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Safety Profile of the Tetanus-Diphtheria-Acellular Pertussis Combination Vaccine as a Single Booster (5th dose) among Spanish Children Aged 4-6 years Old with Different Vaccination Schedules

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Abstract

Objective: A post-authorisation commitment to the Spanish Regulatory Agency was made to evaluate the safety of the tetanus, diphtheria and acellular pertussis vaccine Triaxis® (Tdap5) administered as a booster (5th dose) in 4-6 year old Spanish children according to the Summary of Product Characteristics (SmPC) and local vaccination guidelines. The primary objective was to determine the incidence of injection site reactions (ISRs) and systemic adverse events (sys-AEs) after Tdap5 administration.

Methods: A multicentre, noninterventional, onearm cohort study with a 30-day follow-up after vaccination with Tdap5. The study was carried out by 22 primary care paediatricians in the autonomous communities (ACs) of Madrid and Andalusia, which have different vaccination schedule recommendations for the 5th dose: children are vaccinated with Tdap5 at ages 5-6 in Andalusia whereas in Madrid the vaccine is administered at age 4 co-administered with Measles, Mumps and Rubella vaccine. Adverse events (AEs) were collected by the investigator through direct assessment in the clinic immediately following vaccination and a 30-day diary card completed by parents/legal representatives.

Results: A total of 553 participants were analysed; 229 (41.4%) in Madrid and 324 (58.6%) in Andalusia and follow-up was complete in 98.2%. The incidence per person-month was 4.67 for all AEs, 3.13 for adverse reactions (ARs), 2.83 for ISRs, 3.52 for solicited AEs, 0.78 for unsolicited AEs and 1.31 for sys-AEs. The incidence of serious adverse events (SAEs) was 0.005 per person-month, based on three cases of which two (Syncope and Type III hypersensitivity reaction) were considered vaccine-related and all recovered. The most frequent reactions were ISRs: pain, 67.3%; inflammation, 35.5%; erythema, 38.9%.

Conclusions: The results confirm the expected safety profile of Tdap5 in routine clinical practice when administered in 4-6 year old Spanish children. No safety signal has been identified and the safety profile of Tdap5 is consistent with the SmPC.

Keywords: PASS; Vaccine; Diphtheria; Tetanus; Pertussis; Triaxis; Safety

Abbreviations

ACs: Autonomous Communities; AEs: Adverse Events; ARs: Adverse Reactions; CRF: Case Report Form; DTAP: Diphtheria, Tetanus and Acellular Pertussis (First 3 Doses And 4th Booster Dose); ICH: International Conference on Harmonisation; ISRs: Injection-Site Reactions; MEDDRA: Medical Dictionary for Regulatory Activities; MMR: Measles, Mumps and Rubella Vaccine; PASS: Post-Authorisation Safety Study; SAEs: Serious Adverse Events; SARs: Serious Adverse Reactions; SMPC: Summary Of Product Characteristics; Sys-AEs, Systemic Adverse Events; Sys-ARs: Systemic Adverse Reactions; TDAP5: Tetanus, Diphtheria, and Acellular Pertussis Vaccine (5th Booster Dose).

Introduction

Trivalent combination whole-cell vaccines against tetanus, diphtheria and pertussis infections have been extensively used in childhood immunization since the 1940s, resulting in a significant decline in disease rates and incidence of pertussis in children [1]. Yet whole cell vaccines have been associated with reactogenicity issues including fever, local reactions (erythema, swelling and pain), mild systemic adverse events (sys-AEs) (drowsiness, anorexia and

fretfulness) and, less frequently, more severe neurological events such as convulsions and hypotonic hyporesponsive episodes [2-4]. Concerns regarding the safety of whole cell vaccines prompted the development of reformulated vaccines with acellular pertussis component that have readily been incorporated into routine immunisation schedules worldwide [5].

Triaxis® (Sanofi Pasteur, Toronto, Ontario, Canada; also licensed as Covaxis® or Adacel®) containing tetanus toxoid, reduced antigen content of diphtheria toxoid and five acellular pertussis components (pertussis toxoid, filamentous haemagglutinin, pertactin and fimbriae types 2 and 3), adsorbed on aluminium phosphate (Tdap5) [6] received marketing authorisation in Spain in 2010. According to the Spanish recommendation, Tdap5 is indicated in children from 4 years of age upwards as a booster (5th dose). Vaccination schedules of **Tdap5** differ between Spanish local governmental administrative regions, called Autonomous Communities (ACs) [7]; some ACs systematically co-administer Tdap5 with Measles, Mumps and Rubella vaccine (MMR) while others do not and age at vaccination also differs.

There is good evidence from randomised trials of the robust immunogenicity and the low levels of reactogenicity and AEs of Tdap5 in children aged 46 years [8,9]. However, data on AEs from post-marketing surveillance studies on vaccination of Tdap5 administered as a 5th dose in routine clinical practice were lacking. One recent safety study assessed the risk of SAEs in the same population (4-6 year old children) and with the same dose of the diphtheria (full content), tetanus, and acellular pertussis vaccine (DTaP; 5th dose) as in the present study but following exposure to the DTaP and inactivated polio virus combined vaccine [10].

