11. RESULTS

11.1. Participants

Tables for subject disposition are presented in the appendices - Section 16, Table 15, Table 16, Table 17, Table 18.

From a total of 168,662 HPV vaccinated female subjects in CPRD, 103,081 (61.12%) were eligible for the exposed cohort and 65,000 subjects were randomly selected (Table 15). The vast majority of subjects with a *Cervarix* dose in the 01-SEP-2008 to 31-August-2010 date range were within the target age range of 9-25 years and were not vaccinated with an unspecified HPV vaccine or *Gardasil*.

Corresponding results are presented for the historical female cohort in Table 16, for the concurrent male cohort in Table 17, and historical male cohort in Table 18.

Table 6 describes the selected subjects for the main study population and sensitivity analyses according to the four cohorts:

Table 6 Subject dispositions for the four cohorts

Case definition	Exposed cohort (n)	Non-exposed female cohort (n)	Concurrent male cohort (n)	Historical non-exposed male cohort (n)	Total
Known date of first symptom	64,964	64,973	64,974	64,965	259,876
Known or imputed date of first symptom	64,998	64,994	64,988	64,978	259,958
Diagnosis date	64,998	64,994	64,988	64,978	259,958

11.2. Descriptive data

11.2.1. Demographic characteristics of the overall study population for Main analysis

Demographic characteristics are shown in Table 7 for the overall study population (N=259,876; Table 6).

The overall population for main analysis contained 259,876 subjects.

11.2.1.1. Demographic characteristics

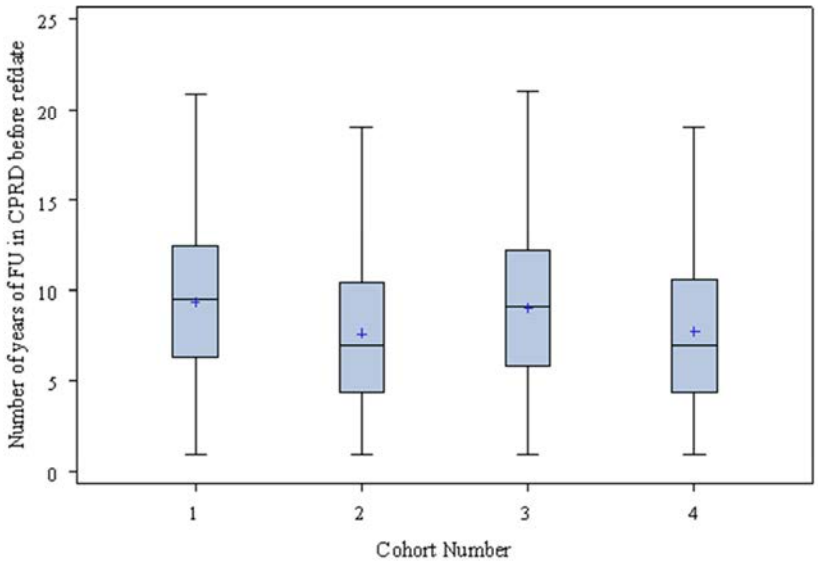
Table 7 Demographic characteristics for overall study population

Demographic Characteristics		Exposed Female Cohort (N=64964)	Non-Exposed Female Cohort (N=64973)	Concurrent Male Cohort N=(64974)	Historical Male Cohort (N=64965)	Total (N=259876)
		n (%) or n (value)	n (%) or n (value)	n (%) or n (value)	n (%) or n (value)	n (%) or n (value)
Age at reference date	Mean (SD)	15.33 (2.09)	15.42 (2.10)	15.27 (2.09)	16 (2.01)	15.51 (2.10)
Age at reference date [by age classes]	9-17 years	58736 (90.4%)	58655 (90.2%)	59242 (91.2%)	56232 (86.6%)	232865 (89.6%)
	18-25 years	6228 (9.5%)	6318 (9.7%)	5732 (8.8%)	8733 (13.5%)	27011 (10.3%)
Geographical distribution	North England	36818 (56.7%)	34646 (53.3%)	35906 (55.3%)	33247 (51.2%)	140617 (54.1%)
	Midlands	8396 (12.9%)	8556 (13.2%)	8423 (13.0%)	8724 (13.4%)	34099 (13.1%)
	South England	19648 (30.2%)	21733 (33.4%)	20616 (31.7%)	22971 (35.4%)	84968 (32.7%)
	Northern Ireland Scotland Wales	102 (0.2%)	38 (0.1%)	29 (0.0%)	23 (0.0%)	192 (0.1%)
HES link	Yes	38656 (59.5%)	36148 (55.6%)	3783 (58.2%)2	37616 (57.9%)	150252 (57.8%)
Number of years of follow-up in CPRD GOLD at reference date	Mean (SD)	9.40 (4.25)	7.64 (4.26)	9.05 (4.3)	7.77 (4.4)	8.46 (4.38)
Number of Healthcare resources utilization[$] (in quartile) the year prior to reference date	0 to 1 consult.	12203 (18.8%)	17940 (27.6%)	21057 (32.4%)	22445 (34.5%)	73645 (28.3%)
	2 to 4 consult.	15746 (24.2%)	17056 (26.3%)	17448 (26.9%)	18262 (28.1%)	68512 (26.4%)
	5 to 9 consult.	16113 (24.8%)	14454 (22.2%)	13362 (20.6%)	13186 (20.3%)	57115 (22.0%)
	≥ 10 consult.	20902 (32.2%)	15523 (23.9%)	13107 (20.2%)	11072 (17.0%)	60604 (23.3%)
Number of Healthcare resources utilization[$] the year prior to reference date	Mean (SD)	8.79 (10.21)	6.95 (9.07)	6.03 (8.41)	5.29 (7.24)	6.77 (8.9)
Exposure to Live or Other vaccines[£] in the year prior to the reference date	Yes	11435 (17.6%)	11008 (16.9%)	9163 (14.1%)	10394 (16%)	42200 (16.2%)
Exposure to Live or Other vaccines[£] in the 1 year follow-up period	Yes	10966 (16.9%)	7765 (12.0%)	7435 (11.4%)	6253 (9.6%)	32419 (12.5%)

$ including e.g. GP consultations, prescriptions, and laboratory tests
£Given the small number of novel adjuvanted vaccinees, only Live and Other vaccines were included
SD=Standard Deviation

The number of years of follow-up in CPRD GOLD by cohort is further summarized in Figure 6.

Figure 6 Summary of follow-up time for each of the four cohorts



1=Exposed female; 2= Non-exposed female; 3 = Non-exposed concurrent male; 4 = Non-exposed historical male

Looking at the healthcare resources utilization (including e.g. GP consultations, prescriptions, and laboratory tests) during the year prior to reference date, the results reflected the assumption that the medical records for current cohorts were more exhaustively reported (Table 34). The difference between the two female cohorts suggested a potential difference in healthcare behaviours. This factor was taken into account in the adjusted analyses.

11.2.1.2. Exposure to other vaccines (One year prior to reference date up to end of follow-up period)

Regarding the novel adjuvanted vaccines which was limited to the H1N1 pandemic influenza vaccines, 636 subjects received this type of vaccine in the year previous to the reference date (311 in the exposed female cohort and 325 in the concurrent male cohort; Table 35).

11.2.1.3. Exposure to *Cervarix* vaccines

Among the exposed cohort, 22.2% of the subjects received their 1st Cervarix dose in 2008, 68.2% in 2009 and 9.7% in 2010 (Table 37). The mean time between the reference date and the last Cervarix dose was 175.28 days (range: 0.0 - 1493 days). In total, 78.1% of the subjects received 3 doses of Cervarix, 14.3% received 2 doses and 7.4% received only 1 dose of Cervarix. Less than 1% of subjects (0.2% or 110 subjects) received

4 doses of Cervarix (Table 37). The overall number of administered Cervarix doses in the exposed cohort is equal to 176124 among the exposed cohort (n=64964; Table 37).

11.3. Outcome data

Figure 7 describes the various steps to identify cases of AD (Section 10.5.1).

After complete review of the individual subject profiles, 466 (44.3%) AD subjects were selected from the 1052 subjects selected originally on the basis of the computer algorithms, with five subjects having 2 AD simultaneously to give a total of 471 AD (Figure 7). Among the identified 466 AD subjects, 384 (82.4%) subjects have been confirmed with a first date of symptom (Table 23) of which 155 (40.4%) were eligible for the main analysis because their first symptom date and date of disease diagnosis were within the 1 year observation period (Table 27).

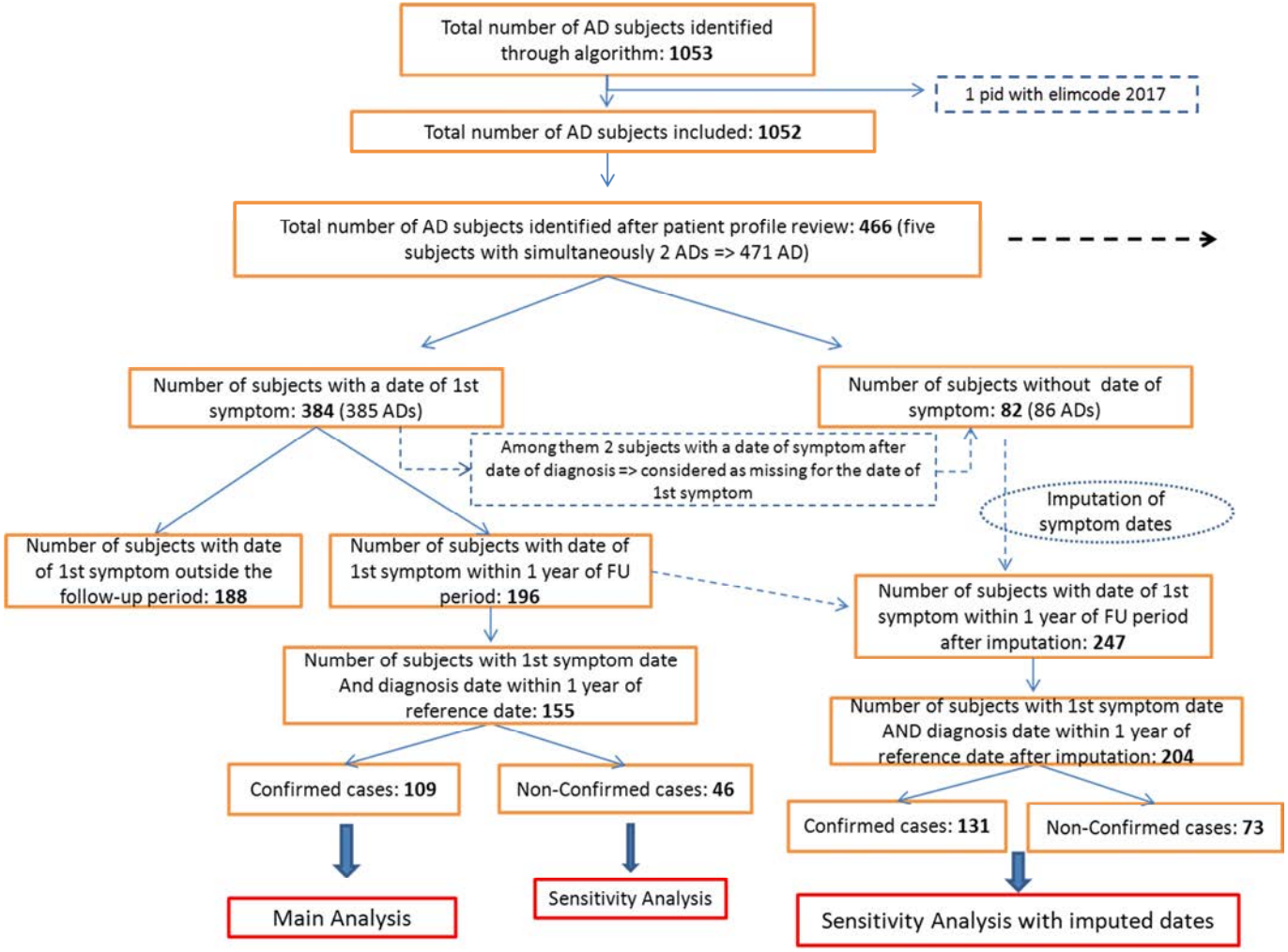
A second review step was conducted by a panel of experts for cases where the (date of) diagnosis, first symptom and/or first abnormal laboratory test could not be confirmed (Section 10.5.1 and 10.5.3). A total of 109 (70.3%) out of 155 subjects with a first symptom date and date of diagnosis within one year from the reference date were selected as confirmed cases for the main analysis (Figure 7 and Table 27).

For a sensitivity analysis, all cases with a missing date of first symptom were also included by using an imputed date of first symptom together with the subjects that had a known first symptom date i.e. both types of case to form a larger sample(Table 26, Table 29). After physician review, a total of 131 (64.2%) out of 204 subjects were confirmed as cases for this analysis (Table 30).

An additional sensitivity analysis was based on the date of disease diagnosis and included 193 (63.5%) confirmed autoimmune disease cases out of 304 subjects (see Figure 8).

