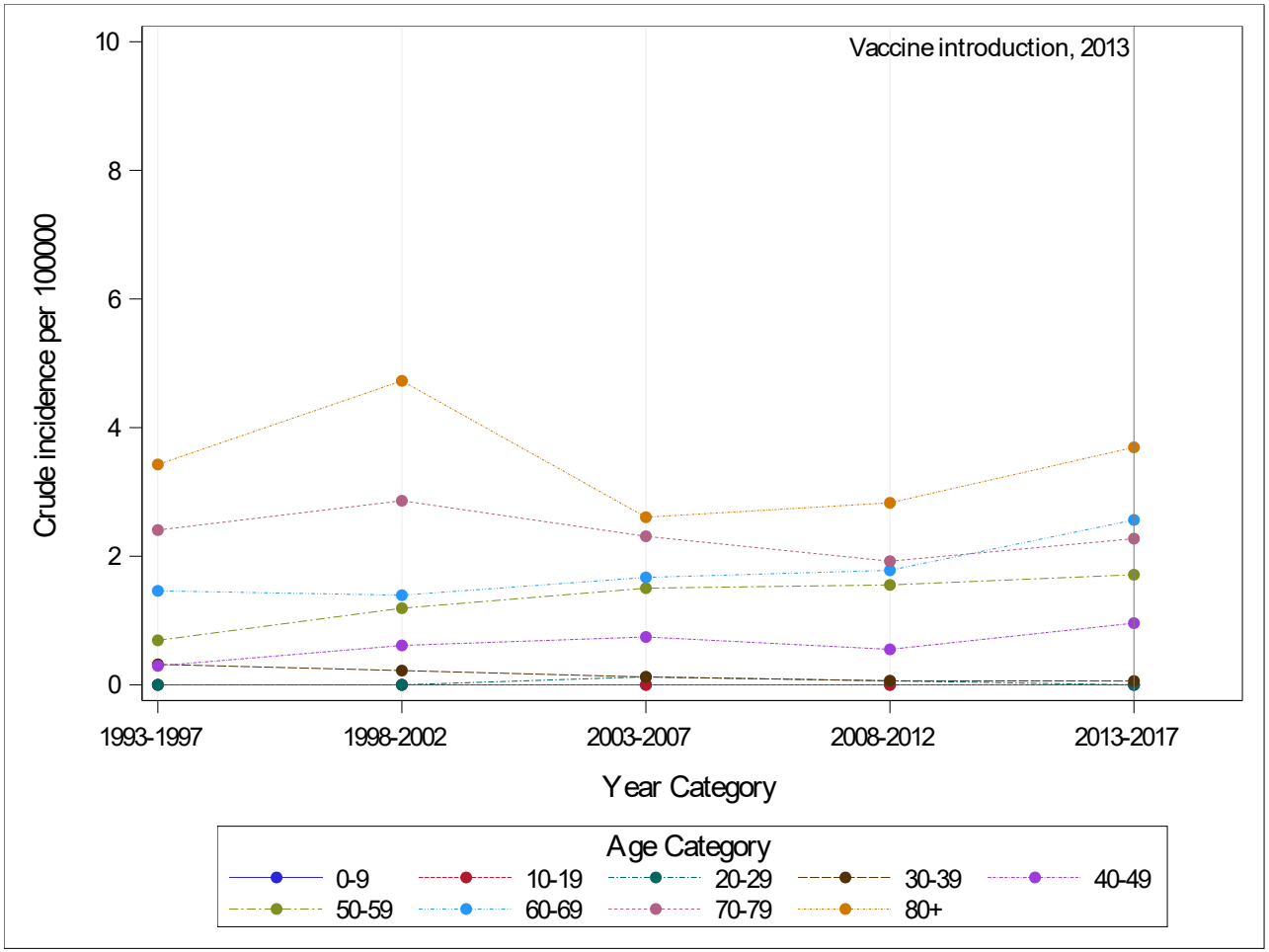
N = population in each category
n = number of anal cancer cases reported in each category
Study period: Pre Cervarix launch (Year 1992 – Year 2012), Post Cervarix launch (Year 2013 – Year 2019)
Crude Incidence per 100000 = (n/N)*100000
95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.3.3.1 Trend over time in the crude incidence of anal cancer by age category for Male - Finland



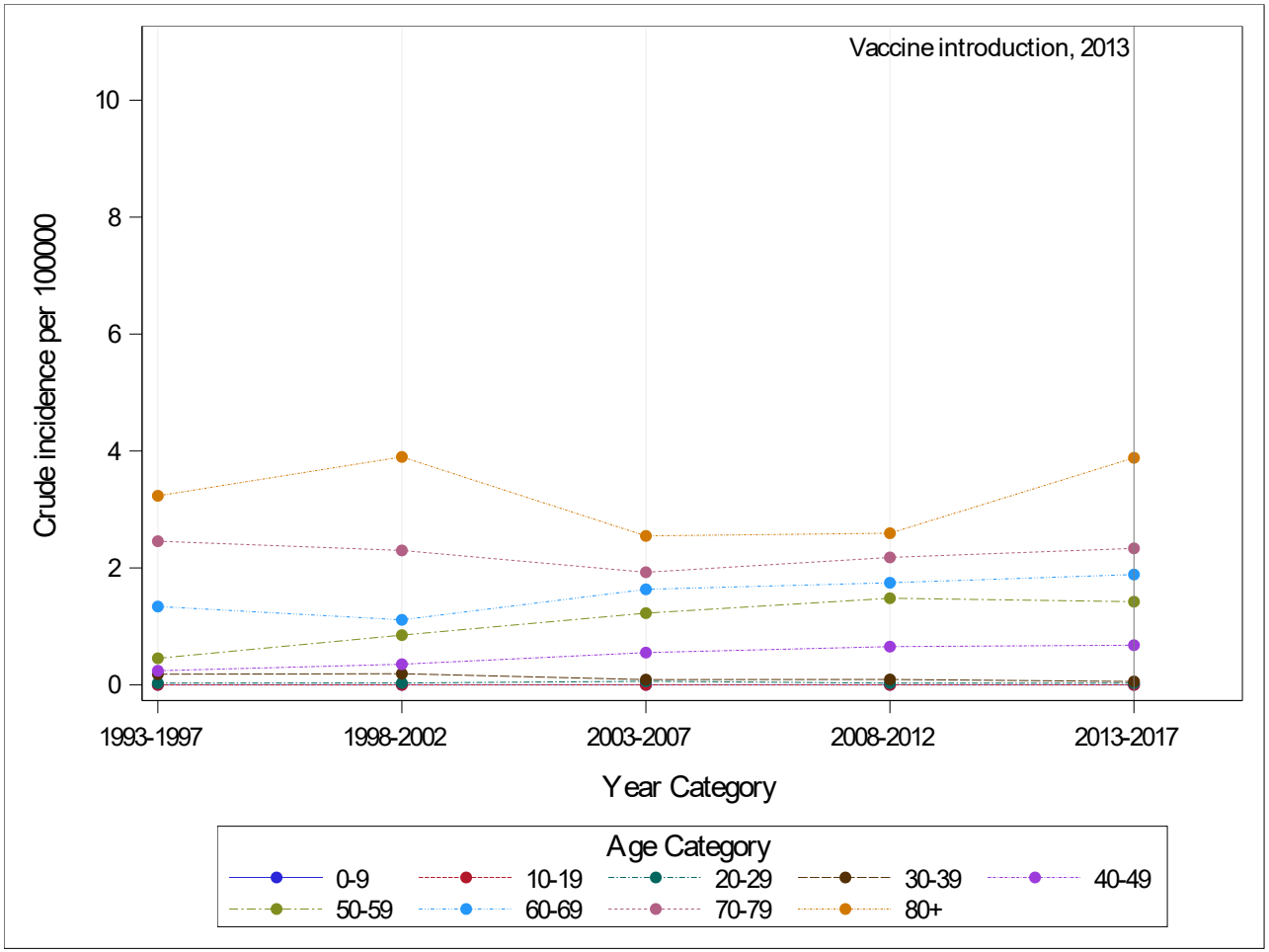
Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.3.3.2 Trend over time in the crude incidence of anal cancer by age category for Female - Finland



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.3.3.3 Trend over time in the crude incidence of anal cancer by age category - Finland



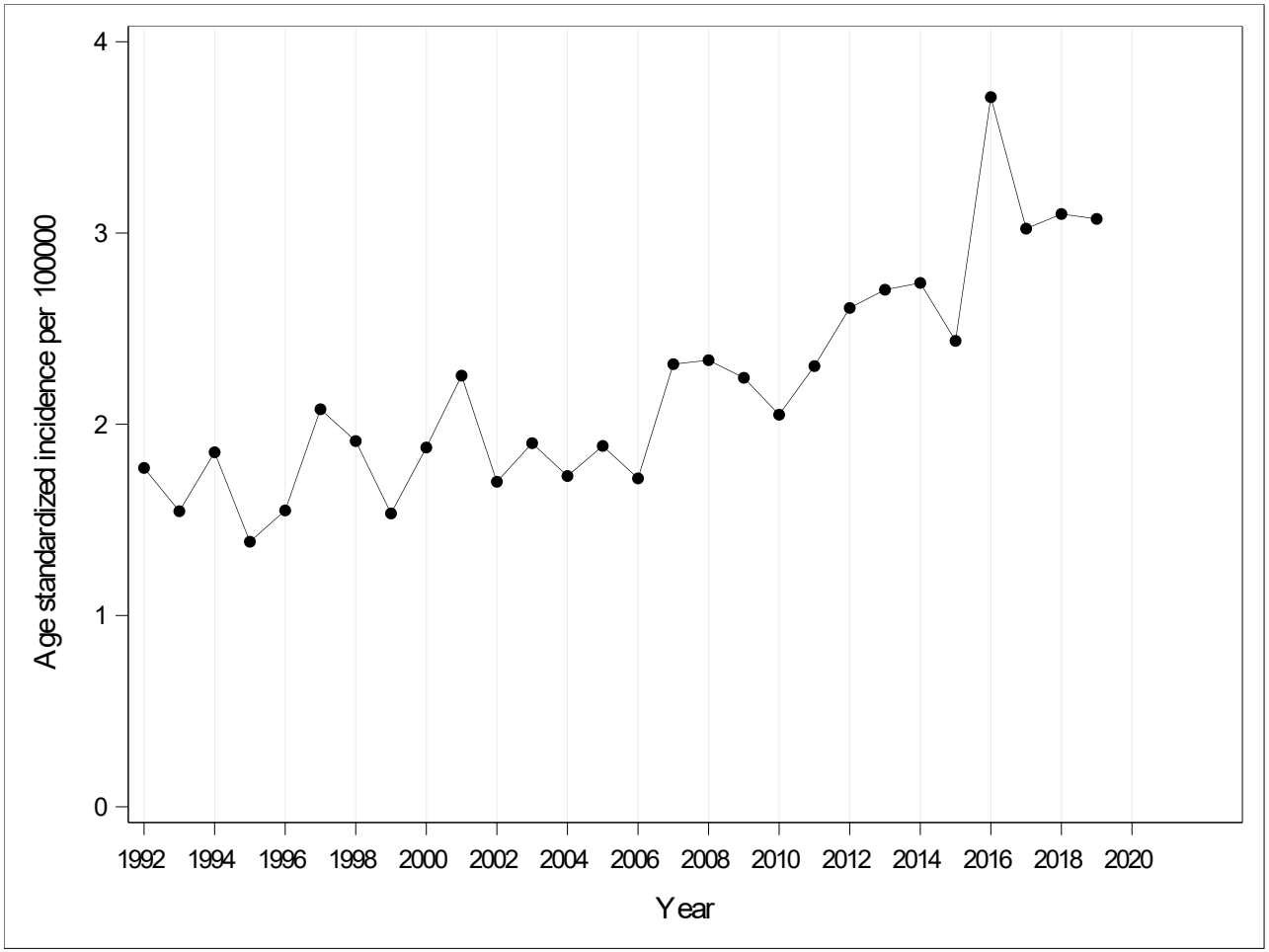
Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Table 14.2.3.4 Incidence of small intestine cancer by calendar year - Finland

			Age standardized Incidence per 100000			Crude Incidence per 100000		
				95% CI			95% CI	
Calendar Year	N	n	Value	LL	UL	Value	LL	UL
1992	5029002	68	1.772	1.117	2.809	1.352	1.050	1.714
1993	5054982	58	1.545	0.956	2.499	1.147	0.871	1.483
1994	5077912	72	1.853	1.182	2.906	1.418	1.109	1.786
1995	5098754	55	1.386	0.828	2.320	1.079	0.813	1.404
1996	5116826	64	1.549	0.936	2.564	1.251	0.963	1.597
1997	5132320	86	2.079	1.357	3.184	1.676	1.340	2.069
1998	5147349	81	1.912	1.223	2.990	1.574	1.250	1.956
1999	5159646	67	1.534	0.923	2.548	1.299	1.006	1.649
2000	5171302	83	1.878	1.197	2.947	1.605	1.278	1.990
2001	5181115	101	2.254	1.492	3.407	1.949	1.588	2.369
2002	5194901	77	1.699	1.052	2.746	1.482	1.170	1.853
2003	5206295	87	1.901	1.205	2.999	1.671	1.338	2.061
2004	5219732	81	1.729	1.080	2.769	1.552	1.232	1.929
2005	5236611	88	1.887	1.209	2.945	1.680	1.348	2.070
2006	5255580	85	1.717	1.049	2.811	1.617	1.292	2.000
2007	5276955	114	2.314	1.544	3.468	2.160	1.782	2.595
2008	5300484	117	2.335	1.555	3.506	2.207	1.826	2.645
2009	5326314	114	2.243	1.485	3.386	2.140	1.765	2.571
2010	5351427	108	2.050	1.329	3.162	2.018	1.656	2.437
2011	5375276	121	2.304	1.540	3.448	2.251	1.868	2.690
2012	5401267	139	2.608	1.775	3.832	2.573	2.163	3.039
2013	5426674	148	2.703	1.850	3.951	2.727	2.306	3.204
2014	5451270	151	2.739	1.881	3.987	2.770	2.346	3.249
2015	5471753	138	2.436	1.622	3.657	2.522	2.119	2.980
2016	5487308	211	3.711	2.689	5.120	3.845	3.344	4.401
2017	5503297	174	3.023	2.125	4.299	3.162	2.709	3.668
2018	5513130	180	3.099	2.167	4.434	3.265	2.805	3.778
2019	5517919	182	3.074	2.158	4.377	3.298	2.837	3.814

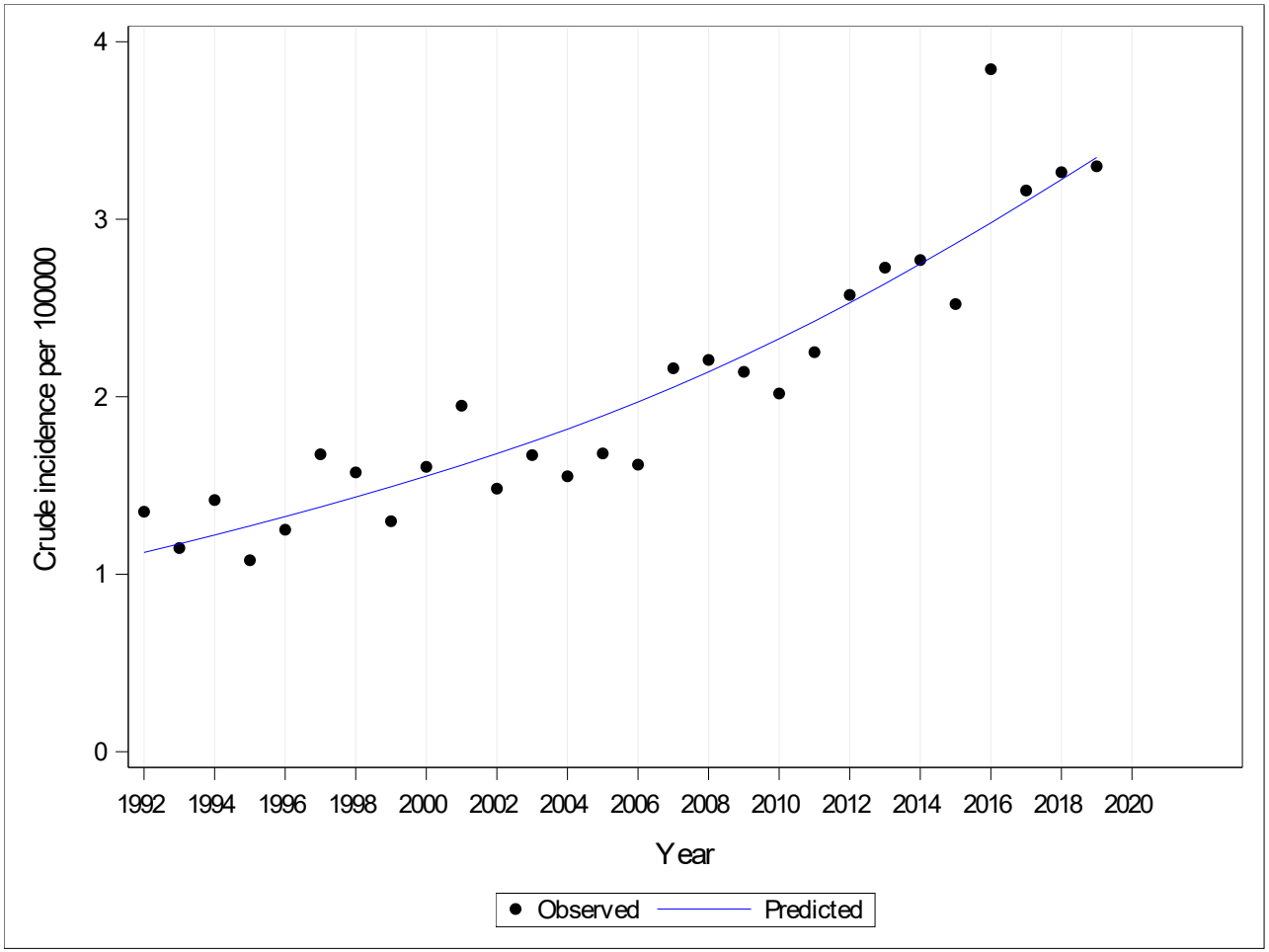
N = population in each category
n = number of small intestine cancer cases reported
Study period: Pre Cervarix launch (Year 1992 – Year 2012), Post Cervarix launch (Year 2013 – Year 2019)
Age standardized Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))
CI=confidence interval; LL=lower limit; UL=upper limit
Age standardized Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.3.4.1 Trend over time in the age standardized incidence of small intestine cancer - Finland



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.3.4.2 Trend over time in the crude incidence of small intestine cancer - Finland



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP
Line - Represents the predicted incidence , Period - Represents the observed Incidence

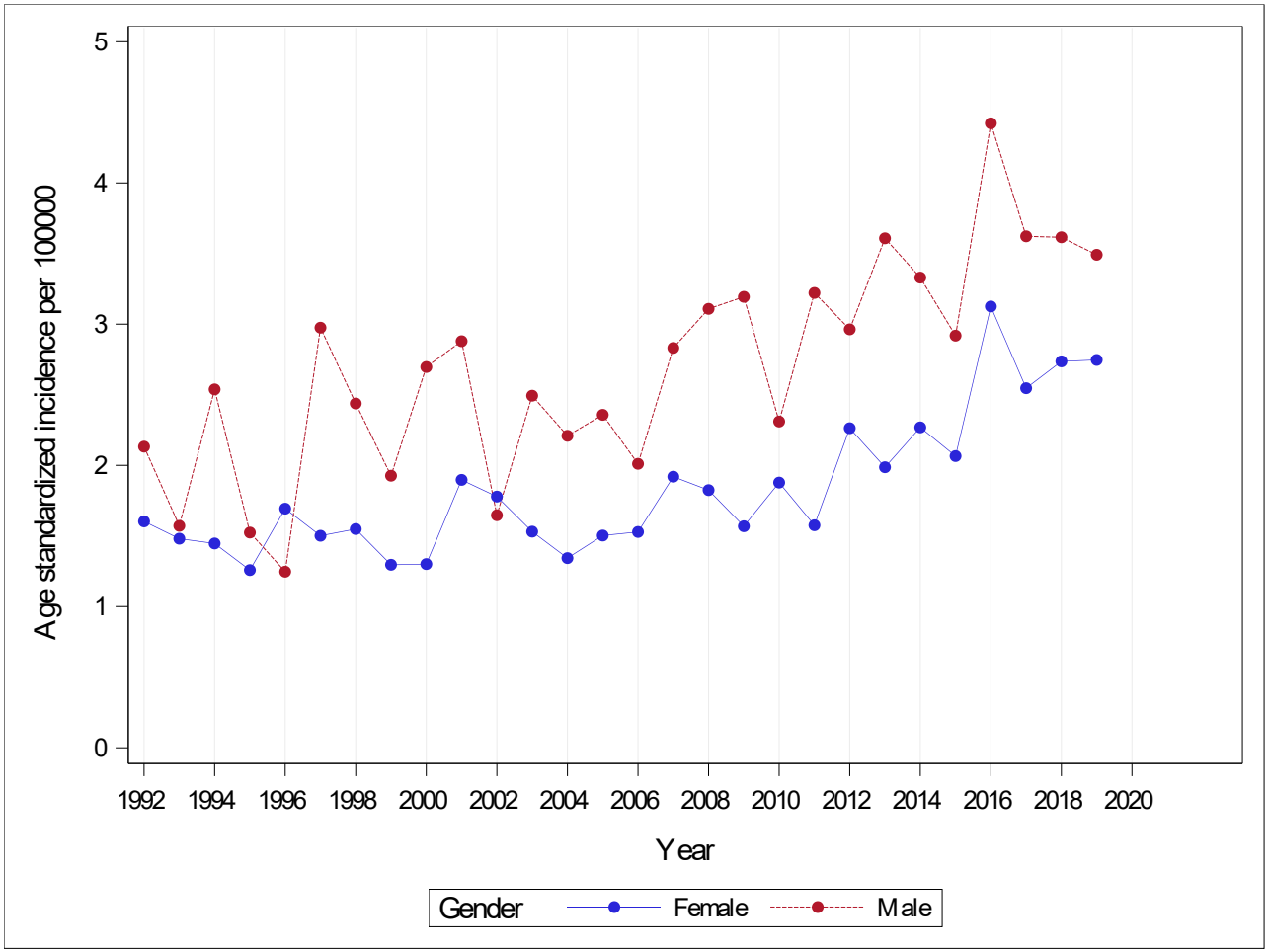
Table 14.2.3.5 Incidence of small intestine cancer by calendar year and gender - Finland

				Age standardized Incidence per 100000			Crude Incidence per 100000		
					95% CI			95% CI	
Calendar Year	Gender	N	n	Value	LL	UL	Value	LL	UL
1992	Male	2443042	32	2.133	1.414	3.218	1.310	0.896	1.849
	Female	2585960	36	1.603	0.980	2.622	1.392	0.975	1.927
1993	Male	2457282	24	1.572	0.966	2.557	0.977	0.626	1.453
	Female	2597700	34	1.481	0.914	2.400	1.309	0.906	1.829
1994	Male	2470196	39	2.538	1.736	3.710	1.579	1.123	2.158
	Female	2607716	33	1.447	0.869	2.409	1.265	0.871	1.777
1995	Male	2481649	25	1.524	0.924	2.515	1.007	0.652	1.487
	Female	2617105	30	1.258	0.737	2.148	1.146	0.773	1.636
1996	Male	2491701	24	1.247	0.703	2.211	0.963	0.617	1.433
	Female	2625125	40	1.693	1.048	2.735	1.524	1.089	2.075
1997	Male	2500596	50	2.975	2.095	4.224	2.000	1.484	2.636
	Female	2631724	36	1.502	0.908	2.482	1.368	0.958	1.894
1998	Male	2509098	43	2.438	1.644	3.615	1.714	1.240	2.308
	Female	2638251	38	1.549	0.943	2.546	1.440	1.019	1.977
1999	Male	2516075	35	1.927	1.236	3.003	1.391	0.969	1.935
	Female	2643571	32	1.296	0.742	2.264	1.210	0.828	1.709
2000	Male	2523026	50	2.697	1.858	3.913	1.982	1.471	2.613
	Female	2648276	33	1.301	0.764	2.217	1.246	0.858	1.750
2001	Male	2529341	53	2.879	2.017	4.110	2.095	1.570	2.741
	Female	2651774	48	1.897	1.203	2.991	1.810	1.335	2.400
2002	Male	2537597	31	1.647	1.021	2.657	1.222	0.830	1.734
	Female	2657304	46	1.779	1.104	2.866	1.731	1.267	2.309
2003	Male	2544916	48	2.493	1.693	3.672	1.886	1.391	2.501
	Female	2661379	39	1.531	0.912	2.569	1.465	1.042	2.003
2004	Male	2552893	45	2.209	1.456	3.352	1.763	1.286	2.359
	Female	2666839	36	1.343	0.792	2.279	1.350	0.945	1.869
2005	Male	2562077	48	2.358	1.581	3.516	1.873	1.381	2.484
	Female	2674534	40	1.503	0.918	2.461	1.496	1.068	2.037
2006	Male	2572350	44	2.011	1.290	3.136	1.710	1.243	2.296
	Female	2683230	41	1.529	0.898	2.603	1.528	1.097	2.073
2007	Male	2583742	61	2.831	1.968	4.073	2.361	1.806	3.033
	Female	2693213	53	1.920	1.234	2.987	1.968	1.474	2.574
2008	Male	2596787	67	3.108	2.209	4.373	2.580	2.000	3.277
	Female	2703697	50	1.825	1.145	2.908	1.849	1.373	2.438
2009	Male	2611653	70	3.194	2.280	4.473	2.680	2.089	3.386
	Female	2714661	44	1.569	0.953	2.582	1.621	1.178	2.176
2010	Male	2625067	53	2.310	1.545	3.454	2.019	1.512	2.641
	Female	2726360	55	1.878	1.190	2.963	2.017	1.520	2.626
2011	Male	2638416	74	3.221	2.296	4.519	2.805	2.202	3.521
	Female	2736860	47	1.576	0.971	2.559	1.717	1.262	2.284
2012	Male	2652534	72	2.963	2.058	4.267	2.714	2.124	3.418
	Female	2748733	67	2.263	1.505	3.402	2.437	1.889	3.096
2013	Male	2666622	88	3.608	2.608	4.992	3.300	2.647	4.066
	Female	2760052	60	1.987	1.277	3.091	2.174	1.659	2.798
2014	Male	2680364	84	3.330	2.379	4.660	3.134	2.500	3.880
	Female	2770906	67	2.269	1.495	3.443	2.418	1.874	3.071
2015	Male	2691863	76	2.919	2.028	4.201	2.823	2.224	3.534
	Female	2779890	62	2.066	1.318	3.238	2.230	1.710	2.859
2016	Male	2701490	114	4.422	3.293	5.938	4.220	3.481	5.069

				Age standardized Incidence per 100000			Crude Incidence per 100000		
					95% CI			95% CI	
Calendar Year	**Gender**	**N**	**n**	**Value**	**LL**	**UL**	**Value**	**LL**	**UL**
	Female	2785818	97	3.125	2.200	4.440	3.482	2.824	4.248
2017	Male	2712327	94	3.622	2.635	4.980	3.466	2.801	4.241
	Female	2790970	80	2.546	1.731	3.747	2.866	2.273	3.567
2018	Male	2719131	96	3.615	2.614	5.000	3.531	2.860	4.311
	Female	2793999	84	2.736	1.859	4.027	3.006	2.398	3.722
2019	Male	2723290	95	3.491	2.515	4.846	3.488	2.822	4.264
	Female	2794629	87	2.747	1.882	4.008	3.113	2.493	3.840

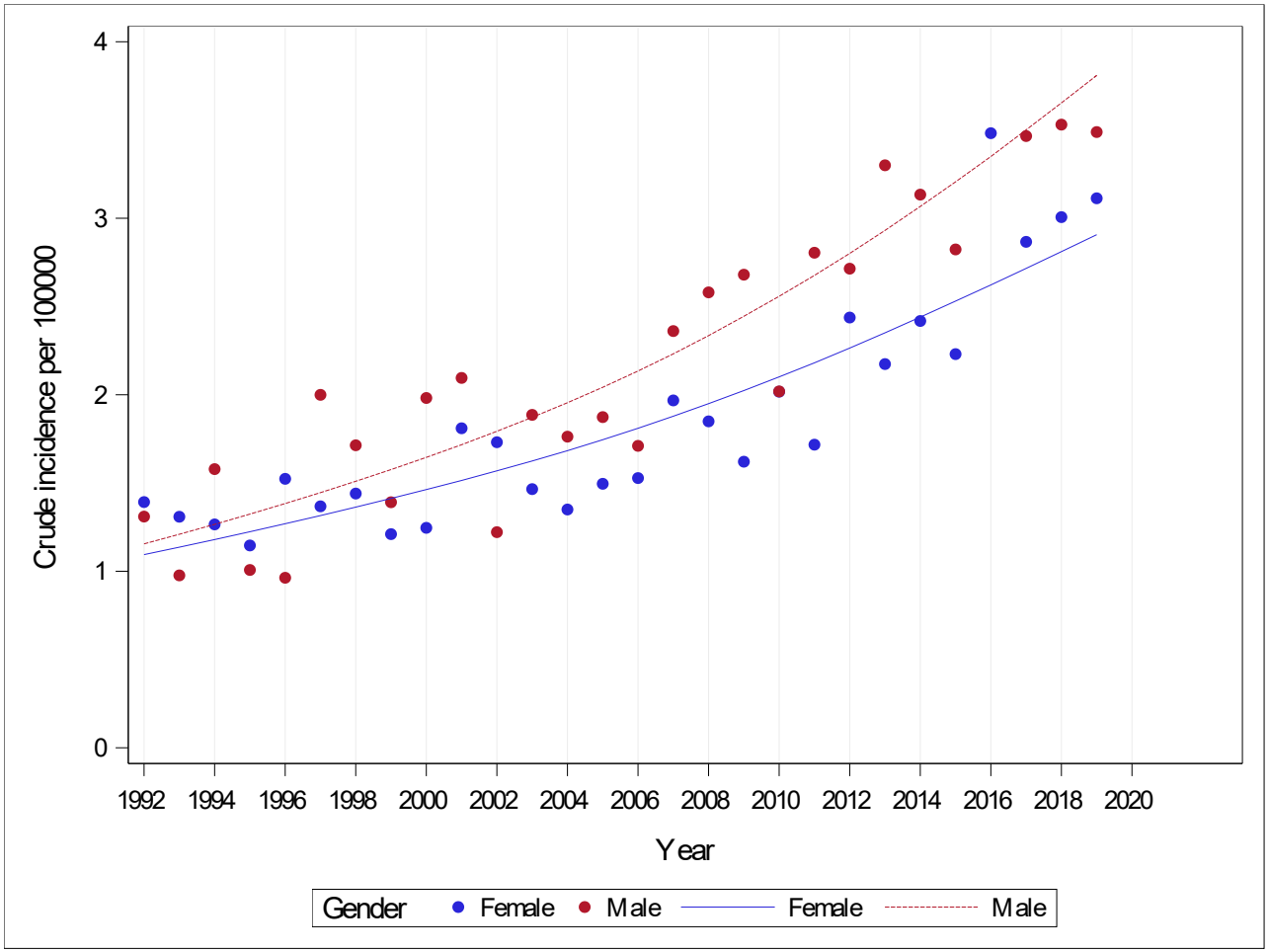
N = population in each category
n = number of small intestine cancer cases reported
Study period: Pre Cervarix launch (Year 1992 – Year 2012), Post Cervarix launch (Year 2013 – Year 2019)
Age standardized Incidence per 100000: Value = Sum product (Crude Incidence in each age category*(population in each age category / Total population))
CI=confidence interval; LL=lower limit; UL=upper limit
Age standardized Incidence 95% CI Computed based on Normal approximation of the log transformed Maximum Likelihood Estimate method
Crude Incidence per 100000 = (n/N)*100000
Crude Incidence 95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.3.5.1 Trend over time in the age standardized incidence of small intestine cancer by gender - Finland



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.3.5.2 Trend over time in the crude incidence of small intestine cancer by gender - Finland



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP
Line - Represents the predicted incidence , Period - Represents the observed Incidence

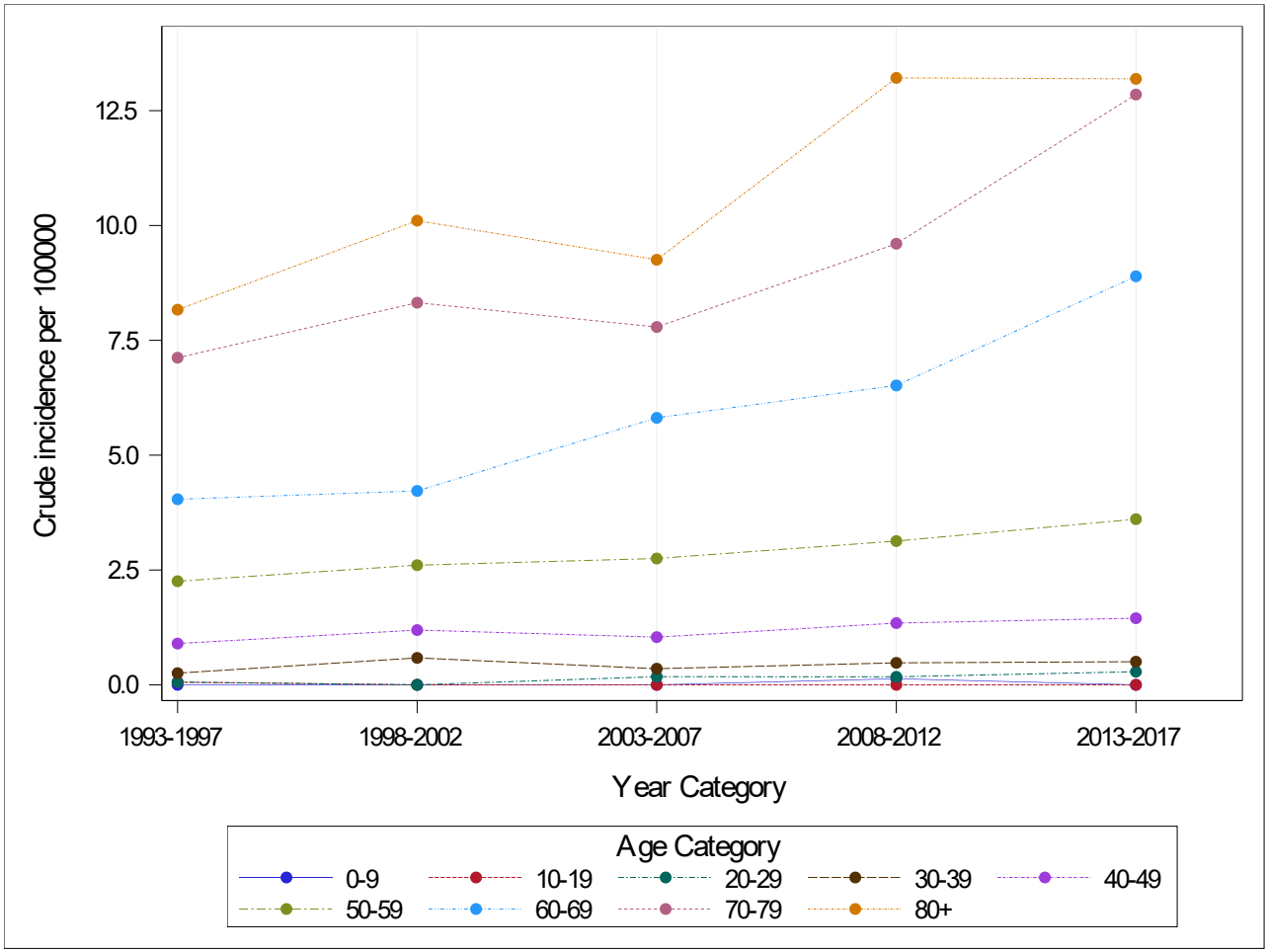
Table 14.2.3.6 Crude incidence of small intestine cancer for year and age category by gender - Finland

		Male					Female					Total				
					95% CI					95% CI					95% CI	
Year category	Age category (in years)	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL
1993-1997	0-9	1638586	0	0.000	0.000	0.225	1571027	0	0.000	0.000	0.235	3209613	0	0.000	0.000	0.115
	10-19	1669111	1	0.060	0.002	0.334	1595900	0	0.000	0.000	0.231	3265011	1	0.031	0.001	0.171
	20-29	1698826	1	0.059	0.001	0.328	1628026	2	0.123	0.015	0.444	3326852	4	0.120	0.033	0.308
	30-39	1963539	5	0.255	0.083	0.594	1883780	5	0.265	0.086	0.619	3847319	10	0.260	0.125	0.478
	40-49	2113675	19	0.899	0.541	1.404	2034451	11	0.541	0.270	0.967	4148126	30	0.723	0.488	1.032
	50-59	1418449	32	2.256	1.543	3.185	1444230	31	2.146	1.458	3.047	2862679	63	2.201	1.691	2.816
	60-69	1089091	44	4.040	2.936	5.424	1299694	36	2.770	1.940	3.835	2388785	80	3.349	2.656	4.168
	70-79	589735	42	7.122	5.133	9.627	1038601	42	4.044	2.914	5.466	1628336	84	5.159	4.115	6.387
	80+	220412	18	8.167	4.840	12.907	583661	46	7.881	5.770	10.513	804073	64	7.959	6.130	10.164
1998-2002	0-9	1594551	0	0.000	0.000	0.231	1531947	0	0.000	0.000	0.241	3126498	0	0.000	0.000	0.118
	10-19	1660061	0	0.000	0.000	0.222	1587266	0	0.000	0.000	0.232	3247327	0	0.000	0.000	0.114
	20-29	1623542	0	0.000	0.000	0.227	1552243	1	0.064	0.002	0.359	3175785	1	0.031	0.001	0.175
	30-39	1874615	11	0.587	0.293	1.050	1803331	10	0.555	0.266	1.020	3677946	21	0.571	0.353	0.873
	40-49	2013179	24	1.192	0.764	1.774	1958249	13	0.664	0.353	1.135	3971428	37	0.932	0.656	1.284
	50-59	1765432	46	2.606	1.908	3.475	1762388	47	2.667	1.959	3.546	3527820	93	2.636	2.128	3.230
	60-69	1137046	48	4.221	3.113	5.597	1291236	37	2.865	2.018	3.950	2428282	85	3.500	2.796	4.328
	70-79	709224	59	8.319	6.333	10.731	1117857	48	4.294	3.166	5.693	1827081	107	5.856	4.799	7.077
	80+	237487	24	10.106	6.475	15.037	634659	41	6.460	4.636	8.764	872146	65	7.453	5.752	9.499
2003-2007	0-9	1494678	0	0.000	0.000	0.247	1431670	0	0.000	0.000	0.258	2926348	0	0.000	0.000	0.126
	10-19	1659335	0	0.000	0.000	0.222	1591346	1	0.063	0.002	0.350	3250681	1	0.031	0.001	0.171
	20-29	1686842	3	0.178	0.037	0.520	1611047	1	0.062	0.002	0.346	3297889	4	0.121	0.033	0.311
	30-39	1706324	6	0.352	0.129	0.765	1637248	7	0.428	0.172	0.881	3343572	13	0.389	0.207	0.665
	40-49	1925875	20	1.038	0.634	1.604	1880922	20	1.063	0.649	1.642	3806797	40	1.051	0.751	1.431
	50-59	1999443	55	2.751	2.072	3.581	1995835	40	2.004	1.432	2.729	3995278	95	2.378	1.924	2.907
	60-69	1255823	73	5.813	4.556	7.309	1376685	46	3.341	2.446	4.457	2632508	119	4.520	3.745	5.409
	70-79	795898	62	7.790	5.973	9.986	1125581	49	4.353	3.221	5.755	1921479	111	5.777	4.752	6.957
	80+	291760	27	9.254	6.099	13.464	728861	45	6.174	4.503	8.261	1020621	72	7.055	5.520	8.884
2008-2012	0-9	1499145	2	0.133	0.016	0.482	1433513	0	0.000	0.000	0.257	2932658	2	0.068	0.008	0.246
	10-19	1620800	0	0.000	0.000	0.228	1556859	0	0.000	0.000	0.237	3177659	0	0.000	0.000	0.116

		Male					Female					Total				
					95% CI					95% CI					95% CI	
Year category	Age category (in years)	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL	N	n	Crude Incidence per 100 000	LL	UL
	20-29	1716435	3	0.175	0.036	0.511	1632637	1	0.061	0.002	0.341	3349072	4	0.119	0.033	0.306
	30-39	1670331	8	0.479	0.207	0.944	1586803	6	0.378	0.139	0.823	3257134	14	0.430	0.235	0.721
	40-49	1859727	25	1.344	0.870	1.984	1812946	16	0.883	0.504	1.433	3672673	41	1.116	0.801	1.514
	50-59	1916879	60	3.130	2.389	4.029	1930826	41	2.123	1.524	2.881	3847705	101	2.625	2.138	3.190
	60-69	1580384	103	6.517	5.320	7.904	1684532	72	4.274	3.344	5.383	3264916	175	5.360	4.595	6.216
	70-79	874753	84	9.603	7.659	11.889	1144303	66	5.768	4.461	7.338	2019056	150	7.429	6.288	8.718
	80+	386003	51	13.212	9.837	17.372	847892	61	7.194	5.503	9.241	1233895	112	9.077	7.474	10.922
2013-2017	0-9	1537441	0	0.000	0.000	0.240	1470340	0	0.000	0.000	0.251	3007781	0	0.000	0.000	0.123
	10-19	1536273	0	0.000	0.000	0.240	1469844	0	0.000	0.000	0.251	3006117	0	0.000	0.000	0.123
	20-29	1745667	5	0.286	0.093	0.668	1662465	0	0.000	0.000	0.222	3408132	5	0.147	0.048	0.342
	30-39	1786571	9	0.504	0.230	0.956	1684667	8	0.475	0.205	0.936	3471238	17	0.490	0.285	0.784
	40-49	1723907	25	1.450	0.938	2.141	1667775	24	1.439	0.922	2.141	3391682	49	1.445	1.069	1.910
	50-59	1857739	67	3.607	2.795	4.580	1869050	64	3.424	2.637	4.373	3726789	130	3.488	2.914	4.142
	60-69	1798999	160	8.894	7.569	10.384	1911218	97	5.075	4.116	6.191	3710217	257	6.927	6.106	7.828
	70-79	996070	128	12.851	10.721	15.279	1231597	90	7.308	5.876	8.982	2227667	218	9.786	8.530	11.175
	80+	469999	62	13.192	10.114	16.911	920680	83	9.015	7.180	11.176	1390679	145	10.427	8.799	12.268