The objective of this post-authorisation safety study (PASS), which was a commitment between the sponsor and the Spanish Regulatory Agency, was to evaluate the overall safety profile of Tdap5 in Spanish children 4 to 6 year old as a 5th dose in routine clinical practice. Differences in the safety profile of Tdap5 due to local variations in vaccination recommendations among ACs were also investigated.

Methods

Study design

This was a single country, multi-centre, observational, one-arm cohort descriptive PASS that sought to assess the safety of Tdap5 in 4-6 year old Spanish children. The study was carried out by 22 paediatricians from primary health care centres distributed among the two ACs, of Madrid and Andalusia. In Madrid vaccination with Tdap5 is recommended at age 4 years co-administered with the 2nd dose of the MMR vaccine, vaccination calendars in Andalusia recommend the administration of the vaccine alone in children aged 5-6. Participants were followed over a period of 30 days after administration of Tdap5 (inclusion visit, 7-day follow-up visit and 30-day review). At the inclusion visit, for each included child, data on demographics, concomitant vaccination, prior vaccination, comorbidities, concomitant medication, any AEs occurring during the first 15 minutes following vaccination and treatment for immediate AEs were collected on a paper Case Report Form (CRF) by the investigator. Parents/legal representatives were provided with a thermometer, a ruler and a diary card which consisted of two different portions: for the first 7 days of follow up (Day 0-Day 7) and the other for Day 8Day 30 followup. The parent/legal representative recorded data on the description, start and stop dates, intensity (mild, moderate, or severe), treatment, hospitalization or visit to another physician of any AE on the diary card from 15 minutes after the time of vaccination (Day 0) to Day 30 after vaccination. At the 7-day follow-up visit, the investigator interviewed the parent/legal representative to evaluate AEs through the assessment of the participant diary card. At the end of the 30-day follow-up period, the completed patient diary card was returned to the investigator. The protocol was reviewed and approved by the Ethics Committee of Hospital Universitario La Paz, Madrid, and the Spanish Regulatory Agency. The Guidelines for Good Pharmacoepidemiology Practices [11], the Declaration of Helsinki [12] and the European Medicines Agency Guide on Methodological Standards in Pharmacoepidemiology [13] were followed.

Study population

Children aged 4 to 6 years who attended the investigator´s office between March and July 2012 to receive a booster of Tdap5 as part of the routine vaccination schedule were invited to participate. Only children that had completed a full course of immunisation with DTaP vaccines (4 doses) and whose parents or legal representatives gave informed consent at the inclusion visit were eligible. The presence of contra-indications or cautions to vaccination in accordance with the Spanish version of the EU SmPC and prior vaccination with a 5th dose of Tdap5 were exclusion criteria. The sample size was estimated at 556 participants to obtain 500 evaluable participants on the basis of the number of children that would allow detection of severe AEs (ISRs and sys-AEs) with an incidence rate of 1%, a precision of alpha of 5% and a 10% drop-out rate.

Outcome measures

The primary safety endpoint of the study was the incidence of all injection-site reactions (ISRs), which are considered related to the Tdap5 vaccine, and sys-AEs, which may or may not be related to the Tdap5 vaccine, that occurred during the study. Specific AEs, as described in the SmPC, were solicited (observed and reported under the conditions prelisted in the diary card and considered as related to vaccination) during the first 7 days following vaccination and included ISRs (pain, erythema, swelling) and sys-AEs (anorexia, headache, diarrhea, tiredness, nausea, vomiting, rash, generalized aching or muscular weakness, arthralgia or joint swelling, pyrexia, chills, and axillary adenopathy). Any other AEs that occurred within the first seven days and all AEs that occurred after the seventh day were considered as unsolicited (observed and reported in the diary card with no specific condition prelisted). Assessments were made on the relationship of AEs to the vaccine, intensity and seriousness of AE/adverse reactions (ARs), concomitant medication and vaccines, and hospitalizations and visits to the physician. The secondary endpoint was the incidence of serious adverse events (SAEs) after Tdap5 administration. The seriousness was assessed based on International Conference on Harmonisation (ICH) Guidelines/European Directives and Volume 9A of the Guidelines on Pharmacovigilance for Medicinal Products for Human Use [14]. The causal relationship of AEs was assessed clinically by the investigator without the use of any algorithms. Events were assessed as “related” if there was a reasonable possibility, evidence or arguments to suggest a causal relationship between the vaccine and the AE. Missing or unknown relationship were considered as “related”. The sponsor also evaluated the causal relationship between the vaccine and the AE however changes to the causality established by the investigator were not permitted.

