In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

GlaxoSmithKline Biologicals, SA

Study detailed title

Meta-analysis of the risk of autoimmune thyroiditis diseases, Guillain-Barré syndrome, and inflammatory bowel disease following vaccination with *Cervarix*.

Study Report for Study 205639 (EPI-HPV-069 VS MA)

Development Phase Not Applicable for this meta-analysis

Study initiation date: (Analysis start)	22 April 2016
Study completion date: (Analysis complete)	29 Jul 2016
Data lock point (Date of database freeze):	Not applicable
Date of report:	Amendment 2 Final: 16 May 2017
Earlier Study Reports	Report: 26 August 2016 Report Amendment 1: 31 March 2017

Study Report revision history: The study report dated 31 March 2017 was amended on 16 May 2017 to correct errors in the table (Table 8: Crude Odds Ratio of autoimmune thyroiditis, GBS, and IDB: pooled table) pertaining to primary objective results.

Sponsor Signatory: Frank Struyf
Clinical and Epidemiology Research & Development
Project Lead,
Clinical R&D,
GSK Biologicals

This study was performed according to the principles of GCP including the archiving of essential documents.

Based on GSK Biologicals' Study Report INS-BIO-CLIN-1010 v05

SYNOPSIS

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** Not applicable	**Name of active substance:** Not applicable

Study No.:
205639 (EPI-HPV-069 VS MA)

Title of the study:
Meta-analysis of the risk of autoimmune thyroiditis diseases, Guillain-Barré syndrome (GBS), and inflammatory bowel disease (IBD) following vaccination with *Cervarix*.

Investigators and study centres:
Not applicable.

Publication (reference):
None at the time of this report.

Study period: **Study initiation date** (Analysis start)**:** 22 April 2016 **Study completion date** (Analysis complete)**:** 29 July 2016 **Data lock point (Date of database freeze):** Not applicable	**Phase:** Not applicable for this epidemiological study

Indication: Not applicable

Objective:
The objective of this meta-analysis was to estimate the overall risk of three autoimmune diseases, following *Cervarix* vaccination:

- Autoimmune thyroiditis,
- GBS,
- IBD.

Methodology: This meta-analysis included all data from *Cervarix* clinical trials identified in the 2015 Development Safety Update Report (DSUR) (Data Lock Point [DLP] 17 November 2015) and post marketing observational studies which met the defined inclusion and exclusion criteria.

Studies included in the meta-analysis:

- Clinical studies identified in the 2015 DSUR (DLP: 17 November 2015) which met inclusion criteria (a control group not exposed to any HPV vaccine, inclusion of female subjects, and the study which enrolled subjects aged 9 years and above) were part of this meta-analysis. The extension studies beyond two years after the first *Cervarix* vaccination and the ongoing blinded studies were excluded.
- Post marketing observational studies (EPI-HPV-040 VS UK [116239], EPI-HPV-011 [112677] and Agence Nationale de Sécurité du Médicament [ANSM] study).

Criteria for evaluations:
Endpoint:
The endpoint was the occurrence of cases of autoimmune thyroiditis, GBS, and IBD during a maximum period of two years (42 days for GBS for the primary analysis) after the first dose of *Cervarix* and an equivalent time period in non-exposed subjects.

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** Not applicable	**Name of active substance:** Not applicable

Statistical methods: The risk of developing the three autoimmune diseases, autoimmune thyroiditis, GBS and IBD, post first dose of *Cervarix* was estimated as the overall odds ratio (OR) using the following three approaches:

- **Pooled table or 'crude' method:** combining total number of cases and subjects in both exposed and unexposed arms;
- **Meta-analysis method with continuity correction*:** Both fixed and random-effect overall OR estimates were computed
- **Beta-binomial regression method**: A method which could use the single and double-zero studies without using continuity correction. This was recently recommended [Kuss, 2015].

** The meta-analysis with continuity correction was pre-defined as the main analysis, where as other methods were sensitivity analyses.*

Study population:

- Data from 18 clinical trials (DLP: 17 November 2015), HPV-040, EPI-HPV-040, EPI-HPV-011 and ANSM observational study were included in this meta-analysis.
- The mean age of subjects in the exposed and the non-exposed group was 16.05 years and 13.71 years, respectively (this difference is due to the ANSM study).
- More than 95% of subjects were enrolled in studies conducted in France (88.4%) and UK (7.9%). (ANSM study and the EPI-HPV-040 study, which involved a large number of subjects, were carried out in France and the UK, respectively).

Summary:

Primary objective results:

Autoimmune thyroiditis:

- The overall OR from variance-inverse meta-analysis, was 2.01 (95% CI: 1.30; 3.11). The other methods gave similar estimates (2.46 for the pooled analysis and 2.17 for the Beta-Binomial model). This excess risk was estimated to be 17 cases per 100,000 exposed subjects.
- The sensitivity analysis, excluding the ANSM study, provided similar results of overall OR estimates ranging between 2.04 and 2.33.

GBS:

- The overall OR from the variance-inverse meta-analysis was 11.14 (95% CI: 2.01; 61.92) during the 42 days follow-up period. The pooled analysis gave a similar estimate (11.07).
- The results of the GBS analysis were driven by the two exposed cases observed in the ANSM study which were conservatively assumed to have occurred during the 42 days after vaccination.
- During the two-year follow-up period, the sensitivity analysis reported low overall OR estimates ranging between 1.89 (pooled analysis) to 3.83 (variance-inverse meta-analysis).

IBD:

- The overall OR from variance-inverse meta-analysis, was 1.11 (95% CI: 0.75; 1.66). Other methods gave similar estimates (1.03 from the pooled analysis and 1.20 for the Beta-Binomial model).

Interpretations:

The current results can be interpreted using the pre-defined criteria developed for an observational safety study with the quadrivalent HPV vaccine [Arnheim-Dahlström, 2013].

Arnheim-Dahlström et al, in the analysis of serious adverse events following vaccination with the quadrivalent HPV vaccine (in health databases in Denmark and Sweden), [Arnheim-Dahlström, 2013] have defined a safety signal outcome with a significant rate ratio increase (lower bound of 95% confidence interval >1.0) with at least five vaccine exposed cases. Three criteria were considered as strengthening signals: analysis based on 20 or more vaccine exposed cases (reliability), rate ratio 3.0 or more (strength), and significantly increased rate ratio in country specific analyses (consistency).

Considering the above criteria following conclusions can be drawn:

- **Autoimmune thyroiditis**: Both main and sensitivity analyses showed evidence of a small increased risk of autoimmune thyroiditis (OR estimate around 2.0 with an upper limit of the 95% CI around 3.0 for the main analysis and 4.0 for the sensitivity analysis). According to Arnheim-

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** Not applicable	**Name of active substance:** Not applicable

Dahlström criteria [Arnheim-Dahlström, 2013], this increased risk is regarded as a safety signal but not as a strengthening signal since the OR is less than 3.0. There was insufficient evidence to conclude on a causal relationship between *Cervarix* and autoimmune thyroiditis.

- **GBS**: The results were driven by the two exposed cases in ANSM study were conservatively assumed to have occurred during the within 42 days follow-up period. A conclusion regarding the risk of GBS cannot be drawn because of the broad confidence interval (CI) (95% CI: 2.01; 61.92). According to Arnheim-Dahlström criteria [Arnheim-Dahlström, 2013], this risk estimate is not reliable since there were less than five vaccine exposed cases during the predefined risk period. The results of the study do not confirm an association between *Cervarix* and GBS.
- **IBD**: There was no evidence of an increased risk of IBD since the OR estimates was close to unity with an upper limit of the 95% CI lower than 2.0.

Overall conclusions

- The present meta-analysis of 18 GSK clinical trials, one cluster randomized trial, two GSK post-marketing epidemiological studies and one non-GSK post-marketing study which represents more than 150,000 *Cervarix* exposed subjects and 1,500,000 non-exposed subjects does not support an increased risk of GBS and IBD.
- A small increased risk of autoimmune thyroiditis is observed as previously described in EPI-HPV-040 and ANSM studies. However, there is insufficient evidence to conclude on a causal relationship with *Cervarix* vaccination.

References:

Lisen Arnheim-Dahlström, Björn Pasternak, Henrik Svanström, Pär Sparén, Anders Hviid. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. *BMJ* 2013; 347: f5906.

Kuss O. Statistical methods for meta-analysis including information from studies without any events – add nothing to nothing and succeed nevertheless. *Statist. Med*. 2015, 34:1097-1116.

Date of report: Amendment 2 Final: 16 May 2017

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

AE:	Adverse Event
ANSM:	Agence National de Sécurité du Médicament et des Produits de Santé
Anti-TPO:	Anti-Thyroid Peroxidase
CDP:	Clinical Development Plan
CI:	Confidence Interval
CPRD:	Clinical Practice Research Datalink
CSF:	Cerebral Spinal Fluid
DLP:	Data Lock Point
DSUR:	Development Safety Update Report
GBS:	Guillain-Barré Syndrome
GSK:	GlaxoSmithKline
HAV:	Hepatitis A Virus
HPV:	Human Papilloma Virus
HR:	Hazard Ratio
IBD:	Inflammatory Bowel Disease
ICD:	International Classification Disease
LL:	Lower Limit of the confidence interval
MedDRA:	Medical Dictionary for Regulatory Activities
N:	Number
N.A:	Not Applicable
OR:	Odds Ratio
PGRx:	Pharmacoepidemiological General Research eXtension
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SD:	Standard Deviation
SE:	Standard Error
TFL:	Tables Figures and Listing template annexed to SAP
TSH:	Thyroid Stimulating Hormone
UK:	United Kingdom
UL:	Upper Limit of the confidence interval
VAR:	Variance

TRADEMARKS

The following trademarks are used in the present report.

Note: In the body of the study report and in synopsis, the names of the vaccines will be written without the superscript symbol ™ or ® and in *italics*.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Cervarix™	Bivalent human papillomavirus (Types 16 and 18) recombinant vaccine

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Gardasil® (Merck and Company, Inc)	Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine

1. ETHICS

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

Not applicable.

1.2. Ethical conduct of the study

The studies included in this meta-analysis was conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki, the principles of "good clinical practice" (GCP) and all applicable regulatory requirements.

1.3. Subject information and consent

Not applicable.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

GSK staff were responsible for the conception and design of this meta-analysis study, the analysis of the data and the interpretation of the results. No investigator external to GSK was involved.

The literature review activity was performed by:

Pallas,
Health and research Consultancy,
Conradstraat 18 E7,
3013 AP Rotterdam,
Netherlands

2.1. Study report revision history (Amended on 16 May 2017)

The study report dated 31 March 2017 was amended on 16 May 2017 to correct errors in the table (Table 8: Crude Odds Ratio of autoimmune thyroiditis, GBS, and IDB: pooled table) pertaining to primary objective results.

3. INTRODUCTION

The risk of autoimmune diseases after vaccination with *Cervarix* has been evaluated in some studies. However no evidence of an overall increased risk of autoimmune diseases has been detected in pooled analyses of clinical studies [Verstraeten, 2008, Angelo, 2014] and post-licensure observational studies [ANSM, 2015, GlaxoSmithKline Biologicals Study Report 116239 (EPI-HPV-040 VS UK), GlaxoSmithKline Biologicals Study Report 112677 (EPI-HPV-011 VS FR PMS)]. The primary endpoints of these studies were generally composite endpoints combining various diseases. The ability to analyse the risk of individual autoimmune diseases is limited due to a low incidence rate of these diseases in the general population. However, analyses of a few individual autoimmune diseases have been performed and the following have been identified for future investigation:

- **Autoimmune thyroiditis**: EPI-HPV-040, an observational study was conducted in the United Kingdom (UK) using data from Clinical Practice and Research Database (CPRD) [GlaxoSmithKline Biologicals Study Report 116239 (EPI-HPV-040 VS UK)] and data from a retrospective cohort study in French Healthcare Databases conducted by the French Agence Nationale de Sécurité du Médicament (ANSM [ANSM, 2015]. These studies showed a significantly increased risk following *Cervarix* vaccination (Risk ratio [RR]= 3.75 [95% Confidence Interval (CI): 1.25; 11.31] and Hazard Ratio (HR)= 2.43 [1.27; 4.66] respectively) while neither the pooled GSK clinical data [Verstraeten, 2008, Angelo, 2014] nor the EPI-HPV-011 case-control study [GlaxoSmithKline Biologicals Study Report 112677 (EPI-HPV-011 VS FR PMS)] showed evidence of an increased risk.
- **Guillain-Barré syndrome (GBS)**: No case of GBS was reported in either EPI-HPV-040 or in the GSK pooled clinical data. However the ANSM study detected a statistically significant increased risk of GBS following *Cervarix* vaccination (HR=8.14 [95% CI 1.70-38.92]).
- **Inflammatory bowel disease (IBD)**: Pooled clinical data analyses and all GSK-sponsored post-licensure observational studies conducted did not show an increased risk of IBD following *Cervarix* vaccination. However, a slightly significant increased risk of IBD following HPV vaccination (pooled bivalent and quadrivalent vaccines) was observed in the ANSM study (HR= 1.19 95%CI: 1.02; 1.39). This disease was also identified for future investigation. The ANSM study also observed a decreasing risk of IBD over time following the first dose of HPV vaccine ($HR_{0\text{-}3\ months}$: 1.30 [95% CI 0.94-1.79]; $HR_{3\text{-}12\ months}$: 1.23 [95% CI 0.99-1.52]; $HR_{>12months}$: 1.12 [95% CI 0.91-1.38]). Hence, the Scientific Committee of the study considered that a very low statistical association does not allow the conclusion of an excess risk for this disease.

In order to better assess a potential risk of these three autoimmune diseases, GSK Biologicals performed a meta-analysis for these three diseases. All available data generated from GSK clinical studies and data from post-licensure observational studies which met the inclusion and exclusion criteria were used.

4. STUDY OBJECTIVE

The objective of this meta-analysis was to estimate the overall risk of three autoimmune diseases, following *Cervarix* vaccination:

- Autoimmune thyroiditis
- GBS
- IBD.

5. INVESTIGATIONAL PLAN

5.1. Study design

5.1.1. Overall study design – Description

This meta-analysis included all data from clinical trials identified in the 2015 Development Safety Update Report (DSUR) (DLP: 17 November 2015) and post marketing observational studies which met the defined inclusion and exclusion criteria.

5.1.2. Selection of studies

All GSK clinical studies and post-marketing observational studies were assessed in order to determine whether the studies were relevant with respect to the objective pursued. The study performed by ANSM was also included.

Data were identified from all GSK sponsored studies, investigator-sponsored studies [ISS]) studies where *Cervarix* was administered as well as non-GSK studies listed in the Committee for Medicinal Products for Human Use (CHMP) Type II variation assessment report (EMEA/H/C/000721/II/0069[assessment report for EPI-HPV-040]). A supplementary literature review was performed by Pallas (DLP: 3rd December 2015), to check whether any additional studies could potentially be included in the meta-analysis. There were no studies of potential interest identified for the meta-analysis during the literature review.

Clinical studies identified in the 2015 DSUR (DLP: 17 November 2015) and which met the following criteria were included in the meta-analysis.

5.1.2.1. Inclusion criteria

- Inclusion of a control group not exposed to any HPV vaccine;
- Inclusion of female subjects;
- The study/studies which enrolled subjects aged 9 years and above

5.1.2.2. Exclusion criteria

The extension studies beyond two years after the first vaccination of *Cervarix* and the ongoing blinded studies were excluded.

A list of included clinical studies included in the meta-analysis is provided in Table 1. Because a large number of studies and low incidence rate of the outcomes, data from all included clinical studies were pooled and considered as a single source (study) in the meta-analysis, except the HPV-040 study.

The following data sources (Figure 1) were included in the meta-analysis:

- Pooled clinical studies: Primarily 22 clinical studies were considered but data from 18 clinical trials were included (HPV-007, HPV-013 EXT M18, HPV-013 EXT M24 studies were excluded as these studies started three years after vaccination) (DLP: 17 November 2015).
- Study HPV-040(#): a cluster randomised clinical trial in Finland; only the exposed and non-exposed female subjects were included;
- Study EPI-HPV-040: an observational retrospective cohort study using the Clinical Practice Research Datalink (CPRD), United Kingdom (UK) database. The follow-up period was limited to 12 months after the first dose of *Cervarix*. Only the two female (exposed and non-exposed) cohorts were used in the meta-analysis, the male non-exposed cohort was excluded [GlaxoSmithKline Biologicals Study Report 116239 (EPI-HPV-040 VS UK)].
- Study EPI-HPV-011: This study included surveillance and estimation of risk of autoimmune diseases. Only the risk results were included in the meta-analysis. The estimation of risk was a case-referent study using the Pharmacoepidemiological General Research extension (PGRx) methodology [GlaxoSmithKline Biologicals Study Report 112677 (EPI-HPV-011 VS FR PMS)].
- ANSM observational study: a longitudinal observational exposed vs. non-exposed study based on national healthcare administrative databases in France. The exposed cohort included both *Cervarix* and *Gardasil* vaccinated subjects. For the purpose of the current meta-analysis, only *Cervarix* exposed subjects were included. The non-exposed cohort included subjects non-exposed to *Cervarix* and *Gardasil* [ANSM, 2015].

(#): HPV-040 study is a cluster randomized study. Because of this particular design (the other clinical studies were parallel group studies), the large sample size and the different methodology for safety follow-up (passive safety surveillance via national registries), this study was considered as a separate study in the meta-analysis.

Figure 1 List of data sources

Data Source reference	Design	Raw data	N exposed subjects	N control subjects	Risk period	Diseases (Terms/codes)	N of cases (Exp/Ctrl)	Source	Comment
Clinical studies (2015 DSUR)	pooled 19 clinical studies	Y	21.699	17.763	Up to 2 years after vaccination	Autoimmune thyroiditis	6/1	DSUR 2015 dataset	N of cases are N including all studies in the 2015 DSUR (Total N = 33942 exposed and 21316 non-exposed subjects) , a few studies will be excluded : * Extension studies >= 2 years post-dose 1, * No control group or Ctrl grp= Gardasil, * Ongoin DB, * Paediatric population
						Basedow's disease	6/1		
						Colitis ulcerative	4/1		
						Crohn's disease	2/2		
						Inflammatory bowel disease	1/1		
						Proctitis ulcerative	1/0		
						Guillain-barre syndrome	0/0		
HPV-040	Cluster randomized trial (Finland)	Y	12.399	8.119	Median : 4,21 Years	Autoimmune thyroiditis	5/1	Analysis dataset	
			Only Female subje			Thyroiditis	1/0		
						Colitis ulcerative	15/8		
						Crohn's disease	8/6		
						Proctitis ulcerative	3/1		
						Guillain-barre syndrome	0/0		
EPI-HPV-040	*Retrospective Cohort study in CPRD (UK)*	*Y*	*64.705*	*64.841*	*1 yr after 1st dose*	Autoimmune thyroiditis (confir	*15/4*	Analysis Dataset	
						Autoimmune hypothyroidit	16		
						Crohn diseases	6/5		
						Ulcerative Colitis	4/5		
						GBS	0/0		
PGRx (LASE EPI-HPV-011	Case-control in France	N	NA	NA 42 days any dose 24 months after any dose		GBS (n Cases / N ctrl)	N case/ctrl 13 / 130	Final Report	0 cases exposed vs. 0 ctrl exposed
						GBS (n Cases / N ctrl)	13 / 130		0 cases exposed vs. 1 ctrl exposed
						Auto Immune Thyroditis	106/876		0 cases exposed vs. 9 ctrl exposed
ANSM	Cohort study in France	N	55.545	1.410.596	24 months	IBD	12/523	ANSM - Final report, September 2015	
						Coeliac disease (incl in IBI	2/119		
						Thyroiditis	10/209		
						GBS	2/18		

N of cases (Exp/Ctrl): For EPI-HPV-011 study, both definite and possible autoimmune thyroiditis have been included.