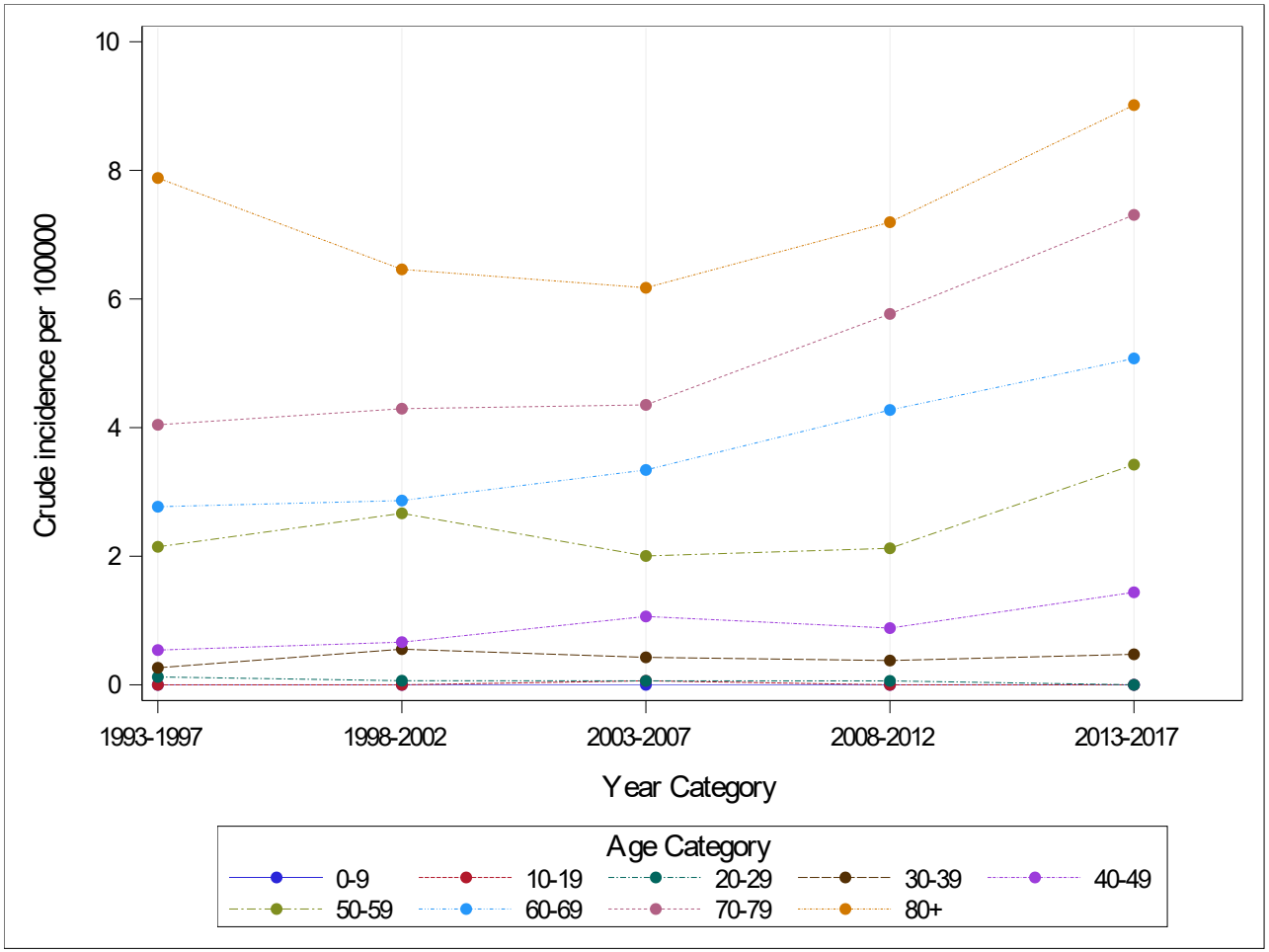
N = population in each category
n = number of small intestine cancer cases reported in each category
Study period: Pre Cervarix launch (Year 1992 – Year 2012), Post Cervarix launch (Year 2013 – Year 2019)
Crude Incidence per 100000 = (n/N)*100000
95% CI= exact poisson confidence interval; LL=lower limit; UL=upper limit

Figure 14.2.3.6.1 Trend over time in the crude incidence of small intestine cancer by age category for Male - Finland



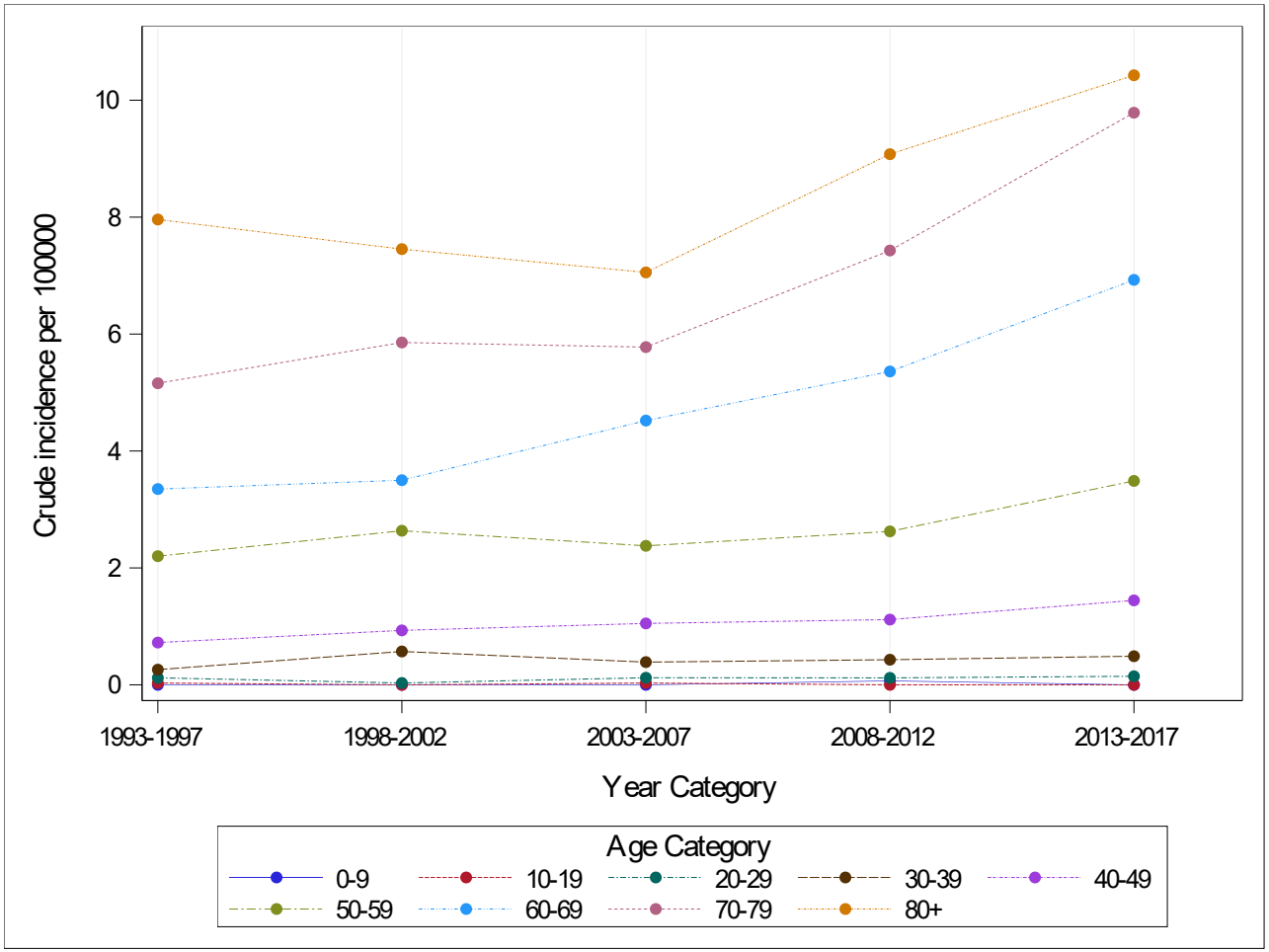
Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.3.6.2 Trend over time in the crude incidence of small intestine cancer by age category for Female - Finland



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Figure 14.2.3.6.3 Trend over time in the crude incidence of small intestine cancer by age category - Finland



Note: The vaccine introduction year is considered as the year Cervarix was introduced in the NIP

Table 14.2.3.7 Univariate Poisson regression model for incidence of anal cancer - Finland

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	147685401	1079	1.029	1.021	1.038	<.0001	2.91

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.3.7.1 Univariate Poisson regression model for incidence of anal cancer for Pre-Cervarix launch (Year 1992 – Year 2012) - Finland

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	109314050	709	1.030	1.019	1.041	<.0001	2.99

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.3.7.2 Univariate Poisson regression model for incidence of anal cancer for Post-Cervarix launch (Year 2013 – Year 2019) - Finland

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	38371351	370	0.989	0.906	1.080	0.8076	-1.09

N = overall population at risk
n = total number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of anal cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.3.8 Multivariate Poisson regression model for incidence of anal cancer - Finland

				Adjusted incidence ratio (e(β))				
					95% CI			
Characteristics	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
Calendar year		147685401	1079	1.015	1.002	1.028	0.0200	-
Age category (in years)	0-29	53414167	6	Reference	-	-	-	<.0001
	30-39	19791287	24	10.833	4.222	27.795	<.0001	-
	40-49	21084704	101	42.947	18.038	102.256	<.0001	-
	50-59	19972250	236	103.556	44.107	243.134	<.0001	-
	60-69	16366462	270	141.523	60.354	331.853	<.0001	-
	70-79	10988423	250	192.931	82.214	452.749	<.0001	-
	80+	6068108	192	256.890	109.101	604.877	<.0001	-
Study period	Pre-Cervarix launch	109314050	709	Reference	-	-	-	0.6372
	Post-Cervarix launch	38371351	370	1.052	0.852	1.298	0.6372	-
Gender	Female	75390276	679	Reference	-	-	-	<.0001
	Male	72295125	400	0.738	0.647	0.842	<.0001	-

N = population at risk in each category
n = number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk)+ intercept + (β1 × calendar year) +(β2 × age category) + (β3 × study period) + (β4 × gender)
Adjusted incidence ratio (e(β)) = change in incidence of anal cancer compared to the reference category of each independent variable adjusted for other covariates (Exponentiated regression coefficient – β)
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Study period: Pre-Cervarix launch (Year 1992 – Year 2012), Post-Cervarix launch (Year 2013 – Year 2019)

Table 14.2.3.8.1 Multivariate Poisson regression model for incidence of anal cancer by age category - Finland

					Adjusted incidence ratio (e(β))				
						95% CI			
Age Category (in years)	**Characteristics**	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
0-29	Calendar year		53414167	6	1.030	0.929	1.141	0.5778	-
	Study period	Pre-Cervarix launch	40269932	5	Reference	-	-	-	0.3943
		Post-Cervarix launch	13144235	1	0.412	0.054	3.166	0.3943	-
	Gender	Female	26110814	3	Reference	-	-	-	0.9391
		Male	27303353	3	0.956	0.306	2.993	0.9391	-
30-39	Calendar year		19791287	24	0.966	0.905	1.033	0.3119	-
	Study period	Pre-Cervarix launch	14911135	21	Reference	-	-	-	0.6830
		Post-Cervarix launch	4880152	3	0.729	0.160	3.321	0.6830	-
	Gender	Female	9662340	14	Reference	-	-	-	0.3183
		Male	10128947	10	0.683	0.323	1.444	0.3183	-
40-49	Calendar year		21084704	101	1.057	1.015	1.102	0.0073	-
	Study period	Pre-Cervarix launch	16374376	71	Reference	-	-	-	0.3011
		Post-Cervarix launch	4710328	30	0.699	0.354	1.378	0.3011	-
	Gender	Female	10378830	61	Reference	-	-	-	0.0354
		Male	10705874	40	0.636	0.417	0.970	0.0354	-
50-59	Calendar year		19972250	236	1.071	1.038	1.104	<.0001	-
	Study period	Pre-Cervarix launch	14778125	151	Reference	-	-	-	0.1134
		Post-Cervarix launch	5194125	85	0.694	0.442	1.091	0.1134	-
	Gender	Female	10012559	145	Reference	-	-	-	0.0015
		Male	9959691	91	0.630	0.474	0.838	0.0015	-
60-69	Calendar year		16366462	270	1.025	0.999	1.052	0.0628	-
	Study period	Pre-Cervarix launch	11194243	162	Reference	-	-	-	0.7988
		Post-Cervarix launch	5172219	108	1.055	0.698	1.596	0.7988	-
	Gender	Female	8583391	164	Reference	-	-	-	0.0085
		Male	7783071	106	0.707	0.545	0.915	0.0085	-
70-79	Calendar year		10988423	250	0.984	0.959	1.010	0.2252	-
	Study period	Pre-Cervarix launch	7706257	175	Reference	-	-	-	0.3255
		Post-Cervarix launch	3282166	75	1.262	0.794	2.005	0.3255	-
	Gender	Female	6432644	153	Reference	-	-	-	0.4550

					Adjusted incidence ratio (e(β))				
						95% CI			
Age Category (in years)	**Characteristics**	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
		Male	4555779	97	0.902	0.688	1.183	0.4550	-
80+	Calendar year		6068108	192	0.973	0.943	1.003	0.0793	-
	Study period	Pre-Cervarix launch	4079982	124	Reference	-	-	-	0.0705
		Post-Cervarix launch	1988126	68	1.645	0.959	2.822	0.0705	-
	Gender	Female	4209698	139	Reference	-	-	-	0.4159
		Male	1858410	53	0.865	0.610	1.227	0.4159	-

N = population at risk in each category
n = number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk)+ intercept + (β1 × calendar year) + (β2 × study period) + (β3 × gender)
Adjusted incidence ratio (e(β)) = change in incidence of anal cancer compared to the reference category of each independent variable adjusted for other covariates (Exponentiated regression coefficient – β)
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Study period: Pre-Cervarix launch (Year 1992 – Year 2012), Post-Cervarix launch (Year 2013 – Year 2019)

Table 14.2.3.8.2 Multivariate Poisson regression model for incidence of anal cancer by gender - Finland

					Adjusted incidence ratio (e(β))				
						95% CI			
Gender	**Characteristics**	**Categories**	**N**	**n**	**Value**	**LL**	**UL**	**P-value for the category of the variable**	**P-value for the variable**
Male	Calendar year		72295125	400	1.031	1.009	1.053	0.0049	-
	Age category (in years)	0-29	27303353	3	Reference	-	-	-	<.0001
		30-39	10128947	10	9.039	2.327	35.112	0.0015	-
		40-49	10705874	40	34.379	10.009	118.088	<.0001	-
		50-59	9959691	91	81.491	24.309	273.180	<.0001	-
		60-69	7783071	106	119.010	35.593	397.925	<.0001	-
		70-79	4555779	97	185.440	55.374	621.017	<.0001	-
		80+	1858410	53	243.834	71.713	829.074	<.0001	-
	Study period	Pre-Cervarix launch	53400038	257	Reference	-	-	-	0.4299
		Post-Cervarix launch	18895087	143	0.872	0.622	1.224	0.4299	-
Female	Calendar year		75390276	679	1.006	0.990	1.022	0.4535	-
	Age category (in years)	0-29	26110814	3	Reference	-	-	-	<.0001
		30-39	9662340	14	12.631	3.384	47.140	0.0002	-
		40-49	10378830	61	51.493	15.139	175.147	<.0001	-
		50-59	10012559	145	125.173	37.421	418.704	<.0001	-
		60-69	8583391	164	163.139	48.838	544.953	<.0001	-
		70-79	6432644	153	204.826	61.273	684.699	<.0001	-
		80+	4209698	139	281.546	84.119	942.341	<.0001	-
	Study period	Pre-Cervarix launch	55914012	452	Reference	-	-	-	0.2469
		Post-Cervarix launch	19476264	227	1.172	0.896	1.534	0.2469	-

N = population at risk in each category
n = number of anal cancer cases reported
Model is calculated by log(No. of anal cancer cases) = log (population at risk)+ intercept + (β1 × calendar year) + (β2 × age category) + (β3 × study period)
Adjusted Incidence ratio (e(β)) = change in incidence of anal cancer compared to the reference category of each independent variable adjusted for other covariates (Exponentiated regression coefficient – β)
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit
Study period: Pre-Cervarix launch (Year 1992 – Year 2012), Post-Cervarix launch (Year 2013 – Year 2019)

Table 14.2.3.9 Univariate Poisson regression model for incidence of small intestine cancer - Finland

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	147685401	3050	1.042	1.036	1.048	<.0001	4.16

N = overall population at risk
n = total number of small intestine cancer cases reported
Model is calculated by log(No. of small intestine cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of small intestine cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.3.9.1 Univariate Poisson regression model for incidence of small intestine cancer for Pre-Cervarix launch (Year 1992 – Year 2012) - Finland

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	109314050	1866	1.034	1.026	1.043	<.0001	3.41

N = overall population at risk
n = total number of small intestine cancer cases reported
Model is calculated by log(No. of small intestine cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of small intestine cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.3.9.2 Univariate Poisson regression model for incidence of small intestine cancer for Post-Cervarix launch (Year 2013 – Year 2019) - Finland

			Incidence ratio (e(β))				
				95% CI			
Characteristics	**N**	**n**	**Value**	**LL**	**UL**	**p-value**	**Annual Percentage Change (%)**
Calendar year	38371351	1184	1.039	0.991	1.090	0.1136	3.94

N = overall population at risk
n = total number of small intestine cancer cases reported
Model is calculated by log(No. of small intestine cancer cases) = log (population at risk) + intercept + (β × calendar year)
Incidence ratio (e(β)) = change in incidence of small intestine cancer with every year increase (Exponentiated regression coefficient – β)
Annual Percentage Change = (Incidence ratio - 1) × 100
95% CI = Wald confidence interval; LL = lower limit; UL = upper limit

Table 14.2.3.10 Trend overtime of anal cancer cases by observed counts versus predicted counts - Finland

					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	26	24	-2	-8.33	-88.67	37.8
1993	20	25	5	20	-44.03	55.56
1994	31	26	-5	-19.23	-100.79	29.2
1995	23	26	3	11.54	-55.03	49.52
1996	22	27	5	18.52	-43.07	53.59
1997	33	28	-5	-17.86	-95.01	28.77
1998	35	29	-6	-20.69	-97.43	26.22
1999	26	30	4	13.33	-46.53	48.74
2000	38	31	-7	-22.58	-96.98	23.72
2001	28	32	4	12.5	-45.3	47.31
2002	28	33	5	15.15	-40.39	48.72
2003	30	34	4	11.76	-44.16	46
2004	35	35	0	0	-59.76	37.41
2005	42	36	-6	-16.67	-82.09	25.25
2006	34	38	4	10.53	-42.11	43.67
2007	40	39	-1	-2.56	-59.42	34.02
2008	43	40	-3	-7.5	-65.35	30.11
2009	44	42	-2	-4.76	-59.89	31.36
2010	37	43	6	13.95	-33.54	44.56
2011	52	45	-7	-15.56	-72.22	22.47
2012	42	46	4	8.7	-38.73	39.91
2013	59	48	-11	-22.92	-79.91	16.02
2014	59	49	-10	-20.41	-75.86	17.56
2015	56	51	-5	-9.8	-60.46	24.86
2016	44	53	9	16.98	-23.82	44.34
2017	37	54	17	31.48	-4.1	54.9
2018	46	56	10	17.86	-21.32	44.39
2019	70	58	-12	-20.69	-70.93	14.78

Note:Poisson model has been used to predict the counts using the pre-vaccination period from 1992-Most recent available year‘s data

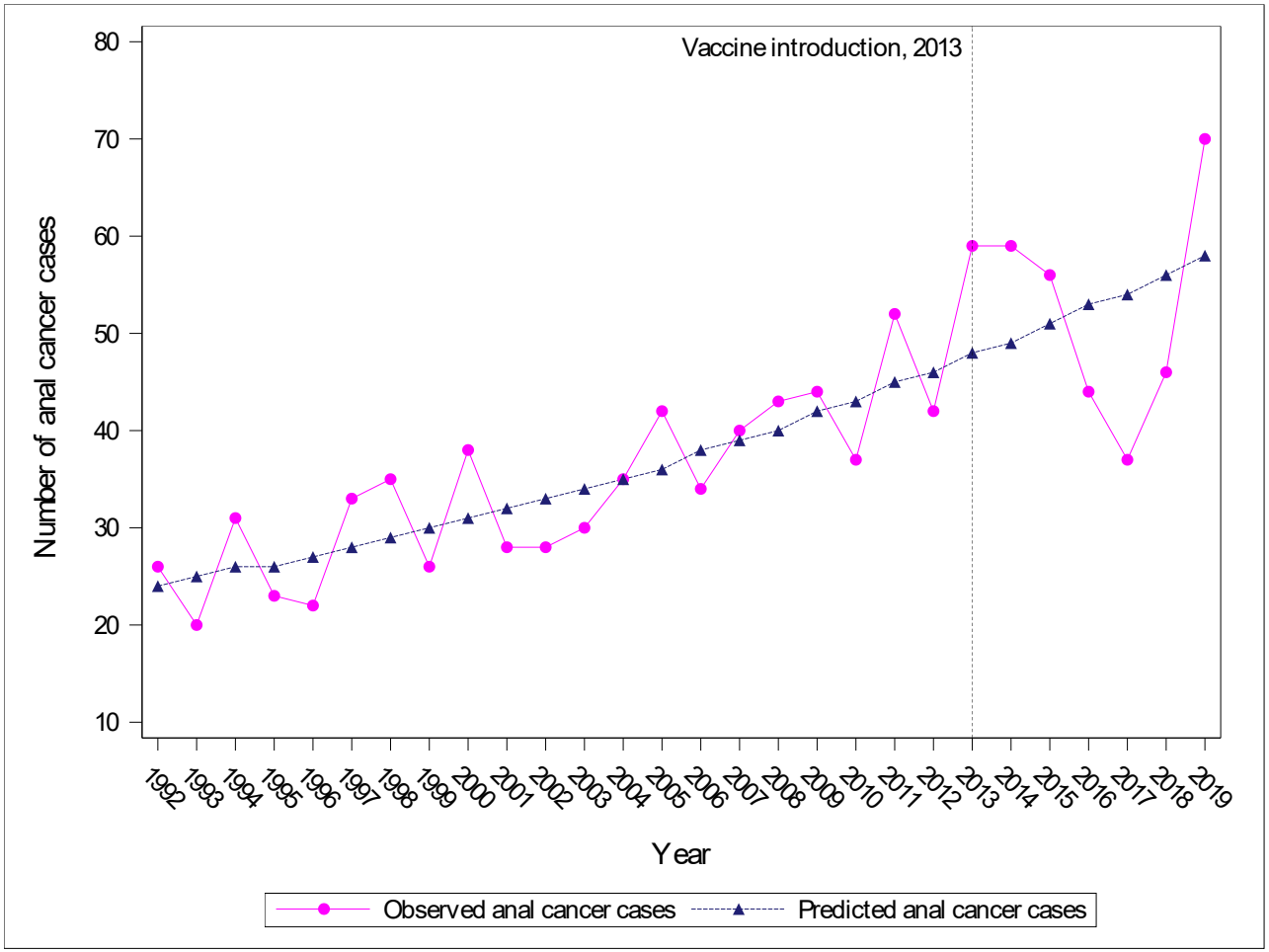
Model is calculated by, log(No. of anal cancer cases) = log (Population at risk) + intercept + (β × calendar year)

%Reduction = ((predicted counts –observed counts)/ predicted counts)×100

Wald’s 95% CI and %reduction was estimated using Poisson model for non-zero observed counts

*Positive sign indicates the reduction and negative sign indicates the increase in observed counts

Figure 14.2.3.10.1 Predicted and observed counts of anal cancer cases - Finland



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Table 14.2.3.11 Trend overtime of anal cancer cases by observed counts versus predicted counts, by age category - Finland

30-39 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	1	1	0	0	-1498.75	93.75
1993	0	1	1	-	-	-
1994	1	1	0	0	-1498.75	93.75
1995	2	1	-1	-100	-2105.64	81.86
1996	2	1	-1	-100	-2105.64	81.86
1997	2	1	-1	-100	-2105.64	81.86
1998	2	1	-1	-100	-2105.64	81.86
1999	2	1	-1	-100	-2105.64	81.86
2000	0	1	1	-	-	-
2001	1	1	0	0	-1498.75	93.75
2002	2	1	-1	-100	-2105.64	81.86
2003	1	1	0	0	-1498.75	93.75
2004	0	1	1	-	-	-
2005	0	1	1	-	-	-
2006	1	1	0	0	-1498.75	93.75
2007	1	1	0	0	-1498.75	93.75
2008	0	1	1	-	-	-
2009	1	1	0	0	-1498.75	93.75
2010	0	1	1	-	-	-
2011	1	1	0	0	-1498.75	93.75
2012	1	1	0	0	-1498.75	93.75
2013	1	1	0	0	-1498.75	93.75
2014	0	1	1	-	-	-
2015	1	1	0	0	-1498.75	93.75
2016	0	1	1	-	-	-
2017	0	1	1	-	-	-
2018	1	1	0	0	-1498.75	93.75
2019	0	1	1	-	-	-

40-49 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	2	2	0	0	-609.91	85.91
1993	2	2	0	0	-609.91	85.91
1994	1	2	1	50	-451.41	95.47
1995	2	2	0	0	-609.91	85.91
1996	1	2	1	50	-451.41	95.47
1997	4	3	-1	-33.33	-495.74	70.16
1998	1	3	2	66.67	-220.45	96.53
1999	5	3	-2	-66.67	-597.39	60.17
2000	4	3	-1	-33.33	-495.74	70.16
2001	2	3	1	33.33	-298.98	88.86
2002	2	3	1	33.33	-298.98	88.86
2003	3	3	0	0	-395.45	79.82
2004	5	4	-1	-25	-365.49	66.43
2005	7	4	-3	-75	-497.8	48.77
2006	3	4	1	25	-235.1	83.21
2007	3	4	1	25	-235.1	83.21
2008	6	4	-2	-50	-431.54	57.67
2009	4	5	1	20	-197.92	78.52
2010	3	5	2	40	-151.06	85.66
2011	4	5	1	20	-197.92	78.52
2012	7	5	-2	-40	-341.1	55.57
2013	4	6	2	33.33	-136.24	81.19
2014	8	6	-2	-33.33	-284.27	53.74
2015	3	6	3	50	-99.92	87.5
2016	4	7	3	42.86	-95.2	83.27
2017	4	7	3	42.86	-95.2	83.27
2018	4	7	3	42.86	-95.2	83.27
2019	3	8	5	62.5	-41.35	90.05

50-59 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	2	2	0	0	-609.91	85.91
1993	2	3	1	33.33	-298.98	88.86
1994	4	3	-1	-33.33	-495.74	70.16
1995	3	3	0	0	-395.45	79.82
1996	1	3	2	66.67	-220.45	96.53
1997	3	4	1	25	-235.1	83.21
1998	3	4	1	25	-235.1	83.21
1999	2	5	3	60	-106.17	92.24
2000	8	5	-3	-60	-389.08	47.66
2001	9	6	-3	-50	-321.42	46.61
2002	8	7	-1	-14.29	-215.16	58.56
2003	6	7	1	14.29	-155.05	71.19
2004	8	8	0	0	-166.44	62.47
2005	13	9	-4	-44.44	-237.91	38.26
2006	9	10	1	10	-121.48	63.43
2007	13	10	-3	-30	-196.47	43
2008	12	11	-1	-9.09	-147.23	51.86
2009	12	11	-1	-9.09	-147.23	51.86
2010	11	12	1	8.33	-107.74	59.55
2011	13	13	0	0	-115.71	53.64
2012	9	14	5	35.71	-48.52	72.17
2013	15	15	0	0	-104.56	51.11
2014	14	16	2	12.5	-79.27	57.29
2015	12	17	5	29.41	-47.8	66.29
2016	7	18	11	61.11	6.89	83.76
2017	5	19	14	73.68	29.52	90.17
2018	11	21	10	47.62	-8.64	74.74
2019	21	22	1	4.55	-73.57	47.51

60-69 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	3	5	2	40	-151.06	85.66
1993	8	5	-3	-60	-389.08	47.66
1994	3	6	3	50	-99.92	87.5
1995	5	6	1	16.67	-173.05	74.57
1996	8	6	-2	-33.33	-284.27	53.74
1997	8	6	-2	-33.33	-284.27	53.74
1998	11	6	-5	-83.33	-395.73	32.2
1999	7	6	-1	-16.67	-247.15	60.79
2000	5	7	2	28.57	-125.05	77.33
2001	3	7	4	57.14	-65.73	88.92
2002	1	7	6	85.71	-16.11	98.24
2003	8	7	-1	-14.29	-215.16	58.56
2004	9	7	-2	-28.57	-245.23	52.12
2005	9	8	-1	-12.5	-191.58	56.59
2006	7	8	1	12.5	-141.29	68.27
2007	10	9	-1	-11.11	-173.44	54.85
2008	13	10	-3	-30	-196.47	43
2009	11	10	-1	-10	-159.01	53.28
2010	7	11	4	36.36	-64.16	75.33
2011	16	12	-4	-33.33	-181.84	36.92
2012	10	12	2	16.67	-92.88	64
2013	17	13	-4	-30.77	-169.23	36.48
2014	13	14	1	7.14	-97.55	56.35
2015	16	14	-2	-14.29	-134.15	44.22
2016	14	15	1	6.67	-93.35	54.95
2017	10	15	5	33.33	-48.39	70.05
2018	16	15	-1	-6.67	-115.75	47.26
2019	22	15	-7	-46.67	-182.72	23.91

70-79 years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	12	8	-4	-50	-266.95	38.68
1993	3	8	5	62.5	-41.35	90.05
1994	10	8	-2	-25	-216.72	50.67
1995	9	8	-1	-12.5	-191.58	56.59
1996	5	8	3	37.5	-91.05	79.55
1997	13	8	-5	-62.5	-292.06	32.65
1998	11	8	-3	-37.5	-241.84	44.69
1999	3	8	5	62.5	-41.35	90.05
2000	15	9	-6	-66.67	-280.84	27.06
2001	7	9	2	22.22	-108.84	71.03
2002	6	9	3	33.33	-87.3	76.27
2003	6	9	3	33.33	-87.3	76.27
2004	9	8	-1	-12.5	-191.58	56.59
2005	7	8	1	12.5	-141.29	68.27
2006	7	8	1	12.5	-141.29	68.27
2007	8	8	0	0	-166.44	62.47
2008	8	8	0	0	-166.44	62.47
2009	9	8	-1	-12.5	-191.58	56.59
2010	7	8	1	12.5	-141.29	68.27
2011	8	8	0	0	-166.44	62.47
2012	12	8	-4	-50	-266.95	38.68
2013	12	8	-4	-50	-266.95	38.68
2014	13	8	-5	-62.5	-292.06	32.65
2015	9	8	-1	-12.5	-191.58	56.59
2016	8	8	0	0	-166.44	62.47
2017	10	9	-1	-11.11	-173.44	54.85
2018	9	9	0	0	-151.92	60.3
2019	14	10	-4	-40	-215.18	37.81

80+ years						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	6	6	0	0	-210.06	67.75
1993	4	6	2	33.33	-136.24	81.19
1994	12	6	-6	-100	-432.88	24.94
1995	2	6	4	66.67	-65.15	93.27
1996	5	6	1	16.67	-173.05	74.57
1997	3	6	3	50	-99.92	87.5
1998	7	6	-1	-16.67	-247.15	60.79
1999	7	6	-1	-16.67	-247.15	60.79
2000	6	6	0	0	-210.06	67.75
2001	5	6	1	16.67	-173.05	74.57
2002	9	6	-3	-50	-321.42	46.61
2003	6	6	0	0	-210.06	67.75
2004	4	6	2	33.33	-136.24	81.19
2005	6	6	0	0	-210.06	67.75
2006	6	6	0	0	-210.06	67.75
2007	4	6	2	33.33	-136.24	81.19
2008	4	6	2	33.33	-136.24	81.19
2009	7	6	-1	-16.67	-247.15	60.79
2010	8	6	-2	-33.33	-284.27	53.74
2011	10	6	-4	-66.67	-358.57	39.43
2012	3	6	3	50	-99.92	87.5
2013	10	6	-4	-66.67	-358.57	39.43
2014	10	6	-4	-66.67	-358.57	39.43
2015	15	6	-9	-150	-544.33	3
2016	11	6	-5	-83.33	-395.73	32.2
2017	8	6	-2	-33.33	-284.27	53.74
2018	5	6	1	16.67	-173.05	74.57
2019	10	6	-4	-66.67	-358.57	39.43

Note:Poisson model has been used to predict the counts using the pre-vaccination period from 1992-Most recent available year‘s data

Model is calculated by, log(No. of anal cancer cases) = log (Population at risk) + intercept + (β × calendar year)

%Reduction = ((predicted counts –observed counts)/ predicted counts)×100

Wald’s 95% CI and %reduction was estimated using Poisson model for non-zero observed counts

*Positive sign indicates the reduction and negative sign indicates the increase in observed counts

The predicted counts are not estimated for 0-9, 10-19, 20-29 age groups because the number of observed counts for the pre vaccination period is less than 5

Figure 14.2.3.11.1 Predicted and observed counts of anal cancer cases, by 0-9 years - Finland

The predicted counts are not estimated for 0-9 age groups because the number of observed counts for the pre vaccination

period is less than 5

Figure 14.2.3.11.2 Predicted and observed counts of anal cancer cases, by 10-19 years - Finland

The predicted counts are not estimated for 10-19 age groups because the number of observed counts for the pre vaccination

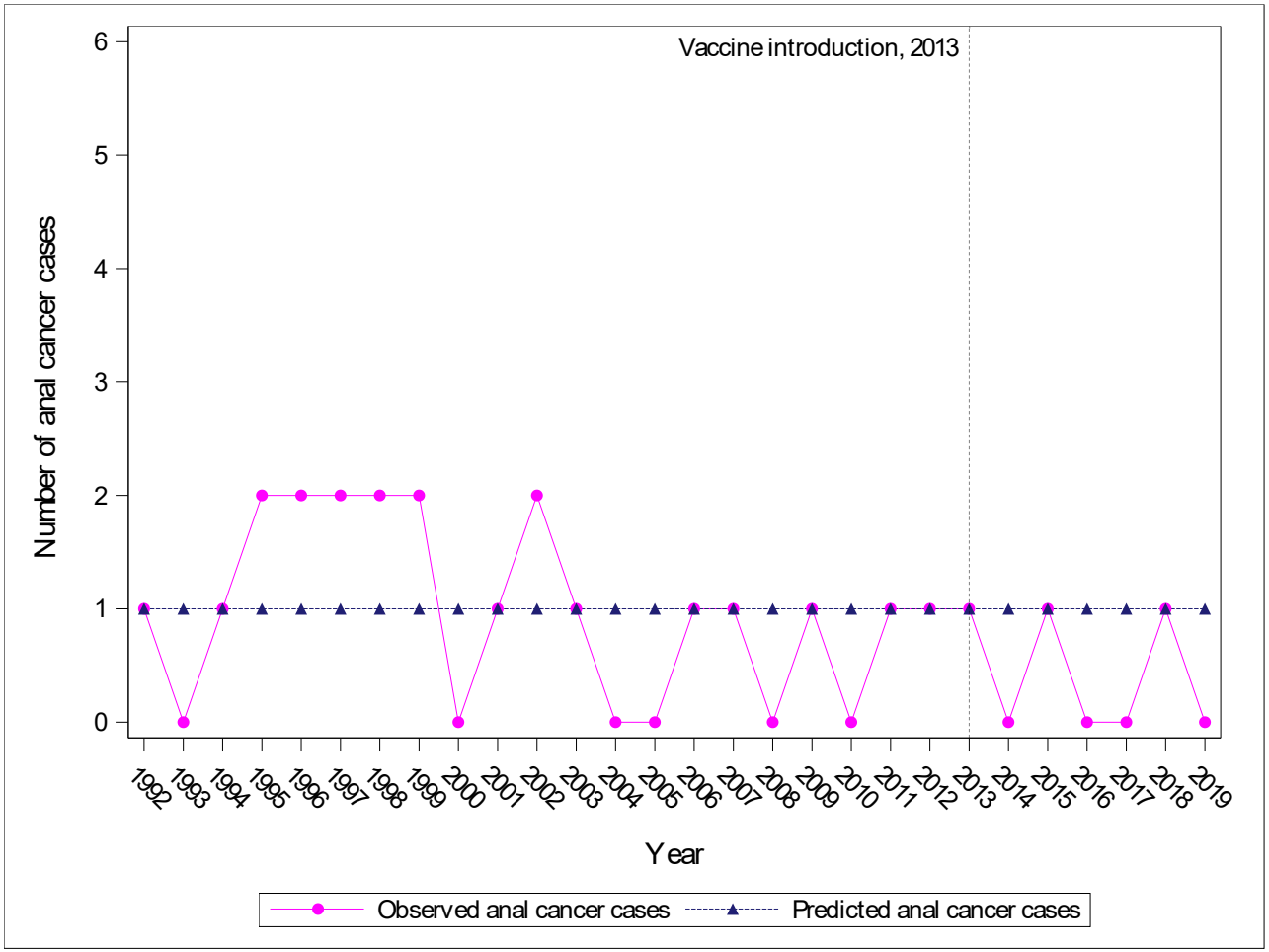
period is less than 5

Figure 14.2.3.11.3 Predicted and observed counts of anal cancer cases, by 20-29 years - Finland

The predicted counts are not estimated for 20-29 age groups because the number of observed counts for the pre vaccination

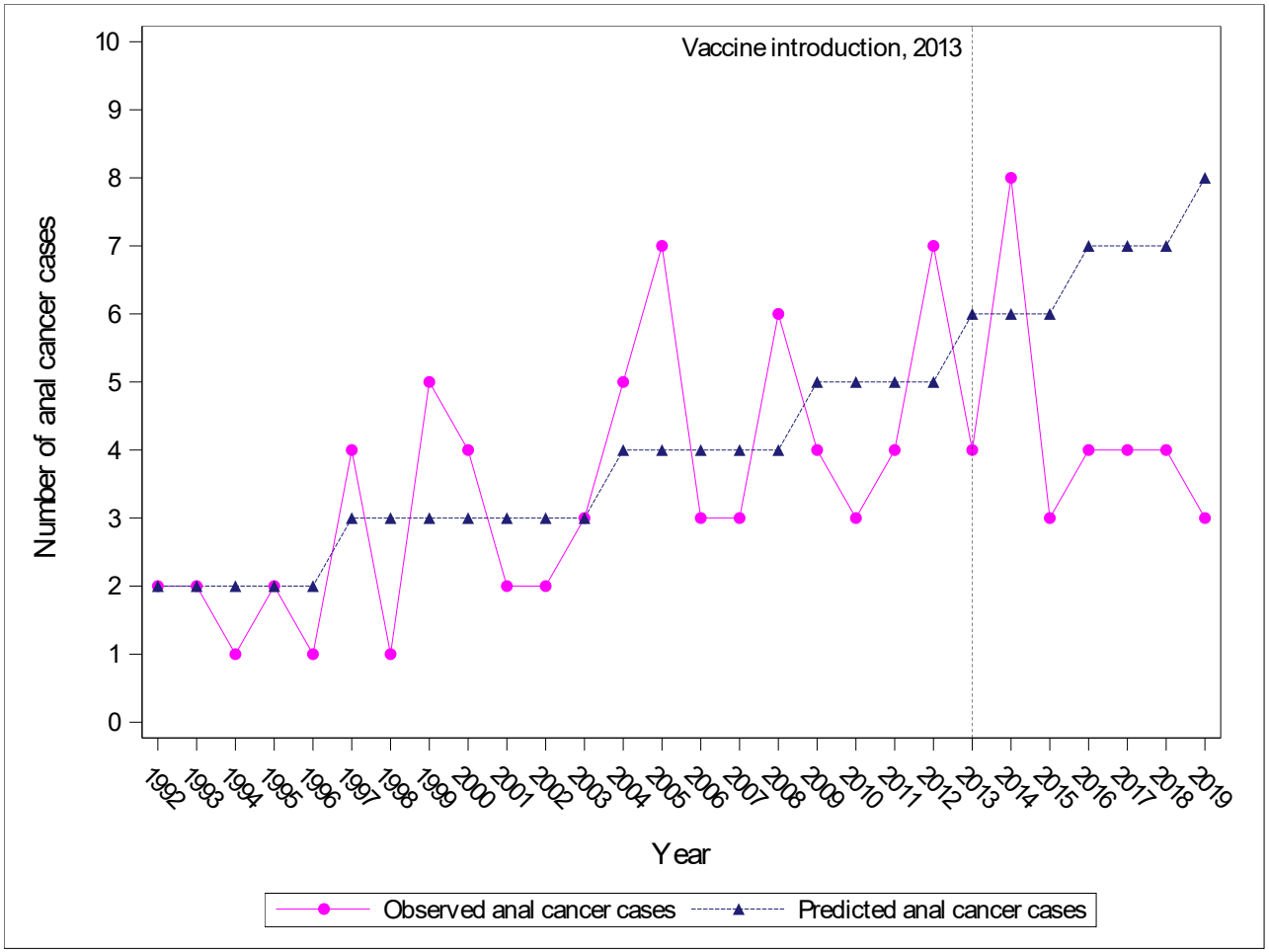
period is less than 5

Figure 14.2.3.11.4 Predicted and observed counts of anal cancer cases, by 30-39 years - Finland