Statistical analysis

The main summary measures calculated were the incidence of AEs and the incidence of SAEs per person-month to allow for the changing hazard rate in the time windows of Day 0, Days 0-7 and Days 8-30. The term 'frequency' is the number of participants who have suffered from at least one AE of the type described with the total number of participants as the denominator. The term 'percentage' will be used for statistics with the number of AEs as the denominator. Incidence rates were calculated as the number of AEs or ARs divided by the corresponding denominator at-risk multiplied by 30 to provide an incidence rate per month (30 days). The at-risk denominator was calculated by multiplying the total number of participants who started at the beginning of the considered period of time (persons at risk) by the total amount of days in which each participant remained at risk within that period until he/she suffered the first event of the type being considered. This denominator varies for the different analyses based on the different follow-up time periods (e.g. Day 0 to Day 7, Day 8 to Day 30, Day 0 to 30), the population considered (e.g. all sample, Madrid, Andalusia), and the type of event (e.g. solicited, ISR, etc.), employed for the different analyses. Ninety five percent confidence intervals were calculated for incidence rates based on the Poisson distribution. Where data of an AE were missing to assign causality with the vaccine, the AE was analysed as being related to vaccination. Where data were missing to assess intensity, no replacement of the missing qualifier was made. Where confirmed information was available from parents/legal representatives on the presence/absence of AEs for the whole follow-up period of at least 30 days, the data for that participant considered as 'complete data'. This confirmation could have been obtained either through the CRF or by phone. Additional post-hoc analyses were conducted for ISRs related to pruritus, induration and warmth and the timing of ARs to assess the association with Tdap5 or MMR vaccination.

Results

Participants

A total of 553 children aged 4-6 were analysed in the study, comprising those who were vaccinated, fulfilled all inclusion and non-inclusion criteria and were correctly enrolled: 229 (41.4%) in Madrid and 324 (58.6%) in Andalusia. Of the 611 participants that initially constituted the Eligible Population, 3 subjects were excluded because they were later found not to fulfil all selection criteria and the other 58 subjects were not enrolled as 33 refused to participate, 8 due to a lack of time and the remaining 17 for other unspecified causes (Figure 1). The recruitment rate of the study expressed as a proportion of the Eligible Population was 90.5%. Enrolment was broadly similar in the two ACs; at 87.1% in Madrid and 93.1% in Andalusia. The 7-day follow-up visit was not performed in 9 participants (1.6%), 8 of whom were from Madrid. The reasons cited for each participant were: an aunt of the child came for the day 7 visit, notebook lost, personal problems, unrelated serious adverse event (bicycle accident), work reasons, unknown, lost to follow up and not reported (2 participants). Of these 9 participants, 5 became study dropouts and 4 parents/legal representatives of the participants provided the data by phone. At day 30 of the follow-up the total number of dropouts was 10 (1.8% of 553). All dropouts were losses to follow-up except for one participant who withdrew consent during the follow-up period. Complete data were available for a total of 487 (88.1% of 553) participants (86.5% in Madrid and 89.2% in Andalusia). However, participants with incomplete data still had evaluable data depending on the variable to be analysed. Baseline characteristics of the study population are displayed in Table 1.

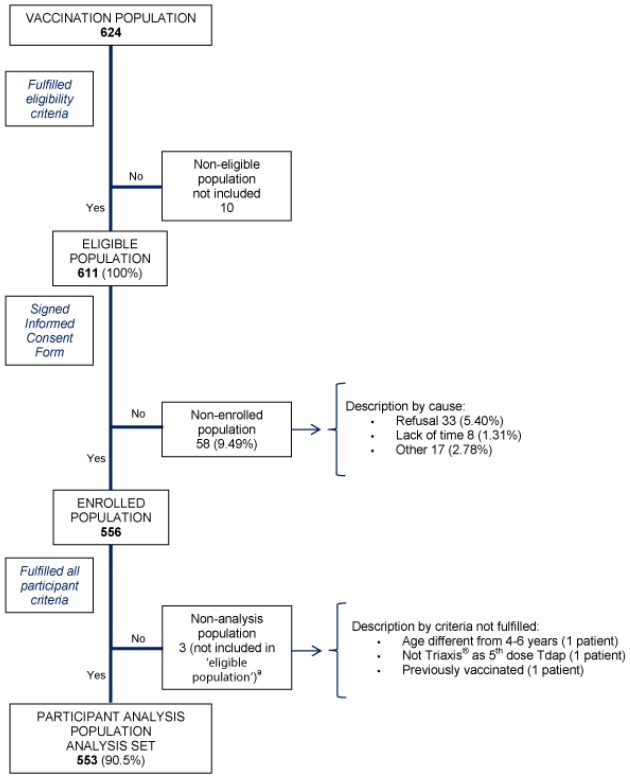

Figure 1: Flow chart of study population. **A** Three patients were later excluded and are not included in the eligible population.

They differ in mean age and the proportion of participants co-vaccinated between the two ACs due to different vaccination calendars. On the day of vaccination, acute disease was reported in 3.6% of participants and chronic disease was reported in 10.1% of participants (Table 1).