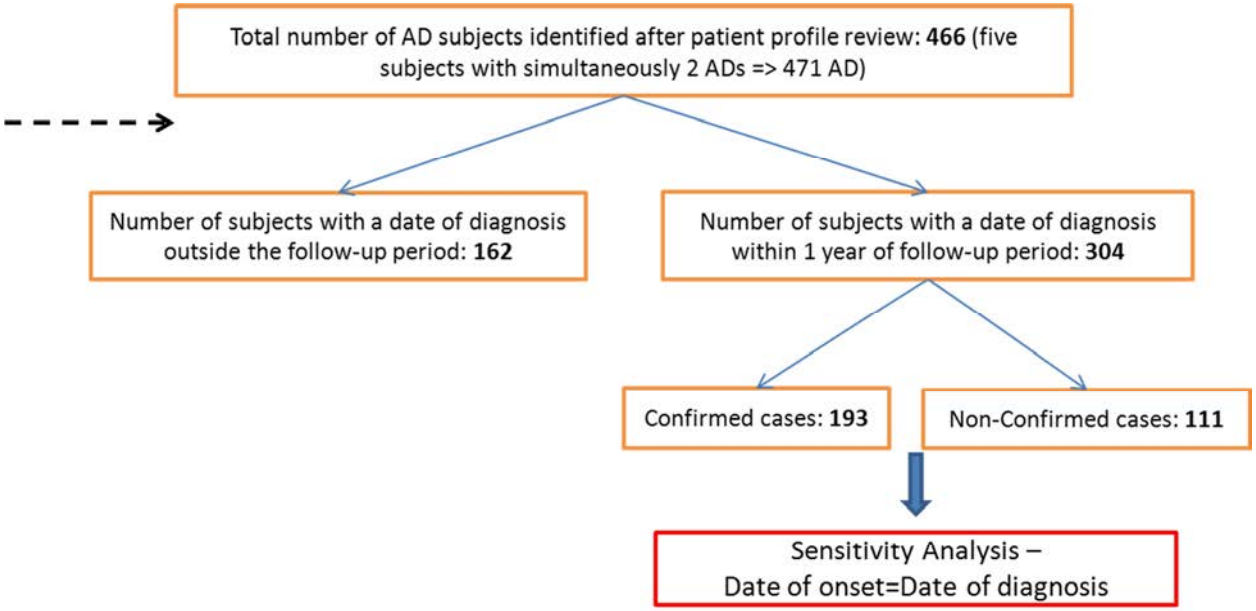
To better understand how the first and second sensitivity analysis populations were selected, Figure 9 depicts the median time between date of diagnosis and date of first symptom for the different AD. For example, for 149 subjects with autoimmune thyroiditis (AI thyroiditis) who had a known date of first symptom, the median time between diagnosis and date of first symptom was 126 days. The other diseases with more than 20 subjects contributing a first symptom were: autoimmune uveitis, Crohn's disease, type 1 diabetes mellitus and ulcerative colitis. The time between date of diagnosis and date of first symptom for each of the autoimmune diseases is further summarised in Table 25.

Figure 7 Selection of subjects for the main and imputed date of first symptom sensitivity analysis



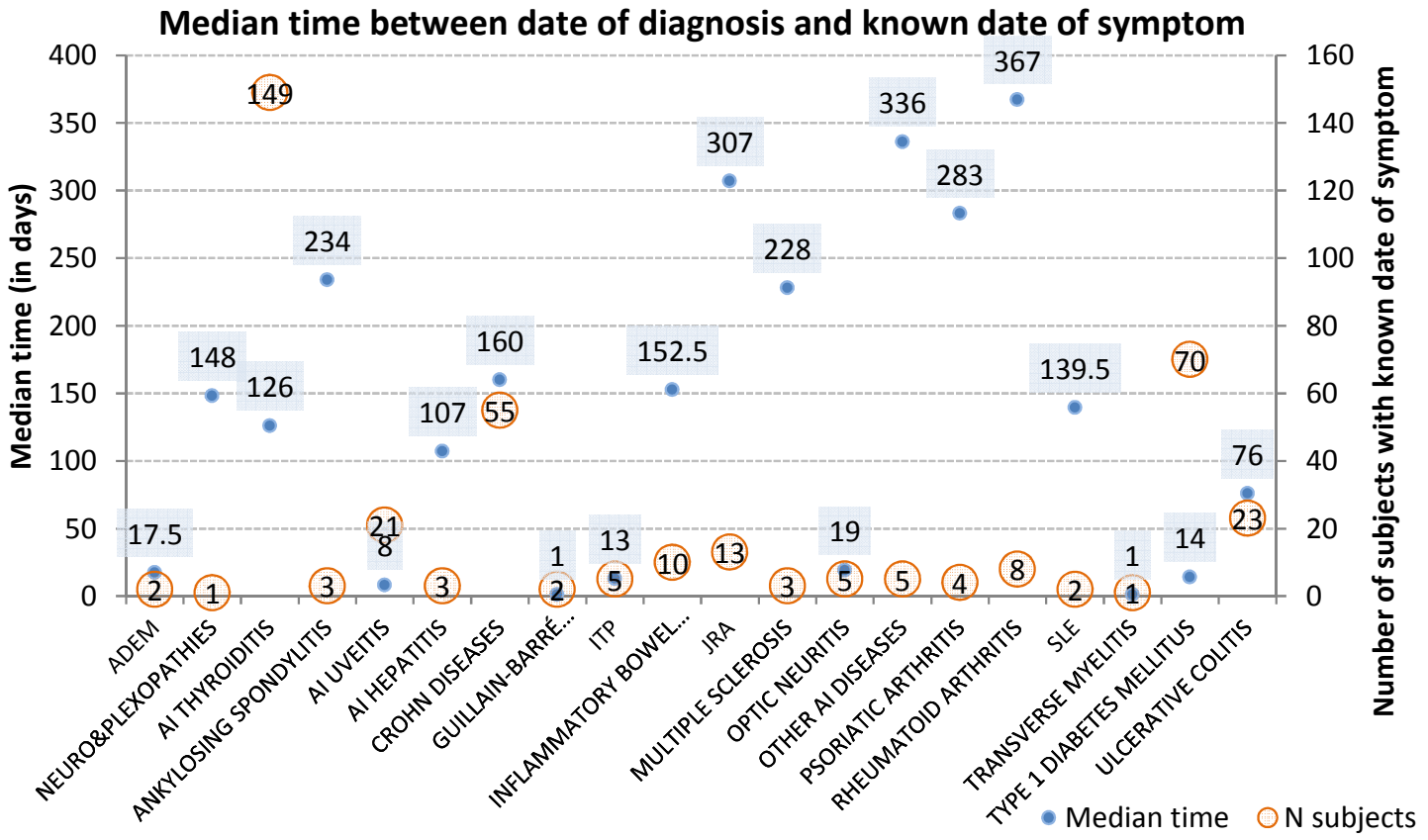
AD = Autoimmune Disease; Confirmation of cases was performed after patient profile review; the 46 non-confirmed cases were combined with the 109 confirmed cases in an extra sensitivity analysis for the Main study population.
Subjects for the Imputed dates sensitivity analyses had either an imputed 1st date of symptom or a known date of 1st symptom i.e. both types of case are included to form a larger sample. Sensitivity analyses for subjects with imputed/known 1st symptom dates were repeated using either confirmed cases only or confirmed and non-confirmed cases.

Figure 8 Selection of subjects for the date of disease diagnosis sensitivity analysis



AD = Autoimmune Disease; Confirmation of cases was performed after patient profile review; Date of onset was assumed to be the same as date of disease diagnosis in this sensitivity analysis. Sensitivity analyses were repeated using either confirmed cases only or confirmed and non-confirmed cases.

Figure 9 Relationship between date of diagnosis and date of first symptom



ADEM: Acute Disseminated Encephalomyelitis; Neuro&Plexopathies: AI Peripheral Neuropathies and Plexopathies; ITP: Idiopathic Thrombocytopenic Purpura; JRA: Juvenile Rheumatoid Arthritis; SLE: Systemic Lupus Erythematous.

11.3.1. Demographic characteristics of the Confirmed Cases in the Main Analysis population

Demographic characteristics are shown in Table 8 for the confirmed cases in the main analysis population (N=109), with reference to the overall population in the main analysis where differences might have greater epidemiological importance.

Table 8 Demographic characteristics for confirmed cases in the main analysis population

Demographic Characteristics		Exposed Female Cohort (N=38)	Non-Exposed Female Cohort (N=28)	Concurrent Male Cohort (N=27)	Historical Male Cohort (N=16)	Total (N=109)
		n (%) or n (value)	n (%) or n (value)	n (%) or n (value)	n (%) or n (value)	n (%) or n (value)
Age at reference date	Mean (SD)	15.92 (1.96)	15.37 (2.48)	14.75 (2.41)	15.70 (2.15)	15.46 (2.26)
Age at reference date [by age classes]	9-17 years	33 (86.9%)	24 (85.7%)	24 (88.9%)	13 (81.3%)	94 (86.2%)
	18-25 years	5 (13.2%)	4 (14.3%)	3 (11.1%)	3 (18.8%)	15 (13.8%)
Geographical distribution	North England	4 (10.5%)	5 (17.9%)	10 (37.0%)	2 (12.5%)	21 (19.3%)
	Midlands	8 (21.1%)	1 (3.6%)	3 (11.1%)	5 (31.3%)	17 (15.6%)
	South England	17 (44.7%)	14 (50.0%)	6 (22.2%)	7 (43.8%)	44 (40.4%)
	Ireland Scotland Wales	9 (23.7%)	8 (28.6%)	8 (29.6%)	2 (12.5%)	27 (24.8%)
HES link	Yes	25 (65.8%)	14 (50.0%)	14 (51.9%)	10 (62.5%)	53 (57.8%)
Number of years of follow-up in CPRD GOLD at reference date	Mean (SD)	10.12 (4.62)	7.84 (5.02)	9.52 (3.74)	8.60 (4.34)	9.16 (4.52)
Number of Healthcare resources utilization[$] (in quartile) the year prior to reference date	0 to 1 consult.	5 (13.2%)	3 (10.7%)	5 (18.5%)	2 (12.5%)	15 (13.8%)
	2 to 4 consult.	10 (26.3%)	9 (32.1%)	11 (40.7%)	7 (43.8%)	37 (33.9%)
	5 to 9 consult.	8 (21.1%)	8 (28.6%)	6 (22.2%)	3 (18.8%)	25 (22.9%)
	≥ 10 consult.	15 (39.5%)	8 (28.6%)	5 (18.5%)	4 (25.0%)	32 (29.4%)
Number of Healthcare resources utilization[$] the year prior to	Mean (SD)	10.53 (10.62)	7.50 (6.69)	6.33 (6.96)	5.75 (4.73)	8.01 (8.26)
Exposure to Any vaccines[§] in the year prior to the reference date	Yes	10 (26.3%)	3 (10.7%)	0 (0.0%)	5 (31.3%)	18 (16.5%)
Exposure to Any vaccines[§] in the 1 year follow-up period	Yes	4 (10.5%)	0 (0.0%)	0 (0.0%)	0. (0.0%)	4 (3.7%)

§Any vaccines included Live attenuated, novel adjuvanted and other vaccines
$ including e.g. GP consultations, prescriptions, and laboratory tests
SD=Standard Deviation

Regarding the confirmed cases included in the sensitivity analysis where date of onset equals the date of disease diagnosis (193 confirmed cases among a total of 304 cases; Table 77 and Table 86), the age at reference date was significantly different between the two male cohorts (p-value=0.01; Table 85). The mean age was 14.96 years (range: 11.76 – 19.45 years) for concurrent male cohort vs. 16.07 years (range: 12.03 – 18.56 years) for historical male cohort. For the female cohorts, the mean age was 15.88 years (range: 12.22 - 20.03) for exposed females and 15.22 years (range: 12.17 - 18.81) for non-exposed female subjects, and this difference was not statistically significant (Table 84). Statistically significant differences were observed for age in female and male cohorts for confirmed cases included in the analysis with imputed date (n=131; Table 59) [p-value=0.013 for female (Table 66) and 0.0094 for male (Table 67)].

For the sensitivity analysis where date of onset equals the date of disease diagnosis, the geographical distribution was significantly different between the two female cohorts (p-value=0.033; Table 84). The proportions in the respective 4 regions were 8.5% (n=5; Table 77), 20.3% (n=12), 37.3% (n=22), 33.9% (n=20) for exposed female vs. 18.9% (n=10), 5.7% (n=3), 50.9% (n=27), 24.5% (n=13) for non-exposed female cohort.

Regarding the confirmed cases included in the sensitivity analyses (both case definitions) the difference for number of years of follow-up in CPRD GOLD remained significant between the two female cohorts (p-values < 0.05): for imputed date analysis (Table 75) and date of disease diagnosis=date of onset (Table 84).

Full details of the demographics are provided in the following tables:

1. Main analysis – All cases: Table 50 to Table 58
2. Imputed date of diagnosis sensitivity analysis – Confirmed cases: Table 59 to Table 67
3. Imputed date of diagnosis sensitivity analysis – All cases: Table 68 to Table 76
4. Date of onset=Date of diagnosis sensitivity analysis – Confirmed cases: Table 77 to Table 85
5. Date of onset=Date of diagnosis sensitivity analysis – All cases: Table 86 and Table 94

11.4. Main results

11.4.1. Primary Objective

The primary study objective is given in Section 8.1and the primary study endpoint is described in Section 10.4.1.

11.4.1.1. Frequency of AD – Main Analysis

In the main analysis population, there was a total of 3 confirmed cases of neuroinflammatory/ophthalmic autoimmune disease (1 in non-exposed female cohort, 1 in concurrent male and 1 in historical male cohort; Table 96) and 106 confirmed cases of other autoimmune diseases (38 in exposed cohort, 27 in non-exposed female cohort, 26 in concurrent male cohort and 15 in historical male cohort) within the 1 year follow-up period. By considering all the cases, confirmed and non-confirmed cases, there were a total of 16 neuroinflammatory/ophthalmic cases (4 in exposed female cohort, 7 in non-exposed female cohort, 3 in concurrent male and 2 in historical male cohort; Table 95) and 139 cases of other autoimmune diseases (51 in exposed female cohort, 41 in non-exposed female cohort, 28 in concurrent male and 19 in historical male cohort).

The number of cases and the incidence of the co-primary endpoints by cohort and also for selected individual diseases are summarised in Table 9. The same summaries are also provided for the sensitivity analyses using either the imputed date of first symptom (Table 10) or the sensitivity analyses based on date of disease diagnosis (Table 11).

