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Statistical Analysis Plan

Study alias & e-track number(s): EPI-HPV-069 VS MA (205639)

Detailed Title:	Meta-analysis of the risk of autoimmune thyroiditis diseases, Guillain-Barré Syndrome, and Inflammatory Bowel Disease with Cervarix Vaccination.
SAP version	Version 1
SAP date	24-MAR-2016
Scope:	All data pertaining to the above study
Co-ordinating author:	[redacted] (Head of Epi Biostatistics)
Other author(s):	[redacted] Epidemiologist
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The complete statistical analysis plan and results presentation is divided into 2 parts: the first part detailing the analyses to be performed (known as SAP, current document) and a second part, annex(-es) (called TFL) describing the flow and format of tables, figures and listings.

LIST OF ABBREVIATIONS

AE	Adverse event
ANSM	Agence National de Sécurité du Médicament et des Produits de Santé
Anti-TPO	Anti-Thyroid Peroxidase
DLP	Data Lock Point
DSUR	Development Safety Update Report
CDP	Clinical Development Plan
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
CSF	Cerebral Spinal Fluid
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

1. DOCUMENT HISTORY

Date	Description	Protocol Version
24-FEB-2016	Version 1	NA

2. RATIONALE

The risk of autoimmune diseases after vaccination with Cervarix has been evaluated in some studies. No evidence of an overall increased risk of autoimmune diseases has been detected in pooled analyses of clinical studies[1,2] and in post-licensure observational studies[3,4,5]. The primary endpoints of these studies were generally composite endpoints combining various diseases. Analysis of the risk of specific autoimmune diseases is limited due to a low incidence rate of those 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[4] and ANSM[3] studies showed a significant increased risk following Cervarix vaccination (RR= 3.75 (95% CI: 1.25; 11.31)) and HR= 2.43 (1.27; 4.66)) while neither the pooled GSK clinical data nor the EPI-HPV-011 case-control study[5] showed evidence of an increased risk[1,2];

- Guillain-Barré Syndrome: No case was reported in either EPI-HPV-040, EPI-HPV-011, or the GSK pooled clinical data. However the ANSM study detected a statistically significant increased risk following Cervarix vaccination (HR=6.53 (1.44; 29,65));

- Inflammatory Bowel Disease (IBD): The pooled clinical data analyses and all GSK-Sponsored post-licensure observational studies conducted so far 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 Scientific Committee of the study considered that the very low statistical association does not allow the conclusion of an excess risk for this disease.

In order to better assess a potential risk, the company committed (EMA commitment) to perform a meta-analysis for these three diseases. All available data generated from GSK clinical studies and any post-licensure observational studies will be used.

3. OBJECTIVES

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

- Autoimmune Thyroiditis,
- Guillain-Barré Syndrome,
- Inflammatory Bowel Disease.

4. STUDY DESIGN

This meta-analysis will include all data available on 17 November 2015 (Data Lock Point for the pooled clinical database). This analysis will include data from clinical studies and post-marketing observational studies.

5. SELECTION OF STUDIES

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

Data were identified from all GSK (sponsored and ISS) studies as well as non-GSK studies listed in the CHMP Type II variation assessment report-Procedure N°EMEA/H/C/000721/II/0069. A supplementary literature review was performed by Pallas (DLP: 3rd December 2015), Health Research and Consultancy, to check whether any additional studies could potentially be included in the meta-analysis (see Annex 1).

Only one additional study was found in Pallas literature search (Khatum et al. 2012). However this study will not be included the very short follow-up period, only 14 days after vaccination, which is not relevant for the current objective.

The following data sources (Table 2) will be included in the meta-analysis:

1. Clinical studies identified in the 2015 DSUR (DLP: 17Nov2015) and which meet the following criteria
   - Inclusion of a control group not exposed to any HPV vaccine;
   - Inclusion female subjects;
   - The study enrolled subjects aged 9 years and above.