	Madrid	Andalusia	Overall
	n=229	n=324	n=553
Age, years			
Mean (SD)	4.2 (0.20)	5.9 (0.29)	5.2 (0.89)
Gender, (n (%))[1]			
Male	103 (45.0)	161 (49.7)	264 (47.7)
Female	126 (55.0)	163 (50.3)	289 (52.3)
Concomitant vaccination, (n (%))a	227 (99.1)	4 (1.2)	231 (41.8)
Haemophilus influenzae type b vaccines	1 (0.4)	0 (0.0)	1 (0.4)
Measles vaccines	226 (98.7)	1 (25.0)	227 (97.4)
Meningococcal vaccines	0 (0.0)	1 (25.0)	1 (0.4)

Pneumococcal vaccines	1 (0.4)	0 (0.0)	1 (0.4)
Poliomyelitis vaccines	1 (0.4)	0 (0.0)	1 (0.4)
Varicella Zoster vaccines	0 (0)	2 (50.0)	2 (0.9)
Disease on day of inclusion, (n (%))a			
Acute disease	6 (2.6)	14 (4.3)	20 (3.6)
Chronic disease	24 (10.5)	32 (9.9)	56 (10.1)
Medication prior to inclusion[2], (n (%))a	11 (4.8)	5 (1.5)	16 (2.9)
Concomitant medication, (n (%))a	23 (10.0)	33 (10.2)	56 (10.1)
Medication used to treat ARs, (n (%))a	36 (7.0)	89 (13.5)	125 (10.6)
Medication used to treat ARs, (n (%))[3]			
Antibiotics for topical use	0 (0.0)	2 (3.2)	2 (2.1)
Antihistamines for systemic use	1 (2.9)	1 (1.6)	2 (2.1)
Antiinflammatory and antirheumatic products, NSAIDs	21 (61.8)	51 (82.3)	72 (75.0)
Antivaricose therapy	0 (0.0)	1 (1.6)	1 (1.0)
Corticosteroids for systemic use	0 (0.0)	2 (3.2)	2 (2.1)
Corticosteroids	1 (2.9)	2 (3.2)	3 (3.1)
Other analgesics and antipyretics	10 (29.4)	3 (4.8)	13 (13.5)
Motility stimulants	1 (2.9)	0 (0.0)	1 (1.0)
SD: Standard Deviation an (%) is expressed as a percentage of the total participant analysis population. The participant analysis population or analysis set consists of all participants enrolled in the study that were compliant with inclusion/non-inclusion criteria and were therefore included in the analysis.			
bRefers to medication taken in the 7 days prior to vaccination day.cn (%) is expressed as a percentage of the total number of different medications used to treat adverse events reported during the study.			

Table 1: Baseline characteristics of Study Population.

Incidence of adverse events

The overall incidence of AEs reported during the complete study period (Day 0-30) was 4.67 per person-month (CI: 4.27-5.10) (Table 2), based on a total of 1998 AEs occurring in 481 out of 553 subjects. The median duration for AEs was 2 days. The incidence per person-month was 3.52 for solicited AEs (CI: 3.21-3.85) and 0.78 for unsolicited AEs (CI: 0.70-0.88). The incidence of sys-AEs was 1.31 per person-month (CI: 1.18-1.45).

Incidence of adverse reactions

The overall incidence of ARs was 3.13 per person-month (CI: 2.85-3.43) with an incidence of ISRs of 2.83 per person-month (CI: 2.57-3.11) and an incidence of 0.32 per person-month (0.27-0.37) for systemic adverse reactions (sys-ARs). The incidence of ARs of severe intensity was 0.31 per person-month (CI: 0.260-0.370) (Table 2). Treatment was administered in 10% of ARs for a mean duration of 1.9 days and 88.5% were anti-inflammatory, anti-rheumatic and other analgesic and antipyretic drugs (Table 1).

Overall, the incidence of ARs showed no differences between ACs, age and co-vaccination except for ARs of mild intensity which were lower in Andalusia (1.50 per person-month, CI: 1.31-1.72) than in Madrid (2.03 per person-month, CI: 1.74-2.36) (Table 2).

	Overall	**Madrid**	**Andalusia**	**MMR Concomitant**
	Incidence (CI95%)	Incidence (CI95%)	Incidence (CI95%)	Incidence (CI95%)
Incidence of AEs by AC and co-vaccination with MMR				
All AEs	4.67 (4.27-5.10)	4.75 (4.14-5.44)	4.61 (4.11-5.17)	4.73 (4.12-5.41)
ISR	2.83 (2.57-3.11)	2.69 (2.32-3.11)	2.94 (2.59-3.31)	2.68 (2.31-3.10)
Systemic Events	1.31 (1.18-1.45)	1.32 (1.12-1.54)	1.31 (1.14-1.49)	1.33 (1.13-1.56)
Solicited	3.52 (3.21-3.85)	3.78 (3.28-4.34)	3.35 (2.97-3.77)	3.76 (3.26-4.32)
Unsolicited	0.78 (0.70-0.88)	0.80 (0.67-0.95)	0.77 (0.66-0.90)	0.80 (0.67-0.96)
Incidence of SAEs by AC and co-vaccination MMR				
All SAEs	0.005 (0.002-0.013)	0.009 (0.003-0.024)	0.003 (0.001-0.011)	0.009 (0.003-0.024)
ISR	0.002 (0.000-0.007)	0	0.003 (0.001-0.011)	0
Systemic Events	0.004 (0.001-0.01)	0.009 (0.003-0.024)	0	0
Solicited	0	0	0	0
Unsolicited	0.005 (0.002-0.013)	0.009 (0.003-0.024)	0.003 (0.001-0.011)	0.009 (0.003-0.024)
Incidence of ARs by AC and co-vaccination with MMR				
SARs	0.004 (0.001-0.010)	0.004 (0.001-0.016)	0.003 (0.001-0.011)	0.004 (0.001-0.016)
ARs	3.13 (2.85-3.43)	3.30 (2.85-3.80)	3.02 (2.67-3.40)	3.28 (2.84-3.78)
ARs intensity				
Mild	1.70 (1.53-1.88)	2.03 (1.74-2.36)	1.50 (1.31-1.72)	1.98 (1.69-2.31)
Moderate	0.54 (0.47-0.62)	0.44 (0.35-0.55)	0.62 (0.52-0.73)	0.45 (0.36-0.56)
Severe	0.31 (0.26-0.37)	0.29 (0.23-0.38)	0.33 (0.26-0.40)	0.30 (0.23-0.39)