Table 1 List of GSK clinical studies included in the meta-analysis

			Meta-analysis of selected autoimmune diseases		
Study E-track	**Study Alias**	**Group DSUR group = study group**	**Included in meta-analysis**	**Comments**	**N subjects (Exposed/Control)**
580299_001	HPV-001	HPV in CDP=HPV Control in CDP=Placebo	Yes		560/553
580299_007	+ follow-up: HPV-007	HPV in CDP=HPV Control in CDP=Placebo	Yes	But limited to two years after first dose	
580299_008	HPV-008	HPV in CDP=HPV Control in CDP=HAV	Yes		9328/6337
580299_009	HPV-009	HPV in CDP=HPV Control in CDP=HAV	Yes		3729/3737
580299_013	HPV-013	HPV in CDP=HPV Control in CDP=HAV	Yes		1035/1032
104896	HPV-013 (Ext M18)	HPV in CDP=HPV Control in CDP=HAV	Yes		
104902	HPV-013 (Ext M24)	HPV in CDP=HPV Control in CDP=HAV	Yes		
104820	HPV-015	HPV in CDP=HPV Control in CDP=Placebo	Yes		2881/2871
107863	HPV-020	HPV in CDP=HPV Control in CDP=Placebo	Yes		91/59
106069	HPV-021	HPV in CDP=HPV Control in CDP=Placebo	Yes		450/226
111567	HPV-026	HPV in CDP=HPV Control in CDP=HBV	Yes		76/76
110886	HPV-029	HPV in CDP=HPV Control in CDP=HAB	Yes		542/271
111507	HPV-030	HPV in CDP=HPV Control in CDP=HBV	Yes		494/247
104479	HPV-031	HPV in CDP=HPV Control in CDP=Placebo	Yes		176/178
104798	HPV-032	HPV in CDP=HPV Control in CDP=HAV	Yes		519/521
104951	HPV-033	HPV in CDP=HPV Control in CDP=HAV	Yes		160/161
106001	HPV-035	HPV in CDP=HPV Control in CDP=Placebo	Yes		150/150
105926	HPV-036	HPV in CDP=HPV Control in CDP=Placebo	Yes		135/136
107291	HPV-038	HPV in CDP=HPV Control in CDP=Placebo	Yes		149/76
112022	HPV-058	HPV in CDP= HPV Control in CDP=Placebo	Yes		374/376
114590	HPV-069	HPV in CDP=HPV Control in CDP=HBV	Yes		606/606

5.2. Statistical methods

The statistical analyses were performed using the Statistical Analysis Systems (SAS) version 9.2 on windows and StatXact-8.1 procedure for SAS.

5.2.1. Endpoint

The endpoint was the occurrence of cases of autoimmune thyroiditis, GBS, and IBD during a maximum period of two years (42 days for GBS for the primary analysis) after the first dose of *Cervarix* and an equivalent time period in non-exposed subjects.

5.2.1.1. Case definition

Different case definitions were used in the various studies and are described in Table 2. In brief:

- GSK clinical studies and HPV-040 used the MedDRA terminology.
- Study EPI-HPV-040 used read code and ICD-10 codes; a patient profile review was performed to confirm the new onsets of autoimmune disease. Some cases, as well as a random 10% sample from each of the categories of autoimmune diseases were reviewed by a panel of medical specialists.
- The ANSM study used definitions based on the occurrence of ICD-10 codes for the event of interest in hospitalization or long duration disease reports. For thyroiditis, different ICD-10 codes were used, including both cases of autoimmune and non-autoimmune origin. Only an aggregated number of cases of thyroiditis were mentioned in the report. It was not possible to determine if these cases of thyroiditis were autoimmune in origin.
- Study EPI-HPV-011 identified cases of autoimmune disorders through a network of specialist centres (internal medicine, neurology, rheumatology, paediatric, endocrinology and dermatology departments) at university and general hospitals across France. The study used specific study definitions, distinguishing “definite” and “possible” cases. Only “definite” cases were considered for the meta-analysis. The index date for the cases was the date of the first clinical sign or symptom suggestive of the autoimmune disorder.

Table 2 presents the clinical definitions which were used in the meta-analysis:

Table 2 Clinical definition across the studies

Event of interest	MedDRA Primary System Organ Class and Preferred Term		Read code + ICD10 Codes	ICD-10	Study clinical definition
	GSK pooled clinical studies	HPV-040	EPI-HPV-040#	ANSM	PGRx
Autoimmune Thyroiditis	- Basedow's disease (10004161) - Autoimmune thyroiditis (10049046)	- Basedow's disease (10004161) - Autoimmune thyroiditis (10049046)	Confirmed cases: - Autoimmune thyroiditis - Basedow's disease - Grave's disease - Hashimoto's disease - De Quervain's thyroiditis - Riedel's thyroiditis (ICD-10: E05, E06.1, E06.3, E06.5)	- At least one hospitalization with principal diagnosis of stay or related diagnosis of thyroiditis - Or long term diseases ICD10 code of thyroiditis$	Auto Immune Thyroditis: definite case according to study definitions including Grave's disease and Hashimoto disease£
GBS	No case	- GBS G61.0: (10018767)	Confirmed cases of GBS # (G61.0, G60)	GBS code G61.0 Occurrence of ALD30 (long term diseases) for GBS Or at least one hospitalization of a minimal 6 days length with a principal diagnosis of stay or related diagnosis for GBS Or at least two hospitalization with a principal diagnosis of stay or related diagnosis for GBS	GBS definite case (level 1) according to the Brighton collaboration case definition: requires clinical, electrophysiologic, and CSF data consistent with the onset of GBS
Inflammatory Bowel Disease	- Colitis ulcerative (10009900) - Crohn's disease (10011401) - Inflammatory bowel disease (10021972) - Proctitis ulcerative (10036783)	- Colitis ulcerative (10009900) - Crohn's disease (10011401) - Proctitis ulcerative (10036783) K 50.0; K 51.0; K51.2	Confirmed cases of: - Crohn's diseases (K50) - Ulcerative colitis (K51)	- ALD30 (long term disease) for IBD - or at least one hospitalization with a principal diagnosis of stay or related diagnosis for IBD AND - one hospitalization for lower digestive before or at the time of diagnosis	Not assessed

Event of interest	MedDRA Primary System Organ Class and Preferred Term		Read code + ICD10 Codes	ICD-10	Study clinical definition
	GSK pooled clinical studies	HPV-040	EPI-HPV-040#	ANSM	PGRx
				- ICD-10 codes K50 Crohn disease K51 Ulcerative colitis	

#:In addition to the specific IDC10 codes listed in the table,other codes were used to capture possible cases. Among these only the cases confirmed by a medical review were included

£: Definite case of autoimmune thyroiditis = Hypothyroidism consistent with incident autoimmune thyroiditis AND anti-peroxydase (anti-TPO) AND increased TSH > 7mU/L; Definite case of Grave's disease= Presence of exophthalmia or palsy or tachycardio or weight loss or weight gain AND anti-TSH-receptor AND decreased TSH

$ ICD-10 code E034 Atrophy of thyroid (acquired) ; E035 Myxedema coma; E038 Other specified hypothyroidism ; E039 Hypothyroidism, unspecified; E040 Nontoxic diffuse goiter; E048 Other specified nontoxic goiter ; E049 Nontoxic goiter, unspecified; E050 Thyrotoxicosis with diffuse goiter; E055 Acute thyrotoxicosis; E058 Other thyrotoxicosis; E059 Thyrotoxicosis, unspecified; E060 Acute thyroiditis; E061 Subacute thyroiditis; Chronic thyroiditis with transient thyrotoxicosis; E063 Autoimmune thyroiditis; E065 Other chronic thyroiditis; E069 Thyroiditis, unspecified

A sensitivity analysis of autoimmune thyroiditis was performed including studies using codes from autoimmune origin (i.e. excluding the ANSM data).

5.2.1.2. Risk period definition

The risk period to assess autoimmune disease post-vaccination was determined based on the onset of the disease (either acute or insidious), possible or known pathologic mechanisms involved, and the type of vaccine [Tavares Da Silva, 2013].

Irrespective of the underlying mechanisms, one may assume that the development of autoimmunity (if a causal association between the event and vaccination existed) requires several weeks, which is similar to the classical time frame of several weeks suggested for the onset of post-infectious autoimmune phenomena [Tavares Da Silva, 2013, Allos, 1997].

The following risk periods were considered for each event of interest:

- For autoimmune thyroiditis and IBD, a risk period of up to two years after first vaccination was considered. An equivalent period was used for non-exposed subjects. Since the clinical course of autoimmune thyroiditis and IBD is generally insidious, a long interval between vaccination and disease onset was considered. A risk period of up to 2 years was primarily assumed but one of the studies in this meta-analysis had a shorter follow-up of 12 months. However, considering this 12 months of follow-up after the last vaccination was a reasonable maximum theoretical risk interval [Tavares Da Silva, 2013]. All included studies except the EPI-HPV-040 had a per-protocol follow-up period of at least two years. The follow-up period of the EPI-HPV-040 was limited to 12 months after the first vaccination.
- For GBS, a risk period of 42 days after each vaccination was used for the main analysis. For GBS (disease of acute onset), the period of increased risk was shown to be concentrated within 6 weeks after the 1976–1977 swine flu vaccination

[Langmuir, 1979, Schonberger, 1979, Wise, 2012]. Therefore a 6 week time window was used for the assessment of cases of GBS potentially associated with vaccination. Also, for the Brighton Collaboration working group [Sejvar, 2011], the recommended risk period for acute neurologic illnesses such as acute disseminated encephalomyelitis was at least 42 days. The number of GBS cases occurring during this 42 day risk period was not available for the ANSM study. The two cases observed in the Cervarix vaccinated group of the ANSM study were conservatively assumed to have occurred within 42 days post-vaccination. For the unvaccinated cohort, the total number of GBS cases (18) occurring during the full follow-up period (30.6 months) for the non exposed subjects was known. This number included cases occurring in the non-vaccinated cohort but also in the vaccinated cohort before vaccination. The number of cases occurring in the non-vaccinated cohort was estimated based on the total person-time reported in the non-vaccinated cohort and in the vaccinated cohort before vaccination. The number of cases occurring during an equivalent 42-day post-dose period was also estimated from the overall incidence rate during the total follow-up period and the total number of unvaccinated subjects. In addition, since the mean follow-up period was longer for the non-exposed than for the exposed subjects (30.2 months versus 19.8 months), the number of cases for two year analysis was calculated as N = 24 * observed number / follow-up (in months).

5.3. Study characteristics

Demographic characteristics (age, country, region, follow-up time, etc.) were summarized by study and overall. Descriptive statistics included N (number of subjects), mean, SD, median, minimum and maximum for continuous variable and N (%) for categorical variables.

These statistics was computed from raw data for GSK studies (except for EPI-HPV-011) and from aggregated data for non-GSK studies.

5.4. Risk estimate

The risk of developing the three autoimmune diseases, autoimmune thyroiditis, GBS and IBD, post first dose of *Cervarix* was estimated using meta-analysis methods.

Since the incidence of the outcomes of interest is very low, Odds Ratio (OR) was used. ORs were computed from both cohort and case-control studies.

A meta-analysis of rare events was challenging because of studies with no event in one arm ('single-zero') or even both arms ('double-zero') [Sweeting, 2004; Bradburn, 2007; Vollset, 1991].

Three approaches were used:

Meta-analysis method* with continuity correction: A continuity correction was applied to all studies to overcome the single and double-zero issue. Various continuity corrections have been proposed [Sweeting, 2004] such as constant continuity correction k (for example k=0.5 is commonly used in many softwares), continuity correction

reciprocal of the opposite treatment arm size and empirical continuity correction. The advantage of this method was that all studies could be included, and any meta-analysis calculation method (inverse variance-weighted method, Peto's method, Mantel-Haenszel's method, etc.) could be applied, all individual studies could also be depicted in forest plots and the heterogeneity among studies could be estimated and tested.

The continuity correction factor in the exposed arm was computed as

$$C_e=0.5\ N_e/N_T$$

Where, C_e is continuity factor in the exposed arm, N_e is the total number of subjects in the exposed arm and N_T is the total number of subjects in both arms.

The continuity correction factor in the non-exposed arm was similarly computed by substituting N_e by N_{ne} , the total number of subjects in the unexposed arm. Both fixed- and random-effect models were computed. The inverse-weighted variance method was used for the fixed-effect model.

Heterogeneity among studies was tested using the Cochran Q test. The degree of the heterogeneity was assessed by the i^2 index [Huedo-Medina, 2006]. For the random-effect model, a component of inter-study variance was added in the overall variance [DerSimonian, 1986].

Pooled table or 'crude' method: Data from all studies were pooled in a single fourfold table and an overall estimate was computed using standard methods. The main limitation was that this method ignored the data which were collected from several studies and the underlying assumption of a constant estimate across all studies.

Beta-binomial regression method: A method which could use the single and double-zero studies without using continuity correction. The latter was recently recommended [Kuss, 2015].

** The meta-analysis with continuity correction was pre-defined as the main analysis. Secondary analysis were performed with two other methods, as a sensitivity assessment of the results obtained with the meta-analysis with continuity correction method.*

5.4.1. Sequence of analyses

Not applicable

5.5. Data quality assurance at study level

A Contract Research Organisation (CRO), Pallas, was employed to perform a supplementary literature review activity to check whether any additional studies could potentially be included in the meta-analysis (in addition to the studies identified) according to an agreed contract. The CRO responsibilities were conducted according to SOPs agreed between GSK and the CRO.

5.6. Changes in the conduct of the study or planned analyses

5.6.1. Protocol amendments

Not applicable.

5.6.2. Other changes

Following were the changes from the analyses planned in the final SAP dated 24 March 2016:

- **The ANSM study**: The mean follow-up period (FU) was longer for the non-vaccinated subjects than the vaccinated subjects (30.2 months versus 19.8 months). Since the defined risk period was two years, the number of cases for two year follow-up was calculated as

  N = 24 * observed number / FU (months).

- **Pooled table or 'crude' method**: the case-control study EPI-HPV-011 has not been included for computation of the crude OR estimate because this method did not allow combining cohort and case control studies.
- **Beta-binomial regression method**: two models were analysed including and excluding the EPI-HPV-011 study.

5.6.3. *Re-analysis analysis*

In December 2016, an issue was detected with the computation of the OR for the ANSM study.

This study included a non-vaccinated cohort and vaccinated cohort who received Cervarix or Gardasil. Exposure to HPV vaccine was considered to be a time-dependent variable. The same individual could therefore initially contribute as a non-exposed subject and then as an exposed subject if ever vaccinated with an HPV vaccine. In order to align the ANSM results with other studies, the number of events observed in the non-vaccinated cohort had to be computed. This number was incorrectly computed in the original analysis.

The total number of events in the non-exposed subjects presented in the ANSM report included cases observed in the non-vaccinated cohort but also cases observed in the vaccinated cohort before vaccination. The estimated number of events in the non-vaccinated cohort had to be re-computed taking into account the total person-time of the non-vaccinated cohort and the total person-time of the vaccinated subjects before vaccination. Please refer to the additional analysis request form (AAR 001:ANALYSIS_E1_02) for details.

Confidence interval for I^2 (heterogenecity assessment) were computed.

6. STUDY POPULATION RESULTS

6.1. Study dates

The analysis start was on 22 April 2016 and the analysis was completed on 29 July 2016.

Add dates of re-analysis

6.2. Subject disposition

- Overall, the pooled GSK studies, the cluster randomised study (HPV-040) and the two observational cohort studies (ANSM and EPI-HPV-040) included 154,398 (9.3%) subjects vaccinated with *Cervarix* and 1,504,322 (90.7%) control subjects (Table 3).
- The imbalance in number of subject numbers between the groups is due to the ANSM study (55,545 subjects vaccinated with *Cervarix* vs. 1,410,596 subjects not vaccinated with HPV vaccine during follow-up).
- The sole case-control study, EPI-HPV-011, included 106 cases of autoimmune thyroiditis and 876 matched controls and 13 cases of GBS and 130 matched controls (Table 4).

6.3. Demographic characteristics and other baseline characteristics

Demographic characteristics are summarized in Table 5 to Table 7.

- The mean age of subjects in the exposed and the non-exposed group was 16.05 years and 13.71 years, respectively (this difference is due to the ANSM study) (Table 6).
- More than 95% of subjects were enrolled in studies conducted in France (88.4%) and UK (7.9%). (ANSM study and the EPI-HPV-040 study, which involved a large number of subjects, were carried out in France and the UK, respectively) (Table 7).
- There is also an imbalance in the distribution by country between the exposed and non-exposed subjects.
    - The UK, France, Finland, Costa Rica and Philippines recruited 42.3%, 36.0%, 9.6%, 2.4% and 1% of the exposed subjects whereas all the other countries reported below 1% of the exposed subjects.
    - France and the UK recruited 93.8% and 4.3%, respectively, of the non-exposed subjects whereas all the other countries reported below 1% of the non-exposed subjects.

7. PRIMARY OBJECTIVE RESULTS

The results of the analysis of the three diseases are presented in Table 8 to Table 21 and Figure 2 to Figure 6.

Autoimmune Thyroiditis:

- The OR of autoimmune thyroiditis ranged from 0.004 (EPI-HPV-011) to 3.75 (EPI-HPV-040) (Figure 2).
- The overall OR from variance-inverse meta-analysis, was 2.01 (95% CI: 1.30; 3.11). The other methods gave similar estimates (2.46 from the pooled analysis [Table 8] and 2.17 for the Beta-Binomial model [Table 14]). This excess risk was estimated to be 17 cases per 100,000 exposed subjects (Table 8).
- The sensitivity analysis, excluding the ANSM study, provided similar results of overall OR estimates ranging between 2.04 and 2.33 (Figure 6).

GBS:

- GBS cases were reported only in the ANSM study and the EPI-HPV-011 studies. None of the cases reported in the EPI-HPV-011 had received vaccination during the 42 days follow-up. This finding did not allow computation of OR estimate (Figure 5).
- The overall OR from the variance-inverse meta-analysis, during the 42 days follow-up period was 11.14 (95% CI: 2.01; 61.92) (Figure 5). The other methods gave similar estimates (11.07 [Table 9]). The Beta-Binomial model gave a lower risk estimate (OR=4.6) but this estimate was questionable because of convergence issues (Table 19).
- During the two years follow-up period, the sensitivity analysis reported lower overall OR estimates ranging between 1.89 (pooled analysis) to 3.83 (variance-inverse meta-analysis) (Figure 3).
- The results of the GBS analysis were driven by the two cases observed in the vaccinated cohort of the ANSM study. The time to onset of these two cases was unknown. In the most conservative approach, we assumed that these two cases had occurred within the 42-days follow-up.
- The time to onset of the 18 GBS cases reported in the non-exposed subjects of the ANSM study was unknown. Under the conservative assumption of constant incidence rate during the 30 months of follow-up, only 1.8 cases would have occurred during similar 42-days follow-up period in the non-exposed cohort.

