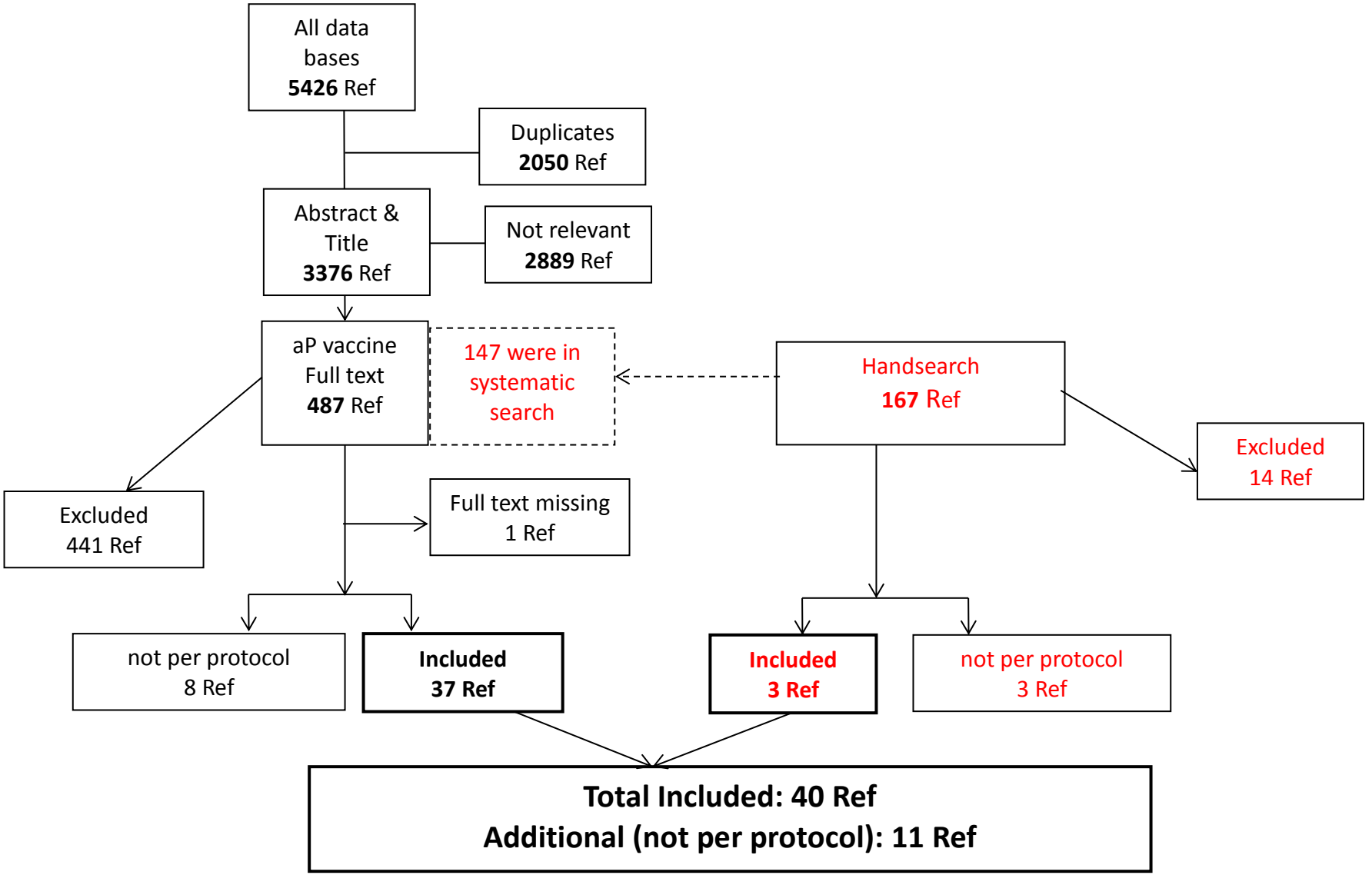
Review on aP schedules and absolute effect - Figures and Tables

Version August 19, 2014

Figure 1. Flow chart of reference screening



J. Mueller/EHESP

Draft August 19, 2014

Figure 2. Overview of type of evidence available from included studies

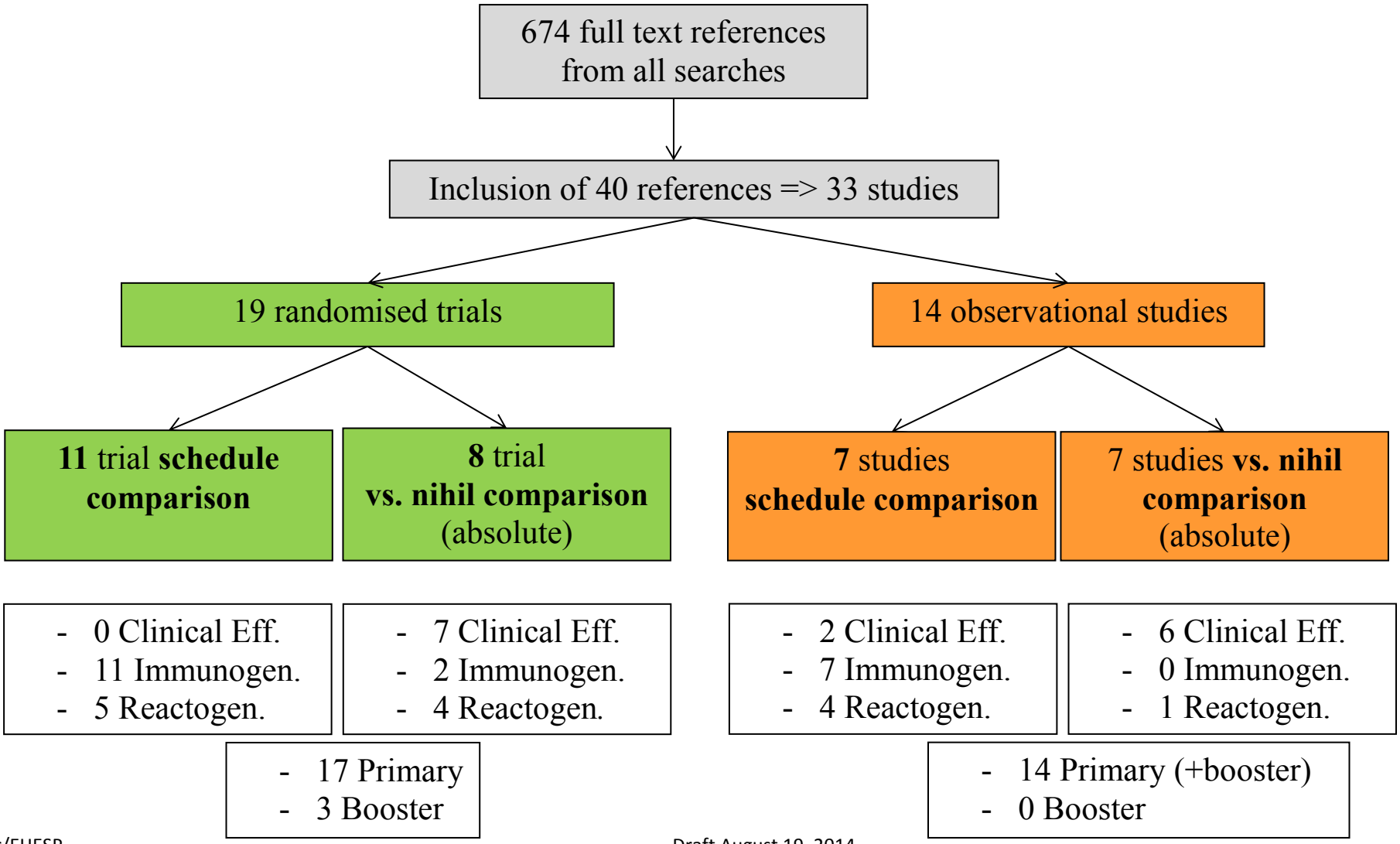


Figure 3. Overview of type of additional evidence available from not-per-protocol studies