   The extension studies beyond 2 years after the first vaccination and the ongoing double-blind studies were excluded. An exhaustive list of included and excluded clinical studies is provided in Table 3. Because of many studies and low incidence rate of the outcomes, data from all included clinical studies will be pooled and

considered a single source (study) in the meta-analysis, except the HPV-040 study;

2. HPV-040(#): a cluster randomised clinical trial in Finland; only the exposed and non-exposed female subjects will be included;

3. EPI-HPV-040: an observational retrospective cohort study using the CPRD (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 will be used in the meta-analysis, the male non-exposed cohorts will be excluded;

4. EPI-HPV-011: This study includes a surveillance study and a risk study. Only the risk study will be included in the meta-analysis. The risk study is a case-referent study using the PGRx (Pharmacoepidemiological General Research eXtension) methodology.[5]

5. ANSM observational study: a longitudinal observational exposed vs. non-exposed study based on national healthcare administrative databases in France. Exposed cohort included both Cervarix and Gardasil vaccinated subjects. For the purpose of the current meta-analysis only Cervarix exposed subjects will be included. The non-exposed cohort included subjects non-exposed to Cervarix and Gardasil[3]

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

6. ENDPOINTS

The endpoints are the occurrence of cases of autoimmune thyroiditis, Guillain-Barré Syndrome, and Inflammatory Bowel Disease during maximum 2 years after the first dose of Cervarix and an equivalent time period in non-exposed subjects.

The various studies used different clinical definitions (system coding and terminology) for the autoimmune diseases as well as various follow-up periods after vaccination. For harmonization, a clinical definition and risk period will be used, as detailed in the following subsections.

6.1. Case definition

Different case definitions were used in the various studies. GSK clinical studies and HPV-040 used MedDRA terminology, EPI-HPV-040 used Read code and ICD-10 codes,

ANSM used ICD-10, and EPI-HPV-011 used specific study definitions / Brighton Collaboration criteria definition.

The granularity level of the clinical definition varied across the studies. The ANSM used ICD10 code; however thyroiditis cases from autoimmune and non-autoimmune origin have been reported under the generic term 'Thyroiditis'.

The following clinical definitions will be used in the meta-analysis:

Table 1 Clinical definition across the studies

Clinical Definition	MedDRA Primary System Organ Class and Preferred		Read code + ICD10 Codes	ICD-10	Study clinical definition
	GSK pooled clinical studies	**HPV-040**	**EPI-HPV-040#**	**ANSM**	**GPRx**
Autoimmune Thyroiditis	- Basedow's disease (10004161) - Autoimmune thyroiditis (10049046)	- Basedow's disease (10004161) - Autoimmune thyroiditis (10043778)	- Autoimmune thyroiditis - Basedow's disease (ICD-10 : E05, E06.1, E06.3, E06.5)	- Thyroiditis $	- Auto Immune Thyroditis: definite case according to study definitions including Grave's disease and Hashimoto disease £
Guillain-Barré Syndrome	- *No case*	- Guillain-Barre syndrome G61.0: (10018767)	- Guillain-Barré syndrome # (G61.0, G60)	- G61.0 exclusively	- Guillain-Barré definite case according to the Brighton collaboration case definition &
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	- Crohn's diseases (K50) - Ulcerative colitis (K51)	-K50 Crohn disease -K51 Ulcerative colitis	*Not assessed*

#:*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 (Level 1): Requires clinical, electrophysiologic, and CSF data consistent with the onset of GBS

£: Definite case of autoimmune hypothyroiditis = 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