IBD:

- The OR of IBD ranged from 0.80 (Pooled clinical trials) to 2.00 (EPI-HPV-040) (Figure 4).
- The overall OR from variance-inverse meta-analysis, was 1.11 (95% CI: 0.75; 1.66) for the random-effect model and for the fixed-effect model (Table 11). Other

methods gave similar estimates (1.03 from the pooled analysis [Table 8] and 1.20 for the Beta-Binomial model [Table 16]).

8. STUDY STRENGTHS, LIMITATIONS, INTERPRETATIONS AND OVERALL CONCLUSIONS

8.1. Study strengths

- The main strength of this meta-analysis was the total number of subjects, data from more than 150,000 exposed and 1,500,000 unexposed subjects was used for the analyses. Large cohorts are needed to assess possible risk of such rare events such as autoimmune diseases.
- Another strength of this study was the consistency of the overall risk estimates (OR) provided by the various methods for autoimmune thyroiditis and inflammatory bowel disease. Overall OR estimates for auto-immune thyroiditis was 2.01 for the main analysis and ranged between 2.04 to 2.46 for the sensitivity analyses. The overall OR estimates for IBD was 1.1 and ranged between 1.03 and 1.20 in the sensitivity analysis. For GBS, the overall OR from the variance-inverse meta-analysis (Figure 4) was 11.14 (95% CI: 2.00; 61.9) during the 42 days after any vaccination. The 'pooled table' method gave similar estimates (11.07), whereas the beta-binomial model gave lower a risk estimate (4.60). The latter estimate should be considered with caution because of convergence issue.

8.2. Limitations

The current meta-analysis had the following limitations:

- There was no access to the raw data for the two studies (EPI-HPV-011 study and ANSM study) and only aggregated data (total number of cases and total number of subject per group) were available. This precluded the adjustment for any covariate as well as sensitivity analysis for the other risk period. The risk period used in the present analysis was two years after first vaccination for autoimmune thyroiditis and IBD.
- Case definitions were not consistent across all studies (Section 5.2.1.1). To overcome this issue, mapping of various definitions/codes was proposed. The general term 'thyroiditis' was used in the ANSM study, this term indeed included a variety of thyroiditis diseases (18 different ICD-10 codes including also non-autoimmune thyroiditis). However the lack of individual ICD-10 data prohibited a more specific analysis using all studies. No case of thyroiditis from the ANSM study was excluded from the analysis. It was assumed that the majority of cases of thyroiditis were from autoimmune origin. A sensitivity analysis on autoimmune thyroiditis was performed using all studies except the ANSM study. The sensitivity analysis performed removing results from the ANSM study provided fairly similar results to the principal analysis, and it is thus unlikely that the difference in thyroiditis case definition may have biased the results.

- The date of identification of the outcome varied among studies. Some studies used the date of diagnosis (ANSM and EPI-HPV-011studies), while other studies used the date of first clinical sign/symptom (EPI-HPV-040) to identify the cases. Ideally the date of first symptoms was to be used as the disease onset. Date of symptoms onset was more easily known in prospective clinical trials than in retrospective database studies (although in the EPI-HPV-040 study, using the CPRD database, symptom onset was derived from a medical review of the subject profiles). Some cases considered as "occurring" during the risk period could have had an onset prior to vaccination (or equivalent date in unvaccinated subjects) and in contrary, events with onset date within the risk period, but diagnosis reported after the risk period could have been missed during this analysis.
- The level of case validation of diagnosis also ranged from a full medical validation in the prospective clinical trials to no validation at all in the ANSM study and intermediate level in the EPI-HPV-040 study.
- Heterogeneity in study types was also considered as a limitation. The goal was to use all the available data, this implied combining different study designs such as a pool of randomized clinical trials, a cluster randomized study, two observational cohort studies and a case-control study. Heterogeneity among studies was expected. This heterogeneity assessed by the i^2 index appeared to be very low ($I^2 = 0.00\%$ for all analysis). This low heterogeneity estimate should be carefully interpreted in view of its very broad confidence limits (95% upper limit around 80%). Low heterogeneity is probably linked to the limited number of studies (only five). This resulted in virtually identical fixed-effect and random-effect estimates of the overall OR.
- A two year risk period after first dose was used for autoimmune thyroiditis and IBD. However for GBS, this risk period was not appropriate. Most studies considered a risk window of 42 days following vaccination for assessing risk of GBS [Schonberger, 1979; Hughes, 2006; Romio, 2009]. In order to assess the risk during this 42-day window, the number of cases in the unvaccinated cohort during the full 2-year follow-up period of the ANSM study were to be estimated from the overall incidence. This estimation assumed a constant incidence rate over the full follow-up period which could be a potential limitation.
- The statistical parameter of interest was the OR. OR was estimated from both cohort and case-control studies. Since the low incidence of the outcomes (<1%), OR was virtually identical to RR. However, the ANSM study was a cohort study but the exposure was a time-depending variable. When a Cox regression analysis with time-depending exposure was used, the estimated parameter was HR. In this study, exposure was not considered as time-dependent. The only option to include the ANSM study results was to recompute OR.
- OR calculation did not take into account the actual follow-up period. All studies except one (EPI-HPV-040) had a follow-up period of at least two years. However, subjects could withdraw from the study at any time. It was assumed that early termination did not depend on the exposure. This assumption was reasonable for all studies except for the ANSM study, due to time-dependent definition of exposure (non-exposed subjects could switch to exposed when they were vaccinated, and then the non-exposed censoring was depending on the exposure).

- Three methods were proposed to overcome the issues related to single-zero and double-zero. Different methods could provide different overall estimates. However, the results show consistent estimates among various methods.
- There was imbalance between the exposed and non-exposed subjects regarding the age (mean age = 16.05 and 13.71 years in the exposed and non-exposed subjects, respectively) and distribution per country (93.8% of the non-exposed subjects were located in France whereas 42.3% of the exposed subjects were from the UK). However, the imbalance in the distribution by country does not seem to bias the results since exclusion of the ANSM study did change the results and the meta-analysis method took into account between-study heterogeneity.
- Results of the analysis of GBS were difficult to interpret because of the over-weight of the sole ANSM study where cases of GBS were reported and the assumption of constant incidence rate during the 30 months of follow-up in the non-exposed cohort. The very broad CI of the OR estimate demonstrates the uncertainty of the risk estimation.

8.3. Interpretations

The current results can be interpreted using the below pre-defined criteria developed for an observational safety study with the quadrivalent HPV vaccine [Arnheim-Dahlström, 2013].

Arnheim-Dahlström et al, in the analysis of serious adverse events following vaccination with the quadrivalent HPV vaccine (in health databases in Denmark and Sweden), [Arnheim-Dahlström, 2013] have defined a safety signal outcome with a significant rate ratio increase (lower bound of 95% confidence interval >1.0) with at least five vaccine exposed cases. Three criteria were considered as strengthening signals: analysis based on 20 or more vaccine exposed cases (reliability), rate ratio 3.0 or more (strength), and significantly increased rate ratio in country specific analyses (consistency).

Considering the above criteria following conclusions can be drawn:

- **Auto-immune thyroiditis**: Both the main and the sensitivity analysis showed evidence of a small increased risk of autoimmune thyroiditis (OR estimate around 2.0 with an upper limit of the 95% CI around 3.0 for the main analysis and 4.0 for the sensitivity analysis). According to Arnheim-Dahlström *et al* criteria [Arnheim-Dahlström, 2013], this increased risk is regarded as a safety signal but not as a strengthening signal since the OR is less than 3.0. There was insufficient evidence to conclude on a causal relationship between *Cervarix* and autoimmune thyroiditis.
- **GBS**: The results were driven by the 2 exposed cases in ANSM which were conservatively assumed to have occurred during the 42 days follow-up period. A conclusion regarding the risk of GBS cannot be drawn because of the broad confidence interval (CI) (95% CI: 2.01; 61.92). According to Arnheim-Dahlström *et al*. criteria [Arnheim-Dahlström, 2013], this risk estimate is not reliable since there were less than five vaccine exposed cases during the predefined risk period. The results of the study do not confirm an association between *Cervarix* and GBS.

- **IBD**: There was no evidence of an increased risk of IBD since the OR estimates was close to unity with an upper limit of the 95% CI lower than 2.0.

8.4. Overall conclusions

- The present meta-analysis of 18 GSK clinical trials, one cluster randomized trial, two GSK post-marketing epidemiological studies and one non-GSK post-marketing study which represents more than 150,000 *Cervarix* exposed subjects and 1,500,000 non-exposed subjects does not support an increased risk of GBS and IBD.

- A small increased risk of autoimmune thyroiditis is observed as previously described in EPI-HPV-040 and ANSM studies. However, despite this observed association there is insufficient evidence to prove a causal relationship with *Cervarix* vaccination.

9. TABLES AND FIGURES

9.1. Study population

Table 3 Subjects disposition in cohort studies

Study ref	N of exposed subjects	% exposed	N of non-exposed subjects	% non- exposed
ANSM	55545	3.79	1410596	96.21
EPI-HPV-040	64998	50.00	64994	50.00
HPV-040	12400	60.43	8119	39.57
Pooled clin	21455	51.00	20613	49.00
Total	154398	9.31	1504322	90.69

Table 4 Subjects disposition in case-control studies

Source	Auto-immune Disease	N of Cases	(%)	N of Controls	(%)
EPI-HPV-011	1.AI thyro	106	10.79	876	89.21
EPI-HPV-011	2.GBS	13	9.09	130	90.91

Table 5 Demographic characteristics

			Group		
Study Ref			Exposed	Non- exposed	All
EPI-HPV-040	Age (years)	N	64998	64994	129992
		Mean	15.33	15.42	15.37
		Std	2.09	2.10	2.10
		Median	15.3	15.7	15.4
		Min	9.4	9.4	9.4
		Max	24.9	24.8	24.9
HPV-040	Age (years)	N	12400	8119	20519
		Mean	14.07	14.09	14.08
		Std	0.75	0.75	0.75
		Median	14.0	14.0	14.0
		Min	12.0	12.0	12.0
		Max	16.0	16.0	16.0
Pooled clin	Age (years)	N	21455	20613	42068
		Mean	22.12	22.44	22.28
		Std	8.07	8.02	8.05
		Median	21.0	21.0	21.0
		Min	9.0	8.0	8.0
		Max	72.0	68.0	72.0
All	Age (years)	N	98853	93726	192579
		Mean	16.65	16.85	16.74
		Std	5.06	5.12	5.09
		Median	15.6	16.2	16.0
		Min	9.0	8.0	8.0
		Max	72.0	68.0	72.0

ANSM and EPI-HPV-011 studies not included

Table 6 Demographic characteristics of cohort studies: age

Treat	N	Mean Age (Years)
Exposed	154398	16.05
Non-exposed	1504322	13.71

The case-control EPI-HPV-011 not included

Table 7 Demographic characteristics of cohort studies: countries

study ref	Country	N exposed	%	N non- exposed	%	N total	%
ANSM	France	55545	100.00	1410596	100.00	1466141	100.00
EPI-HPV-040	United Kingdom	64998	100.00	64994	100.00	129992	100.00
HPV-040	Finland	12400	100.00	8119	100.00	20519	100.00
Pooled clin	Australia	429	2.00	423	2.05	852	2.03
	Belgium	161	0.75	164	0.80	325	0.77
	Brazil	1161	5.41	1148	5.57	2309	5.49
	Canada	565	2.63	525	2.55	1090	2.59
	China	980	4.57	982	4.76	1962	4.66
	Colombia	100	0.47	100	0.49	200	0.48
	Costa Rica	3729	17.38	3737	18.13	7466	17.75
	Czech Republic	60	0.28	59	0.29	119	0.28
	Denmark	142	0.66	70	0.34	212	0.50
	Finland	2409	11.23	2399	11.64	4808	11.43
	France	19	0.09	20	0.10	39	0.09
	Germany	639	2.98	637	3.09	1276	3.03
	Honduras	135	0.63	133	0.65	268	0.64
	Hong Kong	150	0.70	150	0.73	300	0.71
	Hungary	178	0.83	90	0.44	268	0.64
	India	176	0.82	178	0.86	354	0.84
	Italy	18	0.08	19	0.09	37	0.09
	Japan	519	2.42	521	2.53	1040	2.47
	Korea	309	1.44	237	1.15	546	1.30
	Korea Republic of	27	0.13	27	0.13	54	0.13
	Malaysia	135	0.63	136	0.66	271	0.64
	Mexico	1133	5.28	1136	5.51	2269	5.39
	Netherlands	394	1.84	281	1.36	675	1.60
	Norway	36	0.17	36	0.17	72	0.17
	Panama	84	0.39	84	0.41	168	0.40
	Peru	88	0.41	88	0.43	176	0.42
	Philippines	1601	7.46	1604	7.78	3205	7.62
	Portugal	102	0.48	110	0.53	212	0.50
	Russian Federation	152	0.71	148	0.72	300	0.71
	Senegal	229	1.07	113	0.55	342	0.81
	Singapore	117	0.55	117	0.57	234	0.56
	South Africa	91	0.42	59	0.29	150	0.36
	Spain	267	1.24	273	1.32	540	1.28
	Sweden	505	2.35	293	1.42	798	1.90
	Taiwan	852	3.97	851	4.13	1703	4.05
	Tanzania	221	1.03	113	0.55	334	0.79
	Thailand	1179	5.50	1173	5.69	2352	5.59
	United Kingdom	269	1.25	273	1.32	542	1.29
	United States	2094	9.76	2106	10.22	4200	9.98

study ref	Country	N exposed	%	N non- exposed	%	N total	%
Total	Australia	429	0.28	423	0.03	852	0.05
	Belgium	161	0.10	164	0.01	325	0.02
	Brazil	1161	0.75	1148	0.08	2309	0.14
	Canada	565	0.37	525	0.03	1090	0.07
	China	980	0.63	982	0.07	1962	0.12
	Colombia	100	0.06	100	0.01	200	0.01
	Costa Rica	3729	2.42	3737	0.25	7466	0.45
	Czech Republic	60	0.04	59	0.00	119	0.01
	Denmark	142	0.09	70	0.00	212	0.01
	Finland	14809	9.59	10518	0.70	25327	1.53
	France	55564	35.99	1410616	93.77	1466180	88.39
	Germany	639	0.41	637	0.04	1276	0.08
	Honduras	135	0.09	133	0.01	268	0.02
	Hong Kong	150	0.10	150	0.01	300	0.02
	Hungary	178	0.12	90	0.01	268	0.02
	India	176	0.11	178	0.01	354	0.02
	Italy	18	0.01	19	0.00	37	0.00
	Japan	519	0.34	521	0.03	1040	0.06
	Korea	309	0.20	237	0.02	546	0.03
	Korea Republic of	27	0.02	27	0.00	54	0.00
	Malaysia	135	0.09	136	0.01	271	0.02
	Mexico	1133	0.73	1136	0.08	2269	0.14
	Netherlands	394	0.26	281	0.02	675	0.04
	Norway	36	0.02	36	0.00	72	0.00
	Panama	84	0.05	84	0.01	168	0.01
	Peru	88	0.06	88	0.01	176	0.01
	Philippines	1601	1.04	1604	0.11	3205	0.19
	Portugal	102	0.07	110	0.01	212	0.01
	Russian Federation	152	0.10	148	0.01	300	0.02
	Senegal	229	0.15	113	0.01	342	0.02
	Singapore	117	0.08	117	0.01	234	0.01
	South Africa	91	0.06	59	0.00	150	0.01
	Spain	267	0.17	273	0.02	540	0.03
	Sweden	505	0.33	293	0.02	798	0.05
	Taiwan	852	0.55	851	0.06	1703	0.10
	Tanzania	221	0.14	113	0.01	334	0.02
	Thailand	1179	0.76	1173	0.08	2352	0.14
	United Kingdom	65267	42.27	65267	4.34	130534	7.87
	United States	2094	1.36	2106	0.14	4200	0.25

The case-control EPI-HPV-011 was not included

9.2. Primary objective results

Table 8 Crude Odds Ratio (OR) of autoimmune thyroiditis, GBS, and IDB: pooled table (Amended 16 May 2017)

Odds Ratio										
Auto-immune Disease	**study ref**	**N events in exposed subj**	**Total N of exposed subj**	**N events in non-exposed subj**	**Total N of non-exposed subj**	**Estimate of Relative Risk**	**Lower CL, Odds Ratio**	**Upper CL, Odds Ratio**	**Exact Lower CL, Odds Ratio**	**Exact Upper CL, Odds Ratio**
1.AI thyro	ANSM	12.1	55545	161.6	1410596	1.91	1.06	3.42	0.95	3.38
	EPI-HPV-040	15.0	64998	4.0	64994	3.75	1.24	11.30	1.19	15.52
	HPV-040	5.0	12400	3.0	8119	1.09	***0.26***	4.57	0.21	7.03
	Pooled clin	12.0	21455	6.0	20613	1.92	0.72	5.12	0.67	6.24
	Overall	44.1	154398	174.6	1504322	2.46	1.77	3.43	1.72	3.43
2.GBS	ANSM	2.4	55545	12.5	1410596	4.93	1.25	19.53	0.46	19.01
	EPI-HPV-040	0.0	64998	0.0	64994					
	HPV-040	0.0	12400	0.0	8119					
	Pooled clin	0.0	21455	0.0	20613					
	Overall	2.4	154398	12.5	1504322	1.89	0.48	7.49	0.18	7.29
3.IBD	ANSM	14.5	55545	384.4	1410596	0.96	0.57	1.62	0.55	1.66
	EPI-HPV-040	10.0	64998	5.0	64994	2.00	0.68	5.85	0.62	7.46
	HPV-040	13.0	12400	6.0	8119	1.42	0.54	3.74	0.50	4.55
	Pooled clin	5.0	21455	6.0	20613	0.80	***0.24***	2.62	0.19	3.15
	Overall	42.5	154398	401.4	1504322	1.03	0.75	1.42	0.74	1.43

The case-control study EPI-HPV-011 is not included

Table 9 Crude Odds Ratio (OR) of GBS 42 days: pooled table

Odds Ratio										
Auto-immune Disease	study ref	N events in exposed subj	Total N of exposed subj	N events in non-exposed subj	Total N of non-exposed subj	Estimate of Relative Risk	Lower CL, Odds Ratio	Upper CL Odds Ratio	Exact Lower CL, Odds Ratio	Exact Upper CL, Odds Ratio
2.GBS	ANSM	2.0	55545	1.8	1410596	28.84	3.81	218.6	1.84	350.4
	EPI-HPV-040	0.0	64998	0.0	64994					
	HPV-040	0.0	12400	0.0	8119					
	Pooled clin	0.0	21455	0.0	20613					
	Overall	2.0	154398	1.8	1504322	11.07	1.46	83.87	0.71	134.4

