09 September 2022

Immune thrombocytopenia following vaccination with DTaP-IPV or TdaP-IPV in children

Administrative details of the data analysis	
Substance(s)	Diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccine (adsorbed), diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccine (adsorbed) reduced antigens content
Condition/ADR(s)	Immune thrombocytopenia
Short title of topic	Immune thrombocytopenia and DTaP-IPV / TdaP-IPV vaccines
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1. Rationale and background

Immune thrombocytopenia (ITP) is known to occur after many types of infections, including numerous vaccine-preventable diseases.(1) In approximately two-thirds of ITP cases, there is a history of a preceding infectious illness in the days to weeks before ITP onset.(1) Because vaccines are designed to induce an immune response that mimics natural infection to produce immunologic protection, it is possible that vaccines besides might trigger ITP.(1) There have been case reports of ITP after childhood vaccines, including MMR, hepatitis B vaccine (HBV), diphtheria-tetanus pertussis vaccine (DTP), and hepatitis A vaccine (Hep A).(2-5) However, the risk of ITP after childhood vaccines other than MMR is not well known. (3) The World Health Organization (WHO) recommends diphtheria, tetanus, and pertussis and poliomyelitis immunization during infancy for all children worldwide.(6) The combined vaccine diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccine (adsorbed), also referred to as DTaP-IPV, is indicated for primary vaccination in infants and for booster in children who have previously received a primary vaccination. The diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccine (adsorbed), reduced antigens content, also referred to as TdaP-IPV, is indicated for re-vaccination of children (≥4 years). (7)

To support regulatory discussions around these combined vaccines (DTaP-IPV or TdaP-IPV), it was proposed to generate estimates on the use of these combined vaccines in the general population, and incidence rates for ITP in the general and exposed population across three European databases IQVIA™ Medical Research Data (IMRD) UK, IQVIA™ Disease Analyser France, and IQVIA™ Disease Analyser Germany.

2. Research question and objectives

This study aimed at describing:

- How the diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines (DTaP-IPV or TdaP-IPV) were used in the general population?
- How has use of the vaccine changed with time?
- What was the event rate of immune thrombocytopenia in the general population?
- What was the event rate in the population exposed to the vaccine?

3. Research methods

3.1. Study design

This was a cohort study describing vaccine exposure, population incidence rates of immune thrombocytopenia, and (where possible) incidence rates of immune thrombocytopenia in the vaccine exposed population.

3.2. Setting and study population

The study population was the general population (UK) and patients visiting general practices (France and Germany). Analyses were carried out in France, Germany, and UK databases as sufficient numbers of exposures/events were recorded.

3.3. Data sources

The following databases were used: IQVIA™ Medical Research Data (IMRD) UK, IQVIA™ Disease Analyser France, and IQVIA™ Disease Analyser Germany . Brief descriptions of these databases are provided in Annex 1.

3.4. Variables

Exposure

In IMRD (UK) database, vaccine exposure was identified using diagnostic Read codes (READ Coded Clinical Terms, datadictionary.nhs.uk), which are commonly used to record administered vaccines in general practice (i.e., as diagnostic). Although less common, vaccine exposure can also be identified from prescription data, and these were also used in the analysis.

In the IQVIA™ Disease Analyser France and Germany databases, vaccine exposure was identified from prescription data. Paediatric practices and GP practices was included in Germany based on prescribing data showing that 92.7% of patients that received a prescription for the vaccines of interest since 2011 (59,883 out of 64,615 patients) were identified in these practices. Paediatricians are also part of the primary care in Germany, where children may visit a paediatrician instead of a GP.

Annex 2 shows the codes that were used for each database.

Outcome

Immune thrombocytopaenia was identified through Read codes for IMRD (UK) database and ICD10 codes for the IQVIA™ Disease Analyser Germany and France databases (See Annex 2). The main analysis was based on codes considered to be more specific for immune thrombocytopenia, and excluded codes for secondary thrombocytopenia and thrombocytopenia, unspecified.

Other variables

Vaccine utilisation and event rates for immune thrombocytopenia was stratified by age group, gender, and year administered. Age was categorised as: <3 years, 3-6 years, 7-11 years, 12-17 years, 18 years and more.

3.5. Statistical analysis

3.5.1. Main statistical methods

a. **Vaccine exposure:** We described vaccine exposure as counts of patients with a first exposure stratified by age, sex, and year of general practice visit.

b. **Event rates in the general population**: We described the incidence of new onset immune thrombocytopenia in patients contributing patient time to the databases listed above. Patients were required to have a minimum observation time of 365 days prior to entering into each period in order to establish whether events observed during the period are incident (first-ever) cases. Patients were excluded from the analysis if they have any prior history of any of the selected codes for thrombocytopenia in the database. The study period varied according to the years of coverage in the three databases (UK, France and Germany). For IMRD (UK) database, the covered period was from 2004 to 2019. For IQVIA™ Disease Analyser France and Germany databases, the covered period was from 2011 to 2021.

- Numerator: The numerator consisted of the number of patients who experience the event of interest (immune thrombocytopenia) during the yearly or quarterly time period. Patients with a baseline history of immune thrombocytopenia were excluded. Included patients contributed only to one event.
- Denominator: The denominator was defined as patient follow-up time. As with the numerators, patients with a baseline history of immune thrombocytopenia at the start of each quarter were excluded. Patient follow-up time was truncated at the occurrence of the first event after which they did not contribute to the analysis.

  Follow-up time was calculated using the following formula:

  Follow up time (years) = ((end date for the period – start date for the period + 1))/365

  Time was truncated where patients left the study cohort part way through a time period, where they have an event or at the end of the study period.

The incidence rate for immune thrombocytopenia was defined as the number of events divided by the total follow up time. The incidence rate was calculated using the following formula:

Incidence rate = (number of new onset events)/(total follow up time (years))

The incidence is presented as the number of events per 100,000 person-years and was calculated for the entire population as well as stratified by year, gender, and age group. Confidence intervals around incidence rates were calculated using exact method.

c. **Event rates among exposed patients:** To describe the event rate of new onset immune thrombocytopenia following exposure to the vaccine, a rate was calculated using a similar methodology described in section (b) above but restricted to only those patients known to have been exposed to the vaccine. Exposed patients were followed up for a maximum of 1-month and 3 months following first exposure. Thus, the incidence rate was calculated as new onset events divided by the total duration of follow-up time in years. Patients were censored from the analysis if they leave the population (i.e., moved practice, die, or reached the end of follow-up for their practice).

3.5.2. Sensitivity analysis

In a sensitivity analysis code for secondary thrombocytopenia and thrombocytopenia unspecified were also included.

Analyses were completed by EMA researchers using SAS. In accordance with database rules on the management of low cell counts, cells with low numbers (<6 in the IMRD database and <10 in IQVIA™ Disease Analyzer France, THIN® Spain, Italy and Romania) were removed prior to publication of this report. Additional cells may have been redacted (events/patients typically being rounded up to the nearest 10) if needed in order to ensure that the aforementioned low cell counts cannot be re-identified. This may include both events/patients and follow-up times.

3.6. Quality control

The study was conducted according to the ENCePP code of conduct (European Medicines Agency 2018). Standard operating procedures or internal process guidance were adhered to for the conduct of the

study. These procedures include rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results.

All documents underwent at least one round a review by an experienced reviewer, while the results from the statistical analysis were either reviewed or checked via double coding.

The quality control of the data is the responsibility of the data holder.