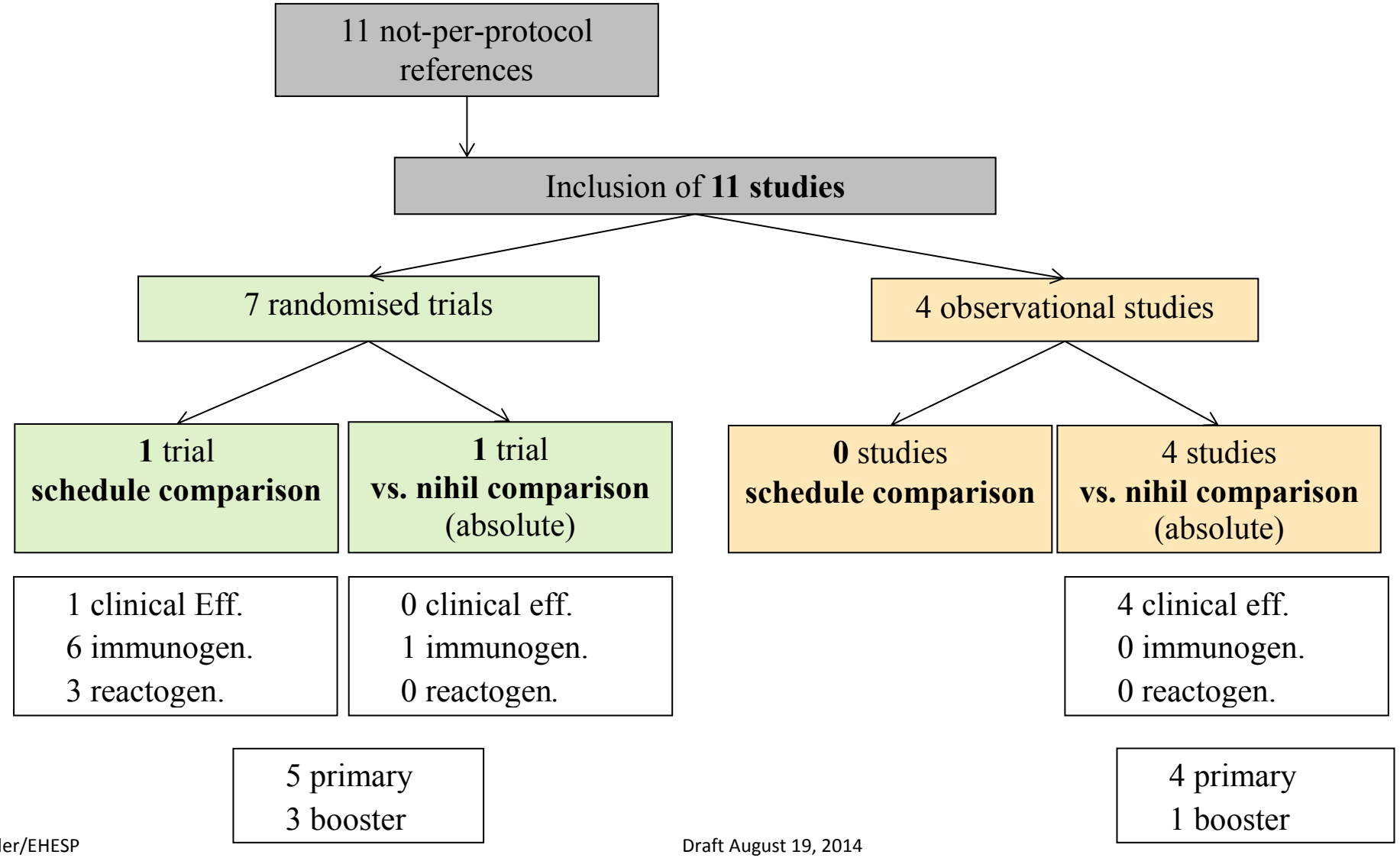


Table 1. Included studies on aP vaccination impact

Author	Design	Primary/booster	Comparison	Schedule	VE	Imgen.	Reactogen.
Anonym. 1988, Storsaeter 1990	RCT	primary	vs nihil	2d, 5-11mo + 7-13wks later	X		
Belloni 2003	RCT	primary	schedule	birth + 3,5,11mo		X	
Biritwum 1985	RCT	primary	schedule	2 vs 3 d		X	
Bisgard 2005	CC	primary	vs nihil	diff doses vs 0 doses	X		
Carlsson 1998	RCT	primary	schedule	3,5,12 vs 2,4,6,13 mo		X	X
Giammanco 1998	cohort	primary	schedule	2,4,6 vs. 3,5,11 mo		X	X
Greco 1996, Giuliano 1998	RCT	primary	vs nihil	2,4,6 mo	X	X	X
Gustafsson 1996	RCT	primary	vs nihil	2,4,6 mo	X	X	X
Halasa 2008	RCT	primary	schedule	birth + 2,4,6 +17 mo		X	
Hoppenbrouwers 1999	RCT	primary	schedule	2,4,6 vs 3,4,5 + 12-14 mo		X	X
Just 1991	RCT	primary	schedules	3,4,5 vs 2,4,6 mo		X	
Kamiya 1992	cohort	primary	schedules	2,4,6 vs 3,5,7 mo		X	X
Kimura 1991	cohort	primary	schedule	3 doses at 3-8 vs. 9-23 mo		X	
Knuf 2008 Knuf 2010	RCT	primary booster	schedule	birth + 2,4,6 mo		X	X
Li 2011 (I and II)	RCT	primary primary+booster	schedule	2,3,4 vs 3,4,5 mo		X	X
Liese 1997	CC	primary	vs nihil	2,4,6 mo	X		
Miller 1997	cohort (synopsis)	primary	schedule	3,5,8-10, vs 2,3,4 mo		X	X
Olin 1998, Olin 1997	cohort	primary	schedule	2,4,6 vs 3,5,12 mo	X	X	
Salmaso 1998, Salmaso 2001	cohort post RCT	primary	vs nihil	2,4,6 mo	X		
Scheifele 2005	RCT	booster	schedule	15 vs 16 vs 17 vs 18 mo		X	X

Schmitt 1996	cohort	primary	vs nihil	3,4,5 mo	X		
Schmitt-Grohe 1997, Überall 1997	cohort	primary+booster	vs nihil	3, 4.5, 6 + 15-18mo			X
Simodon 1997	RCT	primary	vs nihil	2,4,6 mo	X		
Simodon 1999	RCT	primary	schedule	2,3,4 vs 2,4,6		X	
Stehr 1998 (=> Schmitt-Grohe 1997)	cohort	primary	vs nihil	3, 4.5, 6 + 15-18mo	X		
Storsaeter 1992 (=> Anon. 1988)	RCT HH	primary	vs nihil	3 d (2-mo interval) from age 6 mo	X		
Taranger 2000	cohort	primary primary+booster	schedule	2,4,6 vs. 3,5,12 mo	X	X	X
Tomoda 1997	cohort	primary	schedule	2d vs 3d + boost @ 12 mo		X	
Trollfors 1995	RCT	primary	vs nihil	3,5,12 mo	X		X
Trollfors 1997 (=> Trollfors 1995)	RCT HH	primary	vs nihil	3,5,12 mo	X		
Taranger 1997 (=> Trollfors 1995)	cohort post RCT	primary	vs nihil	3,5,12 mo	X		
Wood 2010	RCT	primary	schedules	birth + 2,4,6 mo birth, 1 + 2,4,6; 2,4,6 mo		X	
Zepp 2007	RCT	booster	vs nihil	12-23 mo			X

Abbreviations: VE, vaccine effectiveness/efficacy; RCT, Randomized clinical trial; HH, household contacts; d, doses; mo, months; w, weeks; CC, case control study

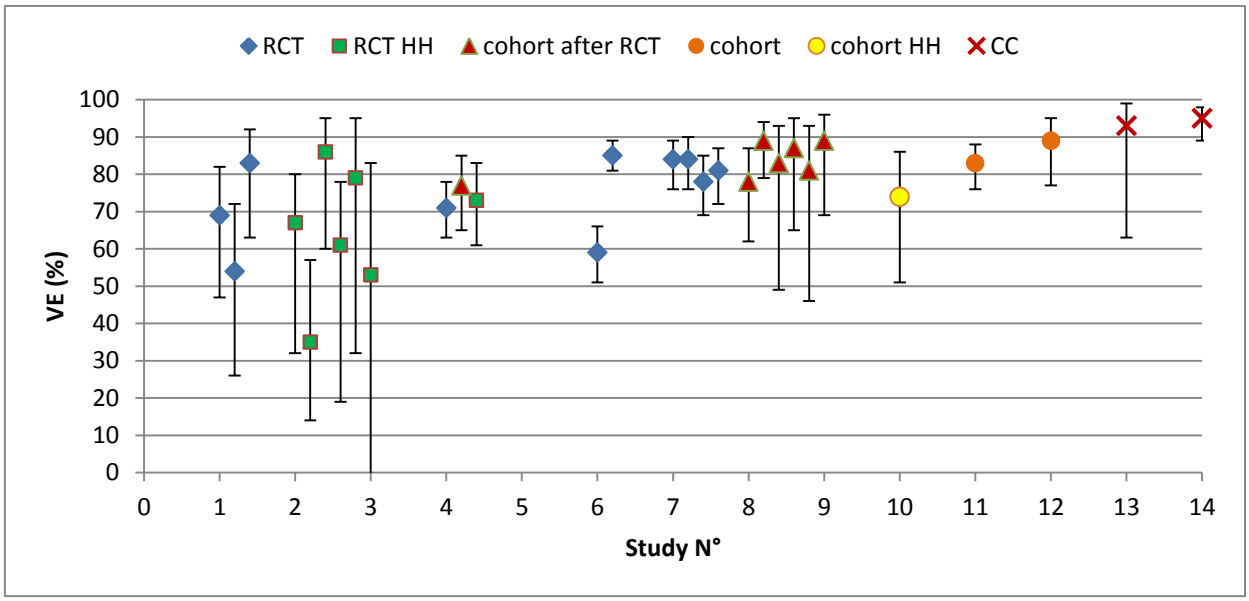
Table 2. Additional studies on aP vaccination impact, not per protocol