Table 9 Incidence rate of new onset of autoimmune diseases – Known date of first symptom

Female Cohort Results						
		Exposed F cohort (Tot PY=64705)		Non-Exposed F cohort (Tot PY=64841)		
Diseases		n	Incidence [n/100,000 PY] (95%CI)	n	Incidence [n/100,000 PY] (95%CI)	Adjusted IRR* (95%CI)
Co-primary endpoints						
Neuroinflammatory/ Ophthalmic autoimmune diseases	Confirmed cases	0	0.00 (0.00; 5.70)	1	1.54 (0.04; 8.59)	ND
	All cases	4	6.18 (1.68; 15.83)	7	10.80 (4.34; 22.24)	0.57 (0.17; 1.96)
Other autoimmune diseases	Confirmed cases	38	58.73 (51.56; 80.61)	27	41.64 (27.44; 60.58)	1.41 (0.86; 2.31)
	All cases	51	78.82 (58.69; 103.63)	41	63.23 (45.38; 85.78)	1.25 (0.83; 1.88)
Individual diseases with more than 10 cases in F cohorts						
Autoimmune thyroiditis	Confirmed cases	15	23.18 (12.98; 38.24)	4	6.17 (1.68; 15.80)	3.75 (1.25; 11.31)
	All cases	26	40.18 (26.25; 58.88)	18	27.76 (16.45; 43.87)	1.45 (0.79; 2.64)
Crohn's disease	Confirmed cases	6	9.27 (3.40; 20.18)	5	7.71 (2.50; 18.00)	1.21 (0.37; 3.95)
	All cases	8	12.36 (5.34; 24.26)	5	7.71 (2.50; 18.00)	1.61 (0.53; 4.91)
Type 1 diabetes mellitus	Confirmed cases	8	12.36 (5.34; 24.36)	16	24.68 (14.10; 40.07)	0.50 (0.21; 1.17) 0.30 (0.11; 0.83)[$]
	All cases	8	12.36 (5.34; 24.36)	16	24.68 (14.10; 40.07)	0.50 (0.24; 1.17)

Male Cohort Results						
		Concurrent M cohort (Tot PY=64859)		Historical M cohort (Tot PY=64868)		
Diseases		n	Incidence [n/100,000 PY] (95%CI)	n	Incidence [n/100,000 PY] (95%CI)	Adjusted IRR* (95%CI)
Co-primary endpoints						
Neuroinflammatory/ Ophthalmic autoimmune diseases	Confirmed cases	1	1.54 (0.04; 8.59)	1	1.54 (0.04; 8.59)	0.95 (0.06; 15.18)
	All cases	3	4.63 (0.95; 13.52)	2	3.08 (0.37; 11.14)	1.73 (0.29; 10.47)
Other autoimmune diseases	Confirmed cases	26	40.09 (26.19; 58.74)	15	23.12 (12.94; 38.14)	1.77 (0.94; 3.35)
	All cases	28	43.17 (28.69; 62.39)	19	29.29 (17.64; 45.74)	1.52 (0.85; 2.73)
Individual diseases with more than 10 cases in F cohorts						
Autoimmune thyroiditis	Confirmed cases	0	0.00 (0.00; 5.69)	0	0.00 (0.00; 5.69)	ND
	All cases	2	3.08 (0.37; 11.14)	3	4.63 (0.95; 13.52)	0.76 (0.13; 4.60)
Crohn's disease	Confirmed cases	4	6.17 (1.68; 15.79)	1	1.54 (0.04; 8.59)	4.22 (0.47; 38.02)
	All cases	4	6.17 (1.68; 15.79)	2	3.08 (0.37;11.14)	2.06 (0.38; 11.34)
Type 1 diabetes mellitus	Confirmed cases	20	30.84 (18.84; 47.62)	8	12.33 (5.32; 24.30)	2.46 (1.08; 5.60)
	All cases	20	30.84 (18.84; 47.62)	8	12.33 (5.32; 24.30)	2.46 (1.08; 5.60)

ND= Not Done; IRR*= Incidence Rate Ratio adjusted for age group [9-17]-[18-25]; [$] - adjusted for the difference between male cohorts

Table 10 Incidence rate of new onset of autoimmune diseases – Imputed date of first symptom sensitivity analysis

Female Cohort Results						
		Exposed F cohort (Tot PY=64730)		Non-Exposed F cohort (Tot PY=64844)		
Diseases		n	Incidence [n/100,000 PY] (95%CI)	n	Incidence [n/100,000 PY] (95%CI)	Adjusted IRR* (95%CI)
Co-primary endpoints						
Neuroinflammatory/ Ophthalmic autoimmune diseases	Confirmed cases	0	0.00 (0.00; 5.70)	1	1.54 (0.04; 8.59)	1.00 (0.06; 16.08)
	All cases	5	7.72 (2.51; 18.03)	9	13.88 (6.35; 26.35)	0.56 (0.19; 1.66)
Other autoimmune diseases	Confirmed cases	42	64.89 (46.76;87.71)	33	50.89 (35.03;71.47)	1.27 (0.81; 2.01)
	All cases	60	92.69 (70.73; 119.31)	52	80.19 (59.89; 105.16)	1.16 (0.79; 1.67)
Individual diseases with more than 10 cases in F cohorts						
Autoimmune thyroiditis	Confirmed cases	16	24.72 (14.13; 40.14)	8	12.34 (5.33; 24.31)	2.00 (0.86; 4.67)
	All cases	32	49.44 (33.81; 69.79)	27	41.64 (27.44; 60.58)	1.19 (0.71; 1.98)
Crohn's disease	Confirmed cases	7	10.81 (4.35; 22.28)	5	7.71 (2.50; 17.99)	1.41 (0.45; 4.43)
	All cases	9	13.90 (6.36; 26.39)	5	7.71 (2.50; 17.99)	1.81 (0.61; 5.39)
Type 1 diabetes mellitus	Confirmed cases	10	15.45 (7.41; 28.41)	18	27.76 (16.45; 43.87)	0.56 (0.26; 1.21)
	All cases	10	15.45 (7.41; 28.41)	18	27.76 (16.45; 43.87)	0.56 (0.26; 1.21)
Male Cohort Results						
		Concurrent M cohort (Tot PY=64865)		Historical M cohort (Tot PY=64874)		
Diseases		n	Incidence [n/100,000 PY] (95%CI)	n	Incidence [n/100,000 PY] (95%CI)	Adjusted IRR* (95%CI)
Co-primary endpoints						
Neuroinflammatory/ Ophthalmic autoimmune diseases	Confirmed cases	2	3.08 (0.37; 11.14)	1	1.54 (0.04; 8.59)	1.89 (0.17; 20.94)
	All cases	7	10.79 (4.34; 22.24)	4	6.17 (1.68; 15.79)	1.82 (0.53; 6.24)
Other autoimmune diseases	Confirmed cases	33	50.88 (35.02; 71.45)	19	29.29 (17.63; 45.74)	1.78 (1.01; 3.14)
	All cases	38	58.58 (41.46; 80.41)	29	44.70 (29.94;64.20)	1.35 (0.83; 2.19)
Individual diseases with more than 10 cases in F cohorts						
Autoimmune thyroiditis	Confirmed cases	1	1.54 (0.04; 8.69)	0	0.00 (0.00; 5.69)	ND
	All cases	5	7.71 (2.50; 17.99)	7	10.79 (4.34; 22.23)	0.73 (0.23; 2.31)
Crohn's disease	Confirmed cases	5	7.71 (2.50; 17.99)	1	1.54 (0.04; 8.59)	5.19 (0.60; 44.68)
	All cases	5	7.71 (2.50; 17.99)	2	3.08 (0.37; 11.14)	2.55 (0.49; 13.23)
Type 1 diabetes mellitus	Confirmed cases	23	35.46 (22.48; 53.21)	12	18.50 (9.56; 32.31)	1.89 (0.94; 3.82)
	All cases	23	35.46 (22.48; 53.21)	14	21.58 (11.80; 36.21)	1.65 (0.85; 3.20)

IRR*= Incidence Rate Ratio adjusted for age group [9-17]-[18-25]

Table 11 Incidence rate of new onset of autoimmune diseases – Date of onset=Date of disease diagnosis sensitivity analysis

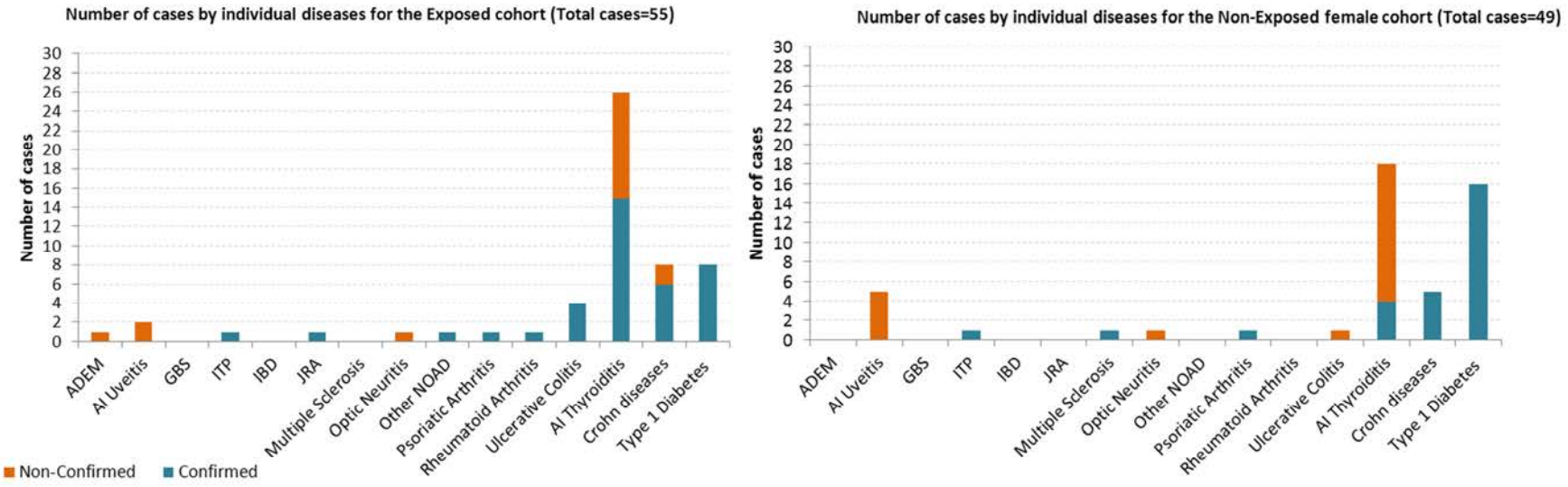
Female Cohort Results						
		Exposed F cohort (Tot PY=64852)		non-Exposed F cohort (Tot PY=64893)		
Diseases		n	Incidence [n/100,000 PY] (95%CI)	n	Incidence [n/100,000 PY] (95%CI)	Adjusted IRR* (95%CI)
Co-primary endpoints						
Neuroinflammatory/ Ophthalmic autoimmune diseases	Confirmed cases	1	1.54 (0.04; 8.59)	1	1.54 (0.04; 8.59)	1.00 (0.6; 16.10)
	All cases	6	9.25 (3.40; 20.14)	10	15.41 (7.39; 28.34)	0.60 (0.21; 1.65)
Other autoimmune diseases	Confirmed cases	58	89.44 (67.91; 115.62)	52	80.13 (59.85; 105.08)	1.12 (0.77; 1.62)
	All cases	87	134.15 (107.45; 165.48)	85	130.99 (104.63; 161.97)	1.024 (0.76; 1.38)
Individual diseases with more than 10 cases in F cohorts						
Autoimmune thyroiditis	Confirmed cases	23	35.47 (22.48; 53.22)	15	23.12 (12.94; 38.13)	1.53 (0.80; 2.94)
	All cases	48	74.01 (54.57; 98.13)	46	70.89 (51.90; 94.55)	1.04 (0.69; 1.56)
Crohn's disease	Confirmed cases	11	16.96 (8.47; 30.35)	9	13.87 (6.34; 26.33)	1.23 (0.51; 2.96)
	All cases	13	20.05 (10.67; 34.28)	9	13.87 (6.34; 26.33)	1.45 (0.62; 3.39)
Type 1 diabetes mellitus	Confirmed cases	11	16.96 (8.47; 30.35)	20	30.82 (18.83; 47.60)	0.55 (0.26; 1.15)
	All cases	11	16.96 (8.47; 30.35)	20	30.82 (18.83; 47.60)	0.55 (0.26; 1.15)

Male Cohort Results						
		Concurrent M cohort (Tot PY=64897)		Historical M cohort (Tot PY=64891)		
Diseases		n	Incidence [n/100,000 PY] (95%CI)	n	Incidence [n/100,000 PY] (95%CI)	Adjusted IRR* (95%CI)
Co-primary endpoints						
Neuroinflammatory /Ophthalmic autoimmune diseases	Confirmed cases	2	3.08 (0.37; 11.13)	1	1.54 (0.04; 8.59)	1.89 (0.17; 20.94)
	All cases	9	13.87 (6.34; 26.33)	3	4.62 (0.95; 13.51)	3.11 (0.84; 11.52)
Other autoimmune diseases	Confirmed cases	45	69.34 (50.58; 92.78)	33	50.85 (35.01; 71.42)	1.39 (0.88; 2.18)
	All cases	56	86.29 (65.18; 112.06)	48	73.97 (54.54; 98.07)	1.19 (0.81; 1.75)
Individual diseases with more than 10 cases in F cohorts						
Autoimmune thyroiditis	Confirmed cases	2	3.08 (0.37; 11.13)	0	0.00 (0.00; 5.69)	ND
	All cases	10	15.41 (7.39; 28.34)	8	12.33 (5.32; 24.29)	1.25 (0.49; 3.18)
Crohn's disease	Confirmed cases	15	23.11 (12.94; 38.12)	8	12.33 (5.32; 24.29)	1.94 (0.82; 4.59)
	All cases	16	24.65 (14.09; 40.04)	10	15.41 (7.39; 28.34)	1.64 (0.74; 3.62)
Type 1 diabetes mellitus	Confirmed cases	23	35.44 (22.47; 53.18)	12	18.49 (9.56; 32.30)	1.89 (0.94; 3.82)
	All cases	23	35.44 (22.47; 53.18)	14	21.58 (11.80; 36.20)	1.65 (0.85; 3.20)