4. Results

4.1. Descriptive data

4.1.1. Vaccine utilisation

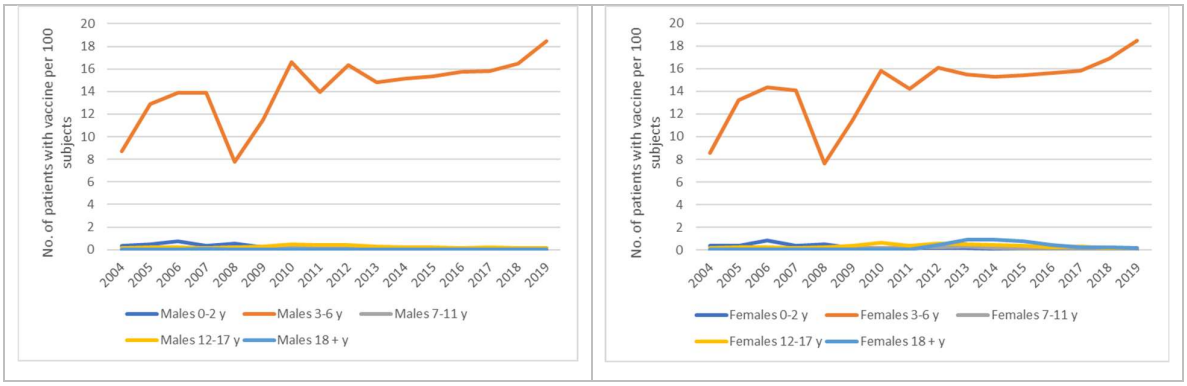
IMRD (UK)

Table 1 shows the yearly number of patients with a prescription, and Figure 1 shows the prevalence of use (i.e., the percentage of all subjects in the database) of diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines by age, sex and year. Use in the 3–6-year age range predominated, reflecting NHS childhood vaccination schedules in recent years.

Table 1 Number of patients in the IMRD (UK) database with a prescription for diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines (DTaP-IPV or TdaP-IPV) stratified by age, sex and year

	0-2 years		3-6 years		7-11 years		12-17 years		18 + years	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
2003	41	29	1,224	958	23	7	17	19	63	64
2004	47	44	1,555	1,324	14	<6	38	35	67	66
2005	65	49	2,453	2,211	32	20	74	56	75	93
2006	109	119	2,804	2,601	32	30	74	66	121	142
2007	68	82	2,990	2,721	25	21	64	54	180	164
2008	92	79	1,781	1,628	51	28	82	81	75	103
2009	42	39	2,542	2,399	58	49	123	122	100	119
2010	29	33	4,095	3,714	43	48	208	225	139	125
2011	55	48	4,935	4,765	65	67	210	162	183	207
2012	44	51	5,187	4,758	119	85	222	259	212	2,314
2013	65	56	5,810	5,708	95	102	150	228	237	5,291
2014	29	27	6,574	6,310	88	67	140	241	257	5,883
2015	22	15	7,292	6,980	72	54	165	268	305	5,323
2016	28	23	7,877	7,420	55	58	106	156	301	3,413
2017	24	7	7,969	7,545	57	57	146	190	208	1,974
2018	21	18	8,243	7,928	74	47	80	109	205	1,613
2019	25	15	9,073	8,606	80	82	106	119	322	1,579

*Figure 1 Yearly prevalence of use in the IMRD (UK) database for diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines (DTaP-IPV or TdaP-IPV) in males and females between 2011 and 2019 by age group **



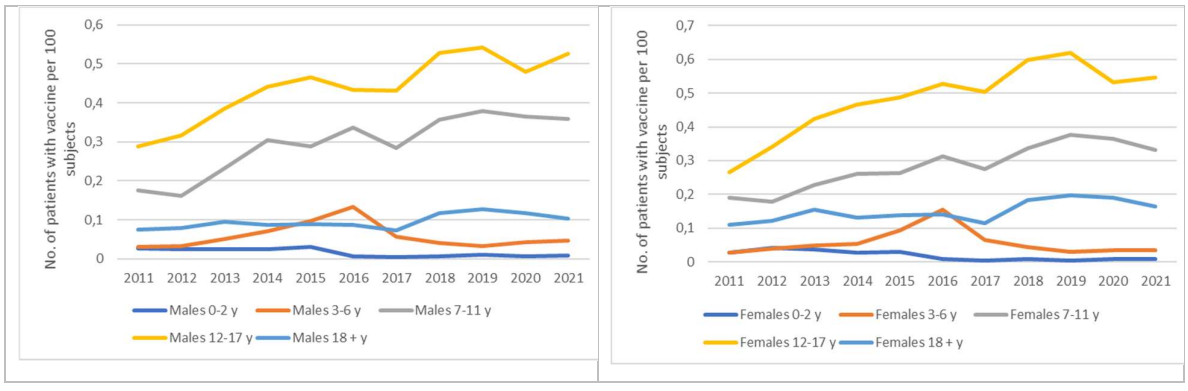
IQVIA™ Disease Analyser Germany

Table 2 shows the yearly number of patients with a prescription, and Figure 2 shows prevalence of use (i.e. the percentage of all subjects in the database) of diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines by age, sex and year. A low level of use was observed. The highest level of use was observed in the age groups 7-11 and 12-17 years, where an increase in use was noted between 2011 and 2019.

Table 2 Number of patients in the IQVIA™ Disease Analyser Germany database with a prescription for diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines (DTaP-IPV or TdaP-IPV) stratified by age, sex and year

	0-2 years		3-6 years		7-11 years		12-17 years		18 + years	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
2011	18	15	25	25	191	162	260	275	1156	941
2012	30	16	39	30	193	162	368	337	1425	1068
2013	28	17	52	51	266	250	502	450	1968	1412
2014	22	19	59	73	317	340	580	542	1784	1365
2015	25	24	107	100	327	330	628	585	1951	1455
2016	9	5	194	154	423	425	762	602	2264	1611
2017	5	5	83	67	386	372	756	622	1946	1415
2018	8	6	58	49	471	465	887	752	3162	2246
2019	5	9	39	40	506	471	900	751	3389	2422
2020	7	5	39	46	438	404	710	606	3088	2126
2021	8	7	36	45	325	320	637	584	2554	1745

*Figure 2 Yearly prevalence of use in the IQVIA DA Germany database for diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines (DTaP-IPV or TdaP-IPV) in males and females between 2011 and 2021 by age group **



* The prevalence might be overestimated during the last year(s) due to an artificial decrease in the denominator (but not numerator) towards the database end that depends on the frequency of visits.

The corresponding results for vaccines with and without reduced antigen content are shown in Annex 3 (**Tables S1-S2** and **Figures S1-S2**). Most of the use concerned vaccines with reduced antigen content.

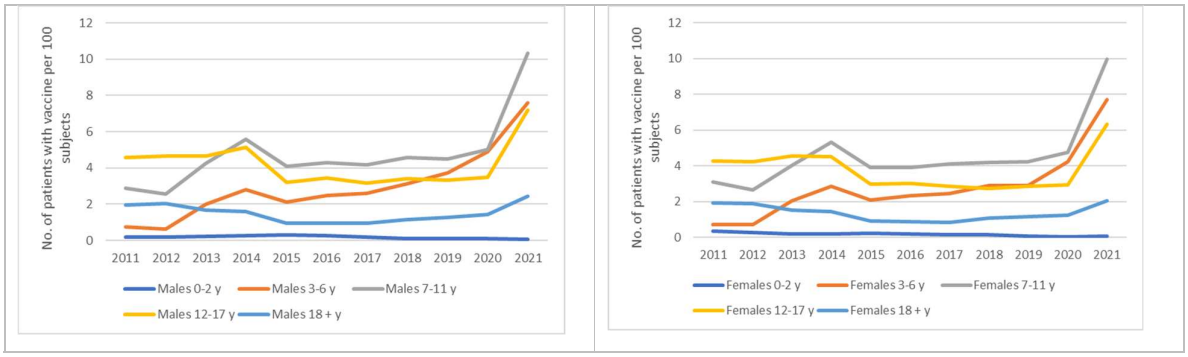
IQVIA™ Disease Analyser France

Table 3 shows the yearly number of patients with a prescription, and Figure 3 the prevalence of use (i.e. the percentage of all subjects in the database) of diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines by age, sex and year. In France the highest level of use was observed in the age group 7-11 years, followed by the age groups 3-6 years and 12-17 years.

Table 3 Number of patients in the IQVIA™ Disease Analyser France database with a prescription for diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines (DTaP-IPV or TdaP-IPV) stratified by age, sex and year

	0-2 years		3-6 years		7-11 years		12-17 years		18 + years	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
2011	16	27	98	83	414	426	715	636	2694	3101
2012	20	23	92	98	418	406	834	719	3258	3582
2013	24	21	351	324	804	715	979	904	3156	3393
2014	38	24	583	538	1263	1099	1309	1052	3606	3831
2015	44	29	487	427	1040	891	909	771	2413	2674
2016	39	23	610	497	1201	948	1036	828	2606	2763
2017	26	20	637	519	1157	1014	974	804	2707	2789
2018	17	20	746	607	1267	1026	1044	758	3298	3655
2019	14	11	858	586	1200	1011	1006	799	3741	4054
2020	12	<10	906	709	1130	959	915	717	4004	4154
2021	10	<10	1328	1182	1840	1549	1536	1295	5920	6080

*Figure 1 Yearly prevalence of use in the IQVIA DA France database for diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines (DTaP-IPV or TdaP-IPV) in males and females between 2011 and 2021 by age group **



* The prevalence might be overestimated during the last year(s) due to an artificial decrease in the denominator (but not numerator) towards the database end that depends on the frequency of visits.