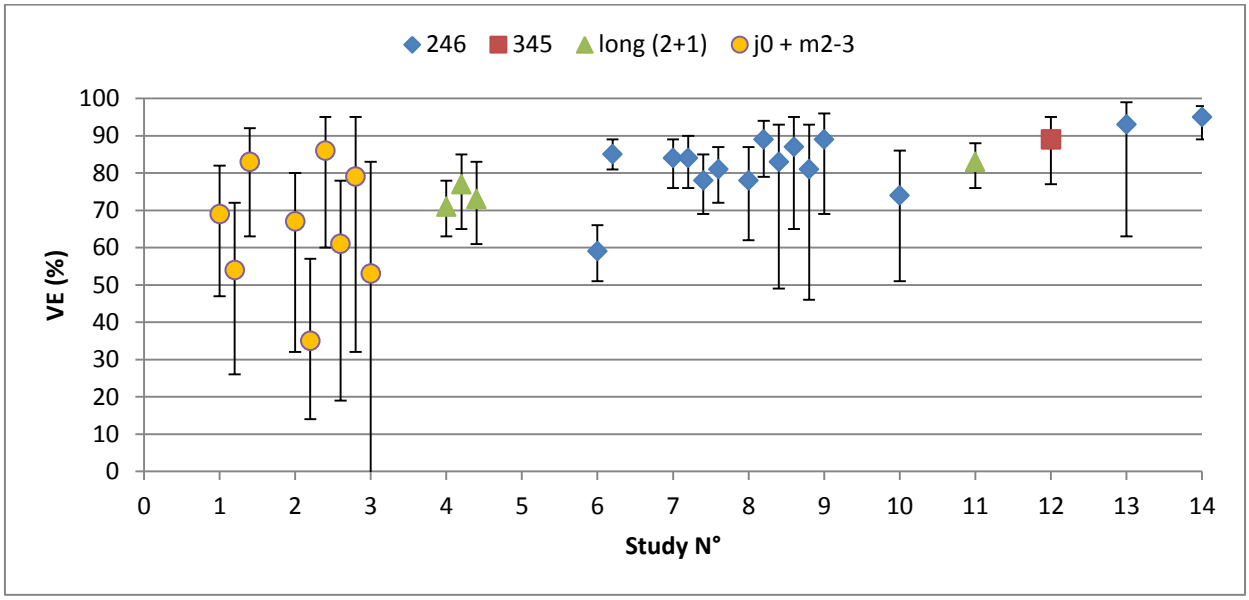
Author	Design	Primary /booster	Comparison	Schedule	VE	Imgen.	Reactogen.
Aoyama 1985	HH cohort	primary	vs nihil	unknown	X	VE	
Blennow 1986	RCT	primary	schedule	2 vs 3d, various schedules		X	X
Blennow 1988	RCT	primary	schedule	2 vs 3d, various schedules		X	X
Blennow 1989 *(I)*	RCT	primary	schedule	2 vs 3d, various schedules		X	
Blennow 1989 *(II)*	RCT	primary, booster	schedule	2d + 1d vs 3d + 1d		X	X
Blennow 1990	RCT, HH	booster	schedule	different ages	X	X	
Campbell 2012	screening	primary, booster	vs nihil	various schedules	X		
Cassone 1997	RCT	primary	vs nihil	2,4,6 mo		X	
Hviid 2004	cohort	primary	vs nihil	3,5,12 mo	X		
Mortimer 1990	cohort HH	primary	vs nihil	2-4 d after 2y	X		
Shinefield 2006	RCT	booster	schedule	Day 0 or Day 42		X	x

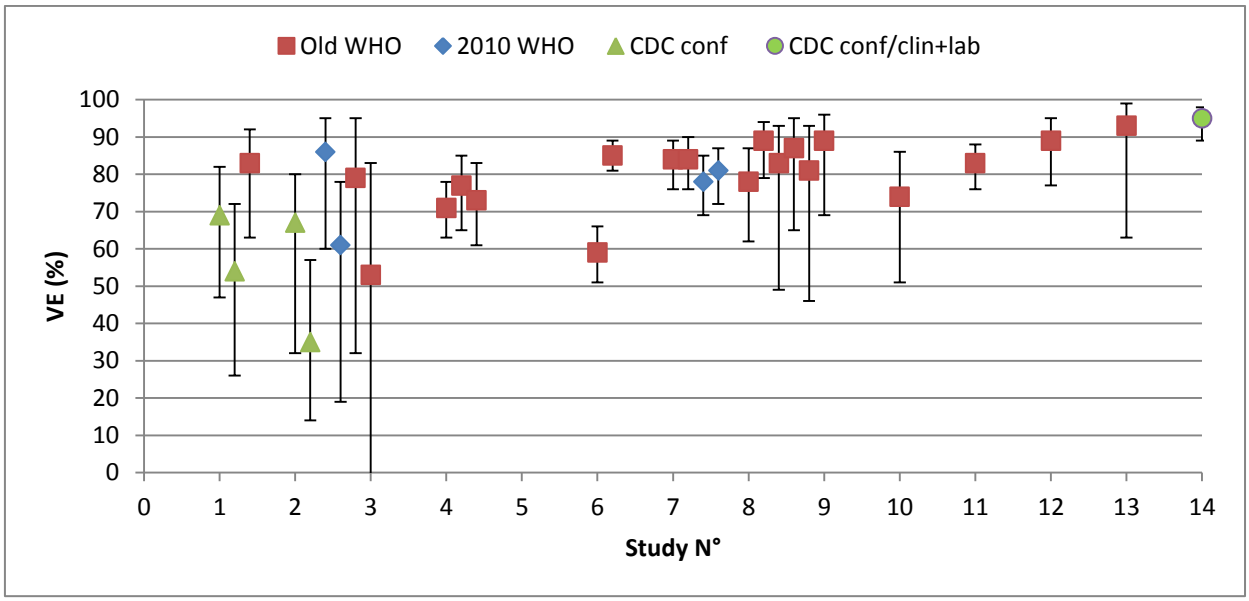
Figure 4. Overview of vaccine efficacy/effectiveness estimates from included studies, by potential factors of heterogeneity (risk of bias; cased definition; schedule evaluated)

N°	Study	Design	Schedule	Vaccine	Case definition	Age
1	Anonymous	RCT	j0 + m2-3*	2c jnih	CDC conf	<2.5y
1.2	Anonymous	RCT	j0 + m2-3	1c jnih	CDC conf	<2.5y
1.4	Anonymous	RCT	j0 + m2-3	1c jnih	Old WHO	<2.5y
2	Storsaeter 1992	RCT HH	j0 + m2-3	1c jnih	CDC conf	<2.5y
2.2	Storsaeter 1992	RCT HH	j0 + m2-3	2c jnih	CDC conf	<2.5y
2.4	Storsaeter 1992	RCT HH	j0 + m2-3	1c jnih	2010 WHO	<2.5y
2.6	Storsaeter 1992	RCT HH	j0 + m2-3	2c jnih	2010 WHO	<2.5y
2.8	Storsaeter 1992	RCT HH	j0 + m2-3	1c jnih	Old WHO	<2.5y
3	Storsaeter 1992	RCT HH	j0 + m2-3	2c jnih	Old WHO	<2.5y
4	Trollfors 1995	RCT	long (2+1)	1c am	Old WHO	<2.5y
4.2	Taranger 1997	cohort after RCT	long (2+1)	1c am	Old WHO	2.5-3y
4.4	Trollfors 1997	RCT HH	long (2+1)	1c am	Old WHO	<2.5y
6	Gustafsson	RCT	246	2c skb	Old WHO	<3y
6.2	Gustafsson	RCT	246	5c co	Old WHO	<3y
7	Greco	RCT	246	3c skb	Old WHO	<2y
7.2	Greco	RCT	246	3c chi	Old WHO	<2y
7.4	Greco	RCT	246	3c skb	2010 WHO	<2y
7.6	Greco	RCT	246	3c chi	2010 WHO	<2y
8	Salmaso 1998	cohort after RCT	246	3c skb	Old WHO	2-3y
8.2	Salmaso 1998	cohort after RCT	246	3c chi	Old WHO	2-3y
8.4	Salmaso 2001	cohort after RCT	246	3c skb	Old WHO	3y
8.6	Salmaso 2001	cohort after RCT	246	3c skb	Old WHO	4y
8.8	Salmaso 2001	cohort after RCT	246	3c chi	Old WHO	3y
9	Salmaso 2001	cohort after RCT	246	3c chi	Old WHO	4y
10	Simodon	cohort HH	246	2c mé	Old WHO	<4y
11	Stehr	cohort	long (2+1)	4c wy	Old WHO	<3y
12	Schmitt	cohort	345	2c skb	Old WHO	<4y
13	Liese	CC	246	2c mé	Old WHO	<2y
14	Bisgard	CC	246	1-4c	CDC conf/clin+lab	<5y

