Risk of Recurrence of Adverse Events Following Immunization: A Systematic Review

Joseline Guetsop Zafack, MD, MPH,[a] Gaston De Serres, MD, PhD,[a,b,c] Marilou Kiely, RN, MSc,[a,c] Marie-Claude Gariépy, MSc,[b] Isabelle Rouleau, PhD,[d] Karina Anne-Marie Top, MD, MSc,[e] for the Canadian Immunization Research Network

abstract

CONTEXT: Reimmunizing patients who had an adverse event following immunization (AEFI) is sometimes a challenge because there are limited data on the risk and severity of AEFI recurrence.

OBJECTIVE: To summarize the literature on the risk of AEFI recurrence.

DATA SOURCES: PubMed, Embase, and Cochrane library.

STUDY SELECTION: We included articles in English or French published before September 30, 2016. Articles were selected if they estimated the risk of AEFI recurrence in at least 5 individuals. Studies with experimental vaccines were excluded.

DATA EXTRACTION: Data on study design, setting, population, vaccines, and AEFI recurrence were extracted.

RESULTS: Twenty-nine articles were included. Among patients with a history of hypotonic hyporesponsive episode (n = 398), anaphylaxis (n = 133), or seizures (n = 60) who were reimmunized, events recurred in 0% to 0.8%. Allergic-like events recurred in 30 of 594 reimmunized patients. Fever recurred in 0% to 84% of 836 reimmunized patients, depending on the vaccine and dose number. Among children with extensive limb swelling after the fourth dose of diphtheria-tetanus-acellular pertussis vaccine, recurrence was higher when the fifth dose was given withthe full-antigen formulation (78%) compared with the reduced-antigen formulation (53%, P = .02)

LIMITATIONS: Many studies, included few patients, and those with severe AEFIs were often not reimmunized.

CONCLUSIONS: Despite vaccines being administered to millions of people annually, there are few studies in which researchers evaluated AEFI recurrence. Published studies suggest that reimmunization is usually safe. However in these studies, severe cases were often not reimmunized.

[a]*Department of Social and Preventive Medicine, Laval University, Quebec, Canada;* [b]*Axe maladies infectieuses et immunitaires,Centre de recherche du CHU de Québec-Université Laval, Quebec, Canada;* [c]*Direction des risques biologiques et de la santé au travail, Institut National de Santé Publique du Québec, Quebec, Canada;* [d]*Ministère de la Santé et des Services Sociaux du Québec, Montreal, Canada; and Departments of* [e]*Pediatrics and Community Health and Epidemiology, Dalhousie University and Canadian Center for Vaccinology, IWK Health Centre, Halifax, Nova Scotia, Canada*

Drs De Serres and Rouleau and Ms Gariépy participated in the conceptualization of the study, the design of the study, and interpretation of data, and they critically reviewed the manuscript; Ms Kiely participated in the collection and interpretation of data and critically reviewed the manuscript; Dr Top participated in the

To cite: Zafack JG, De Serres G, Kiely M, et al. Risk of Recurrence of Adverse Events Following Immunization: A Systematic Review. *Pediatrics*. 2017;140(3):e20163707

For vaccines to be fully effective and induce long-term protective immunity, individuals should receive all recommended doses. Vaccine recipients who experienced an adverse event following immunization (AEFI) are sometimes afraid that the adverse event might recur with future immunizations, and this can lead to avoidance or delay of subsequent immunizations. Most existing recommendations regarding the management of patients who had an AEFI are based on expert opinion and supported by limited scientific data.[1,2]

The aim of this systematic review was to summarize the literature on the risk of AEFI recurrence (defined as an occurrence of the same AEFI after the administration of another dose of the same vaccine or vaccines sharing common antigens) and identify predictors of recurrence. In addition, we sought to determine if the risk of an adverse event following reimmunization was higher in patients who already had the same adverse event at the previous immunization compared with those who did not. These results are expected to inform physicians when discussing continuation of immunization with patients who previously experienced an AEFI and to support future immunization guidelines for these patients.

METHODS

We conducted a systematic review of studies published in English and French before September 30, 2016 in Medline via PubMed, Embase, and the Cochrane library. Ethical approval was not required because only published articles were included in this review.

The search strategy was developed in consultation with an experienced medical library scientist using the preferred reporting items for systematic reviews and meta-analysis of observational studies recommendations.[3,4] The search combined keywords (with corresponding synonyms, Medical Subject Headings and Emtree terms) referring to our intervention (ie, "reimmunization" and "immunization") and outcome (ie, "adverse events"). No restriction on study type or population was used to get a full perspective of the research that has been done to date. The search strategy in Medline via PubMed is available in Supplemental Table 5.

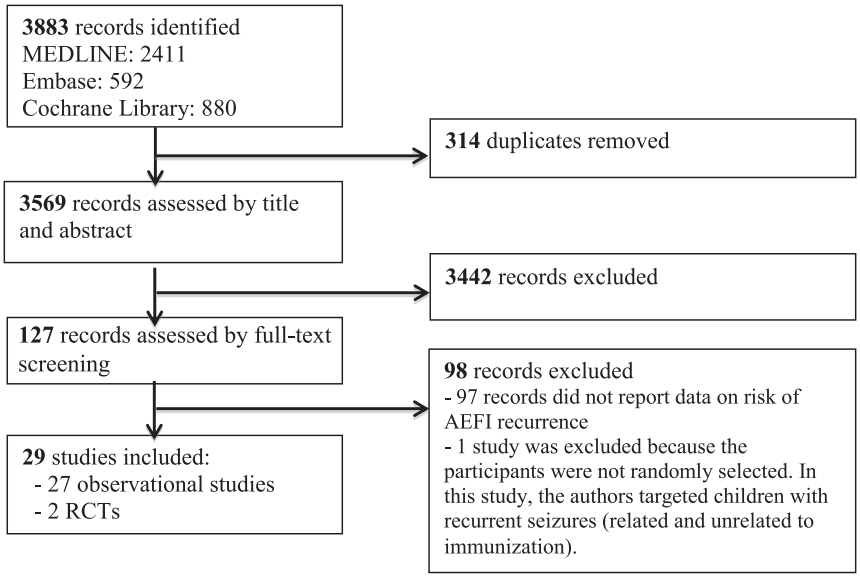

FIGURE 1
Flow diagram of search process.

The titles and abstracts of the publications identified were independently screened for eligibility by 2 investigators (J.G.Z., M.K.); interrater discrepancies were resolved by discussion and consensus. Additional articles were identified by reviewing the reference lists of retrieved articles. J.G.Z. selected the full-text articles. A flow diagram outlining the selection process is presented in Fig 1. We included all studies in which researchers estimated the risk of AEFI recurrence or that described the outcome of reimmunization among patients with a history of AEFI. Exclusion criteria were the following: experimental vaccines (eg, malaria), cancer vaccines, vaccines administered at more than 5-year intervals (eg, yellow fever) and studies in which fewer than 5 patients were reimmunized. Recurrence was defined as the occurrence of the same adverse event following reimmunization. Reimmunization was defined as administration of vaccine(s) that had common antigens with those implicated in the initial AEFI. The case definitions of each evaluated AEFI are presented in Table 1.

For each study, the risk of bias with respect to our review question was assessed by using a standardized form adapted from the guidelines of the National Institute for Health and Care Excellence[6] and Risk Of Bias In Non-Randomized Studies - of Interventions[7] (Supplemental Tables 6, Supplemental Fig 3 and 4). Risk of bias was rated as "low," "moderate," "serious," "critical," or "unclear."[7]

Data on country, year of publication, study design, vaccine(s), population, duration of follow-up, and AEFI recurrence were extracted from the articles that met eligibility criteria and were entered into a spreadsheet. Risk of AEFI recurrence