ARs leading to a visit	0.03 (0.02-0.04)	0.01 (0.0-0.03)	0.03 (0.02-0.06)	0.03 (0.00-0.03)
ISR	2.83 (2.57-3.11)	2.69 (2.32-3.11)	2.94 (2.59-3.31)	2.68 (2.31-3.10)
Unsolicited	0.16 (0.13-0.20)	0.15 (0.11-0.21)	0.17 (0.13-0.22)	0.15 (0.10-0.21)
Solicited	2.69 (2.44-2.95)	2.69 (2.32-3.11)	2.68 (2.37-3.03)	2.68 (2.30-3.09)
Systemic Events	0.32 (0.27-0.37)	0.47 (0.38-0.59)	0.22 (0.18-0.28)	0.48 (0.38-0.59)
Unsolicited	0.03 (0.02-0.05)	0.04 (0.02-0.07)	0.02 (0.01-0.04)	0.04 (0.02-0.07)
Solicited	0.30 (0.25-0.35)	0.46 (0.36-0.57)	0.20 (0.16-0.26)	0.46 (0.36-0.57)
AEs Time of onset				
Day0	18.39 (16.54-20.40)	17.55 (14.83-20.65)	18.98 (16.56-21.67)	17.50 (14.77-20.60)
Day0-Day7	8.70 (7.91-9.54)	8.99 (7.77-10.34)	8.50 (7.51-9.58)	8.95 (7.73-10.31)
Day8-Day30	0	0	0	0

Table 2: Incidence of adverse events, serious adverse events and adverse reactions (per person-month) by autonomous community and co-vaccination with MMR.

Incidence of serious adverse events/serious adverse reactions

As shown in Table 2, the overall incidence of SAEs was 0.005 person-month (CI: 0.002-0.013), based on 3 cases occurring in 3 of the 553 participants: 2 SAEs were considered vaccine-related and all recovered (syncope and type III hypersensitivity reaction). Moderate syncope was experienced by a 4-year old female 45 minutes after receiving Tdap5 co-vaccinated with MMR. No corrective treatment was administered. Severe type III hypersensitivity reaction, classified as an ISR and probably corresponding to extensive limb swelling, occurred in a 5-year-old male 1 day after Tdap5 administration not co-vaccinated with MMR. Corticosteroids were administered to reduce inflammation. One SAE was considered as unrelated to Tdap5 (face injury; 4-year-old male experienced severe right malar intense traumatism 2 days after Tdap5 administration co-vaccinated with MMR) according to the investigator. The median duration of SAEs was 4 days for all SAEs, which were all unsolicited. Based on one case (the above mentioned type III hypersensitivity reaction), the incidence of serious ISRs was 0.002 per person-month (CI: 0.000-0.007).

Frequency of adverse events/adverse reactions

As shown in table 3, for all sys-AEs (1102), 62.9% of participants reported at least 1 sys-AE and 24.6% had at least 1 sys-AE that was considered by the investigator as vaccine-related. The median duration of sys-ARs was 2 days. The maximum number of participants with sys-AEs was on Day 0 (15.6%) and the fewest during Day 8-30 (0.2%). The most common solicited sys-ARs (frequency greater than 1%) were: 13.7% for asthenia/fatigue (tiredness), 8.0% for anorexia, 5.6% for headache, 4.3% for fever, 4.0% for generalized aching and muscular weakness, 2.9% for chills, 2.7% for arthralgia/joint swelling, 1.6% for rash and 1.3% for nausea. The frequency of unsolicited sys-ARs at the Medical Dictionary for Regulatory Activities (MedDRA) preferred term level was less than 1%.