* 2 doses at 5-11 mo and 7-13 wks later


RCT
RCT HH
cohort after RCT
cohort
cohort HH
CC
VE (%)
Study N°


246
345
long (2+1)
j0 + m2-3
VE (%)
Study N°


Old WHO
2010 WHO
CDC conf
CDC conf/clin+lab
VE (%)
Study N°

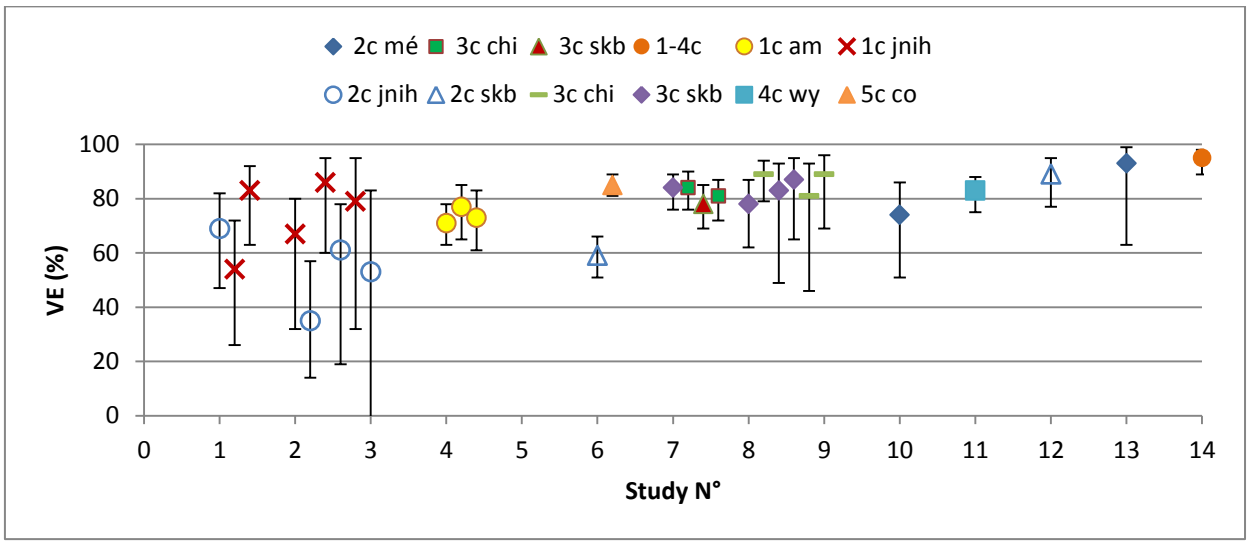

2c mé
3c chi
3c skb
1-4c
1c am
1c jnih
2c jnih
2c skb
3c chi
3c skb
4c wy
5c co
VE (%)
Study N°

Table 4. GRADE evidence profile (included studies): primary DT vaccination, birth dose vs. no birth dose

Quality assessment						Summary of finding	Final Grade: quality of evidence
Number of studies per design	**Limitations (risk of bias)**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Ratio (birth / no birth dose)** min – max	**1-4**
Clinical efficacy/effectiveness							
0 studies							
Immunogenicity anti-FHA							
@ age 2 mo							
GMT (U/ml)							
1 RCT	Low	-	High	Moderate	Unclear	1.00	2
@ age 3 mo							
% ≥5 EL.U/ml							
1 RCT	Low	-	High	Moderate	Unclear	1.04	2
GMT (U/ml)							
2 RCT	Low	Moderate	High	Low	Unclear	1.33 – 7.50	3
@ age 4 mo							
GMT (U/ml)							
1 RCT	Low	-	High	Moderate	Unclear	5.00	2
@ age 5 mo							
% ≥5 EL.U/ml							
1 RCT	Low	-	High	Moderate	Unclear	1.00	2
GMT (U/ml)							
2 RCT	Low	Moderate	High	Low	Unclear	1.67 - 5.81	3
@ age 6 mo							
% Seroconverted							
2 RCT	Low	High	High	Low	Unclear	0.96 - 4.16	1
GMT (U/ml)							
3 RCT	Low	High	High	Low	Unclear	1.00 - 3.61	2
@ age 7 mo							
% Seroconverted							
1 RCT	Low	-	High	Moderate	Unclear	0.83	2
% ≥5 EL.U/ml							
1 RCT	Low	-	High	Moderate	Unclear	1.00	2

GMT (U/ml)							
2 RCT	Low	Moderate	High	Low	Unclear	0.96 – 1.20	3
@ age 8 mo							
GMT (U/ml)							
1 RCT	Low	-	High	Moderate	Unclear	1.18	2
@ pre-booster							
% Seroconverted							
1 RCT	Low	-	High	Moderate	Unclear	1.00	2
GMT (U/ml)							
2 RCT	Low	High	High	Low	Unclear	0.67 – 1.65	2
@ at post-booster							
% Seroconverted							
2 RCT	Low	Low	High	Low	Unclear	0.77 – 0.92	3
GMT (U/ml)							
2 RCT	Low	High	High	Low	Unclear	0.64 – 1.37	2
Immunogenicity anti-PT							
@ age 2 mo							
GMT (U/ml)							
1 RCT	Low	-	High	Moderate	Unclear	1.40	2
@ age 3 mo							
% ≥5 EL.U/ml							
1 RCT	Low	-	High	Moderate	Unclear	2.13	2
GMT (U/ml)							
2 RCT	Low	High	High	Low	Unclear	0.68 – 8.33	2
@ age 4 mo							
GMT (U/ml)							
1 RCT	Low	-	High	Moderate	Unclear	3.75	2
@ age 5 mo							
% ≥5 EL.U/ml							
1 RCT	Low	-	High	Moderate	Unclear	1.00	2
GMT (U/ml)							
2 RCT	Low	Moderate	High	Low	Unclear	1.07 – 3.19	3
@ age 6 mo							
% Seroconverted							
2 RCT	Low	Low	High	Low	Unclear	0.57 - 0.75	3
GMT (U/ml)							
3 RCT	Low	High	High	Low	Unclear	0.67 – 2.00	2

@ age 7 mo							
% Seroconverted							
1 RCT	Low	-	High	Moderate	Unclear	0.53	2
% ≥5 EL.U/ml							
1 RCT	Low	-	High	Moderate	Unclear	1.00	2
GMT (U/ml)							
2 RCT	Low	High	High	Low	Unclear	0.63 – 1.00	2
@ age 8 mo							
GMT (U/ml)							
1 RCT	Low	-	High	Moderate	Unclear	1.00	2
@ pre-booster							
% Seroconverted							
1 RCT	Low	-	High	Moderate	Unclear	0	2
GMT (U/ml)							
2 RCT	Low	Moderate	High	Low	Unclear	0.83 – 1.38	3
@ at post-booster							
% Seroconverted							
2 RCT	Low	High	High	Low	Unclear	0.23 - 0.96	2
GMT (U/ml)							
2 RCT	Low	Moderate	High	Low	Unclear	0.41 – 0.82	3
Reactogenicity							
Fever (> 38.0°C)							
8 days after birth dose							
1 RCT	Low	-	Low	Moderate	Unclear	1	3
8 days after any dose (birth or routine 3-dose schedule)							
1 RCT	Low	-	Low	Moderate	Unclear	0.92	3
8 days after booster							
1 RCT	Low	-	Low	Moderate	Unclear	1.86	3
Irritability							
8 days after birth dose							
1 RCT	Low	-	Low	Moderate	Unclear	0.90	3
8 days after any dose (birth or routine 3-dose schedule)							
1 RCT	Low	-	Low	Moderate	Unclear	0.95	3
8 days after booster							
1 RCT	Low	-	Low	Moderate	Unclear	0.98	3
Local pain							
8 days after birth dose							

1 RCT	Low	-	Low	Moderate	Unclear	0.98	3
8 days after any dose (birth or routine 3-dose schedule)							
1 RCT	Low	-	Low	Moderate	Unclear	0.83	3
8 days after booster							
1 RCT	Low	-	Low	Moderate	Unclear	0.73	3
Local redness							
8 days after birth dose							
1 RCT	Low	-	Low	Moderate	Unclear	0.95	3
8 days after any dose (birth or routine 3-dose schedule)							
1 RCT	Low	-	Low	Moderate	Unclear	0.89	3
8 days after booster							
1 RCT	Low	-	Low	Moderate	Unclear	1.03	3
Local swelling							
8 days after birth dose							
1 RCT	Low	-	Low	Moderate	Unclear	0.93	3
8 days after any dose (birth or routine 3-dose schedule)							
2 RCT	Moderate* - low	-	Low	Low	Unclear	0.64 - 0.67	3
8 days after booster							
1 RCT	Low	-	Low	Moderate	Unclear	1.57	3

RCT: Belloni 2003, Halasa 2008, Knuf 2008, Knuf 2010, Wood 2010

* one RCT was nonblinded to parents who documented reactions, the other controlled by another vaccine

Table 5. GRADE evidence profile (included studies): primary DT vaccination, 2 vs. 3 primary doses