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

6.2. Risk period definition

The risk period to assess autoimmune disease post-vaccination should be determined based on the onset of the disease (either acute or insidious), possible or known pathologic mechanisms involved, and the type of vaccine[15]. Whatever the underlying mechanisms, one may assume that the development of autoimmunity (if a causal association between the event and vaccination existed) requires several weeks to develop; which is similar to the classical time frame of several weeks suggested for the onset of post-infectious autoimmune phenomena[15,16].
For Guillain-Barré syndrome (disease of acute onset), the period of increased risk was shown to be concentrated within 6 weeks after the 1976–1977 swine flu vaccination[17-19]. Therefore a 6 week time window is generally used for the assessment of cases of Guillain-Barré syndrome potentially associated with vaccines. Also, for the Brighton Collaboration working group[20], the recommended risk period for acute neurologic illnesses such as acute disseminated encephalomyelitis is at least 42 days.
Concerning autoimmune thyroiditis and IBD, because the clinical course of the diseases is generally insidious, a longer interval between vaccination and disease onset can be considered. Assuming that in the hypothetical event of a causal association, the development of autoimmunity after vaccination requires a few weeks to develop, about one year after the last vaccination would be a reasonable maximum theoretical risk interval[15].

The periods of follow-up varied among studies. We have defined the risk period for each disease based on the above considerations to be appropriate as follows:

- For autoimmune thyroiditis and IBD, a risk period of up to 2 years after first vaccination will be used. An equivalent period is used for non-exposed subjects. All included studies except the EPI-HPV-040 had a per-protocol follow-up period of at least 2 years. The follow-up period of the EPI-HPV-040 was limited to 12 months after first vaccination.
- For GBS, a risk period of 42 days after each vaccination will be used. The number of GBS cases occurring during this specific period is not available for the ANSM study. The two cases observed in the Cervarix vaccinated subjects are documented in the GSK safety database and both occurred within 42-day post-vaccination. For the unvaccinated cohort, the total number of GBS cases (18) occurring during the full follow-up period (2 years) is known. The number of cases occurring during an equivalent 42-

day post-dose period will be estimated from the overall incidence rate during the total follow-up period and the total number of unvaccinated subjects.

A sensitivity analysis for GBS will be however done using the 2 years risk period after first vaccination, as for the autoimmune thyroiditis and IBD.

Table 2: 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 Only Female subje	Median : 4,21 Years	Autoimmune thyroiditis	5/1	Analsysis dataset	
						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		

Table 3: List of GSK clinical studies (Source: ANALYSIS_E13/ 2015 DSUR)

			Meta-analysis of selected autoimmune diseases		
Study E-track	**Study Alias**	**Group DSUR group = study group**	**Included in meta-analysis**	**Reason for exclusion/Comments**	**N subjects (Exp/Ctrl)**
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 2 years after first dose	
109616	HPV-023 Y7	HPV in CDP=HPV Control in CDP=Placebo	No	Follow-up period after more than 2 years post-dose 1	
109624	HPV-023 Y8	HPV in CDP=HPV Control in CDP=Placebo	No	Follow-up period after more than 2 year post-dose 1	
109625	HPV-023 Y9	HPV in CDP=HPV Control in CDP=Placebo	No	Follow-up period after more than 2 year post-dose 1	
580299_008	HPV-008	HPV in CDP=HPV Control in CDP=HAV	Yes		9316/6325
112024	+ follow-up: HPV-052 (Ext 008)	HPV in CDP=HPV Control in CDP=HAV	No	Follow-up period after more than 2 year post-dose 1	
580299_009	HPV-009	HPV in CDP=HPV Control in CDP=HAV	Yes		3730/3736
108933	HPV-010	HPV in CDP=HPV Control in CDP=Gardasil	No	Control group is HPV vaccine	
580299_011	HPV-011	HPV in CDP=HPV Control in CDP=HBV	Yes		181/89
580299_012	HPV-012	HPV in CDP=HPV	No	No control group (all groups received HPV)	
107476	HPV-012 (Ext M18)	HPV in CDP=HPV	No	No control group	
107477	HPV-012 (Ext M24)	HPV in CDP=HPV	No	No control group	
107479	HPV-012 (Ext M36)	HPV in CDP=HPV	No	No control group	
107481	HPV-012 (Ext M48)	HPV in CDP=HPV	No	No control group	
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		
104904	HPV-013 (Ext M36)	HPV in CDP=HPV	No	Follow-up period after more than 2 year post-dose 1	
104918	HPV-013 (Ext	HPV in CDP=HPV	No	Follow-up period after	