IRR*= Incidence Rate Ratio adjusted for age group [9-17]-[18-25]

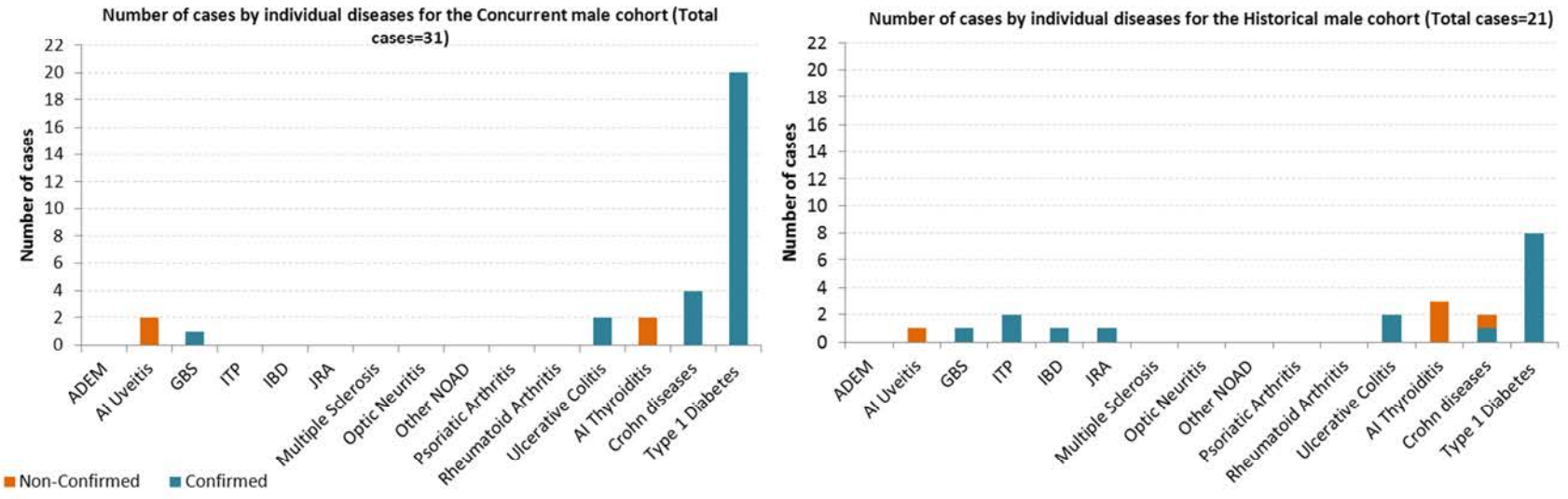
The number of individual cases, both confirmed and unconfirmed, are illustrated in the following two figures, first for the two female cohorts (Figure 10) and then for the two male cohorts (Figure 11).

Figure 10 Number of cases (confirmed and non-confirmed) in female cohorts



Note: In the non-exposed female cohort, 1 subject simultaneously had a confirmed diabetes and non-confirmed thyroiditis
ADEM: Acute Disseminated Encephalomyelitis; AI: AutoImmune; GBS: Guillain-Barré Syndrome; ITP: Idiopathic Thrombocytopenic Purpura; IBD: Inflammatory Bowel Disease; JRA: Juvenile Rheumatoid Arthritis.

Figure 11 Number of cases (confirmed and non-confirmed) in male cohorts



ADEM: Acute Disseminated Encephalomyelitis; AI: AutoImmune; GBS: Guillain-Barré Syndrome; ITP: Idiopathic Thrombocytopenic Purpura; IBD: Inflammatory Bowel Disease; JRA: Juvenile Rheumatoid Arthritis.

11.4.1.2. Time disease-specific analysis

Please refer Section 10.4.2 for details of the study secondary endpoints.

Regarding the two-month disease-specific period after Cervarix vaccination or reference date for male cohorts, a total of two confirmed GBS cases were observed in male cohorts within the 1 year follow-up period (Table 98). Among them only 1 case was observed within the specific period of 2 months and this case was from the historical male cohort (Table 99 and Table 100). The GBS case outside the specific 2 month period was observed in the concurrent male cohort (Table 98). No case of autoimmune haemolytic anaemia was observed during the study period.

A total of four confirmed ITP cases were observed within the 1 year follow-up period (Table 98 and also 2nd bullet point of Section 10.4.2). Three cases were within the specific period of 6 months; one from the exposed cohort, one from the non-exposed female cohort and one from the historical male cohort (Table 102). The case outside the specific period of 6 months was observed in the historical male cohort (Table 98).

Because of the small number of cases within the 2 and 6 month follow-up periods, the IRR (Incidence Rate Ratio) calculations (secondary endpoint) were not performed (see Table 99 to Table 102).

11.4.1.3. Cohort comparison

The incidence rate ratios (IRR) are described for the main analysis which only takes account of confirmed cases. The results for the main analysis with known dates of symptom onset are compared to the two sensitivity analyses which either use imputed date of symptom onset or date of onset equals date of diagnosis, in the following Figures:

1. IRR results for the two co-primary endpoints (refer to Section 10.4.1): Figure 12;
2. IRR results for the individual diseases if more than 10 cases of the AD were observed in both female cohorts (refer to Section 10.9.1.4): Figure 13.

For the neuroinflammatory and ophthalmic diseases (1st co-primary endpoint, confirmed cases), the adjusted IRR for male cohorts was 0.95 [95%CI: 0.06-15.18] (Table 120) and it was not done for females due to only one case in the non-exposed cohort (Table 105).

For the other autoimmune diseases (2nd co-primary endpoint, confirmed cases), the adjusted IRRs were 1.41 [95%CI: 0.86-2.31] for the exposed and non-exposed female cohorts (Table 108) and 1.77 [95%CI: 0.94-3.35] for the concurrent and historical male cohorts (Table 123).

When these types of analysis were repeated for the two additional case definitions, the results for the co-primary endpoints were similar to the main analysis:

1. For imputed date of first symptom sensitivity analysis: For 1st co-primary endpoint, refer to Table 212, and Table 228;

2. For imputed date of first symptom sensitivity analysis: For 2nd co-primary endpoint refer to Table 216, and Table 231;
3. For Date of onset=Date of disease diagnosis sensitivity analysis: For 1st co-primary endpoint, refer to Table 344, and Table 359;
4. For Date of onset=Date of disease diagnosis sensitivity analysis: For 2nd co-primary endpoint, refer to Table 347 and Table 362.

Regarding the individual diseases analysis, the inferential statistics were performed for the diseases with more than 10 cases in both female cohorts. The following diseases were included according to this rule: autoimmune thyroiditis, Crohn's disease and Type 1 diabetes mellitus.

For autoimmune thyroiditis, the IRR was 3.75 [95%CI: 1.25-11.31] (Table 136) for confirmed cases in the two female cohorts meaning that the risk is higher and statistically significant in the exposed cohort vs. non-exposed cohort. When considering confirmed and non-confirmed cases the IRR was 1.45 [95%CI: 0.79-2.64] (Table 140) and became non-significant. For the concurrent and historical male cohorts, no confirmed cases were observed, when considering all the cases the IRR was 0.76 [95%CI: 0.13-4.60] (Table 144).

When the two additional case definitions/sensitivity analyses were investigated for autoimmune thyroiditis, the IRRs were lower or equal to 2 and were not significant due to an increase of cases in both female cohorts (for imputed date analysis refer to Table 246, Table 249, Table 252, Table 256, and for date of onset analysis refer to Table 379, Table 382, Table 385, Table 389).

For the Crohn's disease cases, the IRRs were 1.21 [95%CI: 0.37-3.95] for female cohorts (Table 150) and 4.22 [95%CI: 0.47-38.02] for male cohorts (Table 154). Similar results were observed for the two additional case definitions (for imputed date analysis refer to Table 268, Table 272, Table 275, Table 279, and for date of onset analysis refer to Table 401, Table 405, Table 408, Table 412).

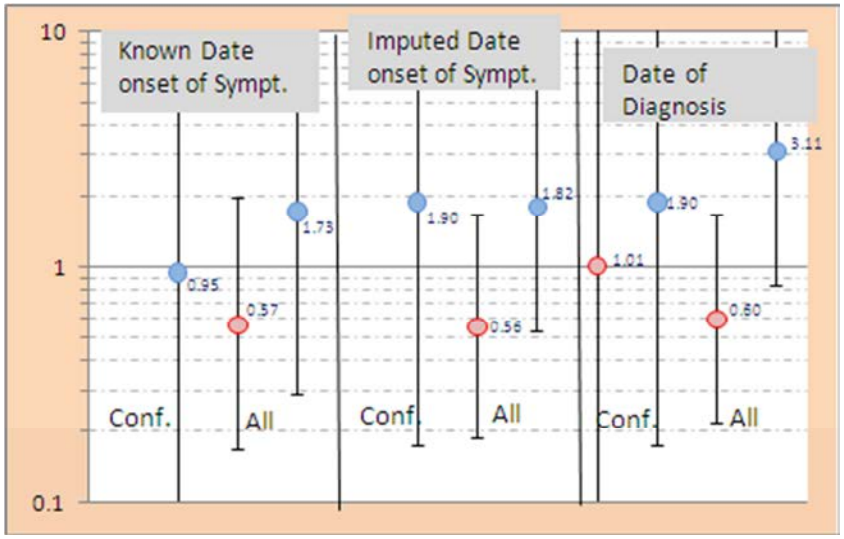
For type 1 diabetes, the IRRs were 0.50 [95%CI: 0.21-1.17] in exposed and non-exposed female cohorts (Table 180) and 2.46 [95%CI: 1.08-5.60] in concurrent and historical male cohorts (Table 184) meaning that the risk was higher and statistically significant in the concurrent male cohort vs. historical male cohort. An adjustment for the male effect was required according to the protocol-specified rule and the IRR when comparing the female cohort with the historical female cohort after adjustment was 0.30 [95%CI: 0.11-0.83] (Table 598).

By analyzing the two additional case definitions, a similar pattern was observed in female (exposed and non-exposed) and male (concurrent and historical) cohorts without significant different for both confirmed and confirmed+non-confirmed cases (for imputed date analysis refer to Table 305, Table 309, Table 313, Table 317 and for date of onset analysis refer to Table 446, Table 450, Table 454, Table 458).

Figure 12 Incidence Rate Ratio results summary for the two co-primary endpoints [1]

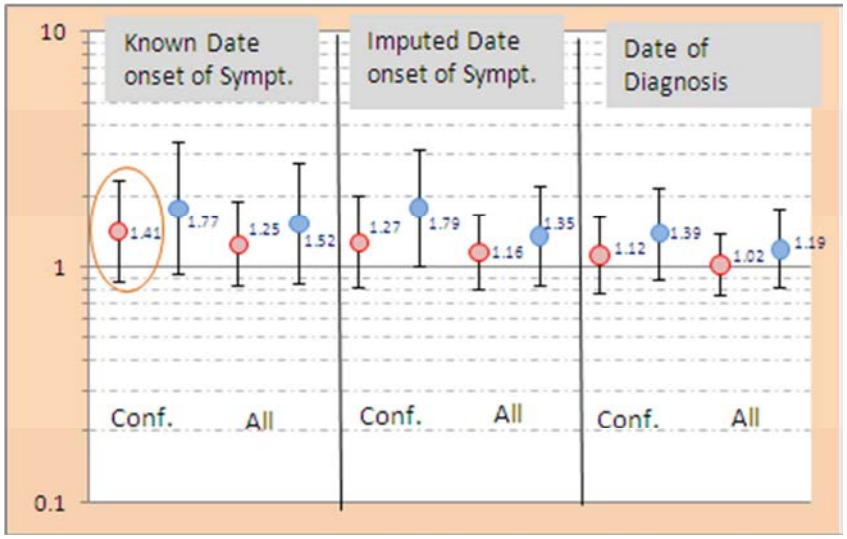
Neuroinflammatory/Ophthalmic diseases [2]

(1st co-primary endpoint)



Other autoimmune diseases [3]

(2nd co-primary endpoint)



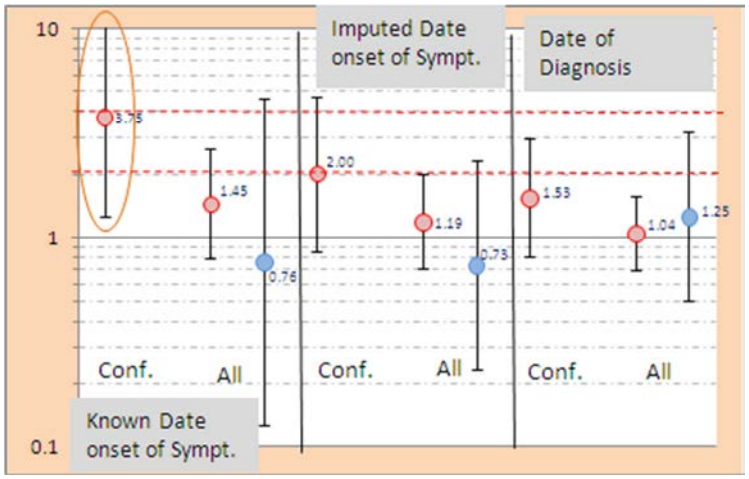
[1] The incidence rate ratios are the comparison of exposed vs. non-exposed female cohorts (red circle) and concurrent vs. historical male cohorts (blue circle) either for the confirmed cases only (Conf.) or both confirmed and non-confirmed cases (All) analyses. These analyses were repeated for the main analysis where the date of symptom onset was known, the imputed date of first symptom sensitivity analysis including both cases with a known date of first symptom and an imputed date of first symptom,, and also the date of onset=date of disease diagnosis analysis.