The corresponding results for vaccines with and without reduced antigen content are shown in Annex 3 (**Tables S3-S4** and Figures **S3-S4**).

4.1.2. Event rates in the general population

The population event rate for immune thrombocytopenia overall and by gender and age group is shown in **Table 4** for the IMRD (UK) database (2004-2019), in **Table 5** for the IQVIA™ Disease Analyser Germany database (2011-2021) and in **Table 6** for IQVIA™ Disease Analyser France database (2011-2021).

4.2. Main results

4.2.1. Event rates among exposed patients

IMRD UK

A comparison of background and vaccine-exposed incident rates of immune thrombocytopenia in the IMRD (UK) database between 2004 and 2019 stratified by gender and age group is shown in **Table 4**. In the analysis looking at the 31 days following vaccine exposure, there was a single event only, however, the 95% confidence interval for the observed event rates overlapped with the expected event range in the population. Seven patients had a diagnosis of immune thrombocytopenia during up to 90 days of follow-up. There was a cluster of cases in females in the 3-6 years category.

IQVIA™ Disease Analyser Germany

Between 2011 and 2021 the event rate for immune thrombocytopenia in patients exposed to the vaccines compared to background rates in the general population in the IQVIA™ Disease Analyser Germany database, overall and by gender and age group is shown in **Table 5**. No patient had a diagnosis of immune thrombocytopenia during up to 90 days of follow-up. The upper confidence intervals were relatively high due to a limited number of follow-up years.

IQVIA™ Disease Analyser France

Between 2011 and 2021 the event rate for immune thrombocytopenia in patients exposed to the vaccines compared to background rates in the general population in the IQVIA™ Disease Analyser France database, overall and by gender and age group is shown in **Table 6**. A single patient had a diagnosis of immune thrombocytopenia during up to 90 days of follow-up. The 95% confidence interval for the observed event rates were within the expected event range in the population.

Table 4. *Incidence of new onset immune thrombocytopenia* in the general population and in patients exposed to vaccines in the* ***IMRD (UK) database*** *per 100,000 years of follow-up between 2004 and 2019 overall, and by gender and age group*

	General population		Exposed patients to vaccines			
	Background rates		Follow-up (FU) for one month (31 days)		Follow-up for three months (90 days)	
	IR per 100,000 person-years	95% CI	IR per 100,000 person-years	95% CI	IR per 100,000 person-years	95% CI
Overall	**4.88**	(4.57-5.20)	**6.64**	(0.17-37.00)	**16.38**	(6.59-33.75)
Male	**4.53**	(4.11-4.98)	**0.00**	(0.00-53.88)	**5.15**	(0.13-28.67)
Female	**5.23**	(4.78-5.71)	**12.18**	(0.31-67.84)	**25.76**	(9.45-56.06)
0-2 years	**10.33**	(8.07-13.04)	**0.00**	(0.00-7600)	**0.00**	(0.00-2673)
3-6 years	**6.69**	(5.13-8.57)	**8.09**	(0.20-45.07)	**17.10**	(6.28-37.23)
7-11 years	**3.12**	(2.17-4.34)	**0.00**	(0.00-3244)	**0.00**	(0.00-1141)
12-17 years	**2.64**	(1.85-3.65)	**0.00**	(0.00-1075)	**0.00**	(0.00-378.5)
18 + years	**4.85**	(4.50-5.22)	**0.00**	(0.00-168.2)	**16.10**	(0.41-89.71)

* Immune thrombocytopenia was defined as Read codes that correspond to an ICD 10 code of D69.3 or D69.4.

IR= incidence rate; 95% CI confidence interval for incidence rate

Table 5. *Incidence of new onset immune thrombocytopenia* in the general population and in patients exposed to vaccines in the* ***IQVIA™ Disease Analyser Germany database*** *per 100,000 years of follow-up between 2011 and 2021 overall, and by gender and age group*

	General population				Exposed patients to vaccines							
	Background rates				Follow-up (FU) for one month (31 days)				Follow-up for three months (90 days)			
	Years of follow-up	No. of outcomes	IR per 100,000 person-years	95% CI	Years of follow-up	No. of outcomes	IR per 100,000 person-years	95% CI	Years of follow-up	No. of outcomes	IR per 100,000 person-years	95% CI
Overall	29.549.204	2064	**6,98**	(6,69-7,29)	3.482	0	**0,00**	(0,00-105,94)	9.630	0	**0,00**	(0,00-38,31)
Male	14.108.983	1001	**7,09**	(6,66-7,55)	1.921	0	**0,00**	(0,00-192,03)	5.310	0	**0,00**	(0,00-69,47)
Female	15.440.222	1063	**6,88**	(6,48-7,31)	1.561	0	**0,00**	(0,00-236,33)	4.320	0	**0,00**	(0,00-85,38)
0-2 years	496.158	74	**14,91**	(11,71-18,72)	4	0	**0,00**	(0,00-87658,92)	12	0	**0,00**	(0,00-30825,11)
3-6 years	1.589.129	138	**8,68**	(7,30-10,26)	49	0	**0,00**	(0,00-7548,58)	136	0	**0,00**	(0,00-2720,69)
7-11 years	1.864.834	104	**5,58**	(4,56-6,76)	426	0	**0,00**	(0,00-865,39)	1.179	0	**0,00**	(0,00-312,99)
12-17 years	1.906.671	82	**4,30**	(3,42-5,34)	694	0	**0,00**	(0,00-531,78)	1.904	0	**0,00**	(0,00-193,72)
18 + years	23.692.412	1666	**7,03**	(6,70-7,38)	2.309	0	**0,00**	(0,00-159,77)	6.340	0	**0,00**	(0,00-57,64)

* Immune thrombocytopenia was defined as an ICD 10 code of D69.3 or D69.4.
IR= incidence rate; 95% CI confidence interval for incidence rate

***Table 6**. Incidence of new onset immune thrombocytopenia* in the general population and in patients exposed to vaccines in the **IQVIA™ Disease Analyser France database** per 100,000 years of follow-up between 2011 and 2021 overall, and by gender and age group*

	General population		Exposed patients to vaccines			
	Background rates		Follow-up (FU) for one month (31 days)		Follow-up for three months (90 days)	
	IR per 100,000 person-years	95% CI	IR per 100,000 person-years	95% CI	IR per 100,000 person-years	95% CI
Overall	**1,52**	(1,18-1,93)	**0,00**	(0,00-64,02)	**6,29**	(0,16-35,07)
Male	**0,99**	(0,62-1,52)	**0,00**	(0,00-131,12)	**0,00**	(0,00-47,59)
Female	**1,99**	(1,46-2,64)	**0,00**	(0,00-125,11)	**12,29**	(0,31-68,48)
0-2 years	**1,84**	(0,05-10,26)	**0,00**	(0,00-55845,75)	**0,00**	(0,00-20357,44)
3-6 years	**3,03**	(1,22-6,24)	**0,00**	(0,00-595,08)	**59,29**	(1,50-330,37)
7-11 years	**1,34**	(0,37-3,43)	**0,00**	(0,00-383,73)	**0,00**	(0,00-139,64)
12-17 years	**0,29**	(0,01-1,62)	**0,00**	(0,00-444,53)	**0,00**	(0,00-161,21)
18 + years	**1,55**	(1,17-2,02)	**0,00**	(0,00-110,30)	**0,00**	(0,00-39,86)

* Immune thrombocytopenia was defined as an ICD 10 code of D69.3 or D69.4.
IR= incidence rate; 95% CI confidence interval for incidence rate

4.3. Other analyses, including sensitivity analyses

The sensitivity analyses included a broader set of codes for immune thrombocytopenia, including more generic terms such as "secondary thrombocytopenia" and "thrombocytopenia, unspecified".