			Meta-analysis of selected autoimmune diseases		
Study E-track	**Study Alias**	**Group DSUR group = study group**	**Included in meta-analysis**	**Reason for exclusion/Comments**	**N subjects (Exp/Ctrl)**
	M48)			more than 2 year post-dose 1	
111375	HPV-025	HPV in CDP=HPV	No	No control group and follow-up period after more than 2 year post-dose 1 (extension of HPV-013)	
103514	HPV-014	HPV in CDP=HPV	No	No control group	
105879	HPV-014 (Ext M18)	HPV in CDP=HPV	No	No control group	
105880	HPV-014 (Ext M24)	HPV in CDP=HPV	No	No control group	
105881	HPV-014 (Ext M36)	HPV in CDP=HPV	No	No control group	
105882	HPV-014 (Ext M48)	HPV in CDP=HPV	No	No control group	
112772	HPV-060	HPV in CDP=HPV	No	No control group and follow-up period after more than 2 year post-dose 1 (extension of HPV-014)	
104820	HPV-015	HPV in CDP=HPV Control in CDP=Placebo	Yes		2881/2871
113617	+ follow-up: HPV-062 (Ext 015)	Blinded in CDP= HPV+Placebo	No	Follow-up period more than 2 years post-dose 1	
104772	HPV-016	HPV in CDP=HPV	No	No control group	
107682	HPV-018	HPV in CDP=HPV	No	No control group	
109823	HPV-019	Blinded in CDP= HPV+Gardasil	No	Control group is HPV vaccine	
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
109628	HPV-024	HPV in CDP=HPV	No	No control group and follow-up period after more than 2 year post-dose 1 (extension of HPV-007)	
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

			Meta-analysis of selected autoimmune diseases		
Study E-track	**Study Alias**	**Group DSUR group = study group**	**Included in meta-analysis**	**Reason for exclusion/Comments**	**N subjects (Exp/Ctrl)**
104798	HPV-032	HPV in CDP=HPV Control in CDP=HAV	Yes		519/521
112949	+ follow-up: HPV-063	HPV in CDP=HPV Control in CDP=HAV	No	Follow-up period more than 2 years post-dose 1	
104951	HPV-033	HPV in CDP=HPV Control in CDP=HAV	Yes		160/161
107336	HPV-034	HPV in CDP=HPV	No	No control group	
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
107638	HPV-039	Blinded in CDP=HPV+Placebo	No	DBF after data lock point	
108464	HPV-042	HPV in CDP= HPV	No	No control group	
109179	HPV-044	HPV in CDP= HPV	No	No control group	
110168	HPV-046	HPV in CDP= HPV	No	No control group	
110659	HPV-048	HPV in CDP= HPV	No	No control group	
111758	HPV-055	HPV in CDP= HPV	No	No control group	
111712	HPV-056	HPV in CDP= HPV	No	No control group	
111955	HPV-057	HPV in CDP= HPV	No	No control group	
112022	HPV-058	HPV in CDP= HPV Control in CDP=Placebo	Yes		374/376
113618	HPV-066	HPV in CDP= HPV	No	No control group	
113621	HPV-067	HPV in CDP= HPV	No	No control group	
114379	HPV-068	HPV in CDP= HPV	No	No control group	
114590	HPV-069	HPV in CDP=HPV Control in CDP=HBV	Yes		606/606
114700	HPV-070	HPV in CDP= HPV	No	No control group	
115411	HPV-071	Blinded in CDP=HPV+Gardasil	No	Ongoing study and Control group is HPV vaccine	
115887	HPV-073	HPV in CDP=HPV Control in CDP=MMR_DTPa	No	Pediatric study (4-6 years of age at time of vaccination)	
108160	HPV-100	HPV in CDP=HPV	No	No control group	
109836	HPV-NG-001	HPV in CDP=HPV	No	No control group	
102114	HPV-TETRA-050 (incl. ESFU)	HPV in CDP=HPV	No	No control group	
102115	HPV-TETRA-051 (incl. ESFU)	HPV in CDP=HPV	No	No control group	
108052	+ follow-	HPV in CDP=HPV	No	No control group	