[2] For the neuroinflammatory and ophthalmic diseases (1st co-primary endpoint, confirmed cases), the adjusted IRR was not estimable for the female cohort comparison because no case(s) was observed in the exposed cohort (Table 105).

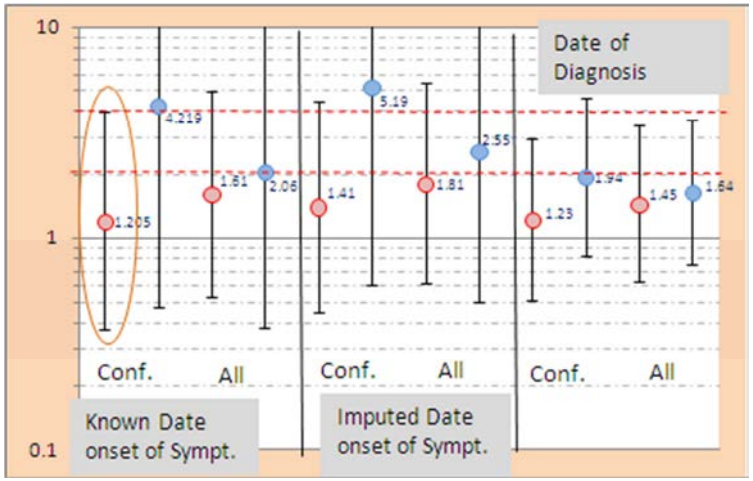
[3] The orange circle denotes the key main analysis for the 'Other autoimmune diseases'.

Figure 13 Incidence Rate Ratio results summary for the individual AD [1]

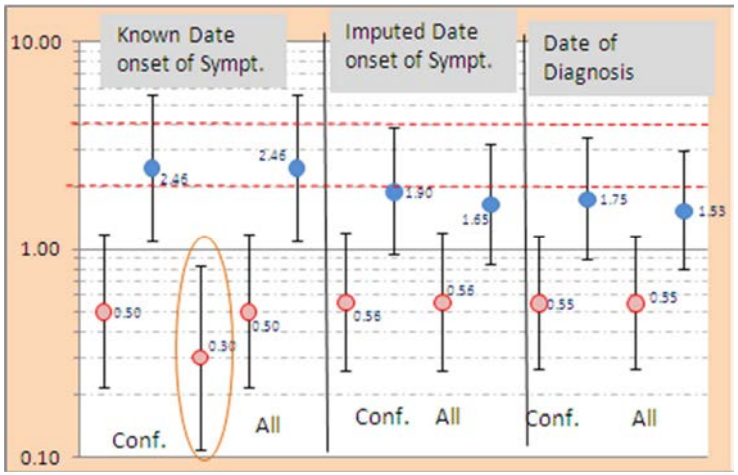
Autoimmune Thyroiditis



Crohn's disease



Type 1 Diabetes Mellitus



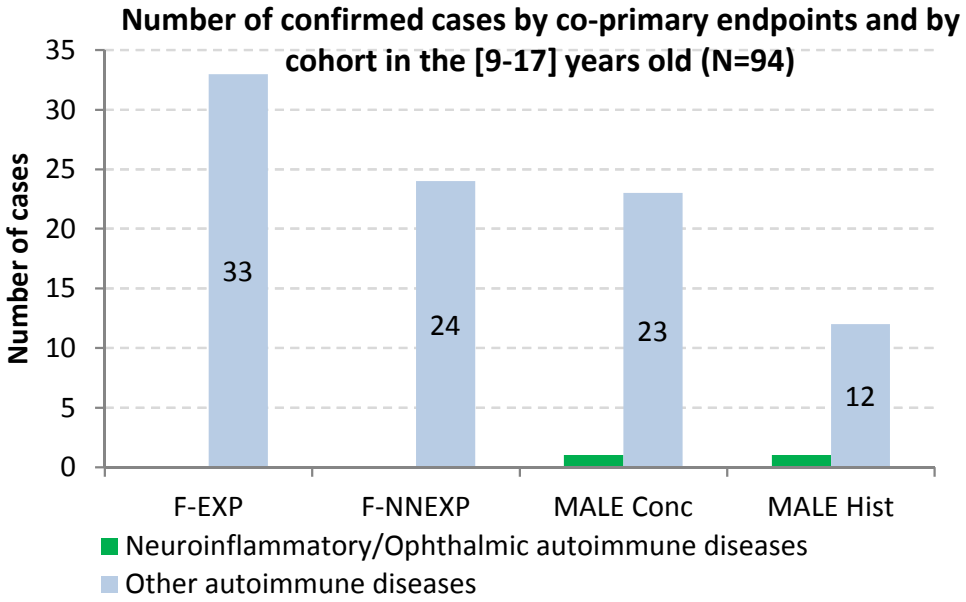
[1] See Footnote 1 of Figure 12. The point estimate marked with an orange circle for Type 1 Diabetes mellitus corresponds to the IRR adjusted for the significant difference observed between the two male cohorts. The orange circle for Autoimmune thyroiditis and Crohn's disease denotes the key main analysis for these individual diseases.

11.4.1.4. Analysis by age groups

Given that around 90% of the overall population was in the age group [9-17] years old, 86.2% of the confirmed cases were observed in this 9-17 years age range (2 cases of neuroinflammatory/ophthalmic diseases and 92 cases of other autoimmune diseases Table 476, and for confirmed cases in the 18-25 years age group refer to Table 477).

The distribution of confirmed cases by the four cohorts in the 9-17 years age group is summarized in Figure 14.

Figure 14 Confirmed cases in the 9-17 years age group



By analyzing the individual diseases, similar results were observed in the [9-17] year age group for autoimmune thyroiditis and Type 1 diabetes mellitus compared to the corresponding analysis for all ages. Crohn's disease was not analysed as less than 10 cases were observed in the age group.

For [9-17] year age group:

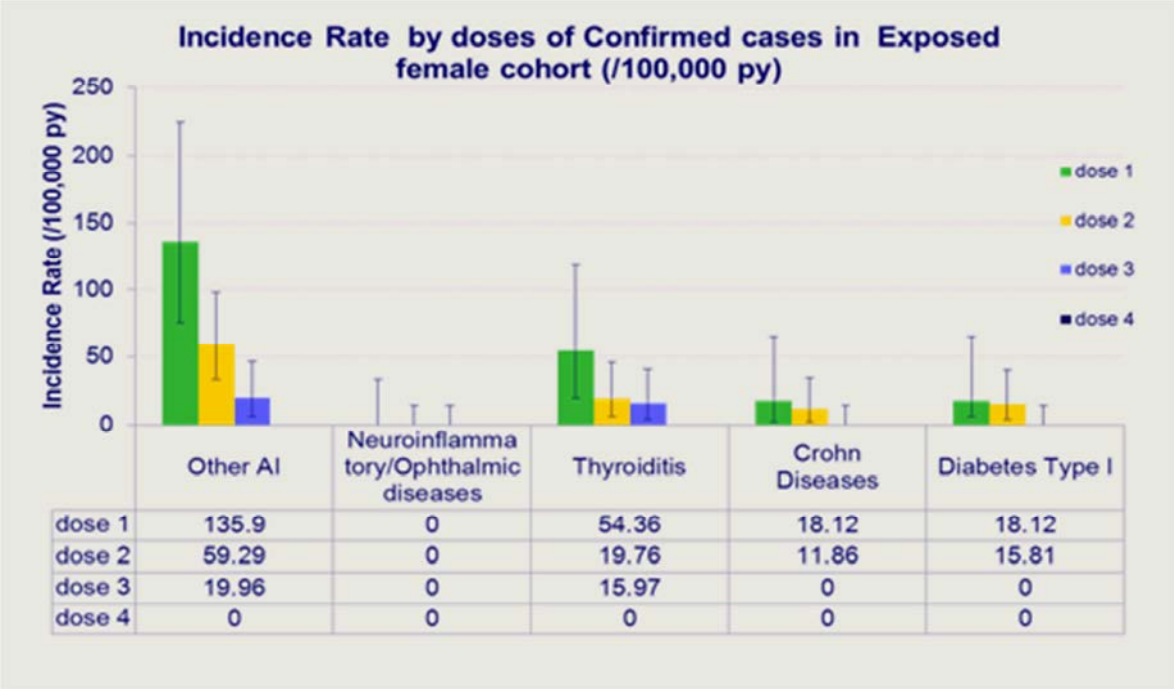
- For autoimmune thyroiditis in female cohorts: Table 507 and Table 515;
- For type 1 diabetes mellitus in female cohorts: Table 511 and Table 519;
- For type 1 diabetes mellitus in male cohorts: Table 513 and Table 521.

11.4.1.5. Analysis by dose

The analysis by dose was only performed for the exposed female cohort. Figure 15 illustrates the incidence rates by doses for the co-primary endpoints, and individual diseases where there were more than 10 cases in both female cohorts.

The results for Neuroinflammatory/Ophthalmic autoimmune diseases and Other autoimmune diseases by *Cervarix* dose 1, 2, 3 and 4 are summarised in Table 532 through to Table 547, and by *Cervarix* dose 1, 2, 3 and 4 for autoimmune thyroiditis in Table 548 to Table 555, for Crohn's disease in Table 556 to Table 563, and type 1 diabetes mellitus in Table 564 to Table 571.

Figure 15 Incidence rates by dose in exposed female cohorts



	Other AI	Neuroinflammatory/Ophthalmic diseases	Thyroiditis	Crohn Diseases	Diabetes Type I
dose 1	135.9	0	54.36	18.12	18.12
dose 2	59.29	0	19.76	11.86	15.81
dose 3	19.96	0	15.97	0	0
dose 4	0	0	0	0	0

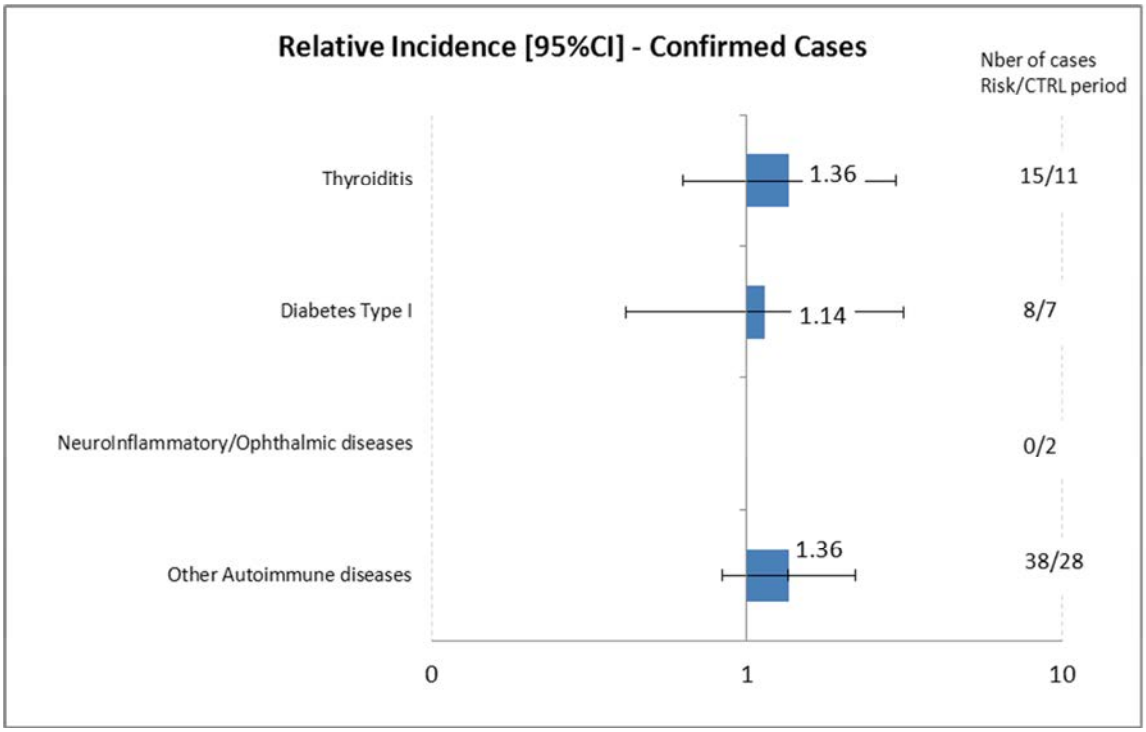
11.4.1.6. Self-controlled case-series (SCCS) analysis

A total of 250 subjects from the exposed cohort were selected for the SCCS analysis (Table 31). A SCCS analysis was performed on the cases in the exposed female cohort. The risk period was defined as one year after the first dose, the buffer period was defined as 6 month after the risk period and the control period was defined as one year after the buffer period. The relative risk between risk period and control period was calculated by co-primary endpoints and for the diseases with more than 10 cases in both risk and control periods. Note that an exclusion criterion was applied to the cases, if the disease onset was within the defined risk period but the date of diagnosis was after the risk period, then the case was excluded from the SCCS analysis. The same rule was indeed applied for cases occurring in the control period because no diagnosis that occurred after the end of the control period was included in the study. The reason for the use of this rule was to avoid a bias in the number of cases occurring in the risk period. Indeed, the exposed cohort was followed up to 30 months in the CPRD database, with this FU period we could expected to have more cases with a first symptom date in the risk period than in the control period. The results are summarized graphically in Figure 16 and results are further described in the following tables:

For the Main SCCS analysis using all cases:

- For Neuroinflammatory/Ophthalmic diseases: Table 580 and Table 581;
- For Other AD: Table 572 and Table 573;
- For type 1 diabetes: Table 574 and Table 575;
- For Thyroid diseases: Table 576 and Table 577;
- For Crohn's disease: Table 578 and Table 579.