4.3.1. Event rates in the general population

The event rates for immune thrombocytopenia in the sensitivity analysis in the **IMRD (UK) database** are shown in **Table 7**. In general, the background event rates were typically 5 times higher compared to the main analysis, reflecting the inclusion of the additional diagnostic codes. This increase was more pronounced in the youngest (<2 years) and oldest (18+) age categories.

The event rates for immune thrombocytopenia in the sensitivity analysis in the **IQVIA™ Disease Analyser Germany database** are shown in **Table 8**. The event rate was more than 10 times higher compared to the main analysis. The increase was more pronounced in the two oldest age groups.

The event rates for immune thrombocytopenia in the sensitivity analysis in the **IQVIA™ Disease Analyser France database** are shown in **Table 9.** Also, in France the event rate was more than 10 times higher compared to the main analysis. The increase was more pronounced in males and in the two oldest age groups.

4.3.2. Event rates among exposed patients

IMRD UK

The event rates for the broader definition of immune thrombocytopenia in patients exposed to the vaccines in IMRD (UK) database overall and stratified by gender and age group is shown in **Table 7**. In the 31-day post-exposure analysis the number of events remained low in comparison with the main analysis and confidence intervals were overlapping with the expected population event rates. In the 90-days analysis, a numerically higher event rate was observed among female exposed patients and those aged over 18 years.

Further sensitivity analyses were therefore carried out considering the age and gender distribution in exposed patients was different from the general population. **Table S5** in Annex 3 shows an exploratory

analysis where background and vaccine exposed event rates are presented stratified by gender and age with additional age categories (19-45 years, >45 years). This analysis shows that the increased event rate noted for the broader endpoint definition at 90 days is based on a cluster of cases in females aged 19 to 45 years. These women could have been vaccinated whilst pregnant and pregnancy is associated with increased risk of thrombocytopenia. See discussion.

IQVIA™ Disease Analyser Germany

In the sensitivity analysis, the event rate for immune thrombocytopenia in patients exposed to the vaccines in Germany overall and by gender and age group is shown in **Table 8**. Although a numerically higher event rate was observed among exposed patients (around two-fold) in the 31-day post-exposure analysis in comparison to the main analysis, confidence intervals were overlapping with the expected population event rates. In the 90-days analysis event rates in exposed patients were somewhat lower, and still overlapping with expected population event rates.

IQVIA™ Disease Analyser France

In the sensitivity analysis, the event rate for immune thrombocytopenia in patients exposed to the vaccines in France overall and by gender and age group is shown in **Table 9**. Only one case was observed within 31 days and four cases were observed within 90 days. Event rates were similar to expected population event rates.

Table 7. *Incidence of new onset immune thrombocytopenia* in the general population and in patients exposed to vaccines in the* ***IMRD (UK) database*** *per 100,000 years of follow-up between 2004 and 2019 overall, and by gender and age group*

	General population		Exposed patients to vaccines			
	Background rates		Follow-up (FU) for one month (31 days)		Follow-up for three months (90 days)	
	IR per 100,000 person-years	95% CI	IR per 100,000 person-years	95% CI	IR per 100,000 person-years	95% CI
Overall	**23.21**	(22.52-23.90)	**19.93**	(4.11-58.26)	**51.53**	(32.29-78.01)
Male	**26.08**	(25.06-27.12)	**0.00**	(0.00-53.91)	**15.45**	(3.19-45.14)
Female	**20.32**	(19.42-21.25)	**36.55**	(7.54-106.8)	**81.63**	(49.15-127.5)
0-2 years	**25.05**	(21.44-29.08)	**0.00**	(0.00-7600)	**0.00**	(0.00-2673)
3-6 years	**8.74**	(6.94-10.86)	**8.09**	(0.20-45.1)	**19.96**	(8.03-41.13)
7-11 years	**4.55**	(3.39-5.98)	**0.00**	(0.00-3244)	**0.00**	(0.00-1141)
12-17 years	**7.62**	(6.23-9.24)	**0.00**	(0.00-1076)	**0.00**	(0.00-378.7)
18 + years	**26.88**	(26.05-27.73)	**91.39**	(11.07-330)	**242.1**	(135.5-399.2)

* Immune thrombocytopenia was defined as Read codes that correspond to ICD 10 codes D69.3, D69.4, D69.5 or D69.6.

IR= incidence rate; 95% CI confidence interval for incidence rate

Table 8. *Incidence of new onset immune thrombocytopenia* in the general population and in patients exposed to vaccines in the* ***IQVIA™ Disease Analyser Germany database*** *per 100,000 years of follow-up between 2011 and 2021 overall, and by gender and age group*

	General population				Exposed patients to vaccines							
	Background rates				Follow-up (FU) for one month (31 days)				Follow-up for three months (90 days)			
	Years of follow-up	No. of outcomes	IR per 100,000 person-years	95% CI	Years of follow-up	No. of outcomes	IR per 100,000 person-years	95% CI	Years of follow-up	No. of outcomes	IR per 100,000 person-years	95% CI
Overall	29.539.049	24.187	**81,88**	(80,85-82,92)	3.482	6	**172,33**	(63,24-375,09)	9.629	11	**114,24**	(57,03-204,41)
Male	14.103.321	13.216	**93,71**	(92,08-95,32)	1.921	4	**208,24**	(56,74-533,18)	5.309	7	**131,86**	(53,01-271,67)
Female	15.435.728	10.971	**71,08**	(69,73-72,42)	1.561	2	**128,14**	(15,52-462,88)	4.320	4	**92,60**	(25,23-237,09)
0-2 years	496.058	321	**64,71**	(57,81-72,19)	4	0	**0,00**	(0,00-87658,9)2	12	0	**0,00**	(0,00-30825,11)
3-6 years	1.588.904	568	**35,75**	(32,86-38,81)	49	0	**0,00**	(0,00-7548,58)	136	0	**0,00**	(0,00-2720,69)
7-11 years	1.864.612	539	**28,91**	(26,51-31,45)	426	0	**0,00**	(0,00-865,39)	1.179	0	**0,00**	(0,00-312,99)
12-17 years	1.906.377	793	**41,60**	(38,75-44,60)	694	1	**144,17**	(3,65-803,26)	1.904	2	**105,05**	(12,72-379,47)
18 + years	23.683.098	21.966	**92,75**	(91,49-93,98)	2.309	5	**216,57**	(70,32-505,41)	6.399	9	**140,66**	(64,32-267,01)

* Immune thrombocytopenia was defined as an ICD 10 code of D69.3, D69.4, D69.5 or D69.6.
IR= incidence rate; 95% CI confidence interval for incidence rate

Table 9. *Incidence of new onset immune thrombocytopenia* in the general population and in patients exposed to vaccines in the* ***IQVIA™ Disease Analyser France database*** *per 100,000 years of follow-up between 2011 and 2021 overall, and by gender and age group*

	General population		Exposed patients to vaccines			
	Background rates		Follow-up (FU) for one month (31 days)		Follow-up for three months (90 days)	
	IR per 100,000 person-years	95% CI	IR per 100,000 person-years	95% CI	IR per 100,000 person-years	95% CI
Overall	**22,71**	(21,33-24,15)	**17,36**	(0,44-96,70)	**25,18**	(6,86-64,46)
Male	**25,48**	(23,37-27,73)	**35,54**	(0,90-198,04)	**38,70**	(7,98-113,10)
Female	**20,23**	(18,46-22,13)	**0,00**	(0,00-125,11)	**12,29**	(0,31-68,48)
0-2 years	**1,84**	(0,05-10,26)	**0,00**	(0,00-55845,75)	**0,00**	(0,00-20357,44)
3-6 years	**4,32**	(2,07-7,95)	**0,00**	(0,00-595,08)	**59,29**	(1,50-330,37)
7-11 years	**3,02**	(1,38-5,73)	**0,00**	(0,00-383,73)	**0,00**	(0,00-139,64)
12-17 years	**4,66**	(2,66-7,57)	**0,00**	(0,00-444,53)	**0,00**	(0,00-161,21)
18 + years	**27,63**	(25,92-29,41)	**29,90**	(0,76-166,60)	**32,42**	(6,69-94,74)

* Immune thrombocytopenia was defined as an ICD 10 code of D69.3, D69.4, D69.5 or D69.6.
IR= incidence rate; 95% CI confidence interval for incidence rate

5. Discussion

5.1. Key results

Observed use of diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines (DTaP-IPV or TdaP-IPV) differed between the UK, France and Germany databases with a greater overall use as well as a predominant use of the vaccine in children 3-6 years in the UK database. The lowest level of use was observed in the Germany database. Compared to the UK database, use was comparatively greater in children 7-11 years and 12-17 years in France database and Germany database. However, it is important to take into account that a more complete ascertainment of these vaccinations was possible in the UK database where vaccinations were recorded both as prescriptions and as vaccine administrations. In Germany and France databases, data was only available for prescriptions. In Germany, vaccines are mainly prescribed when they are required outside of the routine vaccination schedule whereas vaccines that are included in vaccination schedules are administered without a prescription. In France, we were unable to find out to what extent vaccines were administered without a prescription.