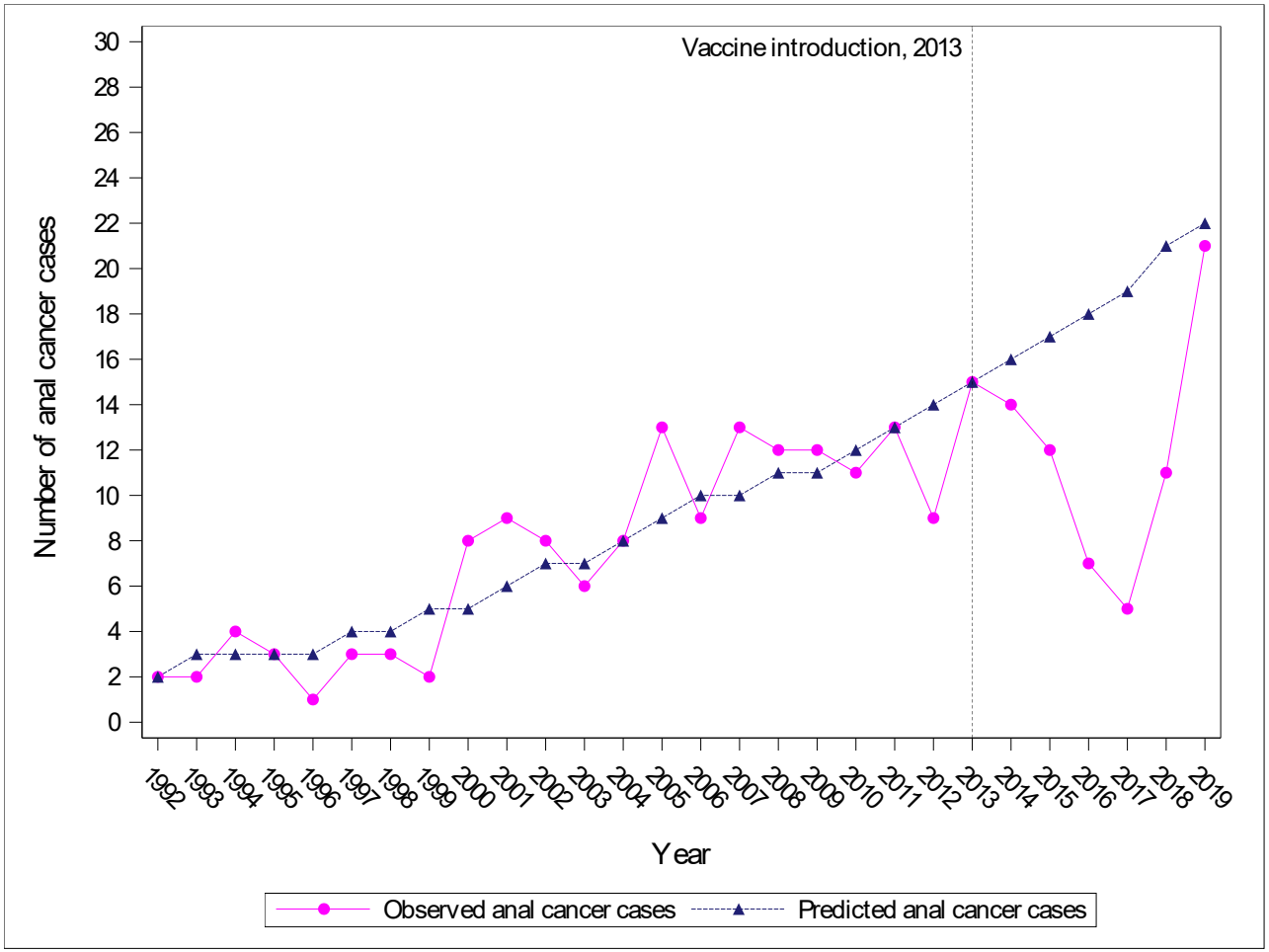
Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.3.11.5 Predicted and observed counts of anal cancer cases, by 40-49 years - Finland



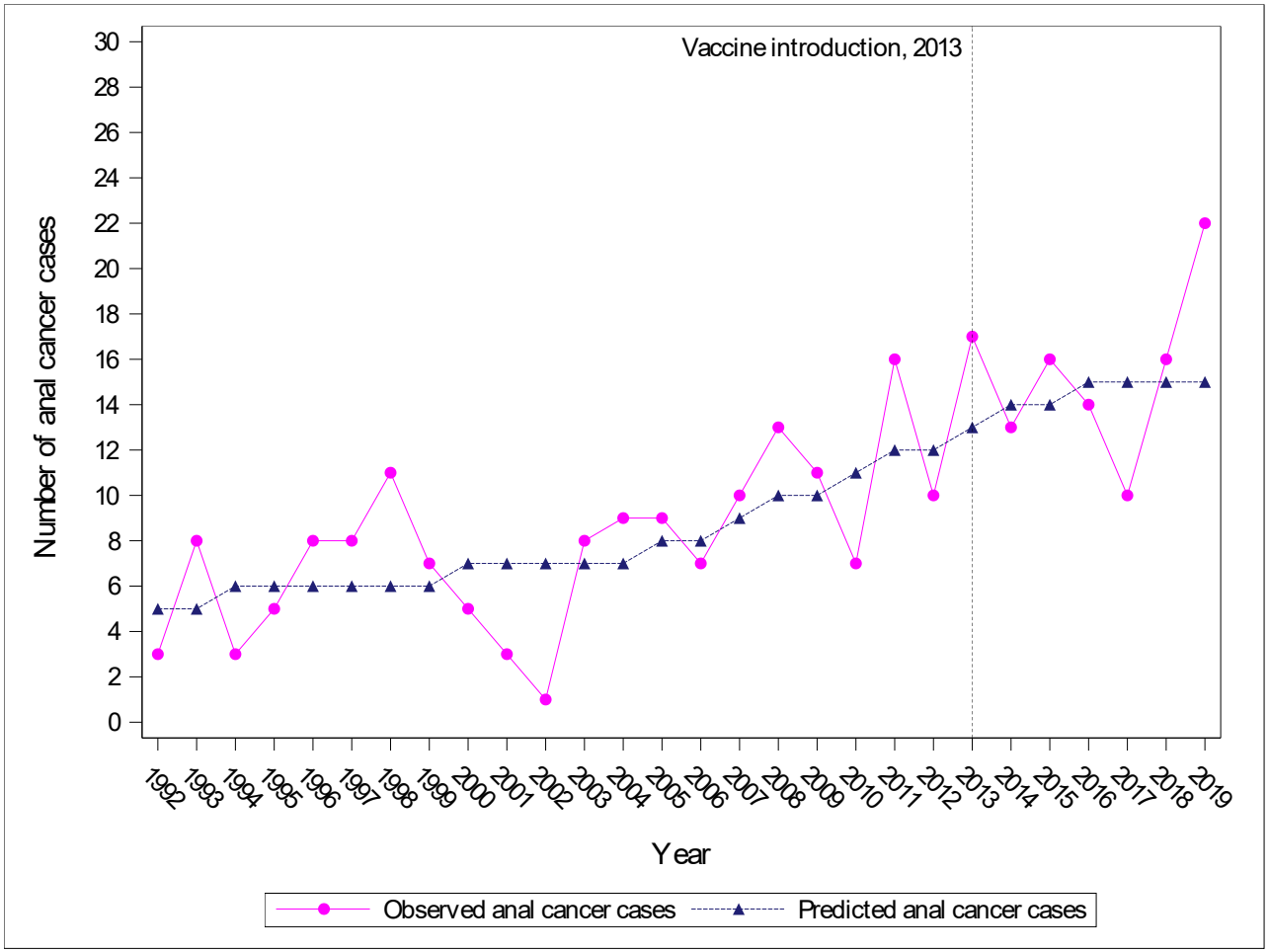
Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.3.11.6 Predicted and observed counts of anal cancer cases, by 50-59 years - Finland



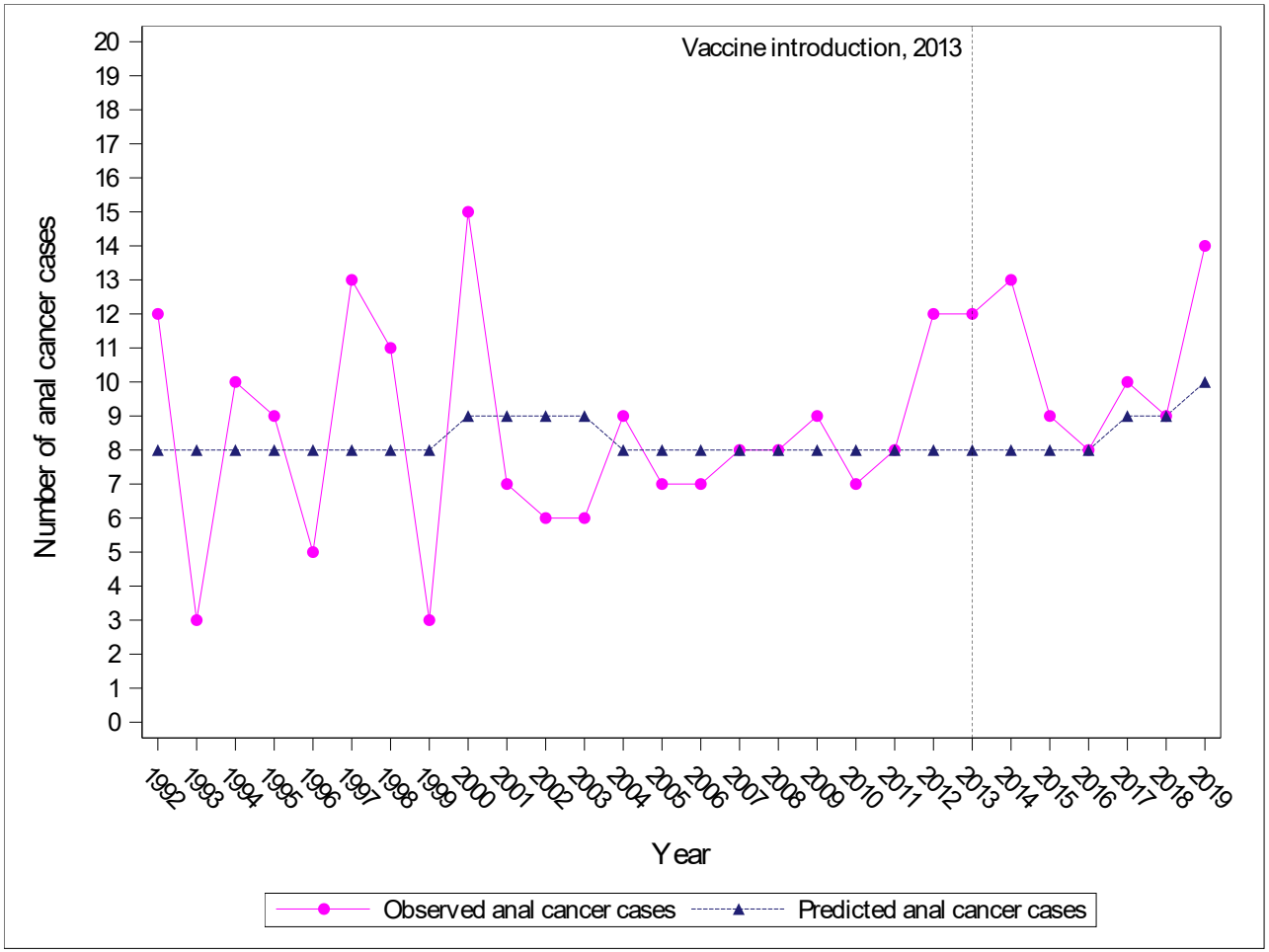
Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.3.11.7 Predicted and observed counts of anal cancer cases, by 60-69 years - Finland



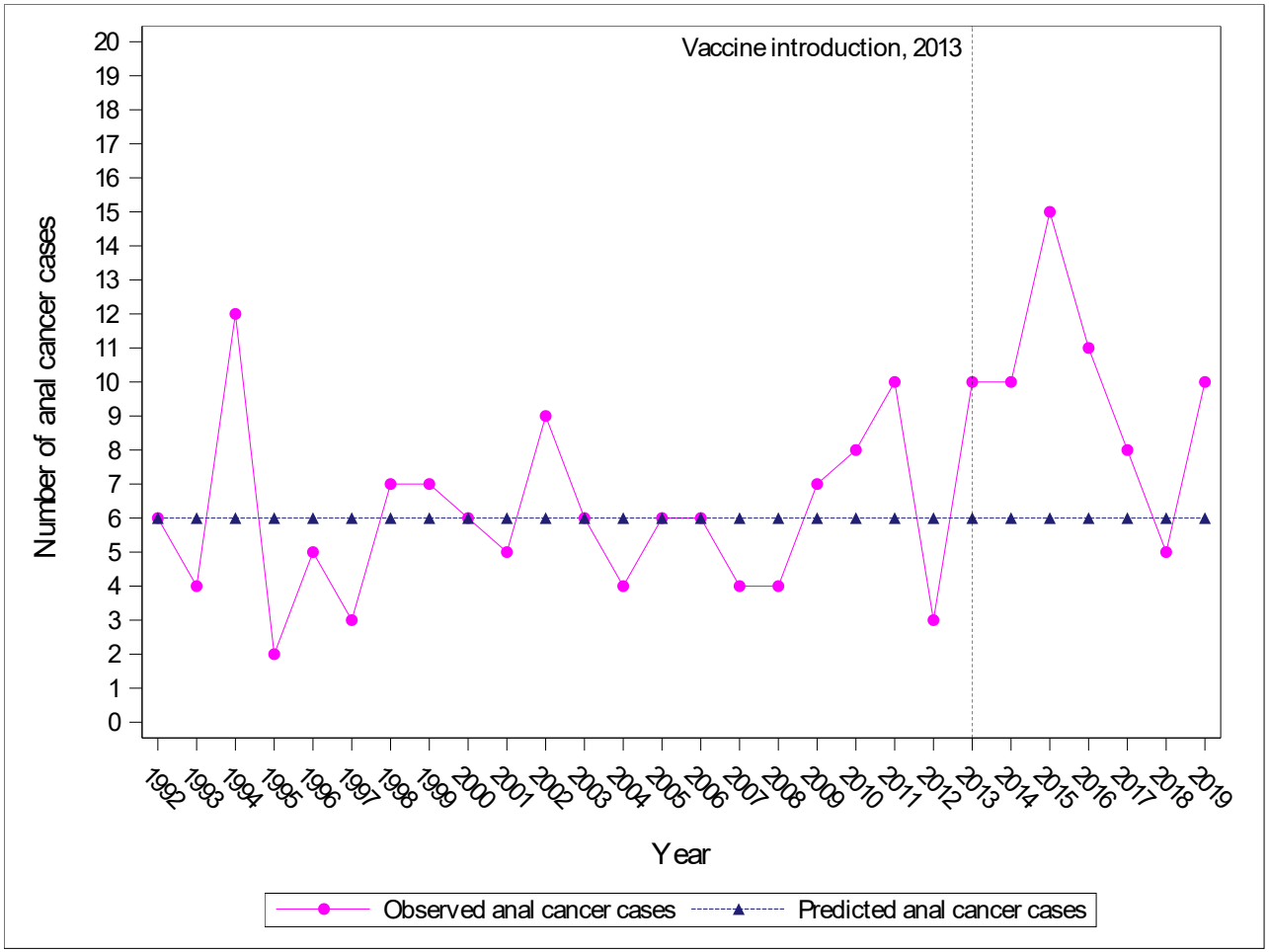
Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.3.11.8 Predicted and observed counts of anal cancer cases, by 70-79 years - Finland



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.3.11.9 Predicted and observed counts of anal cancer cases, by 80 years and above - Finland



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Table 14.2.3.12 Trend overtime of anal cancer cases by observed counts versus predicted counts, by gender - Finland

Male						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	11	7	-4	-57.14	-305.36	39.08
1993	9	7	-2	-28.57	-245.23	52.12
1994	6	8	2	25	-116.15	73.98
1995	12	8	-4	-50	-266.95	38.68
1996	8	8	0	0	-166.44	62.47
1997	8	9	1	11.11	-130.39	65.7
1998	9	9	0	0	-151.92	60.3
1999	6	10	4	40	-65.09	78.19
2000	12	10	-2	-20	-177.74	48.15
2001	7	11	4	36.36	-64.16	75.33
2002	4	12	8	66.67	-3.35	89.25
2003	10	12	2	16.67	-92.88	64
2004	17	13	-4	-30.77	-169.23	36.48
2005	13	14	1	7.14	-97.55	56.35
2006	11	14	3	21.43	-73.07	64.33
2007	14	15	1	6.67	-93.35	54.95
2008	23	16	-7	-43.75	-172.09	24.05
2009	21	17	-4	-23.53	-134.14	34.83
2010	15	18	3	16.67	-65.35	58
2011	21	19	-2	-10.53	-105.58	40.58
2012	20	20	0	0	-85.85	46.19
2013	28	21	-7	-33.33	-134.78	24.28
2014	19	22	3	13.64	-59.56	53.25
2015	19	24	5	20.83	-44.52	56.63
2016	11	25	14	56	10.58	78.35
2017	17	26	9	34.62	-20.5	64.52
2018	22	28	6	21.43	-37.33	55.05
2019	27	29	2	6.9	-57.25	44.88

Female						
					95% CI	
Year	Observed counts	Predicted counts	Difference (Predicted-Observed)	%Reduction*	LL	UL
1992	15	17	2	11.76	-76.68	55.93
1993	11	18	7	38.89	-29.38	71.14
1994	25	18	-7	-38.89	-154.56	24.22
1995	11	18	7	38.89	-29.38	71.14
1996	14	19	5	26.32	-46.96	63.05
1997	25	19	-6	-31.58	-138.92	27.54
1998	26	20	-6	-30	-132.87	27.43
1999	20	20	0	0	-85.85	46.19
2000	26	20	-6	-30	-132.87	27.43
2001	21	21	0	0	-83.1	45.38
2002	24	21	-3	-14.29	-105.28	36.37
2003	20	22	2	9.09	-66.57	50.38
2004	18	22	4	18.18	-52.54	56.11
2005	29	23	-6	-26.09	-117.94	27.05
2006	23	23	0	0	-78.24	43.9
2007	26	24	-2	-8.33	-88.67	37.8
2008	20	24	4	16.67	-50.85	53.96
2009	23	25	2	8	-62.08	47.78
2010	22	25	3	12	-56.07	50.38
2011	31	26	-5	-19.23	-100.79	29.2
2012	22	26	4	15.38	-49.29	52.04
2013	31	27	-4	-14.81	-92.34	31.46
2014	40	28	-12	-42.86	-131.55	11.86
2015	37	28	-9	-32.14	-115.9	19.12
2016	32	29	-3	-10.34	-82.38	33.24
2017	20	30	10	33.33	-17.39	62.14
2018	24	30	6	20	-36.84	53.23
2019	43	31	-12	-38.71	-120.12	12.59

Note:Poisson model has been used to predict the counts using the pre-vaccination period from 1992-Most recent available year‘s data

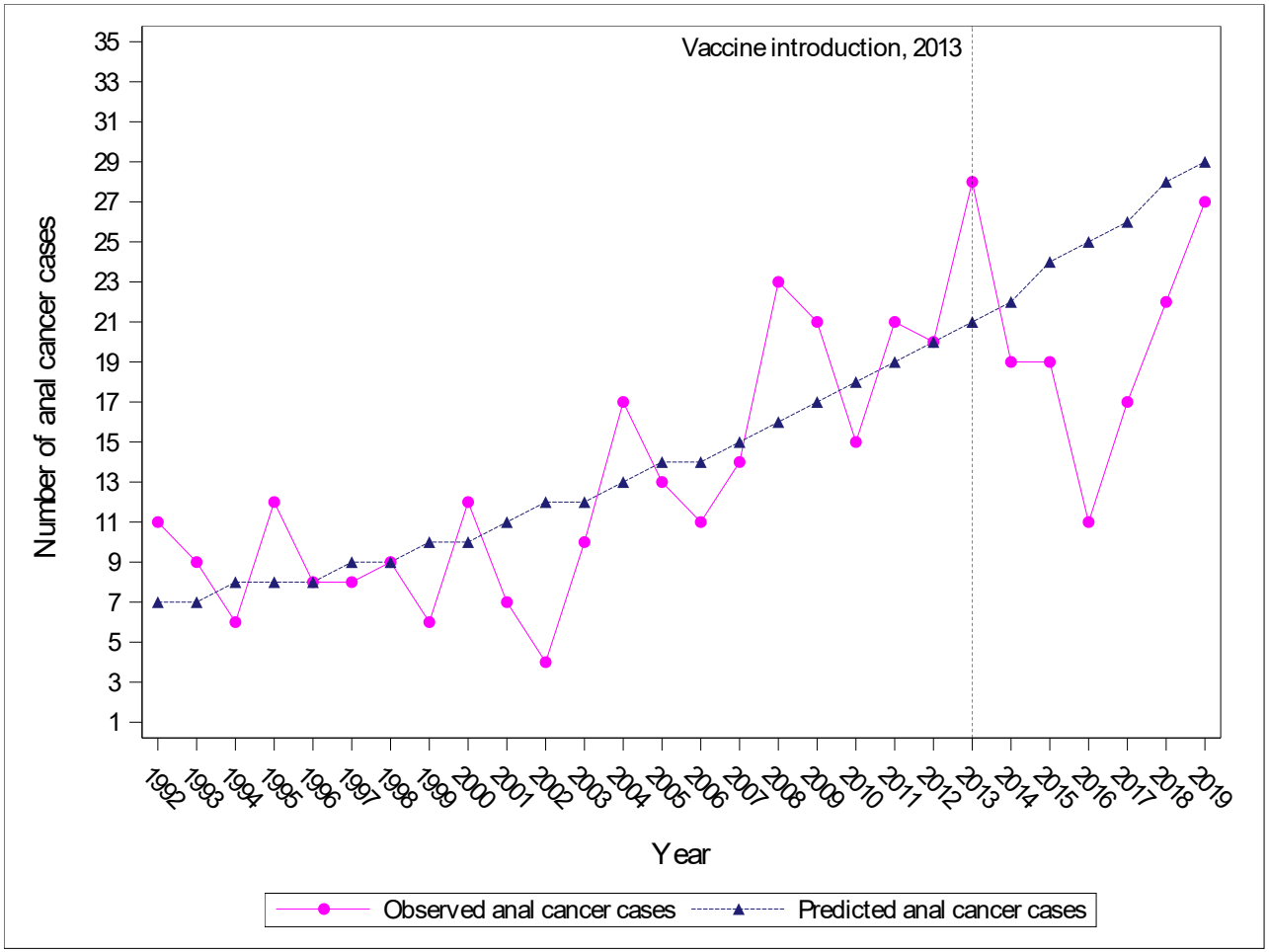
Model is calculated by, log(No. of anal cancer cases) = log (Population at risk) + intercept + (β × calendar year)

%Reduction = ((predicted counts –observed counts)/ predicted counts)×100

Wald’s 95% CI and %reduction was estimated using Poisson model for non-zero observed counts

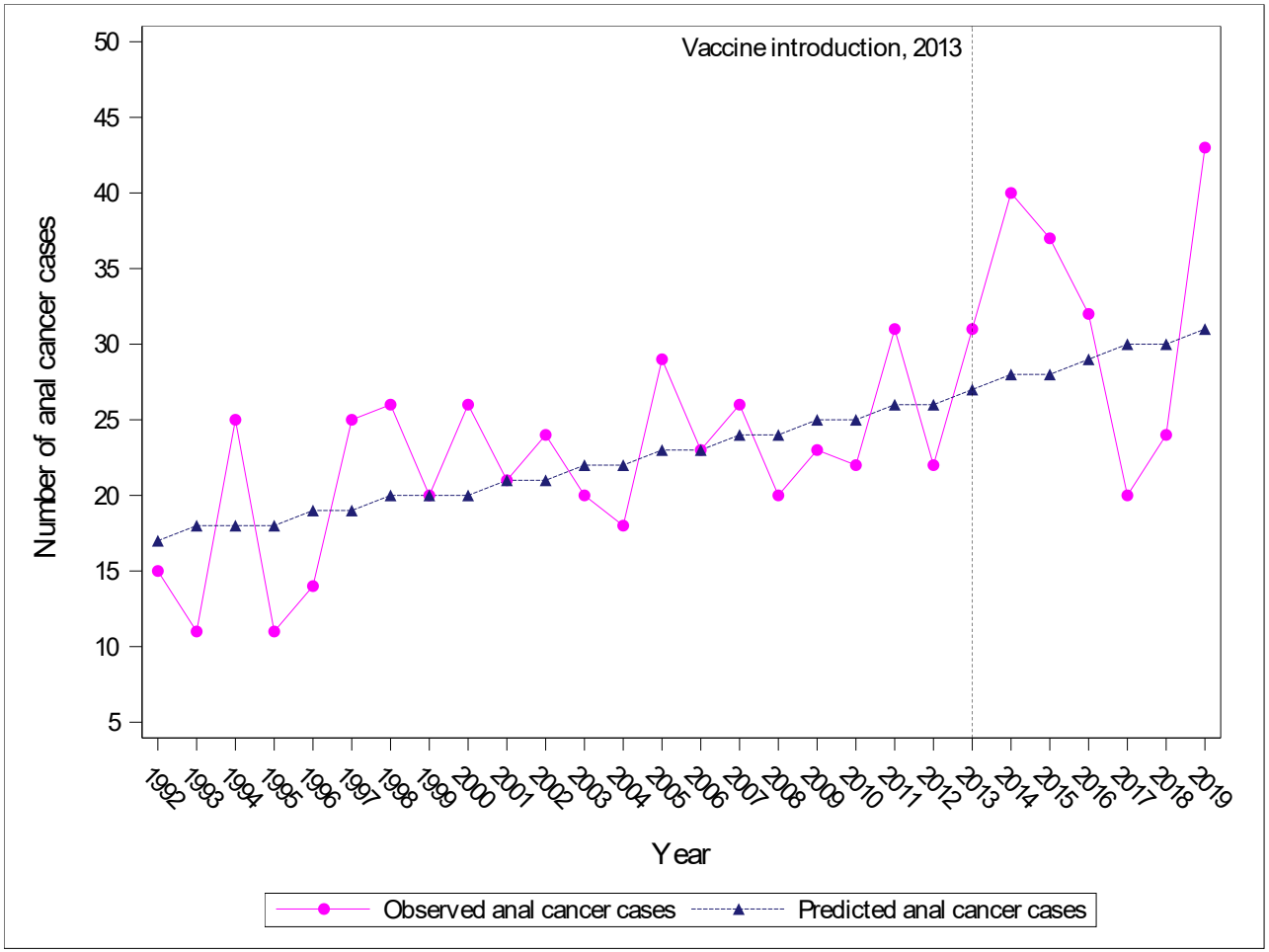
*Positive sign indicates the reduction and negative sign indicates the increase in observed counts

Figure 14.2.3.12.1 Predicted and observed counts of anal cancer cases, by Male - Finland



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Figure 14.2.3.12.2 Predicted and observed counts of anal cancer cases, by Female - Finland



Note: The vaccine introduction year is considered as the year when Cervarix was introduced in the NIP

Table 14.2.3.13 Summary of HPV vaccine coverage in Females by year - Finland

Year	HPV vaccine coverage (%)
2013	75.70
2014	73.20
2015	76.20
2016	74.80
2017	76.00
2018	81.00
2019	79.10
2020	71.00

Table 14.2.3.14 Summary of birth cohort by year and gender - Finland

Year	Gender	Birth cohort
2007	Male	30136
	Female	28593
	Total	58729
2008	Male	30415
	Female	29115
	Total	59530
2009	Male	30795
	Female	29635
	Total	60430
2010	Male	31309
	Female	29671
	Total	60980
2011	Male	30546
	Female	29415
	Total	59961
2012	Male	30308
	Female	29185
	Total	59493
2013	Male	29858
	Female	28276
	Total	58134
2014	Male	29272
	Female	27960
	Total	57232
2015	Male	28469
	Female	27003
	Total	55472
2016	Male	26812
	Female	26002
	Total	52814
2017	Male	25674
	Female	24647
	Total	50321
2018	Male	24630
	Female	22947
	Total	47577
2019	Male	23186
	Female	22427
	Total	45613

Table 14.2.3.15 Feasibility assessment: Number of anal cancer cases and time frame predicted for the Vaccine effectiveness - Finland

		Case-Control Ratio 1:1		Case-Control Ratio 1:2		Case-Control Ratio 1:3		Case-Control Ratio 1:4	
Vaccine Coverage	Vaccine Effectiveness	Number of cases required	Year	Number of cases required	Year	Number of cases required	Year	Number of cases required	Year
30	30	1019	2111	720	2098	624	2094	577	2092
	40	514	2090	364	2083	317	2080	294	2079
	50	290	2079	208	2074	181	2072	168	2071
	60	176	2072	126	2068	111	2067	103	2066
	70	109	2067	81	2064	70	2062	66	2062
	80	69	2063	52	2060	46	2059	43	2059
	90	42	2059	33	2057	29	2056	27	2056
40	30	867	2106	612	2094	529	2090	489	2088
	40	433	2087	307	2080	265	2078	244	2076
	50	242	2077	173	2072	150	2070	138	2069
	60	144	2070	104	2067	90	2065	83	2064
	70	88	2065	65	2063	56	2061	52	2061
	80	55	2062	40	2059	35	2058	33	2058
	90	33	2058	25	2056	22	2055	21	2055
60	30	820	2106	577	2094	497	2090	456	2088
	40	399	2087	281	2081	242	2078	222	2077
	50	217	2078	153	2072	131	2070	121	2069
	60	126	2071	90	2067	77	2065	70	2064
	70	74	2066	53	2063	46	2061	42	2061
	80	44	2062	31	2059	27	2058	25	2057
	90	25	2058	18	2056	16	2055	14	2054
80	30	1158	2127	811	2109	694	2103	636	2100
	40	549	2099	384	2089	328	2085	299	2084
	50	289	2085	202	2079	172	2076	156	2075
	60	160	2077	112	2072	95	2070	86	2069
	70	90	2071	64	2067	53	2065	48	2064
	80	49	2067	35	2063	30	2062	26	2061
	90	25	2062	17	2059	14	2058	13	2057
90	30	1994	2176	1395	2143	1191	2132	1087	2126

		Case-Control Ratio 1:1		Case-Control Ratio 1:2		Case-Control Ratio 1:3		Case-Control Ratio 1:4	
Vaccine Coverage	**Vaccine Effectiveness**	**Number of cases required**	**Year**	**Number of cases required**	**Year**	**Number of cases required**	**Year**	**Number of cases required**	**Year**
	40	930	2125	649	2107	551	2101	502	2098
	50	480	2101	334	2090	283	2087	257	2085
	60	259	2089	181	2082	152	2079	138	2077
	70	140	2081	98	2075	82	2072	74	2071
	80	73	2075	51	2070	42	2068	38	2067
	90	34	2070	22	2065	18	2063	17	2062

Average female birth cohort for the last 10 years (2010-2019) available data = 26753.3
Average incidence (per 100000) available from latest 5 years period (2015-2019):
20-29: 0
30-39: 0.058
40-49: 0.676
50-59: 2.12
60-69: 2.472
70-79: 2.044
80+: 3.174
Year = Year to reach the number of cases required for the completion of case-control study
Life Expectancy of 85 years in Finland has been considered as the upper limit of age for the feasibility assessment

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16. ANNEXES

Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1.	217743	09 June 2022	Annex 1: List of stand-alone documents
2.	217743	09 June 2022	Annex 2: Glossary of Terms
3.	217743	09 June 2022	Annex 3: Trademarks
4.	217743	09 June 2022	Annex 4: Changes in the conduct of the study
5.	217743	09 June 2022	Annex 5: Additional information

Annex 2 Glossary of Terms

Case-control study: A form of epidemiological study where the study population is selected based on whether the participants do (cases) or do not (controls) have the particular outcome (disease) under study. The groups are then compared with respect to exposure/characteristic of interest.

Commitment: Agreement made with Regulatory Authorities as specific condition of regulatory approval and authorisation, either made at the time of product approval or during the lifecycle of the approved product.

Database: A database is a set of pre-existing tables and views containing data. The term “pre-existing” implies that the analysis will be done on retrospective data and the term “views” implies that the data can be made readily available in an electronic format through a straightforward extract, without re-encoding and manual manipulation (like a transpose, a translation, split of a field into several fields, etc).

Database study: A study involving the use of pre-existing data maintained in an electronic format; this will not include collection of new data that requires (re-) encoding via case report form/electronic case report form and retesting of human biological samples.

Epidemiological study: An observational or interventional study without administration of medicinal product(s) as described in a research protocol.

Participant: Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database.

Synonym: subject

Post-Authorisation Safety Study:	A pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product. This includes all GSK sponsored non-interventional studies and clinical trials conducted anywhere in the world that are in accordance with the terms of the European marketing authorisation and where the investigation of safety is the specific stated objective. Note: The phrase 'In accordance with the terms of the European marketing authorisation' means that the product is used according to the European label (e.g. within the recommended dose range, the approved formulation, indication, etc.).
Retrospective study:	A study that looks backward in time (e.g. at events that occurred in the past; outcomes and exposure can no longer be influenced), usually using medical records, databases or interviews in order to address one or more study objectives.
Study population:	Sample of population of interest.
Surveillance:	The ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.
Targeted Safety Study:	Studies specifically planned or conducted to examine an actual or hypothetical safety concern in a product marketed anywhere in the world. This includes any GSK sponsored pharmaco-epidemiological study or clinical trial conducted anywhere in the world with the aim of identifying or quantifying a safety hazard. Although all clinical trials collect safety information as a matter of routine, only those initiated to examine a specific safety concern are considered a TSS.

Annex 3 Trademarks

The following trademark is used in the present report.

Note: In the body of the report (including the abstract), the name of the vaccine is written without the superscript symbol ™ or ® and in *italics*.

Trademark Information

Trademark of the GSK group of companies	Generic description
Cervarix	Human papillomavirus (HPV) Types 16 and 18 vaccine (recombinant, AS04-adjuvanted)

Trademark not owned by the GSK group of companies	Generic description
GARDASIL (Merck & CO., Inc.)	Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine

Annex 4 Changes in the conduct of the study

There was a protocol amendment (dated 2 June 2022) and a SAP amendment (dated 2 June 2022) issued after the start of the study. The interim analysis was not performed for all 5 selected European countries as planned in the protocol. It was only performed for 3 European countries: Finland, the Netherlands and England. The analysis was not performed for Denmark and Norway. In Denmark, *Cervarix* was only introduced in the NIP from February 2016 until November 2017 and the doses applied thereafter have been reported mainly from the private market (refer to Annex 5). The vast majority of females vaccinated against HPV in Denmark have received the quadrivalent HPV vaccine (refer to Annex 5). In Norway, *Cervarix* was only introduced in the NIP in September 2017 (refer to Annex 5). Hence, a decision was made to focus the study on those countries that administered *Cervarix* for at least 5 birth cohorts (either routine or catch-up campaign cohorts), or that have implemented *Cervarix* in their NIPs in a continuous manner since the introduction in their NIP (refer to Section 9.2 of the protocol [Appendix 17.1.1] for details on country eligibility criteria). The analysis for Denmark and Norway maybe performed during the final analysis, planned in 2026, depending on the data availability during that time.

Annex 5 Additional information

The table below presents details on vaccination schedules and vaccine coverage in the 5 selected European countries.

Country	Date HPV vaccine first introduced	Vaccine given	Immunisation schedule	Age cohort	Catch-up campaigns	Vaccine coverage	Date modification immunisation schedule	Modification immunisation schedule
Denmark	January 2009	Quadrivalent HPV (*Gardasil*)	0m, 2m, 6m	12 yo girls (born 1996) (GP-based)	13-15 yo girls Women born 1985-1992 (August 2012 to December 2013)	79% 3-dose	August 2014 February 2016 November 2017 July 2019	*Gardasil* (0m, 6m) *Cervarix* (0m, 6m) *Gardasil 9* (0m, 6m) for girls *Gardasil 9* (0m, 6m) for boys 12 yo on 1 July 2019 or later
Finland	November 2013	Bivalent HPV (*Cervarix*)	0m, 1m, 6m	11-12 yo (born 2005) (school-based)	13-15 yo girls (November 2013)	68% 3-dose in 2015 72% 3-dose in 2016	Autumn 2020	*Cervarix* (0m, 6m) girls and boys 12 yo + Catch-up for boys in grades 7-9 (2020-21 and 2021-22)
Netherlands	September 2009	Bivalent HPV (*Cervarix*)	0m, 1m, 6m	12 yo girls 10 yo girls/boys	13-16 yo girls (2009/2010) 12-18 yo girls/boys (2022/2023)	58% 3-dose (cohort 1998)	January 2014 January 2022	*Cervarix* (0m, 6m) *Cervarix* (0m, 6m) girls and boys
Norway	August 2009	Quadrivalent HPV (*Gardasil*)	0m, 2m, 6m	12 yo (born 1997) (school-based)	Girls born in 1991 or later (2016-2018)	1997 cohort-65% 3-dose in 2011 2004 cohort-83% 3-dose in 2016/2017 school year	September 2017 September 2018	*Cervarix* (0m, 6m) girls *Cervarix* (0m, 6m) girls and boys 12 yo

Country	Date HPV vaccine first introduced	Vaccine given	Immunisation schedule	Age cohort	Catch-up campaigns	Vaccine coverage	Date modification immunisation schedule	Modification immunisation schedule
England	September 2008	Bivalent HPV (*Cervarix*)	0m, 1m, 6m	12-13 yo girls (school-based)	14 to < 18 yo	86.7% 3-dose in 2013/2014 83.9% 2-dose in 2018/2019 64.7% 2-dose in 2019/2020	September 2012 September 2014 April 2018 September 2019	*Gardasil* (0m, 2m, 6m) for girls *Gardasil* (0m, 6m, or 12m) for girls *Gardasil* (0m, 6m) for MSM ≤ 45 yo *Gardasil 9* (0m, 6m, or 12m) for boys 12-13 yo + Catch-up girls and boys up to 25th birthday

GP: General practitioner; HPV: human papillomavirus; m: month; yo: years old; MSM: Men who have sex with men.

PASS INFORMATION

Title:	An observational, retrospective database post-authorisation safety study (PASS) to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced *Cervarix* in their National Immunisation Programmes (NIP)
Protocol version identifier:	217743 (EPI-HPV-099 VS EUR DB)
Date of last version of the protocol:	Protocol Amendment 2 Final: 25 May 2022
EU PAS Register No:	To be determined
Active substance:	HPV-16 L1 VLP protein HPV-18 L1 VLP protein
Medicinal product:	Bivalent human papillomavirus (HPV-16/18 L1 VLP AS04) recombinant vaccine
Product reference:	EMEA/H/C/000721
Procedure number:	To be allocated
Marketing Authorisation Holder (MAH):	GlaxoSmithKline Biologicals SA Rue de l'Institut, 89 1330 Rixensart, Belgium
Joint PASS:	No
Research question and objectives: **(Amended 25 May 2022)**	To assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal cancer in females and males
Countries of study:	Finland, the Netherlands, England, Denmark, and Norway
Author:	PPD , Epidemiology Lead, GlaxoSmithKline Biologicals SA

MARKETING AUTHORISATION HOLDER

MAH:	GlaxoSmithKline Biologicals SA Rue de l'Institut, 89 1330 Rixensart, Belgium
MAH contact person: **(Amended 25 May 2022)**	PPD **,** ***MD*** ***Clinical & Epidemiology Project Lead*** ***GlaxoSmithKline Biologicals SA***

Based on GSK Biologicals' protocol template for post-authorisation safety studies v17.1

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2. LIST OF ABBREVIATIONS

AIN	Anal intraepithelial neoplasia
APC	Annual percentage change
CI	Confidence interval
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
EU-RMP	European Union Risk Management Plan
GPP	Good Pharmacoepidemiology Practices
GSK	GlaxoSmithKline Biologicals SA
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
IACR	International Association of Cancer Registries
ICD	International Classification of Diseases
MAH	Marketing Authorisation Holder
MPL	3-*O*-desacyl-4'-monophosphoryl lipid A
MSM	Men who have sex with men
NCR	Netherlands Cancer Registry
NCRAS	National Cancer Registration and Analysis Service
NIP	National Immunisation Programme
PASS	Post-authorisation safety study
PHE	Public Health England
SCC	Squamous cell carcinoma
TSS	Targeted safety study
UK	United Kingdom
VE	Vaccine effectiveness
VLP	Virus-like particle
WHO	World Health Organisation

3. RESPONSIBLE PARTIES

(Amended 25 May 2022)

Biologicals SA (GSK) has the overall responsibility for the conduct of the study.