Figure 16 Relative incidence (95% CI) between risk and control periods for confirmed cases



When the SCCS analysis was compared to the cohort results described in Section 11.4.1.3, the overall results for other autoimmune diseases did not suggest a significant increase in risk of these diseases as the relative incidence was 1.36 in the SCCS analysis (Figure 16) or 1.41 for female cohorts (exposed versus non-exposed) (Table 108). For autoimmune thyroiditis, the statistically significant IRR for female confirmed cases (Section 11.4.1.3), was not observed in the SCCS analysis (Figure 16).

11.4.2. Secondary objectives

The secondary objective was to describe the incidence of pre-specified AD in the follow-up time periods of a) two months, b) six months and c) one year from the reference date (Section 8.2).

Given that there were small numbers of cases within the selected follow-up time periods (two and six months), the IRR calculations were not performed.

For the one year period, this was by definition the main analysis.

11.5. Other analyses

11.5.1. Exploratory objectives

The exploratory objective was the assessment of the presence of a temporal clustering of the individual AD in relation to the two co-primary endpoints and secondary endpoints (Section 8.3). A similar rule was applied for the individual analysis of three diseases: Crohn's disease, type 1 diabetes, and AI thyroiditis if there were more than 10 cases in each of the four cohorts (exposed and non-exposed female, concurrent and historical male). The analysis was performed by using the SatScan tool [SaTScan, 2014] as described in Section 10.9.1.4.

No significant cluster was detected in the exposed female cohort with the temporal test for the three case definitions (main analysis + sensitivity analyses) and the two time-windows.

SatScan results for the exposed female cohort are presented in Table 599 and Table 603 (main analysis), Table 607 and Table 611 (imputed date) and Table 615 and Table 619 (diagnosis date).

One cluster was observed in the non-exposed female cohort when the imputed case definition (cases with imputed date of first symptom plus cases with a known date of first symptom) for the other autoimmune diseases (all and only confirmed cases) was used. A significant cluster of 5 confirmed cases over a 3 day-period was detected, this period occurred 118 days after the reference date.

SatScan results for the non-exposed female cohort are presented in Table 600 and Table 604 (main analysis), Table 608 and Table 612 (imputed date) and Table 616 and Table 620 (diagnosis date).

A significant cluster was found in the concurrent male cohort when the case definition was used for the main analysis. The cluster was observed for other autoimmune diseases in which all cases were type 1 diabetes cases. A total of 4 type 1 diabetes cases were observed over a period of 1 day. The cluster of cases (n=4) occurred 5 days after the reference date. The same significant cluster was observed for the concurrent male cohort for other autoimmune diseases and type 1 diabetes when using the imputed case definition. The temporary analysis of AI thyroiditis was not performed because for the concurrent male cohort there were only 2 AI thyroiditis cases.

Similarly, a significant cluster was observed for the concurrent male cohort when the case definition based on the date of diagnosis was used. The cluster (n=21 cases) occurred over a period of 52 days and 111 days after the reference date for all the autoimmune diseases. When only the confirmed other autoimmune diseases were considered, the cluster included 19 cases over a period of 57119 days and occurred 11149 days after the reference date.

SatScan results for the concurrent male cohort are presented in Table 601 and Table 605(main analysis), Table 609 and Table 613 (imputed date) and Table 617 and Table 621 (diagnosis date).

No significant cluster was observed for the historical male cohort. SatScan results for the historical male cohort are presented in Table 602 and Table 606 (main analysis), Table 610 and Table 614 (imputed date) and Table 618 and Table 622 (diagnosis date).

11.5.2. Post-hoc analyses

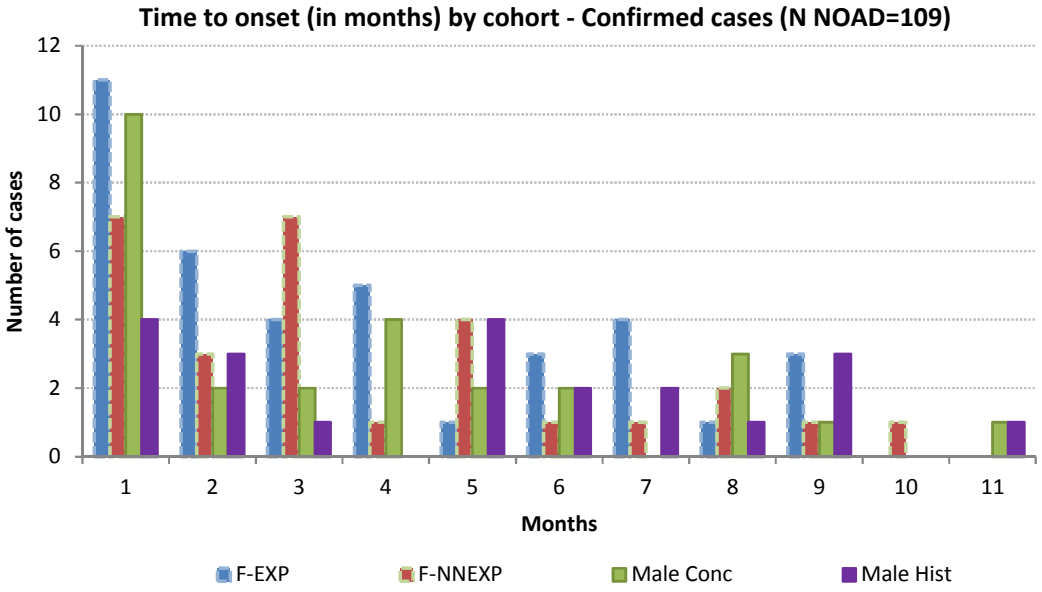
In addition to the analysis presented in the statistical methods section (Section 10.9), the following post-hoc analyses were performed (Section 10.9.4).

11.5.2.1. Time to onset analysis

A time-to-onset analysis of all the confirmed cases and, in particular, the autoimmune thyroiditis diseases cases was performed. The frequency of autoimmune diseases during the one year follow-up period by exposed/non-exposed status is presented in Table 631 (confirmed and non-confirmed cases) and Table 642 (confirmed cases).

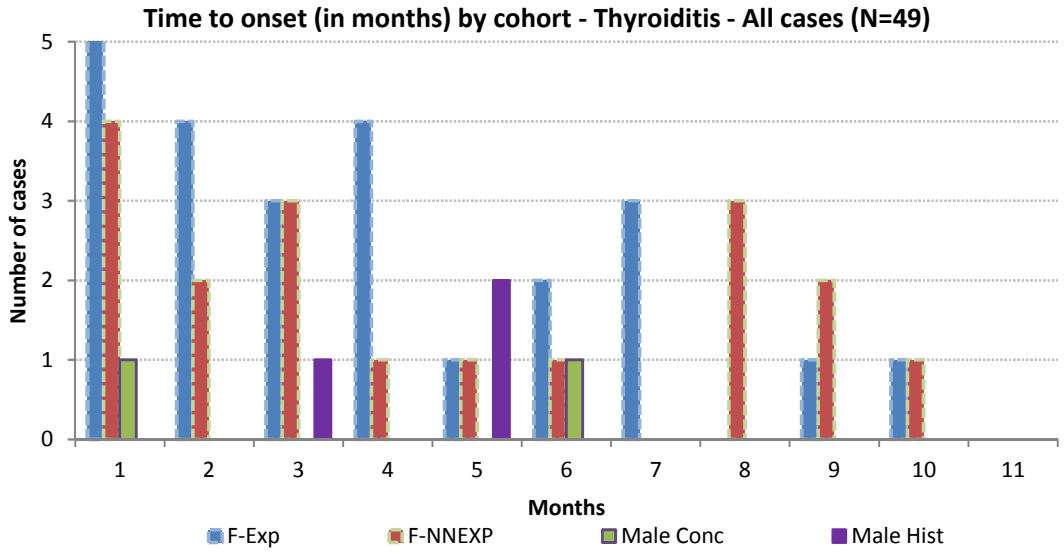
The time to onset for the confirmed cases (all autoimmune diseases) in each cohort is presented in the Figure 17. The number of cases tends to decrease overtime in the four cohorts.

Figure 17 Time to onset of confirmed autoimmune diseases by cohort



The time to onset of autoimmune thyroiditis cases in each cohort is presented in Figure 18. Most cases of any cohort occurred during the first 6 months.

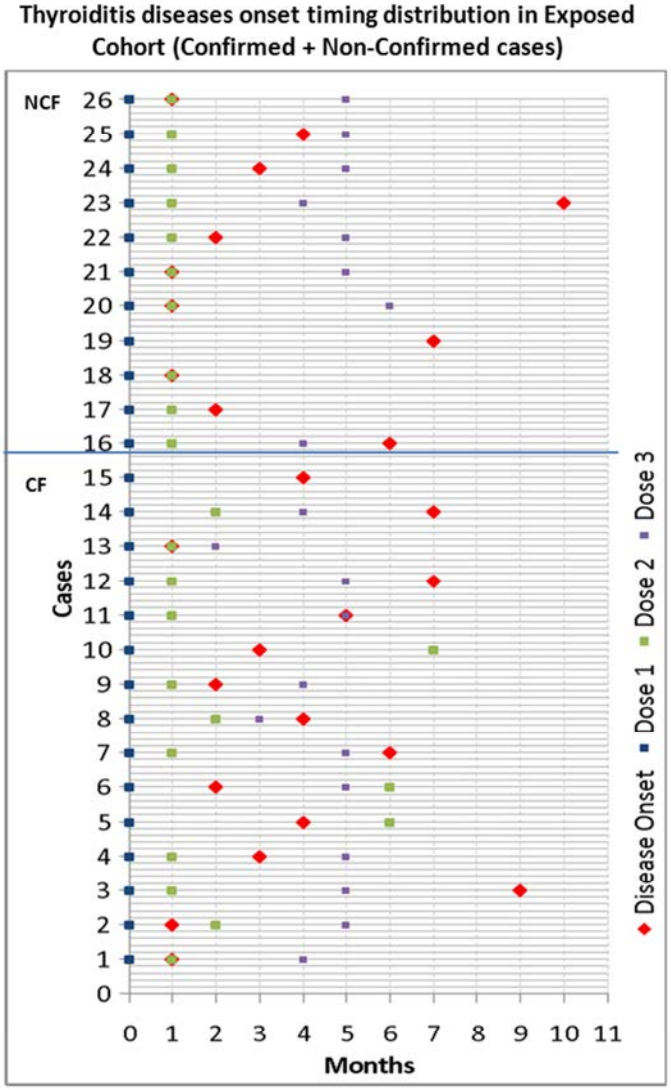
Figure 18 Time to onset of autoimmune thyroiditis cases by cohort



The disease onset for the autoimmune thyroiditis cases according to *Cervarix* vaccination is presented in Figure 19. The graphic analysis shows a random pattern of the disease onset.

The decrease in the number of cases over time could be explained by the study design. Indeed the autoimmune diseases were detected through algorithms identifying the disease diagnosis within one year from the reference date. From the disease diagnosis, the 1st date of symptom was identified by medical review of patient profiles which could lead to a higher identification of disease onset during the first few months after reference date.

Figure 19 Disease onset for the autoimmune thyroiditis cases according to Cervarix vaccination



Cases 2-4 & 16 are hyperthyroiditis , Case11 is a Down Syndrome and the others cases are hypothyroiditis

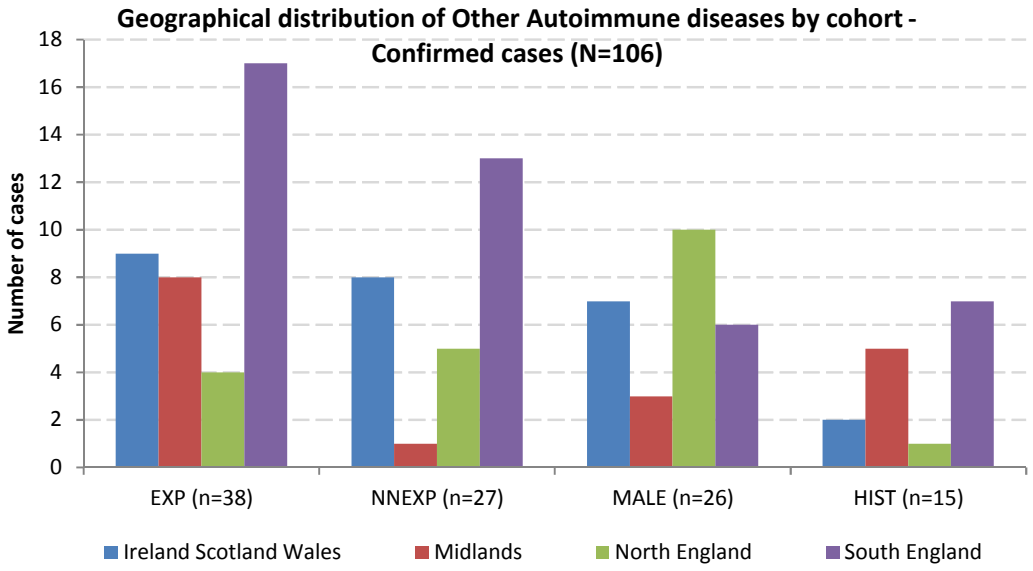
11.5.2.2. Geographical distribution

The geographical distribution of the cases was analysed. The data are presented in Table 623 and Table 624 (geographical distribution of the two co-primary endpoints), Table 625 and Table 626 (thyroid cases) Table 627 and Table 628 (Diabetes type 1 cases), Table 629 and Table 630 (Crohn's disease cases).