In the UK database, children 3-6 years of age vaccinated with DTaP-IPV or TdaP-IPV had a higher incidence of immune thrombocytopenia than the general population during 90 days of follow-up in the main analysis where a more stringent definition of immune thrombocytopenia was used. In the sensitivity analysis where a less stringent definition for immune thrombocytopenia was used there was a higher-than-expected incidence in patients 18 years or older. Further analyses revealed a cluster of cases in females aged 19 to 45 years. These subjects are likely to have been vaccinated whilst pregnant (an indication for the tetravalent vaccines) and pregnancy is associated with increased risk of thrombocytopenia, with 5-10% of patients have low platelet counts during pregnancy (8) It is therefore likely that the high event rate observed in females over 18 years is attributed to pregnancy rather than an effect of the vaccine.

In Germany and France databases, there was no clear evidence of an increased rate of thrombocytopenia in exposed patients in any of the analyses.

5.2. Interpretation

Children 0-2 years and 3-6 years had the highest population rates of immune thrombocytopenia in the main analysis in all three databases. In the UK database, most children vaccinated with DTaP-IPV or TdaP-IPV were 3-6 years of age. During 90 days of follow-up a higher-than-expected incidence of immune thrombocytopenia was observed in vaccinated children in this age group, which could support the possibility that immune thrombocytopenia could be an adverse event of the vaccines. However, alternative explanations cannot be ruled out. Similar findings were not observed in this age group in

Germany or France databases, but more vaccinated children in Germany and France were in the older age groups 7-11 years and 12-17 years.

5.3. Limitations

Incomplete ascertainment of vaccine exposure in all data sources, particularly in the IQVIA™ Disease Analyser Germany and France databases. These databases contain data on patient encounters from primary care, i.e., data are mostly based on general practitioner's prescriptions. Vaccines covered by national vaccination schemes might, however, be administered without an individual patient prescription or the vaccine might be administered outside of the GP practice, and such vaccinations would not be recorded in the databases. Thus, these data may play a subordinate role, particularly for vaccinations covered by the national health insurance (NHI), and the extent to which the available information in our databases reflects the true use of the vaccines of interest in the population is unknown. It is also possible that the vaccine utilization pattern is different in patients that have received the vaccine through a prescription compared to all patients that have received the vaccine. Hence, the generalizability of our results may be limited. In the IMRD (UK) database, the use of a surrogate for vaccine exposure (i.e., diagnostic coding) might be subject to misclassification and potentially inaccurate recoding of date of vaccination. In addition, it is not possible to distinguish between the DTaP-IPV and TdaP-IPV (reduced antigens content) versions of the vaccine in the IMRD (UK) database.

A high level of uptake of the vaccine in the pre-school age group (typically 85% in the UK) and incomplete ascertainment of exposure means that a meaningful unexposed cohort cannot be identified, so a comparative analysis was not possible. For IQVIA DA Germany, where patients are identified only on the basis of primary care consultations the size of the general population might be underestimated as persons not visiting primary care are not included in the database.

For IMRD (UK), this analysis was based on a surrogate measure of vaccine exposure which unlike other medicinal exposures on the database, is not recorded at the time it is administered. This means it is unlikely that the ascertainment of the exposure is complete. This means a comparison between exposed and unexposed cohort of patients is not possible.

The outcome of immune thrombocytopaenia has not been validated. In view of this both narrow and broad endpoint definitions were used.

In the UK the tetravalent vaccine is used as a "preschool" booster in children between 3 years 4 months and 5 years of age. Nationally collated statistics for England show uptake of the vaccine is high, typically over 85% coverage (NHS Digital 2021. Childhood Vaccination Coverage Statistics - 2020-21. Available from https://digital.nhs.uk/data-and-information/publications/statistical/nhs-immunisation-statistics). This means there is even if ascertainment of exposure was complete, it would be difficult to construct an unexposed cohort against which to assess the relative frequency of events in exposed subjects.

With the delivery of healthcare services having been disrupted by the COVID-19 pandemic, data from the UK from 2020 onwards was excluded as in 2020 and 2021 there was a marked decline in diagnoses of immune thrombocytopenia.

The comparison of background with exposed event rates is potentially problematic. The background event rates will be derived from a population who have predominantly had the exposure, with this pe-school vaccine typically attaining 85% coverage. Such a comparison is not ideal as there will be a tendency to bias the results towards the null (i.e., not finding a difference between the vaccine exposed and background event rates); however, the 4-year age grouping and restriction to 31- and 90-days post vaccination should restrict the extend of any such bias.

6. References

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Annexes

Annex 1 - Information on Databases and Healthcare systems included

IQVIA™ Medical Research Data (IMRD) EMIS UK

IQVIA™ Medical Research Data (IMRD) EMIS UK is a primary care database from the UK. GPs play a gatekeeper role in the healthcare system in the UK, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

IQVIA™ Disease Analyzer Germany

IQVIA™ Disease Analyzer Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of general practitioners (GP) practices are included, which covers all patients consulting a practice. Data from IQVIA™ Disease Analyzer Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases and is considered one of the largest national medical databases worldwide. IQVIA™ Disease Analyzer Germany includes more than 2,500 practices and 3,100 physicians (13 speciality groups) representing over 15,000,000 patients. This database used to be named IMS® Germany and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

IQVIA™ Disease Analyzer France

IQVIA™ Disease Analyzer France collects anonymised patient medical records since 1997 through a representative panel of GPs. The physician sample represents approximately 2% of physicians and is weighted by age and gender of the physician, doctor region and the SNIR of the physician (National Official Indicator of the GP volume of activity in terms of visits and consultations). Some 99% of the French population is insured, but there are differences regarding level of coverage. IQVIA™ Disease Analyzer France includes around 1,000 GPs and represents more than 4,000,000 of patients and considered representative for the French population. This database used to be named IMS France and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

Annex 2 - Codelists

CODES USED TO IDENTIFY EXPOSURE

IMRD (UK) database — Drug codes

drugcodeid	description
3178941000033118	Repevax vaccine suspension for injection 0.5ml pre-filled syringes (Sanofi Pasteur)
3198741000033110	Infanrix-IPV vaccine suspension for injection 0.5ml pre-filled syringes (GlaxoSmithKline UK Ltd)
9298541000033119	Boostrix-IPV suspension for injection 0.5ml pre-filled syringes (GlaxoSmithKline UK Ltd)