The case-control study EPI-HPV-011 is not included

Table 10 Crude Odds Ratio (OR) of auto-immune thyroiditis: pooled table excluding ANSM

Auto-immune Disease	study ref	N events in exposed subj	Total N of exposed subj	N events in non-exposed subj	Total N of non-exposed subj	Estimate of Relative Risk	Lower CL, Odds Ratio	Upper CL Odds Ratio	Exact Lower CL, Odds Ratio	Exact Upper CL, Odds Ratio
1.AI thyro	EPI-HPV-040	15.0	64998	4.0	64994	3.75	1.24	11.30	1.19	15.52
	HPV-040	5.0	12400	3.0	8119	1.09	0.26	4.57	0.21	7.03
	Pooled clin	12.0	21455	6.0	20613	1.92	0.72	5.12	0.67	6.24
	Overall	32.0	98853	13.0	93726	2.33	1.23	4.45	1.19	4.85

Table 11 Inverse-Variance analysis Odds Ratios (OR) - two years risk period

Odds Ratio								
Auto-immune Disease	study ref	N events in exposed subj	Total N of exposed subj	N events in non-exposed subj	Total N of non-exposed subj	Estimate of Relative Risk	Lower CL, Odds Ratio	Upper CL Odds Ratio
1.AI thyro	ANSM	12.1	55545.0	161.6	1410596	1.9051	1.0627	3.4154
	EPI-HPV-011	0.0	9.0	106.5	974.0	0.0041	0.0000	1.56791E10
	EPI-HPV-040	15.0	64998.0	4.0	64994.0	3.7504	1.2447	11.3005
	HPV-040	5.0	12400.0	3.0	8119.0	1.0913	0.2607	4.5676
	Pooled clin	12.0	21455.0	6.0	20613.0	1.9220	0.7212	5.1220
	Fixed effec	.	.	.	.	2.0113	1.3020	3.1072
	Random effe	.	.	.	.	2.0113	1.3020	3.1072
2.GBS	ANSM	2.4	55545.0	12.5	1410596	4.9349	1.2468	19.5317
	EPI-HPV-011	0.0	1.0	13.5	143.0	0.0334	0.0000	8.83876E12
	EPI-HPV-040	0.3	64998.5	0.2	64994.5	1.0000	0.0039	255.6031
	HPV-040	0.3	12400.6	0.2	8119.4	1.0000	0.0035	289.5783
	Pooled clin	0.3	21455.5	0.2	20613.5	1.0000	0.0039	255.8929
	Fixed effec					3.8328	1.0824	13.5726
	Random effe					3.8328	1.0824	13.5726
3.IBD	ANSM	14.5	55545.0	384.4	1410596	0.9610	0.5693	1.6223
	EPI-HPV-011							
	EPI-HPV-040	10.0	64998.0	5.0	64994.0	2.0000	0.6836	5.8517
	HPV-040	13.0	12400.0	6.0	8119.0	1.4191	0.5392	3.7350
	Pooled clin	5.0	21455.0	6.0	20613.0	0.8006	0.2443	2.6236
	Fixed effec	.	.	.	.	1.1127	0.7469	1.6578
	Random effe	.	.	.	.	1.1127	0.7469	1.6578

Obs	Auto-immune Disease	Cochran Q	P-value	i^2	95% LL I2	95% UL I2
1	1.AI thyro	2.143	0.709	0.00	0.00	79.20
2	2.GBS	0.875	0.928	0.00	0.00	79.20
3	3.IBD	1.985	0.575	0.00	0.00	84.69

Table 12 Inverse-Variance analysis Odds Ratios (OR) - GBS 42 days

Odds Ratio							
Auto-immune Disease	***N events in exposed subjects***	**N events in exposed subj**	***N events in non-exposed subj***	***Total N of non-exposed subj***	***Estimate of Relative Risk***	***Lower CL, Odds Ratio***	***Upper CL, Odds Ratio***
2.GBS ANSM	2.00	55545.00	1.76	1410596	28.8441	3.8057	218.6151
EPI-HPV-011	0.00	0.00	13.50	144.00			
EPI-HPV-040	0.25	64998.50	0.25	64994.50	1.0000	0.0039	255.6031
HPV-040	0.30	12400.60	0.20	8119.40	1.0000	0.0035	289.5783
Pooled clin	0.26	21455.51	0.24	20613.49	1.0000	0.0039	255.8929
Fixed effec					11.1415	2.0049	61.9156
Random effe					11.1415	2.0049	61.9156

Obs	Auto-immune Disease	N studies	Cochran Q	P-value	i^2	95% LL I2	95% UL I2
2	2.GBS	4	2.995	0.392	0.00	0.00	84.69

Table 13 Inverse-Variance analysis Odds Ratios (OR) of auto-immune thyroiditis - two years risk period excluding ANSM

Odds Ratio								
Auto-immune Disease	study ref	N events in exposed subj	Total N of exposed subj	N events in non-exposed subj	Total N of non-exposed subj	Estimate of Relative Risk	Lower CL, Odds Ratio	Upper CL Odds Ratio
1.AI thyro	EPI-HPV-011	0.00	9.01	106.50	973.99	0.004	0.000	1.57E10
	EPI-HPV-040	15.00	64998.00	4.00	64994.00	3.750	1.245	11.301
	HPV-040	5.00	12400.00	3.00	8119.00	1.091	0.261	4.568
	Pooled clin	12.00	21455.00	6.00	20613.00	1.922	0.721	5.122
	Fixed effec					2.152	1.121	4.131
	Random effe					2.152	1.121	4.131

Obs	Auto-immune Disease	Cochran Q	P-value	i^2	*95% LL I2*	*95% UL I2*
1	1.AI thyro	2.069	0.558	0.00	0.00	84.69

Table 14 Beta-binomial regression model: Odds Ratios (OR) - thyroiditis (two years, without EPI-HPV-011)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	2.166	1.115	4.206	0.022

Table 15 Beta-binomial regression model: Odds Ratios (OR) - GBS (two years, without EPI-HPV-011)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	1.741	0.171	17.666	0.639

Table 16 Beta-binomial regression model: Odds Ratios (OR) - IBD (two years, without EPI-HPV-011)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	1.201	0.498	2.897	0.684

Table 17 Beta-binomial regression model: Odds Ratios (OR) - thyroiditis (two years, with EPI-HPV-011)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	0.860	0.235	3.145	0.820

Table 18 Beta-binomial regression model: Odds Ratios (OR) - GBS (two years, with EPI-HPV-011)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	0.515	0.046	5.771	0.591

Table 19 Beta-binomial regression model: Odds Ratios (OR) - GBS (42 days)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	4.601	0.016	1336.9	0.598

Table 20 Beta-binomial regression model: Odds Ratios (OR) - thyroiditis (2years, excluding ANSM and EPI-HPV-011)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	2.038	0.819	5.068	0.126

Table 21 Beta-binomial regression model: Odds Ratios (OR) - thyroiditis (2years, excluding ANSM but with EPI-HPV-011)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	0.800	0.182	3.516	0.768

Figure 2 Risk of Auto-immune thyroiditis during two years after the first dose of *Cervarix* (bars show 95% CI)

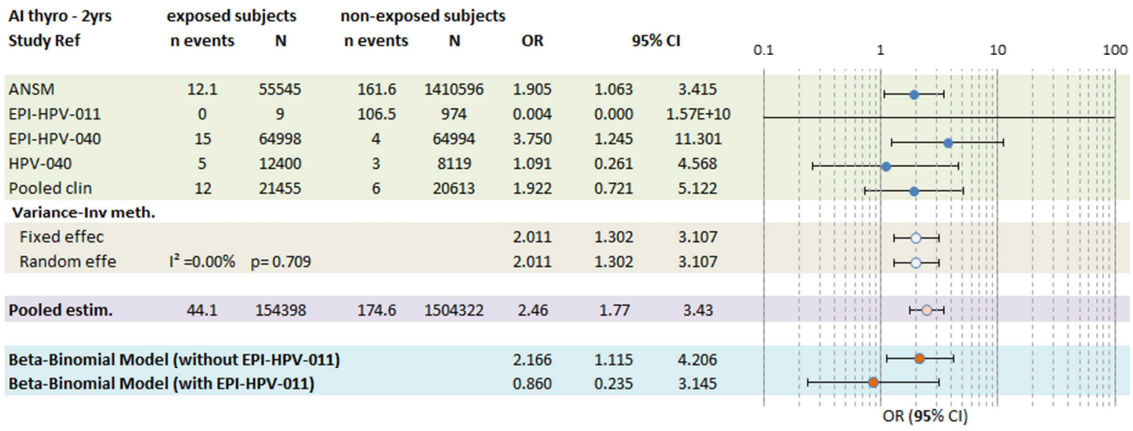


Figure 3 **Risk of Guillain-Barré syndrome during two years after the first dose of *Cervarix* (bars show 95% CI)**

GBS - 2 yrs FU	exposed subjects		non-exposed subjects				
Study Ref	n events	N	n events	N	OR	95% CI	
ANSM	2.4	55545	12.5	1410596	4.935	1.247	19.532
EPI-HPV-011	0	1	13.5	143	0.033	0.000	8.84E+12
EPI-HPV-040	0.3	64998.5	0.2	64994.5	1.000	0.004	255.603
HPV-040	0.3	12400.6	0.2	8119.4	1.000	0.004	289.578
Pooled clin	0.3	21455.5	0.2	20613.5	1.000	0.004	255.893
Variance-Inv meth.							
Fixed effec					3.833	1.082	13.573
Random effe	I^2 =0.00%	p= 0.928			3.833	1.082	13.573
Pooled estim.	2.4	154398	12.5	1504322	1.89	0.48	7.49
Beta-Binomial Model (without EPI-HPV-011)					1.741	0.171	17.666
Beta-Binomial Model (with EPI-HPV-011)					0.511	0.046	5.722

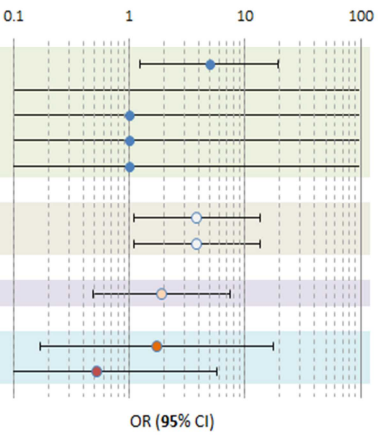


Figure 4 **Risk of inflammatory bowel disease during two years after the first dose of *Cervarix* (bars show 95% CI)**

IBD - 2 Yr FU	exposed subjects		non-exposed subjects				
Study Ref	n events	N	n events	N	OR	95% CI	
ANSM	14.5	55545	384.4	1410596	0.961	0.569	1.622
EPI-HPV-040	10	64998	5	64994	2.000	0.684	5.852
HPV-040	13	12400	6	8119	1.419	0.539	3.735
Pooled clin	5	21455	6	20613	0.801	0.244	2.624
Variance-Inv meth.							
Fixed effec					1.113	0.747	1.658
Random effe	I^2 =0.00%	0.575			1.113	0.747	1.658
Pooled estim.	42.5	154398	401.4	1504322	1.03	0.75	1.42
Beta-Binomial Model (without EPI-HPV-011)					1.201	0.498	2.897

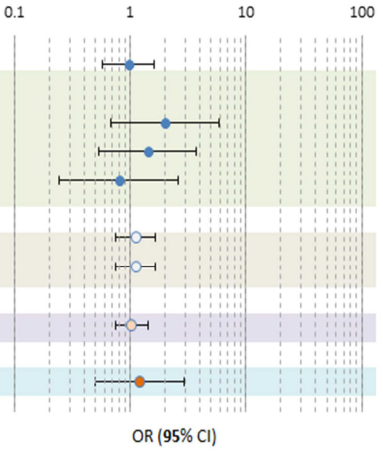


Figure 5 **Risk of Guillain-Barré syndrome during 42 days after each dose of *Cervarix* (bars show 95% CI)**

GBS - 42 days	exposed subjects		non-exposed subjects				
Study Ref	n events	N	n events	N	OR	95% CI	
ANSM	2	55545	1.76	1410596	28.844	3.806	218.615
EPI-HPV-011	0	0	13.5	144			
EPI-HPV-040	0.25	64998.5	0.25	64994.5	1.000	0.004	255.603
HPV-040	0.3	12400.6	0.2	8119.4	1.000	0.004	289.578
Pooled clin	0.26	21455.51	0.24	20613.49	1.000	0.004	255.893
Variance-Inv meth.							
Fixed effec					11.142	2.005	61.916
Random effe	I^2 =0.00%	p= 0.392			11.142	2.005	61.916
Pooled estim.	2	154398	1.8	1504322	11.07	1.46	83.87
Beta-Binomial Model (without EPI-HPV-011)§					4.601	0.016	1336.9

§: because of convergence issues the estimate is questionable

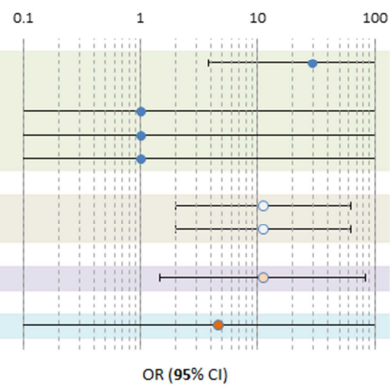
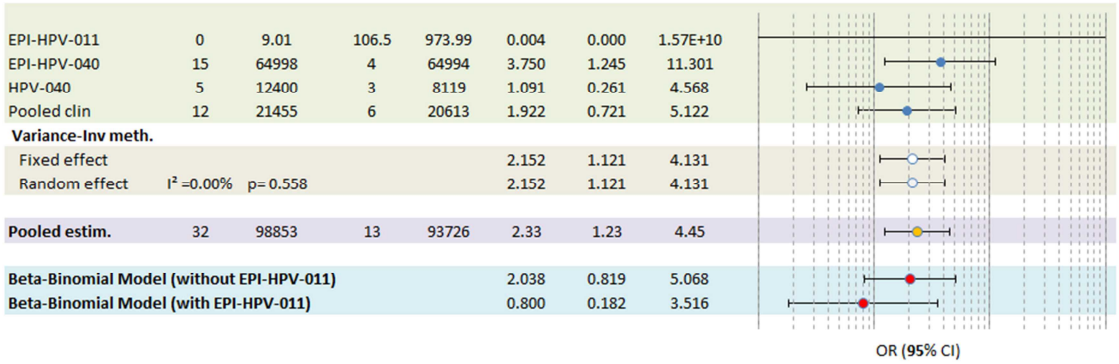


Figure 6 **Risk of autoimmune thyroiditis during two years after the first dose of *Cervarix* (bars show 95% CI) – ANSM study excluded**



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11. STUDY REPORT AUTHORS /CONTRIBUTING AUTHORS

Scientific Writer: PPD

Statistician: PPD

Study Delivery Lead: PPD

Central Safety Contact: PPD

Clinical Safety and Pharmacovigilance Director: PPD

Epidemiologists: PPD

Regulatory Affairs Representative: PPD

N + 1 of Epidemiologist: PPD

12. SERIOUS ADVERSE EVENTS / OTHER SIGNIFICANT ADVERSE EVENTS / PREGNANCY

Not applicable.

MODULAR APPENDICES

List of modular appendices available for the study report and ICH-specific appendices - Study Information equivalent numbering

Modular appendices	ICH numbering
Protocol and protocol amendments.	16.1.1
Sample Case Report form (unique pages only).	16.1.2
List of IECs or IRBs & List of Investigators and other important participants in the study	16.1.3 & 16.1.4
Representative written information for patient and sample consent forms.	16.1.3
Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study	16.1.4
Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement	16.1.5
Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used (if applicable).	16.1.6
Randomization list (patient identification and treatment assigned).	16.1.7
Audit certificates (if available).	16.1.8
Documentation of statistical methods	16.1.9
Documentation of inter-laboratory standardization methods and quality assurance procedures, if used	16.1.10
Publications based on the study.	16.1.11
Important publications referenced in the report	16.1.12
Individual listings	16.2
Case report forms (CRFs /eCRFs) CRFs /eCRFs for deaths, other SAEs and withdrawals due to adverse events	16.3 16.3.1

Protocol and protocol amendments

Since this was a meta-analysis study protocol was not prepared.

Sample Case Report Form

Not applicable

List of investigators, IEC/IRB and distribution of subjects

Not applicable.

Representative written information for patient and sample consent forms

Since this was a meta-analysis study no consent was needed from the subjects. Hence model ICF was not prepared.

Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

Not applicable

Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer

GlaxoSmithKline Biologicals
Vaccine Value and Health Science
Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the study report amendment 2, including appendices

STUDY TITLE: Meta-analysis of the risk of autoimmune thyroiditis diseases, Guillain-Barré Syndrome, and Inflammatory Bowel Disease following vaccination with *Cervarix*.

Study: 205639 (EPI-HPV-069 VS MA) Development Phase: Not applicable for this epidemiological study

I have read this report amendment 2 and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory:	Frank Struyf
Title of Sponsor Signatory:	Clinical and Epidemiology Research & Development Project Lead, Clinical R&D, GSK Biologicals
Signature:	
Date:	

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869fe3820ea620ab1b11101e33642abe75093eba 1.0 5/24/2017 8:03:17 PM - -
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Study Report Amendment Summary Document

GlaxoSmithKline Biologicals
Vaccine Value and Health Science
Clinical Study Report Amendment Summary Document

Report number: 205639 (EPI-HPV-069 VS MA)

Study title: Meta-analysis of the risk of autoimmune thyroiditis diseases, Guillain-Barré syndrome, and inflammatory bowel disease following vaccination with *Cervarix*.

Amendment date: 16 May 2017

Rationale/background for changes:

During the preparation of study results posting, it was noted that two values were missing from the table pertaining to primary objective results (Table 8: Crude odds ratio for autoimmune thyroiditis, Guillain-Barre syndrome and inflammatory bowel disease). This error occurred during manual conversion of table from the statistical report to @std format (human error) during the original report development. Hence the report is being amended to add the missing values in the table.

The changes do not alter the study conclusions.

Table 8 describing the Crude odds ratio for autoimmune thyroiditis, Guillain-Barre syndrome and inflammatory bowel disease was amended.

Amendment Approved by:

Name of Sponsor Signatory: FRANK STRUYF

Title of Sponsor Signatory: CEPL

PPD

Signature:

Date: 24 May 2017

Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used

Not applicable.

Randomization list

Not applicable

Audit certificates

Not applicable

Documentation of statistical methods

Refer to the study report

Documentation of inter-laboratory standardization methods and quality assurance procedures

Not applicable

Publications based on the study

Not applicable

Important publications referenced in the report

No key references have been identified and the other ones will be available on request.

Individual listings

Not Applicable

CRF /eCRFs for deaths, other SAEs and withdrawals due to adverse events

Not applicable

GlaxoSmithKline Biologicals, SA

Study detailed title

Meta-analysis of the risk of autoimmune thyroiditis diseases, Guillain-Barré syndrome, and inflammatory bowel disease following vaccination with *Cervarix*.