Quality assessment						Summary of finding	Final Grade: quality of evidence
Number of studies per design	**Limitations (risk of bias)**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Ratio (2 / 3 doses)** min – max	**1-4**
Clinical efficacy/effectiveness							
1 cohort	Moderate	-	Low	Moderate	Unclear	VE -167%	1
Immunogenicity anti-FHA							
GMC							
@ age 6/7 mo							
2 RCT	Low	High	High	Low	Unclear	0.80 - 1.50	2
3 cohorts (1 with 3 vacc)	Moderate	Low	High	Low	Unclear	0.53 – 0.77	2
@ age 12-13 mo (7 mo post primary)							
1 RCT	Low	-	High	Moderate	Unclear	0.56	2
@ 1 mo post booster (12-15 mo, 21mo)							
1 RCT	Low	-	High	Moderate	Unclear	1.02	2
1 cohort	Moderate	-	High	Moderate	Unclear	0.75	1
@ 1-3 yrs post booster							
1 cohort	Moderate	-	High	Moderate	Unclear	0.81	1
Immunogenicity anti-PT							
GMC							
@ age 6/7 mo							
2 RCT	Low	Moderate	High	Low	Unclear	0.65- 1.05	2
3 cohorts (1 with 3 vacc)	Moderate	Low	High	Low	Unclear	0.52 – 0.62	2
@ age 12-15 mo (7-9 mo post primary)							
1 RCT	Low	-	High	Moderate	Unclear	0.75	2
1 cohort	Moderate	-	High	Moderate	Unclear	1.40	1
@ 1 mo post booster (12-15 mo, 21mo)							
1 RCT	Low	-	High	Moderate	Unclear	1.08	2
2 cohorts	Moderate	Low	High	Moderate	Unclear	0.95 - 1.00	2
@ 1-3 yrs post booster							
2 cohorts	Moderate	Moderate	High	Moderate	Unclear	0.89 - 1.31	1
Reactogenicity							

Rectal temperature ≥38.0°C, 24h							
@ after last primary							
1 cohort	Moderate	-	Low	Moderate	Unclear	0.88	2
@ after booster							
1 RCT, 1 cohort*	Moderate	Low	Low	Low	Unclear	1.17 – 1.40	2
Erythema ≥2 cm							
@ after last primary							
1 cohort	Moderate	-	Low	Moderate	Unclear	0.75	2
@ after booster							
RCT, 1 cohort*	Moderate	Low	Low	Low	Unclear	1.41 – 1.58	2
Swelling ≥2 cm							
@ after last primary							
1 cohort	Moderate	-	Low	Moderate	Unclear	0.65	2
@ after booster							
RCT, 1 cohort*	Moderate	Low	Low	Low	Unclear	1.21 – 1.43	2

RCT : Carlsson, Biritwum; Cohorts: Taranger 2000, Tomoda, Giammanco, Olin 1998

* both studies non-blinded; cohort conducted within an RCT

Table 6. GRADE evidence profile (included studies): primary DT vaccination, accelerated vs. long schedule

Quality assessment						Summary of finding	Final Grade: quality of evidence
Number of studies per design	**Limitations (risk of bias)**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Ratio (accel. / long)** min – max	**1-4**
Clinical efficacy/effectiveness (1 cohort study, relative VE (%) by definition)							
From 1st dose							
Up to > 13mo (SKB)							
Old WHO	Moderate	-	Low	High	Unclear	36.7 (-28.2 – 67.3)	1
Cough+culture	Moderate	-	Low	High	Unclear	23.1 (-31.6 – 53.1)	1
Up to > 28mo (Chiron, Connaught)							
Old WHO	Moderate	-	Low	High	Unclear	-40.8 – 3.8	1
Cough+culture	Moderate	-	Low	High	Unclear	-16.3	1
From 9 mo post 1st dose							
Up to > 13mo (SKB)							
Old WHO	Moderate	-	Low	High	Unclear	-2.0 (-257 – 68.3)	1
Cough+culture	Moderate	-	Low	High	Unclear	0 (-144 – 55.8)	1
Up to > 28mo (Chiron, Connaught)							
Old WHO	Moderate	-	Low	High	Unclear	-212 – -75.4	1
Cough+culture	Moderate	-	Low	High	Unclear	-117 – -81.8	1
Immunogenicity anti-FHA							
GMC							
@ 4-6 wks post 3rd dose							
3 cohorts (2 with 2 vacc.)	High*	Low	High	Low	Unclear	0.62 – 0.90	1
@ 12-18 mo post 3rd dose							
1 cohort (2 vaccines)	Moderate	High	High	Moderate	Unclear	0.62 – 1.14	1
% with detectable titers							
@ 4-6 wks post 3rd dose							
1 cohort (2 vaccines)	High*	Low	High	Moderate	Unclear	1.00 – 1.03	1
@ 12-18 mo post 3rd dose							
1 cohort (2 vaccines)	Moderate	Moderate	High	Moderate	Unclear	1.03 – 1.27	1
Immunogenicity anti-PT							
GMC							
@ 4-6 wks post 3rd dose							

3 cohorts (2 with 2 vacc)	High*	High	High	Low	Unclear	0.74 – 1.48	1
@ 12-18 mo post 3rd dose							
1 cohort (2 vaccines)	Moderate	High	High	Moderate	Unclear	0.38 – 2.80	1
% with detectable titers							
@ 4-6 wks post 3rd dose							
1 cohort (2 vaccines)	High*	Low	High	Moderate	Unclear	1.01 – 1.02	1
@ 12-18 mo post 3rd dose							
1 cohort (2 vaccines)	Moderate	Low	High	Moderate	Unclear	1.00	1
Reactogenicity							
Rectal temperature ≥38.0°C, 24h							
Within 24h (any dose)							
1 cohort (2 vaccines)	Moderate	-	Low	Low	Unclear	0.89 – 0.77	2
Within 8 days (any dose)							
1 cohort	Moderate	-	Low	Low	Unclear	0.94	2
Erythema ≥2 cm							
Within 24h (any dose)							
1 cohort (2 vaccines)	Moderate	-	Low	Low	Unclear	0.21 – 0.24	2
Within 8 days (any dose)							
1 cohort	Moderate	-	Low	Low	Unclear	0.38	2
Swelling ≥2 cm							
Within 24h (any dose)							
1 cohort (2 vaccines)	Moderate	-	Low	Low	Unclear	0.11 – 0.16	2
Within 8 days (any dose)							
1 cohort	Moderate	-	Low	Low	Unclear	0.20	2
Any pain							
Within 8 days (any dose)							
1 cohort	Moderate	-	Low	Low	Unclear	0.92	2
Persistent crying							
Within 8 days (any dose)							
1 cohort	Moderate	-	Low	Low	Unclear	1.21 – 1.43	2
Any systemic symptom							
Within 24h (any dose)							
1 cohort (2 vaccines)	Moderate	-	Low	Low	Unclear	0.77 – 0.80	2

Cohort: Olin 1998, Miller 1997, Giammanco 1998

* High risk of biased comparison, as long schedule group older at 3rd dose

Result summary and GRADE evidence profiles

Tables 4-6 present GRADE evidence profiles for by objectives addressed by several studies with a comparable outcome (birth dose, 2 vs. 3 primary doses, and accelerated vs. long schedule). The following summarizes the overall retrieved evidence (not-per-protocol studies not yet included). Reactogenicity was only included for evaluation of effects of birth dose, 2 vs. 3 primary doses, and accelerated vs. long schedule (see meta-analysis K. Soares-Weiser).

Objective a. (effect of the number of doses on the outcomes)

The comparison of 2 vs. 3 primary doses was addressed by six studies (**Table 5**). 2 compared to 3 primary doses (including boosting at 12-15 mo, last 1° dose through age 3 yrs) are less effective (-167% *ns*) (*GRADE 1*). GMT are similar or lower (factor 0.5) at age 6/7 mo and around booster (*GRADE 1-2*). Reactogenicity of a 2-dose primary schedule is lower during the 1st year of life, but higher at booster (*GRADE 2*).

Objective b. (effect of age at initiation of vaccination on the outcomes)

The effect of an additional birth dose was addressed by four studies (*GRADE 2-3*) (**Table 4**). Results were inconsistent even within studies and antigens tested, with a tendency to slightly lower reactogenicity at any dose in a birth-dose schedule.

The effect of initiation of a 3+1 schedule at 3 vs. 2 month of age was addressed by one RCT (1-mo intervals) and one cohort study (2-mo intervals). The proportions of seroconverters or GMTs after the 3rd dose or a booster are similar (*GRADE 2-3*). Delaying the initiation of a 3+1 schedule from 3-8 months to 9-23 mo does not substantially increase immunogenicity (*GRADE 1*).

Objective c. (effect of length of interval on the outcomes)

The comparison between accelerated (3+0) and long (2+1) schedules was addressed by three studies (*GRADE 1*) (**Table 6**). Clinical effectiveness was substantially lower from age 9 months on (time of 3rd dose in long schedule), irrespective of vaccine product. In analyses counting already from the 1st on (age 2 or 3 month), clinical effectiveness was inconsistent (lower to higher) across vaccines, outcome definitions and follow-up durations. At 1 or 12-18 months following 3rd dose (ages at 3rd dose differ by 4 months), immunogenicity was not consistently higher with the accelerated schedule. Reactogenicity was relatively consistently lower.

The comparison of 1-mo to 2-mo intervals within a 3-dose primary schedule was addressed by 2 studies (*GRADE 1*). The proportion of seroconverters and GMT are similar one month after the third dose. Of note is that the shorter schedule in one study implied later initiation.

Objective d. (effect of any vaccination on the outcomes) was addressed by in total 13 studies on clinical efficacy/effectiveness and two studies on immunogenicity.

Across various study designs, schedules and outcome definitions, absolute VE of 3 doses (3+0 or 2+1) is 59-95% (*GRADE 2-4*) and of 2 doses, 35-86% (*GRADE 4*).

Using 3-dose schedules, VE tended to be lower in randomized studies (60-85%) than in purely observational (excluding unblinded RCT) studies (83-95%). In RCT using the old WHO definition and

studying children <3yrs old, 1-component vaccines used in a 3,5,12-mo schedule had slightly lower VE (71-73%, N=1) than 3-component vaccines used in a 2,4,6-mo schedule (78-84%, N=1).