PPD , ***MD, Clinical & Epidemiology Project Lead, GlaxoSmithKline Biologicals SA.***

4. ABSTRACT

Title	An observational, retrospective database post-authorisation safety study (PASS) to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced *Cervarix* in their National Immunisation Programmes (NIP).
Version and date of the protocol	Protocol Amendment 2 Final: 25 May 2022
Main author	PPD, Epidemiology Lead, GlaxoSmithKline Biologicals SA
Rationale and background	Anal cancer is an uncommon type of cancer, representing around 0.3% of all incident cancers diagnosed in 2020 worldwide [Sung, 2021]. Squamous cell carcinoma (SCC) is the most frequent histopathological type of anal cancer [Hoff, 2017]. There is evidence to suggest that human papillomavirus (HPV) infection is associated with anal cancer, particularly with SCC [Hoff, 2017; De Martel, 2020]. Moreover, in a recent worldwide study, HPV deoxyribonucleic acid (DNA) was detected in more than 88% of anal cancers and more than 95% of anal intraepithelial neoplasia (AIN) grades 2/3. The most frequently detected virus type, detected in over 80.7% of invasive anal cancer cases was HPV-16,followed by HPV-18 (3.6% of cases) [Alemany, 2015; Clifford, 2019]. Over the last 4 decades, anal cancer incidence has been gradually increasing and is more common in women than in men, except for certain high-risk groups such as human immunodeficiency virus (HIV)-infected people, and this raise is more relevant in high-income countries [Lum, 2020]. Risk factors for anal cancer are HPV infection, including a former HPV-related malignancy, HIV infection, more than 10 lifetime sexual partners, ano-receptive intercourse, chronic immunosuppression, cigarette smoking, a history of gynaecological or haematologic malignancy, and age. Hence, HIV and immunocompromised patients, and men who have sex with men (MSM) are particularly vulnerable populations [Nelson, 2017; Van der Zee, 2013; Clifford, 2021]. GlaxoSmithKline Biologicals SA (GSK) has developed a prophylactic HPV vaccine, *Cervarix*, based on L1 proteins of HPV-16 and HPV-18 formulated with AS04

(comprising of aluminium hydroxide [Al(OH)3] and 3-O-desacyl-4'-monophosphoryl lipid A [MPL]).

Cervarix is a vaccine for use from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to certain oncogenic HPV types.

In the context of the European Union Risk Management Plan (EU-RMP) for *Cervarix*, a safety concern was raised linked to missing information on the impact and effectiveness of the vaccine against anal lesions and cancer, since it was not prospectively evaluated in clinical trials.

This study will assess the data on anal cancer in countries where *Cervarix* vaccination has been introduced in the NIP. Five European countries were initially preselected: Finland, the Netherlands, England, Denmark, and Norway to perform a trend analysis and to assess feasibility for a case-control study.

Research question and objectives

(Amended 25 May 2022)

The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal cancer in females and males.

Primary Objectives:

- To assess trends and changes over time in the age-standardised incidence of anal cancer by sex, HPV type and histological classification for each country* separately.
- To assess trends and changes over time in the crude incidence of anal cancer by age category, by sex, HPV type and histological classification for each country* separately.

Secondary Objective:

- To conduct a feasibility assessment for a case-control study to determine the effectiveness of *Cervarix* against anal cancer.

**Five European countries are considered for this study, and each country will be selected based on a set of criteria (please refer to Section 9.2 for country eligibility criteria).*

Study design

(Amended 25 May 2022)

- **Type of study and design**: This is a Targeted Safety Study (TSS) and a PASS. The study is designed as an observational, retrospective database study.
- **Study population**: Females and males of all age groups in the 5 selected European countries.

  Please refer to Section 9.2 for country eligibility criteria.
- **Data collection**: Retrospective data collection from national cancer registries.
- **Study period**:
  - Pre-*Cervarix* launch period (i.e., before *Cervarix* introduction in the NIP): The start and end calendar year for each country will be considered based on the data availability in their respective cancer registries.
  - Post-*Cervarix* launch period (i.e., after *Cervarix* introduction in the NIP): The start calendar year for each country will be the date when *Cervarix* was introduced in their NIP. An interim analysis will be performed in 2022. For ***the*** analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.
- This study will be a trend analysis of incidence of anal cancer in 5 selected European countries.
- The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine *Cervarix* effectiveness against anal cancer can be performed.
- Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed. Small intestine cancer is relatively rare, with an occurrence of similar magnitude to anal cancer.

	Small intestine cancer also has a similar mean age of diagnosis as anal cancer, and there is no screening programme for it. It is not associated with HPV infection. This analysis may allow to control for potential changes in cancer surveillance systems and reporting over time.
Population	The study population will include females and males of all age groups in the 5 selected European countries. Please refer to Section 9.2 for country eligibility criteria.
Variables **(Amended 25 May 2022)**	**Primary endpoint:** • Occurrence and age-standardised incidence of anal cancer during the period (i.e., pre- and post-*Cervarix* launch period) by sex, HPV type and histological classification for each country* separately. • Occurrence and crude incidence of anal cancer during the study period (i.e., pre- and post-*Cervarix* launch period) by age category, by sex, HPV type and histological classification for each country* separately. ***Note:*** Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed, by age category and sex for each country* separately. Please refer to Section 7 for details on choice of control. **Secondary endpoint:** • ***Expected number of anal cancer cases needed to conduct the case-control study based on the vaccine coverage rate and the expected VE and other factors for each country* separately.*** ***Note: Other feasibility assessment checks with findings for the conduct of a case-control study will be further described in the study report.*** **Five European countries are considered for this study and each country will be selected based on a set of criteria (please refer to Section 9.2 for country eligibility criteria).*

Data sources

(Amended 25 May 2022)

- Eurostat will be the source for data on the European Standard Population for age distribution used to estimate the age-standardised incidence rates [Pace, 2013]. It will also be the source for the population data and birth cohort data, except for England, for which the source for population data will be the UK Health Security Agency and for birth cohort data it will be Office for National Statistics.
- Vaccine coverage data will be retrieved from the respective websites of national public health institutes.
- This study will collect anal cancer data from the following national cancer registries:
  - The Finnish Cancer Registry [FCR]
  - The Netherlands Cancer Registry [NCR]
  - National Cancer Registration and Analysis Service [NCRAS] ***(UK)***
  - The Danish Cancer Registry [Danish Cancer Registry]
  - The Cancer Registry of Norway [CRN]
- ***Vaccination registries:***
  - ***Finnish National Vaccination Registry since 2009***
  - ***Dutch vaccination registry (Prœventis) since 2005***
  - ***Immunisations are registered in Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002) (UK)***
  - ***Danish vaccination registry since 2009, although compulsory as of 15 November 2015***
  - ***Norwegian vaccination registry since 1995***

Note: More details on vaccine coverage data and data collection are provided in Section 9.4.

Study size **(Amended 25 May 2022)**	Sample size computation ***for the primary objective*** is not applicable, as there is no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 5 selected European countries will be collected within the established timeframe. Please refer to Section 9.3 for details on variables and Section 9.4 for details on data sources. *Note: National cancer registries are nationwide and thus this study is population-based.*
Data analysis	Analysis will be performed using the country-specific data extracted from the national cancer registries as per defined population and timeframe (please refer to Section 9.1.1 for details on study population and study period). *Note: Details on primary analysis and secondary analysis are provided in Section 9.7.*
Milestones	The first round of data collection is planned to start in Quarter 3, 2021 and end in Quarter 4, 2021. The second round of data collection is planned to start in Quarter 3, 2026 and end in Quarter 4, 2026. The interim report is planned for Quarter 1, 2022. The final report of study results is planned for Quarter 1, 2027. *Note*: *The above-mentioned timelines are tentative and are subject to change*.

5. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	31 March 2022	Section 4 Abstract, Section 8 Primary objective and Section 9.3.1.1 Primary endpoint	Primary objective and its corresponding endpoint updated	For clarity: The primary objective and its corresponding endpoint has been split into 2 independent objectives and endpoints, respectively (i.e., for age-standardised incidence and for crude incidence)
		Section 4 Abstract and Section 9.1.1 Discussion of study design	Study population updated	For better interpretation of the study results so it can be comparable with publications across countries and to align with the age definition as per the European standardised population, the entire age group from 0 – 80+ population will be considered instead of the adult population (>18 years of age)
		Section 4 Abstract and Section 9.1.1 Discussion of study design	Study population updated	Study period (i.e., pre- and post-*Cervarix* launch period) will be considered based on the *Cervarix* introduction in the National Immunisation Programme (NIP)
		Section 4 Abstract, Section 7 Rationale and background, Section 8 Research question and objectives, Section 9.4.3 Websites of national public health institutes and Section 9.9 Limitations of the research methods	County specified: Changed from United Kingdom (UK) to England	For the UK, all analyses will be based specifically on data from England, and not data from UK. The National Cancer Registration and Analysis Service (NCRAS) is the cancer registry in England. As the population of England comprises around 84% of the total UK population, the NCRAS is considered to be representative of the population in the UK
		Section 9.7.2.1 Primary analysis	Inclusion of Poisson / Negative binomial regression model for pre- and post-*Cervarix* launch periods	The trend in the incidence of anal cancer and small intestine cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer/small intestine cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. APC will be

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
				estimated based on the parameter estimates of the regression model. The same model will be generated for the pre- and post-*Cervarix* launch periods separately
		Section 4 Abstract and Section 9.4.3 Eurostat	Data source updated	Eurostat will be the source for population data and birth cohort data, except for England, for which the source for population data will be UK Health Security Agency and for birth cohort data it will be Office for National Statistics
		Section 9.7.2 Statistical analysis	Updated to clarify HPV type and histological classification assessment	A sentence has been added to clarify HPV type and histological classification assessment
		Title page, Section 3 Responsible parties and Section 4 Abstract	Sponsor signatory updated	Change in the study team
2	25 May 2022	Section 4 Abstract, Section 8.2 Secondary objective and Section 9.3.1.2 Secondary endpoint	Secondary objective and its corresponding endpoint updated	• The feasibility assessment for a case-control study to determine the effectiveness of *Cervarix* will be conducted only against anal cancer. The data for anal lesions is not available in the cancer registries • Expected number of anal cancer cases is the endpoint which can be used to estimate the time frame by when the estimated sample size for a case-control study would be reached
		Section 9.1.2 Feasibility assessment	Feasibility assessment updated	Additional information added for clarity
		Section 4 Abstract, Section 9.4 Data sources	Data sources updated	Vaccination registry for each of the 5 selected European countries was added
		Section 9.7.2.2 Secondary analysis	Secondary analysis updated	Additional information added for clarity
		Section 9.9 Strengths and limitations of the research methods	Updated to add the strengths of the study	Additional points on strengths of the study included
		Title page and Section 3 Responsible parties	Marketing Authorisation Holder (MAH) contact person updated	The sponsor signatory should be the MAH contact person

The summary of the amendment is provided in Annex 5.

6. MILESTONES

Note: The timelines mentioned below are tentative and are subject to change.

Milestone	Planned date
Start of first round data collection	Quarter 3, 2021
End of first round data collection	Quarter 4, 2021
Interim report 1	Quarter 1, 2022
Start of second round data collection	Quarter 3, 2026
End of second round data collection	Quarter 4, 2026
Registration in the EU PAS register	To be determined
Final report of study results	Quarter 1, 2027

7. RATIONALE AND BACKGROUND

Cervarix is a prophylactic HPV vaccine developed by GSK. It is based on the L1 proteins of HPV-16 and HPV-18 formulated with AS04 (comprising of aluminium hydroxide [$Al(OH)_3$] and 3-*O*-desacyl-4'-monophosphoryl lipid A), indicated for use from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to certain oncogenic HPV types [*Cervarix* Summary of Product Characteristics, 2020].

In the context of the EU-RMP for *Cervarix*, a safety concern was raised linked to missing information on the impact and effectiveness of the vaccine against anal lesions and cancer, since it was not prospectively evaluated in clinical trials.

Anal cancer is an uncommon type of cancer, representing around 0.3% of all incident cancers diagnosed in 2020 worldwide [Sung, 2021]. SCC is the most frequent histopathological type of anal cancer [Hoff, 2017]. There is evidence to suggest that HPV infection is associated with anal cancer, particularly with SCC [Hoff, 2017; De Martel, 2020]. Moreover, in a recent worldwide study, HPV DNA was detected in more than 88% of anal cancers and more than 95% of anal AIN grades 2/3. The most frequently detected virus type, detected in over 80.7% of invasive anal cancer cases was HPV-16, followed by HPV-18 (3.6% of cases) [Alemany, 2015; Clifford, 2019]. Over the last 4 decades, anal cancer incidence has been gradually increasing and is more common in women than in men, except for certain high-risk groups such as HIV-infected people, and this raise is more relevant in high-income countries [Lum, 2020]. Risk factors for anal cancer are HPV infection, including a former HPV-related malignancy, HIV infection, more than 10 lifetime sexual partners, ano-receptive intercourse, chronic immunosuppression, cigarette smoking, a history of gynaecological or haematologic malignancy, and age. Hence, HIV and immunocompromised patients, and MSM are particularly vulnerable populations [Nelson, 2017; Van der Zee, 2013; Clifford, 2021].

An observational study of effectiveness of *Cervarix* against HPV anal positivity in Dutch women showed a pooled vaccine effectiveness of approximately 90% for HPV-16/18 [Woestenberg, 2020], with adjusted VEs of 88.2% (95% confidence interval [CI],

41.3%– 97.6%) against anal HPV-16 and 91.9% (95% CI, 30.5%–99.1%) against anal HPV-18 [Woestenberg, 2020]. The results also demonstrated cross-protection against anal HPV-45 and HPV-31 and a high correlation between anal and cervicovaginal VE. The results support the notion that *Cervarix* may offer protection against HPV-related anal cancer (including cross-protection against HPV-31/33/45) [Clifford, 2019].

Population-based cancer registries are platforms that collect, store, validate and analyse data on incidence and survival of the most relevant types of cancer and are crucial for the planning and evaluation of prevention activities. For instance, the World Health Organisation (WHO) global initiative to eliminate cervical cancer points to sound surveillance and monitoring systems as crucial to monitor the evolution of cervical cancer incidence and the impact of interventions over time [WHO; Piñeros, 2021].

This study will assess the data on anal cancer in countries where *Cervarix* vaccination has been introduced in the NIP. Five European countries were initially preselected: Finland, the Netherlands, England, Denmark, and Norway to perform a trend analysis and to assess feasibility for a case-control study.

Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed. Small intestine cancer is relatively rare, with an occurrence of similar magnitude to anal cancer. Small intestine cancer also has a similar mean age of diagnosis as anal cancer, and there is no screening programme for it. It is not associated with HPV infection. This analysis may allow to control for potential changes in cancer surveillance systems and reporting over time.

8. RESEARCH QUESTION AND OBJECTIVES

(Amended 25 May 2022)

The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries aiming to determine the impact and effectiveness of *Cervarix* against anal cancer in females and males.

Please refer to Section 6 for details on study milestones.

8.1. Primary objectives

- To assess trends and changes over time in the age-standardised incidence of anal cancer by sex, HPV type and histological classification for each country* separately.
- To assess trends and changes over time in the crude incidence of anal cancer by age category, by sex, HPV type and histological classification for each country* separately.

8.2. Secondary objective

(Amended 25 May 2022)

- To conduct a feasibility assessment for a case-control study to determine the effectiveness of *Cervarix* against anal cancer.

**Five European countries are considered for this study and each country will be selected based on a set of criteria (please refer to Section 9.2 for country eligibility criteria).*

9. RESEARCH METHODS

9.1. Study design

9.1.1. Discussion of study design

- Type of study and design: This is a TSS and a PASS. The study is designed as an observational, retrospective database study.
- Study population: Females and males of all age groups in the 5 selected European countries.

Please refer to Section 9.2 for country eligibility criteria.

- Data collection: Retrospective data collection from national cancer registries ***and national vaccination registries***.
- Study period:
  - Pre-*Cervarix* launch period (i.e., before *Cervarix* introduction in the NIP): The start and end calendar year for each country will be considered based on the data availability in their respective cancer registries.
  - Post-*Cervarix* launch period (i.e., after *Cervarix* introduction in the NIP): The start calendar year for each country will be the date when *Cervarix* was introduced in their NIP. An interim analysis will be performed in 2022. For ***the*** analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.
- This study will be a trend analysis of incidence of anal cancer in 5 selected European countries.
- Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed. Small intestine cancer is relatively rare, with an occurrence of similar magnitude to anal cancer. Small intestine cancer also has a similar mean age of diagnosis as anal cancer, and there is no screening programme for it. It is not associated with HPV infection. This analysis may allow to control for potential changes in cancer surveillance systems and reporting over time.

9.1.2. Feasibility assessment

(Amended 25 May 2022)

As mentioned above , the objectives of the feasibility assessment are:

- ***To describe the main requirements for the conduct of an additional study assessing the effectiveness of Cervarix in the prevention of anal cancer***
- ***To assess a case-control study design and the data sources that would meet those requirements.***

The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries ***and national vaccination registries*** will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine ***Cervarix*** effectiveness against anal cancer can be performed.

9.1.3. Case definition

In this study, for case identification of anal cancer and small intestine cancer, [International Classification of Diseases (ICD)-10] codes will be used.

For histological classification of anal cancer, the WHO ICD-O-2 (or) 3 will be used based on the coding version of the cancer registries in the selected countries.

9.2. Setting

The following country eligibility criteria should be checked in order to perform analysis:

- Should have a stable, consolidated and validated cancer registry.
- The cancer registry should preferably be population-based and nationwide.
- Administration of *Cervarix* for at least 5 birth cohorts (either routine or catch-up campaign cohorts) within the NIP.

9.3. Variables

(Amended 25 May 2022)

The following variables will be assessed for each country separately:

- Incidence of anal cancer by age category, by sex, by HPV type (if available), by histological classification (if available) and by calendar year.
- Number of anal cancer cases by age category, by sex, by HPV type (if available), by histological classification (if available) and by calendar year.
- Incidence of small intestine cancer by age category, by sex and by calendar year.
- Number of small intestine cancer cases by age category, by sex and by calendar year.

- Population data by age category, by sex and by calendar year.
- Birth cohort data, by sex and by calendar year.
- HPV vaccine coverage of the eligible birth cohorts by calendar year and by age category and by sex if possible.

9.3.1. Endpoints

9.3.1.1. Primary endpoints

(Amended 25 May 2022)

- Occurrence and age-standardised incidence of anal cancer during the study period (i.e., pre- and post- *Cervarix* launch period) by sex, HPV type and histological classification for each country* separately.
- Occurrence and crude incidence of anal cancer during the study period (i.e., pre- and post-*Cervarix* launch period) by age category, by sex, HPV type and histological classification for each country* separately.

Note: Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed by age category and sex for each country* separately.

Please refer to Section 7 for details on choice of control.

9.3.1.2. Secondary endpoint

(Amended 25 May 2022)

- ***Expected number of anal cancer cases needed to conduct the case-control study based on the vaccine coverage rate and the expected VE and other factors for each country* separately.***

Note: Other feasibility assessment checks with findings for the conduct of a case-control study will be further described in the study report.

**Five European countries are considered for this study and each country will be selected based on a set of criteria (please refer to Section 9.2 or country eligibility criteria).*

9.4. Data sources

(Amended 25 May 2022)

9.4.1. National cancer registries

This study will collect anal cancer data from the following national cancer registries:

- The Finnish Cancer Registry [FCR]:

The Cancer Registry of the National Institute for Health and Welfare maintained by the Finnish Cancer Society, contains data on all cancer cases and suspected cancer cases detected in Finland. The health care organisations in Finland are obliged to report this information. The registry holds data on anal cancer cases reported from 1953 to 2019. The reporting of cancer cases has been mandatory since 1961 [International Association of Cancer Registries (IACR)].

Information on cancer cases (from hospitals, physicians, pathology laboratories, and death certificates) are available from Statistics Finland. In order to ensure correctness of data, the notifiers are requested to check accuracy of information about primary site, patient identity, and date of diagnosis. A physician oversees or performs coding. Since 1967, Finland is using personal identification numbers for identification of cases. This allows for accurate follow-up of patients (including death) through official sources. Formal evaluations are also conducted in addition to the continuous quality control procedures [IACR].

FCR data is subjected to computerised checks for validity and internal consistency. Comparability of data is ensured by following the ICD-O-3 introduced in 2007, and earlier codes were converted to ICD-O-3. The completeness of the FCR for all sites was estimated at 95% (96% for solid tumours and 86% for non-solid tumours). The FCR publishes annual statistics with a delay of approximately 2 years. This is due to a latency of one full calendar year for submitting cancer data for registration and having access to data on causes of death [Leinonen, 2017].

- The Netherlands Cancer Registry [NCR]:

NCR is a population-based cancer registry with nationwide coverage since 1989. Cancer diagnoses are notified by the nationwide network and registry of histology and cytopathology (PALGA) and in addition through linkage with the Landelijke Medische Registratie hosted by Dutch Hospital Data. Each cancer case is coded by trained registration clerks (internal education of 1 year) according to ICD-O-3 based on information gathered from medical files at the hospital. Date of diagnosis is coded according to international coding rules and mostly based on the date of first pathological confirmation, or if unavailable, date of first hospital admission [Van der Willik, 2020].

The database is managed by the Netherlands Comprehensive Cancer Organisation (IKNL). NCR is the only oncological hospital registry in the Netherlands with data on all cancer patients. Data on incidence, prevalence, survival, mortality and risk are included in the website and are available at a national level from 1989 to 2020. However, data available for 2019 and 2020 are provisional.

- National Cancer Registration and Analysis Service ***(UK)*** [NCRAS]:

NCRAS is managed by Public Health England (PHE) and captures a wide range of data sources, including data such as: histopathology and haematology services, medical records, radiotherapy departments, hospices, independent hospitals, screening services, death certificates, general practitioners, other UK cancer registries. The registry holds data on anal cancer from 1993 to ***2018***. The final registrations are released approximately 1 year following the end of a diagnosis year, but it can take up to 5 years to achieve 100% completeness [Henson, 2020].

Each year, NCRAS collects data on over 300 000 cases of cancer, which includes patient details (i.e., their name, age, address sex, and date of birth etc), and also data about the type of cancer, how advanced it is and the treatment the patient receives.

In order to allow contemporaneous, comprehensive and cost-effective data collection and to ensure quality assurance, the registry obtains data from across the National Health Service. The data quality in term of validity, completeness, timeliness etc. is assessed. Quality checks are performed both at the level of individual records as well as at the level of the registry. In addition, records are validated against other records and against expected values [Henson, 2020].

- The Danish Cancer Registry [Danish Cancer Registry]:

The Danish Cancer Registry was founded in 1942 and contains data of the incidence of cancer among the Danish population from 1943 to 2019. The purpose of the cancer registry is to collect and process data on new cases of cancer, in order to produce statistics on the incidence and prevalence of cancer in Denmark, to provide information for the planning of the Danish health services, and to provide a basis for research into the causes of cancer and the course of cancer diseases. Reporting to the cancer registry has been mandatory since 1987. From 2004 to 2008 it underwent a process of modernisation. As a result, the reporting became electronic through integration of patient administrative systems and the manual coding was partly replaced by an automatic coding logic.

The Danish cancer registry has been repeatedly validated for data quality (validity and completeness). Internal validation for lung and breast cancer detected low proportions of errors or missing reports. Moreover, the automated registration ensures high quality and data completeness. Continued improvements following validation studies are implemented [Validation of The Danish Cancer Registry and selected Clinical Cancer Databases; Lund, 2013].

- The Cancer Registry of Norway [CRN]:

The Cancer Registry of Norway was established in 1951 and includes data on anal cancer from 1953 to 2019. It is organised as an independent institution under the Oslo University Hospital Trust. Annual data on cancer are published in the *Cancer in Norway* report. Cancer statistics of Norway from 2019 were published in October 2020 [Cancer in Norway, 2019]. Suspected cancer cases (without a verified cancer diagnosis), and cancer first diagnosed by autopsy, need to be mandatorily notified. The cancer registry is in charge for the national screening programmes: Breast Cancer Screening Programme and Cervical Cancer Screening Programme. The cancer registry regulations demands the

following 3 main objectives for the cancer registry: registration, research and information.

In Norway, population-based data with high-quality cancer incidence are favourable. Such data requires mandatory reporting, unique personal identification numbers and more than 50 years of experience in cancer registration [Larsen, 2009].

A study of the data quality at the Cancer Registry of Norway showed that data from the registry are reasonably accurate, and that completeness (close-to-completeness) and timely reporting is among the best in Europe [Larsen, 2009].

9.4.2. Vaccination registries

Country	*Vaccination registry*
Finland	*Finnish National Vaccination Registry since 2009*
The Netherlands	*Dutch vaccination registry (Præventis) since 2005*
England	*Immunisations are registered in the Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002)*
Denmark	*Danish vaccination registry since 2009, although compulsory as of 15 November 2015 (UK)*
Norway	*Norwegian vaccination registry since 1995*

9.4.3. Eurostat

Eurostat will be the source for data on the European Standard Population for age distribution used to estimate the age-standardised incidence rates [Pace, 2013]. It will also be the source for population data and birth cohort data**,** except for England, for which the source for population data will be UK Health Security Agency and for birth cohort data it will be Office for National Statistics.

9.4.4. Websites of national public health institutes

- Vaccine coverage data will be retrieved from the respective websites of national public health institutes:
  - Finland
  - The Netherlands
  - England
  - Denmark
  - Norway

Please refer to Annex 4 for details on vaccination schedules and vaccine coverage in the selected 5 European countries.

9.5. Study size

(Amended 25 May 2022)

Sample size computation ***for the primary objective*** is not applicable, as there is no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 5 selected European countries will be collected within the established timeframe.

Please refer to Section 9.3 for details on variables and Section 9.4 for details on data sources.

Note: National cancer registries are nationwide and thus this study is population-based.

9.6. Data management

9.6.1. Data collection

Please refer to Section 9.3 for details on study variables and Section 9.4 for details on study data sources.

9.7. Data analysis

9.7.1. Analysis set

The country-specific data extracted from the national cancer registries as per defined population and timeframe.

Please refer to Section 9.1.1 for details on study population and study period.

9.7.2. Statistical Analysis

All analyses will be performed for each country separately. The analysis planned by HPV type and histological classification will be performed based on the data availability during the time of the analysis.

9.7.2.1. Primary analysis

(Amended 25 May 2022)

To assess trends and changes over time in incidence of anal cancer by age category and by sex.

- Age-standardised incidence with 95% CI during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by sex.

Note: Age-standardised incidence rates of anal cancer will be calculated by calendar year and sex using the European Standard Population (age distribution).

Additionally,

- Crude incidence with 95% CI during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post-*Cervarix* launch period) will be presented by age category, sex, HPV type and histological classification.
- The trend in the incidence of anal cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. Annual Percentage Change (APC) will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-*Cervarix* launch periods separately.
- The trend in the incidence of anal cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer incidences as outcome variable; calendar year, age category, study period (pre-launch = 0 and post-launch = 1), HPV type and sex as the independent variables (risk factors). The model will include the population followed up as the offset variable. Similar analysis will be performed by subcategories – age category, sex, HPV type and histological classification.
- Observed and predicted counts of the anal cancer cases will be presented by calendar year. Predicted counts of the anal cancer cases will be estimated using the Poisson / Negative binomial regression univariate model with number of anal cancer cases as the outcome variable and year as the independent variable on the pre-vaccination data.
  Percentage reduction of the anal cancer cases in the observed counts compared to the predicted will be presented with its Wald's 95% CI.
  Similar analysis will be performed by subcategories – age category, sex, HPV type and histological classification.

Analysis for negative control:

- Age-standardised incidence with 95% CI of small intestine cancer during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by age category and sex.

Note: Age-standardised incidence rates of small intestine cancer will be calculated by calendar year and sex using the European Standard Population (age distribution).

- Crude incidence with 95% CI of small intestine cancer during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by age category, sex.

- The trend in the incidence of small intestine cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of small intestine cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. APC will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-*Cervarix* launch periods separately.

9.7.2.2. Secondary analysis

(Amended 25 May 2022)

To assess ***the*** feasibility for ***the conduct of*** a case-control study to determine the effectiveness of *Cervarix* against anal cancer in each country.

The number of expected anal cancer cases (estimated sample size) required to demonstrate the expected vaccine effectiveness will be determined. ***Also the timeframe for generating meaningful VE estimates will be assessed for each country of interest.***

The cases would be those in the cancer registry with HPV-related anal cancer, whereas controls would be subjects with a non-HPV related cancer. Controls would be sex- and age-matched, retrieved from the same cancer registry to ensure that the comparison group is representative of the source population as that of the cases. ***Investigations will need to be done to understand if brand-specific HPV (Cervarix) vaccination status of the cases and controls could be retrieved from national vaccine registries effectively linked to national cancer registries by country of interest.***

9.8. Quality control

To ensure compliance with Good Pharmaco-epidemiology Practices (GPP) or other applicable guidelines and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study.

9.9. *Strengths and* limitations of the research methods

(Amended 25 May 2022)

The study has the following ***strengths and*** limitations:

Strengths

- ***Use of nationwide longitudinal data from national cancer registries using the same case definition (aligned with ICD-10 codes).***
- ***A harmonised and coordinated approach in the analysis allowing comparisons across countries and with external similar studies.***

- ***Use of an HPV negative control (i.e., small intestine cancer) would permit to assess for potential bias owed to changes in the surveillance and reporting system of anal cancer over time.***

Limitations

- ***The cancer registry of Finland does not provide the number of cancer cases when less than 5 cases are reported in a given year, by sex and age category, due to potential risk of patient identification. Therefore, in those instances, the number of cancer cases will be back-computed using the provided crude incidence and population data. This may introduce some bias by round-offs and back-calculation.***
- Limitations in the cancer registry data such as accuracy in the cancer diagnosis methods, case ascertainment, misclassification of primary location (i.e., misclassification as rectal cancer).
- Lack of/limited information on the existence of targeted anal cancer screening programmes (i.e., directed towards at-risk groups such as MSM, HIV-positive patients, or subjects previously diagnosed of an HPV-related cancer), that may lead to overdiagnosis and may also have an impact on temporal incidence trends.
- Lack of information of the aetiology of the anal cancer cases (i.e., whether HPV-related) may introduce some bias and limit the interpretation. Additionally, if no causative HPV type could be provided, further sub-analysis of the incidence by HPV type will be limited by this constraint.
- Percentage of anal cancers with unspecified histology (unspecified carcinomas or unspecified morphology).
- Variations in registry practices in diagnosis and information collection may introduce some bias in international comparisons (i.e., consistency of histological classifications).
- Changes in trends may occur over time for reasons other than HPV vaccination (i.e., changes in the surveillance and reporting system, increment of anal cancer diagnosis due to increased awareness among physicians, implementation of an anal cancer screening programme).

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

GSK will not have access to individual data (i.e., only aggregated data by age group will be provided). No protected personal data will be transferred to GSK.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable since this study is an observational, retrospective PASS, based on data extracted from the national cancer registry databases.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Posting of information on publicly available registers and publication policy

Studies that do not evaluate vaccines are progressed for publication in the scientific literature when the results provide important scientific or medical knowledge or are relevant for patient care, and will be considered for disclosure on the GSK website and in publicly accessible regulatory registry(ies) such as EU PAS register as applicable.

12.2. Provision of study results to investigators/database owners

Where required by applicable regulatory requirements, an investigator/database owner signatory will be identified for the potential review of the results and approval of the study report.

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(Amended 25 May 2022)

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Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1	217743	25 May 2022	List of stand-alone documents
2	217743	25 May 2022	Glossary of terms
3	217743	25 May 2022	Sponsor information
4	217743	25 May 2022	Additional information
5	217743	25 May 2022	ENCePP checklist for study protocols

Annex 2 Glossary of terms

Case-control study:	A form of epidemiological study where the study population is selected based on whether the participants do (cases) or do not (controls) have the particular outcome (disease) under study. The groups are then compared with respect to exposure/characteristic of interest.
Commitment:	Agreement made with Regulatory Authorities as specific condition of regulatory approval and authorisation, either made at the time of product approval or during the lifecycle of the approved product.
Database:	A database is a set of pre-existing tables and views containing data. The term "pre-existing" implies that the analysis will be done on retrospective data and the term "views" implies that the data can be made readily available in an electronic format through a straightforward extract, without re-encoding and manual manipulation (like a transpose, a translation, split of a field into several fields, etc).
Database study:	A study involving the use of pre-existing data maintained in an electronic format; this will not include collection of new data that requires (re-) encoding via CRF/eCRF and retesting of human biological samples.
Epidemiological study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
eTrack:	GSK's tracking tool for clinical/epidemiological studies.
Participant:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database. Synonym: subject
Protocol amendment:	The International Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants,

	scope of the investigation, study design, or scientific integrity of the study.
Post-Authorisation Safety Study:	A pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product. This includes all GSK sponsored non-interventional studies and clinical trials conducted anywhere in the world that are in accordance with the terms of the European marketing authorisation and where the investigation of safety is the specific stated objective. Note: The phrase 'In accordance with the terms of the European marketing authorisation' means that the product is used according to the European label (e.g. within the recommended dose range, the approved formulation, indication, etc.).
Retrospective study:	A study that looks backward in time (e.g. at events that occurred in the past; outcomes and exposure can no longer be influenced), usually using medical records, databases or interviews in order to address one or more study objectives.
Study population:	Sample of population of interest.
Surveillance:	The ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.
Targeted Safety Study:	Studies specifically planned or conducted to examine an actual or hypothetical safety concern in a product marketed anywhere in the world. This includes any GSK sponsored pharmaco-epidemiological study or clinical trial conducted anywhere in the world with the aim of identifying or quantifying a safety hazard. Although all clinical trials collect safety information as a matter of routine, only those initiated to examine a specific safety concern are considered a targeted safety study.

Annex 3 Sponsor Information

(Amended 25 May 2022)

1. Sponsor:

GlaxoSmithKline Biologicals (GSK)
Rue de l'Institut, 89, B-1330 Rixensart
Belgium

2. Sponsor medical expert for the study:

PPD **, *MD, Clinical & Epidemiology Project Lead, GlaxoSmithKline Biologicals SA.***

Refer to the local study contact information document.

Annex 4 Additional information

(Amended 25 May 2022)

The table below presents details on vaccination schedules and vaccine coverage in the 5 selected European countries.

Country	Date HPV vaccine first introduced	Vaccine given	Immunisation schedule	Age cohort	Catch-up campaigns	Vaccine coverage	Date modification immunisation schedule	Modification immunisation schedule
Denmark	January 2009	Quadrivalent HPV (*Gardasil*)	0m, 2m, 6m	12 yo girls (born 1996) (GP-based)	13-15 yo girls Women born 1985-1992 (August 2012 to December 2013)	79% 3-dose	August 2014 February 2016 November 2017 July 2019	*Gardasil* (0m, 6m) *Cervarix* (0m, 6m) *Gardasil 9* (0m, 6m) for girls *Gardasil 9* (0m, 6m) for boys 12 yo on 1 July 2019 or later
Finland	November 2013	Bivalent HPV (*Cervarix*)	0m, 1m, 6m	11-12 yo (born 2005) (school-based)	13-15 yo girls (November 2013)	68% 3-dose in 2015 72% 3-dose in 2016	Autumn 2020	*Cervarix* (0m, 6m) girls and boys 12 yo + Catch-up for boys in grades 7-9 (2020-21 and 2021-22)
Netherlands	September 2009	Bivalent HPV (*Cervarix*)	0m, 1m, 6m	12 yo girls 10 yo girls/boys	13-16 yo girls (2009/2010) ***12-18 yo girls/boys (2022/2023)***	58% 3-dose (cohort 1998)	January 2014 ***January 2022***	*Cervarix* (0m, 6m) *Cervarix* (0m, 6m) girls and boys
Norway	August 2009	Quadrivalent HPV (*Gardasil*)	0m, 2m, 6m	12 yo (born 1997) (school-based)	Girls born in 1991 or later (2016-2018)	1997 cohort-65% 3-dose in 2011 2004 cohort- 83% 3-dose in 2016/2017 school year	September 2017 September 2018	*Cervarix* (0m, 6m) girls *Cervarix* (0m, 6m) girls and boys 12 yo

Country	Date HPV vaccine first introduced	Vaccine given	Immunisation schedule	Age cohort	Catch-up campaigns	Vaccine coverage	Date modification immunisation schedule	Modification immunisation schedule
England	September 2008	Bivalent HPV (*Cervarix*)	0m, 1m, 6m	12-13 yo girls (school-based)	14 to < 18 yo	86.7% 3-dose in 2013/2014 83.9% 2-dose in 2018/2019 64.7% 2-dose in 2019/2020	September 2012 September 2014 April 2018 September 2019	*Gardasil* (0m, 2m, 6m) for girls *Gardasil* (0m, 6m or 12m) for girls *Gardasil* (0m, 6m) for MSM ≤ 45 yo *Gardasil 9* (0m, 6m or 12m) for boys 12-13 yo + Catch-up girls and boys up to 25th birthday

HPV: human papillomavirus; m: month; ***MSM: Men who have sex with men;*** yo: years old.

Annex 5 Amendments and administrative changes to the protocol

GlaxoSmithKline Biologicals SA

Vaccines R & D
Protocol Amendment 1

eTrack study number and Abbreviated Title:	217743 (EPI-HPV-099 VS EUR DB)
Amendment number:	Amendment 1 Final
Amendment date:	Final: 31 March 2022

Rationale/background for changes:

The protocol amendment 1 was developed to account for the following changes:

1. For clarity, the primary objective and its corresponding endpoint has been split into 2 independent objectives and endpoints, respectively (i.e., for age-standardised incidence and for crude incidence).
2. For better interpretation of the study results so it can be comparable with publications across countries and to align with the age definition as per the European standardised population, the entire age group from 0 – 80+ population will be considered instead of the adult population (>18 years of age).
3. Study period (i.e., pre- and post-*Cervarix* launch period) will be considered based on the *Cervarix* introduction in the National Immunisation Programme (NIP).
4. For the UK, all analyses will be based specifically on data from England, and not data from UK. The National Cancer Registration and Analysis Service (NCRAS) is the cancer registry in England. As the population of England comprises around 84% of the total UK population, the NCRAS is considered to be representative of the population in the UK.
5. Inclusion of Poisson / Negative binomial regression model for pre- and post-*Cervarix* launch periods: The trend in the incidence of anal cancer and small intestine cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer/small intestine cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. APC will be estimated based on the parameter estimates of the regression model.
   The same model will be generated for the pre- and post-*Cervarix* launch periods separately.
6. Eurostat will be the source for population data and birth cohort data, except for England, for which the source for population data will be UK Health Security Agency and for birth cohort data it will be Office for National Statistics.
7. The analysis planned by HPV type and histological classification will be performed based on the data availability during the time of the analysis.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

In the PASS information page:

Research question and objectives: To assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, ~~the United Kingdom (UK)~~***England***, Denmark and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer in females and males

Countries of study: Finland, the Netherlands, ~~the UK~~***England***, Denmark and Norway

Author: PPD ~~, MD, Clinical and Epidemiology R&D Project Lead, HPV, Hepatitis and Pneumococcal vaccines, GlaxoSmithKline Biologicals SA~~ PPD **,** ***Epidemiology Lead, GlaxoSmithKline Biologicals SA***

MAH contact person: PPD ~~, MD, Clinical and Epidemiology R&D Project Lead, HPV, Hepatitis and Pneumococcal vaccines, GlaxoSmithKline Biologicals SA~~ PPD **,** ***Epidemiology Lead, GlaxoSmithKline Biologicals SA***

In Section 3 Responsible parties:

PPD ~~(Clinical and Epidemiology R&D Project Lead) is GSK's designated contact person for this study~~PPD **,** ***Epidemiology Lead, GlaxoSmithKline Biologicals SA***.

In Section 4 Abstract:

Main author: PPD ~~, MD, Clinical and Epidemiology R&D Project Lead, HPV, Hepatitis and Pneumococcal vaccines, GlaxoSmithKline Biologicals SA~~ PPD **,** ***Epidemiology Lead, GlaxoSmithKline Biologicals SA***

Rationale and background: In the context of the European Union Risk Management Plan (EU-RMP) for *Cervarix*, a safety concern was raised linked to missing information on the impact and~~/or~~ effectiveness of the vaccine against anal lesions and cancer, since it was not prospectively evaluated in clinical trials.

This study will assess the data on anal cancer in countries where *Cervarix* vaccination has been introduced in the NIP. Five European countries were initially preselected: Finland, the Netherlands, ~~the United Kingdom (UK)~~***England***, Denmark and Norway to perform a trend analysis and to assess feasibility for a case-control study.

Research question and objectives: The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, ~~the UK~~ ***England***, Denmark and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer in females and males.

Primary Objective:

- To assess trends and changes over time in ***the age-standardised*** incidence of anal cancer by ~~age,~~ sex, HPV type and histological classification for each country* separately.
- ***To assess trends and changes over time in the crude incidence of anal cancer by age category, by sex, HPV type and histological classification for each country* separately.***

Secondary Objective:

- To conduct a feasibility assessment for a case-control study to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer.

Study design:

Study population: Females and males ~~aged 18 years** and above~~***of all age groups*** in the 5 selected European countries.

Study period:

- Pre-*Cervarix* launch period (i.e., before *Cervarix* ~~commercialisation~~***introduction in the NIP***): ~~From 1992 to 2006 inclusive~~***The start and end calendar year for each country will be considered based on the data availability in their respective cancer registries***.
- Post-*Cervarix* launch period ***(i.e., after Cervarix introduction in the NIP)***: ~~From 2007 to 2026 (i.e., final analysis)~~***The start calendar year for each country will be the date when Cervarix was introduced in their NIP***. An interim analysis will be performed in 202***2***~~1~~. For each analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.

The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine vaccine impact and~~/or~~ effectiveness against anal lesions and cancer can be performed.

Population:

The study population will include females and males ~~aged 18** years and above~~***of all age groups*** in the 5 selected European countries.

~~***The exact lower limit of age will depend on each cancer registry.***~~

Variables:

Primary endpoint:

- Occurrence and ***the age-standardised*** incidence of anal cancer during the period ~~from 1992 until the most recent and complete available calendar year in the cancer registries~~ (i.e., ~~during~~ pre- and post- *Cervarix* launch period) by ~~age,~~ sex, HPV type and histological classification for each country* separately.
- ***Occurrence and the crude incidence of anal cancer during the study period (i.e., pre- and post-Cervarix launch period) by age category, by sex, HPV type and histological classification for each country* separately.***

Note: Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed, by age ***category*** and sex for each country* separately.