TABLE 1 Case Definitions of AEFIs

AEFI	Case Definitions	Duration of Follow-up[a]
ALEs	ALE	24 h[b]
	ALE documented by a health care provider	
	or	
	ALE occurred after immunization. This includes 1 or more of the following symptoms:	
	cutaneous signs: urticaria, skin rash, or angioedema	
	respiratory signs: throat tingling, dyspnea, wheezing, cough, or hoarseness	
	cardiovascular signs: facial flushing, hypotension, or tachycardia	
	Anaphylaxis	24 h[b]
	Anaphylactic reaction documented by a health care provider	
	or	
	Rapidly progressive acute hypersensitivity reaction with multiorgan system involvement	
	presenting as, or rapidly progressing to, a life-threatening reaction	
	ORS	24 h
	Adverse event occurring after influenza immunization and characterized by	
	bilateral conjunctivitis, facial edema, or respiratory symptoms (cough, sore throat, hoarseness, dyspnea, chest tightness) beginning 2–24 h after influenza immunization and resolving within 48 h after onset (2000–2001 case definition)	
	or	
	bilateral conjunctivitis, facial edema, or respiratory symptoms onset ≤24 h after immunization, with no restriction on duration of symptoms (2001–2002 case definition)	
Apnea	Cessation of respiration for 20 s or more; bradycardia as a drop in heart rate to <100 beats per min ± desaturation with oxygen ≤90%	48 h
	Signs absent for 24 h or 48 h before immunization and present in the subsequent 48 h period	
Decreased appetite	Anorexia or poor appetite	48 h
Drowsiness or sleepiness	Drowsiness: unusually sleepy or inactive	48 h
	Sleepiness: uncharacteristic drowsiness or napping	
ELS	Swelling (with or without redness) centered at the site of the injection and fulfilling at least one of the following characteristics:	5–15 d
	swelling to the nearest joint	
	swelling extending beyond the nearest joint	
	swelling from joint to joint	
	swelling for more than 3 d duration	
	swelling requiring hospitalization and/or medical attention, including general practitioner review	
	swelling or redness ≥100 mm	
Fever	Temperature ≥38°C	6–48 h[b]
Henoch-Schonlein purpura	Allergic purpura or nonthrombocytopenic purpura occurring within 30 d of immunization	30 d
HHE[c]	Sudden onset of reduced muscle tone, hyporesponsiveness, and change of skin color (pallor or cyanosis)	24–72 h[b]
Pain	Mild to moderate: discomfort thought to be related to the injection site	48 h
	Moderate to severe: crying or protesting to touch of the immunized limb or when the latter was moved	
Persistent crying	Crying after immunization lasting more than 3 h	48 h
	or	
	Prolonged crying and refusing to play or persistent crying that could not be comforted	
Redness, swelling at injection site	Redness ≥0.5 cm	48 h[b]
	Redness ≥2.5 cm	
	Redness ≥5 cm	
	Swelling ≥0.5 cm	
	Swelling ≥2.5 cm	
	Swelling ≥5 cm	
	or	
	Redness and/or swelling ≥0.5 cm	
Seizures	Seizures or syncopal seizures documented by a health care provider	Unspecified
Vomiting	Vomiting within 48 h of immunization	48 h

[a] Duration after immunization.

[b] In some studies, duration of follow-up was not reported by the authors.

[c] In the study by Duvernoy and Braun,[5] authors included children up to 10 years of age.

was calculated as follows: the number of patients with recurrence divided by the total number of patients reimmunized. Owing to the differences between the studies, a DerSimonian and Laird random-effects approach was used for the pooled estimates. The variances of the risks estimated in the individual studies were stabilized with the Freeman-Tukey transformation before pooling.[8] Heterogeneity was assessed by using the I^2 statistics, interpreted as low (0%–40%), moderate (30%–60%), substantial (50%–90%), and considerable (75%–100%) heterogeneity.[9] Subgroup analyses per vaccine dose number and type (eg, whole-cell or acellular pertussis) were conducted to explore clinical heterogeneity.

We compared the occurrence of adverse events following reimmunization in various subgroups, including vaccine recipients with a history of AEFI versus those without, type of vaccine administered, and severity of the initial AEFI. Comparisons were performed by using risk ratios (RRs) with 95% confidence intervals (CIs), 2-tailed χ^2 tests, or Fisher's exact tests with statistical significance defined as $P < .05$. Pooled analyses were performed with Stata version 13.0 and the remaining with SAS, version 9.3.

RESULTS

Among the 3883 articles retrieved, 29 met the inclusion criteria, 6 of which (20%) were identified from the reference lists of other articles (Fig 1).[5,10–37] The articles were published between 1982 and 2016. Most (n = 27, 93%) studies were observational,[5,10–24,27–37] and 14 (48%) were prospective (Table 2). In the various studies, AEFIs were collected through patient and/or parental reports (n = 12), physician report or patient and/or parental report (n = 7), hospital records and/or chart review (n = 7), passive surveillance database (n = 2), or physician report (n = 1) (Table 2). Most studies included only children aged <18 years (n = 18, 62%), of which 12 (67%) studies included only children ≤6 years. The remaining studies included adults aged 18 years or older (n = 3, 10%) or both children and adults (n = 8, 28%). All studies included both sexes, except for 2 studies in which researchers described adverse events following human papilloma virus (HPV) immunization in girls.[14,30] Researchers evaluated the recurrence risk of the following AEFIs: allergic-like events (ALEs) (n = 13), hypotonic hyporesponsive episodes (HHEs) (n = 7), fever (n = 5), extensive limb swelling (ELS) (n = 3), seizures (n = 3), pain (n = 3), apnea (n = 2), decreased appetite (n = 2), persistent crying (n = 2), drowsiness (n = 2), vomiting (n = 2), and Henoch-Schonlein purpura (n = 1). Typically, several vaccines or adverse events were evaluated in the same study; researchers in 9 studies assessed the risk of recurrence of 1 specific AEFI (fever, apnea, ELS, oculorespiratory syndrome [ORS], ALE, or HHE) after administration of 1 or several vaccines (Table 2). Among the studies in which researchers assessed vaccine-specific risks of AEFI recurrence, the most frequently studied vaccines were the diphtheria-tetanus-acellular pertussis vaccine (full-antigen, DTaP or reduced-antigen, dTap formulations) or diphtheria-tetanus whole-cell pertussis vaccine (DTwP) (n = 12), followed by inactivated influenza vaccine (IIV) (n = 6), HPV vaccine (n = 2), diphtheria-tetanus toxoids vaccine (DT) (n = 1), and New Zealand meningococcal B vaccine (n = 1).

Overall, the risk of bias in the individual studies was rated as low in 8 (28%) of the studies, moderate in 15 (52%), and serious in 6 (21%) (Fig 2).

ALEs

Allergic-like signs and symptoms can be caused by a variety of conditions. Three of these conditions were described in the studies retrieved: ALEs, anaphylaxis, and ORS. ORS is a non–immunoglobin E–mediated adverse event that typically starts 2 to 24 hours after influenza immunization and often affects 2 systems, causing bilateral conjunctivitis, facial edema, and upper respiratory signs and symptoms (cough, sore throat, hoarseness, dyspnea, chest tightness, and lingual and/or pharyngeal edema).[38]

Researchers in 8 studies described reimmunization of patients with a history of ALEs after immunization.[16–20,22,30,37] Before reimmunization, all patients underwent a clinical evaluation (description of the ALE and medical history) by a specialist (an allergist, pediatrician, or emergency physician), with or without skin testing with the vaccine. Overall, 594 children and adults were reimmunized at a hospital or clinic: 148 were reimmunized with a single full dose, 59 received 2 graded doses, and for 389 patients, the reimmunization protocol was not described. However, for 373 (96%) of these patients, the authors specified that individualized precautions (eg, premedication, temporally separated single injections, and alternative brand and/or administration in a hospital as a single dose or 4 graded doses) were applied when deemed necessary. Among the 594 patients reimmunized, ALEs recurred in 30 (5% [95% CI, 3.3 to 6.8]), none of whom experienced anaphylaxis. All recurrences were mild and self-limited except for 1 female child with severe food and respiratory allergies who developed urticaria and bronchospasm after being reimmunized with measles-mumps-rubella (MMR) vaccine. Her symptoms subsided immediately after treatment. The risk of recurrence of ALEs was higher in 1 study based on the German passive