Study Report for Study 205639 (EPI-HPV-069 VS MA)

Development Phase Not Applicable for this meta-analysis

Study initiation date: (Analysis start)	22 April 2016
Study completion date: (Analysis complete)	29 Jul 2016
Data lock point (Date of database freeze):	Not applicable
Date of report:	Amendment 1 Final: 31 March 2017
Earlier Study Reports	Report 26 August 2016

Study Report revision history: The study report dated 26 August 2016 was amended on 31 March 2017 to correct errors in the results in the original report.

Sponsor Signatory: Frank Struyf
Clinical and Epidemiology Research & Development
Project Lead,
Clinical R&D,
GSK Biologicals

This study was performed according to the principles of GCP including the archiving of essential documents.

Based on GSK Biologicals' Study Report INS-BIO-CLIN-1010 v05

SYNOPSIS

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** Not applicable	**Name of active substance:** Not applicable

Study No.:
205639 (EPI-HPV-069 VS MA)

Title of the study:
Meta-analysis of the risk of autoimmune thyroiditis diseases, Guillain-Barré syndrome (GBS), and inflammatory bowel disease (IBD) following vaccination with *Cervarix*.

Investigators and study centres:
Not applicable.

Publication (reference):
None at the time of this report.

Study period: **Study initiation date** (Analysis start)**:** 22 April 2016 **Study completion date** (Analysis complete)**:** 29 July 2016 **Data lock point (Date of database freeze):** Not applicable	**Phase:** Not applicable for this epidemiological study

Indication: Not applicable

Objective:
The objective of this meta-analysis was to estimate the overall risk of three autoimmune diseases, following *Cervarix* vaccination:

- Autoimmune thyroiditis,
- GBS,
- IBD.

Methodology: This meta-analysis included all data from *Cervarix* clinical trials identified in the 2015 Development Safety Update Report (DSUR) (Data Lock Point [DLP] 17 November 2015) and post marketing observational studies which met the defined inclusion and exclusion criteria.

Studies included in the meta-analysis:

- Clinical studies identified in the 2015 DSUR (DLP: 17 November 2015) which met inclusion criteria (a control group not exposed to any HPV vaccine, inclusion of female subjects, and the study which enrolled subjects aged 9 years and above) were part of this meta-analysis. The extension studies beyond two years after the first *Cervarix* vaccination and the ongoing blinded studies were excluded.
- Post marketing observational studies (EPI-HPV-040 VS UK [116239], EPI-HPV-011 [112677] and Agence Nationale de Sécurité du Médicament [ANSM] study).

Criteria for evaluations:
Endpoint:
The endpoint was the occurrence of cases of autoimmune thyroiditis, GBS, and IBD during a maximum period of two years (42 days for GBS for the primary analysis) after the first dose of *Cervarix* and an equivalent time period in non-exposed subjects.

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** Not applicable	**Name of active substance:** Not applicable

Statistical methods: The risk of developing the three autoimmune diseases, autoimmune thyroiditis, GBS and IBD, post first dose of *Cervarix* was estimated as the overall odds ratio (OR) using the following three approaches:

- **Pooled table or 'crude' method:** combining total number of cases and subjects in both exposed and unexposed arms;
- **Meta-analysis method with continuity correction*:** Both fixed and random-effect overall OR estimates were computed
- **Beta-binomial regression method**: A method which could use the single and double-zero studies without using continuity correction. This was recently recommended [Kuss, 2015].

** The meta-analysis with continuity correction was pre-defined as the main analysis, where as other methods were sensitivity analyses.*

Study population:

- Data from 18 clinical trials (DLP: 17 November 2015), HPV-040, EPI-HPV-040, EPI-HPV-011 and ANSM observational study were included in this meta-analysis.
- The mean age of subjects in the exposed and the non-exposed group was 16.05 years and 13.71 years, respectively (this difference is due to the ANSM study).
- More than 95% of subjects were enrolled in studies conducted in France (88.4%) and UK (7.9%). (ANSM study and the EPI-HPV-040 study, which involved a large number of subjects, were carried out in France and the UK, respectively).

Summary:

Primary objective results: (Amended on 31 March 2017)

Autoimmune thyroiditis:

- The overall OR from variance-inverse meta-analysis, was ***2.01*** (95% CI: ***1.30; 3.11***). The other methods gave similar estimates (***2.46*** for the pooled analysis and ***2.17*** for the Beta-Binomial model). This excess risk was estimated to be ***17*** cases per 100,000 exposed subjects.
- The sensitivity analysis, excluding the ANSM study, provided similar results of overall OR estimates ranging between 2.04 and 2.33.

GBS:

- The overall OR from the variance-inverse meta-analysis was ***11.14*** (95% CI: ***2.01; 61.92***) during the 42 days follow-up period. The ***pooled analysis gave a*** similar estimate (***11.07***).
- The results of the GBS analysis were driven by the two ***exposed*** cases observed in the ANSM study ***which were conservatively assumed to have occurred during the 42 days after vaccination.***
- ***During the two year follow-up period, the sensitivity analysis reported low overall OR estimates ranging between 1.89 (pooled analysis) to 3.83 (variance-inverse meta-analysis).***

IBD:

- The overall OR from variance-inverse meta-analysis, was ***1.11*** (95% CI: ***0.75; 1.66***). Other methods gave similar estimates (***1.03*** from the pooled analysis and ***1.20*** for the Beta-Binomial model).

Interpretations:

The current results can be interpreted using the pre-defined criteria developed for an observational safety study with the quadrivalent HPV vaccine [Arnheim-Dahlström, 2013].

Arnheim-Dahlström in the analysis of serious adverse events following vaccination with the quadrivalent HPV vaccine (in health databases in Denmark and Sweden), [Arnheim-Dahlström, 2013] have defined a safety signal outcome with a significant rate ratio increase (lower bound of 95% confidence interval >1.0) with at least five vaccine exposed cases. Three criteria were considered as strengthening signals: analysis based on 20 or more vaccine exposed cases (reliability), rate ratio 3.0 or more (strength), and significantly increased rate ratio in country specific analyses (consistency).

Considering the above criteria following conclusions can be drawn:

- **Autoimmune thyroiditis**: Both main and sensitivity analyses showed evidence of a small increased risk of autoimmune thyroiditis (OR estimate around 2.0 with an upper limit of the 95% CI around ***3.0*** for the main analysis and ***4.0*** for the sensitivity analysis). According to Arnheim-

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** Not applicable	**Name of active substance:** Not applicable

Dahlström criteria [Arnheim-Dahlström, 2013], this increased risk is regarded as a safety signal but not as a strengthening signal since the OR is less than 3.0. There was insufficient evidence to conclude on a causal relationship between *Cervarix* and autoimmune thyroiditis.

- **GBS**: The results were driven by the two exposed cases in ANSM study ***were conservatively assumed to have occurred during the*** within 42 days follow-up period. A conclusion regarding the risk of GBS cannot be drawn because of the broad confidence interval (CI) (95% CI: ***2.01; 61.92***). According to Arnheim-Dahlström criteria [Arnheim-Dahlström, 2013], this risk estimate is not reliable since there were less than five vaccine exposed cases during the predefined risk period. The results of the study do not confirm an association between *Cervarix* and GBS.
- **IBD**: There was no evidence of an increased risk of IBD since the OR estimates was close to unity with an upper limit of the 95% CI lower than 2.0.

Overall conclusions

- The present meta-analysis of 18 GSK clinical trials, one cluster randomized trial, two GSK post-marketing epidemiological studies and one non-GSK post-marketing study which represents more than 150,000 *Cervarix* exposed subjects and 1,500,000 non-exposed subjects does not support an increased risk of GBS and IBD.
- A small increased risk of autoimmune thyroiditis is observed as previously described in EPI-HPV-040 and ANSM studies. However, there is insufficient evidence to conclude on a causal relationship with *Cervarix* vaccination.

References:

Lisen Arnheim-Dahlström, Björn Pasternak, Henrik Svanström, Pär Sparén, Anders Hviid. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. *BMJ* 2013; 347: f5906.

Kuss O. Statistical methods for meta-analysis including information from studies without any events – add nothing to nothing and succeed nevertheless. *Statist. Med*. 2015, 34:1097-1116.

Date of report: Amendment 1 Final: 31 March 2017

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

AE:	Adverse Event
ANSM:	Agence National de Sécurité du Médicament et des Produits de Santé
Anti-TPO:	Anti-Thyroid Peroxidase
CDP:	Clinical Development Plan
CI:	Confidence Interval
CPRD:	Clinical Practice Research Datalink
CSF:	Cerebral Spinal Fluid
DLP:	Data Lock Point
DSUR:	Development Safety Update Report
GBS:	Guillain-Barré Syndrome
GSK:	GlaxoSmithKline
HAV:	Hepatitis A Virus
HPV:	Human Papilloma Virus
HR:	Hazard Ratio
IBD:	Inflammatory Bowel Disease
ICD:	International Classification Disease
LL:	Lower Limit of the confidence interval
MedDRA:	Medical Dictionary for Regulatory Activities
N:	Number
N.A:	Not Applicable
OR:	Odds Ratio
PGRx:	Pharmacoepidemiological General Research eXtension
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SD:	Standard Deviation
SE:	Standard Error
TFL:	Tables Figures and Listing template annexed to SAP
TSH:	Thyroid Stimulating Hormone
UK:	United Kingdom
UL:	Upper Limit of the confidence interval
VAR:	Variance

TRADEMARKS

The following trademarks are used in the present report.

Note: In the body of the study report and in synopsis, the names of the vaccines will be written without the superscript symbol ™ or ® and in *italics*.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Cervarix™	Bivalent human papillomavirus (Types 16 and 18) recombinant vaccine

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Gardasil® (Merck and Company, Inc)	Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine

1. ETHICS

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

Not applicable.

1.2. Ethical conduct of the study

The studies included in this meta-analysis was conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki, the principles of "good clinical practice" (GCP) and all applicable regulatory requirements.

1.3. Subject information and consent

Not applicable.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

GSK staff were responsible for the conception and design of this meta-analysis study, the analysis of the data and the interpretation of the results. No investigator external to GSK was involved.

The literature review activity was performed by:

Pallas,
Health and research Consultancy,
Conradstraat 18 E7,
3013 AP Rotterdam,
Netherlands

2.1. Study report revision history (Amended on 31 March 2017)

The study report dated 26 August 2016 was amended on 31 March 2017 to correct errors in the results in the original report. Please refer to the report amendment summary for more details of the rationale for the amendment.

3. INTRODUCTION

The risk of autoimmune diseases after vaccination with *Cervarix* has been evaluated in some studies. However no evidence of an overall increased risk of autoimmune diseases has been detected in pooled analyses of clinical studies [Verstraeten, 2008, Angelo, 2014] and post-licensure observational studies [ANSM, 2015, GlaxoSmithKline Biologicals Study Report 116239 (EPI-HPV-040 VS UK), GlaxoSmithKline Biologicals Study

Report 112677 (EPI-HPV-011 VS FR PMS)]. The primary endpoints of these studies were generally composite endpoints combining various diseases. The ability to analyse the risk of individual autoimmune diseases is limited due to a low incidence rate of these diseases in the general population. However, analyses of a few individual autoimmune diseases have been performed and the following have been identified for future investigation:

- **Autoimmune thyroiditis**: EPI-HPV-040, an observational study was conducted in the United Kingdom (UK) using data from Clinical Practice and Research Database (CPRD) [GlaxoSmithKline Biologicals Study Report 116239 (EPI-HPV-040 VS UK)] and data from a retrospective cohort study in French Healthcare Databases conducted by the French Agence Nationale de Sécurité du Médicament (ANSM [ANSM, 2015]. These studies showed a significantly increased risk following *Cervarix* vaccination (Risk ratio [RR]= 3.75 [95% Confidence Interval (CI): 1.25; 11.31] and Hazard Ratio (HR)= 2.43 [1.27; 4.66] respectively) while neither the pooled GSK clinical data [Verstraeten, 2008, Angelo, 2014] nor the EPI-HPV-011 case-control study [GlaxoSmithKline Biologicals Study Report 112677 (EPI-HPV-011 VS FR PMS)] showed evidence of an increased risk.
- **Guillain-Barré syndrome (GBS)**: No case of GBS was reported in either EPI-HPV-040 or in the GSK pooled clinical data. However the ANSM study detected a statistically significant increased risk of GBS following *Cervarix* vaccination (HR=8.14 [95% CI 1.70-38.92]).
- **Inflammatory bowel disease (IBD)**: Pooled clinical data analyses and all GSK-sponsored post-licensure observational studies conducted did not show an increased risk of IBD following *Cervarix* vaccination. However, a slightly significant increased risk of IBD following HPV vaccination (pooled bivalent and quadrivalent vaccines) was observed in the ANSM study (HR= 1.19 95%CI: 1.02; 1.39). This disease was also identified for future investigation. The ANSM study also observed a decreasing risk of IBD over time following the first dose of HPV vaccine ($HR_{0\text{-}3\ months}$: 1.30 [95% CI 0.94-1.79]; $HR_{3\text{-}12\ months}$: 1.23 [95% CI 0.99-1.52]; $HR_{>12months}$: 1.12 [95% CI 0.91-1.38]). Hence, the Scientific Committee of the study considered that a very low statistical association does not allow the conclusion of an excess risk for this disease.

In order to better assess a potential risk of these three autoimmune diseases, GSK Biologicals performed a meta-analysis for these three diseases. All available data generated from GSK clinical studies and data from post-licensure observational studies which met the inclusion and exclusion criteria were used.

4. STUDY OBJECTIVE

The objective of this meta-analysis was to estimate the overall risk of three autoimmune diseases, following *Cervarix* vaccination:

- Autoimmune thyroiditis
- GBS

- IBD.

5. INVESTIGATIONAL PLAN

5.1. Study design

5.1.1. Overall study design – Description

This meta-analysis included all data from clinical trials identified in the 2015 Development Safety Update Report (DSUR) (DLP: 17 November 2015) and post marketing observational studies which met the defined inclusion and exclusion criteria.

5.1.2. Selection of studies

All GSK clinical studies and post-marketing observational studies were assessed in order to determine whether the studies were relevant with respect to the objective pursued. The study performed by ANSM was also included.

Data were identified from all GSK sponsored studies, investigator-sponsored studies [ISS]) studies where *Cervarix* was administered as well as non-GSK studies listed in the Committee for Medicinal Products for Human Use (CHMP) Type II variation assessment report (EMEA/H/C/000721/II/0069[assessment report for EPI-HPV-040]). A supplementary literature review was performed by Pallas (DLP: 3rd December 2015), to check whether any additional studies could potentially be included in the meta-analysis. There were no studies of potential interest identified for the meta-analysis during the literature review.

Clinical studies identified in the 2015 DSUR (DLP: 17 November 2015) and which met the following criteria were included in the meta-analysis.

5.1.2.1. Inclusion criteria

- Inclusion of a control group not exposed to any HPV vaccine;
- Inclusion of female subjects;
- The study/studies which enrolled subjects aged 9 years and above

5.1.2.2. Exclusion criteria

The extension studies beyond two years after the first vaccination of *Cervarix* and the ongoing blinded studies were excluded.

A list of included clinical studies included in the meta-analysis is provided in Table 1. Because a large number of studies and low incidence rate of the outcomes, data from all included clinical studies were pooled and considered as a single source (study) in the meta-analysis, except the HPV-040 study.

The following data sources (Figure 1) were included in the meta-analysis:

- Pooled clinical studies: Primarily 22 clinical studies were considered but data from 18 clinical trials were included (HPV-007, HPV-013 EXT M18, HPV-013 EXT M24 studies were excluded as these studies started three years after vaccination) (DLP: 17 November 2015).
- Study HPV-040(#): a cluster randomised clinical trial in Finland; only the exposed and non-exposed female subjects were included;
- Study EPI-HPV-040: an observational retrospective cohort study using the Clinical Practice Research Datalink (CPRD), United Kingdom (UK) database. The follow-up period was limited to 12 months after the first dose of *Cervarix*. Only the two female (exposed and non-exposed) cohorts were used in the meta-analysis, the male non-exposed cohort was excluded [GlaxoSmithKline Biologicals Study Report 116239 (EPI-HPV-040 VS UK)].
- Study EPI-HPV-011: This study included surveillance and estimation of risk of autoimmune diseases. Only the risk results were included in the meta-analysis. The estimation of risk was a case-referent study using the Pharmacoepidemiological General Research extension (PGRx) methodology [GlaxoSmithKline Biologicals Study Report 112677 (EPI-HPV-011 VS FR PMS)].
- ANSM observational study: a longitudinal observational exposed vs. non-exposed study based on national healthcare administrative databases in France. The exposed cohort included both *Cervarix* and *Gardasil* vaccinated subjects. For the purpose of the current meta-analysis, only *Cervarix* exposed subjects were included. The non-exposed cohort included subjects non-exposed to *Cervarix* and *Gardasil* [ANSM, 2015].

(#): HPV-040 study is a cluster randomized study. Because of this particular design (the other clinical studies were parallel group studies), the large sample size and the different methodology for safety follow-up (passive safety surveillance via national registries), this study was considered as a separate study in the meta-analysis.

Figure 1 List of data sources

Data Source reference	Design	Raw data	N exposed subjects	N control subjects	Risk period	Diseases (Terms/codes)	N of cases (Exp/Ctrl)	Source	Comment
Clinical studies (2015 DSUR)	pooled 19 clinical studies	Y	21.699	17.763	Up to 2 years after vaccination	Autoimmune thyroiditis	6/1	DSUR 2015 dataset	N of cases are N including all studies in the 2015 DSUR (Total N = 33942 exposed and 21316 non-exposed subjects) , a few studies will be excluded : * Extension studies >= 2 years post-dose 1, * No control group or Ctrl grp= Gardasil, * Ongoin DB, * Paediatric population
						Basedow's disease	6/1		
						Colitis ulcerative	4/1		
						Crohn's disease	2/2		
						Inflammatory bowel disease	1/1		
						Proctitis ulcerative	1/0		
						Guillain-barre syndrome	0/0		
HPV-040	Cluster randomized trial (Finland)	Y	12.399	8.119	Median : 4,21 Years	Autoimmune thyroiditis	5/1	Analysis dataset	
			Only Female subje			Thyroiditis	1/0		
						Colitis ulcerative	15/8		
						Crohn's disease	8/6		
						Proctitis ulcerative	3/1		
						Guillain-barre syndrome	0/0		
EPI-HPV-040	*Retrospective Cohort study in CPRD (UK)*	*Y*	*64.705*	*64.841*	*1 yr after 1st dose*	Autoimmune thyroiditis (confir	*15/4*	Analysis Dataset	
						Autoimmune hypothyroidit	16		
						Crohn diseases	6/5		
						Ulcerative Colitis	4/5		
						GBS	0/0		
PGRx (LASE EPI-HPV-011	Case-control in France	N	NA	NA 42 days any dose 24 months after any dose		GBS (n Cases / N ctrl)	N case/ctrl 13 / 130	Final Report	0 cases exposed vs. 0 ctrl exposed
						GBS (n Cases / N ctrl)	13 / 130		0 cases exposed vs. 1 ctrl exposed
						Auto Immune Thyroditis	106/876		0 cases exposed vs. 9 ctrl exposed
ANSM	Cohort study in France	N	55.545	1.410.596	24 months	IBD	12/523	ANSM - Final report, September 2015	
						Coeliac disease (incl in IBI	2/119		
						Thyroiditis	10/209		
						GBS	2/18		

N of cases (Exp/Ctrl): For EPI-HPV-011 study, both definite and possible autoimmune thyroiditis have been included.