IMRD (UK) database – Read ("diagnostic") codes

readtermid	term
CODES INCLUDED	
65I4	Booster diphtheria, tetanus, acellular pertussis (DTaP) and polio vaccination
65I5	First diphtheria, tetanus, acellular pertussis (DTaP) and polio vaccination
65I6	Second diphtheria, tetanus, acellular pertussis (DTaP) and polio vaccination
65I7	Third diphtheria, tetanus, acellular pertussis (DTaP) and polio vaccination
65I8	Low dose diphtheria, tetanus, five component acellular pertussis and inactivated polio vaccination
65I9	Booster diphtheria, tetanus, acellular pertussis and inactivated polio vaccination
^ESCT1348496	Administration of diphtheria and pertussis and poliomyelitis and tetanus vaccine
^ESCT1348680	Administration of booster dose of diphtheria and acellular pertussis and poliomyelitis and tetanus vaccine
^ESCT1408279	Administration of low dose diphtheria and acellular pertussis five component and inactivated poliomyelitis and tetanus vaccine
CODES EXCLUDED: pattern of use is triple DTP and polio vaccinations used separately	
65I	DTP (triple)+polio vaccination
65I3	Third DTP (triple)+polio vaccination
65I2	Second DTP (triple)+polio vaccination
ZV063	Diphtheria, pertussis and tetanus triple and polio vaccination
65IZ	Diphtheria, pertussis and tetanus triple and polio vaccination
65I1	First DTP (triple)+polio vaccination
EMISQPR3	Pre-school triple DTaP+polio vaccination
^ESCTFI463311	First diphtheria, pertussis and tetanus triple and polio vaccination
^ESCTSE463313	Second diphtheria, pertussis and tetanus triple and polio vaccination
^ESCTTH463315	Third diphtheria, pertussis and tetanus triple and polio vaccination
CODES EXCLUDED: seldom used in this patient cohort	
EMISNQTH5	Third DTaP and polio vaccination
EMISNQSE6	Second DTaP and polio vaccination
65IA	Post exposure diphtheria, tetanus, acellular pertussis and inactivated polio vaccination
^ESCT1245743	[V]Diphtheria-tetanus-pertussis with poliomyelitis (DTP + polio) vaccination
^ESCT1348700	Administration of first dose of diphtheria and acellular pertussis and poliomyelitis and tetanus vaccine

readtermid	term
^ESCT1348704	Administration of second dose of diphtheria and acellular pertussis and poliomyelitis and tetanus vaccine
^ESCT1348708	Administration of third dose of diphtheria and acellular pertussis and poliomyelitis and tetanus vaccine
^ESCT1348716	Administration of diphtheria and acellular pertussis and inactivated poliomyelitis and tetanus vaccine
^ESCT1396218	Administration of second dose of diphtheria and pertussis and poliomyelitis and tetanus vaccine
^ESCT1396222	Administration of third dose of diphtheria and pertussis and poliomyelitis and tetanus vaccine
^ESCT1396226	Administration of first dose of diphtheria and pertussis and poliomyelitis and tetanus vaccine

IQVIA™ Disease AAnalyser Germany database

Diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines *with reduced antigen content (TdaP-IPV)*

Therapy_No	Therapy_Name
GE11373313	REPEVAX GRK>> FE.SPR.M.KAN .5ML (N1)
GE9685922	BOOSTR.P.ALT GRK>> FERT SPR 10 .5ML (N2)
GE6614665	REPEVAX KHP>> FE.SPR.M.KAN .5ML (N1)
GE15557681	REPEVAX ORI>> FE.SPR.M.KAN .5ML (N1)
GE9471276	REPEVAX ORI>> FE.SPR.M.KAN 20 .5ML (N3)
GE5971080	REPEVAX EUP>> FE.SPR.M.KAN ALT 10 .5ML (N2)
GE10352021	BOOSTRIX POL.ORI>> FERT SPR ALT 10 .5ML (N2)
GE2623226	REPEVAX FE.SPR.O.KAN .5ML (N1)
GE12616043	REPEVAX GRK>> FE.SPR.M.KAN 20 .5ML (N3)
GE3724640	REPEVAX FE.SPR.O.KAN 10 .5ML
GE17582448	BOOSTRIX POL.ORI>> FERT SPR 10 .5ML (N2)
GE9216858	REPEVAX ORI>> F.SP.M.K.ALT ALT 10 .5ML (N2)
GE1406554	BOOSTRIX POLIO FERT SPR .5ML (N1)
GE9550344	BOOSTRIX POL.CC4>> FERT SPR 10 .5ML (N2)
GE20665036	REPEVAX ORI>> FE.SPR.M.KAN 10 .5ML
GE10075364	BOOSTRIX POL.ORI>> FERT SPR .5ML (N1)
GE6407747	BOOSTRIX POL.EUP>> FERT SPR 10 .5ML (N2)
GE11045043	REPEVAX CC4>> FERT SPR 10 .5ML (N2)
GE16339451	BOOSTR.P(GRK)EU0>> FERT SPR 10 .5ML (N2)
GE11525279	REPEVAX GRK>> FE.SPR.O.KAN 10 .5ML (N2)
GE6787291	REPEVAX KHP>> FE.SPR.M.KAN ALT 20 .5ML
GE7929871	BOOSTRIX POL.KHP>> FERT SPR .5ML (N1)
GE8062894	BOOSTRIX POL.KHP>> FERT SPR 10 .5ML (N2)
GE16199159	BOOSTR.P(GRK)EU0>> FERT SPR .5ML (N1)
GE8193035	REPEVAX E-M>> FE.SPR.M.KAN .5ML (N1)
GE18098870	REPEVAX ORI>> FE.SPR.M.KAN ALT 10 .5ML
GE21023974	REPEVAX KHP>> FE.SPR.M.KAN 20 .5ML
GE5071243	BOOSTRIX POL.CC4>> FERT SPR .5ML (N1)

GE9370813	REPEVAX ORI>> FE.SPR.M.KAN ALT .5ML (N1)
GE47756	REPEVAX DURCHSTECHFL .5ML (N1)
GE5809233	REPEVAX EUP>> FE.SPR.M.KAN .5ML (N1)
GE5873256	REPEVAX EUP>> FE.SPR.M.KAN ALT 20 .5ML (N3)
GE9636567	BOOSTR.P.ALT GRK>> FERT SPR .5ML (N1)
GE8211332	REPEVAX E-M>> FE.SPR.M.KAN 10 .5ML (N2)
GE10051777	BOOSTRIX POL.E-M>> FERT SPR .5ML (N1)
GE6177006	BOOSTRIX POL.EUP>> FERT SPR .5ML (N1)
GE10347685	BOOSTRIX POL.ML8>> FERT SPR .5ML (N1)
GE19880976	REPEVAX A4X>> FE.SPR.M.KAN 10 .5ML
GE10808037	REPEVAX CC4>> FERT SPR .5ML (N1)
GE4274941	REPEVAX FE.SPR.M.KAN 10 .5ML
GE11078230	BOOSTRIX POL.E-M>> FERT SPR 10 .5ML (N2)
GE15917397	REPEVAX ORI>> FE.SPR.O.KAN ALT 10 .5ML (N2)
GE11396018	REPEVAX GRK>> FE.SPR.O.KAN 20 .5ML (N3)
GE6753317	REPEVAX KHP>> FE.SPR.M.KAN 10 .5ML
GE12266298	REPEVAX GRK>> FE.SPR.M.KAN 10 .5ML (N2)
GE4137383	REPEVAX FE.SPR.M.KAN .5ML (N1)
GE13021189	REPEVAX CC4>> FERT SPR 20 .5ML (N3)
GE446491	BOOSTRIX POLIO FERT SPR 10 .5ML (N2)
GE3084377	REPEVAX FE.SPR.O.KAN 20 .5ML
GE17773926	REPEVAX EUP>> FE.SPR.M.KAN 10 .5ML
GE50425	REPEVAX DURCHSTECHFL 10 .5ML
GE257495	REPEVAX DURCHSTECHFL 20 .5ML
GE8221291	REPEVAX E-M>> FE.SPR.M.KAN ALT 20 .5ML (N3)
GE19885931	REPEVAX A4X>> FE.SPR.M.KAN .5ML (N1)

Diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines *without reduced antigen content (DTaP-IPV)*

Therapy_No	Therapy_Name
GE489129	TETRAVAC FERT SPR 25 .5ML
GE7980966	TETRAVAC ORI>> FE.SPR.M.KAN 10 .5ML (N2)
GE168136	TETRAVAC FERT SPR .5ML (N1)
GE13373428	TETRAVAC E-M>> FE.SPR.M.KAN 10 .5ML (N2)
GE13178310	TETRAVAC E-M>> FE.SPR.M.KAN .5ML (N1)
GE2491127	TETRAVAC EUP>> FE.SPR.M.KAN 10 .5ML (N2)
GE6416649	TETRAVAC ORI>> FE.SPR.M.KAN .5ML (N1)
GE340416	TETRAVAC FERT SPR 10 .5ML
GE1431776	TETRAVAC EUP>> FE.SPR.M.KAN .5ML (N1)
GE9543906	TETRAVAC AC9>> FE.SPR.M.KAN 10 .5ML (N2)
GE853361	TETRAVAC FERT SPR 50 .5ML
GE8808837	TETRAVAC AC9>> FE.SPR.M.KAN .5ML (N1)