TABLE 2 Description of the 29 Studies Included in the Review

Author, Publication Year	Country	Type of Study	Method of Ascertainment of the AEFI	Age at Reimmunization	Vaccine(s)	Adverse Event(s)
Andrews et al[29] 1998	Australia	Cohort (prospective)	Physician report, patient and/or parental report	2 mo–15 y	DTwP-Hib	Anorexia, drowsiness, HHE, pain, persistent crying, redness and/or swelling
Baraff et al[10] 1985	United States	Cohort (prospective)	Patient report (active search)[a]	<1 y	DTP	Fever, injection site reaction
Broos et al[27] 2010	Netherlands	Cohort (prospective)	Patient and/or parental report[a]	6–48 mo	Influenza	Fever
Clifford et al[34] 2011	Australia	Cohort (retrospective)	Hospital records, chart review	<1 y	Various[b]	Apnea
Crawford et al[33] 2011	Australia	Cohort (retrospective)	Enhanced passive surveillance data (reports from patients and HCP)	8–26 y	HPV	Syncopal seizures, syncope
Cronin et al[17] 2012	Ireland	Cohort (prospective)	Physician, patient and/or parental report[a]	Children[c]	Various[b]	ALE
De Serres et al[25] 2004	Canada	RCT	Patient and/or parental report[a]	>17 y	Influenza	ALE (ORS)
Deloria et al[15] 1995	United States	Cohort (prospective)	Patient and/or parental report[a]	4–6 mo	DTaP/WCL	Anorexia, drowsiness, fever, pain, persistent crying, vomiting
DuVernoy et al[5] 2000	United States	Cohort (prospective)	Patient and/or parental report[a]	2 mo–10 y	DTaP±Hib, DTwP±Hib	HHE
Edelman et al[11] 1999	Finland	Cohort (prospective)	Patient and/or parental report[a]	3–5 mo	DTaP	Local redness and/or swelling
Flatz-Jequier et al[35] 2008	Switzerland	Cohort (retrospective)	Chart review	2–4 mo	DTaP-IPV-Hib±HepB	Apnea
Gold et al[30] 2000	Australia	Cohort (retrospective)	Physician report, patient and/or parental report[a]	1 mo–15 y	Various[b]	Seizures, HHE
Goodwin et al[31] 1999	Australia	Cohort (retrospective)	Chart review	4–18 mo	DTP	HHE
Grenier et al[23] 2004	Canada	Cohort (retrospective)	Patient and/or parental report[a]	Children and adults	Influenza	ALE (ORS)
Jacobs et al[16] 1982	United States	Cohort (retrospective)	Physician report, patient and/or parental report[a]	17–27 y	DT	ALE, anaphylaxis
Kang et al[18] 2008	Australia	Cohort (retrospective)	Physician report, patient and/or parental report	12–26 y	HPV	ALE
Long et al[28] 1990	United States	Cohort (prospective)	Patient and/or parental report[a]	2–20 mo	DTP	Drowsiness, fever, pain
Marshall et al[14] 2006	Australia	Cohort (prospective, subgroup analysis of an RCT)	Patient and/or parental report[a]	4–6 y	DTaP, dTap	ELS
Micheletti et al[22] 2012	Italy	Cohort (retrospective)	Chart review, physician	2 mo–87 y[d]	Various[b]	ALE
Nicolosi et al[19] 2014	Italy	Cohort (retrospective)	Hospital records	4 mo–16 y	Various[b]	ALE, fever, seizures, HHE
Quinn et al[12] 2011	Australia	Cohort (prospective)	Patient and/or parental report[a]	4–6 y	DTaP, dTap	ELS
Rennels et al[13] 2008	United States	Cohort (prospective)	Patient and/or parental report[a]	4–6 y	DTaP	ELS
Seitz et al[21] 2009	Germany	Cohort (prospective)	Physician report	13–79 y	Various[b]	ALE (anaphylaxis)
Sexton et al[36] 2009	New Zealand	Cohort (prospective)	Hospital records (that were reviewed by pediatricians to ensure diagnostic consistency)	6 wk–9 y	NZ-MenB	Thrombocytopenia

TABLE 2 Continued

Author, Publication Year	Country	Type of Study	Method of Ascertainment of the AEFI	Age at Reimmunization	Vaccine(s)	Adverse Event(s)
Skowronski et al[24] 2002	Canada	Cohort (retrospective)	Patient and/or parent report[a]	>17 y	Influenza	ALE (ORS)
Skowronski et al[26] 2003	Canada	RCT	Physician report, patient and/or parental report[a]	33–74 y	Influenza	ALE (ORS)
Top et al[37] 2016	Canada	Cohort (prospective)	Physician report, patient and/or parental report[a]	2 mo–65 y	Various[b]	ALE, injection site reaction
Vermeer-de Bondt et al[32] 1998	Netherlands	Cohort (retrospective)	Chart review	4–6 y	DTP-IPV	HHE
Zent et al[20] 2002	Germany	Cohort (retrospective)	Passive surveillance database (reports of HCP and legal bodies)	Children and adults	Various[b]	ALE

DT, diphtheria and tetanus toxoids; HCP, health care provider; NZ-MenB, New Zealand outer membrane meningococcal serogroup B vaccine.
[a] In these studies, there was an active surveillance: the patient or parents either had a diary to record the AEFIs or received phone calls or e-mails to collect information on adverse events after reimmunization.
[b] Various vaccines: DTaP±Hib/HepB/IPV; hepatitis A or B, meningococcal vaccines, pneumococcal vaccines, MMR, influenza, HPV, or tick-borne encephalitis.
[c] Children <18 years old.
[d] Mean age was 13 years, and median age was 7.5 years.

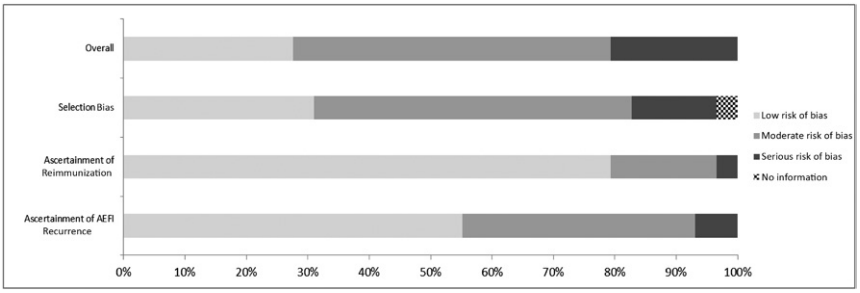

FIGURE 2
Risk of bias in the individual studies.

surveillance system[17] (61.5%, 8 of 13) than in the 7 hospital- or clinic-based studies (3.8%, 22 of 581, $P < .0001$).

Researchers in 2 studies evaluated the risk of recurrence of anaphylaxis in 133 patients receiving various vaccines[16,21] (Table 3). All but 1 had negative skin testing with the vaccine. Ninety-five (71%) were reimmunized with a single dose, and 38 (29%) were reimmunized with 3 graded doses (10%, 30%, and 60% of the total dose at 1-hour intervals). No anaphylaxis or ALEs occurred after reimmunization.

The risk of recurrence of ORS after immunization only with IIV was evaluated in 4 studies.[23–26] The risk of recurrence estimated by the 2 randomized controlled trials (RCTs)[25,26] was higher than that estimated by researchers in the 2 retrospective studies[23,24] (67 of 180 = 37% vs 48 of 488 = 10%, $P < .001$). The estimated risk of recurrence varied from year to year depending on the manufacturer of the vaccine but was not influenced by age, sex, number of previous influenza vaccine doses, or the severity of the previous ORS episode. Patients with a history of ORS were 3.3 to 4 times more likely to develop ORS compared with vaccine recipients without such history. In the study by Skowronski et al,[24] 4 of 6 patients described their recurrence as milder, and the remaining 2 considered their recurrence as being of the same severity as the first episode. Recurrences did not dissuade patients from continuing immunization.

Injection Site Reactions

Three types of injection site reactions were assessed: ELS, pain, and redness and/or swelling at the injection site. In 3 studies, 55 of 98 (56% [95% CI, 9.8 to 46.3]) children with ELS after the fourth dose of DTaP had a recurrence after the fifth dose (DTaP/ reduced-antigen diphtheria-tetanus-acellular pertussis vaccine [dTap]).[5,9,10] Among the 55 children who had a recurrence, none had fever >38.5°C. The injected arm was spontaneously painful (without touch or movement) in 3 subjects, and symptoms were severe enough to prevent daily activities in 3 patients. In the study conducted by Quinn et al,[12] 64% of patients reported spontaneous resolution of the ELS within 4 days of immunization. All 55 children recovered completely within 19 days of immunization. In 2 studies, children were reimmunized with either the full- (DTaP) or reduced-antigen (dTap) vaccine.[12,14] The risk of recurrence of swelling was 1.5-fold higher when using DTaP (31 of 40, 78%) compared with dTap (20 of 38, 53%) $P = .02$. After reimmunization, patients in both the DTaP and dTap