Table 1 List of GSK clinical studies included in the meta-analysis

			Meta-analysis of selected autoimmune diseases		
Study E-track	**Study Alias**	**Group DSUR group = study group**	**Included in meta-analysis**	**Comments**	**N subjects (Exposed/Control)**
580299_001	HPV-001	HPV in CDP=HPV Control in CDP=Placebo	Yes		560/553
580299_007	+ follow-up: HPV-007	HPV in CDP=HPV Control in CDP=Placebo	Yes	But limited to two years after first dose	
580299_008	HPV-008	HPV in CDP=HPV Control in CDP=HAV	Yes		***9328/6337***
580299_009	HPV-009	HPV in CDP=HPV Control in CDP=HAV	Yes		***3729/3737***
580299_013	HPV-013	HPV in CDP=HPV Control in CDP=HAV	Yes		1035/1032
104896	HPV-013 (Ext M18)	HPV in CDP=HPV Control in CDP=HAV	Yes		
104902	HPV-013 (Ext M24)	HPV in CDP=HPV Control in CDP=HAV	Yes		
104820	HPV-015	HPV in CDP=HPV Control in CDP=Placebo	Yes		2881/2871
107863	HPV-020	HPV in CDP=HPV Control in CDP=Placebo	Yes		91/59
106069	HPV-021	HPV in CDP=HPV Control in CDP=Placebo	Yes		450/226
111567	HPV-026	HPV in CDP=HPV Control in CDP=HBV	Yes		76/76
110886	HPV-029	HPV in CDP=HPV Control in CDP=HAB	Yes		542/271
111507	HPV-030	HPV in CDP=HPV Control in CDP=HBV	Yes		494/247
104479	HPV-031	HPV in CDP=HPV Control in CDP=Placebo	Yes		176/178
104798	HPV-032	HPV in CDP=HPV Control in CDP=HAV	Yes		519/521
104951	HPV-033	HPV in CDP=HPV Control in CDP=HAV	Yes		160/161
106001	HPV-035	HPV in CDP=HPV Control in CDP=Placebo	Yes		150/150
105926	HPV-036	HPV in CDP=HPV Control in CDP=Placebo	Yes		135/136
107291	HPV-038	HPV in CDP=HPV Control in CDP=Placebo	Yes		149/76
112022	HPV-058	HPV in CDP= HPV Control in CDP=Placebo	Yes		374/376
114590	HPV-069	HPV in CDP=HPV Control in CDP=HBV	Yes		606/606

5.2. Statistical methods

The statistical analyses were performed using the Statistical Analysis Systems (SAS) version 9.2 on windows and StatXact-8.1 procedure for SAS.

5.2.1. Endpoint

The endpoint was the occurrence of cases of autoimmune thyroiditis, GBS, and IBD during a maximum period of two years (42 days for GBS for the primary analysis) after the first dose of *Cervarix* and an equivalent time period in non-exposed subjects.

5.2.1.1. Case definition

Different case definitions were used in the various studies and are described in Table 2. In brief:

- GSK clinical studies and HPV-040 used the MedDRA terminology.
- Study EPI-HPV-040 used read code and ICD-10 codes; a patient profile review was performed to confirm the new onsets of autoimmune disease. Some cases, as well as a random 10% sample from each of the categories of autoimmune diseases were reviewed by a panel of medical specialists.
- The ANSM study used definitions based on the occurrence of ICD-10 codes for the event of interest in hospitalization or long duration disease reports. For thyroiditis, different ICD-10 codes were used, including both cases of autoimmune and non-autoimmune origin. Only an aggregated number of cases of thyroiditis were mentioned in the report. It was not possible to determine if these cases of thyroiditis were autoimmune in origin.
- Study EPI-HPV-011 identified cases of autoimmune disorders through a network of specialist centres (internal medicine, neurology, rheumatology, paediatric, endocrinology and dermatology departments) at university and general hospitals across France. The study used specific study definitions, distinguishing “definite” and “possible” cases. Only “definite” cases were considered for the meta-analysis. The index date for the cases was the date of the first clinical sign or symptom suggestive of the autoimmune disorder.

Table 2 presents the clinical definitions which were used in the meta-analysis:

Table 2 Clinical definition across the studies

Event of interest	MedDRA Primary System Organ Class and Preferred Term		Read code + ICD10 Codes	ICD-10	Study clinical definition
	GSK pooled clinical studies	HPV-040	EPI-HPV-040#	ANSM	PGRx
Autoimmune Thyroiditis	- Basedow's disease (10004161) - Autoimmune thyroiditis (10049046)	- Basedow's disease (10004161) - Autoimmune thyroiditis (10049046)	Confirmed cases: - Autoimmune thyroiditis - Basedow's disease - Grave's disease - Hashimoto's disease - De Quervain's thyroiditis - Riedel's thyroiditis (ICD-10: E05, E06.1, E06.3, E06.5)	- At least one hospitalization with principal diagnosis of stay or related diagnosis of thyroiditis - Or long term diseases ***ICD10*** code of thyroiditis$	Auto Immune Thyroditis: definite case according to study definitions including Grave's disease and Hashimoto disease£
GBS	No case	- GBS G61.0: (10018767)	Confirmed cases of GBS # (G61.0, G60)	GBS code G61.0 Occurrence of ALD30 (long term diseases) for GBS Or at least one hospitalization of a minimal 6 days length with a principal diagnosis of stay or related diagnosis for GBS Or at least two hospitalization with a principal diagnosis of stay or related diagnosis for GBS	GBS definite case (level 1) according to the Brighton collaboration case definition: requires clinical, electrophysiologic, and CSF data consistent with the onset of GBS
Inflammatory Bowel Disease	- Colitis ulcerative (10009900) - Crohn's disease (10011401) - Inflammatory bowel disease (10021972) - Proctitis ulcerative (10036783)	- Colitis ulcerative (10009900) - Crohn's disease (10011401) - Proctitis ulcerative (10036783) K 50.0; K 51.0; K51.2	Confirmed cases of: - Crohn's diseases (K50) - Ulcerative colitis (K51)	- ALD30 (long term disease) for IBD - or at least one hospitalization with a principal diagnosis of stay or related diagnosis for IBD AND - one hospitalization for lower digestive before or at the time of diagnosis	Not assessed

Event of interest	MedDRA Primary System Organ Class and Preferred Term		Read code + ICD10 Codes	ICD-10	Study clinical definition
	GSK pooled clinical studies	HPV-040	EPI-HPV-040#	ANSM	PGRx
				- ICD-10 codes K50 Crohn disease K51 Ulcerative colitis	

#:In addition to the specific IDC10 codes listed in the table,other codes were used to capture possible cases. Among these only the cases confirmed by a medical review were included

£: Definite case of autoimmune thyroiditis = Hypothyroidism consistent with incident autoimmune thyroiditis AND anti-peroxydase (anti-TPO) AND increased TSH > 7mU/L; Definite case of Grave's disease= Presence of exophthalmia or palsy or tachycardio or weight loss or weight gain AND anti-TSH-receptor AND decreased TSH

$ ICD-10 code E034 Atrophy of thyroid (acquired) ; E035 Myxedema coma; E038 Other specified hypothyroidism ; E039 Hypothyroidism, unspecified; E040 Nontoxic diffuse goiter; E048 Other specified nontoxic goiter ; E049 Nontoxic goiter, unspecified; E050 Thyrotoxicosis with diffuse goiter; E055 Acute thyrotoxicosis; E058 Other thyrotoxicosis; E059 Thyrotoxicosis, unspecified; E060 Acute thyroiditis; E061 Subacute thyroiditis; Chronic thyroiditis with transient thyrotoxicosis; E063 Autoimmune thyroiditis; E065 Other chronic thyroiditis; E069 Thyroiditis, unspecified

A sensitivity analysis of autoimmune thyroiditis was performed including studies using codes from autoimmune origin (i.e. excluding the ANSM data).

5.2.1.2. Risk period definition

The risk period to assess autoimmune disease post-vaccination was determined based on the onset of the disease (either acute or insidious), possible or known pathologic mechanisms involved, and the type of vaccine [Tavares Da Silva, 2013].

Irrespective of the underlying mechanisms, one may assume that the development of autoimmunity (if a causal association between the event and vaccination existed) requires several weeks, which is similar to the classical time frame of several weeks suggested for the onset of post-infectious autoimmune phenomena [Tavares Da Silva, 2013, Allos, 1997].

The following risk periods were considered for each event of interest:

- For autoimmune thyroiditis and IBD, a risk period of up to two years after first vaccination was considered. An equivalent period was used for non-exposed subjects. Since the clinical course of autoimmune thyroiditis and IBD is generally insidious, a long interval between vaccination and disease onset was considered. A risk period of up to 2 years was primarily assumed but one of the studies in this meta-analysis had a shorter follow-up of 12 months. However, considering this 12 months of follow-up after the last vaccination was a reasonable maximum theoretical risk interval [Tavares Da Silva, 2013]. All included studies except the EPI-HPV-040 had a per-protocol follow-up period of at least two years. The follow-up period of the EPI-HPV-040 was limited to 12 months after the first vaccination.
- For GBS, a risk period of 42 days after each vaccination was used for the main analysis. For GBS (disease of acute onset), the period of increased risk was shown to be concentrated within 6 weeks after the 1976–1977 swine flu vaccination

[Langmuir, 1979, Schonberger, 1979, Wise, 2012]. Therefore a 6 week time window was used for the assessment of cases of GBS potentially associated with vaccination. Also, for the Brighton Collaboration working group [Sejvar, 2011], the recommended risk period for acute neurologic illnesses such as acute disseminated encephalomyelitis was at least 42 days. The number of GBS cases occurring during this 42 day risk period was not available for the ANSM study. The two cases observed in the *Cervarix* vaccinated group of the ANSM study were ***conservatively assumed to have occurred*** within 42 days post-vaccination. For the unvaccinated cohort, the total number of GBS cases (18) occurring during the full follow-up period (30.6 months) ***for the non exposed subjects*** was known. ***This number included cases occurring in the non-vaccinated cohort but also in the vaccinated cohort before vaccination. The number of cases occurring in the non-vaccinated cohort was estimated based on the total person-time reported in the non-vaccinated cohort and in the vaccinated cohort before vaccination.*** The number of cases occurring during an equivalent 42-day post-dose period was ***also*** estimated from the overall incidence rate during the total follow-up period and the total number of unvaccinated subjects. In addition, since the mean follow-up period was longer for the non-exposed than for the exposed subjects (30.2 months versus 19.8 months), the number of cases for two year analysis was calculated as N = 24 * observed number / follow-up (in months).

5.3. Study characteristics

Demographic characteristics (age, country, region, follow-up time, etc.) were summarized by study and overall. Descriptive statistics included N (number of subjects), mean, SD, median, minimum and maximum for continuous variable and N (%) for categorical variables.

These statistics was computed from raw data for GSK studies (except for EPI-HPV-011) and from aggregated data for non-GSK studies.

5.4. Risk estimate

The risk of developing the three autoimmune diseases, autoimmune thyroiditis, GBS and IBD, post first dose of *Cervarix* was estimated using meta-analysis methods.

Since the incidence of the outcomes of interest is very low, Odds Ratio (OR) was used. ORs were computed from both cohort and case-control studies.

A meta-analysis of rare events was challenging because of studies with no event in one arm ('single-zero') or even both arms ('double-zero') [Sweeting, 2004; Bradburn, 2007; Vollset, 1991].

Three approaches were used:

Meta-analysis method* with continuity correction: A continuity correction was applied to all studies to overcome the single and double-zero issue. Various continuity corrections have been proposed [Sweeting, 2004] such as constant continuity correction k

(for example k=0.5 is commonly used in many softwares), continuity correction reciprocal of the opposite treatment arm size and empirical continuity correction. The advantage of this method was that all studies could be included, and any meta-analysis calculation method (inverse variance-weighted method, Peto's method, Mantel-Haenszel's method, etc.) could be applied, all individual studies could also be depicted in forest plots and the heterogeneity among studies could be estimated and tested.

The continuity correction factor in the exposed arm was computed as

$$C_e=0.5\ N_e/N_T$$

Where, C_e is continuity factor in the exposed arm, N_e is the total number of subjects in the exposed arm and N_T is the total number of subjects in both arms.

The continuity correction factor in the non-exposed arm was similarly computed by substituting N_e by N_{ne} , the total number of subjects in the unexposed arm. Both fixed- and random-effect models were computed. The inverse-weighted variance method was used for the fixed-effect model.

Heterogeneity among studies was tested using the Cochran Q test. The degree of the heterogeneity was assessed by the i^2 index [Huedo-Medina, 2006]. For the random-effect model, a component of inter-study variance was added in the overall variance [DerSimonian, 1986].

Pooled table or 'crude' method: Data from all studies were pooled in a single fourfold table and an overall estimate was computed using standard methods. The main limitation was that this method ignored the data which were collected from several studies and the underlying assumption of a constant estimate across all studies.

Beta-binomial regression method: A method which could use the single and double-zero studies without using continuity correction. The latter was recently recommended [Kuss, 2015].

** The meta-analysis with continuity correction was pre-defined as the main analysis. Secondary analysis were performed with two other methods, as a sensitivity assessment of the results obtained with the meta-analysis with continuity correction method.*

5.4.1. Sequence of analyses

Not applicable

5.5. Data quality assurance at study level

A Contract Research Organisation (CRO), Pallas, was employed to perform a supplementary literature review activity to check whether any additional studies could potentially be included in the meta-analysis (in addition to the studies identified) according to an agreed contract. The CRO responsibilities were conducted according to SOPs agreed between GSK and the CRO.

5.6. Changes in the conduct of the study or planned analyses

5.6.1. Protocol amendments

Not applicable.

5.6.2. Other changes

Following were the changes from the analyses planned in the final SAP dated 24 March 2016:

- **The ANSM study**: The mean follow-up period (FU) was longer for the ***non-vaccinated subjects*** than the ***vaccinated*** subjects (30.2 months versus 19.8 months). Since the defined risk period was two years, the number of cases for two year follow-up was calculated as

  N = 24 * observed number / FU (months).

- **Pooled table or 'crude' method**: the case-control study EPI-HPV-011 has not been included for computation of the crude OR estimate because this method did not allow combining cohort and case control studies.
- **Beta-binomial regression method**: two models were analysed including and excluding the EPI-HPV-011 study.

5.6.3. *Re-analysis*

In December 2016, an issue was detected with the computation of the OR for the ANSM study.

This study included a non-vaccinated cohort and vaccinated cohort who received Cervarix or Gardasil. Exposure to HPV vaccine was considered to be a time-dependent variable. The same individual could therefore initially contribute as a non-exposed subject and then as an exposed subject if ever vaccinated with an HPV vaccine. In order to align the ANSM results with other studies, the number of events observed in the non-vaccinated cohort had to be computed. This number was incorrectly computed in the original analysis.

The total number of events in the non-exposed subjects presented in the ANSM report included cases observed in the non-vaccinated cohort but also cases observed in the vaccinated cohort before vaccination. The estimated number of events in the non-vaccinated cohort had to be re-computed taking into account the total person-time of the non-vaccinated cohort and the total person-time of the vaccinated subjects before vaccination. Please refer to the additional analysis request form (AAR 001:ANALYSIS_E1_02) for details.

Confidence interval for I^2 (heterogenecity assessment) were computed.

6. STUDY POPULATION RESULTS

6.1. Study dates

The analysis start was on 22 April 2016 and the analysis was completed on 29 July 2016.

Add dates of re-analysis

6.2. Subject disposition

- Overall, the pooled GSK studies, the cluster randomised study (HPV-040) and the two observational cohort studies (ANSM and EPI-HPV-040) included 154,398 (9.3%) subjects vaccinated with *Cervarix* and 1,504,322 (90.7%) control subjects (Table 3).
- The imbalance in number of subject numbers between the groups is due to the ANSM study (55,545 subjects vaccinated with *Cervarix* vs. 1,410,596 subjects not vaccinated with HPV vaccine during follow-up).
- The sole case-control study, EPI-HPV-011, included 106 cases of autoimmune thyroiditis and 876 matched controls and 13 cases of GBS and 130 matched controls (Table 4).

6.3. Demographic characteristics and other baseline characteristics

Demographic characteristics are summarized in Table 5 to Table 7.

- The mean age of subjects in the exposed and the non-exposed group was 16.05 years and 13.71 years, respectively (this difference is due to the ANSM study) (Table 6).
- More than 95% of subjects were enrolled in studies conducted in France (88.4%) and UK (7.9%). (ANSM study and the EPI-HPV-040 study, which involved a large number of subjects, were carried out in France and the UK, respectively) (Table 7).
- There is also an imbalance in the distribution by country between the exposed and non-exposed subjects.
    - The UK, France, Finland, Costa Rica and Philippines recruited 42.3%, 36.0%, 9.6%, 2.4% and 1% of the exposed subjects whereas all the other countries reported below 1% of the exposed subjects.
    - France and the UK recruited 93.8% and 4.3%, respectively, of the non-exposed subjects whereas all the other countries reported below 1% of the non-exposed subjects.

7. PRIMARY OBJECTIVE RESULTS (AMENDED ON 31 MARCH 2017)

The results of the analysis of the three diseases are presented in Table 8 to Table 21 and Figure 2 to Figure 6.

Autoimmune Thyroiditis:

- The OR of autoimmune thyroiditis ranged from 0.004 (EPI-HPV-011) to 3.75 (EPI-HPV-040) (Figure 2).
- The overall OR from variance-inverse meta-analysis, was ***2.01*** (95% CI: ***1.30; 3.11***). The other methods gave similar estimates (2.46 from the pooled analysis [Table 8] and ***2.17*** for the Beta-Binomial model [Table 14]). This excess risk was estimated to be ***17*** cases per 100,000 exposed subjects (Table 8).
- The sensitivity analysis, excluding the ANSM study, provided similar results of overall OR estimates ranging between 2.04 and 2.33 (Figure 6).

GBS:

- GBS cases were reported only in the ANSM study and the EPI-HPV-011 studies. None of the cases reported in the EPI-HPV-011 had received vaccination during the 42 days follow-up. This finding did not allow computation of OR estimate (Figure 5).
- The overall OR from the variance-inverse meta-analysis, during the 42 days follow-up period was ***11.14*** (95% CI: ***2.01; 61.92***) (Figure 5). The other methods gave similar estimates (***11.07*** [Table 9]). The Beta-Binomial model ***gave a lower risk estimate (OR=4.6) but this estimate was questionable because of convergence issues (Table 19***).
- During the two years follow-up period, the sensitivity analysis reported ***lower*** overall OR estimates ranging between ***1.89*** (pooled analysis) to ***3.83*** (variance-inverse meta-analysis) (Figure 3).
- The results of the GBS analysis were driven by the two cases observed in the vaccinated cohort of the ANSM study. ***The time to onset of these two cases was unknown. In the most conservative approach, we assumed that these two cases had occurred*** within the 42-days follow-up.
- The time to onset of the 18 GBS cases reported in the non-exposed subjects of the ANSM study was unknown. Under the conservative assumption of constant incidence rate during the 30 months of follow-up, only ***1.8*** cases would have occurred during similar 42-days follow-up period in the non-exposed cohort.