IQVIA™ Disease Analyser France database

Diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines *with reduced antigen content (TdaP-IPV)*

Therapy_No	Therapy_Name
FR16942	REPEVAX SER.PRE+AIGU 0.5ML 1
FR17913	BOOSTRIXTETRA SER PREREMPL 0.5ML 1

Diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines *without reduced antigen content (DTaP-IPV)*

Therapy_No	Therapy_Name
FR8080	INFANRIX POLIO SER PREREMPL 0.5ML ENF 1
FR9527	TETRAVAC ACELLUL. SER.PRE+AIGU 0.5ML 1
FR12217	INFANRIX TETRA SER PREREMPL 0.5ML 1

Diphtheria, tetanus, pertussis (acellular) and polio (inactivated) vaccines without unknown antigen content

Therapy_No	Therapy_Name
FR14546	VAC DTCAP LAB. IND SER PREREMPL 0.5ML 1

OUTCOMES CODES

IMRD (UK) database

IMRD codes corresponding to ICD10 D69.3

Read Code	Description
D3130	Idiopathic thrombocytopenic purpura
D3130-1	Idiopathic purpura
42P2-1	Autoimmune thrombocytopenia
D3130-2	ITP - idiopathic thrombocytopenic purpura
D313-5	Thrombocytopenic purpura
D313-1	Evan's syndrome
D313-3	Idiopathic purpura
D313-2	Idiopathic thrombocytopenic purpura
C3912-1	Thrombocytopenic eczema with immunodeficiency
^ESCTIM301968	Immune thrombocytopenic purpura
^ESCTEV372490	Evans syndrome

IMRD codes corresponding to ICD10 D69.4

Read Code	Description
D3133	[X]Essential thrombocytopenia NOS
Dyu32	[X]Other primary thrombocytopenia
D313z-1	Essential thrombocytopenia NOS

Read Code	Description
D3131-1	Hereditary thrombocytopenia NEC
D313	Primary thrombocytopenia
D3131	Congenital thrombocytopenic purpura
D313z	Primary thrombocytopenia NOS
D313y	Other specified primary thrombocytopenia

IMRD codes corresponding to ICD10 D69.5 & D69.6

Read Code	Description
D3133	[X]Essential thrombocytopenia NOS
Dyu32	[X]Other primary thrombocytopenia
D313z-1	Essential thrombocytopenia NOS
D3131-1	Hereditary thrombocytopenia NEC
D313	Primary thrombocytopenia
D3131	Congenital thrombocytopenic purpura
D313z	Primary thrombocytopenia NOS
D313y	Other specified primary thrombocytopenia
Read Code	Description

IQVIA™ Disease Analyser Germany and France databases

ICD10	Description
D69.3	Idiopathic thrombocytopenic purpura
D69.4	Other primary thrombocytopenia
D69.5	Secondary thrombocytopenia
D69.6	Thrombocytopenia, unspecified

Annex 3 – Supplementary results

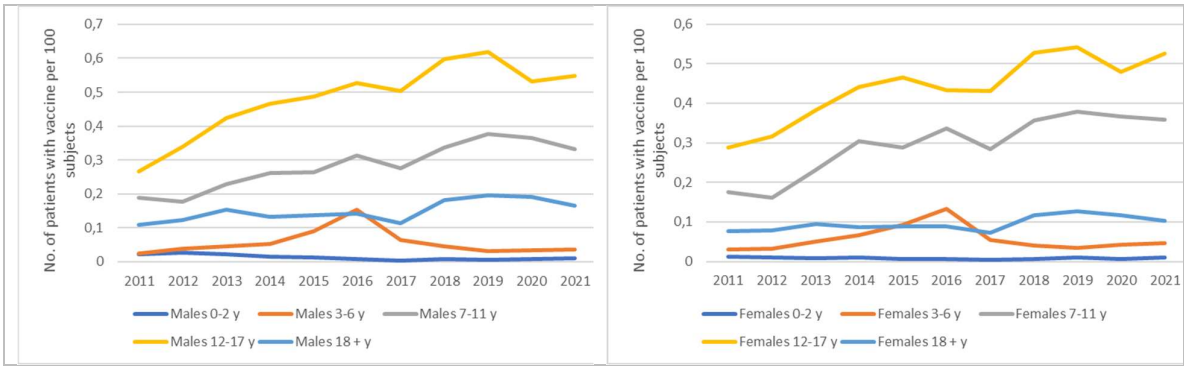
*Table S1 Number of patients in the IQVIA™ Disease Analyser **Germany database** with a prescription for diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines **with reduced antigen content** (TdaP-IPV) stratified by age, sex and year*

	0-2 years		3-6 years		7-11 years		12-17 years		18 + years	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
2011	14	7	23	25	191	162	259	275	1152	940
2012	19	6	38	29	193	162	368	337	1424	1065
2013	17	6	48	49	266	250	502	446	1967	1410
2014	12	7	58	69	316	340	580	542	1781	1362
2015	10	5	103	95	327	330	628	585	1950	1454
2016	7	5	194	154	423	425	762	602	2264	1610
2017	3	4	83	66	386	372	756	622	1943	1412
2018	8	6	58	49	471	465	887	752	3162	2246
2019	5	9	39	40	506	471	900	751	3389	2422
2020	7	5	39	46	438	404	710	606	3088	2126
2021	8	7	36	45	325	320	637	584	2554	1745

*Table S2 Number of patients in the IQVIA™ Disease Analyser **Germany database** with a prescription for diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines **without reduced antigen content** (DTaP-IPV) stratified by age, sex and year*

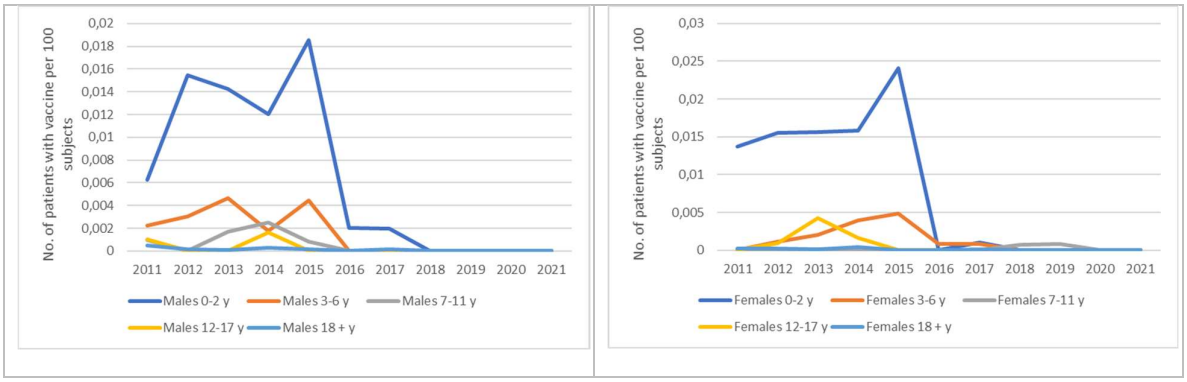
	0-2 years		3-6 years		7-11 years		12-17 years		18 + years	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
2011	4	8	2	0	1	0	1	0	5	3
2012	11	10	3	1	0	0	0	1	2	3
2013	11	11	5	2	2	0	0	5	1	2
2014	10	12	2	4	3	0	2	2	4	6
2015	16	19	5	5	1	0	0	0	2	1
2016	2	0	0	1	0	0	0	0	0	1
2017	2	1	0	1	0	0	0	0	3	3
2018	0	0	0	0	0	1	0	0	0	0
2019	0	0	0	0	0	1	0	0	0	0
2020	0	0	0	0	0	0	0	0	0	0
2021	0	0	0	0	0	0	0	0	0	0

*Figure S1 Yearly prevalence of use in IQVIA™ Disease Analyser **Germany database** of diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines **with reduced antigen content** (TdaP-IPV) in males and females between 2011 and 2021 by age group **



* The prevalence might be overestimated during the last year(s) due to an artificial decrease in the denominator (but not numerator) towards the database end that depends on the frequency of visits.