Data sources: Eurostat will be the source for data on the European Standard Population for age distribution used to estimate the age-standardised incidence rates for the 5 selected European countries [Pace, 2013]. It will also be the source for the population data and birth cohort data, ***except for England, for which the source for population data will be the UK Health Security Agency and for birth cohort data it will be Office for National Statistics.***

This study will collect anal cancer data from the following national cancer registries:

- National Cancer Registration and Analysis Service [NCRAS] ~~in the UK~~

In Section 7 Rationale and background: In the context of the EU-RMP for *Cervarix*, a safety concern was raised linked to missing information on the impact and~~/or~~ effectiveness of the vaccine against anal lesions and cancer, since it was not prospectively evaluated in clinical trials.

This study will assess the data on anal cancer in countries where *Cervarix* vaccination has been introduced in the NIP. Five European countries were initially preselected: Finland, the Netherlands, ~~the UK~~***England***, Denmark and Norway to perform a trend analysis and to assess feasibility for a case-control study.

In Section 8 Research question and objectives: The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, ~~the UK~~ ***England***, Denmark and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer in females and males.

Primary Objective:

- To assess trends and changes over time in ***the age-standardised*** incidence of anal cancer by ~~age,~~ sex, HPV type and histological classification for each country* separately.

- ***To assess trends and changes over time in the crude incidence of anal cancer by age category, by sex, HPV type and histological classification for each country* separately.***

Secondary Objective:

- To conduct a feasibility assessment for a case-control study to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer.

In Section 9.1.1 Discussion of study design:

- Study population: Females and males ~~aged 18** years and above~~***of all age groups*** in the 5 selected European countries.

~~***The exact lower limit of age will depend on each cancer registry.***~~

- Study period:
  - Pre-*Cervarix* launch period (i.e., before *Cervarix* ~~commercialisation~~***introduction in the NIP***): ~~From 1992 to 2006 inclusive~~***The start and end calendar year for each country will be considered based on the data availability in their respective cancer registries***.
  - Post-*Cervarix* launch period ***(i.e., after Cervarix introduction in the NIP)***: ~~From 2007 to 2026 (i.e., final analysis)~~***The start calendar year for each country will be the date when Cervarix was introduced in their NIP***. An interim analysis will be performed in 202***2***~~1~~. For each analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.

In Section 9.1.2. Feasibility assessment: The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine vaccine impact and~~/or~~ effectiveness against anal lesions and cancer can be performed.

In Section 9.1.3 Case definition

In this study, for case identification ***of anal cancer and small intestine cancer,*** [International Classification of Diseases (ICD)-10~~]/ International Classification of Diseases for Oncology, third Edition (ICD-O-3)~~ codes will be used~~ (i.e., C21 for anal cancer and C17 for small intestine cancer)~~.

For histological classification of anal cancer, the WHO ICD-O-2 (or) 3 will be used based on the coding version of the cancer registries in the selected countries.~~Cancer registries in the selected countries use the WHO ICD-O-3 for classification and coding of neoplasms.~~

In Section 9.3 Variables: The following variables will be assessed for each country separately:

- Incidence of anal cancer by age ***category***, by sex, by HPV type ***(if available)***, by histological classification ***(if available)*** and by calendar year.
- Number of anal cancer cases by age ***category***, by sex, by HPV type ***(if available)***, by histological classification ***(if available)*** and by calendar year.
- Incidence of small intestine cancer by age ***category***, by sex and by calendar year.
- Number of small intestine cancer cases by age ***category***, by sex and by calendar year.
- Age distribution data as per European Standard Population ***and UK Health Security agency (for England)***.
- Population data by age ***category***, by sex and by calendar year.
- Birth cohort data by age ***category***, by sex and by calendar year.
- HPV vaccine coverage of the eligible birth cohorts by calendar year and by age ***category*** and by sex if possible.

In Section 9.3.1.1 Primary endpoint:

- Occurrence and ***the age-standardised*** incidence of anal cancer during the period ~~from 1992 until the most recent and complete available calendar year in the cancer registries~~ (i.e., ~~during~~ pre- and post- *Cervarix* launch period) by ~~age,~~ sex, HPV type and histological classification for each country* separately.

- ***Occurrence and the crude incidence of anal cancer during the study period (i.e., pre- and post-Cervarix launch period) by age category, by sex, HPV type and histological classification for each country* separately.***

Note: Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed, by age ***category*** and sex for each country* separately.

In Section 9.4.2 Eurostat: Eurostat will be the source for data on the European Standard Population for age distribution used to estimate the age-standardised incidence rates [Pace, 2013]. It will also be the source for population data and birth cohort data***, except for England, for which the source for population data will be UK Health Security Agency and for birth cohort data it will be Office for National Statistics.***

In Section 9.4.3 Websites of national public health institutes:

- Vaccine coverage data will be retrieved from the respective websites of national public health institutes:
  - ~~**The UK**~~ ***England***

In Section 9.7.2. Statistical Analysis: All analyses will be performed for each country separately. ***The analysis planned by HPV type and histological classification will be performed based on the data availability during the time of the analysis.***

In Section 9.7.2.1. Primary analysis: To assess trends and changes over time in incidence of anal cancer by age ***category*** and by sex. ~~Additionally, based on availability of data, the same will be assessed also by HPV type and by histological classification.~~

- Age-standardised incidence ***with 95% CI*** during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by ~~age category and~~sex. ~~Additionally, based on availability of data, the same will be assessed also by HPV type and by histological classification.~~

Note: Age-standardised incidence rates of anal cancer will be calculated by calendar year and sex using the European Standard Population (age distribution)***, except for England, for which the source for population data will be UK Health Security Agency.***

Additionally,

- ***Crude i***ncidence ***with 95% CI*** ~~rates~~ during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by age category, sex, HPV type and histological classification.
- The trend in the incidence of anal cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. Annual Percentage Change (APC) will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-Cervarix launch periods separately.
- The trend in the incidence of anal cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer incidences as outcome variable; ***calendar year,*** age category, study period (pre-launch = 0 and post-launch = 1), ***HPV type and*** sex and histological classification as the independent variables ***(risk factors)***. The model will include the population followed up as the offset variable.
  Similar analysis will be performed by subcategories – age category, sex, HPV type and histological classification.

Analysis for negative control:

- Age-standardised incidence ***with 95% CI*** of small intestine cancer during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by age category and sex.

Note: Age-standardised incidence rates of small intestine cancer will be calculated by calendar year and sex using the European Standard Population (age distribution)***, except for England, for which the source for population data will be UK Health Security Agency.***

- ***Crude*** incidence ***with 95% CI*** of small intestine cancer during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by age category, sex.
- The trend in the incidence of small intestine cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of small intestine cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. APC will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-Cervarix launch periods separately.

In Section 9.7.2.2 Secondary analysis: To assess feasibility for a case-control study to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer in each country.

In Section 9.9 Limitations of the research methods:

- The cancer registr***y***~~ies~~ of Finland~~, the Netherlands and the UK~~ cannot provide year of ~~birth~~***cancer*** data for calendar years with less than 5 cases due to potential risk for patient identification. Therefore, ***in those instances, the number of cases will be back-computed using the provided crude incidence and population data***~~the sub-group incidence analysis by age will be limited by this constraint~~.
- ~~For the UK, incidence data may derive from regional registries and data might not be representative of the entire country since reports to this cancer registry only cover England.~~

In Section 13 References:

Office for National Statistics: Home - Office for National Statistics (ons.gov.uk). Accessed: 31 March 2022.

The UK Health Security Agency (UKHSA): https://www.gov.uk/government/organisations/uk-health-security-agency. Accessed: 31 March 2022.

GlaxoSmithKline Biologicals SA

Vaccines R & D
Protocol Amendment 2

eTrack study number and Abbreviated Title:	217743 (EPI-HPV-099 VS EUR DB)
Amendment number:	Amendment 2 Final
Amendment date:	Final: 25 March 2022

Rationale/background for changes:

The protocol amendment 2 was developed to account for the following changes:

1. Secondary objective and its corresponding endpoint was updated:
   - The feasibility assessment for a case-control study to determine the effectiveness of *Cervarix* will be conducted only against anal cancer. The data for anal lesions is not available in the cancer registries
   - Expected number of anal cancer cases is the endpoint which can be used to estimate the time frame by when the estimated sample size for a case-control study would be reached.
2. Feasibility assessment was updated to add additional information for clarity.
3. Vaccination registry for each of the 5 selected European countries was added.
4. Secondary analysis was updated to add additional information for clarity.
5. Additional points on strengths of the study were included.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

In the PASS information page:

Research question and objectives: To assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal ~~lesions and~~ cancer in females and males

In the Marketing authorisation holder page:

MAH contact person: PPD ~~, Epidemiology Lead, GlaxoSmithKline Biologicals SA~~PPD ***, MD, Clinical & Epidemiology Project Lead, GlaxoSmithKline Biologicals SA***

In Section 3 Responsible parties: PPD ~~, Epidemiology Lead, GlaxoSmithKline Biologicals SA~~PPD ***, MD, Clinical & Epidemiology Project Lead, GlaxoSmithKline Biologicals SA***

In Section 4 Abstract:

Research question and objectives: To assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal ~~lesions and~~ cancer in females and males

Secondary objective:

- To conduct a feasibility assessment for a case-control study to determine the ~~impact and~~ effectiveness of *Cervarix* against anal cancer.

Study design:

Data collection: Retrospective data collection from national cancer registries ***and national vaccination registries***.

Study period:

- Post-*Cervarix* launch period (i.e., after *Cervarix* introduction in the NIP): The start calendar year for each country will be the date when *Cervarix* was introduced in their NIP. An interim analysis will be performed in 2022. For ***the*** ~~each~~ analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.

- The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine ***Cervarix*** ~~vaccine~~ impact and effectiveness against anal ~~lesions and~~ cancer can be performed.

Variables:

Primary endpoint:

- Occurrence and ~~the~~ age-standardised incidence of anal cancer during the period (i.e., pre- and post- *Cervarix* launch period) by sex, HPV type and histological classification for each country* separately.
- Occurrence and ~~the~~ crude incidence of anal cancer during the study period (i.e., pre- and post-*Cervarix* launch period) by age category, by sex, HPV type and histological classification for each country* separately.

Secondary endpoint:

- ~~Incidence of anal cancer during the pre-~~*~~Cervarix~~* ~~launch period for each country* separately.~~ ***Expected number of anal cancer cases needed to conduct the case-control study based on the vaccine coverage rate and the expected VE and other factors for each country* separately.***

Note: Other feasibility assessment checks with findings for the conduct of a case-control study will be further described in the study report.

Data sources:

  - National Cancer Registration and Analysis Service [NCRAS] ***(UK)***
- ***Vaccination registries:***
  - ***Finnish National Vaccination Registry since 2009***
  - ***Dutch vaccination registry (Præventis) since 2005***
  - ***Immunisations are registered in Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002) (UK)***
  - ***Danish vaccination registry since 2009, although compulsory as of 15 November 2015***
  - ***Norwegian vaccination registry since 1995***

Study size:

Sample size computation ***for the primary objective*** is not applicable, as there is no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 5 selected European countries will be collected within the established timeframe.

In Section 8 Research question and objectives:

The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries aiming to determine the impact and effectiveness of *Cervarix* against anal ~~lesions and~~ cancer in females and males.

In Section 8.2 Secondary objective:

- To conduct a feasibility assessment for a case-control study to determine the impact and effectiveness of *Cervarix* against anal ~~lesions and~~ cancer.

In Section 9.1.1 Discussion of study design:

Data collection: Retrospective data collection from national cancer registries ***and national vaccination registries***.

Study period:

- Post-*Cervarix* launch period (i.e., after *Cervarix* introduction in the NIP): The start calendar year for each country will be the date when *Cervarix* was introduced in their NIP. An interim analysis will be performed in 2022. For ***the*** ~~each~~ analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.

In Section 9.1.2 Feasibility assessment

As mentioned above , the objectives of the feasibility assessment are:

- ***To describe the main requirements for the conduct of an additional study assessing the effectiveness of Cervarix in the prevention of anal cancer***
- ***To assess a case-control study design and the data sources that would meet those requirements.***

The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries ***and national vaccination registries*** will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine ***Cervarix*** effectiveness against anal cancer can be performed.

In Section 9.3 Variables:

- ~~Age distribution data as per European Standard Population and UK Health Security agency (for England).~~

In Section 9.3.1.1 Primary endpoints:

- Occurrence and ~~the~~ age-standardised incidence of anal cancer during the study period (i.e., pre- and post- *Cervarix* launch period) by sex, HPV type and histological classification for each country* separately.
- Occurrence and ~~the~~ crude incidence of anal cancer during the study period (i.e., pre- and post-*Cervarix* launch period) by age category, by sex, HPV type and histological classification for each country* separately.

In Section 9.3.1.2 Secondary endpoint:

- ~~Incidence of anal cancer during the pre-*Cervarix* launch period for each country* separately.~~ ***Expected number of anal cancer cases needed to conduct the case-control study based on the vaccine coverage rate and the expected VE and other factors for each country* separately.***

Note: Other feasibility assessment checks with findings for the conduct of a case-control study will be further described in the study report.

In Section 9.4 Data sources:

- National Cancer Registration and Analysis Service ***(UK)*** [NCRAS]:

NCRAS is managed by Public Health England (PHE) and captures a wide range of data sources, including data such as: histopathology and haematology services, medical records, radiotherapy departments, hospices, independent hospitals, screening services, death certificates, general practitioners, other UK cancer registries. The registry holds data on anal cancer from 1993 to ***2018***. The final registrations are released approximately 1 year following the end of a diagnosis year, but it can take up to 5 years to achieve 100% completeness [Henson, 2020].

Added Section 9.4.2 Vaccination registries:

Country	***Vaccination registry***
Finland	***Finnish National Vaccination Registry since 2009***
The Netherlands	***Dutch vaccination registry (Præventis) since 2005***
England	***Immunisations are registered in the Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002)***
Denmark	***Danish vaccination registry since 2009, although compulsory as of 15 November 2015 (UK)***
Norway	***Norwegian vaccination registry since 1995***

In Section 9.5 Study size:

Sample size computation ***for the primary objective*** is not applicable, as there is no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 5 selected European countries will be collected within the established timeframe.

In Section 9.7.2.2 Secondary analysis:

To assess ***the*** feasibility for ***the conduct of*** a case-control study to determine the impact and effectiveness of *Cervarix* against anal ~~lesions and~~ cancer in each country.

~~Step1:~~ **The** ~~N~~number of expected anal cancer cases (estimated sample size) required to demonstrate the expected vaccine effectiveness based on the vaccine coverage data will be determined. ***Also the timeframe for generating meaningful VE estimates will be assessed for each country of interest.***

~~***Step2:*** Assuming that the number of anal cancer cases will increase over time, based on the incidence data of anal cancer cases, birth cohort, vaccine effectiveness and HPV vaccination coverage, assessment of the time frame for conducting the matched case-control study will be done.~~
The cases would be those in the cancer registry with HPV-related anal cancer, whereas controls would be subjects with a non-HPV related cancer. Controls would be sex- and age- matched, retrieved from the same cancer registry to ensure that the comparison group is representative of the source population as that of the cases. ***Investigations will need to be done to understand if brand-specific HPV (Cervarix) vaccination status of***

the cases and controls could be retrieved from national vaccine registries effectively linked to national cancer registries by country of interest.

In Section 9.9 *Strengths and* limitations of the study:

The study has the following ***strengths and*** limitations:

Strengths

- ***Use of nationwide longitudinal data from national cancer registries using the same case definition (aligned with ICD-10 codes).***
- ***A harmonised and coordinated approach in the analysis allowing comparisons across countries and with external similar studies.***
- ***Use of an HPV negative control (i.e., small intestine cancer) would permit to assess for potential bias owed to changes in the surveillance and reporting system of anal cancer over time.***

Limitations

- ~~The cancer registry of Finland cannot provide year of cancer data for calendar years with less than 5 cases due to potential risk for patient identification. Therefore, in those instances, the number of cases will be back-computed using the provided crude incidence and population data~~***The cancer registry of Finland does not provide the number of cancer cases when less than 5 cases are reported in a given year, by sex and age category, due to potential risk of patient identification. Therefore, in those instances, the number of cancer cases will be back-computed using the provided crude incidence and population data. This may introduce some bias by round-offs and back-calculation.***

In Section 13 References:

~~World Health Organization (WHO). Draft Global Strategy towards eliminating cervical cancer as a public health problem 2020. Available from: https://www.who.int/publications/m/item/draft-global-strategy-towards-eliminating-cervical-cancer-as-a-public-health-problem. Accessed: 31 March 2022.~~

WHO International Classification of Diseases for Oncology, 2nd and 3rd Edition (ICD-O-2 and ICD-O-3). Available from: https://apps.who.int/iris/handle/10665/39441 (ICD-O-2); https://www.who.int/standards/classifications/other-classifications/international-classification-of-diseases-for-oncology (ICD-O-3). Accessed: 25 May 2022.

Annex 6 Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	217743 (EPI-HPV-099 VS EUR DB)
Date of protocol amendment	Amendment 2 Final: 25 May 2022
Title	An observational, retrospective database post-authorisation safety study (PASS) to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced *Cervarix* in their National Immunisation Programmes (NIP)
Sponsor signatory	Nadia Meyer, MD Clinical & Epidemiology Project Lead GlaxoSmithKline Biologicals SA
Signature	_____
Date	_____

Note: Not applicable if an alternative signature process (e.g. electronic signature or email approval) is used to get the sponsor approval.

Annex 7 ENCePP Checklist for study protocols

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4, 6
1.1.2 End of data collection[2]	☒	☐	☐	4, 6
1.1.3 Progress report(s)	☐	☐	☒	-
1.1.4 Interim report(s)	☒	☐	☐	4, 6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	4, 6

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	4, 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4, 9.1.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	-
2.1.5 If applicable, that there is no a priori hypothesis?	☒	☐	☐	4, 9.5

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	4, 9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	4, 7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	-
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	-

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	4, 9.1.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	4, 9.1.1
4.2.2 Age and sex	☒	☐	☐	4, 9.1.1
4.2.3 Country of origin	☒	☐	☐	4, 9.1.1
4.2.4 Disease/indication	☒	☐	☐	4, 7
4.2.5 Duration of follow-up	☐	☐	☒	-
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☒	-

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	-
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	-
5.3 Is exposure categorised according to time windows?	☐	☐	☒	-
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	-
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	-
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	-

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3, 9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	-
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	-

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	-
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	-
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	-

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	-

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	4, 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	4, 9.4
9.1.3 Covariates and other characteristics?	☐	☐	☒	-
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	4, 9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	4, 9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	4, 9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	-
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.1.3
9.3.3 Covariates and other characteristics?	☐	☐	☒	-
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	-

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	4, 9.7.2
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	-
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	-
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	-
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	-
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	-

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	4, 9.4
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	-

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	-
12.1.2 Information bias?	☐	☐	☒	-
12.1.3 Residual/unmeasured confounding?	☐	☐	☒	-
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	4, 9.1.2

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☒	☐	-
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	-
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12.1, 12.2
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.1

Comments:

***Note*: The Sponsor confirms his/her agreement with the completed ENCePP checklist by signing the Protocol Sponsor Signatory Approval page.**

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: An observational, retrospective database post-authorisation safety study (PASS) to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced *Cervarix* in their National Immunisation Programmes (NIP).

Study Number: 217743

Compound Number: *580299*

Abbreviated Title: EPI-HPV-099 VS EUR DB

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

Regulatory Agency Identifier Number(s) To be determined

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1. Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	7 November 2021	Final (12 July 2021)	Not Applicable	Original version
Amendment 1	02 Jun 2022	Amendment 1 (25 May 2022)	Primary objective updated for more clarity	Primary objective, study period (based on the introduction of *Cervarix* in NIP)and data source (European standard population) aligned to the update in the protocol amendment.
			Study population updated	For better interpretation of the study results so it can be comparable with publications across countries and to align with the age definition as per the European standard population, inclusion of all age groups instead of adult population (>18 years of age).
			County specified: Changed from United Kingdom (UK) to England	For the UK, all analyses will be based specifically on data from England, and not data from UK. The National Cancer Registration and

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				Analysis Service (NCRAS) is the cancer registry in England
			Inclusion of Poisson / Negative binomial regression model for pre- and post-*Cervarix* launch periods	To see the change in trends pre and post Cervarix launch periods; to have more clarity and to compare the trend.
			Inclusion of year variable in multivariate Poisson / Negative binomial regression model.	To adjust the segmented effect of the model, the year variable is added in the multivariate Poisson / Negative binomial regression model.
			Secondary endpoint updated	More appropriate is to mention the number of anal cancer cases as the endpoint to evaluate the time frame to conduct a case control study, based on the vaccine coverage rate, expected vaccine effectiveness and other factors like crude incidence and birth cohort.

2. INTRODUCTION

The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, ***England***, Denmark and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal lesions and cancer in females and males.

2.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To assess trends and changes over time in ***the age-standardised*** incidence of anal cancer by sex, HPV type and histological classification for each country* separately. • ***To assess trends and changes over time in the crude incidence of anal cancer by age category, by sex, HPV type and histological classification for each country* separately.***	• Occurrence and ***the age-standardised*** incidence of anal cancer during the ***study*** period (i.e., pre- and post-*Cervarix* launch period) ***by*** sex, HPV type and histological classification for each country* separately. • ***Occurrence and the crude incidence of anal cancer during the study period (i.e., pre- and post-Cervarix launch period) by age category, by sex, HPV type and histological classification for each country* separately.*** ***Note:*** Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed by age ***category*** and sex for each country* separately.
Secondary	
• To conduct a feasibility assessment for a case-control study to determine the impact and effectiveness of *Cervarix* against anal lesions and cancer.	• ***Expected number of anal cancer cases needed to conduct the case-control study based on the vaccine coverage rate and the expected VE and other factors for each country* separately.***

Objectives	Endpoints
	Note: Other feasibility assessment checks with findings for the conduct of a case-control study will be further described in the study report.

*Five European countries are considered for this study and each country will be selected based on a set of criteria defined in section 2.2.

Primary estimand

The primary analysis of interest is to observe the trend and changes in ***the age-standardised incidence and crude*** incidence of anal cancer cases over time (during pre- and post- *Cervarix* launch period)

The estimand is described by the following attributes:

- Population: Anal cancer cases / crude incidence in the Netherlands, Finland, Denmark, England and Norway as per the cancer registries during pre- and post-*Cervarix* launch period.
- Variable / endpoint: ***The age-standardised incidence*** by sex, by calendar year, HPV type (if available) and histological classification ***(if available) and crude*** incidence of anal cancer by age category, by sex, by calendar year, HPV type (if available) and histological classification ***(if available).***
- Summary measure: Age standardised ***and crude*** incidence over time.

2.2. Study Design

Overview of Study Design and Key Features	
Design Features	• **Type of study and design**: This is a Targeted Safety Study (TSS) and a PASS. The study is designed as an observational, retrospective database study. • **Study population**: Females and males ***of all age groups*** in the 5 selected European countries. Please refer to Section 9.2 of the protocol for country eligibility criteria. • **Data collection**: Retrospective data collection from national cancer registries ***and national vaccination registries***. • **Study period**: – Pre-*Cervarix* launch period (i.e., before *Cervarix* ***introduction in the NIP***): ***The start and end calendar year for each country***

Overview of Study Design and Key Features	
	will be considered based on the data availability in their respective cancer registries. – Post-*Cervarix* launch period: ***(i.e., after Cervarix introduction in the NIP): The start calendar year for each country will be the date when Cervarix was introduced in their NIP.*** An interim analysis will be performed in 202***2***. For each analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered. • This study will be a trend analysis of incidence of anal cancer in 5 selected European countries. • Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed. Small intestine cancer is relatively rare, with an occurrence of similar magnitude to anal cancer. Small intestine cancer also has a similar mean age of diagnosis as anal cancer, and there is no screening programme for it. It is not associated with HPV infection. This analysis may allow to control for potential changes in cancer surveillance systems and reporting over time.
Interim Analysis	An interim analysis will be performed in 2021-22. For each analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.
Feasibility assessment	***As mentioned above , the objectives of the feasibility assessment are:*** • ***To describe the main requirements for the conduct of an additional study assessing the effectiveness of Cervarix in the prevention of anal cancer*** • ***To assess a case-control study design and the data sources that would meet those requirements.*** The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries ***and national vaccination registries*** will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether a case-control study to determine ***Cervarix*** effectiveness against anal lesions and cancer can be performed.
Case Definition	In this study, for case identification ***of anal cancer and small intestine cancer,*** [International Classification of Diseases (ICD)-10] codes will be used.

Overview of Study Design and Key Features	
	For histological classification of anal cancer, the WHO ICD-O-2 (or) 3 will be used based on the coding version of the cancer registries in the selected countries.
Setting	The following country eligibility criteria should be checked in order to perform analysis: • Should have a stable, consolidated and validated cancer registry. • The cancer registry should preferably be population-based and nationwide. • Administration of *Cervarix* for at least 5 birth cohorts (either routine or catch-up campaign cohorts) within the NIP.
Variables	The following variables will be assessed for each country separately: • Incidence of anal cancer by age category, by sex, by HPV type (if available), by histological classification ***(if available)*** and by calendar year. • Number of anal cancer cases by age category, by sex, by HPV type (if available), by histological classification ***(if available)*** and by calendar year. • Incidence of small intestine cancer by age ***category***, by sex and by calendar year. • Number of small intestine cancer cases by age ***category***, by sex and by calendar year. • Age distribution data as per European Standard Population ***(for all countries)*** • Population data by age ***category***, by sex and by calendar year. • Birth cohort data by sex and by calendar year. • HPV vaccine coverage of the eligible birth cohorts by calendar year, age category (if available) and by sex (if available).

2.3. Data Source

2.3.1. National Cancer Registries

This study will collect anal cancer data from the following national cancer registries:

- The Finnish Cancer Registry [FCR]:

The Cancer Registry of the National Institute for Health and Welfare maintained by the Finnish Cancer Society, contains data on all cancer cases and suspected cancer cases detected in Finland. The health care organisations in Finland are obliged to report this information. The registry holds data on anal cancer cases reported from 1953 to 2019. The reporting of cancer cases has been mandatory since 1961 [International Association of Cancer Registries (IACR)].

Information on cancer cases (from hospitals, physicians, pathology laboratories, and death certificates) are available from Statistics Finland. In order to ensure correctness of data, the notifiers are requested to check accuracy of information about primary site, patient identity, and date of diagnosis. A physician oversees or performs coding. Since 1967, Finland is using personal identification numbers for identification of cases. This allows for accurate follow-up of patients (including death) through official sources. Formal evaluations are also conducted in addition to the continuous quality control procedures (IACR).

FCR data is subjected to computerised checks for validity and internal consistency. Comparability of data is ensured by following the ICD-O-3 introduced in 2007, and earlier codes were converted to ICD-O-3. The completeness of the FCR for all sites was estimated at 95% (96% for solid tumours and 86% for non-solid tumours). The FCR publishes annual statistics with a delay of approximately 2 years. This is due to a latency of one full calendar year for submitting cancer data for registration and having access to data on causes of death [Leinonen, 2017].

- The Netherlands Cancer Registry [NCR]:

NCR is a population-based cancer registry with nationwide coverage since 1989. Cancer diagnoses are notified by the nationwide network and registry of histology and cytopathology (PALGA) and in addition through linkage with the Landelijke Medische Registratie hosted by Dutch Hospital Data. Each cancer case is coded by trained registration clerks (internal education of 1 year) according to ICD-O-3 based on information gathered from medical files at the hospital. Date of diagnosis is coded according to international coding rules and mostly based on the date of first pathological confirmation, or if unavailable, date of first hospital admission [Van der Willik, 2020].

The database is managed by the Netherlands Comprehensive Cancer Organisation (IKNL). NCR is the only oncological hospital registry in the Netherlands with data on all cancer patients. Data on incidence, prevalence, survival, mortality and risk are included in the website and are available at a national level from 1989 to 2020. However, data available for 2019 and 2020 are provisional for the interim analysis.

- National Cancer Registration and Analysis Service [NCRAS]:

NCRAS is managed by Public Health England (PHE) ***(UK Health Security Agency)*** and captures a wide range of data sources, including data such as: histopathology and haematology services, medical records, radiotherapy departments, hospices, independent hospitals, screening services, death certificates, general practitioners, other UK cancer registries. The registry holds data on anal cancer from 1993 to ***2018***. The final registrations are released approximately 1 year following the end of a diagnosis year, but it can take up to 5 years to achieve 100% completeness [Henson, 2020].

Each year, NCRAS collects data on over 300 000 cases of cancer, which includes patient details (i.e., their name, age, address, sex, and date of birth etc), and also data about the type of cancer, how advanced it is and the treatment the patient receives.

In order to allow contemporaneous, comprehensive and cost-effective data collection and to ensure quality assurance, the registry obtains data from across the National Health Service. The data quality in term of validity, completeness, timeliness etc. is assessed. Quality checks are performed both at the level of individual records as well as at the level of the registry. In addition, records are validated against other records and against expected values [Henson, 2020].

- The Danish Cancer Registry [Danish Cancer Registry.]:

The Danish Cancer Registry was founded in 1942 and contains data of the incidence of cancer among the Danish population from 1943 to 2019. The purpose of the cancer registry is to collect and process data on new cases of cancer, in order to produce statistics on the incidence and prevalence of cancer in Denmark, to provide information for the planning of the Danish health services, and to provide a basis for research into the causes of cancer and the course of cancer diseases. Reporting to the cancer registry has been mandatory since 1987. From 2004 to 2008 it underwent a process of modernisation. As a result, the reporting became electronic through integration of patient administrative systems and the manual coding was partly replaced by an automatic coding logic.

The Danish cancer registry has been repeatedly validated for data quality (validity and completeness). Internal validation for lung and breast cancer detected low proportions of errors or missing reports. Moreover, the automated registration ensures high quality and data completeness. Continued improvements following validation studies are implemented [Validation of The Danish Cancer Registry ; Lund , 2013].

- The Cancer Registry of Norway [CRN]:

The Cancer Registry of Norway was established in 1951 and includes data on anal cancer from 1953 to 2019. It is organised as an independent institution under the Oslo University Hospital Trust. Annual data on cancer are published in the *Cancer in Norway* report. Cancer statistics of Norway from 2019 were published in October 2020 [Cancer in Norway , 2019]. Suspected cancer cases (without a verified cancer diagnosis), and cancer first diagnosed by autopsy, need to be mandatorily notified. The cancer registry is in charge for the national screening programmes: Breast Cancer Screening Programme and Cervical Cancer Screening Programme. The cancer registry regulations demand the following 3 main objectives for the cancer registry: registration, research and information.

In Norway, population-based data with high-quality cancer incidence are favourable. Such data requires mandatory reporting, unique personal identification numbers and more than 50 years of experience in cancer registration [Larsen, 2009].

A study of the data quality at the Cancer Registry of Norway showed that data from the registry are reasonably accurate, and that completeness (close-to-completeness) and timely reporting is among the best in Europe [Larsen, 2009].

2.3.2. Vaccination Registries

Country	*Vaccination registry*
Finland	*Finnish National Vaccination Registry since 2009*
The Netherlands	*Dutch vaccination registry (Præventis) since 2005*
England	*Immunisations are registered in the Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002)*
Denmark	*Danish vaccination registry since 2009, although compulsory as of 15 November 2015*
Norway	*Norwegian vaccination registry since 1995*

2.3.3. Eurostat

Eurostat: will be the source for data on the European Standard Population for age distribution used to estimate the age-standardised incidence rates [Pace, 2013]. It will also be the source for population data and birth cohort data***, except for England, for which the source for population data will be UK Health Security Agency and for birth cohort data it will be Office for National Statistics.***

2.3.4. Websites of national public health institutes

- Vaccine coverage data will be retrieved from the respective websites of national public health institutes:
  - Vaccine coverage: For Finland (*Cervarix* introduction in NIP: November 2013)
  - Vaccine coverage: For The Netherlands (*Cervarix* introduction in NIP: September 2009)
  - Vaccine coverage: For England (*Cervarix* introduction in NIP: September 2008)
  - Vaccine coverage: For Denmark (*Cervarix* introduction in NIP: February 2016)
  - Vaccine coverage: For Norway (*Cervarix* introduction in NIP: September 2017)

3. STATISTICAL HYPOTHESES

No formal hypothesis assessment has been done for this study.

3.1. Multiplicity Adjustment

Not applicable as there is no hypothesis testing.

4. ANALYSIS SETS

Definition of the analysis sets and elimination codes will not be applicable.

Analysis will be based on country-specific data extracted from the national cancer registries as per defined population and timeframe.

Please refer to Section 2.2 for details on study population and study period.

5. STATISTICAL ANALYSES

5.1. General Considerations

General Methodology

- All primary and secondary endpoint analyses will be performed for each country separately.
- Exact Poisson 95% CI will be presented for incidences (Ulm K, 1990)
- Normal approximation of the log transformed Maximum Likelihood Estimate method will be used to derive the 95% CI of age standardised incidences (H.K.T. Ng et al, 2008).
- The Wald's 95% CI will be presented for the Poisson / negative binomial regression estimates and for the percentage reduction of the anal cancer cases in the observed counts compared to the predicted counts.

5.2. Primary Endpoints Analyses

To assess trends and changes over time in incidence of anal cancer by age category and by sex. Additionally, based on availability of data, the same will be assessed also by HPV type (if available) and by histological classification ***(if available).***

- Age-standardised incidence with 95% CI during the period from 1992 or later (based on the data availability in the cancer registries) until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by calendar year and sex. Additionally, based on availability of data, the same will be assessed also by HPV type (if available) and by histological classification ***(if available)***.

Note: Age-standardised incidences of anal cancer will be calculated by calendar year and sex using the European Standard Population (age distribution). Computation of age standardised incidence in the interim and final analysis ***will be based on the data source in the section 2.3.3***

Additionally,

- Crude incidences with 95% during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post-*Cervarix* launch period) will be presented by age category, sex, HPV type (if available) and histological classification (if available).
- The trend in the incidence of anal cancer will be assessed using the Poisson / negative binomial regression model. The model will include number of anal cancer cases as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. Annual Percentage Change (APC) will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-Cervarix launch periods separately.
- The trend in the incidence of anal cancer will be assessed using the Poisson / negative binomial regression model. The model will include number of anal cancer cases as outcome variable; ***calendar year,*** age category, study period (pre-launch = 0 and post-launch = 1) ***HPV type, and*** sex as the independent variables (risk factors). The model will include the population followed up as the offset variable.
  Similar analyses will be performed by subcategories – age category, sex, HPV type (if available) and histological classification ***(if available)***.
- Observed and predicted counts of anal cancer cases will be presented by calendar year. Predicted counts of the anal cancer cases will be estimated using a Poisson / negative binomial regression univariate model with number of anal cancer cases as the outcome variable and year as the independent variable on the pre-vaccination data.
  Percentage reduction of the anal cancer cases in the observed counts compared to the predicted will be presented with its Wald's 95% CI.
  Similar analyses will be performed by subcategories – age category, sex, HPV type (if available) and histological classification ***(if available)***.

5.2.1. Definition of endpoints/estimands

Refer to primary estimand in Section 2.1

5.2.2. Main analytical approach

- Age standardised incidence (Ahmad OB, 2001; Anderson RN, 1998) of anal cancer cases per 100000 population during the study period will be derived from the crude incidences extracted from the registries as below.

$$Age\ standardised\ incidence = \sum_{i=1}^{n} Crude\ Incidence\ of\ ith\ age\ category\ * Wi$$

Where n = number of age categories as per the European Standard Population Wi = weight of i^{th} age category = population in i^{th} age category / Total population

Age standardised incidence of anal cancer cases will also be presented by sex overall for each country with 95% CI.

Country-wise age standardised incidence with 95% CI of anal cancer cases by calendar year stratified by sex and overall will also be presented graphically to present the graphical trend. Line graphs will be used for the graphical representation of the trends in age standardised incidence (x-axis : calendar year; y-axis : age standardised incidence).Year of vaccine introduction will also be presented in the same graph.

Additionally,

- Country-wise crude incidence of anal cancer cases with 95% CI by calendar year stratified by sex, age category and overall will also be presented graphically to present the graphical trend. Line graphs will be used for the graphical representation of the incidence (x-axis : calendar year; y-axis : Incidence).Year of vaccine introduction will also be presented in the graph.
- Vaccination coverage rates by calendar year, age-categories (if available), gender (if available) in each country will also be presented.
- The trend in the incidence of anal cancer will be assessed using the Poisson / negative binomial regression model. The model will include number of anal cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. Annual Percentage Change (APC) will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-Cervarix launch periods separately.

5.2.2.1. Poisson Model:

Model : Poisson random variable is a function of predictor information.

$$\log\left(\frac{E(y)}{n_i}\right) = \log\left(\frac{\mu}{n_i}\right) = \beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p \quad \rightarrow (1)$$

Y = Number of anal cancer cases

n_i = population at risk ($\log(n_i)$ is the offset variable)

β's = regression coefficients

5.2.2.2. Assumption of equi-dispersion:

The adequacy of the Poisson regression model of anal cancer incidence will be checked using the Pearson chi-squared goodness-of-fit test.

$\frac{Pearson's\ chi-square}{degrees\ of\ freedom}$ ~ 1 with p-value significant.

If the data violates the equi-dispersion assumption, then the over-dispersion (variance is larger than the mean) or under-dispersion (variance is smaller than the mean), then negative binomial model will be used to model the regression parameters.

Model (1) can be written as,

$$log\left(\frac{\text{Number of anal cancer cases}}{\text{Population at risk}}\right) = \text{intercept} + (\beta 1 \times \text{calendar year}) \quad \rightarrow (2)$$

Note: p-values will be calculated for the regression coefficients and the values < 0.05 will be considered significant.

5.2.2.3. Annual Percentage Change (APC)

Annual Percentage Change (APC) will be estimated to see the unit change in anal cancer incidence using the regression estimates of calendar year in the model:

$$APC = (e\beta - 1) * 100\%;$$

where 'β' is the maximum-likelihood estimate of the true parameter. APC will be presented along with the regression estimates of the calendar year in the model.

5.2.2.4. SAS codes to be used for the Poisson / negative binomial regression model:

```
PROC GENMOD data= <data>;
  CLASS var1(ref=first) var2 … / param=ref;
  MODEL outcome_var = var1 var2…  /DIST=<poisson/negbin> offset =
<log_offset var> TYPE3 WALD;
 SCALE=pearson;
RUN;
```

- The trend in the incidence of anal cancer will be assessed using the Poisson / negative binomial regression model. The model will include number of anal cancer cases as outcome variable; age category, study period (pre-launch = 0 and post-launch = 1), sex, HPV type (if available) as the independent variables. The model will include the population followed up as the offset variable.
- The approach of the Poisson model and the assumptions check (equi-dispersion) will be done as per the details provided in the section 5.2.2.1
- The model to assess the trend of anal cancer incidence is as below.

$$log\left(\frac{\text{Number of anal cancer cases}}{\text{Population at risk}}\right) = \text{intercept} + (\beta1 \times \text{age category}) + (\beta2 \times \text{study period}) + (\beta3 \times \text{sex}) + (\beta4 \times \text{calendar year}) + (\beta5 \times \text{HPV type})$$

- Similar analysis will be performed by subcategories – age category, sex, HPV type (if available) and histological classification (if available).

  – By age category

  $$log\left(\frac{\text{Number of anal cancer cases}}{\text{Population at risk}}\right) = \text{intercept} + (\beta1 \times \text{study period}) + (\beta2 \times \text{sex}) + (\beta3 \times \text{calendar year}) + (\beta4 \times \text{HPV type})$$

  – By Sex:

  $$log\left(\frac{\text{Number of anal cancer cases}}{\text{Population at risk}}\right) = \text{intercept} + (\beta1 \times \text{study period}) + (\beta2 \times \text{age category}) + (\beta3 \times \text{calendar year}) + (\beta4 \times \text{HPV type})$$

  – By HPV type (If available):

  $$log\left(\frac{\text{Number of anal cancer cases}}{\text{Population at risk}}\right) = \text{intercept} + (\beta1 \times \text{study period}) + (\beta2 \times \text{sex}) + (\beta3 \times \text{age category})$$

  – By histological classification:

  $$log\left(\frac{\text{Number of anal cancer cases}}{\text{Population at risk}}\right) = \text{intercept} + (\beta1 \times \text{study period}) + (\beta2 \times \text{sex}) + (\beta3 \times \text{HPV type}) + (\beta4 \times \text{age category})$$

- Observed and predicted counts of the anal cancer cases will be presented by calendar year.
- Predicted counts of the anal cancer cases will be estimated using the Poisson / negative binomial regression univariate model with number of anal cancer cases as the outcome variable and year as the independent variable on the pre-vaccination data. Model that will be used for the estimation of the predicted counts will be as in equation (1).
- Percentage reduction of the anal cancer cases in the observed counts compared to the predicted will be presented with its Wald's 95% CI.

$$Percentage\ reduction = \frac{Predicted\ count\ of\ anal\ cancer\ cases - Observed\ count\ of\ anal\ cancer\ cases}{Predicted\ count\ of\ anal\ cancer\ cases} * 100$$

- Similar analysis will be performed by subcategories – age category, sex, HPV type (if available) and histological classification.
- Predicted and observed counts of anal cancer cases will be presented in line graphs by age category, sex and overall to present the graphical trend (x-axis : calendar year; y-axis : Predicted/observed counts of anal cancer cases). Year of vaccine introduction will also be presented in the graph.