IBD:

- The OR of IBD ranged from ***0.80 (Pooled clinical trials)*** to 2.00 (EPI-HPV-040) (Figure 4).

- The overall OR from variance-inverse meta-analysis, was ***1.11*** (95% CI: ***0.75; 1.66***) for the random-effect model and for the fixed-effect model (Table 11). Other methods gave similar estimates (***1.03*** from the pooled analysis [Table 8] and ***1.20*** for the Beta-Binomial model [Table 16]).

8. STUDY STRENGTHS, LIMITATIONS, INTERPRETATIONS AND OVERALL CONCLUSIONS (AMENDED ON 31 MARCH 2017)

8.1. Study strengths

- The main strength of this meta-analysis was the total number of subjects, data from more than 150,000 exposed and 1,500,000 unexposed subjects was used for the analyses. Large cohorts are needed to assess possible risk of such rare events such as autoimmune diseases.
- Another strength of this study was the consistency of the overall risk estimates (OR) provided by the various methods ***for autoimmune thyroiditis and inflammatory bowel disease***. Overall OR estimates for auto-immune thyroiditis was 2.01 for the main analysis and ***ranged between 2.04*** to ***2.46*** for the sensitivity analyses. The overall OR estimates for IBD ***was 1.1 and ranged between 1.03 and 1.20 in the sensitivity analysis. For GBS, the overall OR from the variance-inverse meta-analysis (Figure 4) was 11.14 (95% CI: 2.00; 61.9) during the 42 days after any vaccination. The 'pooled table' method gave similar estimates (11.07), whereas the beta-binomial model gave lower a risk estimate (4.60). The latter estimate should be considered with caution because of convergence issue.***

8.2. Limitations

The current meta-analysis had the following limitations:

- There was no access to the raw data for the two studies (EPI-HPV-011 study and ANSM study) and only aggregated data (total number of cases and total number of subject per group) were available. This precluded the adjustment for any covariate as well as sensitivity analysis for the other risk period. The risk period used in the present analysis was two years after first vaccination for autoimmune thyroiditis and IBD.
- Case definitions were not consistent across all studies (Section 5.2.1.1). To overcome this issue, mapping of various definitions/codes was proposed. The general term 'thyroiditis' was used in the ANSM study, this term indeed included a variety of thyroiditis diseases (18 different ICD-10 codes including also non-autoimmune thyroiditis). However the lack of individual ICD-10 data prohibited a more specific analysis using all studies. No case of thyroiditis from the ANSM study was excluded from the analysis. It was assumed that the majority of cases of thyroiditis were from autoimmune origin. A sensitivity analysis on autoimmune thyroiditis was performed using all studies except the ANSM study. The sensitivity analysis performed removing results from the ANSM study provided fairly similar results to the principal analysis, and it is thus unlikely that the difference in thyroiditis case definition may have biased the results.
- The date of identification of the outcome varied among studies. Some studies used the date of diagnosis (ANSM and EPI-HPV-011studies), while other studies used the

date of first clinical sign/symptom (EPI-HPV-040) to identify the cases. Ideally the date of first symptoms was to be used as the disease onset. Date of symptoms onset was more easily known in prospective clinical trials than in retrospective database studies (although in the EPI-HPV-040 study, using the CPRD database, symptom onset was derived from a medical review of the subject profiles). Some cases considered as "occurring" during the risk period could have had an onset prior to vaccination (or equivalent date in unvaccinated subjects) and in contrary, events with onset date within the risk period, but diagnosis reported after the risk period could have been missed during this analysis.

- The level of case validation of diagnosis also ranged from a full medical validation in the prospective clinical trials to no validation at all in the ANSM study and intermediate level in the EPI-HPV-040 study.
- Heterogeneity in study types was also considered as a limitation. The goal was to use all the available data, this implied combining different study designs such as a pool of randomized clinical trials, a cluster randomized study, two observational cohort studies and a case-control study. Heterogeneity among studies was expected. This heterogeneity assessed by the i^2 index appeared to be very low ($I^2 = 0.00\%$ ***for all analysis***). This low heterogeneity ***estimate should be carefully interpreted in view of its very broad confidence limits (95% upper limit around 80%). Low heterogeneity*** is probably linked to the limited number of studies (only five). This resulted in virtually identical fixed-effect and random-effect estimates of the overall OR.
- A two year risk period after first dose was used for autoimmune thyroiditis and IBD. However for GBS, this risk period was not appropriate. Most studies considered a risk window of 42 days following vaccination for assessing risk of GBS [Schonberger, 1979; Hughes, 2006; Romio, 2009]. In order to assess the risk during this 42-day window, the number of cases in the unvaccinated cohort during the full 2-year follow-up period of the ANSM study were to be estimated from the overall incidence. This estimation assumed a constant incidence rate over the full follow-up period which could be a potential limitation.
- The statistical parameter of interest was the OR. OR was estimated from both cohort and case-control studies. Since the low incidence of the outcomes (<1%), OR was virtually identical to RR. However, the ANSM study was a cohort study but the exposure was a time-depending variable. When a Cox regression analysis with time-depending exposure was used, the estimated parameter was HR. In this study, exposure was not considered as time-dependent. The only option to include the ANSM study results was to recompute OR.
- OR calculation did not take into account the actual follow-up period. All studies except one (EPI-HPV-040) had a follow-up period of at least two years. However, subjects could withdraw from the study at any time. It was assumed that early termination did not depend on the exposure. This assumption was reasonable for all studies except for the ANSM study, due to time-dependent definition of exposure (non-exposed subjects could switch to exposed when they were vaccinated, and then the non-exposed censoring was depending on the exposure).

- Three methods were proposed to overcome the issues related to single-zero and double-zero. Different methods could provide different overall estimates. However, the results show consistent estimates among various methods.
- There was imbalance between the exposed and non-exposed subjects regarding the age (mean age = 16.05 and 13.71 years in the exposed and non-exposed subjects, respectively) and distribution per country (93.8% of the non-exposed subjects were located in France whereas 42.3% of the exposed subjects were from the UK). However, the imbalance in the distribution by country does not seem to bias the results since exclusion of the ANSM study did change the results and the meta-analysis method took into account between-study heterogeneity.
- Results of the analysis of GBS were difficult to interpret because of the over-weight of the sole ANSM study where cases of GBS were reported and the assumption of constant incidence rate during the 30 months of follow-up in the non-exposed cohort. The very broad CI of the OR estimate demonstrates the uncertainty of the risk estimation.

8.3. Interpretations

The current results can be interpreted using the below pre-defined criteria developed for an observational safety study with the quadrivalent HPV vaccine [Arnheim-Dahlström, 2013].

Arnheim-Dahlström et al, in the analysis of serious adverse events following vaccination with the quadrivalent HPV vaccine (in health databases in Denmark and Sweden), [Arnheim-Dahlström, 2013] have defined a safety signal outcome with a significant rate ratio increase (lower bound of 95% confidence interval >1.0) with at least five vaccine exposed cases. Three criteria were considered as strengthening signals: analysis based on 20 or more vaccine exposed cases (reliability), rate ratio 3.0 or more (strength), and significantly increased rate ratio in country specific analyses (consistency).

Considering the above criteria following conclusions can be drawn:

- **Auto-immune thyroiditis**: Both the main and the sensitivity analysis showed evidence of a small increased risk of autoimmune thyroiditis (OR estimate around 2.0 with an upper limit of the 95% CI around ***3.0*** for the main analysis and ***4.0*** for the sensitivity analysis). According to Arnheim-Dahlström criteria [Arnheim-Dahlström, 2013], this increased risk is regarded as a safety signal but not as a strengthening signal since the OR is less than 3.0. There was insufficient evidence to conclude on a causal relationship between *Cervarix* and autoimmune thyroiditis.
- **GBS**: The results were driven by the 2 exposed cases in ANSM which ***were conservatively assumed to have occurred during the*** 42 days follow-up period. A conclusion regarding the risk of GBS cannot be drawn because of the broad confidence interval (CI) (95% CI: ***2.01; 61.92***). According to Arnheim-Dahlström criteria [Arnheim-Dahlström, 2013], this risk estimate is not reliable since there were less than five vaccine exposed cases during the predefined risk period. The results of the study do not confirm an association between *Cervarix* and GBS.

- **IBD**: There was no evidence of an increased risk of IBD since the OR estimates was close to unity with an upper limit of the 95% CI lower than 2.0.

8.4. Overall conclusions

- The present meta-analysis of 18 GSK clinical trials, one cluster randomized trial, two GSK post-marketing epidemiological studies and one non-GSK post-marketing study which represents more than 150,000 *Cervarix* exposed subjects and 1,500,000 non-exposed subjects does not support an increased risk of GBS and IBD.

- A small increased risk of autoimmune thyroiditis is observed as previously described in EPI-HPV-040 and ANSM studies. However, despite this observed association there is insufficient evidence to prove a causal relationship with *Cervarix* vaccination.

9. TABLES AND FIGURES

9.1. Study population

Table 3 Subjects disposition in cohort studies

Study ref	N of exposed subjects	% exposed	N of non-exposed subjects	% non- exposed
ANSM	55545	3.79	1410596	96.21
EPI-HPV-040	64998	50.00	64994	50.00
HPV-040	12400	60.43	8119	39.57
Pooled clin	21455	51.00	20613	49.00
Total	154398	9.31	1504322	90.69

Table 4 Subjects disposition in case-control studies

Source	Auto-immune Disease	N of Cases	(%)	N of Controls	(%)
EPI-HPV-011	1.AI thyro	106	10.79	876	89.21
EPI-HPV-011	2.GBS	13	9.09	130	90.91

Table 5 Demographic characteristics

			Group		
Study Ref			Exposed	Non- exposed	All
EPI-HPV-040	Age (years)	N	64998	64994	129992
		Mean	15.33	15.42	15.37
		Std	2.09	2.10	2.10
		Median	15.3	15.7	15.4
		Min	9.4	9.4	9.4
		Max	24.9	24.8	24.9
HPV-040	Age (years)	N	12400	8119	20519
		Mean	14.07	14.09	14.08
		Std	0.75	0.75	0.75
		Median	14.0	14.0	14.0
		Min	12.0	12.0	12.0
		Max	16.0	16.0	16.0
Pooled clin	Age (years)	N	21455	20613	42068
		Mean	22.12	22.44	22.28
		Std	8.07	8.02	8.05
		Median	21.0	21.0	21.0
		Min	9.0	8.0	8.0
		Max	72.0	68.0	72.0
All	Age (years)	N	98853	93726	192579
		Mean	16.65	16.85	16.74
		Std	5.06	5.12	5.09
		Median	15.6	16.2	16.0
		Min	9.0	8.0	8.0
		Max	72.0	68.0	72.0

ANSM and EPI-HPV-011 studies not included

Table 6 Demographic characteristics of cohort studies: age

Treat	N	Mean Age (Years)
Exposed	154398	16.05
Non-exposed	1504322	13.71

The case-control EPI-HPV-011 not included

Table 7 Demographic characteristics of cohort studies: countries

study ref	Country	N exposed	%	N non- exposed	%	N total	%
ANSM	France	55545	100.00	1410596	100.00	1466141	100.00
EPI-HPV-040	United Kingdom	64998	100.00	64994	100.00	129992	100.00
HPV-040	Finland	12400	100.00	8119	100.00	20519	100.00
Pooled clin	Australia	429	2.00	423	2.05	852	2.03
	Belgium	161	0.75	164	0.80	325	0.77
	Brazil	1161	5.41	1148	5.57	2309	5.49
	Canada	565	2.63	525	2.55	1090	2.59
	China	980	4.57	982	4.76	1962	4.66
	Colombia	100	0.47	100	0.49	200	0.48
	Costa Rica	3729	17.38	3737	18.13	7466	17.75
	Czech Republic	60	0.28	59	0.29	119	0.28
	Denmark	142	0.66	70	0.34	212	0.50
	Finland	2409	11.23	2399	11.64	4808	11.43
	France	19	0.09	20	0.10	39	0.09
	Germany	639	2.98	637	3.09	1276	3.03
	Honduras	135	0.63	133	0.65	268	0.64
	Hong Kong	150	0.70	150	0.73	300	0.71
	Hungary	178	0.83	90	0.44	268	0.64
	India	176	0.82	178	0.86	354	0.84
	Italy	18	0.08	19	0.09	37	0.09
	Japan	519	2.42	521	2.53	1040	2.47
	Korea	309	1.44	237	1.15	546	1.30
	Korea Republic of	27	0.13	27	0.13	54	0.13
	Malaysia	135	0.63	136	0.66	271	0.64
	Mexico	1133	5.28	1136	5.51	2269	5.39
	Netherlands	394	1.84	281	1.36	675	1.60
	Norway	36	0.17	36	0.17	72	0.17
	Panama	84	0.39	84	0.41	168	0.40
	Peru	88	0.41	88	0.43	176	0.42
	Philippines	1601	7.46	1604	7.78	3205	7.62
	Portugal	102	0.48	110	0.53	212	0.50
	Russian Federation	152	0.71	148	0.72	300	0.71
	Senegal	229	1.07	113	0.55	342	0.81
	Singapore	117	0.55	117	0.57	234	0.56
	South Africa	91	0.42	59	0.29	150	0.36
	Spain	267	1.24	273	1.32	540	1.28
	Sweden	505	2.35	293	1.42	798	1.90
	Taiwan	852	3.97	851	4.13	1703	4.05
	Tanzania	221	1.03	113	0.55	334	0.79
	Thailand	1179	5.50	1173	5.69	2352	5.59
	United Kingdom	269	1.25	273	1.32	542	1.29
	United States	2094	9.76	2106	10.22	4200	9.98

study ref	Country	N exposed	%	N non- exposed	%	N total	%
Total	Australia	429	0.28	423	0.03	852	0.05
	Belgium	161	0.10	164	0.01	325	0.02
	Brazil	1161	0.75	1148	0.08	2309	0.14
	Canada	565	0.37	525	0.03	1090	0.07
	China	980	0.63	982	0.07	1962	0.12
	Colombia	100	0.06	100	0.01	200	0.01
	Costa Rica	3729	2.42	3737	0.25	7466	0.45
	Czech Republic	60	0.04	59	0.00	119	0.01
	Denmark	142	0.09	70	0.00	212	0.01
	Finland	14809	9.59	10518	0.70	25327	1.53
	France	55564	35.99	1410616	93.77	1466180	88.39
	Germany	639	0.41	637	0.04	1276	0.08
	Honduras	135	0.09	133	0.01	268	0.02
	Hong Kong	150	0.10	150	0.01	300	0.02
	Hungary	178	0.12	90	0.01	268	0.02
	India	176	0.11	178	0.01	354	0.02
	Italy	18	0.01	19	0.00	37	0.00
	Japan	519	0.34	521	0.03	1040	0.06
	Korea	309	0.20	237	0.02	546	0.03
	Korea Republic of	27	0.02	27	0.00	54	0.00
	Malaysia	135	0.09	136	0.01	271	0.02
	Mexico	1133	0.73	1136	0.08	2269	0.14
	Netherlands	394	0.26	281	0.02	675	0.04
	Norway	36	0.02	36	0.00	72	0.00
	Panama	84	0.05	84	0.01	168	0.01
	Peru	88	0.06	88	0.01	176	0.01
	Philippines	1601	1.04	1604	0.11	3205	0.19
	Portugal	102	0.07	110	0.01	212	0.01
	Russian Federation	152	0.10	148	0.01	300	0.02
	Senegal	229	0.15	113	0.01	342	0.02
	Singapore	117	0.08	117	0.01	234	0.01
	South Africa	91	0.06	59	0.00	150	0.01
	Spain	267	0.17	273	0.02	540	0.03
	Sweden	505	0.33	293	0.02	798	0.05
	Taiwan	852	0.55	851	0.06	1703	0.10
	Tanzania	221	0.14	113	0.01	334	0.02
	Thailand	1179	0.76	1173	0.08	2352	0.14
	United Kingdom	65267	42.27	65267	4.34	130534	7.87
	United States	2094	1.36	2106	0.14	4200	0.25

The case-control EPI-HPV-011 was not included

9.2. Primary objective results

Table 8 Crude Odds Ratio (OR) of autoimmune thyroiditis, GBS, and IDB: pooled table (Amended on 31 March 2017)

Odds Ratio										
Auto-immune Disease	**study ref**	**N events in exposed subj**	**Total N of exposed subj**	**N events in non-exposed subj**	**Total N of non-exposed subj**	**Estimate of Relative Risk**	**Lower CL, Odds Ratio**	**Upper CL, Odds Ratio**	**Exact Lower CL, Odds Ratio**	**Exact Upper CL, Odds Ratio**
1.AI thyro	ANSM	12.1	55545	***161.6***	1410596	***1.91***	***1.06***	***3.42***	***0.95***	***3.38***
	EPI-HPV-040	15.0	64998	4.0	64994	3.75	1.24	11.30	1.19	15.52
	HPV-040	5.0	12400	3.0	8119	1.09		4.57	0.21	7.03
	Pooled clin	12.0	21455	6.0	20613	1.92	0.72	5.12	0.67	6.24
	Overall	44.1	154398	***174.6***	1504322	***2.46***	***1.77***	***3.43***	***1.72***	***3.43***
2.GBS	ANSM	2.4	55545	***12.5***	1410596	***4.93***	***1.25***	***19.53***	***0.46***	***19.01***
	EPI-HPV-040	0.0	64998	0.0	64994					
	HPV-040	0.0	12400	0.0	8119					
	Pooled clin	0.0	21455	0.0	20613					
	Overall	2.4	154398	***12.5***	1504322	***1.89***	***0.48***	***7.49***	***0.18***	***7.29***
3.IBD	ANSM	14.5	55545	***384.4***	1410596	***0.96***	***0.57***	***1.62***	***0.55***	***1.66***
	EPI-HPV-040	10.0	64998	5.0	64994	2.00	0.68	5.85	0.62	7.46
	HPV-040	13.0	12400	6.0	8119	1.42	0.54	3.74	0.50	4.55
	Pooled clin	5.0	21455	6.0	20613	0.80		2.62	0.19	3.15
	Overall	42.5	154398	***401.4***	1504322	***1.03***	***0.75***	***1.42***	***0.74***	***1.43***

The case-control study EPI-HPV-011 is not included

Table 9 Crude Odds Ratio (OR) of GBS 42 days: pooled table (Amended on 31 March 2017)

Odds Ratio										
Auto-immune Disease	**study ref**	**N events in exposed subj**	**Total N of exposed subj**	**N events in non-exposed subj**	**Total N of non-exposed subj**	**Estimate of Relative Risk**	**Lower CL, Odds Ratio**	**Upper CL Odds Ratio**	**Exact Lower CL, Odds Ratio**	**Exact Upper CL, Odds Ratio**
2.GBS	ANSM	2.0	55545	***1.8***	1410596	***28.84***	***3.81***	***218.6***	1.84	350.4
	EPI-HPV-040	0.0	64998	0.0	64994					
	HPV-040	0.0	12400	0.0	8119					
	Pooled clin	0.0	21455	0.0	20613					
	Overall	2.0	154398	***1.8***	1504322	***11.07***	***1.46***	***83.87***	0.71	134.4