			Meta-analysis of selected autoimmune diseases		
Study E-track	**Study Alias**	**Group DSUR group = study group**	**Included in meta-analysis**	**Reason for exclusion/Comments**	**N subjects (Exp/Ctrl)**
	up:HPV-TETRA-051 (Ext M18)				
107919	HPV-TETRA-051 (Ext M24)	HPV in CDP=HPV	No	No control group	
107921	HPV-TETRA-051 (Ext M36)	HPV in CDP=HPV	No	No control group	
107918	HPV-TETRA-051 (Ext M48)	HPV in CDP=HPV	No	No control group	
111040	HPV-022	HPV in CDP=HPV	No	No control group	

7. STATISTICAL METHODS

7.1. Study characteristics

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

These statistics will be computed from raw data for GSK studies and from aggregated data for non-GSK studies (see 8.1 for details).

7.2. Risk estimate

The risk of developing the three autoimmune diseases post-vaccination will be estimated using meta-analysis methods.

Since the very rare incidence of the outcomes of interest, Odds Ratios (OR) will be used. OR can be computed from both cohort and case-control studies.

Meta-analysis of rare event are challenging because of studies with no event in one 'single-zero' or even both 'double-zero' arms[6,7,8].

Three approaches will be used:

1. Pooled table or 'crude' method. Data from all studies will be pooled in a single fourfold table and an overall estimate will be computed using standard methods. The main limitation is that this method ignores that data were collected from

several studies and the underlying assumption of a constant estimate across all studies.

2. Meta-analysis method with continuity correction. A continuity correction will be applied to all studies to overcome the single- and double- zero issue. Various continuity corrections have been proposed[6]: constant continuity correction k (for example k=0.5 is commonly used in many software's), continuity correction reciprocal of the opposite treatment arm size, empirical continuity correction. Advantage of this method is that all studies can be included, and any meta-analysis calculation method (inverse variance-weighted method, Peto's method, Mantel-Haenszel's method, etc.) can be applied, all individual studies can also be depicted in forest plots, and heterogeneity among studies can be estimated and tested.
3. Beta-binomial regression method which can use the single- and double-zero studies without using continuity correction. This latter has been recently recommended[11].

Method 2 will be the main analysis, the two other methods will be sensitivity analysis.

8. STATISTICAL CALCULATIONS

8.1. Study characteristics

For continuous variables, the overall mean and SD will be computed from study means and variances as follows:

The overall mean, $\bar{x}$:

$$\bar{x} = \frac{\sum_i n_i \bar{x}_i}{\sum_i n_i}$$

Where $\bar{x}_i$ and n_i is the mean and N of observation in study i

The overall standard error (SE):

$$SE = \sqrt{S_p^2}$$

Where S_p^2 is the pooled variance as

$$S_p^2 = \frac{\sum_i (n_i - 1) S_i^2}{\sum_i (n_i - 1)}$$

And S_i^2 is the variance in study ***i***

For categorical variables the total N_j of observation in category *j* will be computed as

$$N_{j=\sum} n_{ij}$$

Where n_{ij} is the number of observations of the study ***i*** in the category ***j***

8.2. Calculation of overall risk estimate

8.2.1. Pooled table method

A single fourfold table with the total number of cases will be set-up for each outcome of interest.