A total of 896 ISRs were recorded in 420 (75.9%) participants which were all considered by the investigator as vaccine-related (Table 4). For all ISRs during the 30 day follow-up, 75.9% of participants had at least 1 ISR and the median duration of ISRs was 2 days. The most common ISRs were: 67.27% for pain, 35.44% for swelling and 38.88% for erythema. Other ISRs included: 7.6% for injection site pruritus, 4.0% for injection site warmth, 1.4% for injection site induration and 1.4% for injection site haematoma. Three ISRs which are not individually listed in the SmPC, pruritus, warmth and induration, were observed at frequencies of 7.6%, 4% and 1.5%, respectively. Post-hoc analysis showed that 75 to 95% of injection-site pruritus, induration and warmth were associated with one or more ISRs and more than 50% were associated with the inflammatory triad of pain, erythema and swelling at the injection site. Table 5 provides a comparison of the frequency (and 95% confidence interval) of ARs reported during the 30-day period after vaccination with Tdap5 in the study and the frequency ranges quoted in the SmPC.

	Events	**Duration (median)**	**Reactions**	**Duration (median)**	**Reactions at Day 0[a]**	**Reactions at Days 0-7[a] n(%)**	**Reactions at Days 8-30[a]n(%)**
	n (%)[a]	**(days)**	**n (%)[a]**	**(days)**	**n(%)**		
[Analysis Population=553 participants]							
[Total number of Systemic Events = 1102]							
Participants with Systemic Events (n (%))	348(62.9)	2	136 (24.6)	2	86 (15.6)	136 (24.6)	1 (0.2)
Participants with Serious Systemic Events (n (%))	2 (0.4)	2.5	1 (0.2)	1	1 (0.2)	1 (0.2)	0 (0.0)
Participants with:							

Solicited systemic AE after Triaxis® between Day 0 and Day 7	249 (45.0)	2	129 (23.3)	2	80 (14.5)	129 (23.3)	-
Severe	32 (5.8)[b]	2	10 (1.8)[c]	2	4 (0.7)[d]	10 (1.8)[c]	-
Serious	0 (0)	-	0 (0)	-	0 (0)	0 (0)	-
Visit to hospital or physician	22 (4.0)	3	3 (0.5)	1	1 (0.2)	3 (0.5)	-
Medication to treat	82 (14.8)	1.5	37 (6.7)	1	17 (3.1)	37 (6.7)	-
Unsolicited systemic AE after Triaxis® between Day 0 and Day 30	239 (43.2)	3	17 (3.1)	2	13 (2.4)	16 (2.9)	1 (0.2)
Severe	41 (7.4)[e]	4	3 (0.5)[f]	1	3 (0.5)	3 (0.5)[g]	0 (0.0)
Serious	2 (0.4)	2.5	1 (0.2)	1	1 (0.2)	1 (0.2)[h]	0 (0.0)
Visit to hospital or physician	122 (22.1)	4	2 (0.4)	4	1 (0.2)	1 (0.2)[h]	1 (0.2)
Medication to treat	181 (32.7)	3	4 (0.7)	2.5	2 (0.4)	3 (0.5)	1 (0.2)
[a]n (%) is expressed as a percentage of the number of participants presenting at least one relevant adverse event/number of analyzable participants.							
[b]Nine participants had missing values for the intensity of one solicited AEs between Day 0 and Day 7.							
[c]One participant had a missing value for the intensity of solicited systemic ARs between Day 0 and Day 7.							
[d]One participant had a missing value for the intensity of a solicited AR at Day 0.							
[e]Two participants had missing values for the intensity of unsolicited systemic AEs at Days 0 to 30.							
[f]One participant had a missing value for the intensity of an unsolicited systemic AR at Days 0 to 30.							
[g]One participant had a missing value for the intensity of an unsolicited systemic AR at Days 0 to 7.							
[h]One participant had missing values to determine seriousness and the need to visit hospital or physician for an unsolicited AR reported between Day 0 and Day 7. The Pharmacovigilance Department confirmed with the investigator that it was not a Serious AR and a visit to the hospital or physician was not made.							

Table 3: Frequency of systemic adverse events and reactions.

	Reactions	Duration (median)	Reactions at Day 0b	Reactions at Days 0-7b	Reactions at Days 8-30b
	n (%)a	(days)			
[Analysis Population=553 participants]					
[Total number of ISR=896]					
Participants with ISR	420 (75.9)	2	318 (57.5)	420 (75.9)	3 (0.5)
Participants with Serious ISR	1 (0.2)	4	0 (0.0)	1 (0.2)	0 (0.0)
Participants with:					
Solicited ISR after Triaxis® between Day 0 and Day 7	414 (74.9)	2	314 (56.8)	414 (74.9)	-
Severe	122 (22.1)	3	32 (5.8)	122 (22.1)[3]	-
Serious	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Visit to hospital or physician	10 (1.8)	5	0 (0.0)	10 (1.8)	-
Medication to treat	54 (9.8)	3	41 (7.4)	54 (9.8)	-