Titers against included antigens after 3 primary doses of any vaccine compared to no vaccination are at least 50-fold higher one month after primary schedule and 4-fold at 15 months later (*GRADE 3*).

Objective e. (effect of booster schedule on the outcomes) was addressed by one study (*GRADE 3*). After a 3-dose primary series before age 8 months, timing of booster between age 15 and 18 months does not impact on immunogenicity or reactogenicity.

Objective f. (effect of any booster vaccination on the outcomes) was addressed by one RCT (*GRADE 3*). Compared to MMR-varicella vaccine, aP as booster at 12-23 mo provokes local reactions substantially more frequently.

Table set 3. Characteristics and criticial appraisal of studies included per protocol

Anonymous, 1988

- ⇨ **Storsaeter, 1992**

Belloni C., 2003

Methods	Site: Italy, January-August 1999 Design: observer-blinded RCT Follow up: up to 24 months after dose 1
Participants	Included: Healthy full-term newborn infants(N=91) Excluded: Gestational age outside of 37-42 weeks, severe illness, perinatal brain damage, congenital abnormalities, or if mother was HIV+
Interventions	**Primary DTaP series (3,5,11 mo), with vs. without birth dose** Vaccines : DTaP (Biocine), 3-component: PT(5µg), FHA(2.5µg), PRN(2.5µg) Dose schedule: Group 1: 0,3,5,11 mo (N=45) : 4 doses, interval 3-2-6 mo Control group: 3,5,11 mo (N=46) : 3 doses, interval 2-6 mo
Outcomes	**Immunogenicity** : Timing of assessment: at 0, 3,5,6, and 12mo (+ mother's serum post-partum) - Each infant was randomly assigned to 2 of the blood collections to reduce the number of phlebotomies Serological assay: **ELISA (IgG: anti-PT, anti-FHA, anti-PRN**), subgroups: birth (n=91), 3mo (n=44), 5mo (n=42), 6mo (n=44), 12mo (n=83), and mothers (n=91) - Response was defined as a 4-fold increment in prevaccination antibody levels with MDL (1.5EU/ml for PT; 1EU/ml for FHA; 3EU/ml for PRN) - Geometric mean titre (GMT) post-immunization (data extracted from text) Reactogenicity: no detailed data reported Clinical effectiveness: no data reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Low risk	Usual criteria for inclusion/exclusion
Random sequence generation (selection bias)	Unclear risk	Randomization procedure not specified
Allocation concealment (selection bias)	Unclear risk	Randomization procedure not specified
Blinding of participants (performance bias)	Risk	Only observer-blinded, but low risk in serological evaluation

Blinding of outcome assessment (detection bias)	Low risk	Not clear whether study nurse or other staff saw trial card. Neonatologist was different at follow-up
Selective reporting	Unclear risk	Protocol not available

Biritwum RB, 1985

Methods	Site: Ghana, 1980s Design: RCT Follow-up: 1 month post vaccination
Participants	Included: children aged 3 mo – 3 yrs (N=119) Excluded: not specified
Interventions	**Primary DTaP series 2 vs. 3 doses (monthly interval)** Vaccines : DTaP (JNIH; 1-component?) Group 1: 2 doses in 1-mo interval Group 2: 3 doses in 1-mo interval
Outcomes	**Immunogenicity** : Timing of assessment: 1 month post last dose Serological assay: **ELISA [micro ELISA?] (IgG anti-PT, anti-FHA**) - GMT (U) pre-post vaccination Clinical efficacy and reactogenicity: no data reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Unclear risk	Inclusion criteria not specified
Random sequence generation (selection bias)	Unclear risk	No method described
Allocation concealment (selection bias)	Unclear risk	No method described
Blinding of participants (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Selective reporting	Unclear risk	Protocol not available

Bisgard K., 2005

Methods	Site: Four US states (Ohio, Colorado, Idaho, Minnesota), 1998-2001 ; Design: age- and area-matched case-control study Telephone contact with parents and care providers (vaccination status)

Participants	Cases (N=184): Confirmed **pertussis cases aged 6-59 months,** reported to local public health officials. 5 controls per case (N=893): sampling from birth registry: children from same region or zip-code are, born the same day.
Exposure	**Primary series (2,4,6 mo) of DTaP, vs. no vaccination** Primary series and booster (12-18 mo) of DTaP, vs. no vaccination Comparison groups: 0 doses of aP Vaccines: 4 different aP vaccines were distributed during the study period Baxter (1c, PT); SP (2c, PT and FHA); GSK (3c, PT, FHA, PRN); Wyeth (4c, Pt, FHA, PRN, Fim2)
Outcomes	**Clinical effectiveness** : **CDC definition of confirmed cases :** o Cough ≥1 day with culture confirmation of *B. pertussis* o illness with ≥14 days of cough with paroxysm, whooping or posttussive vomiting and PCR confirmation or epilink with lab-confirmed case - Odds ratio by immunization status Immunogenicity and reactogenicity: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias (with regard to case and controls)	Moderate risk	Controls randomly chosen from exhaustive population list Matching for age and residency Other characteristics that are different between cases and controls mainly related to socio-economic status, could induce bias
Missing data on exposure	Low risk	Only 11/ 904 children excluded for missing vaccination status
Performance bias	Unclear risk	No details reported
Exposure assessment bias	Moderate risk	Same procedure of assessment for cases and controls: by telephone interview with parent and contact with health care provider.
Selective reporting	Unclear or low risk	Probably all results reported

Carlsson RM., 1998

Methods	Site: Sweden 1994-96 Design: Open, controlled RCT Follow-up: 1 month post booster dose
Participants	Included: healthy term birth infants aged 2 months (N=236)

	Excluded: low birth weight
Interventions	**Primary and booster vaccination DTaP, comparing 3,5,12 mo vs. 2,4,6,13 mo** Vaccine: **Pentavalent DTaP (with IPV, Hib): Pasteur Mérieux 2-component (PT, FHA)** Group 1: 3,5,12-mo-schedule (N=113) Group 2: 2,4,6,13-mo-schedule (N=118)
Outcomes	**Immunogenicity** : Timing of assessment: 4-6 weeks post primary, 7 mo post primary, 4-6 weeks post booster dose Serological assay: **ELISA (IgG anti-PT, anti-FHA**) and PT-neutralising antibody (CHO assay) - Geometric mean titers or concentration - Percentage with titers ≥4, ≥32, ≥256 **Reactogenicity:** Parents' diary during 3 days following vaccination - Incidence expressed in % of subjects (by serial number of dose) - Redness (≥2cm); swelling (≥2cm); - Rectal temperature ≥38.0 or 39.0°C; Clinical effectiveness: no data reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Low risk	Usual exclusion criteria
Random sequence generation (selection bias)	Low risk	Randomisation in blocks of 10
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants (performance bias)	Low and moderate risk	No blinding => low risk for immunogenicity, high risk for reactogenicity
Blinding of outcome assessment (detection bias)	Low and high risk	Serological analyses were blinded high risk for reactogenicity
Selective reporting	Unclear or moderate risk	Protocol not disclosed; authors include manufacturer

Giammanco G., 1998

Methods:	Site : Italy, period not specified Design: Cohort study Follow-up: until one month after the 3rd dose
Participants	Included : Healthy infants weighing ≥2000g at birth (N=565) Excluded: contradiction to vaccination
Interventions	**Primary DTaP series: accelerated vs. long schedule** Vaccines : DTaP –HepB (SKB) Dose schedule: Group 1: 2,4,6 mo (N=208) Group 2: 3,5,11 mo (N=357)
Outcomes	**Immunogenicity**: Timing of assessment: one month after 3rd dose (Group 1: 7 mo; Group 2; 12 mo) and one month after 2nd dose (Group 2: 6 mo) Serological assay: ELISA (IgG anti-FHA, anti-PT, anti-PRN) - GMT (EU/ml), 95% CI) at 1 mo after third dose, and at age 7 mo (group 2) - Seropositivity (%) ≥5 EU/ml **Reactogenicity:** Assessed by diary during 8 days post vaccination (all doses combined by schedule) - Local (pain, redness, swelling), systemic (fever >39.0°C, crying, …) Clinical effectiveness: not reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Selection bias	Unclear risk	Few information on study participants and study population
Attrition Bias	High risk	There was about 35% loss to follow-up.
Performance Bias	Unclear risk	Information not available on the blinding of participants and assessors, or the methods the participants were monitored.
Confounding	Moderate risk	Indication bias possible (but possibly less important in serological evaluation) No correction for possible confounding variables
Detection bias	Unclear risk	Not clear whether testing done in blinded fashion
Selective reporting	Unclear risk	The protocol not provided. Authors include manufacturer