TABLE 3 Risks of Recurrence of AEFIs

	$Vaccine_{dose\ number}$, First Author	Vaccine Recipient's Age	No. of Patients With Recurrence/No. of Patients With a Previous AEFI Reimmunized	Risk of Recurrence % (95% CI)
ALES				
ALEs	DT, Jacobs	17–27 y	0/38	0 (0 to 9)
	HPV, Kang	12–26 y	1/21	5 (1 to 23)
	Various[a], Cronin	Children	0/63	0 (0 to 6)
	Various[a], Gold	1 mo–15 y	0/33	0 (0 to 10)
	Various[a], Micheletti	2 mo–87 y	19/352	5 (4 to 8)
	Various[a], Nicolosi	4 mo–16 y	0/53	0 (0 to 7)
	Various[a], Zent	Children and adults	8/13	62 (36 to 82)
	Various[a], Top	6 mo–65 y	2/21	10 (3 to 29)
		Pooled estimate	I^2 = 84%	4 (0 to 10)
Anaphylaxis	DT, Jacobs	17–27 y	0/95	0 (0 to 4)
	Various[a], Seitz	13–79 y	0/38	0 (0 to 9)
		Pooled estimate	I^2 = 98%	0 (0 to 1)
ORS	IIV, De Serres	17–74 y	52/146	36 (28 to 44)
	IIV, Grenier	Children and adults	42/366	11 (9 to 15)
	IIV, Skowronski 2002	17–74 y	6/122	5 (2 to 10)
	IIV, Skowronski 2003	17–74 y	15/34	44 (29 to 61)
		Pooled estimate	I^2 = 96%	21 (7 to 39)
Injection site reactions				
ELS	$DTaP_5$, Rennels	4–6 y	4/20	20 (8 to 42)
	$DTaP_5$, Quinn	4–6 y	23/27	85 (66 to 96)
	$dTap_5$, Quinn	4–6 y	16/26	62 (41 to 80)
	$DTaP_5$, Marshall	4–6 y	8/13	62 (32 to 86)
	$dTap_5$, Marshall	4–6 y	4/12	33 (10 to 65)
		Pooled estimate	I^2 = 89%	48 (18 to 79)
Pain (mild to severe)	$DTP_{2\&3}$, Baraff	<1 y	336/596	56 (52 to 60)
	$DTwP_2$, Long[b]	4 mo	NR	75
	$DTwP_3$, Long[b]	6 mo	NR	66
	$DTwP_4$, Long[b]	18 mo	NR	85
Pain (moderate to severe)	$DTaP_2$, Deloria	4 mo	8/66	12 (5 to 23)
	$DTaP_3$, Deloria	6 mo	3/33	9 (2 to 24)
	$DTwP_2$, Deloria	4 mo	34/95	36 (26 to 46)
	$DTwP_3$,Deloria	6 mo	22/63	35 (23 to 48)
Redness swelling at injection site				
Redness ≥0.5 cm	$DTP_{2\&3}$, Baraff	<1 y	230/459	50 (45 to 55)
Redness ≥2.5 cm	$DTP_{2\&3}$, Baraff	<1 y	50/196	26 (20 to 32)
Redness ≥5 cm	$DTP_{2\&3}$, Baraff	<1 y	6/66	9 (3 to 19)
Swelling ≥0.5 cm	$DTP_{2\&3}$, Baraff	<1 y	290/517	56 (52 to 60)
Swelling ≥2.5 cm	$DTP_{2\&3}$, Baraff	<1 y	70/241	29 (23 to 35)
Swelling ≥5 cm	$DTP_{2\&3}$, Baraff	<1 y	10/86	12 (6 to 20)
Redness and/or swelling ≥0.5 cm	$DTaP_2$, Edelman	4 mo	8/12	67 (35 to 90)
Redness and/or swelling ≥0.5 cm	$DTaP_3$, Edelman	5 mo	5/22	23 (8 to 45)
Redness and/or swelling ≥0.5 cm	$DTaP_4$, Edelman	24 mo	12/23	52 (31 to 73)
Redness and swelling ≥10 cm	Various[a], Top	6 mo–65 y	4/10	40 (12 to 74)
Systemic adverse events				
Apnea in preterm infants	DTaP, Flatz-Jequier	2–4 mo	6/33	18 (9 to 33)
	Various[a], Clifford	<1 y	7/38	18 (9 to 33)
		Pooled estimate	I^2 = 95%	18 (10 to 28)
Apnea in term infants	Various[a], Clifford	<1 y	0/8	0
Decreased appetite	$DTaP_2$, Deloria	4 mo	28/136	21 (14 to 28)
	$DTaP_3$, Deloria	6 mo	28/130	22 (15 to 30)
	$DTwP_2$, Deloria	4 mo	25/68	37 (25 to 49)
	$DTwP_3$, Deloria	6 mo	13/55	24 (13 to 37)
	$DTP_{2\&3}$, Baraff	<1 y	68/259	26 (21 to 32)
		Pooled estimate	I^2 = 95%	25 (22 to 28)
Drowsiness, sleepiness	$DTaP_2$, Deloria	4 mo	146/503	29 (25 to 33)
	$DTaP_3$, Deloria	6 mo	69/277	25 (20 to 30)

TABLE 3 Continued

	$Vaccine_{dose\ number}$, First Author	Vaccine Recipient's Age	No. of Patients With Recurrence/No. of Patients With a Previous AEFI Reimmunized	Risk of Recurrence % (95% CI)
	$DTwP_2$, Deloria	4 mo	63/153	41 (33 to 49)
	$DTwP_3$, Deloria	6 mo	46/104	44 (35 to 54)
	$DTP_{2\&3}$, Baraff	<1 y	208/486	43 (39 to 47)
		Pooled estimate	I^2 = 95%	35 (33 to 37)
Fever	$DTaP_2$, Deloria	4 mo	6/28	21 (8 to 41)
	$DTaP_3$, Deloria	6 mo	14/76	18 (11 to 29)
	$DTwP_2$ (>38°C), Deloria	4 mo	19/58	33 (21 to 46)
	$DTwP_2$ (>38°C), Baraff	<1 y	113/193	59 (52 to 65)
	$DTwP_2$ (>38.3°C), Long	4 mo	NR	64
	$DTwP_3$ (>38°C), Deloria	6 mo	30/77	39 (28 to 51)
	$DTwP_3$ (>38.3°C), Long	6 mo	NR	62
	$DTwP_4$ (>38.3°C), Long	18 mo	NR	84
	Influenza, Broos	6–48 mo	198/380	52 (47 to 57)
	Various[a], Nicolosi	4 mo–16 y	0/24	0 (0 to 14)
		Pooled estimate	I^2 = 97%	33 (16 to 53)
Henoch-Schonlein purpura	NZ-MenB	6 wk–9 y	1/6	17 (0 to 64)
HHE	DTP, Goodwin	4–18 mo	0/59	0 (0 to 6)
	$DTwP_{2,3,4}$, Andrews	2 mo–15 y	1/5	20 (4 to 62)
	$DTwP_{2,3,4}$, Du Vernoy	2 mo–10 y	0/12	0 (0 to 3)
	$DTwP_2$, Vermeer de Bondt	2 mo–15 y	0/100	0 (0 to 4)
	$DTwP_3$, Vermeer de Bondt	2 mo–15 y	0/74	0 (0 to 5)
	$DTaP_{2,3,4}$, DuVernoy	2 mo–10 y	0/56	0 (0 to 6)
	Various[a], DuVernoy	2 mo–10 y	1/13	7 (0 to 37)
	Various[a], Gold	1 mo–15 y	1/72	1 (0 to 8)
	Various[a], Nicolosi	4 mo–16 y	0/7	0 (0 to 35)
		Pooled estimate	I^2 = 28%	0 (0 to 0.1)
Persistent crying	$DTaP_2$, Deloria	4 mo	24/96	25 (17 to 35)
	$DTaP_3$, Deloria	6 mo	16/108	15 (10 to 23)
	$DTwP_2$, Deloria	4 mo	31/70	44 (32 to 57)
	$DTwP_3$, Deloria	6 mo	24/76	32 (21 to 43)
	DTwP, Andrews	<1 y	0/20	0 (0 to 16)
		Pooled estimate	I^2 = 86%	24 (20 to 29)
Seizures	HPV, Crawford	8–26 y	0/8	0 (0 to 32)
	Various[a], Gold	1 mo–15 y	0/35	0 (0 to 10)
	Various[a], Nicolosi	4 mo–16 y	0/17	0 (0 to 18)
		Pooled estimate	I^2 = 0%	0 (0 to 3)
Vomiting	$DTP_{2\&3}$, Baraff	<1 y	10/89	11 (6 to 20)
	$DTaP_2$, Deloria	4 mo	13/94	14 (8 to 23)
	$DTaP_3$, Deloria	6 mo	10/65	15 (8 to 27)
	$DTwP_2$, Deloria	4 mo	4/20	20 (6 to 44)
	$DTwP_3$, Deloria	6 mo	5/15	33 (12 to 62)
		Pooled estimate	I^2 = 0%	15 (11 to 19)

Pooled estimates were calculated only when the AEFI-specific risks of recurrence were evaluated in 2 studies or more. The study by Long et al[28] was not included in the pooled estimates because raw data were not reported. DT, diphtheria and tetanus toxoids; NR, not reported; NZ-MenB, New Zealand outer membrane meningococcal serogroup B vaccine.