Unsolicited ISR after Triaxis® between Day 0 and Day 30	79 (14.3)	2	21 (3.8)	76 (13.7)	3 (0.5)
Severe	7 (1.3)	4	4 (0.7)	7 (1.3)	0 (0.0)
Serious	1 (0.2)	4	0 (0.0)	1 (0.2)	0 (0.0)
Visit to hospital or physician	3 (0.5)	3	0 (0.0)	3 (0.5)	0 (0.0)
Medication to treat	4 (0.7)	3	1 (0.2)	4 (0.7)	0 (0.0)
Solicited ISR after Triaxis® between Day 0 and Day 7					
Injection-site pain	372 (67.3)	2	303 (54.8)	372 (67.3)	0 (0.0)
Injection-site erythema	215 (38.9)	3	56 (10.1)	215 (38.9)	0 (0.0)
Injection site-swelling	196 (35.4)	3	52 (9.4)	196 (35.4)	0 (0.0)

aAll injection-site reactions are related.

bn (%) is expressed as the number of participants presenting at least once the considered related adverse event/number of analysable participants.

cOne participant had a missing value for the intensity of one solicited ARs between Day 0 and Day 7.

Table 4: Frequency of injection-site reactions.

	Triaxis® SmPC	**Triaxis®PASS**
	%	% (CI)
Metabolism and Nutrition Disorders		
Anorexia (decreased appetite) [1]	≥ 10%	7.95% (5.70-10.21)
Nervous System Disorders		
Headache[a]	≥ 10%	5.60% (3.69-7.52)
Gastrointestinal Disorders		
Diarrhea[a]	≥ 10%	0.36% (0.00-0.08)
Nausea[a]	≥ 1% and <10%	1.27% (3.34-2.20)
Vomiting[a]	≥ 1% and <10%	0.90% (0.11-1.69)
Skin and Subcutaneous System Disorders		
Rash[a]	≥ 1% and <10%	1.63% (0.57-2.68)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia/joint swelling[a]	≥ 1% and <10%	2.71% (1.37-4.07)
Generalized aching or muscular weakness[a]	≥ 1% and <10%	3.98% (2.35-5.61)
General Disorders and Administrative Site Conditions		
Asthenia/Fatigue[a] (tiredness)	≥ 10%	13.74% (10.87-16.61)
Chills[a]	≥ 1% and <10%	2.89% (1.50-4.29)
Pyrexia (fever ≥38°C)[a]	≥ 1% and <10%	4.52% (2.79-6.25)
Axillary adenopathy[a]	≥ 1% and <10%	0.54% (0.00-1.15)
Injection-site pain[a]	≥ 10%	67.27% (63.36-71.18)
Injection-site swelling[a]	≥ 10%	35.44% (31.46-39.43)

Injection-site erythema[a]	≥ 10%	38.88% (34.82-42.94)
Injection-site haematoma[2]	Listed[3]	1.45% (0.45-2.44)
Injection-site induration[b]	Not listed[4]	1.45 % (0.45-2.44)
Injection-site pruritus[b]	Not listedd	7.59 % (5.39-9.80)
Injection-site warmth[b]	Not listedd	3.98 % (2.35-5.61)

[a]These AEs were solicited from Day 0 to Day 7 after Triaxis®.

[b]These AEs were unsolicited from Day 0 to Day 30 after Triaxis®.

[c]Injection site haematoma (bruising) is listed in the SmPC with no precise frequency since it has been spontaneously reported during post marketing use from a population of uncertain size.

[d]Injection-site induration, pruritus and warmth were spontaneously reported during post marketing use. They have not been individually listed in the SmPC because these ISRs are commonly associated with erythema and swelling part of inflammatory local reactions.

Table 5: Comparison of the reported frequencies in the Study and the frequencies stated in the Summary of Product Characteristics of Triaxis® (Tdap5).

Discussion

This post-marketing study demonstrates that the safety profile of Tdap5 administered as a 5th dose in 4-6 year old Spanish children in routine clinical practice is consistent with premarketing data from clinical trials and post-marketing data included in the SmPC. Since no unusual or unexpected AEs were identified in the study, there is no evidence to question the current safety profile of the vaccine. Compared with the solicited ARs listed in the SmPC, this observational study found frequencies which were consistent with the SmPC for solicited AEs based on clinical trials. Some ARs were below the ranges of the SmPC, such as vomiting and diarrhoea and others that were at the lower ranges. The 2 SAEs considered related to the administration of Tdap5 and which recovered are already listed in the current SmPC.The primary objective of the study was to determine the incidence of all ISRs and sys-AEs that occurred during this post-licensure study. ISRs were the most frequently reported reactions in the study and similar to those in the current Spanish version of the SmPC for these kind of reactions and reported in clinical trials of similarly aged children with follow up over 4 days [15] and 7 days [8]. ISRs not individually listed in the SmPC included: injection site pruritus, injection site induration and injection site warmth. These reactions were mainly associated with the inflammatory triad of pain, erythema and swelling at the injection site. Hence no safety signal regarding the occurrence of ISRs after Tdap5 administration was identified in the study.