Giuliano M., 1998 **---** *[overlap with participants of Greco 1996]*

Methods	Site: Italy 1992-93 Design: parallel group double-blind RCT Follow up: 15 months after dose 3 (age 21 months)
Participants	Included: Healthy unvaccinated children < 2 months-old Excluded: contraindications for further doses Only 1572 participants from a larger efficacy trial participated in the immunogenicity study (children whose parents consented to the collection of capillary blood)
Interventions	**Primary series (2,4,6 mo): DTaP vs. DT comparison** Vaccines : 1. DTaP (Cannaught: 3-component, PT, FHA and PRN) 2. DTaP (SKB: 3-component, PT, FHA and PRN) 3. DT (control group)
Outcomes	**Immunogenicity** : Timing of assessment: **1 month** (mean 34.4 days, range 15-95 days) and **15 months** (mean 15.5mo, range 6.3-22.5 mo) **post-third dose** Serological assay: **ELISA (IgG-PT, IgG-FHA, IgG-PRN**) PT-neutralizing antibodies (CHO assay) => additional information Seropositivity criteria: antibody concentration ≥ 4x MLD [minimum level of detection = 8 EU/ml for PT and FHA, 12 EU/ml for PRN; ≥ 160 neutralizing titer] - Percentage seropositive post-immunization - GMC post-immunization Clinical effectiveness and reactogenicity: no data presented (*see Greco 1996*)

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Moderate risk	Inclusion into immunogenicity study based on parental consent after randomisation
Random sequence generation (selection bias)	Low risk	Randomization list provided externally
Allocation concealment (selection bias)	Low risk	Randomisation material and vaccines prepared externally
Blinding of participants (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Laboratory result blinded
Selective reporting	Unclear risk	Protocol not available

Greco D., 1996

Methods	Site: Italy 1992-93 Design: parallel group double-blind RCT Follow up: average 17 months after dose 3 (mean 17.2 mo; age 23 months)
Participants	Included: Healthy unvaccinated children 6-12 week-old (N=15,601) Excluded: contraindications for further doses. Follow-up of 14,832 children (95% of randomized); subsample of 10% for immunogenicity
Interventions	**Primary series (2,4,6 mo): DTaP vs. DT** Vaccines : 1. DTaP (SKM: 3-component, PT, FHA and PRN) 2. DTaP (Chiron Biocine: 3-component, PT, FHA and PRN) 3. DT (Chiron Biocine, control) Dose schedule: **2, 4, 6 months** Number randomized (vaccinated with at least 1 dose): 4696 (group 1), 4672 (group 2), 1555 (group 3)
Outcomes	**Clinical efficacy:** Passive and active case ascertainment; case incidence adjusted for follow up from the day of first dose or 30 days after 3rd dose (intention to treat); **Confirmed pertussis cases: illness with ≥21 paroxysmal cough and evidence of *B. pertussis* infection or positive diagnostic serologic test**. Alternative definitions (cough - paroxysmal cough; duration varying 7 to 60 days) - Incidence rates (person days) per group and N doses (3 or ≥1) - Relative risk and vaccine efficacy **Immunogenicity** : (see also Giuliano 1998) Timing of assessment: **pre-vaccination and 1 month (?) post-third dose** Serological assay: **ELISA (IgG-PT, IgG-FHA, IgG-PRN**) PT-neutralizing antibodies (CHO assay) => additional information Seroconversion criteria: antibody concentration ≥ 4x MLD (minimum level of detection = 8 EU/ml for PT and FHA, 12 EU/ml for PRN; ≥ 160 neutralizing titer) and ≥ 4-fold increase from pre-vaccination - Percentage seroconverted - GMC post-immunization **Reactogenicity:** Parents reported adverse events in a standardized diary Timing of assessment: within 2 days after each vaccine dose - Incidence expressed as rate per 1000 doses

	- Irritability; Rectal temperature ≥38.0°C, ≥40.0°C; Persistent crying ≥3h; Hypotonic, hypo- responsive episodes; Seizures - Local swelling; local tenderness;

Salmaso S., 1998

Extension of RCT follow-up into 33 months of life (stage 2)

Methods	Cohort study (unblinded control group, declined vaccination after RCT) Group 1: N=4327 Group 2: N=4302 Group 3: N=317
Participants	No history of pertussis
Interventions	**Primary series (2,4,6 mo): DTaP vs. DT** Vaccines : 1. DTaP (SKM: 3-component, PT, FHA and PRN) 2. DTaP (Chiron Biocine: 3-component, PT, FHA and PRN) 3. DT (Chiron Biocine, control) Dose schedule: **2, 4, 6 months** Number originally randomized (vaccinated with at least 1 dose): 4696 (group 1), 4672 (group 2), 1555 (group 3)
Outcomes	**Clinical efficacy:** Passive and active case ascertainment; case incidence adjusted for follow up from the day of first dose or 30 days after 3rd dose (intention to treat); **Confirmed pertussis cases: illness with ≥21 paroxysmal cough and evidence of *B. pertussis* infection or positive diagnostic serologic test**. Alternative definitions (cough - paroxysmal cough; duration varying 7 to 60 days) - Vaccine efficacy

Salmaso S., 2001

Extension of RCT follow-up to 59 months (stage 3) of life

Methods	Cohort study (unblended control group, declined vaccination after RCT) Group 1: N=4217 Group 2: N=4215 Group 3: N=266
Participants	Included: Healthy unvaccinated children 6-12 week-old (N=15,601) Excluded: contraindications for further doses. Follow-up of 14,832 children (95% of randomized); subsample of 10% for immunogenicity

Interventions	**Primary series (2,4,6 mo): DTaP vs. DT** Vaccines : 1. DTaP (SKM: 3-component, PT, FHA and PRN) 2. DTaP (Chiron Biocine: 3-component, PT, FHA and PRN) 3. DT (Chiron Biocine, control) Dose schedule: **2, 4, 6 months** Number originally randomized (vaccinated with at least 1 dose): 4696 (group 1), 4672 (group 2), 1555 (group 3)
Outcomes	**Clinical efficacy:** Passive and active case ascertainment; case incidence adjusted for follow up from the day of first dose or 30 days after 3rd dose (intention to treat); **Confirmed pertussis cases: illness with ≥21 paroxysmal cough and evidence of *B. pertussis* infection or positive diagnostic serologic test**. Alternative definitions (cough - paroxysmal cough; duration varying 7 to 60 days) - Vaccine efficacy

Gustafsson L., 1996 (Olin 1997, trial I)

Methods	Site: Sweden 1992-95 Design: parallel group double-blind RCT Follow-up: up to 3 years (average 21 to 23.5 months post dose 3), by nurse show also enrolled and vaccinated infants Cox proportional hazard model
Participants	Included: 9829 healthy unvaccinated children < 2 months-old Excluded: contraindications for further doses, pertussis diagnosis Loss to follow-up after complete vaccination : 205
	Primary series (2,4,6 mo): DTaP vs. DT Vaccines : 1. DTaP: SKB (2- component, PT and FHA) 2. DTaP: Cannaught (5-component, PT, FHA, Fim2/3, PRN 3. DT (Control group, Swedish National Bacteriological Lab, Stockholm) Dose schedule: 2, 4, 6 months Number randomized: 2102 (group 1), 2587 (group 2) , 2574 (control, group 3)
Outcomes	**Clinical effectiveness**: Passive and active case assessment (parent report, telephone call by nurses every 6-8 wks); case incidence adjusted for follow up from the day of first dose (intention to treat **Old WHO definition of confirmed cases** with ≥ 21 days of paroxysmal cough plus culture or serology positive, or epi link with confirmed case. Serological confirmation based on two-fold increase in anti-PT or anti-FHA IgG or IgA (FHA culture/PCR negative for *B. parapertussis).*

- Incidence rate (per person year) and vaccine efficacy, starting post 3rd dose or post 1st dose

Immunogenicity (provides additional, not per protocol evidence) :

Evaluated in one study site only

Timing of assessment: **1 month post-third dose**; high pre-vaccination maternal antibody concentration => not reported

Serological assay: **ELISA (IgG anti-PT, anti-FHA, anti-PRN, anti-Fim2/3**)

- Percentage ≥1 units/ml post-immunization (limit of detection, estimated from figure)
- Median concentration post-immunization (estimated from figure)
- => classed as additional information

Reactogenicity:

Active ascertainment of adverse events during day 1-14 after vaccination (structured questionnaire by telephone)

Timing of assessment: within one day post dose 1, 2, and 3

- Percentage of children with symptom within one day after each dose, and any dose
- Rectal temperature ≥38.0°C; Persistent crying ≥ 1h;
- Local nodule ≥ 2cm; local tenderness; redness ≥2cm;

Risk of Bias	Reviewer judgment	Support for judgment
Inclusion bias	Low risk	No unusual exclusion pattern for all eligibles
Random sequence generation (selection bias)	Low risk	Computer Generated Randomization
Allocation concealment (selection bias)	Low risk	Vaccine supplied in identical vials with unique computer generated randomization number
Blinding of participants (performance bias)	Moderate risk	Double-blind; possibly partial unblinding re. wP due to vaccine aspect (suspension) and side-effects
Blinding of outcome assessment (detection bias)	Moderate risk	Possibly partial unblinding re. wP due to vaccine aspect (suspension) and side-effects; vaccinating nurses did also the follow-up Laboratory results blinded
Selective reporting	Unclear risk	Protocol not available