The case-control study EPI-HPV-011 is not included

Table 10 Crude Odds Ratio (OR) of auto-immune thyroiditis: pooled table excluding ANSM

Auto-immune Disease	**study ref**	**N events in exposed subj**	**Total N of exposed subj**	**N events in non-exposed subj**	**Total N of non-exposed subj**	**Estimate of Relative Risk**	**Lower CL, Odds Ratio**	**Upper CL Odds Ratio**	**Exact Lower CL, Odds Ratio**	**Exact Upper CL, Odds Ratio**
1.AI thyro	EPI-HPV-040	15.0	64998	4.0	64994	3.75	1.24	11.30	1.19	15.52
	HPV-040	5.0	12400	3.0	8119	1.09	0.26	4.57	0.21	7.03
	Pooled clin	12.0	21455	6.0	20613	1.92	0.72	5.12	0.67	6.24
	Overall	32.0	98853	13.0	93726	2.33	1.23	4.45	1.19	4.85

Table 11 Inverse-Variance analysis Odds Ratios (OR) - two years risk period (Amended on 31 March 2017)

Odds Ratio								
Auto-immune Disease	**study ref**	**N events in exposed subj**	**Total N of exposed subj**	**N events in non-exposed subj**	**Total N of non-exposed subj**	**Estimate of Relative Risk**	**Lower CL, Odds Ratio**	**Upper CL Odds Ratio**
1.AI thyro	ANSM	12.1	55545.0	161.6	1410596	***1.9051***	***1.0627***	***3.4154***
	EPI-HPV-011	0.0	9.0	106.5	974.0	0.0041	0.0000	1.56791E10
	EPI-HPV-040	15.0	64998.0	4.0	64994.0	3.7504	1.2447	11.3005
	HPV-040	5.0	12400.0	3.0	8119.0	1.0913	0.2607	4.5676
	Pooled clin	12.0	21455.0	6.0	20613.0	1.9220	0.7212	5.1220
	Fixed effec	.	.	.	.	***2.0113***	***1.3020***	***3.1072***
	Random effe	.	.	.	.	***2.0113***	***1.3020***	***3.1072***
2.GBS	ANSM	2.4	55545.0	12.5	1410596	***4.9349***	***1.2468***	***19.5317***
	EPI-HPV-011	0.0	1.0	13.5	143.0	0.0334	0.0000	8.83876E12
	EPI-HPV-040	0.3	64998.5	0.2	64994.5	1.0000	0.0039	255.6031
	HPV-040	0.3	12400.6	0.2	8119.4	1.0000	0.0035	289.5783
	Pooled clin	0.3	21455.5	0.2	20613.5	1.0000	0.0039	255.8929
	Fixed effec					***3.8328***	***1.0824***	***13.5726***
	Random effe					***3.8328***	***1.0824***	***13.5726***
3.IBD	ANSM	14.5	55545.0	***384.4***	1410596	***0.9610***	***0.5693***	***1.6223***
	EPI-HPV-011							
	EPI-HPV-040	10.0	64998.0	5.0	64994.0	2.0000	0.6836	5.8517
	HPV-040	13.0	12400.0	6.0	8119.0	1.4191	0.5392	3.7350
	Pooled clin	5.0	21455.0	6.0	20613.0	0.8006	0.2443	2.6236
	Fixed effec	.	.	.	.	***1.1127***	***0.7469***	***1.6578***
	Random effe	.	.	.	.	***1.1127***	***0.7469***	***1.6578***

Obs	**Auto-immune Disease**	**Cochran Q**	**P-value**	**i^2**	***95% LL I2***	***95% UL I2***
1	1.AI thyro	***2.143***	***0.709***	0.00	***0.00***	***79.20***
2	2.GBS	***0.875***	***0.928***	0.00	***0.00***	***79.20***
3	3.IBD	***1.985***	***0.575***	***0.00***	***0.00***	***84.69***

Table 12 Inverse-Variance analysis Odds Ratios (OR) - GBS 42 days (Amended on 31 March 2017)

Odds Ratio							
Auto-immune Disease	***N events in exposed subjects***	**N events in exposed subj**	***N events in non-exposed subj***	***Total N of non-exposed subj***	***Estimate of Relative Risk***	***Lower CL, Odds Ratio***	***Upper CL, Odds Ratio***
2.GBS ANSM	2.00	55545.00	***1.76***	1410596	***28.8441***	***3.8057***	***218.6151***
EPI-HPV-011	0.00	0.00	13.50	144.00			
EPI-HPV-040	0.25	64998.50	0.25	64994.50	1.0000	0.0039	255.6031
HPV-040	0.30	12400.60	0.20	8119.40	1.0000	0.0035	289.5783
Pooled clin	0.26	21455.51	0.24	20613.49	1.0000	0.0039	255.8929
Fixed effec					***11.1415***	***2.0049***	***61.9156***
Random effe					***11.1415***	***2.0049***	***61.9156***

Obs	**Auto-immune Disease**	***N studies***	**Cochran Q**	**P-value**	**i^2**	***95% LL I2***	***95% UL I2***
2	2.GBS	***4***	***2.995***	***0.392***	***0.00***	***0.00***	***84.69***

Table 13 Inverse-Variance analysis Odds Ratios (OR) of auto-immune thyroiditis - two years risk period excluding ANSM (Amended on 31 March 2017)

Odds Ratio								
Auto-immune Disease	study ref	N events in exposed subj	Total N of exposed subj	N events in non-exposed subj	Total N of non-exposed subj	Estimate of Relative Risk	Lower CL, Odds Ratio	Upper CL Odds Ratio
1.AI thyro	EPI-HPV-011	0.00	9.01	106.50	973.99	0.004	0.000	1.57E10
	EPI-HPV-040	15.00	64998.00	4.00	64994.00	3.750	1.245	11.301
	HPV-040	5.00	12400.00	3.00	8119.00	1.091	0.261	4.568
	Pooled clin	12.00	21455.00	6.00	20613.00	1.922	0.721	5.122
	Fixed effec					2.152	1.121	4.131
	Random effe					2.152	1.121	4.131

Obs	Auto-immune Disease	Cochran Q	P-value	i^2	*95% LL I2*	*95% UL I2*
1	1.AI thyro	2.069	0.558	0.00	***0.00***	***84.69***

Table 14 Beta-binomial regression model: Odds Ratios (OR) - thyroiditis (two years, without EPI-HPV-011) (Amended on 31 March 2017)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	***2.166***	***1.115***	***4.206***	***0.022***

Table 15 Beta-binomial regression model: Odds Ratios (OR) - GBS (two years, without EPI-HPV-011) (Amended on 31 March 2017)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	***1.741***	***0.171***	***17.666***	***0.639***

Table 16 Beta-binomial regression model: Odds Ratios (OR) - IBD (two years, without EPI-HPV-011) (Amended on 31 March 2017)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	***1.201***	***0.498***	***2.897***	***0.684***

Table 17 Beta-binomial regression model: Odds Ratios (OR) - thyroiditis (two years, with EPI-HPV-011) (Amended on 31 March 2017)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	***0.860***	***0.235***	***3.145***	***0.820***

Table 18 Beta-binomial regression model: Odds Ratios (OR) - GBS (two years, with EPI-HPV-011) (Amended on 31 March 2017)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	***0.515***	0.046	***5.771***	***0.591***

Table 19 Beta-binomial regression model: Odds Ratios (OR) - GBS (42 days) (Amended on 31 March 2017)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	***4.601***	***0.016***	***1336.9***	***0.598***

Table 20 Beta-binomial regression model: Odds Ratios (OR) - thyroiditis (2years, excluding ANSM and EPI-HPV-011)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	2.038	0.819	5.068	0.126

Table 21 Beta-binomial regression model: Odds Ratios (OR) - thyroiditis (2years, excluding ANSM but with EPI-HPV-011)

Effect Measure	Method	Estimate	Lower 95%-CI	Upper 95%-CI	Wald p-Value
Odds Ratio	Beta-Binomial Model	0.800	0.182	3.516	0.768

Figure 2 Risk of Auto-immune thyroiditis during two years after the first dose of *Cervarix* (bars show 95% CI) (Amended on 31 March 2017)

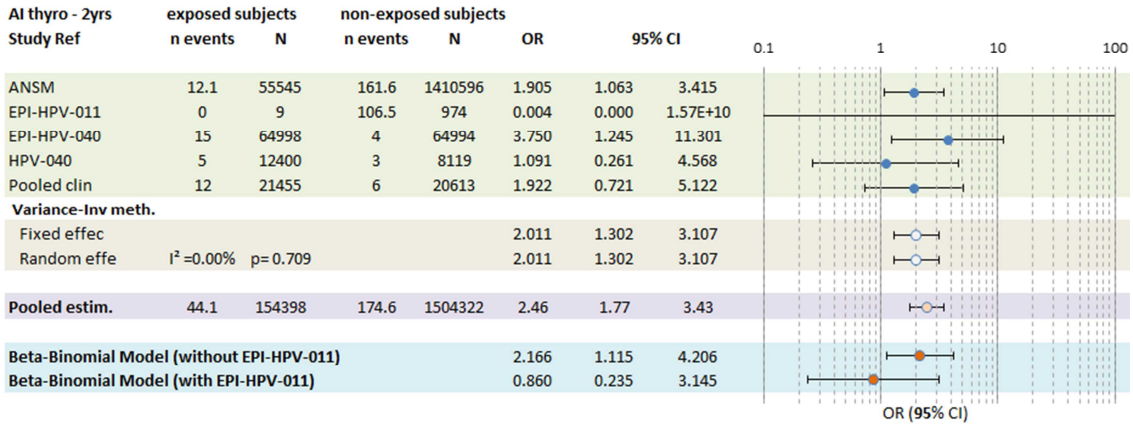


Figure 3 **Risk of Guillain-Barré syndrome during two years after the first dose of *Cervarix* (bars show 95% CI) (Amended on 31 March 2017)**

GBS - 2 yrs FU	exposed subjects		non-exposed subjects				
Study Ref	n events	N	n events	N	OR	95% CI	
ANSM	2.4	55545	12.5	1410596	4.935	1.247	19.532
EPI-HPV-011	0	1	13.5	143	0.033	0.000	8.84E+12
EPI-HPV-040	0.3	64998.5	0.2	64994.5	1.000	0.004	255.603
HPV-040	0.3	12400.6	0.2	8119.4	1.000	0.004	289.578
Pooled clin	0.3	21455.5	0.2	20613.5	1.000	0.004	255.893
Variance-Inv meth.							
Fixed effec					3.833	1.082	13.573
Random effe	I^2 =0.00%	p= 0.928			3.833	1.082	13.573
Pooled estim.	2.4	154398	12.5	1504322	1.89	0.48	7.49
Beta-Binomial Model (without EPI-HPV-011)					1.741	0.171	17.666
Beta-Binomial Model (with EPI-HPV-011)					0.511	0.046	5.722

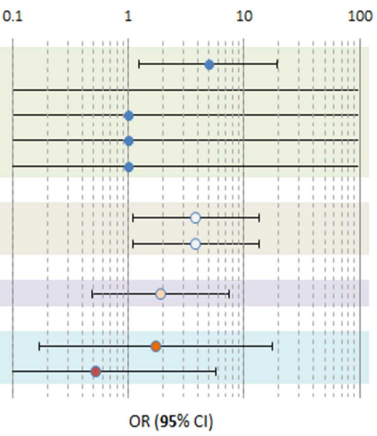


Figure 4 **Risk of inflammatory bowel disease during two years after the first dose of *Cervarix* (bars show 95% CI) (Amended on 31 March 2017)**

IBD - 2 Yr FU	exposed subjects		non-exposed subjects				
Study Ref	n events	N	n events	N	OR	95% CI	
ANSM	14.5	55545	384.4	1410596	0.961	0.569	1.622
EPI-HPV-040	10	64998	5	64994	2.000	0.684	5.852
HPV-040	13	12400	6	8119	1.419	0.539	3.735
Pooled clin	5	21455	6	20613	0.801	0.244	2.624
Variance-Inv meth.							
Fixed effec					1.113	0.747	1.658
Random effe	I^2 =0.00%	0.575			1.113	0.747	1.658
Pooled estim.	42.5	154398	401.4	1504322	1.03	0.75	1.42
Beta-Binomial Model (without EPI-HPV-011)					1.201	0.498	2.897

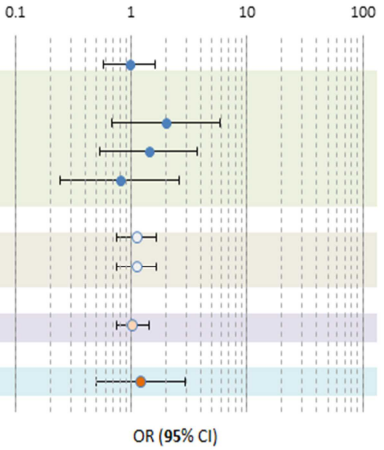


Figure 5 **Risk of Guillain-Barré syndrome during 42 days after each dose of *Cervarix* (bars show 95% CI) (Amended on 31 March 2017)**

GBS - 42 days	exposed subjects		non-exposed subjects				
Study Ref	n events	N	n events	N	OR	95% CI	
ANSM	2	55545	1.76	1410596	28.844	3.806	218.615
EPI-HPV-011	0	0	13.5	144			
EPI-HPV-040	0.25	64998.5	0.25	64994.5	1.000	0.004	255.603
HPV-040	0.3	12400.6	0.2	8119.4	1.000	0.004	289.578
Pooled clin	0.26	21455.51	0.24	20613.49	1.000	0.004	255.893
Variance-Inv meth.							
Fixed effec					11.142	2.005	61.916
Random effe	I^2 =0.00%	p= 0.392			11.142	2.005	61.916
Pooled estim.	2	154398	1.8	1504322	11.07	1.46	83.87
Beta-Binomial Model (without EPI-HPV-011)§					4.601	0.016	1336.9

§: because of convergence issues the estimate is questionable

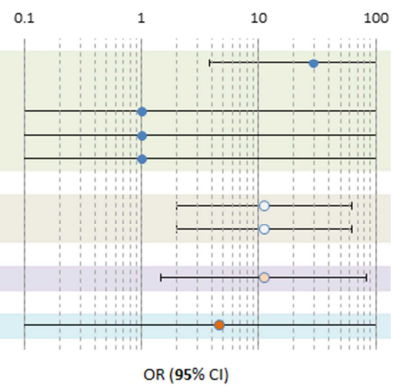
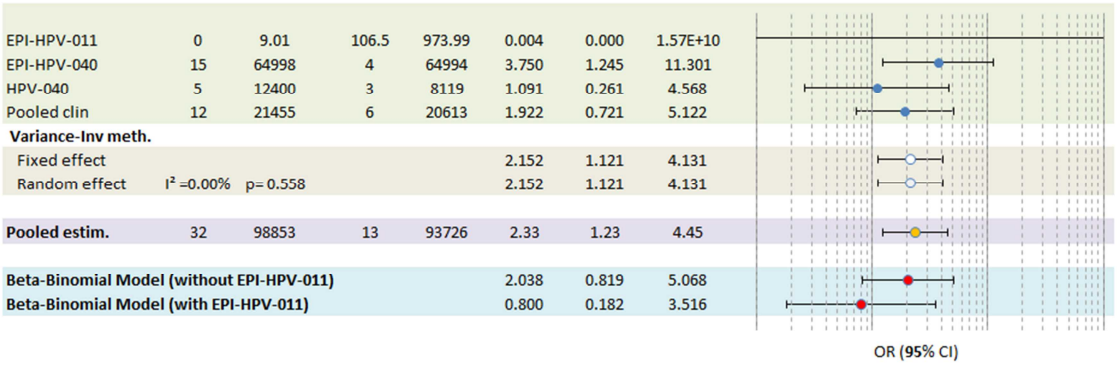


Figure 6 **Risk of autoimmune thyroiditis during two years after the first dose of *Cervarix* (bars show 95% CI) – ANSM study excluded (Amended on 31 March 2017)**



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11. STUDY REPORT AUTHORS /CONTRIBUTING AUTHORS

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Epidemiologists: PPD

Regulatory Affairs Representative: PPD

N + 1 of Epidemiologist: PPD

12. SERIOUS ADVERSE EVENTS / OTHER SIGNIFICANT ADVERSE EVENTS / PREGNANCY

Not applicable.

MODULAR APPENDICES

List of modular appendices available for the study report and ICH-specific appendices - Study Information equivalent numbering

Modular appendices	ICH numbering
Protocol and protocol amendments.	16.1.1
Sample Case Report form (unique pages only).	16.1.2
List of IECs or IRBs & List of Investigators and other important participants in the study	16.1.3 & 16.1.4
Representative written information for patient and sample consent forms.	16.1.3
Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study	16.1.4
Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement	16.1.5
Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used (if applicable).	16.1.6
Randomization list (patient identification and treatment assigned).	16.1.7
Audit certificates (if available).	16.1.8
Documentation of statistical methods	16.1.9
Documentation of inter-laboratory standardization methods and quality assurance procedures, if used	16.1.10
Publications based on the study.	16.1.11
Important publications referenced in the report	16.1.12
Individual listings	16.2
Case report forms (CRFs /eCRFs) CRFs /eCRFs for deaths, other SAEs and withdrawals due to adverse events	16.3 16.3.1

Protocol and protocol amendments

Since this was a meta-analysis study protocol was not prepared.

Sample Case Report Form

Not applicable

List of investigators, IEC/IRB and distribution of subjects

Not applicable.

Representative written information for patient and sample consent forms

Since this was a meta-analysis study no consent was needed from the subjects. Hence model ICF was not prepared.

Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

Not applicable

GlaxoSmithKline Biologicals
Vaccine Value and Health Science
Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the study report amendment 1, including appendices

STUDY TITLE: Meta-analysis of the risk of autoimmune thyroiditis diseases, Guillain-Barré Syndrome, and Inflammatory Bowel Disease following vaccination with *Cervarix*.

Study: 205639 (EPI-HPV-069 VS MA) Development Phase: Not applicable for this epidemiological study

I have read this report amendment 1 and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory:	Frank Struyf
Title of Sponsor Signatory:	Clinical and Epidemiology Research & Development Project Lead, Clinical R&D, GSK Biologicals
Signature:	
Date:	

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Name of Sponsor Signatory: Frank Struyf
Title of Sponsor Signatory: Clinical and Epidemiology Research & Development Project Lead, Clinical R&D, GSK PPD

Signature: PPD

Date: 04 APR 2017

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Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used

Not applicable.

Randomization list

Not applicable

Audit certificates

Not applicable

Documentation of statistical methods

Refer to the study report

Documentation of inter-laboratory standardization methods and quality assurance procedures

Not applicable

Publications based on the study

Not applicable

Important publications referenced in the report

No key references have been identified and the other ones will be available on request.

Individual listings

Not Applicable

CRF /eCRFs for deaths, other SAEs and withdrawals due to adverse events

Not applicable