Analysis for negative control:

- Age standardised incidence of small intestine cancer per 100000 population during the period from 1992 until the most recent and complete available calendar year will be derived from the incidence extracted from the registries as below.

$$Age\ standardised\ incidence = \sum_{i=1}^{n} Incidence\ * \frac{percentage\ in\ n^{th}\ age\ category}{100}$$

Where n = age categories as per the European Standard Population (Age distribution as per section 5.2)

Age standardised incidence of small intestine cancer will also be presented by sex overall for each country.

Country-wise age standardised incidences of small intestine cancer by calendar year stratified by sex and overall will also be presented graphically to present the graphical trend. Line graphs will be used for the graphical representation of the trends in age standardised incidence (x-axis : calendar year; y-axis : age standardised incidence).

Additionally,

- Country-wise crude incidence of small intestine cancer by calendar year stratified by sex, age category and overall will also be presented graphically to present the graphical trend. Line graphs will be used for the graphical representation of the trends in crude incidence (x-axis : calendar year; y-axis : crude incidence).The trend in the incidence of small intestine cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of small intestine cancer cases as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. APC will be estimated based on the parameter estimates of the regression model. ***The same model will be generated for the pre- and post-Cervarix launch periods separately.***
- The Poisson model and the assumptions check (equi-dispersion) will be done as per the details provided in the section 5.2.2.1
- Annual Percentage Change (APC) will be estimated to see the unit change in small intestine cancer incidence using the regression estimates of model as per the section 5.2.2.3.

5.2.3. Sensitivity analyses

Not applicable.

5.3. Secondary Endpoint Analyses

To assess ***the*** feasibility for ***the conduct of a*** case-control study to determine the effectiveness of *Cervarix* against anal lesions and cancer in each country.

A prerequisite to conduct a vaccine case-control study is to have high quality data on:

- Cases, with the definition of cases: Subjects ***of all age groups*** identified in the cancer registries with HPV-related anal cancer.
- Controls, with definition of controls: Subjects ***of all age groups*** in the cancer registries identified with a non-HPV related cancer. Controls will be sex- and age-matched, ***retrieved from the same cancer registry to ensure that the comparison group is representative of the source population as that of the cases.***
- Besides age and sex, other covariates of interest may be extracted from the registries if available in order to adjust further the case control vaccine estimate, if needed, to ensure that other factors that could affect the vaccine effectiveness estimate are evenly distributed between cases and controls. (see below under 5.3.1.2 Additional Considerations).
- HPV vaccination status of each case and each control: Note if the vaccination status is not available in the registries or is not available for majority of the cases and controls in the registries, it will be assessed if there exists a linkage between the cancer registries and national vaccine registries (as per the section 2.3.2) to retrieve this information (see below under 5.3.1.2 Additional Considerations).

- Definitions of "vaccinated" and "unvaccinated" subjects in the registries: The definitions of who is fully vaccinated and who is not may vary by country, as dependents on the nationally recommended immunization schedule in each country.

  - England: Full vaccination consists of the administration of 2 doses of HPV vaccine (at present, Gardasil 9). Boys and girls aged 12 and 13 years are offered the first HPV vaccination in school at Year 8, as the scheme is school based. The second dose is offered 6 to 24 months after the first dose. For the purpose of this analysis, a women will be considered vaccinated if the first dose of HPV (*Cervarix*) was administered at <18 years of age , independent of the administration or timing of subsequent vaccine doses.
  - The Netherlands:
    - Before the 15th birthday: full vaccination consists of 2 doses of the HPV vaccine (at present, *Cervarix*), the first preferably around 12-13 years of age and the second, 6 months later.
    - After the 15th birthday: full vaccination consists of the second dose administered 1 month after the first dose, and the third dose about 6 months after the first dose.
    - For the purpose of this analysis, a women will be considered vaccinated if the first dose of HPV (Cervarix) was administered at ≤ 16 years of age , independent of the administration or timing of subsequent vaccine doses.
  - Finland:
    - Before the 15th birthday: full vaccination consists of 2 doses administered (grades 5 and 6, respectively) (at present, *Cervarix*), with an interval of at least 5 months
    - After the 15th birthday: full vaccination consists of 3 doses at 0, 1 and 6 months.
    - For the purpose of this analysis, a women will be considered vaccinated if the first dose of HPV (*Cervarix*) was administered at ≤ 15 years of age , independent of the administration or timing of subsequent vaccine doses.
  - Norway:
    - Full vaccination consists of 2 doses of HPV vaccine. Boys and girls 12 years old (in grade 7th) receive 2 doses of the HPV vaccine (at present, *Cervarix*) at least 6 months apart.
    - For the purpose of this analysis, a women will be considered vaccinated if the first dose of HPV (*Cervarix*) was administered at ≤18 years of age , independent of the administration or timing of subsequent vaccine doses.

- Denmark: full vaccination consists of the administration of 2 or 3 doses of HPV vaccine, depending on the age:
  - Before their 15th birthday, boys and girls are administered 2 doses of HPV vaccine (Gardasil 9) at 0 and 6 months and the vaccination series must be completed within 13 months. If these intervals are not observed, a total of 3 doses should be given, within three months at least between the second and third dose.
  - After the 15th birthday, 3 doses are administered at 0, 1 month, and 3 months, respectively. All 3 doses must be given within 1 year.
  - For the purpose of this analysis, a women will be considered vaccinated if the first dose of HPV (*Cervarix*) was administered at ≤15 years of age , independent of the administration or timing of subsequent vaccine doses.

- Data on the annual background incidence of anal cancer in subjects ***of all age groups***, annual HPV vaccination coverage rates by country, and expected HPV vaccine effectiveness, and decision on the case-control ratio in order to calculate a precision-based sample size.

Hence, step1 and step2 will be done as part of statistical analysis:

Step1: ***The n***umber of expected anal cancer cases (estimated sample size) required to demonstrate the expected vaccine effectiveness based on the vaccine coverage data will be determined.

Step2: Assuming that the number of anal cancer cases will increase over time, based on the incidence data of anal cancer cases, birth cohort, vaccine effectiveness and HPV vaccination coverage, assessment of the time frame for conducting the matched case-control study ***for generating meaningful VE estimates will be assessed for each country of interest.***

Step 3: There will be an investigation for the other data and variables mentioned above and this in the registries, in the literature and on public health websites (as mentioned under 2.3.4) and elsewhere. The study report will include the full information of the outcome of the feasibility assessment for the conduct of a case-control study.

5.3.1. Secondary endpoint

5.3.1.1. Main analytical approach

The number of expected anal cancer cases will be estimated based on the vaccine coverage rate of the controls and the expected vaccine effectiveness.

Below tables provides the number of expected anal cancer cases with 30% drop out rate required to demonstrate vaccine effectiveness (VE) of 30% to 90%, with 80% power using a two-sided test, alpha=0.05 , with 1, 2, 3 and 4 controls per case and for a vaccine coverage rate in controls of 40% to 90%.

Case-Control Ratio 1:1							
Vaccination rate in controls	**Vaccine Effectiveness**						
	90%	**80%**	**70%**	**60%**	**50%**	**40%**	**30%**
30%	42	69	109	176	290	514	1019
40%	33	55	88	144	242	433	867
60%	25	44	74	126	217	399	820
80%	25	49	90	160	289	549	1158
90%	34	73	140	259	480	930	1994

Case-Control Ratio 1:2							
Vaccination rate in controls	**Vaccine Effectiveness**						
	90%	**80%**	**70%**	**60%**	**50%**	**40%**	**30%**
30%	33	52	81	126	208	364	720
40%	25	40	65	104	173	307	612
60%	18	31	53	90	153	281	577
80%	17	35	64	112	202	384	811
90%	22	51	98	181	334	649	1395

Case-Control Ratio 1:3							
Vaccination rate in controls	**Vaccine Effectiveness**						
	90%	**80%**	**70%**	**60%**	**50%**	**40%**	**30%**
30%	29	46	70	111	181	317	624
40%	22	35	56	90	150	265	529
60%	16	27	46	77	131	242	497
80%	14	30	53	95	172	328	694
90%	18	42	82	152	283	551	1191

Case-Control Ratio 1:4							
Vaccination rate in controls	**Vaccine Effectiveness**						
	90%	**80%**	**70%**	**60%**	**50%**	**40%**	**30%**
30%	27	43	66	103	168	294	577
40%	21	33	52	83	138	244	489
60%	14	25	42	70	121	222	456
80%	13	26	48	86	156	299	636
90%	17	38	74	138	257	502	1087

Method: PASS 2019 Software: Matched Case-Control power analysis (Dupont, 1988)
Vaccine effectiveness = (1 – Odds ratio) *100%

Step 2 analysis will be performed to estimate the time frame for conducting the matched case-control study based on the number of cases from the above tables, crude incidence, birth cohort, vaccine coverage and expected vaccine effectiveness.

Data and steps needed for evaluating the timeframe for conducting the **matched case control study** will be as follows.

- Starting point (year) for the case control study including aged 25 years old (age at which every vaccine eligible birth cohort turns 25 years old) will be identified based on Year of *Cervarix* introduction in each country and the target age group (in years) for vaccination.
- Number of anal cancer cases in each calendar year that can be registered from the starting point (year) will be estimated based on the crude incidence, birth cohort, vaccine coverage and expected vaccine effectiveness as follows.

Note: The starting age-point for the matched case-control study has been arbitrarily established at 25 years as information retrieved from the respective cancer websites in the different selected countries shows that anal cancer very rarely affects people before that age.

$$Number\ of\ anal\ cancer\ cases = \sum_{i=1}^{n} BC\ (100\% - VC\%)(inci\ of\ nth\ age\ cat) + BC\ (VC\%)\ (inci\ of\ nth\ age\ cat)(100 - VE\%)$$

n: number of age categories considered in the study
BC: Birth cohort of each country
VC: Vaccine coverage of each country
inci of nth age cat: Crude incidence of anal cancer of nth age category
VE: Vaccine Effectiveness considered in step1

- Cumulative number of anal cancer cases by calendar year will be estimated.
- Time frame (year) will be identified at which the number of anal cancer cases are reached (based on the step 1).

Note: Life Expectancy of 85 years in Finland, 83 years in England and 84 years in Netherlands will be considered as the upper limit of age for the feasibility assessment. This information is considered from the Worldbank data.

5.3.1.2. Additional considerations

- The study report will include the full information of the outcome of the feasibility assessment for the conduct of a case-control study, hence covering also what variables and factors could be found in the registries or elsewhere to run a case-control study.

- The study report will also include the narrative on assessment of the feasibility to link the vaccine registries and the cancer registries in terms of extraction of data on the individual vaccination status of cases and controls, in case information on vaccination status is not available in the registries, and also on the variables that are potentially associated with both vaccination (*Cervarix*) and the disease of interest

(anal cancer). It needs to be checked if the data variables are available in these registries and this in order to see if the case-control vaccine effectiveness estimate can be adjusted on these variables.

- To account for potential selection bias and confounding, controls will be sex-, and age-matched (three thirds of anal cancer cases occur beyond 50 years of age) and retrieved from the same registry to ensure that the comparison group is representative of the source population that produced the cases. Information on other variables that can act as confounders/effect modifiers and are risk factors for HPV-related anal cancer is to be retrieved to make adjustments during the analytical phase, such as smoking, HIV status/immunosuppression, sexual practices, former gynaecologic HPV-related malignancies, and a proxy variable to socioeconomic factors. The availability of these variables will be assessed and the linkage with other databases to provide this information will be determined.

5.3.1.3. Sensitivity analyses

Not applicable.

5.4. Tertiary Analyses

Not applicable.

5.5. Safety Analyses

Not applicable.

5.6. Other Analyses

Not applicable.

5.7. Interim Analyses

An interim analysis will be performed in 2022. For each analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.

5.8. Changes to Protocol Defined Analyses

- Crude incidence of cancer cases per 100000 will be computed if not available in the registry, by using the national population data.

$$Crude\ incidence\ per\ 100000 = \frac{Number\ of\ cancer\ cases}{Population\ data} * 100000$$

- All analysis for the interim analysis will be performed for 3 countries - Finland, the Netherlands and England. The analysis for the remaining 2 countries Denmark and

Norway will be performed during the final analysis depending on the data availability..

- Study period (start and end calendar year) for each country will be considered based on the data availability in the registries. Eg, e.g., first available year of anal cancer data in the English registry is 1995, and not 1992 as planned in the protocol.

6. SAMPLE SIZE DETERMINATION

Sample size computation ***for the primary objective*** is not applicable for the primary objective, as there is no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 5 selected European countries will be collected within the established timeframe.

7. SUPPORTING DOCUMENTATION

7.1. Appendix 1 Data extraction rules

Cancer data will be extracted directly by GSK when available on line (e.g. Netherlands), or by officers of national cancer registries (e.g. ***England***), with number of cancers displayed by year, sex, age-band (5- ***or 10-*** year ***given the country***) and, for anal cancer, by category of histological type, if available.

ICD-10 codes will be used for selecting the cancers of interest (i.e. C21 for anal cancer and C17 for small intestine cancer) from national registries.
The grouping of the ICD-O histo-morphological types into 3 categories of anal cancer types will be based on the classification used by the International Agency for Research on Cancer (WHO) in their 2021 report 'Cancer Incidence in Five Continents Vol. XI':

Table 4.2. Anus (C21)

1 Carcinoma	**8010–8576**
1.1 Squamous cell carcinoma	8050–8076, 8083–8084, 8123–8124
1.2 Adenocarcinoma	8140–8145, 8190–8231, 8260–8265, 8310, 8401, 8480–8490, 8550–8552, 8570–8574, 8576
1.3 Other specified carcinoma	
1.4 Unspecified carcinoma	8010–8011
2 Melanoma	**8720–8790**
3 Other specified malignant neoplasm	
4 Unspecified malignant neoplasm	**8000–8005**

Source : https://publications.iarc.fr/597

The 3 anal cancer types used will be 'epidermoid' carcinoma or 'squamous cell' carcinoma (group 1.1), 'adenocarcinoma' (group 1.2) , and 'others' (all other codes).

Crude incidence rates will be computed, if not available in the registry, by using the national population data.

European Standardised Rates (ESR) for each country will be computed, by year, and by year and sex, using the 2013 European Standard Population from Pace,2013 as follows :
ESR_anal = sum of (W_i _EU * CR_i)
with CR_i = crude rates for each age class i and
W_i _EU = weight of age class i= Npop in age class i in EU / Npop total in EU from Pace,2013
Rates of Cancer data will be provided in SAS format for statistical analyses.
One dataset will include the raw numbers and crude rates by age range.

Variable	Type	Label
Year	Text	Year
Sex	Text	Sex
Age_range	Text	Age_range
N_Anal	Num.	Nbr of Anal Cancer from registry
CR_Anal	Num.	Crude rates of Anal cancer from registry
N_SI	Num.	Nbr of Small Intestine cancer from registry
CR_SI	Num.	Crude rates of Small Intestine cancer from registry
Wi_EU	Num.	Weight of age class i in Europe with from Eurostat 2013

For anal cancer, an additional dataset will provide the morphological types if available

Variable	*Type*	*Label*
Year	***Text***	***Year***
Sex	***Text***	***Sex***
Age_range	***Text***	***Age_range***
Morph_group	***Num.***	***Morph group***
N_Anal	***Num.***	***Nbr of Anal Cancer from registry***
CR_Anal	***Num.***	***Crude rates of Anal cancer from registry***
Wi_EU	***Num.***	***Weight of age class i in Europe with from Eurostat 2013***

The second dataset will include the CR and ESR rates across ages .

Variable	Type	Label
Year	Text	Year
Sex	Text	Sex
ESR_anal	Num.	European Standardised Rates of Anal Cancer by Sex - pop 2013 for Wi
ESR_SI	Num.	European Standardised Rates of Small Intestine cancer by Sex- pop 2013 for Wi

For anal cancer, an additional dataset will provide the morphological types if available

Variable	*Type*	*Label*
Year	***Text***	***Year***
Sex	***Text***	***Sex***
ESR_anal	***Num.***	***European Standardised Rates of Anal Cancer by Sex - pop 2013 for Wi***
Morph_group	***Num.***	***Morph_group***

- Vaccine coverage data will be retrieved, as per the section 2.3.4, from the respective websites of national public health institutes:

  All vaccine coverage rates will be provided in a single table in SAS format by year (1 column by year) for each country.

Variable	Type
Country	Text
Year	Num
Sex	Text
Vaccine Coverage	Text

- Population data will be retrieved from Eurostat:, unless provided by national cancer registries.

  Data retrieved from Eurostat will be provided in an SAS format table and displayed by calendar year and 5- ***or 10***-year age bands, for male, female and globally.

Variable	Type
Country	Text
Year	Num
Sex	Text
Age range	Text
Population	Num

- Birth cohorts will be retrieved from Eurostat: ***unless provided by national registries.***

  They will be provided in a SAS format table and displayed by calendar year, for male, female and globally.

Variable	Type
Country	Text
Year	Num
Sex	Text
Birth	Num.

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17. APPENDICES

17.1. Study Information

17.1.1. Protocol and protocol amendments

PASS INFORMATION

Title:	An observational, retrospective database post-authorisation safety study (PASS) to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced *Cervarix* in their National Immunisation Programmes (NIP)
Protocol version identifier:	217743 (EPI-HPV-099 VS EUR DB)
Date of last version of the protocol:	Protocol Amendment 2 Final: 25 May 2022
EU PAS Register No:	To be determined
Active substance:	HPV-16 L1 VLP protein HPV-18 L1 VLP protein
Medicinal product:	Bivalent human papillomavirus (HPV-16/18 L1 VLP AS04) recombinant vaccine
Product reference:	EMEA/H/C/000721
Procedure number:	To be allocated
Marketing Authorisation Holder (MAH):	GlaxoSmithKline Biologicals SA Rue de l'Institut, 89 1330 Rixensart, Belgium
Joint PASS:	No
Research question and objectives: **(Amended 25 May 2022)**	To assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal cancer in females and males
Countries of study:	Finland, the Netherlands, England, Denmark, and Norway
Author:	PPD , Epidemiology Lead, GlaxoSmithKline Biologicals SA

MARKETING AUTHORISATION HOLDER

MAH:	GlaxoSmithKline Biologicals SA Rue de l'Institut, 89 1330 Rixensart, Belgium
MAH contact person: **(Amended 25 May 2022)**	PPD **,** ***MD*** ***Clinical & Epidemiology Project Lead*** ***GlaxoSmithKline Biologicals SA***

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2. LIST OF ABBREVIATIONS

AIN	Anal intraepithelial neoplasia
APC	Annual percentage change
CI	Confidence interval
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
EU-RMP	European Union Risk Management Plan
GPP	Good Pharmacoepidemiology Practices
GSK	GlaxoSmithKline Biologicals SA
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
IACR	International Association of Cancer Registries
ICD	International Classification of Diseases
MAH	Marketing Authorisation Holder
MPL	3-*O*-desacyl-4'-monophosphoryl lipid A
MSM	Men who have sex with men
NCR	Netherlands Cancer Registry
NCRAS	National Cancer Registration and Analysis Service
NIP	National Immunisation Programme
PASS	Post-authorisation safety study
PHE	Public Health England
SCC	Squamous cell carcinoma
TSS	Targeted safety study
UK	United Kingdom
VE	Vaccine effectiveness
VLP	Virus-like particle
WHO	World Health Organisation

3. RESPONSIBLE PARTIES

(Amended 25 May 2022)

Biologicals SA (GSK) has the overall responsibility for the conduct of the study.

PPD , ***MD, Clinical & Epidemiology Project Lead, GlaxoSmithKline Biologicals SA.***

4. ABSTRACT

Title	An observational, retrospective database post-authorisation safety study (PASS) to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced *Cervarix* in their National Immunisation Programmes (NIP).
Version and date of the protocol	Protocol Amendment 2 Final: 25 May 2022
Main author	PPD, Epidemiology Lead, GlaxoSmithKline Biologicals SA
Rationale and background	Anal cancer is an uncommon type of cancer, representing around 0.3% of all incident cancers diagnosed in 2020 worldwide [Sung, 2021]. Squamous cell carcinoma (SCC) is the most frequent histopathological type of anal cancer [Hoff, 2017]. There is evidence to suggest that human papillomavirus (HPV) infection is associated with anal cancer, particularly with SCC [Hoff, 2017; De Martel, 2020]. Moreover, in a recent worldwide study, HPV deoxyribonucleic acid (DNA) was detected in more than 88% of anal cancers and more than 95% of anal intraepithelial neoplasia (AIN) grades 2/3. The most frequently detected virus type, detected in over 80.7% of invasive anal cancer cases was HPV-16,followed by HPV-18 (3.6% of cases) [Alemany, 2015; Clifford, 2019]. Over the last 4 decades, anal cancer incidence has been gradually increasing and is more common in women than in men, except for certain high-risk groups such as human immunodeficiency virus (HIV)-infected people, and this raise is more relevant in high-income countries [Lum, 2020]. Risk factors for anal cancer are HPV infection, including a former HPV-related malignancy, HIV infection, more than 10 lifetime sexual partners, ano-receptive intercourse, chronic immunosuppression, cigarette smoking, a history of gynaecological or haematologic malignancy, and age. Hence, HIV and immunocompromised patients, and men who have sex with men (MSM) are particularly vulnerable populations [Nelson, 2017; Van der Zee, 2013; Clifford, 2021]. GlaxoSmithKline Biologicals SA (GSK) has developed a prophylactic HPV vaccine, *Cervarix*, based on L1 proteins of HPV-16 and HPV-18 formulated with AS04

(comprising of aluminium hydroxide [Al(OH)3] and 3-O-desacyl-4'-monophosphoryl lipid A [MPL]).

Cervarix is a vaccine for use from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to certain oncogenic HPV types.

In the context of the European Union Risk Management Plan (EU-RMP) for *Cervarix*, a safety concern was raised linked to missing information on the impact and effectiveness of the vaccine against anal lesions and cancer, since it was not prospectively evaluated in clinical trials.

This study will assess the data on anal cancer in countries where *Cervarix* vaccination has been introduced in the NIP. Five European countries were initially preselected: Finland, the Netherlands, England, Denmark, and Norway to perform a trend analysis and to assess feasibility for a case-control study.

Research question and objectives

(Amended 25 May 2022)

The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal cancer in females and males.

Primary Objectives:

- To assess trends and changes over time in the age-standardised incidence of anal cancer by sex, HPV type and histological classification for each country* separately.
- To assess trends and changes over time in the crude incidence of anal cancer by age category, by sex, HPV type and histological classification for each country* separately.

Secondary Objective:

- To conduct a feasibility assessment for a case-control study to determine the effectiveness of *Cervarix* against anal cancer.

**Five European countries are considered for this study, and each country will be selected based on a set of criteria (please refer to Section 9.2 for country eligibility criteria).*

Study design

(Amended 25 May 2022)

- **Type of study and design**: This is a Targeted Safety Study (TSS) and a PASS. The study is designed as an observational, retrospective database study.
- **Study population**: Females and males of all age groups in the 5 selected European countries.

  Please refer to Section 9.2 for country eligibility criteria.
- **Data collection**: Retrospective data collection from national cancer registries.
- **Study period**:
  - Pre-*Cervarix* launch period (i.e., before *Cervarix* introduction in the NIP): The start and end calendar year for each country will be considered based on the data availability in their respective cancer registries.
  - Post-*Cervarix* launch period (i.e., after *Cervarix* introduction in the NIP): The start calendar year for each country will be the date when *Cervarix* was introduced in their NIP. An interim analysis will be performed in 2022. For ***the*** analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.
- This study will be a trend analysis of incidence of anal cancer in 5 selected European countries.
- The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine *Cervarix* effectiveness against anal cancer can be performed.
- Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed. Small intestine cancer is relatively rare, with an occurrence of similar magnitude to anal cancer.

Small intestine cancer also has a similar mean age of diagnosis as anal cancer, and there is no screening programme for it. It is not associated with HPV infection. This analysis may allow to control for potential changes in cancer surveillance systems and reporting over time.

Population

The study population will include females and males of all age groups in the 5 selected European countries.

Please refer to Section 9.2 for country eligibility criteria.

Variables

(Amended 25 May 2022)

Primary endpoint:

- Occurrence and age-standardised incidence of anal cancer during the period (i.e., pre- and post-*Cervarix* launch period) by sex, HPV type and histological classification for each country* separately.
- Occurrence and crude incidence of anal cancer during the study period (i.e., pre- and post-*Cervarix* launch period) by age category, by sex, HPV type and histological classification for each country* separately.

Note: Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed, by age category and sex for each country* separately.

Please refer to Section 7 for details on choice of control.

Secondary endpoint:

- ***Expected number of anal cancer cases needed to conduct the case-control study based on the vaccine coverage rate and the expected VE and other factors for each country* separately.***

Note: Other feasibility assessment checks with findings for the conduct of a case-control study will be further described in the study report.

**Five European countries are considered for this study and each country will be selected based on a set of criteria (please refer to Section 9.2 for country eligibility criteria).*

Data sources

(Amended 25 May 2022)

- Eurostat will be the source for data on the European Standard Population for age distribution used to estimate the age-standardised incidence rates [Pace, 2013]. It will also be the source for the population data and birth cohort data, except for England, for which the source for population data will be the UK Health Security Agency and for birth cohort data it will be Office for National Statistics.
- Vaccine coverage data will be retrieved from the respective websites of national public health institutes.
- This study will collect anal cancer data from the following national cancer registries:
  - The Finnish Cancer Registry [FCR]
  - The Netherlands Cancer Registry [NCR]
  - National Cancer Registration and Analysis Service [NCRAS] ***(UK)***
  - The Danish Cancer Registry [Danish Cancer Registry]
  - The Cancer Registry of Norway [CRN]
- ***Vaccination registries:***
  - ***Finnish National Vaccination Registry since 2009***
  - ***Dutch vaccination registry (Prœventis) since 2005***
  - ***Immunisations are registered in Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002) (UK)***
  - ***Danish vaccination registry since 2009, although compulsory as of 15 November 2015***
  - ***Norwegian vaccination registry since 1995***

Note: More details on vaccine coverage data and data collection are provided in Section 9.4.

Study size **(Amended 25 May 2022)**	Sample size computation ***for the primary objective*** is not applicable, as there is no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 5 selected European countries will be collected within the established timeframe. Please refer to Section 9.3 for details on variables and Section 9.4 for details on data sources. *Note: National cancer registries are nationwide and thus this study is population-based.*
Data analysis	Analysis will be performed using the country-specific data extracted from the national cancer registries as per defined population and timeframe (please refer to Section 9.1.1 for details on study population and study period). *Note: Details on primary analysis and secondary analysis are provided in Section 9.7.*
Milestones	The first round of data collection is planned to start in Quarter 3, 2021 and end in Quarter 4, 2021. The second round of data collection is planned to start in Quarter 3, 2026 and end in Quarter 4, 2026. The interim report is planned for Quarter 1, 2022. The final report of study results is planned for Quarter 1, 2027. *Note*: *The above-mentioned timelines are tentative and are subject to change*.

5. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	31 March 2022	Section 4 Abstract, Section 8 Primary objective and Section 9.3.1.1 Primary endpoint	Primary objective and its corresponding endpoint updated	For clarity: The primary objective and its corresponding endpoint has been split into 2 independent objectives and endpoints, respectively (i.e., for age-standardised incidence and for crude incidence)
		Section 4 Abstract and Section 9.1.1 Discussion of study design	Study population updated	For better interpretation of the study results so it can be comparable with publications across countries and to align with the age definition as per the European standardised population, the entire age group from 0 – 80+ population will be considered instead of the adult population (>18 years of age)
		Section 4 Abstract and Section 9.1.1 Discussion of study design	Study population updated	Study period (i.e., pre- and post-*Cervarix* launch period) will be considered based on the *Cervarix* introduction in the National Immunisation Programme (NIP)
		Section 4 Abstract, Section 7 Rationale and background, Section 8 Research question and objectives, Section 9.4.3 Websites of national public health institutes and Section 9.9 Limitations of the research methods	County specified: Changed from United Kingdom (UK) to England	For the UK, all analyses will be based specifically on data from England, and not data from UK. The National Cancer Registration and Analysis Service (NCRAS) is the cancer registry in England. As the population of England comprises around 84% of the total UK population, the NCRAS is considered to be representative of the population in the UK
		Section 9.7.2.1 Primary analysis	Inclusion of Poisson / Negative binomial regression model for pre- and post-*Cervarix* launch periods	The trend in the incidence of anal cancer and small intestine cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer/small intestine cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. APC will be

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
				estimated based on the parameter estimates of the regression model. The same model will be generated for the pre- and post-*Cervarix* launch periods separately
		Section 4 Abstract and Section 9.4.3 Eurostat	Data source updated	Eurostat will be the source for population data and birth cohort data, except for England, for which the source for population data will be UK Health Security Agency and for birth cohort data it will be Office for National Statistics
		Section 9.7.2 Statistical analysis	Updated to clarify HPV type and histological classification assessment	A sentence has been added to clarify HPV type and histological classification assessment
		Title page, Section 3 Responsible parties and Section 4 Abstract	Sponsor signatory updated	Change in the study team
2	25 May 2022	Section 4 Abstract, Section 8.2 Secondary objective and Section 9.3.1.2 Secondary endpoint	Secondary objective and its corresponding endpoint updated	• The feasibility assessment for a case-control study to determine the effectiveness of *Cervarix* will be conducted only against anal cancer. The data for anal lesions is not available in the cancer registries • Expected number of anal cancer cases is the endpoint which can be used to estimate the time frame by when the estimated sample size for a case-control study would be reached
		Section 9.1.2 Feasibility assessment	Feasibility assessment updated	Additional information added for clarity
		Section 4 Abstract, Section 9.4 Data sources	Data sources updated	Vaccination registry for each of the 5 selected European countries was added
		Section 9.7.2.2 Secondary analysis	Secondary analysis updated	Additional information added for clarity
		Section 9.9 Strengths and limitations of the research methods	Updated to add the strengths of the study	Additional points on strengths of the study included
		Title page and Section 3 Responsible parties	Marketing Authorisation Holder (MAH) contact person updated	The sponsor signatory should be the MAH contact person

The summary of the amendment is provided in Annex 5.

6. MILESTONES

Note: The timelines mentioned below are tentative and are subject to change.

Milestone	Planned date
Start of first round data collection	Quarter 3, 2021
End of first round data collection	Quarter 4, 2021
Interim report 1	Quarter 1, 2022
Start of second round data collection	Quarter 3, 2026
End of second round data collection	Quarter 4, 2026
Registration in the EU PAS register	To be determined
Final report of study results	Quarter 1, 2027

7. RATIONALE AND BACKGROUND

Cervarix is a prophylactic HPV vaccine developed by GSK. It is based on the L1 proteins of HPV-16 and HPV-18 formulated with AS04 (comprising of aluminium hydroxide [$Al(OH)_3$] and 3-*O*-desacyl-4'-monophosphoryl lipid A), indicated for use from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to certain oncogenic HPV types [*Cervarix* Summary of Product Characteristics, 2020].

In the context of the EU-RMP for *Cervarix*, a safety concern was raised linked to missing information on the impact and effectiveness of the vaccine against anal lesions and cancer, since it was not prospectively evaluated in clinical trials.

Anal cancer is an uncommon type of cancer, representing around 0.3% of all incident cancers diagnosed in 2020 worldwide [Sung, 2021]. SCC is the most frequent histopathological type of anal cancer [Hoff, 2017]. There is evidence to suggest that HPV infection is associated with anal cancer, particularly with SCC [Hoff, 2017; De Martel, 2020]. Moreover, in a recent worldwide study, HPV DNA was detected in more than 88% of anal cancers and more than 95% of anal AIN grades 2/3. The most frequently detected virus type, detected in over 80.7% of invasive anal cancer cases was HPV-16, followed by HPV-18 (3.6% of cases) [Alemany, 2015; Clifford, 2019]. Over the last 4 decades, anal cancer incidence has been gradually increasing and is more common in women than in men, except for certain high-risk groups such as HIV-infected people, and this raise is more relevant in high-income countries [Lum, 2020]. Risk factors for anal cancer are HPV infection, including a former HPV-related malignancy, HIV infection, more than 10 lifetime sexual partners, ano-receptive intercourse, chronic immunosuppression, cigarette smoking, a history of gynaecological or haematologic malignancy, and age. Hence, HIV and immunocompromised patients, and MSM are particularly vulnerable populations [Nelson, 2017; Van der Zee, 2013; Clifford, 2021].

An observational study of effectiveness of *Cervarix* against HPV anal positivity in Dutch women showed a pooled vaccine effectiveness of approximately 90% for HPV-16/18 [Woestenberg, 2020], with adjusted VEs of 88.2% (95% confidence interval [CI],

41.3%– 97.6%) against anal HPV-16 and 91.9% (95% CI, 30.5%–99.1%) against anal HPV-18 [Woestenberg, 2020]. The results also demonstrated cross-protection against anal HPV-45 and HPV-31 and a high correlation between anal and cervicovaginal VE. The results support the notion that *Cervarix* may offer protection against HPV-related anal cancer (including cross-protection against HPV-31/33/45) [Clifford, 2019].

Population-based cancer registries are platforms that collect, store, validate and analyse data on incidence and survival of the most relevant types of cancer and are crucial for the planning and evaluation of prevention activities. For instance, the World Health Organisation (WHO) global initiative to eliminate cervical cancer points to sound surveillance and monitoring systems as crucial to monitor the evolution of cervical cancer incidence and the impact of interventions over time [WHO; Piñeros, 2021].

This study will assess the data on anal cancer in countries where *Cervarix* vaccination has been introduced in the NIP. Five European countries were initially preselected: Finland, the Netherlands, England, Denmark, and Norway to perform a trend analysis and to assess feasibility for a case-control study.

Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed. Small intestine cancer is relatively rare, with an occurrence of similar magnitude to anal cancer. Small intestine cancer also has a similar mean age of diagnosis as anal cancer, and there is no screening programme for it. It is not associated with HPV infection. This analysis may allow to control for potential changes in cancer surveillance systems and reporting over time.

8. RESEARCH QUESTION AND OBJECTIVES

(Amended 25 May 2022)

The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries aiming to determine the impact and effectiveness of *Cervarix* against anal cancer in females and males.

Please refer to Section 6 for details on study milestones.

8.1. Primary objectives

- To assess trends and changes over time in the age-standardised incidence of anal cancer by sex, HPV type and histological classification for each country* separately.
- To assess trends and changes over time in the crude incidence of anal cancer by age category, by sex, HPV type and histological classification for each country* separately.

8.2. Secondary objective

(Amended 25 May 2022)

- To conduct a feasibility assessment for a case-control study to determine the effectiveness of *Cervarix* against anal cancer.

**Five European countries are considered for this study and each country will be selected based on a set of criteria (please refer to Section 9.2 for country eligibility criteria).*

9. RESEARCH METHODS

9.1. Study design

9.1.1. Discussion of study design

- Type of study and design: This is a TSS and a PASS. The study is designed as an observational, retrospective database study.
- Study population: Females and males of all age groups in the 5 selected European countries.

Please refer to Section 9.2 for country eligibility criteria.

- Data collection: Retrospective data collection from national cancer registries ***and national vaccination registries***.
- Study period:
  - Pre-*Cervarix* launch period (i.e., before *Cervarix* introduction in the NIP): The start and end calendar year for each country will be considered based on the data availability in their respective cancer registries.
  - Post-*Cervarix* launch period (i.e., after *Cervarix* introduction in the NIP): The start calendar year for each country will be the date when *Cervarix* was introduced in their NIP. An interim analysis will be performed in 2022. For ***the*** analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.
- This study will be a trend analysis of incidence of anal cancer in 5 selected European countries.
- Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed. Small intestine cancer is relatively rare, with an occurrence of similar magnitude to anal cancer. Small intestine cancer also has a similar mean age of diagnosis as anal cancer, and there is no screening programme for it. It is not associated with HPV infection. This analysis may allow to control for potential changes in cancer surveillance systems and reporting over time.

9.1.2. Feasibility assessment

(Amended 25 May 2022)

As mentioned above , the objectives of the feasibility assessment are:

- ***To describe the main requirements for the conduct of an additional study assessing the effectiveness of Cervarix in the prevention of anal cancer***
- ***To assess a case-control study design and the data sources that would meet those requirements.***

The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries ***and national vaccination registries*** will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine ***Cervarix*** effectiveness against anal cancer can be performed.

9.1.3. Case definition

In this study, for case identification of anal cancer and small intestine cancer, [International Classification of Diseases (ICD)-10] codes will be used.

For histological classification of anal cancer, the WHO ICD-O-2 (or) 3 will be used based on the coding version of the cancer registries in the selected countries.

9.2. Setting

The following country eligibility criteria should be checked in order to perform analysis:

- Should have a stable, consolidated and validated cancer registry.
- The cancer registry should preferably be population-based and nationwide.
- Administration of *Cervarix* for at least 5 birth cohorts (either routine or catch-up campaign cohorts) within the NIP.

9.3. Variables

(Amended 25 May 2022)

The following variables will be assessed for each country separately:

- Incidence of anal cancer by age category, by sex, by HPV type (if available), by histological classification (if available) and by calendar year.
- Number of anal cancer cases by age category, by sex, by HPV type (if available), by histological classification (if available) and by calendar year.
- Incidence of small intestine cancer by age category, by sex and by calendar year.
- Number of small intestine cancer cases by age category, by sex and by calendar year.

- Population data by age category, by sex and by calendar year.
- Birth cohort data, by sex and by calendar year.
- HPV vaccine coverage of the eligible birth cohorts by calendar year and by age category and by sex if possible.

9.3.1. Endpoints

9.3.1.1. Primary endpoints

(Amended 25 May 2022)

- Occurrence and age-standardised incidence of anal cancer during the study period (i.e., pre- and post- *Cervarix* launch period) by sex, HPV type and histological classification for each country* separately.
- Occurrence and crude incidence of anal cancer during the study period (i.e., pre- and post-*Cervarix* launch period) by age category, by sex, HPV type and histological classification for each country* separately.

Note: Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed by age category and sex for each country* separately.

Please refer to Section 7 for details on choice of control.

9.3.1.2. Secondary endpoint

(Amended 25 May 2022)

- ***Expected number of anal cancer cases needed to conduct the case-control study based on the vaccine coverage rate and the expected VE and other factors for each country* separately.***

Note: Other feasibility assessment checks with findings for the conduct of a case-control study will be further described in the study report.

**Five European countries are considered for this study and each country will be selected based on a set of criteria (please refer to Section 9.2 or country eligibility criteria).*

9.4. Data sources

(Amended 25 May 2022)

9.4.1. National cancer registries

This study will collect anal cancer data from the following national cancer registries:

- The Finnish Cancer Registry [FCR]:

The Cancer Registry of the National Institute for Health and Welfare maintained by the Finnish Cancer Society, contains data on all cancer cases and suspected cancer cases detected in Finland. The health care organisations in Finland are obliged to report this information. The registry holds data on anal cancer cases reported from 1953 to 2019. The reporting of cancer cases has been mandatory since 1961 [International Association of Cancer Registries (IACR)].

Information on cancer cases (from hospitals, physicians, pathology laboratories, and death certificates) are available from Statistics Finland. In order to ensure correctness of data, the notifiers are requested to check accuracy of information about primary site, patient identity, and date of diagnosis. A physician oversees or performs coding. Since 1967, Finland is using personal identification numbers for identification of cases. This allows for accurate follow-up of patients (including death) through official sources. Formal evaluations are also conducted in addition to the continuous quality control procedures [IACR].

FCR data is subjected to computerised checks for validity and internal consistency. Comparability of data is ensured by following the ICD-O-3 introduced in 2007, and earlier codes were converted to ICD-O-3. The completeness of the FCR for all sites was estimated at 95% (96% for solid tumours and 86% for non-solid tumours). The FCR publishes annual statistics with a delay of approximately 2 years. This is due to a latency of one full calendar year for submitting cancer data for registration and having access to data on causes of death [Leinonen, 2017].

- The Netherlands Cancer Registry [NCR]:

NCR is a population-based cancer registry with nationwide coverage since 1989. Cancer diagnoses are notified by the nationwide network and registry of histology and cytopathology (PALGA) and in addition through linkage with the Landelijke Medische Registratie hosted by Dutch Hospital Data. Each cancer case is coded by trained registration clerks (internal education of 1 year) according to ICD-O-3 based on information gathered from medical files at the hospital. Date of diagnosis is coded according to international coding rules and mostly based on the date of first pathological confirmation, or if unavailable, date of first hospital admission [Van der Willik, 2020].

The database is managed by the Netherlands Comprehensive Cancer Organisation (IKNL). NCR is the only oncological hospital registry in the Netherlands with data on all cancer patients. Data on incidence, prevalence, survival, mortality and risk are included in the website and are available at a national level from 1989 to 2020. However, data available for 2019 and 2020 are provisional.

- National Cancer Registration and Analysis Service ***(UK)*** [NCRAS]:

NCRAS is managed by Public Health England (PHE) and captures a wide range of data sources, including data such as: histopathology and haematology services, medical records, radiotherapy departments, hospices, independent hospitals, screening services, death certificates, general practitioners, other UK cancer registries. The registry holds data on anal cancer from 1993 to ***2018***. The final registrations are released approximately 1 year following the end of a diagnosis year, but it can take up to 5 years to achieve 100% completeness [Henson, 2020].

Each year, NCRAS collects data on over 300 000 cases of cancer, which includes patient details (i.e., their name, age, address sex, and date of birth etc), and also data about the type of cancer, how advanced it is and the treatment the patient receives.

In order to allow contemporaneous, comprehensive and cost-effective data collection and to ensure quality assurance, the registry obtains data from across the National Health Service. The data quality in term of validity, completeness, timeliness etc. is assessed. Quality checks are performed both at the level of individual records as well as at the level of the registry. In addition, records are validated against other records and against expected values [Henson, 2020].