The results were similar in several subgroups examined, although not powered or tested for differences. Incidence of AEs was broadly similar in: the two ACs of Andalusia and Madrid, those co-vaccinated with MMR vaccine, at ages 4, 5 and 6, and the time elapsed between the 4th and 5th dose of Tdap5. Only the presence of acute and chronic disease at the time of vaccination appeared to increase the incidence of all AEs. Age, co-vaccination and AC did not explain this difference. Overall, no differences were observed between the three age groups in the incidence rates for all AEs, ISRs, solicited ISRs, sys-AEs (solicited or unsolicited), AEs leading to a visit or by time of onset. Differences were observed for unsolicited ISRs and for incidence rates by intensity of the AE, although all of these rates are low. The findings of apparent differences between subgroups should be viewed cautiously as they may be due to the play of chance from the large number of subgroup analyses performed. This caution may apply to the apparent differences observed with reporting of vaccine-related gastrointestinal, musculoskeletal and skin AEs between the ACs, differences in the severity of ISRs between ACs (higher intensity in Andalusia with more visits to hospital or physician and more ISRs treated with medications), and the higher incidence of systemic events in Madrid due to solicited sys-AEs.

The differences in co-vaccination policy and the age at vaccination of the 5th dose of Tdap5 appear not to make a difference in the incidence of AEs, indicating that the practice of vaccinating Tdap5 and MMR concurrently leads to no further increase of AEs. Indeed, a post-hoc analysis showed no consistent evidence that the time between the 4th DTaP and 5th Tdap5 dose influences the severity of ARs and ISRs.

It is also noteworthy that ARs based on 30-day diary cards, and some of the study procedures, may have increased the observed rate of ARs compared to those collected in routine clinical practice. Even with enhanced reporting through a diary system, the rate of AEs was low and no unusual ARs were detected.

The intensity of AEs in one study may be difficult to compare with other studies that may have used different thresholds to categorize intensities [8]. Nevertheless, the categorizations used in this study have partly been based on those recommended by the Brighton Collaboration [16] for systemic AEs and non-measurable ISRs, measurable ISRs, fever and vomiting and diarrhoea.

Where data were missing to assign causality with the vaccine of an AE, the AE was analysed as being related to vaccination (in accordance with ICH recommendations). Although there was few such missing data the bias would exaggerate the incidence of vaccine-related AE.

The conduct of the study indicates that the results are valid and sufficiently precise for the primary and secondary objectives and capable of being generalizable to routine daily clinical practice. Notably, a high proportion of eligible subjects participated in the study indicating that important selection biases are unlikely. Lack of attrition bias is reflected by the high follow-up and the number of participants having complete data. The actual drop-out rate was much lower than the 10% assumed.The study was an observational study carried out in routine clinical practice where the 5thdose of Tdap5 vaccination is normally administered, among community paediatricians in Spain.

Vaccination was only restricted to the terms of use under the Spanish version of the SmPC.

Although data on the characteristics of the two ACs were not collected as part of the study, the sites in the ACs of Andalusia and Madrid cover largely urban populations but with some rural representation, and with a minority of other ethnic groups. The use of a relatively large number of research naïve community paediatricians (22 centres) and not hospital specialists allows for greater generalizability of the results to other similar health care settings. The lack of biased subject selection and the rapid and highly successful recruitment rate indicate that a wide and representative spectrum of children was included, in Spain, who are eligible for the 5th dose of Tdap5 and hence the results will have wide applicability.

The similarity of results among the principal analyses with many subgroups support the wide applicability of the overall findings for: ages 4, 5 and 6, co-vaccination with or without MMR, different ACs and time between the 4th DTaP and 5th Tdap5 vaccination.

The major limitation of the study is the lack of a comparator group. However, the results are not out of keeping with other studies for this age group [8, 10, 15]. The high rate of minor ISRs associated with this vaccination has been observed in other studies with solicited and diary method of data collection; this rate represents a reduction compared with using DTaP combined vaccine for this dose [9] and is comparable with that following the 4th (booster) dose [8].

The study confirmed that the safety profile of Tdap5 as a 5th dose in 4-6 year old children used in routine clinical practice is consistent with results observed in pre-licensure studies and with spontaneously reported events in post marketing surveillance. All AEs and the few SAEs detected were within the range of events that may be expected in this population of children after vaccination with Tdap5 and none caused any clinical concern. Furthermore, the safety profile of Tdap5 does not differ with ages above 4 years old and co-vaccination with MMR vaccines.

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Contributors

Study design: all authors and L. Dominguez, I. Mendez and M. Mariño from Oxon Epidemiology. Analysis and interpretation of data: all authors and B. San José and I. Mendez from Oxon Epidemiology. Drafting of the manuscript: all authors and I. Mendez and E. Artime from Oxon Epidemiology. Revision of the manuscript: all authors. Final manuscript was reviewed and approved by all authors before submission.

Conflict of Interest

C. Lambermont and L. Marcelon are employees of Sanofi Pasteur MSD. I. Bruyère is an employee of Sanofi Pasteur. N. Qizilbash, I. Mendez, L. Dominguez, B. San José, E. Artime and M. Mariño are employees of Oxon Epidemiology, which was awarded a contract to conduct this study for Sanofi Pasteur MSD. J. García-Sicilia and F. Giménez-Sánchez have received honoraria from Sanofi Pasteur MSD.

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