[a] Various vaccines: DTaP±Hib/HepB/IPV; hepatitis A or B, meningococcal vaccines, pneumococcal vaccines, MMR, influenza, HPV, or tick-borne encephalitis.

[b] In this study, the authors reported the risks of recurrence without specifying the number of patients with a previous event who were reimmunized.

groups had seroprotective antibody levels.

Pain at the injection site was evaluated in 3 studies.[10,15,28] Moderate to severe pain recurred more frequently in children reimmunized with whole-cell pertussis vaccines ($DTwP_2$: 36% [95% CI, 26.1 to 45.4]; $DTwP_3$: 35% [95% CI, 23.1 to 46.7]) than acellular pertussis vaccines ($DTaP_2$: 12% [95% CI, 4.2 to 20]; $DTaP_3$: 9% [95% CI, −0.7 to 18.9]). A history of moderate to severe pain at the previous immunization increased the risk of having it again at the next immunization, especially in patients receiving acellular pertussis vaccine (RR: 6.3 [95% CI, 3.4 to 11.5] for DTaP and 2.9 [95% CI, 2.2 to 4.0] for DTwP) (Table 4).

Analysis of redness and swelling at the injection site by Baraff et al[10] showed that the risk of recurrence was inversely proportional to the size of the initial reaction (Table 3).

Apnea

The risk of recurrence of apnea was evaluated in 2 studies.[34,35] In the first study, Flatz-Jequier et al[35] monitored 64 very low birth weight

TABLE 4 RRs Comparing the Incidence of AEFIs in Vaccine Recipients With and Without a History of the Same AEFI

AEFI	$Vaccine_{dose\ number}$, First Author	Vaccine Recipient's Age	Proportion of AEFI in Vaccine Recipients With a History of AEFI (%)	Proportion of AEFI in Vaccine Recipients Without a History of AEFI (%)	RR Comparing Vaccine Recipients With and Without a History of AEFI (95% CI)
Anorexia	$DTaP_2$, Deloria	4 mo	28/136 (21)	108/1634 (7)	3.0 (2.1 to 4.5)
	$DTaP_3$, Deloria	6 mo	28/130 (22)	112/1582 (7)	3.1 (2.1 to 4.4)
	$DTwP_2$, Deloria	4 mo	25/68 (37)	31/289 (11)	3.4 (2.2 to 5.4)
	$DTwP_3$, Deloria	6 mo	13/55 (24)	32/287 (11)	2.1 (1.2 to 3.8)
	$DTP_{2\&3}$, Baraff	<1 y	68/259 (26)	157/982 (16)	1.7 (1.3 to 2.1)
			Pooled estimate	$I^2 = 99$	2.3 (1.2 to 4.5)
Apnea (in preterm infants)	Various[a], Flatz-Jequier	<4 mo	6/33 (18)	0/31 (0)	—
Drowsiness	$DTaP_2$, Deloria	4 mo	144/503 (29)	148/1267 (12)	2.5 (2.0 to 3.0)
	$DTaP_3$, Deloria	6 mo	68/277 (25)	141/1435 (10)	2.5 (1.9 to 3.2)
	$DTwP_2$, Deloria	4 mo	62/153 (41)	46/204 (23)	1.8 (1.3 to 2.5)
	$DTwP_3$, Deloria	6 mo	46/104 (44)	37/238 (16)	2.8 (2.0 to 4.1)
	$DTP_{2\&3}$, Baraff	<1 y	208/486 (43)	188/755 (25)	1.7 (1.5 to 2.0)
			Pooled estimate	$I^2 = 99$	2.1 (1.4 to 3.2)
Fever	$DTaP_2$, Deloria	4 mo	6/28 (21%)	79/1742 (5)	4.7 (2.3 to 9.9)
	$DTaP_3$, Deloria	6 mo	14/76 (18)	114/1636 (7)	2.6 (1.6 to 4.4)
	$DTwP_2$, Deloria	4 mo	19/58 (33)	62/299 (21)	1.6 (1.2 to 2.9)
	$DTP_{2\&3}$ (>38°C), Baraff	<1 y	113/193 (59)	89/237 (38)	1.6 (1.3 to 1.9)
	$DTwP_2$ (>38.3°C), Long[b]	4 mo	NR (64)	NR (42)	1.5
	$DTwP_3$, Deloria	6 mo	30/77 (39)	57/265 (22)	1.8 (1.3 to 2.6)
	$DTwP_3$ (>38.3°C), Long[b]	6 mo	NR (62)	NR (34)	1.8
	$DTwP_4$ (>38.3°C), Long[b]	18 mo	NR (84)	NR (49)	1.7
			Pooled estimate	$I^2 = 99$	2.4 (1.0 to 5.5)
ORS	IIV, De Serres	17–74 y	52/146 (36)	16/146 (11)	3.3 (2.0 to 5.4)
	IIV, Skowronski 2002	17–74 y	6/122 (5)	2/100 (2)	2.5 (0.6 to 11.9)
	IIV, Skowronski 2003	17–74 y	15/34 (44)	3/27 (11)	4.0 (1.3 to 12.3)
			Pooled estimate	$I^2 = 38$	3.3 (2.1 to 5.1)
Pain (mild to severe)	$DTwP_2$, Long[b]	4 mo	NR (75)	NR (41)	1.8
	$DTwP_3$, Long[b]	6 mo	NR (66)	NR (41)	1.6
	$DTwP_4$, Long[b]	18 mo	NR (85)	NR (76)	1.1
Pain (moderate to severe)	$DTaP_2$, Deloria	4 mo	8/66 (12)	27/1704 (2)	7.6 (3.6 to 16.2)
	$DTaP_3$, Deloria	6 mo	3/33 (9)	33/1679 (2)	4.6 (1.5 to 14.3)
	$DTwP_2$, Deloria	4 mo	34/95 (36)	33/262 (13)	2.8 (1.9 to 4.3)
	$DTwP_3$, Deloria	6 mo	22/63 (35)	32/279 (12)	3.0 (1.9 to 4.9)
Persistent crying	$DTaP_2$, Deloria	4 mo	24/96 (25)	96/1674 (6)	4.4 (2.9 to 6.5)
	$DTaP_3$, Deloria	6 mo	16/108 (15)	89/1604 (6)	2.7 (1.6 to 4.4)
	$DTwP_2$, Deloria	4 mo	31/70 (44)	52/287 (18)	2.4 (1.7 to 3.5)
	$DTwP_3$, Deloria	6 mo	24/76 (32)	33/266 (12)	2.5 (1.6 to 4.0)
Vomiting	$DTaP_2$, Deloria	4 mo	13/94 (14)	55/1676 (3)	4.2 (2.4 to 7.4)
	$DTaP_3$, Deloria	6 mo	10/65 (15)	53/1647 (3)	4.8 (2.6 to 9.0)
	$DTwP_2$, Deloria	4 mo	4/20 (20)	11/337 (3)	6.1 (2.1 to 17.5)
	$DTwP_3$, Deloria	6 mo	5/15 (33)	13/327 (4)	8.4 (3.4 to 20.5)

TABLE 4 Continued

AEFI	Vaccine$_{\text{dose number}}$, First Author	Vaccine Recipient's Age	Proportion of AEFI in Vaccine Recipients With a History of AEFI (%)	Proportion of AEFI in Vaccine Recipients Without a History of AEFI (%)	RR Comparing Vaccine Recipients With and Without a History of AEFI (95% CI)
	$DTwP_{2\&3}$, Baraff	<1 y	10/89 (11)	55/1152 (5)	2.2 (1.2 to 4.5)
			Pooled estimate	$I^2 = 98$	3.6 (1.7 to 7.5)

Pooled estimates were calculated only when the AEFI-specific relative risks were evaluated in 2 studies or more. The study by Long et al[28] was not included in the pooled estimates because raw data were not reported. NR, not reported; —, RR could not be estimated.

[a] Dose 2 of the following vaccines: DTaP±Hib/HepB/IPV, pneumococcal conjugated, rotavirus, or respiratory syncytial virus monoclonal antibodies.