	Cases	Non-cases	Total
Exposed	N_{11}	N_{12}	$N_{1.}$
Non-exposed	N_{21}	N_{22}	$N_{2.}$
Total	$N_{.1}$	$N_{.2}$	$N_{..}$

The overall OR_p will be computed as

$$OR_p = \frac{N_{11} N_{22}}{N_{12} N_{21}}$$

The standard error of the log-transformed OR will be computed as

$$SE\left(Log\left(OR_p\right)\right) = \sqrt{\frac{1}{N_{11}} + \frac{1}{N_{12}} + \frac{1}{N_{21}} + \frac{1}{N_{22}}}$$

95% Confidence interval will be computed using a normal approximation method.

Because of the very low number of event, an exact confidence interval for OR will also be computed using an algorithm based on Vollset, Hirji, and Elashoff (1991)[8] implemented in SAS PROC FREQ (SAS 9.2 user's guide)

8.2.2. Inverse Variance OR with continuity correction method

A fourfold table will be set-up for each data source (~studies) after addition of a continuity correction. The continuity correction will be a factor will be a factor reciprocal of the size of the opposite treatment arm size:

$$c_{t=k/N_c}$$

where *Ct* is the correction factor for exposed(treated) arm, *k* a constant and *Nc* the total number of subjects in the non-exposed (control) arm.

This correction factor is preferable to a constant continuity factor such as ½ because of large imbalance in the sample size of the exposed and non-exposed groups in the ANSM study.

OR will be computed for each study as described in 8.2.1. Log(OR) and SE(Log(OR) will be used for the calculation of the overall OR estimate and its 95% CI.

The overall pooled estimate of *Log(OR)* will be computed as the weighted average of individual *Log(OR)*, the weight being the inverse of the variance ($W_F=1/VAR(Log(OR))$).

The overall variance will be computed as the weighted average of individual *VAR(Log(OR))* in the fixed study effect model.

Heterogeneity among study will be tested using the Cochran Q test. The degree of the heterogeneity will be assessed by the i^2 index (Huedo-Medina et al. 2006)[9].

For the random study effect model, a component of inter-study variance will be added in the overall variance (DerSimonian and Liar 1986)[10].

The inter-study variance will be computed as:

$IS\_VAR = 0$ if $Q \leq (k\text{-}1)$

Else $IS\_VAR = [Q-(k-1)]/[\text{sum}(W_F)-\text{sum}(W_F^2)/\text{sum}(W_F)]$

where k is the number of individual estimates, and Q is the sum of weighted square differences between each *Log(OR)* and the pooled fixed estimate.

$Q = \text{sum}\ [W_F * (log(OR)\text{-Fixed pooled}(log(OR))^2]$

The weight for the random pooled estimate of *Log(OR)* will so be equal to

$W_R = 1/[VAR(Log(OR)) + IS\_VAR]$

Results will be presented in tables and in forest plots.

Primary use of the fixed study effect model or random study effect model will be discussed as part of the report based on the level of heterogeneity and any potential bias that might be detected during analysis.

8.2.3. Beta-binomial regression method

This method has been recently recommended based on a large simulation study.[11] This methods does not require continuity correction for single-zero and double-zero.

It assumes that the proportion $p_i = \frac{y_i}{n_i}$ is observed from a binomial distribution $bin(n_i, \pi)$ where π has a beta distribution with parameters α and β. The mean μ of this distribution is $E(\pi) = \mu = \frac{\alpha}{\alpha+\beta}$, and the variance is $Var(\pi) = \frac{\mu(1-\mu)\theta}{1+\theta}$ with $\theta = \frac{1}{\alpha+\beta}$;

For the meta-analysis calculation, each study contributes two proportions, one from the control and one from the treated arm. The overall treatment effect, μ is modelled as:

$$g(\pi) = b_0 + b_t x_t$$

Where g is a common link functions from the GLM family, x_t= 0 for control and 1 for treatment. The link function for log (odds) is the logit link. $Exp(b_t)$ gives an overall estimate of OR.