*Figure S2 Yearly prevalence of use in the IQVIA™ Disease Analyser **Germany database** of diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines **without reduced antigen content** (DTaP-IPV) in males and females between 2011 and 2021 by age group **



* The prevalence might be overestimated during the last year(s) due to an artificial decrease in the denominator (but not numerator) towards the database end that depends on the frequency of visits.

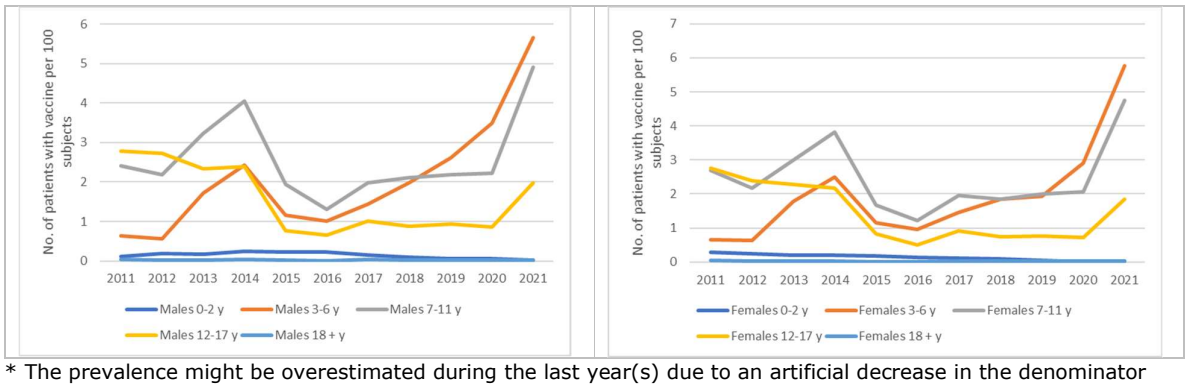
*Table S3 Number of patients in the IQVIA™ Disease Analyser **France database** with a prescription for diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines **with reduced antigen content** (TdaP-IPV) stratified by age, sex and year*

	0-2 years		3-6 years		7-11 years		12-17 years		18 + years	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
2011	10	22	85	77	348	371	435	412	43	69
2012	18	22	83	86	355	331	491	406	43	47
2013	20	20	299	281	612	528	492	453	45	57
2014	32	23	507	468	916	788	605	507	95	92
2015	33	22	265	237	494	382	215	215	28	36
2016	34	18	249	206	365	294	197	140	19	32
2017	23	15	348	310	548	479	310	255	109	100
2018	15	13	473	382	582	449	268	209	73	90
2019	<10	<10	604	393	586	478	285	212	77	77
2020	<10	<10	650	485	503	414	227	179	53	67
2021	<10	<10	988	885	874	740	423	375	60	61

*Table S4 Number of patients in the IQVIA™ Disease Analyser **France database** with a prescription for diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines **without reduced antigen content** (DTaP-IPV) stratified by age, sex and year*

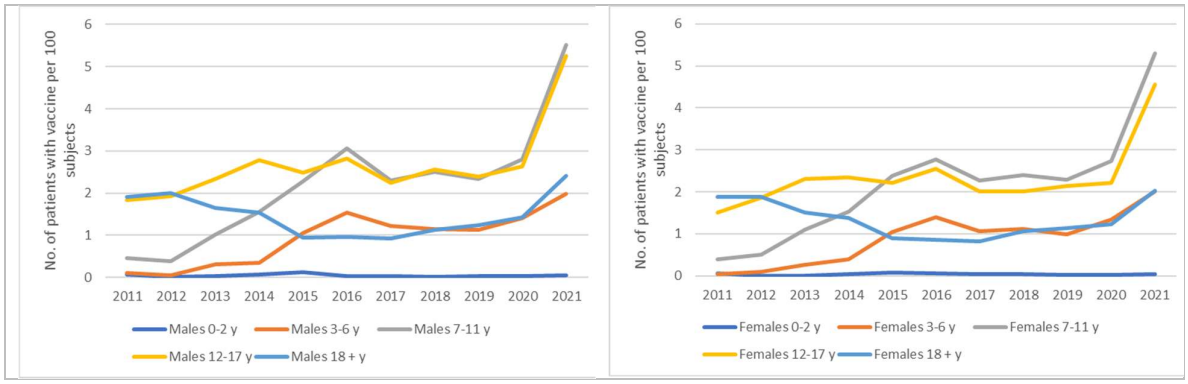
	0-2 years		3-6 years		7-11 years		12-17 years		18 + years	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
2011	<10	<10	14	6	67	55	287	226	2652	3032
2012	<10	<10	<10	13	63	78	347	318	3215	3537
2013	<10	<10	53	42	194	193	494	457	3087	3322
2014	<10	<10	74	73	351	316	709	548	3473	3661
2015	20	10	242	214	581	541	705	575	2375	2629
2016	<10	<10	379	300	855	676	848	697	2572	2712
2017	<10	<10	299	227	634	558	685	561	2587	2682
2018	<10	<10	275	232	694	585	786	557	3220	3546
2019	<10	<10	260	200	628	547	724	595	3646	3955
2020	<10	<10	260	224	631	549	692	543	3933	4073
2021	<10	<10	345	308	980	823	1123	927	5850	6004

*Figure S3 Yearly prevalence of use in IQVIA™ Disease Analyser **France database** of diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines **with reduced antigen content** (TdaP-IPV) in males and females between 2011 and 2021 by age group **



* The prevalence might be overestimated during the last year(s) due to an artificial decrease in the denominator (but not numerator) towards the database end that depends on the frequency of visits.

*Figure S4 Yearly prevalence of use in IQVIA™ Disease Analyser **France database** of diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccines **without reduced antigen content** (DTaP-IPV) in males and females between 2011 and 2021 by age group **



* The prevalence might be overestimated during the last year(s) due to an artificial decrease in the denominator (but not numerator) towards the database end that depends on the frequency of visits.

Table S5. Incidence of new onset immune thrombocytopenia in the general population and in patients exposed to vaccines in the **IMRD (UK) database** per 100,000 years of follow-up between 2004 and 2019 overall, and by gender and age group*

	General population		Exposed patients to vaccines			
	Background rates		Follow-up (FU) for one month (31 days)		Follow-up for three months (90 days)	
	IR per 100,000 person-years	95% CI	IR per 100,000 person-years	95% CI	IR per 100,000 person-years	95% CI
Overall	**23.21**	(22.52-23.90)	**19.93**	(4.11-58.26)	**51.53**	(32.29-78.01)
male < 3 year	**30.64**	(25.13-36.99)	**0.00**	(0.00-14774)	**0.00**	(0.00-5195)
male 3-6 years	**8.77**	(6.32-11.85)	**0.00**	(0.00-57.93)	**5.53**	(0.14-30.83)
male 7-11 years	**4.09**	(2.62-6.08)	**0.00**	(0.00-5922)	**0.00**	(0.00-2083)
male 12-18 years	**6.92**	(5.15-9.10)	**0.00**	(0.00-2329)	**0.00**	(0.00-819.0)
male 19-45 years	**10.99**	(9.92-12.15)	**0.00**	(0.00-3431)	**327.6**	(8.29-1825)
male > 45 years	**48.63**	(46.45-50.89)	**0.00**	(0.00-3047)	**290.5**	(7.36-1619)
female < 3 year	**19.15**	(14.75-24.45)	**0.00**	(0.00-15652)	**0.00**	(0.00-5504)
female 3-6 years	**8.71**	(6.20-11.91)	**16.70**	(0.42-93.05)	**35.31**	(12.96-76.86)
female 7-11 years	**5.06**	(3.33-7.36)	**0.00**	(0.00-7173)	**0.00**	(0.00-2524)
female 12-18 years	**8.45**	(6.33-11.05)	**0.00**	(0.00-2000)	**0.00**	(0.00-704.5)
female 19-45 years	**16.42**	(15.09-17.84)	**110.3**	(13.35-398.3)	**253.3**	(134.9-433.2)
female >45 years	**28.79**	(27.17-30.49)	**0.00**	(0.00-2523)	**0.00**	(0.00-887.6)

* Immune thrombocytopenia was defined as Read codes that correspond to ICD 10 codes D69.3, D69.4, D69.5 or D69.6.
IR= incidence rate; 95% CI confidence interval for incidence rate