[b] In this study, the authors reported the risks of recurrence without specifying the number of patients with a previous event who were reimmunized.

preterm infants (mean birth weight of 886 g, gestational age <32 weeks) during their first 3 immunizations at 2, 3, and 4 months of age, whereas Clifford et al[34] monitored 30 preterm (gestational age <37 weeks) and 8 term (gestational age ≥37 weeks) infants during their first 4 immunizations at 2, 4, 6, and 12 months of age. At the first, second, and third immunizations, all infants received DTaP–injectable polio vaccine (IPV)–*Haemophilus influenzae* type b (Hib)–hepatitis B (HepB) and pneumococcal conjugate vaccines, and some additionally received rotavirus vaccine, influenza vaccine, and respiratory syncytial virus monoclonal antibody. At the fourth immunization, infants received MMR vaccine, Hib, and meningococcal C vaccines. At the second immunization, 13 (18% [95% CI, 9.3 to 27.3]) of 71 preterm infants had a recurrence of apnea that was as severe as the initial episode (Table 3). No recurrences of apnea occurred among the 8 term infants (4 had underlying conditions, including metabolic disorder, cardiac disease, probable viral meningitis, and multiple allergies). Five of the 13 children with recurrences received subsequent immunizations, and none experienced additional episodes of apnea. Clifford et al[34] identified 2 predictors of recurrent apnea: lower birth weight and ongoing hospitalization for complications related to prematurity. A 10-g increase in birth weight was associated with a 6% reduction in the odds of recurrent apnea (odds ratio 0.94 [95% CI, 0.89 to 1.00]). The odds of recurrence were 23 times higher in infants hospitalized for complications related to prematurity (odds ratio 23 [95% CI, 2 to 272]).

HHE

The 6 studies in which researchers evaluated the risk of HHE recurrence[5,19,29–32] included 398 children, of whom 3 (0.8% [95% CI, 0.2 to 2.2]) had a recurrence. In the 4 studies in which researchers specifically identified the risk of HHE recurrence after DTaP or DTwP vaccines, only 1 of the 306 reimmunized children experienced a recurrence (0.3% [95% CI, 0 to 1.8])[6,26,28,29] (Table 3).

Fever

Researchers in 5 studies evaluated the risk of recurrence of fever upon reimmunization with DTaP or DTwP ($n = 3$) vaccines,[10,15,28] influenza vaccine ($n = 1$),[27] or various vaccines ($n = 1$)[19] (Tables 3 and 4).

For DTwP vaccine, the risk of recurrence of fever after the second dose (vaccine recipients aged 4 months) or third dose (vaccine recipients aged 6 months) ranged from 33% to 64%.[10,15,28] The risk was highest after the fourth dose (84%)[28] (Table 3). Fever was also more likely to occur among children with a history of fever after a previous dose versus children without previous fever (pooled RR 1.9 [95% CI, 1.6 to 2.2] Table 4). In the study by Baraff et al,[10] the severity of initial fever (<39°C vs ≥39°C) had no impact on the risk of recurrence.

For DTaP vaccine, the risk of recurrence of fever was estimated at 21% and 18% after the second and third doses, respectively. Fever was more likely to occur among children with a history of fever after the previous dose compared with those without previous fever (RRs of 4.7 [95% CI, 2.3 to 9.9] and 2.6 [95% CI, 1.6 to 4.4] after $DTaP_2$ and $DTaP_3$, respectively) (Table 4). In the study by Deloria et al,[11] recurrence of fever was higher among DTwP recipients compared with DTaP recipients after dose 3 (RR: 2.1 [95% CI, 1.2 to 3.7]) but not dose 2 (RR: 1.5 [95% CI, 0.7 to 3.4]).

Recurrence of fever after influenza immunization occurred in 198 (52% [95% CI, 47.1 to 57.1]) of

380 children aged 6 months to 4 years (Table 3). Recurrences were generally shorter in duration and associated with a lower maximum temperature than the initial episode.[27] The use of antipyretics was not reported by the authors.

Henoch-Schonlein Purpura

Sexton et al[36] evaluated the risk of Henoch-Schonlein purpura recurrence after administration of an outer membrane meningococcal B vaccine to 6 New Zealanders aged <10 years, of whom 3 received 1 additional dose and 3 received 2 additional doses. Among the 6 reimmunized children, 1 presented with mild self-limited proteinuria after the second dose. He received his third vaccine dose without further events.

Seizures

Researchers in 3 studies evaluated the risk of recurrence of seizures after immunization.[19,30,33] Nicolosi et al[19] and Gold et al[30] evaluated the risk of seizures after various vaccines (hepatitis A or B, meningococcal vaccines, pneumococcal vaccines, and MMR; DTaP with or without Hib, HepB, and poliomyelitis antigens [DTaP±Hib/HepB/IPV]); none of the 52 children reimmunized between 1 month and 16 years of age had a recurrence (Table 3). In the third study, Crawford et al[33] reported no recurrences of syncopal seizures among 8 girls aged 8 to 26 years who were reimmunized in the supine position with HPV vaccine. The authors of the studies described above did not specify if any additional measures (eg, antipyretics or anticonvulsants) were taken to reduce recurrence of seizures.

Other AEFIs

Overall, vomiting, persistent crying, decreased appetite, and drowsiness recurred in 15%, 24%, 25%, and 35% of the reimmunized patients, respectively (Table 3).

Pooled Estimates

For most AEFIs, pooled estimates displayed substantial heterogeneity (I^2 > 80%, Tables 3 and 4) that remained high in all subgroup analyses (data not presented).

DISCUSSION

In this review of 29 studies presenting the outcome of reimmunization of patients who experienced AEFIs, it appears that the risk of recurrence of serious AEFIs (anaphylaxis, seizures, or apnea in term infants) was low (<1%). For minor to moderate AEFIs (fever, ELS, ORS, ALEs, sleepiness, thrombocytopenia, decreased appetite, vomiting, or persistent crying), the risk of recurrence ranged from 4% to 48%, and recurrences were generally less severe or equally severe compared with the initial episode.

Researchers in 7 of 8 studies reported a low risk of recurrence of ALEs. The high risk of recurrence (62%) observed by Zent et al[20] may be explained by a reporting bias related to professionals being more likely to report severe or recurrent cases to the passive surveillance system of the German Pharmacovigilance Department, thus leading to an overestimation of the risk of recurrence. None of the 727 patients with a history of ALE or anaphylaxis in the included studies developed anaphylaxis after reimmunization. This finding supports the Joint Task Force on Practice Parameters 2012 practice guidelines, which state that patients who experienced an ALE after immunization can be safely reimmunized when appropriate precautions are taken.[39] However, these findings may not apply to patients with severe ALEs or positive skin tests because they were often not reimmunized in the studies reviewed. There was great variability in the management of patients with an ALE after immunization. Seitz et al[21] reimmunized patients with graded doses despite negative skin testing to the vaccine, suggesting that the ALE was not an immunoglobulin E–mediated reaction. There may be a need for guidelines[39–41] to be evaluated and validated to standardize practices.

Approximately half of children with ELS after the fourth dose of DTaP had a recurrence at reimmunization, but few patients with recurrent events developed systemic signs, symptoms, or an altered general state, and all cases resolved without sequelae. ELS reactions after immunization are dramatic but usually painless. Parents should be reassured that these reactions are usually benign and should not prevent subsequent immunizations that will protect their children against severe diseases. There was no study in which researchers directly compared the risk of ELS among children with and without a past history of ELS, but recurrences appear to occur more frequently than the expected background frequency of 2% to 5% among children 4 to 6 years of age.[42,43] Vaccines with lower diphtheria and pertussis antigens content (dTap and dTap-IPV), which confer protective immunity while reducing the risk of occurrence and/or recurrence of ELS, should be recommended in these patients.[12,14,42–46]

Recurrence of moderate to severe pain at the injection site varied with the type of vaccine. Whereas the absolute risk of pain was higher with DTwP (35%–36%) compared with DTaP (9%–12%), the relative risk comparing patients with versus without a previous event was higher in DTaP recipients (RR: 4.6 to 7.7 for DTaP and 3 for DTwP). Physical interventions (eg, no aspiration, simultaneous injections, or injection in the buttock) and psychological interventions (eg, verbal, video, or music distraction) should be considered to reduce the severity or perception of pain.[47–50]

Children who had a history of fever after immunization were at

higher risk of developing fever after subsequent immunizations, especially with DTaP (RR 2.6 to 4.7 for DTaP versus RR 1.5 to 1.8 for DTwP).[10,15,28] For both vaccines, the risk of recurrence of fever after dose 2 and 3 was similar within each study.[10,15,28] One study revealed an increased risk of recurrence after DTwP dose 4,[28] but we could not evaluate if the difference was statistically significant because the number of patients reimmunized was not reported. Severe fevers (≥39°C and ≥40°C) did not recur, and recurrent febrile episodes were usually milder than the initial episode. Prophylactic antipyretics or reduced-antigen formulation vaccine (ie, dTap) can be used to reduce either the occurrence or the severity of fever,[51–53] but their effect on recurrence is still to be evaluated. Both measures have been associated with a decreased vaccine immunogenicity response, and this should be taken into consideration in the risk/benefit evaluation.[44,45,53,54]

In this review, researchers reported a risk of recurrence after DTaP ±Hib/HepB/IPV and DTwP vaccines of <0.8% in all the studies that included patients with HHE.[5,29,31,32] However, the risk of recurrence after DTwP combined with Hib, injectable poliomyelitis, or HepB antigens, which is currently used in low- and middle-income countries, was not evaluated.