A SAS macro using the SAS PROC NLMIXED has been written by Kuss 2014[11]

This macro will used after validation by an independent re-programing.

8.3 Sensitivity analysis

For inflammatory bowel diseases, no sensitivity analysis are planned.

For autoimmune thyroiditis, a sensitivity analysis will be performed by retrieving the ANSM study.

For GBS, a sensitivity analysis using a 2-year risk period will be performed.

The table below summarizes the main and sensitivity analysis:

Diseases	Risk windows	
	Main analysis	Sensitivity analysis
Autoimmune thyroiditis	2 years	2 years Excluding the ANSM study
Inflammatory Bowel diseases	2 years	NA
Guillain Barre Syndrome	42 days	2 years

9. LIMITATIONS

The proposed meta-analysis has limitations:

1. We do not have access to the raw data for the two studies (EPI-HPV-011 study and ANSM study), only aggregated data (total number of cases and total number of subject per group) is available. This preludes adjustment for any covariate as well as sensitivity analysis for other risk period. The risk period used in the present analysis is 2 years after 1st vaccination..
2. Case definitions are not consistent among all studies (see section 6.1). To overcome this issue, we have proposed mapping of the various definitions/codes. The general term 'thyroiditis' was used in the ANSM study, this term indeed included a variety of thyroiditis: 18 different ICD-10 codes including also non-autoimmune thyroiditis. However the lack of individual ICD-10 data inhibits a more specific analysis using all studies. We will assume that the majority of cases of thyroiditis are from autoimmune origin. A sensitivity analysis on autoimmune thyroiditis will be performed using all studies except the ANSM study.
3. The date of identification of the outcome varies among studies. Some studies used the date of diagnosis (ANSM study, EPI-HPV-011) and some others used the data of first clinical sign/symptom (EPI-HPV-040) to identify the cases. Ideally the date of first symptoms should be used as the disease onset. Date of symptoms onset is 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 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.

4. The level of case validation also ranges 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.
5. Heterogeneity in study types. The goal is to use all the available data, this implies combining different study designs: pool of randomized clinical trials, a cluster randomized study, two observational cohort studies and a case-control study. Heterogeneity among studies is expected. This heterogeneity will be assessed using the i^2 index and the inverse variance meta-analysis method will take into account the variability between-study in the overall estimate.
6. A 2-year risk period after first dose will be used for autoimmune thyroiditis and IBD. However for GBS, this risk period is not appropriate, as discussed in section 6.2. Most studies considered for GBS a risk window of 42 days following vaccination[12-14]. In order to assess the risk during this 42-day window, the number of cases in the unvaccinated cohort of the ANSM study needs to be estimated from the overall incidence during the full 2-year follow-up period. This estimation assumes a constant incidence rate over the full follow-up period which can be doubtful.
7. The statistical parameter of interest is the OR. OR can be estimated from both cohort and case-control study. Since the low incidence of the outcomes (<1%), OR is virtually identical to RR. However, the ANSM study is a cohort study but the exposure is a time-depending variable. The authors properly used a Cox regression analysis with time-depending exposure, the estimated parameter is HR. Here we cannot consider the exposure as time-dependent. The only option to include the ANSM study results is to recomputed OR as described in section 8.
8. OR calculation does 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. We can assume that early termination does not depend on the exposure. This assumption seems reasonable for all studies but the ANSM due to time-dependent definition of exposure: non-exposed subjects could switch to exposed when they were vaccinated, and then the non-exposed censoring is depending on the exposure.
9. Three methods has been proposed to overcome the issues related to single-zero's and double-zero's. Different methods could provide different overall estimate. However, one method (#2) has been defined a priori as the main analysis the two others are sensitivity analyses.

10. REFERENCES

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11. ANNEXES

11.1. Annexe 1: Pallas 2015 - Systematic literature review on Cervarix vaccination and autoimmune diseases- Final report - Rotterdam, January 7th, 2016

11.2. Annexe 2: TFL's