Figure 20 presents the number of confirmed cases in each region and by cohort. The majority of the cases occur in the South England region for the female cohort, while the proportion of cohort subjects in this region is equal to 31.8% for both female cohorts (second most represented region in our study cohorts after North England). However a large proportion of autoimmune disease cases are observed in the

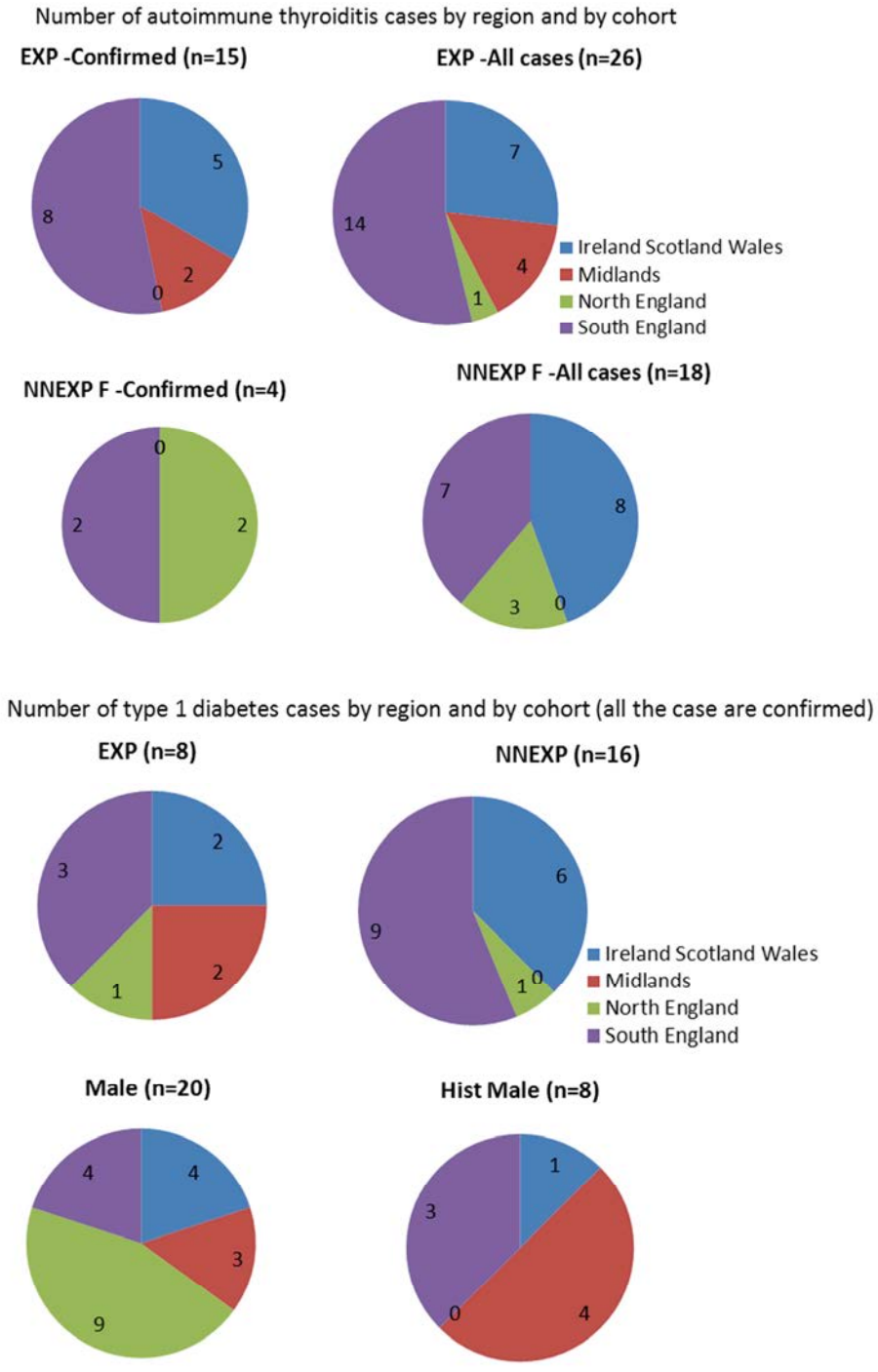
Northern Ireland-Scotland-Wales region (26/106 confirmed cases of other autoimmune diseases) representing 24.5% of the cases in this region, while this region represents less than 0.1% of the overall study population cohorts. This finding triggered another post-hoc analysis of the main case definition endpoint excluding subjects from Northern Ireland, Scotland and Wales.

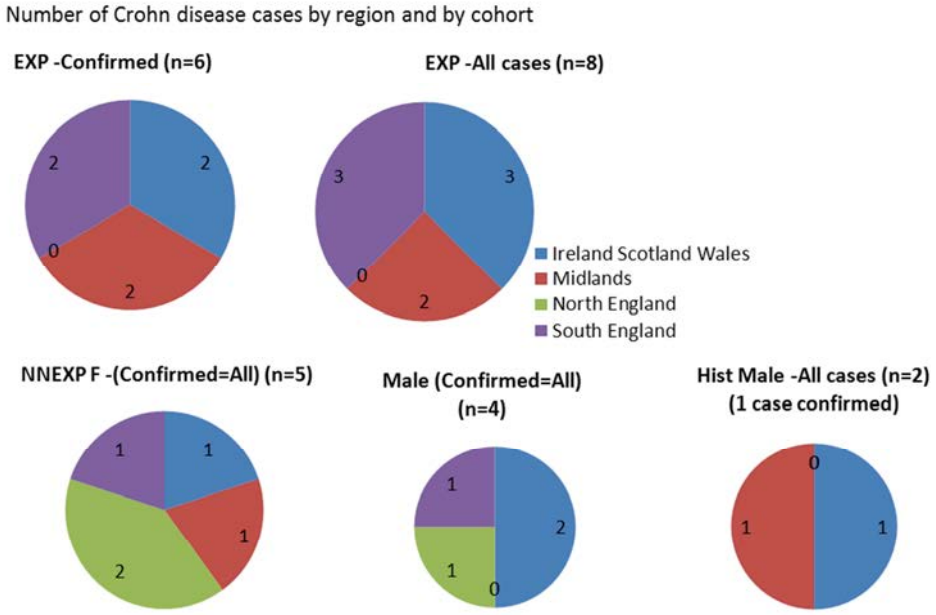
Figure 20 Geographical distribution of confirmed cases for Other autoimmune diseases



When individual diseases (thyroiditis, type 1 diabetes and Crohn's disease) are assessed, the majority of the cases occur in the South England region (Figure 21).

Figure 21 Geographical distribution of Thyroiditis, Type 1 diabetes and Crohn's disease cases by cohort





11.5.2.3. Autoimmune thyroiditis or hypothyroiditis/hyperthryroiditis analysis

An additional medical patient profile review was performed for all the autoimmune thyroiditis cases included in the main analysis (N=49) in order to classify the cases as hypo- or hyperthyroiditis (Table 12). Among the 49 cases, 2 cases (4.1%) were presented separately because the underlying Down's syndrome is known to be associated with increased risk of autoimmune diseases as part of polygrandular syndrome, 40 cases (81.6%) were hypothyroiditis and 7 cases (14.3%) were hyperthyroiditis (thyrotoxicosis).

The classification of thyroiditis cases and HES linkage is presented in Table 632 and Table 633 (all cases) and Table 643 and Table 644 (confirmed cases), respectively.

Table 12 Incidence rate of new onset of autoimmune thyroiditis cases after additional patient profile review – Known date of first symptom

Diseases		Exposed F cohort (Tot PY=64705) n	Exposed F cohort (Tot PY=64705) Incidence (n/100,000 PY) (95% CI)	Non-Exposed F cohort (Tot PY=64841) n	Non-Exposed F cohort (Tot PY=64841) Incidence (n/100,000 PY) (95% CI)	Adjusted IRR* (95%CI)
Hypothyroiditis	Confirmed cases	12	18.55 (9.58;32.40)	4	6.17 (1.68;15.80)	3.00 (0.97; 9.31)
	All cases	22	34.00 (12.95;38.16)	15	23.13 (21.31;51.48)	1.47 (0.76; 2.83)
Hyperthyroiditis	Confirmed cases	2	ND	0	ND	ND
	All cases	3	ND	3	ND	ND
Down's Syndrome	Confirmed cases	1	ND	0	ND	ND
	All cases	1	ND	0	ND	ND

Diseases		Concurrent M cohort (Tot PY=64859) n	Concurrent M cohort (Tot PY=64859) Incidence (n/100,000 PY) (95% CI)	Historical M cohort (Tot PY=64868) n	Historical M cohort (Tot PY=64868) Incidence (n/100,000 PY) (95%CI)	Adjusted IRR* (95% CI)
Hypothyroiditis	Confirmed cases	0	ND	0	ND	ND
	All cases	2	3.08 (0.37;11.14)	1	1.54 (0.04;8.59)	1.90 (0.17; 20.94)
Hyperthyroiditis	Confirmed cases	0	ND	0	ND	ND
	All cases	0	ND	1	ND	ND
Down's Syndrome	Confirmed cases	0	ND	0	ND	ND
	All cases	0	ND	1	ND	ND

ND – Not determined; IRR*= Incidence Rate Ratio adjusted for age group [9-17]-[18-25]

For autoimmune hypothyroiditis, the adjusted IRR was 3.00 [95%CI: 0.97-9.31] for confirmed cases in the two female cohorts, meaning that the risk is higher in the exposed cohort vs. non-exposed cohort (Table 12). When considering confirmed and non-confirmed cases the adjusted IRR was 1.47 [95%CI: 0.76-2.83]. For the male cohorts, no confirmed cases were observed and when considering all the cases the adjusted IRR was 1.90 [95%CI: 0.17-20.94]. These results confirm the point estimates previously calculated before the additional medical review and the classification of autoimmune thyroiditis cases.

The incidence rates of new onset of autoimmune thyroiditis cases are presented in Table 634 to Table 641 (all cases) and in Table 645 to Table 648 (confirmed cases).

11.5.2.4. Exclusion of the Northern Ireland-Scotland-Wales region analysis

The main analysis and incidence rate ratios were calculated after exclusion of the subjects in the Northern Ireland-Scotland &Wales region given the high proportion of cases observed in these region (see Section 11.5.2.2). The Table 13 shows the IRR (95%CI) for

female cohorts after exclusion of the subjects from Northern Ireland-Scotland-Wales region for other autoimmune disease and Crohn's diseases, type 1 diabetes, thyroiditis and hypothyroiditis.

Table 13 Incidence Rate Ratio (95%CI) after exclusion of Northern Ireland-Scotland-Wales region for female cohorts

Diseases	Adjusted IRR* (95%CI)
Other Autoimmune disease	1.53 (0.86 - 2.73)
Crohn's disease	1.01 (0.25 - 4.02)
Type 1 Diabetes Mellitus	0.60 (0.22 - 1.66)
Thyroiditis	2.50 (0.79 - 7.98)
Hypothyroiditis	1.75 (0.51 - 5.98)

IRR*= Incidence Rate Ratio adjusted for age group [9-17]-[18-25]

After exclusion of these regions, the IRRs were statistically non-significant (Table 13). For the autoimmune thyroiditis diseases, the rate ratio is still above 2 and non-statistically significant.

The incidence rates of confirmed 'other autoimmune diseases' were also computed for each of the 13 CPRD regions for female cohorts (Table 14). The incidences for the exposed female cohort in Northern Ireland, Scotland & Wales are between 77 and 400 times higher than the England regions, except for South England where the incidence rate is up to 2 times lower than in Northern Ireland, Scotland and/or Wales regions.

Table 14 Incidence rate of Other autoimmune diseases (confirmed cases) by regions for female cohorts

Regions	Other Autoimmune diseases					
	EXPOSED FEMALE			NON-EXPOSED FEMALE		
	IR (/100,000 py)	LL 95%CI	UP 95%CI	IR (/100,000 py)	LL 95%CI	UP 95%CI
North East	0.00	0.00	14.37	0.00	0.00	16.06
North West	34.42	7.10	100.60	47.56	12.96	121.78
Yorkshire & The Humber	42.46	1.08	236.55	31.05	0.79	172.99
East Midlands	135.91	37.03	347.98	31.96	0.81	178.05
West Midlands	73.69	20.08	188.67	0.00	0.00	68.10
East of England	63.45	7.69	229.27	65.94	17.97	168.83
South West	59.39	12.25	173.55	104.19	28.39	266.78
South Central	83.61	33.62	172.27	34.59	4.19	124.96
London	33.88	0.86	188.78	33.37	4.04	120.56
South East Coast	7 238.80	1 972.30	18 534.10	12 879.10	326.10	71 757.50
Northern Ireland	11 122.10	281.60	61 968.40	144 026.00	46 764.90	336 109.00
Scotland	14 038.40	4 558.20	32 760.80	17 119.80	2 073.30	61 842.40
Wales	10 502.70	2 165.90	30 693.40	10 893.20	275.80	60 693.20

11.6. Adverse events/adverse reactions

Not applicable.