This systematic review has limitations. Although every effort was made to ensure a comprehensive search, some articles may have been missed. Our search was limited to articles published in English or French and did not include the gray literature. Despite the large number of AEFIs targeted in our search, we did not find any studies with 5 individuals or more that estimated the risk of recurrence of several AEFIs. Studies on the recurrence of serious or rare AEFIs are unlikely to be conducted for ethical reasons (risk of death or permanent sequelae) or feasibility (too few patients). All studies were conducted in developed countries; a different pattern of the risk of recurrence might be observed in low- and middle-income countries because of differences in vaccine products, schedules, or ethnicities. Only 2 of the 29 studies reviewed were RCTs. AEFI case definitions, study design, age groups, and targeted vaccines varied from one study to another, which limited the comparability of results. As a result of these clinical and methodological differences, most of the pooled estimates displayed substantial heterogeneity and should be considered with caution. Most study participants were children; adults and especially the elderly may have different recurrence risks. With severe cases being less often reimmunized, the risk of recurrence may have been underestimated. The number of patients per AEFI was frequently small, leading to estimates with broad CIs and limited statistical power to detect a small risk of recurrence. The largest studies (including >500 vaccine recipients with and without a history of an AEFI) were performed before 1995. The paucity of recent large studies is all the more regrettable given that most vaccines currently in use were introduced after 1995 and underwent large pre- and postlicensure safety evaluations. To guide clinicians, prelicensure clinical RCTs should report not only the risk of occurrence of AEFI but also the risk of recurrence when the vaccine requires several doses. In a context of vaccine hesitancy and growing concerns regarding vaccine safety, evaluating the risk of recurrence of all AEFIs should become part of the standard evaluation of vaccine safety. Specialized immunization networks such as the Clinical Immunization Safety Assessment (United States), the Surveillance of Adverse Events Following Vaccination In the Community (Australia), and the Specialized Immunization Clinics (Canada) are ideal platforms for the continuous and prospective evaluation of AEFI recurrence.

CONCLUSIONS

Despite vaccines being administered to millions of people annually, few studies have been conducted by researchers seeking to evaluate the risk of AEFI recurrence. Based on the published literature, reimmunization appears to be safe for patients with mild to moderate AEFIs. However, the data are insufficient to draw firm conclusions regarding the safety of reimmunization after a severe AEFI. High-quality studies by researchers estimating the vaccine-specific risk of recurrence and predictors of recurrence for each AEFI are needed to inform evidence-based immunization practices in this population.

ABBREVIATIONS

AEFI: adverse event following immunization
ALE: allergic-like event
CI: confidence interval
DTaP: diphtheria-tetanus-acellular pertussis vaccine
dTap: reduced-antigen diphtheria-tetanus-acellular pertussis vaccine
DTaP±Hib/HepB/IPV: DTaP with or without Hib, HepB, and IPV
DTP: diphtheria-tetanus toxoids-pertussis vaccine
DTwP: diphtheria, tetanus, whole-cell pertussis vaccine
ELS: extensive limb swelling
HepB: hepatitis B
HHE: hypotonic hyporesponsive episode
Hib: *Haemophilus influenzae* type b
HPV: human papilloma virus
IIV: inactivated influenza vaccine
IPV: injectable polio vaccine
MMR: measles-mumps-rubella
ORS: oculorespiratory syndrome
RCT: randomized controlled trial
RR: risk ratio

interpretation of data and critically reviewed the manuscript; Dr Zafack participated in the conceptualization of the study, the design of the study, and data collection, and she conducted the analyses and drafted the initial manuscript; and all authors approved the final manuscript as submitted.

DOI: https://doi.org/10.1542/peds.2016-3707

Accepted for publication May 19, 2017

Address correspondence to Gaston De Serres, MD, PhD, Institut national de santé publique du Québec, 2400 Avenue d'Estimauville, Quebec City, QC G1E 7G9, Canada. E-mail: gaston.deserres@inspq.qc.ca

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: Except for those listed in the conflicts of interest, the authors have nothing to disclose.

FUNDING: This study was funded by the Canadian Immunization Research Network, which is sponsored by the Public Health Agency of Canada and the Canadian Institutes of Health Research.

POTENTIAL CONFLICT OF INTEREST: Dr De Serres has received investigator-initiated grants from GlaxoSmithKline and Pfizer and travel reimbursement to attend an ad hoc advisory board meeting of GlaxoSmithKline; Dr Top has received in-kind research support from Pfizer and a grant from GlaxoSmithKline; and the other authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2017-1760.

REFERENCES

1. Kroger AT, Sumaya CV, Pickering LK, Atkinson WL; Advisory Committee on Immunization Practices. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2011;60(RR02):1–60. Available at: www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm. Accessed February 26, 2016
2. National Advisory Committee on Immunization. *Canadian Immunization Guide, Part 2. Vaccine Safety*, Evergreen edition. Ottawa (Ontario), Canada: Public Health Agency of Canada; 2017 Available at: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-2-vaccine-safety.html. Accessed May 12, 2017
3. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006–1012
4. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008–2012
5. DuVernoy TS, Braun MM; VAERS Working Group. Hypotonic-hyporesponsive episodes reported to the Vaccine Adverse Event Reporting System (VAERS), 1996-1998. *Pediatrics*. 2000;106(4). Available at: www.pediatrics.org/cgi/content/full/106/4/e52
6. National Institute for Health and Care Excellence. The NICE public health guidance development process. Process and methods guides no. 5 Version 3. 2012. Available at: https://www.nice.org.uk/process/pmg5/chapter/introduction. Accessed May 12, 2016
7. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919
8. Mills EJ, Nachega JB, Buchan I, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. *JAMA*. 2006;296(6):679–690
9. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration; 2011
10. Baraff LJ, Cherry JD, Cody CL, Marcy SM, Manclark CR. DTP vaccine reactions: effect of prior reactions on rate of subsequent reactions. *Dev Biol Stand*. 1985;61:423–428
11. Edelman K, Malmström K, He Q, Savolainen J, Terho EO, Mertsola J. Local reactions and IgE antibodies to pertussis toxin after acellular diphtheria-tetanus-pertussis immunization. *Eur J Pediatr*. 1999;158(12):989–994
12. Quinn P, Gold M, Royle J, et al. Recurrence of extensive injection site reactions following DTPa or dTpa vaccine in children 4-6 years old. *Vaccine*. 2011;29(25):4230–4237
13. Rennels MB, Black S, Woo EJ, Campbell S, Edwards KM. Safety of a fifth dose of diphtheria and tetanus toxoid and acellular pertussis vaccine in children experiencing extensive, local reactions to the fourth dose. *Pediatr Infect Dis J*. 2008;27(5):464–465
14. Marshall HS, Gold MS, Gent R, et al. Ultrasound examination of extensive limb swelling reactions after diphtheria-tetanus-acellular pertussis or reduced-antigen content diphtheria-tetanus-acellular pertussis immunization in preschool-aged children. *Pediatrics*. 2006;118(4):1501–1509
15. Deloria MA, Blackwelder WC, Decker MD, et al. Association of reactions after consecutive acellular or whole-cell pertussis vaccine immunizations. *Pediatrics*. 1995;96(3, pt 2):592–594
16. Jacobs RL, Lowe RS, Lanier BQ. Adverse reactions to tetanus toxoid. *JAMA*. 1982;247(1):40–42
17. Cronin J, Scorr A, Russell S, McCoy S, Walsh S, O'Sullivan R. A review of a paediatric emergency department vaccination programme for patients at risk of allergy/anaphylaxis. *Acta Paediatr*. 2012;101(9):941–945
18. Kang LW, Crawford N, Tang ML, et al. Hypersensitivity reactions to human

papillomavirus vaccine in Australian schoolgirls: retrospective cohort study. *BMJ*. 2008;337:a2642