- The Danish Cancer Registry [Danish Cancer Registry]:

The Danish Cancer Registry was founded in 1942 and contains data of the incidence of cancer among the Danish population from 1943 to 2019. The purpose of the cancer registry is to collect and process data on new cases of cancer, in order to produce statistics on the incidence and prevalence of cancer in Denmark, to provide information for the planning of the Danish health services, and to provide a basis for research into the causes of cancer and the course of cancer diseases. Reporting to the cancer registry has been mandatory since 1987. From 2004 to 2008 it underwent a process of modernisation. As a result, the reporting became electronic through integration of patient administrative systems and the manual coding was partly replaced by an automatic coding logic.

The Danish cancer registry has been repeatedly validated for data quality (validity and completeness). Internal validation for lung and breast cancer detected low proportions of errors or missing reports. Moreover, the automated registration ensures high quality and data completeness. Continued improvements following validation studies are implemented [Validation of The Danish Cancer Registry and selected Clinical Cancer Databases; Lund, 2013].

- The Cancer Registry of Norway [CRN]:

The Cancer Registry of Norway was established in 1951 and includes data on anal cancer from 1953 to 2019. It is organised as an independent institution under the Oslo University Hospital Trust. Annual data on cancer are published in the *Cancer in Norway* report. Cancer statistics of Norway from 2019 were published in October 2020 [Cancer in Norway, 2019]. Suspected cancer cases (without a verified cancer diagnosis), and cancer first diagnosed by autopsy, need to be mandatorily notified. The cancer registry is in charge for the national screening programmes: Breast Cancer Screening Programme and Cervical Cancer Screening Programme. The cancer registry regulations demands the

following 3 main objectives for the cancer registry: registration, research and information.

In Norway, population-based data with high-quality cancer incidence are favourable. Such data requires mandatory reporting, unique personal identification numbers and more than 50 years of experience in cancer registration [Larsen, 2009].

A study of the data quality at the Cancer Registry of Norway showed that data from the registry are reasonably accurate, and that completeness (close-to-completeness) and timely reporting is among the best in Europe [Larsen, 2009].

9.4.2. Vaccination registries

Country	*Vaccination registry*
Finland	*Finnish National Vaccination Registry since 2009*
The Netherlands	*Dutch vaccination registry (Præventis) since 2005*
England	*Immunisations are registered in the Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002)*
Denmark	*Danish vaccination registry since 2009, although compulsory as of 15 November 2015 (UK)*
Norway	*Norwegian vaccination registry since 1995*

9.4.3. Eurostat

Eurostat will be the source for data on the European Standard Population for age distribution used to estimate the age-standardised incidence rates [Pace, 2013]. It will also be the source for population data and birth cohort data**,** except for England, for which the source for population data will be UK Health Security Agency and for birth cohort data it will be Office for National Statistics.

9.4.4. Websites of national public health institutes

- Vaccine coverage data will be retrieved from the respective websites of national public health institutes:
  - Finland
  - The Netherlands
  - England
  - Denmark
  - Norway

Please refer to Annex 4 for details on vaccination schedules and vaccine coverage in the selected 5 European countries.

9.5. Study size

(Amended 25 May 2022)

Sample size computation ***for the primary objective*** is not applicable, as there is no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 5 selected European countries will be collected within the established timeframe.

Please refer to Section 9.3 for details on variables and Section 9.4 for details on data sources.

Note: National cancer registries are nationwide and thus this study is population-based.

9.6. Data management

9.6.1. Data collection

Please refer to Section 9.3 for details on study variables and Section 9.4 for details on study data sources.

9.7. Data analysis

9.7.1. Analysis set

The country-specific data extracted from the national cancer registries as per defined population and timeframe.

Please refer to Section 9.1.1 for details on study population and study period.

9.7.2. Statistical Analysis

All analyses will be performed for each country separately. The analysis planned by HPV type and histological classification will be performed based on the data availability during the time of the analysis.

9.7.2.1. Primary analysis

(Amended 25 May 2022)

To assess trends and changes over time in incidence of anal cancer by age category and by sex.

- Age-standardised incidence with 95% CI during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by sex.

Note: Age-standardised incidence rates of anal cancer will be calculated by calendar year and sex using the European Standard Population (age distribution).

Additionally,

- Crude incidence with 95% CI during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post-*Cervarix* launch period) will be presented by age category, sex, HPV type and histological classification.
- The trend in the incidence of anal cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. Annual Percentage Change (APC) will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-*Cervarix* launch periods separately.
- The trend in the incidence of anal cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer incidences as outcome variable; calendar year, age category, study period (pre-launch = 0 and post-launch = 1), HPV type and sex as the independent variables (risk factors). The model will include the population followed up as the offset variable. Similar analysis will be performed by subcategories – age category, sex, HPV type and histological classification.
- Observed and predicted counts of the anal cancer cases will be presented by calendar year. Predicted counts of the anal cancer cases will be estimated using the Poisson / Negative binomial regression univariate model with number of anal cancer cases as the outcome variable and year as the independent variable on the pre-vaccination data.
  Percentage reduction of the anal cancer cases in the observed counts compared to the predicted will be presented with its Wald's 95% CI.
  Similar analysis will be performed by subcategories – age category, sex, HPV type and histological classification.

Analysis for negative control:

- Age-standardised incidence with 95% CI of small intestine cancer during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by age category and sex.

Note: Age-standardised incidence rates of small intestine cancer will be calculated by calendar year and sex using the European Standard Population (age distribution).

- Crude incidence with 95% CI of small intestine cancer during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by age category, sex.

- The trend in the incidence of small intestine cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of small intestine cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. APC will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-*Cervarix* launch periods separately.

9.7.2.2. Secondary analysis

(Amended 25 May 2022)

To assess ***the*** feasibility for ***the conduct of*** a case-control study to determine the effectiveness of *Cervarix* against anal cancer in each country.

The number of expected anal cancer cases (estimated sample size) required to demonstrate the expected vaccine effectiveness will be determined. ***Also the timeframe for generating meaningful VE estimates will be assessed for each country of interest.***

The cases would be those in the cancer registry with HPV-related anal cancer, whereas controls would be subjects with a non-HPV related cancer. Controls would be sex- and age-matched, retrieved from the same cancer registry to ensure that the comparison group is representative of the source population as that of the cases. ***Investigations will need to be done to understand if brand-specific HPV (Cervarix) vaccination status of the cases and controls could be retrieved from national vaccine registries effectively linked to national cancer registries by country of interest.***

9.8. Quality control

To ensure compliance with Good Pharmaco-epidemiology Practices (GPP) or other applicable guidelines and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study.

9.9. *Strengths and* limitations of the research methods

(Amended 25 May 2022)

The study has the following ***strengths and*** limitations:

Strengths

- ***Use of nationwide longitudinal data from national cancer registries using the same case definition (aligned with ICD-10 codes).***
- ***A harmonised and coordinated approach in the analysis allowing comparisons across countries and with external similar studies.***

- ***Use of an HPV negative control (i.e., small intestine cancer) would permit to assess for potential bias owed to changes in the surveillance and reporting system of anal cancer over time.***

Limitations

- ***The cancer registry of Finland does not provide the number of cancer cases when less than 5 cases are reported in a given year, by sex and age category, due to potential risk of patient identification. Therefore, in those instances, the number of cancer cases will be back-computed using the provided crude incidence and population data. This may introduce some bias by round-offs and back-calculation.***
- Limitations in the cancer registry data such as accuracy in the cancer diagnosis methods, case ascertainment, misclassification of primary location (i.e., misclassification as rectal cancer).
- Lack of/limited information on the existence of targeted anal cancer screening programmes (i.e., directed towards at-risk groups such as MSM, HIV-positive patients, or subjects previously diagnosed of an HPV-related cancer), that may lead to overdiagnosis and may also have an impact on temporal incidence trends.
- Lack of information of the aetiology of the anal cancer cases (i.e., whether HPV-related) may introduce some bias and limit the interpretation. Additionally, if no causative HPV type could be provided, further sub-analysis of the incidence by HPV type will be limited by this constraint.
- Percentage of anal cancers with unspecified histology (unspecified carcinomas or unspecified morphology).
- Variations in registry practices in diagnosis and information collection may introduce some bias in international comparisons (i.e., consistency of histological classifications).
- Changes in trends may occur over time for reasons other than HPV vaccination (i.e., changes in the surveillance and reporting system, increment of anal cancer diagnosis due to increased awareness among physicians, implementation of an anal cancer screening programme).

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

GSK will not have access to individual data (i.e., only aggregated data by age group will be provided). No protected personal data will be transferred to GSK.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable since this study is an observational, retrospective PASS, based on data extracted from the national cancer registry databases.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Posting of information on publicly available registers and publication policy

Studies that do not evaluate vaccines are progressed for publication in the scientific literature when the results provide important scientific or medical knowledge or are relevant for patient care, and will be considered for disclosure on the GSK website and in publicly accessible regulatory registry(ies) such as EU PAS register as applicable.

12.2. Provision of study results to investigators/database owners

Where required by applicable regulatory requirements, an investigator/database owner signatory will be identified for the potential review of the results and approval of the study report.

13. REFERENCES

(Amended 25 May 2022)

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Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1	217743	25 May 2022	List of stand-alone documents
2	217743	25 May 2022	Glossary of terms
3	217743	25 May 2022	Sponsor information
4	217743	25 May 2022	Additional information
5	217743	25 May 2022	ENCePP checklist for study protocols

Annex 2 Glossary of terms

Case-control study:	A form of epidemiological study where the study population is selected based on whether the participants do (cases) or do not (controls) have the particular outcome (disease) under study. The groups are then compared with respect to exposure/characteristic of interest.
Commitment:	Agreement made with Regulatory Authorities as specific condition of regulatory approval and authorisation, either made at the time of product approval or during the lifecycle of the approved product.
Database:	A database is a set of pre-existing tables and views containing data. The term "pre-existing" implies that the analysis will be done on retrospective data and the term "views" implies that the data can be made readily available in an electronic format through a straightforward extract, without re-encoding and manual manipulation (like a transpose, a translation, split of a field into several fields, etc).
Database study:	A study involving the use of pre-existing data maintained in an electronic format; this will not include collection of new data that requires (re-) encoding via CRF/eCRF and retesting of human biological samples.
Epidemiological study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
eTrack:	GSK's tracking tool for clinical/epidemiological studies.
Participant:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database. Synonym: subject
Protocol amendment:	The International Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants,

	scope of the investigation, study design, or scientific integrity of the study.
Post-Authorisation Safety Study:	A pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product. This includes all GSK sponsored non-interventional studies and clinical trials conducted anywhere in the world that are in accordance with the terms of the European marketing authorisation and where the investigation of safety is the specific stated objective. Note: The phrase 'In accordance with the terms of the European marketing authorisation' means that the product is used according to the European label (e.g. within the recommended dose range, the approved formulation, indication, etc.).
Retrospective study:	A study that looks backward in time (e.g. at events that occurred in the past; outcomes and exposure can no longer be influenced), usually using medical records, databases or interviews in order to address one or more study objectives.
Study population:	Sample of population of interest.
Surveillance:	The ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.
Targeted Safety Study:	Studies specifically planned or conducted to examine an actual or hypothetical safety concern in a product marketed anywhere in the world. This includes any GSK sponsored pharmaco-epidemiological study or clinical trial conducted anywhere in the world with the aim of identifying or quantifying a safety hazard. Although all clinical trials collect safety information as a matter of routine, only those initiated to examine a specific safety concern are considered a targeted safety study.

Annex 3 Sponsor Information

(Amended 25 May 2022)

1. Sponsor:

GlaxoSmithKline Biologicals (GSK)
Rue de l'Institut, 89, B-1330 Rixensart
Belgium

2. Sponsor medical expert for the study:

PPD **, *MD, Clinical & Epidemiology Project Lead, GlaxoSmithKline Biologicals SA.***

Refer to the local study contact information document.

Annex 4 Additional information

(Amended 25 May 2022)

The table below presents details on vaccination schedules and vaccine coverage in the 5 selected European countries.

Country	Date HPV vaccine first introduced	Vaccine given	Immunisation schedule	Age cohort	Catch-up campaigns	Vaccine coverage	Date modification immunisation schedule	Modification immunisation schedule
Denmark	January 2009	Quadrivalent HPV (*Gardasil*)	0m, 2m, 6m	12 yo girls (born 1996) (GP-based)	13-15 yo girls Women born 1985-1992 (August 2012 to December 2013)	79% 3-dose	August 2014 February 2016 November 2017 July 2019	*Gardasil* (0m, 6m) *Cervarix* (0m, 6m) *Gardasil 9* (0m, 6m) for girls *Gardasil 9* (0m, 6m) for boys 12 yo on 1 July 2019 or later
Finland	November 2013	Bivalent HPV (*Cervarix*)	0m, 1m, 6m	11-12 yo (born 2005) (school-based)	13-15 yo girls (November 2013)	68% 3-dose in 2015 72% 3-dose in 2016	Autumn 2020	*Cervarix* (0m, 6m) girls and boys 12 yo + Catch-up for boys in grades 7-9 (2020-21 and 2021-22)
Netherlands	September 2009	Bivalent HPV (*Cervarix*)	0m, 1m, 6m	12 yo girls 10 yo girls/boys	13-16 yo girls (2009/2010) ***12-18 yo girls/boys (2022/2023)***	58% 3-dose (cohort 1998)	January 2014 ***January 2022***	*Cervarix* (0m, 6m) *Cervarix* (0m, 6m) girls and boys
Norway	August 2009	Quadrivalent HPV (*Gardasil*)	0m, 2m, 6m	12 yo (born 1997) (school-based)	Girls born in 1991 or later (2016-2018)	1997 cohort-65% 3-dose in 2011 2004 cohort- 83% 3-dose in 2016/2017 school year	September 2017 September 2018	*Cervarix* (0m, 6m) girls *Cervarix* (0m, 6m) girls and boys 12 yo

Country	Date HPV vaccine first introduced	Vaccine given	Immunisation schedule	Age cohort	Catch-up campaigns	Vaccine coverage	Date modification immunisation schedule	Modification immunisation schedule
England	September 2008	Bivalent HPV (*Cervarix*)	0m, 1m, 6m	12-13 yo girls (school-based)	14 to < 18 yo	86.7% 3-dose in 2013/2014 83.9% 2-dose in 2018/2019 64.7% 2-dose in 2019/2020	September 2012 September 2014 April 2018 September 2019	*Gardasil* (0m, 2m, 6m) for girls *Gardasil* (0m, 6m or 12m) for girls *Gardasil* (0m, 6m) for MSM ≤ 45 yo *Gardasil 9* (0m, 6m or 12m) for boys 12-13 yo + Catch-up girls and boys up to 25th birthday

HPV: human papillomavirus; m: month; ***MSM: Men who have sex with men;*** yo: years old.

Annex 5 Amendments and administrative changes to the protocol

GlaxoSmithKline Biologicals SA

Vaccines R & D
Protocol Amendment 1

eTrack study number and Abbreviated Title:	217743 (EPI-HPV-099 VS EUR DB)
Amendment number:	Amendment 1 Final
Amendment date:	Final: 31 March 2022

Rationale/background for changes:

The protocol amendment 1 was developed to account for the following changes:

1. For clarity, the primary objective and its corresponding endpoint has been split into 2 independent objectives and endpoints, respectively (i.e., for age-standardised incidence and for crude incidence).
2. For better interpretation of the study results so it can be comparable with publications across countries and to align with the age definition as per the European standardised population, the entire age group from 0 – 80+ population will be considered instead of the adult population (>18 years of age).
3. Study period (i.e., pre- and post-*Cervarix* launch period) will be considered based on the *Cervarix* introduction in the National Immunisation Programme (NIP).
4. For the UK, all analyses will be based specifically on data from England, and not data from UK. The National Cancer Registration and Analysis Service (NCRAS) is the cancer registry in England. As the population of England comprises around 84% of the total UK population, the NCRAS is considered to be representative of the population in the UK.
5. Inclusion of Poisson / Negative binomial regression model for pre- and post-*Cervarix* launch periods: The trend in the incidence of anal cancer and small intestine cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer/small intestine cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. APC will be estimated based on the parameter estimates of the regression model.
   The same model will be generated for the pre- and post-*Cervarix* launch periods separately.
6. Eurostat will be the source for population data and birth cohort data, except for England, for which the source for population data will be UK Health Security Agency and for birth cohort data it will be Office for National Statistics.
7. The analysis planned by HPV type and histological classification will be performed based on the data availability during the time of the analysis.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

In the PASS information page:

Research question and objectives: To assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, ~~the United Kingdom (UK)~~***England***, Denmark and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer in females and males

Countries of study: Finland, the Netherlands, ~~the UK~~***England***, Denmark and Norway

Author: PPD ~~, MD, Clinical and Epidemiology R&D Project Lead, HPV, Hepatitis and Pneumococcal vaccines, GlaxoSmithKline Biologicals SA~~ PPD **,** ***Epidemiology Lead, GlaxoSmithKline Biologicals SA***

MAH contact person: PPD ~~, MD, Clinical and Epidemiology R&D Project Lead, HPV, Hepatitis and Pneumococcal vaccines, GlaxoSmithKline Biologicals SA~~ PPD **,** ***Epidemiology Lead, GlaxoSmithKline Biologicals SA***

In Section 3 Responsible parties:

PPD ~~(Clinical and Epidemiology R&D Project Lead) is GSK's designated contact person for this study~~PPD **,** ***Epidemiology Lead, GlaxoSmithKline Biologicals SA***.

In Section 4 Abstract:

Main author: PPD ~~, MD, Clinical and Epidemiology R&D Project Lead, HPV, Hepatitis and Pneumococcal vaccines, GlaxoSmithKline Biologicals SA~~ PPD **,** ***Epidemiology Lead, GlaxoSmithKline Biologicals SA***

Rationale and background: In the context of the European Union Risk Management Plan (EU-RMP) for *Cervarix*, a safety concern was raised linked to missing information on the impact and~~/or~~ effectiveness of the vaccine against anal lesions and cancer, since it was not prospectively evaluated in clinical trials.

This study will assess the data on anal cancer in countries where *Cervarix* vaccination has been introduced in the NIP. Five European countries were initially preselected: Finland, the Netherlands, ~~the United Kingdom (UK)~~***England***, Denmark and Norway to perform a trend analysis and to assess feasibility for a case-control study.

Research question and objectives: The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, ~~the UK~~ ***England***, Denmark and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer in females and males.

Primary Objective:

- To assess trends and changes over time in ***the age-standardised*** incidence of anal cancer by ~~age,~~ sex, HPV type and histological classification for each country* separately.
- ***To assess trends and changes over time in the crude incidence of anal cancer by age category, by sex, HPV type and histological classification for each country* separately.***

Secondary Objective:

- To conduct a feasibility assessment for a case-control study to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer.

Study design:

Study population: Females and males ~~aged 18 years** and above~~***of all age groups*** in the 5 selected European countries.

Study period:

- Pre-*Cervarix* launch period (i.e., before *Cervarix* ~~commercialisation~~***introduction in the NIP***): ~~From 1992 to 2006 inclusive~~***The start and end calendar year for each country will be considered based on the data availability in their respective cancer registries***.
- Post-*Cervarix* launch period ***(i.e., after Cervarix introduction in the NIP)***: ~~From 2007 to 2026 (i.e., final analysis)~~***The start calendar year for each country will be the date when Cervarix was introduced in their NIP***. An interim analysis will be performed in 202***2***~~1~~. For each analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.

The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine vaccine impact and~~/or~~ effectiveness against anal lesions and cancer can be performed.

Population:

The study population will include females and males ~~aged 18** years and above~~***of all age groups*** in the 5 selected European countries.

~~***The exact lower limit of age will depend on each cancer registry.***~~

Variables:

Primary endpoint:

- Occurrence and ***the age-standardised*** incidence of anal cancer during the period ~~from 1992 until the most recent and complete available calendar year in the cancer registries~~ (i.e., ~~during~~ pre- and post- *Cervarix* launch period) by ~~age,~~ sex, HPV type and histological classification for each country* separately.
- ***Occurrence and the crude incidence of anal cancer during the study period (i.e., pre- and post-Cervarix launch period) by age category, by sex, HPV type and histological classification for each country* separately.***

Note: Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed, by age ***category*** and sex for each country* separately.

Data sources: Eurostat will be the source for data on the European Standard Population for age distribution used to estimate the age-standardised incidence rates for the 5 selected European countries [Pace, 2013]. It will also be the source for the population data and birth cohort data, ***except for England, for which the source for population data will be the UK Health Security Agency and for birth cohort data it will be Office for National Statistics.***

This study will collect anal cancer data from the following national cancer registries:

- National Cancer Registration and Analysis Service [NCRAS] ~~in the UK~~

In Section 7 Rationale and background: In the context of the EU-RMP for *Cervarix*, a safety concern was raised linked to missing information on the impact and~~/or~~ effectiveness of the vaccine against anal lesions and cancer, since it was not prospectively evaluated in clinical trials.

This study will assess the data on anal cancer in countries where *Cervarix* vaccination has been introduced in the NIP. Five European countries were initially preselected: Finland, the Netherlands, ~~the UK~~***England***, Denmark and Norway to perform a trend analysis and to assess feasibility for a case-control study.

In Section 8 Research question and objectives: The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, ~~the UK~~ ***England***, Denmark and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer in females and males.

Primary Objective:

- To assess trends and changes over time in ***the age-standardised*** incidence of anal cancer by ~~age,~~ sex, HPV type and histological classification for each country* separately.

- ***To assess trends and changes over time in the crude incidence of anal cancer by age category, by sex, HPV type and histological classification for each country* separately.***

Secondary Objective:

- To conduct a feasibility assessment for a case-control study to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer.

In Section 9.1.1 Discussion of study design:

- Study population: Females and males ~~aged 18** years and above~~***of all age groups*** in the 5 selected European countries.

~~***The exact lower limit of age will depend on each cancer registry.***~~

- Study period:
  - Pre-*Cervarix* launch period (i.e., before *Cervarix* ~~commercialisation~~***introduction in the NIP***): ~~From 1992 to 2006 inclusive~~***The start and end calendar year for each country will be considered based on the data availability in their respective cancer registries***.
  - Post-*Cervarix* launch period ***(i.e., after Cervarix introduction in the NIP)***: ~~From 2007 to 2026 (i.e., final analysis)~~***The start calendar year for each country will be the date when Cervarix was introduced in their NIP***. An interim analysis will be performed in 202***2***~~1~~. For each analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.

In Section 9.1.2. Feasibility assessment: The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine vaccine impact and~~/or~~ effectiveness against anal lesions and cancer can be performed.

In Section 9.1.3 Case definition

In this study, for case identification ***of anal cancer and small intestine cancer,*** [International Classification of Diseases (ICD)-10~~]/ International Classification of Diseases for Oncology, third Edition (ICD-O-3)~~ codes will be used~~ (i.e., C21 for anal cancer and C17 for small intestine cancer)~~.

For histological classification of anal cancer, the WHO ICD-O-2 (or) 3 will be used based on the coding version of the cancer registries in the selected countries.~~Cancer registries in the selected countries use the WHO ICD-O-3 for classification and coding of neoplasms.~~

In Section 9.3 Variables: The following variables will be assessed for each country separately:

- Incidence of anal cancer by age ***category***, by sex, by HPV type ***(if available)***, by histological classification ***(if available)*** and by calendar year.
- Number of anal cancer cases by age ***category***, by sex, by HPV type ***(if available)***, by histological classification ***(if available)*** and by calendar year.
- Incidence of small intestine cancer by age ***category***, by sex and by calendar year.
- Number of small intestine cancer cases by age ***category***, by sex and by calendar year.
- Age distribution data as per European Standard Population ***and UK Health Security agency (for England)***.
- Population data by age ***category***, by sex and by calendar year.
- Birth cohort data by age ***category***, by sex and by calendar year.
- HPV vaccine coverage of the eligible birth cohorts by calendar year and by age ***category*** and by sex if possible.

In Section 9.3.1.1 Primary endpoint:

- Occurrence and ***the age-standardised*** incidence of anal cancer during the period ~~from 1992 until the most recent and complete available calendar year in the cancer registries~~ (i.e., ~~during~~ pre- and post- *Cervarix* launch period) by ~~age,~~ sex, HPV type and histological classification for each country* separately.

- ***Occurrence and the crude incidence of anal cancer during the study period (i.e., pre- and post-Cervarix launch period) by age category, by sex, HPV type and histological classification for each country* separately.***

Note: Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed, by age ***category*** and sex for each country* separately.

In Section 9.4.2 Eurostat: Eurostat will be the source for data on the European Standard Population for age distribution used to estimate the age-standardised incidence rates [Pace, 2013]. It will also be the source for population data and birth cohort data***, except for England, for which the source for population data will be UK Health Security Agency and for birth cohort data it will be Office for National Statistics.***

In Section 9.4.3 Websites of national public health institutes:

- Vaccine coverage data will be retrieved from the respective websites of national public health institutes:
  - ~~**The UK**~~ ***England***

In Section 9.7.2. Statistical Analysis: All analyses will be performed for each country separately. ***The analysis planned by HPV type and histological classification will be performed based on the data availability during the time of the analysis.***

In Section 9.7.2.1. Primary analysis: To assess trends and changes over time in incidence of anal cancer by age ***category*** and by sex. ~~Additionally, based on availability of data, the same will be assessed also by HPV type and by histological classification.~~

- Age-standardised incidence ***with 95% CI*** during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by ~~age category and~~sex. ~~Additionally, based on availability of data, the same will be assessed also by HPV type and by histological classification.~~

Note: Age-standardised incidence rates of anal cancer will be calculated by calendar year and sex using the European Standard Population (age distribution)***, except for England, for which the source for population data will be UK Health Security Agency.***

Additionally,

- ***Crude i***ncidence ***with 95% CI*** ~~rates~~ during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by age category, sex, HPV type and histological classification.
- The trend in the incidence of anal cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. Annual Percentage Change (APC) will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-Cervarix launch periods separately.
- The trend in the incidence of anal cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer incidences as outcome variable; ***calendar year,*** age category, study period (pre-launch = 0 and post-launch = 1), ***HPV type and*** sex and histological classification as the independent variables ***(risk factors)***. The model will include the population followed up as the offset variable.
  Similar analysis will be performed by subcategories – age category, sex, HPV type and histological classification.

Analysis for negative control:

- Age-standardised incidence ***with 95% CI*** of small intestine cancer during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by age category and sex.

Note: Age-standardised incidence rates of small intestine cancer will be calculated by calendar year and sex using the European Standard Population (age distribution)***, except for England, for which the source for population data will be UK Health Security Agency.***

- ***Crude*** incidence ***with 95% CI*** of small intestine cancer during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by age category, sex.
- The trend in the incidence of small intestine cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of small intestine cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. APC will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-Cervarix launch periods separately.

In Section 9.7.2.2 Secondary analysis: To assess feasibility for a case-control study to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer in each country.

In Section 9.9 Limitations of the research methods:

- The cancer registr***y***~~ies~~ of Finland~~, the Netherlands and the UK~~ cannot provide year of ~~birth~~***cancer*** data for calendar years with less than 5 cases due to potential risk for patient identification. Therefore, ***in those instances, the number of cases will be back-computed using the provided crude incidence and population data***~~the sub-group incidence analysis by age will be limited by this constraint~~.
- ~~For the UK, incidence data may derive from regional registries and data might not be representative of the entire country since reports to this cancer registry only cover England.~~

In Section 13 References:

Office for National Statistics: Home - Office for National Statistics (ons.gov.uk). Accessed: 31 March 2022.

The UK Health Security Agency (UKHSA): https://www.gov.uk/government/organisations/uk-health-security-agency. Accessed: 31 March 2022.

GlaxoSmithKline Biologicals SA

Vaccines R & D
Protocol Amendment 2

eTrack study number and Abbreviated Title:	217743 (EPI-HPV-099 VS EUR DB)
Amendment number:	Amendment 2 Final
Amendment date:	Final: 25 March 2022

Rationale/background for changes:

The protocol amendment 2 was developed to account for the following changes:

1. Secondary objective and its corresponding endpoint was updated:
   - The feasibility assessment for a case-control study to determine the effectiveness of *Cervarix* will be conducted only against anal cancer. The data for anal lesions is not available in the cancer registries
   - Expected number of anal cancer cases is the endpoint which can be used to estimate the time frame by when the estimated sample size for a case-control study would be reached.
2. Feasibility assessment was updated to add additional information for clarity.
3. Vaccination registry for each of the 5 selected European countries was added.
4. Secondary analysis was updated to add additional information for clarity.
5. Additional points on strengths of the study were included.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

In the PASS information page:

Research question and objectives: To assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal ~~lesions and~~ cancer in females and males

In the Marketing authorisation holder page:

MAH contact person: PPD ~~, Epidemiology Lead, GlaxoSmithKline Biologicals SA~~PPD ***, MD, Clinical & Epidemiology Project Lead, GlaxoSmithKline Biologicals SA***

In Section 3 Responsible parties: PPD ~~, Epidemiology Lead, GlaxoSmithKline Biologicals SA~~PPD ***, MD, Clinical & Epidemiology Project Lead, GlaxoSmithKline Biologicals SA***

In Section 4 Abstract:

Research question and objectives: To assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal ~~lesions and~~ cancer in females and males

Secondary objective:

- To conduct a feasibility assessment for a case-control study to determine the ~~impact and~~ effectiveness of *Cervarix* against anal cancer.

Study design:

Data collection: Retrospective data collection from national cancer registries ***and national vaccination registries***.

Study period:

- Post-*Cervarix* launch period (i.e., after *Cervarix* introduction in the NIP): The start calendar year for each country will be the date when *Cervarix* was introduced in their NIP. An interim analysis will be performed in 2022. For ***the***~~each~~ analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.

- The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine ***Cervarix***~~vaccine~~ impact and effectiveness against anal ~~lesions and~~ cancer can be performed.

Variables:

Primary endpoint:

- Occurrence and ~~the~~ age-standardised incidence of anal cancer during the period (i.e., pre- and post- *Cervarix* launch period) by sex, HPV type and histological classification for each country* separately.
- Occurrence and ~~the~~ crude incidence of anal cancer during the study period (i.e., pre- and post-*Cervarix* launch period) by age category, by sex, HPV type and histological classification for each country* separately.

Secondary endpoint:

- ~~Incidence of anal cancer during the pre-~~*~~Cervarix~~* ~~launch period for each country* separately.~~ ***Expected number of anal cancer cases needed to conduct the case-control study based on the vaccine coverage rate and the expected VE and other factors for each country* separately.***

Note: Other feasibility assessment checks with findings for the conduct of a case-control study will be further described in the study report.

Data sources:

  - National Cancer Registration and Analysis Service [NCRAS] ***(UK)***
- ***Vaccination registries:***
  - ***Finnish National Vaccination Registry since 2009***
  - ***Dutch vaccination registry (Præventis) since 2005***
  - ***Immunisations are registered in Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002) (UK)***
  - ***Danish vaccination registry since 2009, although compulsory as of 15 November 2015***
  - ***Norwegian vaccination registry since 1995***

Study size:

Sample size computation ***for the primary objective*** is not applicable, as there is no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 5 selected European countries will be collected within the established timeframe.

In Section 8 Research question and objectives:

The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries aiming to determine the impact and effectiveness of *Cervarix* against anal ~~lesions and~~ cancer in females and males.

In Section 8.2 Secondary objective:

- To conduct a feasibility assessment for a case-control study to determine the impact and effectiveness of *Cervarix* against anal ~~lesions and~~ cancer.

In Section 9.1.1 Discussion of study design:

Data collection: Retrospective data collection from national cancer registries ***and national vaccination registries***.

Study period:

- Post-*Cervarix* launch period (i.e., after *Cervarix* introduction in the NIP): The start calendar year for each country will be the date when *Cervarix* was introduced in their NIP. An interim analysis will be performed in 2022. For ***the*** ~~each~~ analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.

In Section 9.1.2 Feasibility assessment

As mentioned above , the objectives of the feasibility assessment are:

- ***To describe the main requirements for the conduct of an additional study assessing the effectiveness of Cervarix in the prevention of anal cancer***
- ***To assess a case-control study design and the data sources that would meet those requirements.***

The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries ***and national vaccination registries*** will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine ***Cervarix*** effectiveness against anal cancer can be performed.

In Section 9.3 Variables:

- ~~Age distribution data as per European Standard Population and UK Health Security agency (for England).~~

In Section 9.3.1.1 Primary endpoints:

- Occurrence and ~~the~~ age-standardised incidence of anal cancer during the study period (i.e., pre- and post- *Cervarix* launch period) by sex, HPV type and histological classification for each country* separately.
- Occurrence and ~~the~~ crude incidence of anal cancer during the study period (i.e., pre- and post-*Cervarix* launch period) by age category, by sex, HPV type and histological classification for each country* separately.

In Section 9.3.1.2 Secondary endpoint:

- ~~Incidence of anal cancer during the pre-*Cervarix* launch period for each country* separately.~~ ***Expected number of anal cancer cases needed to conduct the case-control study based on the vaccine coverage rate and the expected VE and other factors for each country* separately.***

Note: Other feasibility assessment checks with findings for the conduct of a case-control study will be further described in the study report.

In Section 9.4 Data sources:

- National Cancer Registration and Analysis Service ***(UK)*** [NCRAS]:

NCRAS is managed by Public Health England (PHE) and captures a wide range of data sources, including data such as: histopathology and haematology services, medical records, radiotherapy departments, hospices, independent hospitals, screening services, death certificates, general practitioners, other UK cancer registries. The registry holds data on anal cancer from 1993 to ***2018***. The final registrations are released approximately 1 year following the end of a diagnosis year, but it can take up to 5 years to achieve 100% completeness [Henson, 2020].

Added Section 9.4.2 Vaccination registries:

Country	***Vaccination registry***
Finland	***Finnish National Vaccination Registry since 2009***
The Netherlands	***Dutch vaccination registry (Præventis) since 2005***
England	***Immunisations are registered in the Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002)***
Denmark	***Danish vaccination registry since 2009, although compulsory as of 15 November 2015 (UK)***
Norway	***Norwegian vaccination registry since 1995***

In Section 9.5 Study size:

Sample size computation ***for the primary objective*** is not applicable, as there is no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 5 selected European countries will be collected within the established timeframe.

In Section 9.7.2.2 Secondary analysis:

To assess ***the*** feasibility for ***the conduct of*** a case-control study to determine the impact and effectiveness of *Cervarix* against anal ~~lesions and~~ cancer in each country.

~~Step1:~~ **The** ~~N~~number of expected anal cancer cases (estimated sample size) required to demonstrate the expected vaccine effectiveness based on the vaccine coverage data will be determined. ***Also the timeframe for generating meaningful VE estimates will be assessed for each country of interest.***

~~***Step2:*** Assuming that the number of anal cancer cases will increase over time, based on the incidence data of anal cancer cases, birth cohort, vaccine effectiveness and HPV vaccination coverage, assessment of the time frame for conducting the matched case-control study will be done.~~
The cases would be those in the cancer registry with HPV-related anal cancer, whereas controls would be subjects with a non-HPV related cancer. Controls would be sex- and age- matched, retrieved from the same cancer registry to ensure that the comparison group is representative of the source population as that of the cases. ***Investigations will need to be done to understand if brand-specific HPV (Cervarix) vaccination status of***

the cases and controls could be retrieved from national vaccine registries effectively linked to national cancer registries by country of interest.

In Section 9.9 *Strengths and* limitations of the study:

The study has the following ***strengths and*** limitations:

Strengths

- ***Use of nationwide longitudinal data from national cancer registries using the same case definition (aligned with ICD-10 codes).***
- ***A harmonised and coordinated approach in the analysis allowing comparisons across countries and with external similar studies.***
- ***Use of an HPV negative control (i.e., small intestine cancer) would permit to assess for potential bias owed to changes in the surveillance and reporting system of anal cancer over time.***

Limitations

- ~~The cancer registry of Finland cannot provide year of cancer data for calendar years with less than 5 cases due to potential risk for patient identification. Therefore, in those instances, the number of cases will be back-computed using the provided crude incidence and population data~~***The cancer registry of Finland does not provide the number of cancer cases when less than 5 cases are reported in a given year, by sex and age category, due to potential risk of patient identification. Therefore, in those instances, the number of cancer cases will be back-computed using the provided crude incidence and population data. This may introduce some bias by round-offs and back-calculation.***

In Section 13 References:

~~World Health Organization (WHO). Draft Global Strategy towards eliminating cervical cancer as a public health problem 2020. Available from: https://www.who.int/publications/m/item/draft-global-strategy-towards-eliminating-cervical-cancer-as-a-public-health-problem. Accessed: 31 March 2022.~~

WHO International Classification of Diseases for Oncology, 2nd and 3rd Edition (ICD-O-2 and ICD-O-3). Available from: https://apps.who.int/iris/handle/10665/39441 (ICD-O-2); https://www.who.int/standards/classifications/other-classifications/international-classification-of-diseases-for-oncology (ICD-O-3). Accessed: 25 May 2022.

Annex 6 Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	217743 (EPI-HPV-099 VS EUR DB)
Date of protocol amendment	Amendment 2 Final: 25 May 2022
Title	An observational, retrospective database post-authorisation safety study (PASS) to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced *Cervarix* in their National Immunisation Programmes (NIP)
Sponsor signatory	Nadia Meyer, MD Clinical & Epidemiology Project Lead GlaxoSmithKline Biologicals SA
Signature	_____
Date	_____

Note: Not applicable if an alternative signature process (e.g. electronic signature or email approval) is used to get the sponsor approval.

Annex 7 ENCePP Checklist for study protocols

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4, 6
1.1.2 End of data collection[2]	☒	☐	☐	4, 6
1.1.3 Progress report(s)	☐	☐	☒	-
1.1.4 Interim report(s)	☒	☐	☐	4, 6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	4, 6

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	4, 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4, 9.1.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	-
2.1.5 If applicable, that there is no a priori hypothesis?	☒	☐	☐	4, 9.5

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	4, 9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	4, 7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	-
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	-

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	4, 9.1.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	4, 9.1.1
4.2.2 Age and sex	☒	☐	☐	4, 9.1.1
4.2.3 Country of origin	☒	☐	☐	4, 9.1.1
4.2.4 Disease/indication	☒	☐	☐	4, 7
4.2.5 Duration of follow-up	☐	☐	☒	-
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☒	-

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	-
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	-
5.3 Is exposure categorised according to time windows?	☐	☐	☒	-
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	-
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	-
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	-

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3, 9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	-
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	-

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	-
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	-
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	-

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	-

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	4, 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	4, 9.4
9.1.3 Covariates and other characteristics?	☐	☐	☒	-
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	4, 9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	4, 9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	4, 9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	-
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.1.3
9.3.3 Covariates and other characteristics?	☐	☐	☒	-
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	-

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	4, 9.7.2
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	-
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	-
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	-
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	-
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	-

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	4, 9.4
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	-

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	-
12.1.2 Information bias?	☐	☐	☒	-
12.1.3 Residual/unmeasured confounding?	☐	☐	☒	-
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	4, 9.1.2

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☒	☐	-
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	-
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12.1, 12.2
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.1

Comments:

***Note*: The Sponsor confirms his/her agreement with the completed ENCePP checklist by signing the Protocol Sponsor Signatory Approval page.**

17.1.2. Study Administrative Table providing information on important participants in the study

Study Administrative Table

Clinical Trial Activity	Performed by	Responsibilities and scope of activities	Site address
Monitoring	Study Delivery Lead (Central Study co-ordinator) PPD	• co-ordinates operational aspects of running the study from preparation of study supplies and data capture tools, to study tracking • has regular contacts with local monitors in order to review the study progress and any issue raised by the local monitor. In this way compliance with the protocol and GCP/ICH guidelines is ensured during preparation, active and cleaning phases of the study • is responsible for maintaining and archiving a comprehensive study file. If required, transitioning of a study from one monitor to another is documented in the study file • is responsible for reviewing the clinical study report	GSK India Global Services Private Limited Level 1,2 & 3, Luxor NorthTower Bagmane Capital Business Park Outer Ring Road, Mahadevapura KR Puram Hobli Bangalore – 560037
Monitoring	Local Monitor	*Prior to study start*: • is responsible for the evaluation of the study site and ensures that the staff and facilities are trained and appropriate for running of the study according to protocol and GCP guidelines • is involved in the preparation of study package for submission to Ethics Committee and/or Independent Review Board (EC/IRBs) and appropriate authorities *At study initiation*: • conducts study specific training *While trial is ongoing*: • discusses all aspects of the trial with the study staff • verifies source documents and Case Report Forms (CRFs) • conducts a 100% review of all Informed Consent documentation	NA

Clinical Trial Activity	Performed by	Responsibilities and scope of activities	Site address
		• checks accountability of investigational product and its storage conditions • checks the collection and storage of biological samples and transport to central laboratory • reviews each SAE report All monitoring visits are documented via a monitoring visit report (MVR), which will be reviewed by the monitor's manager. These reports allow the identification of protocol violation, re-education of site staff and communication of significant issues (SAEs, quality, efficacy and GCP compliance) to the central organisation. In this way the Local Monitors oversee the progress of the clinical trial and ensure that it is conducted, recorded and reported in accordance with the protocol and current GCP/ICH guidelines. The Local Monitor works in close partnership with the Local Medical Adviser and the Central Study Monitor.	
Data Management	Data Manager PPD	• the development of the Case Report Form • the development of checks and listings for data cleaning purposes • the handling/cleaning of study data (in conjunction with the Clinical Development Manager, Central Study and Local Monitors) in order to provide cleaned database for the statistical analysis	GSK India Global Services Private Limited Level 1,2 & 3, Luxor North Tower Bagmane Capital Business Park Outer Ring Road, Mahadevapura KR Puram Hobli Bangalore – 560037
Statistics	Statistician PPD	• is involved in the study design and is responsible for calculating the sample size, preparation of the randomisation list, identification of appropriate statistical tests to analyse the data, conducting the statistical analysis on the data collected, issuing the statistical report and interpretation of the statistical findings • reviews the final study report to ensure that all aspects of the statistical analysis and findings are accurately represented in the final report	GSK India Global Services Private Limited Level 1,2 & 3, Luxor North Tower Bagmane Capital Business Park Outer Ring Road, Mahadevapura KR Puram Hobli Bangalore – 560037

Clinical Trial Activity	Performed by	Responsibilities and scope of activities	Site address
Laboratory assessments	NA	NA	NA
Epidemiology lead	Epidemiologist PPD Sponsor signatory Nadia Meyer	• Provides scientific input for the study protocol, analysis plan and review of data • Reviews the final study report to ensure that clinical/epidemiological and scientific interpretation of the findings are accurately represented in the final report	GlaxoSmithKline EspañaParque Tecnológico de MadridC Severo Ochoa, no 228760 – Tres Cantos Madrid Tfno. 91 807 0300 01 GlaxoSmithKline Vaccines Research & Development (R&D) Building WN23, 1300 Wavre Belgium
Medical writing	Scientific Writer PPD	• In collaboration with the study team, prepares study protocols, Informed Consent Forms (ICFs), protocol amendments and the Study Reports. • Co-ordinates the review of the final study report with the study team (including the investigators) to ensure that the report is an accurate account of the study and findings.	GSK India Global Services Private Limited Level 1,2 & 3, Luxor North Tower Bagmane Capital Business Park Outer Ring Road, Mahadevapura KR Puram Hobli Bangalore – 560037
Central Safety	Central Safety Department	During the conduct of pre-licensure studies, the Central Safety Department is responsible for: • Centralising collection, review and follow-up of all reported SAEs • Analysis of safety issues and review of the safety content of the final study report. • the issue of Expedited Investigator Safety Reports to inform all investigators in the programme and IRBs of unexpected and related SAEs.	NA

Clinical Trial Activity	Performed by	Responsibilities and scope of activities	Site address
Other information			
Location of trial master file	Local Study Monitor Central Study Monitor	The Sponsor's Trial Master file is composed of the country monitoring study file and the central study file.	Electronic trial master file (eTMF)
Site(s) of manufacture	NA	NA	NA
Site of release in Europe	NA	NA	NA

17.1.3. Signatures of sponsor approver

GlaxoSmithKline Biologicals SA
Vaccines R & D
Sponsor signatory approval page

Please note that by signing this page, you take responsibility for the content of the Interim Study Report, including appendices

Study title: An observational, retrospective database post-authorisation safety study (PASS) to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced *Cervarix* in their National Immunisation Programmes (NIP)

Study: 217743 (EPI-HPV-099 VS EUR DB)

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of sponsor signatory:	Nadia Meyer
Title of sponsor signatory:	Clinical and Epidemiology R&D Project Lead, GlaxoSmithKline Biologicals SA
Signature:	
Date:	

17.1.4. Documentation of statistical methods

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: An observational, retrospective database post-authorisation safety study (PASS) to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced *Cervarix* in their National Immunisation Programmes (NIP).