12. DISCUSSION

12.1. Key results

- The present study did not show any evidence of increased risk for the two co-primary endpoints (neuroinflammatory/ophthalmic autoimmune diseases and other autoimmune diseases):
- The analysis of the risk for the individual diseases (diseases with more than 10 cases in both females cohorts) showed:
  - No evidence of increased risk of Crohn's disease:
  - A higher and significant risk of autoimmune thyroiditis in exposed female vs. non-exposed female cohort. When considering both confirmed and non-confirmed cases, the risk in female subjects was reduced and became non-significant.
  - A, not significantly, reduced risk of Type 1 Diabetes mellitus in the exposed female cohort vs. non-exposed female cohort. A significant higher risk in the concurrent vs. historical male cohorts was observed. For the Type 1 Diabetes Mellitus results, a protocol-specified adjusted risk was calculated for the female cohorts based on the significant effect observed in male cohorts, which showed a significant reduced risk.
- The sensitivity analysis based on the two additional case definitions (i.e. imputed date for first symptom and disease diagnosis date) showed similar results for the co-primary endpoints and the individual diseases analysis except for autoimmune thyroiditis.
- The analysis by age group showed similar results for autoimmune thyroiditis and type 1 diabetes in the [9-17] year age group, which represented 90% of the overall study population.
- The analysis by dose in the exposed cohort showed a decrease in incidence after each successive dose for the category of other autoimmune diseases and in the three individual diseases – autoimmune thyroiditis, Crohn's disease and type 1 diabetes. However a similar decrease over time was observed in the unexposed cohorts. This finding could be the result of the procedure used to identify AD. The first important date which was searched for was the diagnosis date and then for subjects with a diagnosis date within one year of the reference date, the date of first symptom was investigated. Hence it is possible that subjects who were diagnosed after the one year time period from the reference date could have been missed in this procedure.
- Most of the autoimmune thyroiditis (confirmed and non-confirmed cases) were hypothyroiditis cases (81.6%).

- Incidence rate of other immune disease and more specifically of hypothyroiditis (confirmed and non-confirmed cases) was particularly high in the three regions of the United Kingdom (Scotland, Northern Ireland and Wales) including in some regions very few subjects at risk (less than 10 person-years (P-Y)). Further discussion of these results occurred with the CPRD research team, but an explanation of these findings is unclear.

12.2. Limitations

To address safety research with very rare outcomes, most epidemiological studies are based on existing disease-specific registries or large healthcare databases, such as CPRD GOLD in the UK. A UK database was chosen because it was one of the first countries to implement *Cervarix* through a school-based Universal Mass Vaccination (UMV) campaign.

CPRD GOLD is a GP database enriched by the possibility to have access to different sources of information: HES data, “free text” (such as specialist letters or hospital discharge reports) and laboratory or imaging results. A feasibility assessment performed before finalisation of the protocol and of the study start was positive despite some limitations such as the rarity of some of the outcomes of interest and the fact that CPRD GOLD is based primarily on GP practices. For this study, a pre-specified list of outcomes of interest was defined and, for most of them, they are mainly diagnosed and characterized in a hospital setting (HES linkage was 57.8% between CPRD GOLD and HES in this study). Occurrence of autoimmune disease in the paediatric and young adult population is rare. GPs might have difficulties to identify and characterize their occurrences and therefore, they might not identify or under-report some symptoms including the first symptoms for identification of onset of disease. Measures were taken to minimise bias in the study design, with the inclusion of unexposed female and male cohorts for comparison and also in the study procedure with the creation of patient profiles and validation by external experts for optimal case ascertainment.

The advantage of CPRD GOLD is that information is available for each subject over a couple of years (most of the time since birth for children and teenagers). Therefore, a cohort design is feasible. Because of the rarity of the outcomes of interest, the study design included four cohorts of 65,000 subjects each. In order to prevent inclusion of vaccinated subjects in an ‘unexposed’ cohort, the vaccinated exposed cohort was compared to a historical unexposed cohort before the start of the *Cervarix* programme in the UK. In addition, two unexposed male cohorts were enrolled in order to assess a possible change over time in the incidence rate of autoimmune diseases in CPRD GOLD independent to *Cervarix* introduction. Finally, for the exposed cohort, an additional SCCS analysis was performed in order to control for all fixed confounders not varying with time during the follow-up period. The detection of potential temporal associations was tested using a temporal cluster analysis.

A limitation was a possible lack of specificity of the pre-defined algorithms. The initial step for case selection was performed using algorithms based on medcodes for the initial extraction. The medical records were not made available for verification of the cases and this is a well-known limitation of using CPRD. However, this limitation was restrained

by manual review of all other available information from other CPRD sources and adjudication of the cases. The multiple sources of information within CPRD GOLD were of added value for assessing the outcomes of interest. However, it was quite complex to combine this information altogether and to perform a manual review of all this medical information (all the details are provided in a separate document named Pallas Methodology Report (Annex 5) prepared by Pallas). The study team created the "patient profiles" and reviewed all the information retrieved from the different sources and this intensive effort allowed the confirmation of 385 (81.7%) cases with first symptoms among 471 cases with date of diagnosis. Variables retrieved from this review were entered in the database to complete as much as possible the data missing from using medcodes only. In addition, after this intensive step, autoimmune disease cases for which the aetiology was uncertain after the first review were validated by a panel of external experts to adjudicate the final classification of these cases. For the cases with no date of onset of first symptoms and/or confirmation of the aetiologies, sensitivity analyses were performed to complement the main analysis based on confirmed cases with a known date for the onset of first symptoms.

The team used an imputation method to substitute unknown first symptom dates. Any imputation has limitations. Here, for reasons of simplification, it was decided to impute the median time between first symptoms and diagnosis for all missing first symptom dates. This has been done by individual disease to take into account disease specificity. For example it is well-known that time between first symptoms and diagnosis is short for diseases such as Guillain-Barré Syndrome and can be very long for other diseases such as SLE or rheumatoid arthritis. Figure 9 clearly reflects these differences. The chosen imputation methods could create artificial temporal clusters, however the incidence rate estimate should not be biased, and the results of the temporal analysis suggested this risk of creating temporal clusters was well-controlled. These imputed first symptom dates were not used for the analysis of temporal cluster of events. Other approaches could potentially be applied such as multiple imputations which would give a more realistic distribution of the disease onset.

For the two co-primary endpoints (neuroinflammatory/ophthalmic autoimmune diseases and other autoimmune diseases; see Section 10.4.1) the present study did not show evidence of increased risk, as detailed in Section 11.4 Main results. Of course, the length of the risk period may not be well-defined per outcome of interest (although even in this study, all known risk periods were taken into account) and this is a limitation for aggregated endpoints. As secondary endpoints, for individual diseases with > 10 cases (Crohn's disease, type 1 diabetes and autoimmune thyroiditis), statistical analyses were performed.

The study team found an increased risk of autoimmune thyroiditis in the vaccinated cohort. However, the background incidence of autoimmune thyroiditis in CPRD for the studied age group was within the same range as the vaccinated cohort in this study, indicating that the incidence rates were still within expected ranges (see background incidence rates of Combined Hashimoto's and Graves' disease for UK in Table 4 and then compare to rates in Table 2 and Table 135). The diagnostic methods for autoimmune thyroiditis might have changed over time, leading to an increase in incidence. This result could also be found by chance. There is always a difficult threshold between increasing

the sample size in the vaccinated cohort to reduce the likelihood of chance findings and making the study too large to be completed in an acceptable timeframe.

One difficulty of these hypothesis-driven studies with search of rare events is that the immune-mediated phenomena following vaccination are still poorly understood. The use of already collected information did not allow any assessment of, for instance, possible polymorphic associations in immune-related genes (genetic predisposition such as some HLA-DR haplotype or certain environmental exposure that may trigger the occurrence of autoimmune diseases. Most of the subjects were followed since birth and a lot of information has been retrieved from the different data sources; however, familial history of autoimmune disease is not always documented. This is an area that probably deserves further investigation in the future.

An additional limitation could be the risk of false negative cases (lack of sensitivity). The case ascertainment as described above ensured a high specificity of the endpoint(s), but the team did not review the subject profiles of the non-cases (because unfeasible for 65,000 subjects per cohort), and this means that possible cases of ADs could have been missed. However a high specificity was required to avoid a bias towards the null hypothesis whereas high sensitivity was not essential.

Studies of rare events typically have low power and therefore only large risk increases can be detected. The present study also shares this limitation. This is the reason two composite co-primary endpoints were defined. The observed incidence of the co-primary endpoint ‘other autoimmune diseases’ was in alignment with the sample size calculation assumptions, but it was lower than expected for the neuroinflammatory diseases. However, the absence of confirmed neuroinflammatory disease cases in the exposed cohort was quite re-assuring.

12.3. Interpretation

The use of the CPRD GOLD database was a unique opportunity as *Cervarix* was used during 3 years for universal mass vaccination of the young women. Despite the fact that this is a GP database, some of the limitations were overcome by an intensive data management including case ascertainment and by the study design.

The present study showed no evidence of increased risk of most conditions in the exposed compared to the unexposed subjects. The observed incidence rates were within the range of background incidences reported in the literature (see Table 3 and Table 4).

A statistically significant increased risk of AI thyroiditis in the exposed female cohort vs. non-exposed female cohort was observed for confirmed cases (see Section 11.4.1.3), although the risk was diluted and became non-significant when looking at confirmed+non-confirmed cases. Most of the reported AI thyroiditis cases were hypothyroiditis (40/49 cases). An over-representation of AI thyroiditis cases was noted for the combined Northern Ireland-Wales-Scotland regions compared to the rest of the UK: 5 of 49 AI thyroiditis cases, but the Northern Ireland-Wales-Scotland regions contributed only 0.07% of the total study population. The estimated background UK incidence rate of AI thyroidits in 10-14 year-old females combining Hashimoto’s disease

(hypothyroiditis) and Graves' disease (hyperthyroiditis) was 3.4 per 100,000 P-Y with another estimate for hyperthyroidism in a Scottish population including adults and children of 99.0 per 100, 000 P-Y (Table 4). Hence for a cohort of 65,000 subjects, the range of expected cases (2.2-64.4) includes the observed 49 cases. No increased incidence of AI thyroiditis was noted in previous Cervarix safety analyses involving the pooling of data from multiple clinical studies [Descamps, 2009; Prophylactic HPV-16/18 L1 VLP Vaccine Formulated with AS04. Investigator Brochure Edition 11, 2012; Angelo, 2014a]. In an interim analysis of a Finnish Cervarix safety/immunogenicity community randomized study, the incidence rate of AI thyroiditis was noted to be 8.3 per 100,000 P-Y which was in line with the background rates in the UK [HPV-040 PRI, 2013; Table 4]. Post-marketing experience with *Cervarix* has not identified an increased rate of AI thyroiditis compared to the background rates in published literature [Angelo, 2014b].

The increased risk of AI thyroiditis in the exposed female cohort vs. non-exposed female cohort for confirmed cases could be the result of a type I error as mentioned in the previous section on sample size considerations.

In a study of the quadrivalent human papillomavirus (HPV4) vaccine administered to women in California, USA, a similar elevation in rate of combined Hashimoto's and Graves' disease and particularly a statistically significant elevation of Hashimoto's disease was noted [Chao, 2011]. In the same study the incidence of type 1 diabetes was also reduced in subjects receiving HPV4 vaccine, with a similar reduction noted in subjects receiving *Cervarix* vaccine in the current study [Chao, 2011; Section 11.4.1.3 including Table 180 & Table 598]. In a case-control study looking at autoimmune disorders following HPV4 vaccination in France, no HPV4-vaccinated subject was noted to develop thyroiditis [Grimaldi-Bensouda, 2014].

With regard to the geographical localisation to Northern Ireland-Wales-Scotland regions, Hunter et al. estimated an incidence of hypothyroiditis in Scotland (Tayside region) of 135 per 100,000 person-years for the period covered from 1993 to 1995 in subjects aged less than 22 years [Hunter, 2000]. In the same Tayside region, [Leese, 2008] showed evidence for increasing incidence of hyperthyroiditis and hypothyroiditis in Tayside between 1994 and 2001, and a growing proportion of these cases in females under 20 years of age.

Overall, the available data do not suggest a safety signal for increased risk of AI thyroiditis following vaccination with Cervarix based on the following:

- No cluster with regards to time to onset and dosing considering the date of disease onset was observed in the 49 cases of AI thyroiditis observed in the study. The individual review of the cases concluded that it was not consistent with vaccination having caused the events, considering the known natural progression of the disease, i.e. these cases could represent pre-existing conditions at the time of vaccination. Similar conclusions were published with the HPV4 vaccine [Chao, 2012].
- The increased risk of AI thyroiditis and hypothyroiditis in vaccinated subjects was decreased when excluding cases from Northern Ireland, Scotland and Wales, which represent 0.07% of the population included in this analysis.

- The increasing incidence of hypothyroiditis over time in Scotland reported in the literature supports the disproportionately large number of cases of AI thyroiditis observed in Northern Ireland-Scotland-Wales in this study [Hunter, 2000; Leese, 2008].

12.4. Generalisability

Based on the present study in the UK, the vaccination with *Cervarix* in young women does not seem to trigger the onset of autoimmune diseases.

The evidence from the current study in CPRD GOLD, past and current clinical studies using *Cervarix* e.g. HPV-040 PRI study, pooled safety analysis for multiple clinical studies and post-marketing experience with *Cervarix*, do not suggest a safety signal for increased risk of autoimmune thyroiditis including hypothyroiditis in subjects receiving *Cervarix* – See Section 12.3 for further details.

13. OTHER INFORMATION

Not applicable.

14. CONCLUSION

Autoimmune diseases are rare chronic inflammatory conditions which can be organ specific or systemic. Loss of immunological tolerance of self-antigens is considered as a trigger for autoimmune diseases. Both intrinsic (inherited) and extrinsic (e.g. environmental) factors could contribute to the pathogenesis. Adjuvanted vaccines are considered as a potential external trigger for onset of autoimmune diseases.

The present study carried out in cohort of 65,000 Cervarix vaccinated women aged 9-25 in the UK does not support an increased risk of autoimmune disease during the period of 1 year following vaccination. These results complement and confirm the findings from the Cervarix clinical trials and Cervarix routine pharmacovigilance.

For the 49 AI thyroiditis cases, no cluster with regards to *Cervarix* dosing and date of disease onset was observed. The individual review of the cases concluded that it is not consistent with vaccination having caused the events, considering the known natural progression of AI thyroiditis, i.e. the cases observed could represent pre-existing conditions at the time of vaccination. Similar conclusions were published for the HPV4 vaccine.

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