19. Nicolosi L, Vittucci A, Mancini R, et al. Vaccine risk assessment in children with a referred reaction to a previous vaccine dose: 2009-2011 retrospective report at the Bambino Gesu' children hospital, Rome, Italy. *Ital J Pediatr*. 2014;40:31
20. Zent O, Arras-Reiter C, Broeker M, Hennig R. Immediate allergic reactions after vaccinations–a post-marketing surveillance review. *Eur J Pediatr*. 2002;161(1):21–25
21. Seitz CS, Bröcker EB, Trautmann A. Vaccination-associated anaphylaxis in adults: diagnostic testing ruling out IgE-mediated vaccine allergy. *Vaccine*. 2009;27(29):3885–3889
22. Micheletti F, Peroni D, Piacentini G, et al. Vaccine allergy evaluation and management at the specialized Green Channel Consultation Clinic. *Clin Exp Allergy*. 2012;42(7):1088–1096
23. Grenier JL, Toth E, De Serres G, et al. Safety of revaccination of patients affected by the oculo-respiratory syndrome (ORS) following influenza vaccination. *Can Commun Dis Rep*. 2004;30(2):9–16
24. Skowronski DM, Strauss B, Kendall P, Duval B, De Serres G. Low risk of recurrence of oculorespiratory syndrome following influenza revaccination. *CMAJ*. 2002;167(8):853–858
25. De Serres G, Skowronski DM, Guay M, et al. Recurrence risk of oculorespiratory syndrome after influenza vaccination: randomized controlled trial of previously affected persons. *Arch Intern Med*. 2004;164(20):2266–2272
26. Skowronski DM, De Serres G, Scheifele D, et al. Randomized, double-blind, placebo-controlled trial to assess the rate of recurrence of oculorespiratory syndrome following influenza vaccination among persons previously affected. *Clin Infect Dis*. 2003;37(8):1059–1066
27. Broos N, van Puijenbroek EP, van Grootheest K. Fever following immunization with influenza A (H1N1) vaccine in children: a survey-based study in the Netherlands. *Drug Saf*. 2010;33(12):1109–1115
28. Long SS, Deforest A, Smith DG, Lazaro C, Wassilak GF. Longitudinal study of adverse reactions following diphtheria-tetanus-pertussis vaccine in infancy. *Pediatrics*. 1990;85(3):294–302
29. Andrews RM, Kempe AE, Sinn KK, Herceg A. Vaccinating children with a history of serious reactions after vaccination or of egg allergy. *Med J Aust*. 1998;168(10):491–494
30. Gold M, Goodwin H, Botham S, Burgess M, Nash M, Kempe A. Re-vaccination of 421 children with a past history of an adverse vaccine reaction in a special immunisation service. *Arch Dis Child*. 2000;83(2):128–131
31. Goodwin H, Nash M, Gold M, Heath TC, Burgess MA. Vaccination of children following a previous hypotonic-hyporesponsive episode. *J Paediatr Child Health*. 1999;35(6):549–552
32. Vermeer-de Bondt PE, Labadie J, Rümke HC. Rate of recurrent collapse after vaccination with whole cell pertussis vaccine: follow up study. *BMJ*. 1998;316(7135):902–903
33. Crawford NW, Clothier HJ, Elia S, Lazzaro T, Royle J, Buttery JP. Syncope and seizures following human papillomavirus vaccination: a retrospective case series. *Med J Aust*. 2011;194(1):16–18
34. Clifford V, Crawford NW, Royle J, et al. Recurrent aponoea post immunisation: informing re-immunisation policy. *Vaccine*. 2011;29(34):5681–5687
35. Flatz-Jequier A, Posfay-Barbe KM, Pfister RE, Siegrist CA. Recurrence of cardiorespiratory events following repeat DTaP-based combined immunization in very low birth weight premature infants. *J Pediatr*. 2008;153(3):429–431
36. Sexton K, McNicholas A, Galloway Y, et al. Henoch-Schönlein purpura and meningococcal B vaccination. *Arch Dis Child*. 2009;94(3):224–226
37. Top KA, Billard MN, Gariepy MC, et al; Canadian Immunization Research Network's (CIRN) Special Immunization Clinics Network investigators. Immunizing patients with adverse events following immunization and potential contraindications to immunization: a report from the special immunization clinics network. *Pediatr Infect Dis J*. 2016;35(12):e384–e391
38. World Health Organization. Weekly epidemiologic record. 2003. Available at: www.who.int/vaccine_safety/committee/reports/wer7804.pdf?ua=1. Accessed January 24, 2016
39. Kelso JM, Greenhawt MJ, Li JT, et al. Adverse reactions to vaccines practice parameter 2012 update. *J Allergy Clin Immunol*. 2012;130(1):25–43
40. Wood RA, Berger M, Dreskin SC, et al; Hypersensitivity Working Group of the Clinical Immunization Safety Assessment (CISA) Network. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. *Pediatrics*. 2008;122(3). Available at: www.pediatrics.org/cgi/content/full/122/3/e771
41. Gold M. A clinical approach to the investigation of suspected vaccine anaphylaxis. *Curr Allergy Clin Immunol*. 2012;25(2):68–70
42. Meyer CU, Habermehl P, Knuf M, Hoet B, Wolter J, Zepp F. Immunogenicity and reactogenicity of acellular pertussis booster vaccines in children: standard pediatric versus a reduced-antigen content formulation. *Hum Vaccin*. 2008;4(3):203–209
43. Rennels MB, Deloria MA, Pichichero ME, et al. Extensive swelling after booster doses of acellular pertussis-tetanus-diphtheria vaccines. *Pediatrics*. 2000;105(1). Available at: www.pediatrics.org/cgi/content/full/105/1/e12
44. Langley JM, Predy G, Guasparini R, et al. An adolescent-adult formulation tetanus and diptheria toxoids adsorbed combined with acellular pertussis vaccine has comparable immunogenicity but less reactogenicity in children 4-6 years of age than a pediatric formulation acellular pertussis vaccine and diphtheria and tetanus toxoids adsorbed combined with inactivated poliomyelitis vaccine. *Vaccine*. 2007;25(6):1121–1125
45. Scheifele DW, Halperin SA, Ochnio JJ, Ferguson AC, Skowronski DM. A modified vaccine reduces the rate of large injection site reactions to the preschool booster dose of

diphtheria-tetanus-acellular pertussis vaccine: results of a randomized, controlled trial. *Pediatr Infect Dis J*. 2005;24(12):1059–1066

46. Skowronski DM, Remple VP, Macnabb J, et al. Injection-site reactions to booster doses of acellular pertussis vaccine: rate, severity, and anticipated impact. *Pediatrics*. 2003;112(6, pt 1). Available at: www.pediatrics.org/cgi/content/full/112/6/e453
47. Petousis-Harris H. Vaccine injection technique and reactogenicity–evidence for practice. *Vaccine*. 2008;26(50):6299–6304
48. Hogan ME, Kikuta A, Taddio A. A systematic review of measures for reducing injection pain during adult immunization. *Vaccine*. 2010;28(6):1514–1521
49. Taddio A, Ilersich AL, Ipp M, Kikuta A, Shah V; HELPinKIDS Team. Physical interventions and injection techniques for reducing injection pain during routine childhood immunizations: systematic review of randomized controlled trials and quasi-randomized controlled trials. *Clin Ther*. 2009;31(suppl 2):S48–S76
50. Birnie KA, Chambers CT, Taddio A, et al; HELPinKids&Adults Team. Psychological interventions for vaccine injections in children and adolescents: systematic review of randomized and quasi-randomized controlled trials. *Clin J Pain*. 2015;31(suppl 10):S72–S89
51. Klar S, Harris T, Wong K, Fediurek J, Deeks SL. Vaccine safety implications of Ontario, Canada's switch from DTaP-IPV to Tdap-IPV for the pre-school booster. *Vaccine*. 2014;32(48):6360–6363
52. Jackson LA, Peterson D, Dunn J, et al. A randomized placebo-controlled trial of acetaminophen for prevention of post-vaccination fever in infants. *PLoS One*. 2011;6(6):e20102
53. Prymula R, Siegrist CA, Chlibek R, et al. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. *Lancet*. 2009;374(9698):1339–1350
54. Das RR, Panigrahi I, Naik SS. The effect of prophylactic antipyretic administration on post-vaccination adverse reactions and antibody response in children: a systematic review. *PLoS One*. 2014;9(9):e106629

Risk of Recurrence of Adverse Events Following Immunization: A Systematic Review

Joseline Guetsop Zafack, Gaston De Serres, Marilou Kiely, Marie-Claude Gariépy, Isabelle Rouleau, Karina Anne-Marie Top and for the Canadian Immunization Research Network

Pediatrics originally published online August 28, 2017;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Risk of Recurrence of Adverse Events Following Immunization: A Systematic Review

Joseline Guetsop Zafack, Gaston De Serres, Marilou Kiely, Marie-Claude Gariépy, Isabelle Rouleau, Karina Anne-Marie Top and for the Canadian Immunization Research Network

Pediatrics originally published online August 28, 2017;