Study Number: 217743

Compound Number: *580299*

Abbreviated Title: EPI-HPV-099 VS EUR DB

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

Regulatory Agency Identifier Number(s) To be determined

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1. Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	7 November 2021	Final (12 July 2021)	Not Applicable	Original version
Amendment 1	02 Jun 2022	Amendment 1 (25 May 2022)	Primary objective updated for more clarity	Primary objective, study period (based on the introduction of *Cervarix* in NIP)and data source (European standard population) aligned to the update in the protocol amendment.
			Study population updated	For better interpretation of the study results so it can be comparable with publications across countries and to align with the age definition as per the European standard population, inclusion of all age groups instead of adult population (>18 years of age).
			County specified: Changed from United Kingdom (UK) to England	For the UK, all analyses will be based specifically on data from England, and not data from UK. The National Cancer Registration and

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				Analysis Service (NCRAS) is the cancer registry in England
			Inclusion of Poisson / Negative binomial regression model for pre- and post-*Cervarix* launch periods	To see the change in trends pre and post Cervarix launch periods; to have more clarity and to compare the trend.
			Inclusion of year variable in multivariate Poisson / Negative binomial regression model.	To adjust the segmented effect of the model, the year variable is added in the multivariate Poisson / Negative binomial regression model.
			Secondary endpoint updated	More appropriate is to mention the number of anal cancer cases as the endpoint to evaluate the time frame to conduct a case control study, based on the vaccine coverage rate, expected vaccine effectiveness and other factors like crude incidence and birth cohort.

2. INTRODUCTION

The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, ***England***, Denmark and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal lesions and cancer in females and males.

2.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To assess trends and changes over time in ***the age-standardised*** incidence of anal cancer by sex, HPV type and histological classification for each country* separately. • ***To assess trends and changes over time in the crude incidence of anal cancer by age category, by sex, HPV type and histological classification for each country* separately.***	• Occurrence and ***the age-standardised*** incidence of anal cancer during the ***study*** period (i.e., pre- and post-*Cervarix* launch period) ***by*** sex, HPV type and histological classification for each country* separately. • ***Occurrence and the crude incidence of anal cancer during the study period (i.e., pre- and post-Cervarix launch period) by age category, by sex, HPV type and histological classification for each country* separately.*** ***Note:*** Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed by age ***category*** and sex for each country* separately.
Secondary	
• To conduct a feasibility assessment for a case-control study to determine the impact and effectiveness of *Cervarix* against anal lesions and cancer.	• ***Expected number of anal cancer cases needed to conduct the case-control study based on the vaccine coverage rate and the expected VE and other factors for each country* separately.***

Objectives	Endpoints
	Note: Other feasibility assessment checks with findings for the conduct of a case-control study will be further described in the study report.

*Five European countries are considered for this study and each country will be selected based on a set of criteria defined in section 2.2.

Primary estimand

The primary analysis of interest is to observe the trend and changes in ***the age-standardised incidence and crude*** incidence of anal cancer cases over time (during pre- and post- *Cervarix* launch period)

The estimand is described by the following attributes:

- Population: Anal cancer cases / crude incidence in the Netherlands, Finland, Denmark, England and Norway as per the cancer registries during pre- and post-*Cervarix* launch period.
- Variable / endpoint: ***The age-standardised incidence*** by sex, by calendar year, HPV type (if available) and histological classification ***(if available) and crude*** incidence of anal cancer by age category, by sex, by calendar year, HPV type (if available) and histological classification ***(if available).***
- Summary measure: Age standardised ***and crude*** incidence over time.

2.2. Study Design

Overview of Study Design and Key Features	
Design Features	• **Type of study and design**: This is a Targeted Safety Study (TSS) and a PASS. The study is designed as an observational, retrospective database study. • **Study population**: Females and males ***of all age groups*** in the 5 selected European countries. Please refer to Section 9.2 of the protocol for country eligibility criteria. • **Data collection**: Retrospective data collection from national cancer registries ***and national vaccination registries***. • **Study period**: – Pre-*Cervarix* launch period (i.e., before *Cervarix* ***introduction in the NIP***): ***The start and end calendar year for each country***

Overview of Study Design and Key Features	
	will be considered based on the data availability in their respective cancer registries. – Post-*Cervarix* launch period: ***(i.e., after Cervarix introduction in the NIP): The start calendar year for each country will be the date when Cervarix was introduced in their NIP.*** An interim analysis will be performed in 202***2***. For each analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered. • This study will be a trend analysis of incidence of anal cancer in 5 selected European countries. • Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed. Small intestine cancer is relatively rare, with an occurrence of similar magnitude to anal cancer. Small intestine cancer also has a similar mean age of diagnosis as anal cancer, and there is no screening programme for it. It is not associated with HPV infection. This analysis may allow to control for potential changes in cancer surveillance systems and reporting over time.
Interim Analysis	An interim analysis will be performed in 2021-22. For each analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.
Feasibility assessment	***As mentioned above , the objectives of the feasibility assessment are:*** • ***To describe the main requirements for the conduct of an additional study assessing the effectiveness of Cervarix in the prevention of anal cancer*** • ***To assess a case-control study design and the data sources that would meet those requirements.*** The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries ***and national vaccination registries*** will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether a case-control study to determine ***Cervarix*** effectiveness against anal lesions and cancer can be performed.
Case Definition	In this study, for case identification ***of anal cancer and small intestine cancer,*** [International Classification of Diseases (ICD)-10] codes will be used.

Overview of Study Design and Key Features	
	For histological classification of anal cancer, the WHO ICD-O-2 (or) 3 will be used based on the coding version of the cancer registries in the selected countries.
Setting	The following country eligibility criteria should be checked in order to perform analysis: • Should have a stable, consolidated and validated cancer registry. • The cancer registry should preferably be population-based and nationwide. • Administration of *Cervarix* for at least 5 birth cohorts (either routine or catch-up campaign cohorts) within the NIP.
Variables	The following variables will be assessed for each country separately: • Incidence of anal cancer by age category, by sex, by HPV type (if available), by histological classification ***(if available)*** and by calendar year. • Number of anal cancer cases by age category, by sex, by HPV type (if available), by histological classification ***(if available)*** and by calendar year. • Incidence of small intestine cancer by age ***category***, by sex and by calendar year. • Number of small intestine cancer cases by age ***category***, by sex and by calendar year. • Age distribution data as per European Standard Population ***(for all countries)*** • Population data by age ***category***, by sex and by calendar year. • Birth cohort data by sex and by calendar year. • HPV vaccine coverage of the eligible birth cohorts by calendar year, age category (if available) and by sex (if available).

2.3. Data Source

2.3.1. National Cancer Registries

This study will collect anal cancer data from the following national cancer registries:

- The Finnish Cancer Registry [FCR]:

The Cancer Registry of the National Institute for Health and Welfare maintained by the Finnish Cancer Society, contains data on all cancer cases and suspected cancer cases detected in Finland. The health care organisations in Finland are obliged to report this information. The registry holds data on anal cancer cases reported from 1953 to 2019. The reporting of cancer cases has been mandatory since 1961 [International Association of Cancer Registries (IACR)].

Information on cancer cases (from hospitals, physicians, pathology laboratories, and death certificates) are available from Statistics Finland. In order to ensure correctness of data, the notifiers are requested to check accuracy of information about primary site, patient identity, and date of diagnosis. A physician oversees or performs coding. Since 1967, Finland is using personal identification numbers for identification of cases. This allows for accurate follow-up of patients (including death) through official sources. Formal evaluations are also conducted in addition to the continuous quality control procedures (IACR).

FCR data is subjected to computerised checks for validity and internal consistency. Comparability of data is ensured by following the ICD-O-3 introduced in 2007, and earlier codes were converted to ICD-O-3. The completeness of the FCR for all sites was estimated at 95% (96% for solid tumours and 86% for non-solid tumours). The FCR publishes annual statistics with a delay of approximately 2 years. This is due to a latency of one full calendar year for submitting cancer data for registration and having access to data on causes of death [Leinonen, 2017].

- The Netherlands Cancer Registry [NCR]:

NCR is a population-based cancer registry with nationwide coverage since 1989. Cancer diagnoses are notified by the nationwide network and registry of histology and cytopathology (PALGA) and in addition through linkage with the Landelijke Medische Registratie hosted by Dutch Hospital Data. Each cancer case is coded by trained registration clerks (internal education of 1 year) according to ICD-O-3 based on information gathered from medical files at the hospital. Date of diagnosis is coded according to international coding rules and mostly based on the date of first pathological confirmation, or if unavailable, date of first hospital admission [Van der Willik, 2020].

The database is managed by the Netherlands Comprehensive Cancer Organisation (IKNL). NCR is the only oncological hospital registry in the Netherlands with data on all cancer patients. Data on incidence, prevalence, survival, mortality and risk are included in the website and are available at a national level from 1989 to 2020. However, data available for 2019 and 2020 are provisional for the interim analysis.

- National Cancer Registration and Analysis Service [NCRAS]:

NCRAS is managed by Public Health England (PHE) ***(UK Health Security Agency)*** and captures a wide range of data sources, including data such as: histopathology and haematology services, medical records, radiotherapy departments, hospices, independent hospitals, screening services, death certificates, general practitioners, other UK cancer registries. The registry holds data on anal cancer from 1993 to ***2018***. The final registrations are released approximately 1 year following the end of a diagnosis year, but it can take up to 5 years to achieve 100% completeness [Henson, 2020].

Each year, NCRAS collects data on over 300 000 cases of cancer, which includes patient details (i.e., their name, age, address, sex, and date of birth etc), and also data about the type of cancer, how advanced it is and the treatment the patient receives.

In order to allow contemporaneous, comprehensive and cost-effective data collection and to ensure quality assurance, the registry obtains data from across the National Health Service. The data quality in term of validity, completeness, timeliness etc. is assessed. Quality checks are performed both at the level of individual records as well as at the level of the registry. In addition, records are validated against other records and against expected values [Henson, 2020].

- The Danish Cancer Registry [Danish Cancer Registry.]:

The Danish Cancer Registry was founded in 1942 and contains data of the incidence of cancer among the Danish population from 1943 to 2019. The purpose of the cancer registry is to collect and process data on new cases of cancer, in order to produce statistics on the incidence and prevalence of cancer in Denmark, to provide information for the planning of the Danish health services, and to provide a basis for research into the causes of cancer and the course of cancer diseases. Reporting to the cancer registry has been mandatory since 1987. From 2004 to 2008 it underwent a process of modernisation. As a result, the reporting became electronic through integration of patient administrative systems and the manual coding was partly replaced by an automatic coding logic.

The Danish cancer registry has been repeatedly validated for data quality (validity and completeness). Internal validation for lung and breast cancer detected low proportions of errors or missing reports. Moreover, the automated registration ensures high quality and data completeness. Continued improvements following validation studies are implemented [Validation of The Danish Cancer Registry ; Lund , 2013].

- The Cancer Registry of Norway [CRN]:

The Cancer Registry of Norway was established in 1951 and includes data on anal cancer from 1953 to 2019. It is organised as an independent institution under the Oslo University Hospital Trust. Annual data on cancer are published in the *Cancer in Norway* report. Cancer statistics of Norway from 2019 were published in October 2020 [Cancer in Norway , 2019]. Suspected cancer cases (without a verified cancer diagnosis), and cancer first diagnosed by autopsy, need to be mandatorily notified. The cancer registry is in charge for the national screening programmes: Breast Cancer Screening Programme and Cervical Cancer Screening Programme. The cancer registry regulations demand the following 3 main objectives for the cancer registry: registration, research and information.

In Norway, population-based data with high-quality cancer incidence are favourable. Such data requires mandatory reporting, unique personal identification numbers and more than 50 years of experience in cancer registration [Larsen, 2009].

A study of the data quality at the Cancer Registry of Norway showed that data from the registry are reasonably accurate, and that completeness (close-to-completeness) and timely reporting is among the best in Europe [Larsen, 2009].

2.3.2. Vaccination Registries

Country	*Vaccination registry*
Finland	*Finnish National Vaccination Registry since 2009*
The Netherlands	*Dutch vaccination registry (Præventis) since 2005*
England	*Immunisations are registered in the Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002)*
Denmark	*Danish vaccination registry since 2009, although compulsory as of 15 November 2015*
Norway	*Norwegian vaccination registry since 1995*

2.3.3. Eurostat

Eurostat: will be the source for data on the European Standard Population for age distribution used to estimate the age-standardised incidence rates [Pace, 2013]. It will also be the source for population data and birth cohort data***, except for England, for which the source for population data will be UK Health Security Agency and for birth cohort data it will be Office for National Statistics.***

2.3.4. Websites of national public health institutes

- Vaccine coverage data will be retrieved from the respective websites of national public health institutes:
  - Vaccine coverage: For Finland (*Cervarix* introduction in NIP: November 2013)
  - Vaccine coverage: For The Netherlands (*Cervarix* introduction in NIP: September 2009)
  - Vaccine coverage: For England (*Cervarix* introduction in NIP: September 2008)
  - Vaccine coverage: For Denmark (*Cervarix* introduction in NIP: February 2016)
  - Vaccine coverage: For Norway (*Cervarix* introduction in NIP: September 2017)

3. STATISTICAL HYPOTHESES

No formal hypothesis assessment has been done for this study.

3.1. Multiplicity Adjustment

Not applicable as there is no hypothesis testing.

4. ANALYSIS SETS

Definition of the analysis sets and elimination codes will not be applicable.

Analysis will be based on country-specific data extracted from the national cancer registries as per defined population and timeframe.

Please refer to Section 2.2 for details on study population and study period.

5. STATISTICAL ANALYSES

5.1. General Considerations

General Methodology

- All primary and secondary endpoint analyses will be performed for each country separately.
- Exact Poisson 95% CI will be presented for incidences (Ulm K, 1990)
- Normal approximation of the log transformed Maximum Likelihood Estimate method will be used to derive the 95% CI of age standardised incidences (H.K.T. Ng et al, 2008).
- The Wald's 95% CI will be presented for the Poisson / negative binomial regression estimates and for the percentage reduction of the anal cancer cases in the observed counts compared to the predicted counts.

5.2. Primary Endpoints Analyses

To assess trends and changes over time in incidence of anal cancer by age category and by sex. Additionally, based on availability of data, the same will be assessed also by HPV type (if available) and by histological classification ***(if available).***

- Age-standardised incidence with 95% CI during the period from 1992 or later (based on the data availability in the cancer registries) until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by calendar year and sex. Additionally, based on availability of data, the same will be assessed also by HPV type (if available) and by histological classification ***(if available)***.

Note: Age-standardised incidences of anal cancer will be calculated by calendar year and sex using the European Standard Population (age distribution). Computation of age standardised incidence in the interim and final analysis ***will be based on the data source in the section 2.3.3***

Additionally,

- Crude incidences with 95% during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post-*Cervarix* launch period) will be presented by age category, sex, HPV type (if available) and histological classification (if available).
- The trend in the incidence of anal cancer will be assessed using the Poisson / negative binomial regression model. The model will include number of anal cancer cases as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. Annual Percentage Change (APC) will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-Cervarix launch periods separately.
- The trend in the incidence of anal cancer will be assessed using the Poisson / negative binomial regression model. The model will include number of anal cancer cases as outcome variable; ***calendar year,*** age category, study period (pre-launch = 0 and post-launch = 1) ***HPV type, and*** sex as the independent variables (risk factors). The model will include the population followed up as the offset variable.
  Similar analyses will be performed by subcategories – age category, sex, HPV type (if available) and histological classification ***(if available)***.
- Observed and predicted counts of anal cancer cases will be presented by calendar year. Predicted counts of the anal cancer cases will be estimated using a Poisson / negative binomial regression univariate model with number of anal cancer cases as the outcome variable and year as the independent variable on the pre-vaccination data.
  Percentage reduction of the anal cancer cases in the observed counts compared to the predicted will be presented with its Wald's 95% CI.
  Similar analyses will be performed by subcategories – age category, sex, HPV type (if available) and histological classification ***(if available)***.

5.2.1. Definition of endpoints/estimands

Refer to primary estimand in Section 2.1

5.2.2. Main analytical approach

- Age standardised incidence (Ahmad OB, 2001; Anderson RN, 1998) of anal cancer cases per 100000 population during the study period will be derived from the crude incidences extracted from the registries as below.

$$Age\ standardised\ incidence = \sum_{i=1}^{n} Crude\ Incidence\ of\ ith\ age\ category\ * Wi$$

Where n = number of age categories as per the European Standard Population Wi = weight of i^{th} age category = population in i^{th} age category / Total population

Age standardised incidence of anal cancer cases will also be presented by sex overall for each country with 95% CI.

Country-wise age standardised incidence with 95% CI of anal cancer cases by calendar year stratified by sex and overall will also be presented graphically to present the graphical trend. Line graphs will be used for the graphical representation of the trends in age standardised incidence (x-axis : calendar year; y-axis : age standardised incidence).Year of vaccine introduction will also be presented in the same graph.

Additionally,

- Country-wise crude incidence of anal cancer cases with 95% CI by calendar year stratified by sex, age category and overall will also be presented graphically to present the graphical trend. Line graphs will be used for the graphical representation of the incidence (x-axis : calendar year; y-axis : Incidence).Year of vaccine introduction will also be presented in the graph.
- Vaccination coverage rates by calendar year, age-categories (if available), gender (if available) in each country will also be presented.
- The trend in the incidence of anal cancer will be assessed using the Poisson / negative binomial regression model. The model will include number of anal cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. Annual Percentage Change (APC) will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-Cervarix launch periods separately.

5.2.2.1. Poisson Model:

Model : Poisson random variable is a function of predictor information.

$$\log\left(\frac{E(y)}{n_i}\right) = \log\left(\frac{\mu}{n_i}\right) = \beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p \quad \rightarrow (1)$$

Y = Number of anal cancer cases

n_i = population at risk ($\log(n_i)$ is the offset variable)

β's = regression coefficients

5.2.2.2. Assumption of equi-dispersion:

The adequacy of the Poisson regression model of anal cancer incidence will be checked using the Pearson chi-squared goodness-of-fit test.

$\frac{Pearson's\ chi-square}{degrees\ of\ freedom}$ ~ 1 with p-value significant.

If the data violates the equi-dispersion assumption, then the over-dispersion (variance is larger than the mean) or under-dispersion (variance is smaller than the mean), then negative binomial model will be used to model the regression parameters.

Model (1) can be written as,

$$log\left(\frac{\text{Number of anal cancer cases}}{\text{Population at risk}}\right) = \text{intercept} + (\beta 1 \times \text{calendar year}) \quad \rightarrow (2)$$

Note: p-values will be calculated for the regression coefficients and the values < 0.05 will be considered significant.

5.2.2.3. Annual Percentage Change (APC)

Annual Percentage Change (APC) will be estimated to see the unit change in anal cancer incidence using the regression estimates of calendar year in the model:

$$APC = (e\beta - 1)*100\%;$$

where 'β' is the maximum-likelihood estimate of the true parameter. APC will be presented along with the regression estimates of the calendar year in the model.

5.2.2.4. SAS codes to be used for the Poisson / negative binomial regression model:

```
PROC GENMOD data= <data>;
  CLASS var1(ref=first) var2 … / param=ref;
  MODEL outcome_var = var1 var2…  /DIST=<poisson/negbin> offset =
<log_offset var> TYPE3 WALD;
 SCALE=pearson;
RUN;
```

- The trend in the incidence of anal cancer will be assessed using the Poisson / negative binomial regression model. The model will include number of anal cancer cases as outcome variable; age category, study period (pre-launch = 0 and post-launch = 1), sex, HPV type (if available) as the independent variables. The model will include the population followed up as the offset variable.
- The approach of the Poisson model and the assumptions check (equi-dispersion) will be done as per the details provided in the section 5.2.2.1
- The model to assess the trend of anal cancer incidence is as below.

$$log\left(\frac{\text{Number of anal cancer cases}}{\text{Population at risk}}\right) = \text{intercept} + (\beta1 \times \text{age category}) + (\beta2 \times \text{study period}) + (\beta3 \times \text{sex}) + (\beta4 \times \text{calendar year}) + (\beta5 \times \text{HPV type})$$

- Similar analysis will be performed by subcategories – age category, sex, HPV type (if available) and histological classification (if available).

  – By age category

  $$log\left(\frac{\text{Number of anal cancer cases}}{\text{Population at risk}}\right) = \text{intercept} + (\beta1 \times \text{study period}) + (\beta2 \times \text{sex}) + (\beta3 \times \text{calendar year}) + (\beta4 \times \text{HPV type})$$

  – By Sex:

  $$log\left(\frac{\text{Number of anal cancer cases}}{\text{Population at risk}}\right) = \text{intercept} + (\beta1 \times \text{study period}) + (\beta2 \times \text{age category}) + (\beta3 \times \text{calendar year}) + (\beta4 \times \text{HPV type})$$

  – By HPV type (If available):

  $$log\left(\frac{\text{Number of anal cancer cases}}{\text{Population at risk}}\right) = \text{intercept} + (\beta1 \times \text{study period}) + (\beta2 \times \text{sex}) + (\beta3 \times \text{age category})$$

  – By histological classification:

  $$log\left(\frac{\text{Number of anal cancer cases}}{\text{Population at risk}}\right) = \text{intercept} + (\beta1 \times \text{study period}) + (\beta2 \times \text{sex}) + (\beta3 \times \text{HPV type}) + (\beta4 \times \text{age category})$$

- Observed and predicted counts of the anal cancer cases will be presented by calendar year.
- Predicted counts of the anal cancer cases will be estimated using the Poisson / negative binomial regression univariate model with number of anal cancer cases as the outcome variable and year as the independent variable on the pre-vaccination data. Model that will be used for the estimation of the predicted counts will be as in equation (1).
- Percentage reduction of the anal cancer cases in the observed counts compared to the predicted will be presented with its Wald's 95% CI.

$$Percentage\ reduction = \frac{Predicted\ count\ of\ anal\ cancer\ cases - Observed\ count\ of\ anal\ cancer\ cases}{Predicted\ count\ of\ anal\ cancer\ cases} * 100$$

- Similar analysis will be performed by subcategories – age category, sex, HPV type (if available) and histological classification.
- Predicted and observed counts of anal cancer cases will be presented in line graphs by age category, sex and overall to present the graphical trend (x-axis : calendar year; y-axis : Predicted/observed counts of anal cancer cases). Year of vaccine introduction will also be presented in the graph.

Analysis for negative control:

- Age standardised incidence of small intestine cancer per 100000 population during the period from 1992 until the most recent and complete available calendar year will be derived from the incidence extracted from the registries as below.

$$Age\ standardised\ incidence = \sum_{i=1}^{n} Incidence\ * \frac{percentage\ in\ n^{th}\ age\ category}{100}$$

Where n = age categories as per the European Standard Population (Age distribution as per section 5.2)

Age standardised incidence of small intestine cancer will also be presented by sex overall for each country.

Country-wise age standardised incidences of small intestine cancer by calendar year stratified by sex and overall will also be presented graphically to present the graphical trend. Line graphs will be used for the graphical representation of the trends in age standardised incidence (x-axis : calendar year; y-axis : age standardised incidence).

Additionally,

- Country-wise crude incidence of small intestine cancer by calendar year stratified by sex, age category and overall will also be presented graphically to present the graphical trend. Line graphs will be used for the graphical representation of the trends in crude incidence (x-axis : calendar year; y-axis : crude incidence).The trend in the incidence of small intestine cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of small intestine cancer cases as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. APC will be estimated based on the parameter estimates of the regression model. ***The same model will be generated for the pre- and post-Cervarix launch periods separately.***
- The Poisson model and the assumptions check (equi-dispersion) will be done as per the details provided in the section 5.2.2.1
- Annual Percentage Change (APC) will be estimated to see the unit change in small intestine cancer incidence using the regression estimates of model as per the section 5.2.2.3.

5.2.3. Sensitivity analyses

Not applicable.

5.3. Secondary Endpoint Analyses

To assess ***the*** feasibility for ***the conduct of a*** case-control study to determine the effectiveness of *Cervarix* against anal lesions and cancer in each country.

A prerequisite to conduct a vaccine case-control study is to have high quality data on:

- Cases, with the definition of cases: Subjects ***of all age groups*** identified in the cancer registries with HPV-related anal cancer.
- Controls, with definition of controls: Subjects ***of all age groups*** in the cancer registries identified with a non-HPV related cancer. Controls will be sex- and age-matched, ***retrieved from the same cancer registry to ensure that the comparison group is representative of the source population as that of the cases.***
- Besides age and sex, other covariates of interest may be extracted from the registries if available in order to adjust further the case control vaccine estimate, if needed, to ensure that other factors that could affect the vaccine effectiveness estimate are evenly distributed between cases and controls. (see below under 5.3.1.2 Additional Considerations).
- HPV vaccination status of each case and each control: Note if the vaccination status is not available in the registries or is not available for majority of the cases and controls in the registries, it will be assessed if there exists a linkage between the cancer registries and national vaccine registries (as per the section 2.3.2) to retrieve this information (see below under 5.3.1.2 Additional Considerations).

- Definitions of "vaccinated" and "unvaccinated" subjects in the registries: The definitions of who is fully vaccinated and who is not may vary by country, as dependents on the nationally recommended immunization schedule in each country.

  - England: Full vaccination consists of the administration of 2 doses of HPV vaccine (at present, Gardasil 9). Boys and girls aged 12 and 13 years are offered the first HPV vaccination in school at Year 8, as the scheme is school based. The second dose is offered 6 to 24 months after the first dose. For the purpose of this analysis, a women will be considered vaccinated if the first dose of HPV (*Cervarix*) was administered at <18 years of age , independent of the administration or timing of subsequent vaccine doses.
  - The Netherlands:
    - Before the 15th birthday: full vaccination consists of 2 doses of the HPV vaccine (at present, *Cervarix*), the first preferably around 12-13 years of age and the second, 6 months later.
    - After the 15th birthday: full vaccination consists of the second dose administered 1 month after the first dose, and the third dose about 6 months after the first dose.
    - For the purpose of this analysis, a women will be considered vaccinated if the first dose of HPV (Cervarix) was administered at ≤ 16 years of age , independent of the administration or timing of subsequent vaccine doses.
  - Finland:
    - Before the 15th birthday: full vaccination consists of 2 doses administered (grades 5 and 6, respectively) (at present, *Cervarix*), with an interval of at least 5 months
    - After the 15th birthday: full vaccination consists of 3 doses at 0, 1 and 6 months.
    - For the purpose of this analysis, a women will be considered vaccinated if the first dose of HPV (*Cervarix*) was administered at ≤ 15 years of age , independent of the administration or timing of subsequent vaccine doses.
  - Norway:
    - Full vaccination consists of 2 doses of HPV vaccine. Boys and girls 12 years old (in grade 7th) receive 2 doses of the HPV vaccine (at present, *Cervarix*) at least 6 months apart.
    - For the purpose of this analysis, a women will be considered vaccinated if the first dose of HPV (*Cervarix*) was administered at ≤18 years of age , independent of the administration or timing of subsequent vaccine doses.

- Denmark: full vaccination consists of the administration of 2 or 3 doses of HPV vaccine, depending on the age:
  - Before their 15th birthday, boys and girls are administered 2 doses of HPV vaccine (Gardasil 9) at 0 and 6 months and the vaccination series must be completed within 13 months. If these intervals are not observed, a total of 3 doses should be given, within three months at least between the second and third dose.
  - After the 15th birthday, 3 doses are administered at 0, 1 month, and 3 months, respectively. All 3 doses must be given within 1 year.
  - For the purpose of this analysis, a women will be considered vaccinated if the first dose of HPV (*Cervarix*) was administered at ≤15 years of age , independent of the administration or timing of subsequent vaccine doses.

- Data on the annual background incidence of anal cancer in subjects ***of all age groups***, annual HPV vaccination coverage rates by country, and expected HPV vaccine effectiveness, and decision on the case-control ratio in order to calculate a precision-based sample size.

Hence, step1 and step2 will be done as part of statistical analysis:

Step1: ***The n***umber of expected anal cancer cases (estimated sample size) required to demonstrate the expected vaccine effectiveness based on the vaccine coverage data will be determined.

Step2: Assuming that the number of anal cancer cases will increase over time, based on the incidence data of anal cancer cases, birth cohort, vaccine effectiveness and HPV vaccination coverage, assessment of the time frame for conducting the matched case-control study ***for generating meaningful VE estimates will be assessed for each country of interest.***

Step 3: There will be an investigation for the other data and variables mentioned above and this in the registries, in the literature and on public health websites (as mentioned under 2.3.4) and elsewhere. The study report will include the full information of the outcome of the feasibility assessment for the conduct of a case-control study.

5.3.1. Secondary endpoint

5.3.1.1. Main analytical approach

The number of expected anal cancer cases will be estimated based on the vaccine coverage rate of the controls and the expected vaccine effectiveness.

Below tables provides the number of expected anal cancer cases with 30% drop out rate required to demonstrate vaccine effectiveness (VE) of 30% to 90%, with 80% power using a two-sided test, alpha=0.05 , with 1, 2, 3 and 4 controls per case and for a vaccine coverage rate in controls of 40% to 90%.

Case-Control Ratio 1:1							
Vaccination rate in controls	**Vaccine Effectiveness**						
	90%	**80%**	**70%**	**60%**	**50%**	**40%**	**30%**
30%	42	69	109	176	290	514	1019
40%	33	55	88	144	242	433	867
60%	25	44	74	126	217	399	820
80%	25	49	90	160	289	549	1158
90%	34	73	140	259	480	930	1994

Case-Control Ratio 1:2							
Vaccination rate in controls	**Vaccine Effectiveness**						
	90%	**80%**	**70%**	**60%**	**50%**	**40%**	**30%**
30%	33	52	81	126	208	364	720
40%	25	40	65	104	173	307	612
60%	18	31	53	90	153	281	577
80%	17	35	64	112	202	384	811
90%	22	51	98	181	334	649	1395

Case-Control Ratio 1:3							
Vaccination rate in controls	**Vaccine Effectiveness**						
	90%	**80%**	**70%**	**60%**	**50%**	**40%**	**30%**
30%	29	46	70	111	181	317	624
40%	22	35	56	90	150	265	529
60%	16	27	46	77	131	242	497
80%	14	30	53	95	172	328	694
90%	18	42	82	152	283	551	1191

Case-Control Ratio 1:4							
Vaccination rate in controls	**Vaccine Effectiveness**						
	90%	**80%**	**70%**	**60%**	**50%**	**40%**	**30%**
30%	27	43	66	103	168	294	577
40%	21	33	52	83	138	244	489
60%	14	25	42	70	121	222	456
80%	13	26	48	86	156	299	636
90%	17	38	74	138	257	502	1087

Method: PASS 2019 Software: Matched Case-Control power analysis (Dupont, 1988)
Vaccine effectiveness = (1 – Odds ratio) *100%

Step 2 analysis will be performed to estimate the time frame for conducting the matched case-control study based on the number of cases from the above tables, crude incidence, birth cohort, vaccine coverage and expected vaccine effectiveness.

Data and steps needed for evaluating the timeframe for conducting the **matched case control study** will be as follows.

- Starting point (year) for the case control study including aged 25 years old (age at which every vaccine eligible birth cohort turns 25 years old) will be identified based on Year of *Cervarix* introduction in each country and the target age group (in years) for vaccination.
- Number of anal cancer cases in each calendar year that can be registered from the starting point (year) will be estimated based on the crude incidence, birth cohort, vaccine coverage and expected vaccine effectiveness as follows.

Note: The starting age-point for the matched case-control study has been arbitrarily established at 25 years as information retrieved from the respective cancer websites in the different selected countries shows that anal cancer very rarely affects people before that age.

$$Number\ of\ anal\ cancer\ cases = \sum_{i=1}^{n} BC\ (100\% - VC\%)(inci\ of\ nth\ age\ cat) + BC\ (VC\%)\ (inci\ of\ nth\ age\ cat)(100 - VE\%)$$

n: number of age categories considered in the study
BC: Birth cohort of each country
VC: Vaccine coverage of each country
inci of nth age cat: Crude incidence of anal cancer of nth age category
VE: Vaccine Effectiveness considered in step1

- Cumulative number of anal cancer cases by calendar year will be estimated.
- Time frame (year) will be identified at which the number of anal cancer cases are reached (based on the step 1).

Note: Life Expectancy of 85 years in Finland, 83 years in England and 84 years in Netherlands will be considered as the upper limit of age for the feasibility assessment. This information is considered from the Worldbank data.

5.3.1.2. Additional considerations

- The study report will include the full information of the outcome of the feasibility assessment for the conduct of a case-control study, hence covering also what variables and factors could be found in the registries or elsewhere to run a case-control study.

- The study report will also include the narrative on assessment of the feasibility to link the vaccine registries and the cancer registries in terms of extraction of data on the individual vaccination status of cases and controls, in case information on vaccination status is not available in the registries, and also on the variables that are potentially associated with both vaccination (*Cervarix*) and the disease of interest

(anal cancer). It needs to be checked if the data variables are available in these registries and this in order to see if the case-control vaccine effectiveness estimate can be adjusted on these variables.

- To account for potential selection bias and confounding, controls will be sex-, and age-matched (three thirds of anal cancer cases occur beyond 50 years of age) and retrieved from the same registry to ensure that the comparison group is representative of the source population that produced the cases. Information on other variables that can act as confounders/effect modifiers and are risk factors for HPV-related anal cancer is to be retrieved to make adjustments during the analytical phase, such as smoking, HIV status/immunosuppression, sexual practices, former gynaecologic HPV-related malignancies, and a proxy variable to socioeconomic factors. The availability of these variables will be assessed and the linkage with other databases to provide this information will be determined.

5.3.1.3. Sensitivity analyses

Not applicable.

5.4. Tertiary Analyses

Not applicable.

5.5. Safety Analyses

Not applicable.

5.6. Other Analyses

Not applicable.

5.7. Interim Analyses

An interim analysis will be performed in 2022. For each analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.

5.8. Changes to Protocol Defined Analyses

- Crude incidence of cancer cases per 100000 will be computed if not available in the registry, by using the national population data.

$$Crude\ incidence\ per\ 100000 = \frac{Number\ of\ cancer\ cases}{Population\ data} * 100000$$

- All analysis for the interim analysis will be performed for 3 countries - Finland, the Netherlands and England. The analysis for the remaining 2 countries Denmark and

Norway will be performed during the final analysis depending on the data availability..

- Study period (start and end calendar year) for each country will be considered based on the data availability in the registries. Eg, e.g., first available year of anal cancer data in the English registry is 1995, and not 1992 as planned in the protocol.

6. SAMPLE SIZE DETERMINATION

Sample size computation ***for the primary objective*** is not applicable for the primary objective, as there is no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 5 selected European countries will be collected within the established timeframe.

7. SUPPORTING DOCUMENTATION

7.1. Appendix 1 Data extraction rules

Cancer data will be extracted directly by GSK when available on line (e.g. Netherlands), or by officers of national cancer registries (e.g. ***England***), with number of cancers displayed by year, sex, age-band (5- ***or 10-*** year ***given the country***) and, for anal cancer, by category of histological type, if available.

ICD-10 codes will be used for selecting the cancers of interest (i.e. C21 for anal cancer and C17 for small intestine cancer) from national registries.
The grouping of the ICD-O histo-morphological types into 3 categories of anal cancer types will be based on the classification used by the International Agency for Research on Cancer (WHO) in their 2021 report 'Cancer Incidence in Five Continents Vol. XI':

Table 4.2. Anus (C21)

1 Carcinoma	**8010–8576**
1.1 Squamous cell carcinoma	8050–8076, 8083–8084, 8123–8124
1.2 Adenocarcinoma	8140–8145, 8190–8231, 8260–8265, 8310, 8401, 8480–8490, 8550–8552, 8570–8574, 8576
1.3 Other specified carcinoma	
1.4 Unspecified carcinoma	8010–8011
2 Melanoma	**8720–8790**
3 Other specified malignant neoplasm	
4 Unspecified malignant neoplasm	**8000–8005**

Source : https://publications.iarc.fr/597

The 3 anal cancer types used will be 'epidermoid' carcinoma or 'squamous cell' carcinoma (group 1.1), 'adenocarcinoma' (group 1.2) , and 'others' (all other codes).

Crude incidence rates will be computed, if not available in the registry, by using the national population data.

European Standardised Rates (ESR) for each country will be computed, by year, and by year and sex, using the 2013 European Standard Population from Pace,2013 as follows :
ESR_anal = sum of (W_i _EU * CR_i)
with CR_i = crude rates for each age class i and
W_i _EU = weight of age class i= Npop in age class i in EU / Npop total in EU from Pace,2013
Rates of Cancer data will be provided in SAS format for statistical analyses.
One dataset will include the raw numbers and crude rates by age range.

Variable	Type	Label
Year	Text	Year
Sex	Text	Sex
Age_range	Text	Age_range
N_Anal	Num.	Nbr of Anal Cancer from registry
CR_Anal	Num.	Crude rates of Anal cancer from registry
N_SI	Num.	Nbr of Small Intestine cancer from registry
CR_SI	Num.	Crude rates of Small Intestine cancer from registry
Wi_EU	Num.	Weight of age class i in Europe with from Eurostat 2013

For anal cancer, an additional dataset will provide the morphological types if available

Variable	*Type*	*Label*
Year	***Text***	***Year***
Sex	***Text***	***Sex***
Age_range	***Text***	***Age_range***
Morph_group	***Num.***	***Morph group***
N_Anal	***Num.***	***Nbr of Anal Cancer from registry***
CR_Anal	***Num.***	***Crude rates of Anal cancer from registry***
Wi_EU	***Num.***	***Weight of age class i in Europe with from Eurostat 2013***

The second dataset will include the CR and ESR rates across ages .

Variable	Type	Label
Year	Text	Year
Sex	Text	Sex
ESR_anal	Num.	European Standardised Rates of Anal Cancer by Sex - pop 2013 for Wi
ESR_SI	Num.	European Standardised Rates of Small Intestine cancer by Sex- pop 2013 for Wi

For anal cancer, an additional dataset will provide the morphological types if available

Variable	*Type*	*Label*
Year	***Text***	***Year***
Sex	***Text***	***Sex***
ESR_anal	***Num.***	***European Standardised Rates of Anal Cancer by Sex - pop 2013 for Wi***
Morph_group	***Num.***	***Morph_group***

- Vaccine coverage data will be retrieved, as per the section 2.3.4, from the respective websites of national public health institutes:

  All vaccine coverage rates will be provided in a single table in SAS format by year (1 column by year) for each country.

Variable	Type
Country	Text
Year	Num
Sex	Text
Vaccine Coverage	Text

- Population data will be retrieved from Eurostat:, unless provided by national cancer registries.

  Data retrieved from Eurostat will be provided in an SAS format table and displayed by calendar year and 5- ***or 10***-year age bands, for male, female and globally.

Variable	Type
Country	Text
Year	Num
Sex	Text
Age range	Text
Population	Num

- Birth cohorts will be retrieved from Eurostat: ***unless provided by national registries.***

  They will be provided in a SAS format table and displayed by calendar year, for male, female and globally.

Variable	Type
Country	Text
Year	Num
Sex	Text
Birth	Num.

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