Halasa N., 2008

Methods	Site: USA, February 2004 – June 2006 Design: parallel group RCT

	Follow-up: until age 18 months
Participants	Included: Healthy full-term newborn infants (2-14 days old) Excluded: See article appendix (usual criteria)
Interventions	**Primary DTaP series (2,4,6,17 mo), with vs. without birth dose** Vaccines : 1. DTaP (Sanofi Pasteur), 4-component: PT(10µg), FHA(5µg), PRN(3µg), FIM (5µg) 2. Hep B (Merck), Control group Dose schedule: Experimental group: 0,2,4,6, 17 mo (N=25) : 5 doses, interval 2-2-2-7 mo Control group: 2,4,6,17 mo (N=25) : 4 doses, interval 2-2-7 mo
Outcomes	**Immunogenicity** : Timing of assessment: at 2-14 days, 6, 7, 17 and 18 months - Mean age of the infants at enrollment was 3.2 days Serological assay: **ELISA (IgG anti-PT, anti-FHA, anti-PRN, anti-FIM**) - Response was defined as a 4-fold increment in prevaccination antibody levels with MDL (2EU/ml for PT; 3EU/ml for FHA; 2EU/ml for PRN) - FIM anti-body IgG also reported - Geometric mean concentrations (GMC) post-immunization (data extracted from table) Reactogenicity: Results were listed as not significant and no data was reported. Clinical effectiveness: no data reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Low risk	Usual criteria for inclusion/exclusion
Random sequence generation (selection bias)	Unclear risk	Randomized study, but method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants (performance bias)	Low risk	Participants were blinded
Blinding of outcome assessment (detection bias)	Unclear or moderate risk	Not reported
Selective reporting	Unclear risk	Protocol not available

Hoppenbrouwers K., 1999

Methods	Site: Belgium, Turkey, 1990s Design: parallel group open RCT Follow-up: up to one month after third dose of primary vaccination (booster not evaluated between schedules)
Participants	Included: 410 healthy unvaccinated children < 2 months-old in three study groups (only two included in this report) Excluded: no details provided Loss to follow-up after complete vaccination : 7.5% in Belgium, 49.2% in Turkey
Intervention	**Primary series DTaP, comparing short to longer schedule (3 doses)** Vaccine : DTaP (Pasteur Mérieux, 2 component PT, FHA) Dose schedule: Group 1: 3,4,5 mo (N=135) Group 2: 2,4,6 mo (N=137)
Outcomes	**Immunogenicity :** Timing of assessment: **1 month post-third dose**; high pre-vaccination maternal antibody concentration => not reported Serological assay: **ELISA (IgG anti-PT, anti-FHA**) - Percentage seroconverted after three doses (≥4-fold rise in concentration) - GMT , total and by country **Reactogenicity**: Parents' diary *Timing of assessment:* within three days post dose 1, 2, and 3 - Percentage of children with symptom within one day after each dose - Rectal temperature ≥38.0°C; irritability; any side reaction (and others not pp) -

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Low risk	No unusual exclusion criteria
Random sequence generation (selection bias)	Low risk	Randomization list
Allocation concealment (selection bias)	Low risk	Randomization list, no further detail
Blinding of participants (performance bias)	Low or moderate risk	Non-blinded => low risk for immunogenicity evaluation, moderate risk for reactogenicity high drop-out in Turkey => potential selection for better tolerance?

Blinding of outcome assessment (detection bias)	Moderate risk	moderate risk for reactogenicity Serology testing was blinded
Selective reporting	Moderate risk	Protocol not available, manufacturer among authors

Just M., 1991

Methods	Site: Switzerland and Turkey, 1989-90 Design: Synopsis of two parallel group double-blind RCT evaluating wP vs. 2 lots of aP vaccine, the two trials using a different schedules. The two trials are presented as using an identical protocol. Follow-up by appointments for vaccination or blood sampling
Participants	Included: Children (total N=313) at age for primary vaccination (2 or 3 months), no details on setting of enrollment Excluded: no details provided 70%-72% follow-up for immunogenicity, 83% for reactogenicity
Interventions	**DTaP 1-mo vs. 2-mo intervals** Vaccines : 2 lots of DTaP (SKB, 2-component: P, FHA) Dose schedule: Group 1: **3,4,5 mo** (N=43 and 33 per lot) - Switzerland Group 2: **2,4,6 mo** (N=43 and 34 per lot) - Turkey
Outcomes	**Immunogenicity** : Timing of assessment: **one month after 3rd dose** Serological assay: **ELISA (IgG anti-FHA)** and **neutralization test anti-PT** *(not per protocol)* - GMT (range) post-vaccination by country group **Reactogenicity:** Study diary kept by parents, revised at visit; comparison between Switzerland and Turkey does not appear appropriate for this outcome - % of children with symptoms 7 days by serial dose and at any of three doses: - Any local or general symptom, any local reaction (redness, swelling, pain), pain, swelling, rectal temp ≥ 38.0°C, severe general symptoms (restlessness, unusual crying) Clinical effectiveness: no data presented
Bias	**Reviewers' judgment** **Support for judgment**

Selection bias	High risk	Comparison of two cohorts (participating in trial) in two countries, without control of any confounding variable
Attrition bias	Moderate risk	30%, similar in both trials
Performance bias	Low or unclear risk	No event reported
Detection bias	Moderate risk	Immunogenicity evaluation, test interpretation possibly biased
Selective reporting	Moderate risk	Study team includes vaccine producer; not exhaustive list of outcomes presented

Kamiya H., 1992

Methods	Site: Japan Design: Cohort study (sequential recruitment into groups) Follow-up until one months after the third dose (4% drop-out)
Participants	Included: children (N=121 in total) No inclusion/exclusion criteria are specified
Interventions	**Primary vaccination, DTaP at 3,5,7 mo vs. 2,4,6 mo with booster 12 later** Vaccine : DTaP (Takeda: 4-component, PT, FHA, pertactin, agglutinogens) Dose schedule: Group 1: **3,5,7 mo + 19 mo** (N=78) Group 2: **2,4,6 mo + 18 mo** (N=43)
Outcomes	**Immunogenicity** : Timing of assessment: **one month pre and post 3rd dose, one month pre and post booster** Serological assay: **ELISA (IgG anti-PT, FHA and PRN**) *Not per protocol*: agglutinating antibodies (microagglutination assay) - GMT (range) pre- and post-vaccination Reactogenicity: parents' questionnaires Timing of assessment: within 24h after vaccination - Pain, redness, swelling - Axillary T° ≥37.5°C, fretfulness, any systemic reaction Clinical effectiveness not reported.

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Moderate risk	Sequential enrolment into groups

Attrition bias	Low risk	Low drop-out rate in both groups
Performance bias	Low risk	No event reported
Detection bias	Moderate risk	Non-blinded study, may have biased reactogenicity
Selective reporting	Unclear risk	Protocol not available

Kimura M., 1991

Methods	Site: Japan Design: Cohort, follow-up until one month post booster (age 16-46 mo)
Participants	Included: Infants aged 3-30 months Excluded: not reported
Intervention	**Primary series DTaP: 3 doses initiated before or after age 9 mo** Schedule: initiation at 3-8 months (N=182) vs. between 9-23 months (N=92); interval 6-10 weeks; booster at 12-18 mo post primary Vaccine: DTaP (Takeda)
Outcomes	Immunogenicity: - Timing of assessment: after 3rd dose - Serology assay: o **ELISA (IgG anti-FHA and anti-PT)** o **Agglutinating antibodies** - GMT (IU/ml) (pre-and post-immunization 3rd primary and booster), by pre-existing antibody - seroconversion (around 3rd primary and booster), for seronegatives pre-immunization Clinical effectiveness and reactogenicity not reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Selection bias	Unclear risk	Few information on study participants and study population
Attrition Bias	High risk	There was about 25% loss to follow-up.
Performance Bias	Unclear risk	Information not available on the blinding of participants and assessors, or the methods the participants were monitored.
Confounding	Moderate risk	Indication bias likely No correction for possible confounding variables
Detection bias	Unclear risk	Not clear whether testing done in blinded fashion
Selective reporting	Unclear risk	The protocol not provided.

Knuf, 2008

Methods	Site: Germany, July 2004 – April 2006 Design: Double-blinded, controlled RCT Follow-up: until age 7 months
Participants	Included: Healthy full-term newborn infants (2-5 days old) Excluded: Not 36 to 42 week gestation; complications in pregnancy; mothers seropositive for Hepatitis B and/or HIV; birth weight <2.5kg and 5-minute APGAR < 7; severe illness at birth; planned pneumococcal or BCG vaccination planned during study period.
Interventions	**Primary DTaP series (2,4,6 mo), with vs. without birth dose** Vaccines : 1. aP stand alone – birth dose (GlaxoSmithKline), 3-component: PT(25µg), FHA(25µg), PRN(8µg) 2. Hep B – birth dose (GlaxoSmithKline), Control group 3. DTaP-HBV-IPV/Hib – 2, 4, 6 month doses (GlaxoSmithKline), Both groups Dose schedule: Experimental group: 0,2,4,6 mo (N=60) : 4 doses, interval 2-2-2 mo Control group: 2,4,6 mo (N=61) : 3 doses, interval 2-2 mo
Outcomes	**Immunogenicity** : Timing of assessment: at 2-5 days, 3, 5, and 7 months - Mean age of the infants at enrollment was 2.9 days - Immunogenicity was performed on the according-to-protocol (ATP) sub-cohort: Experimental group (N=55) and Control group (N=57) - APA cohort: All subjects who had complied with the vaccination schedule defined in the protocol and with available serological data. - **Group numbers fluctuate for serological data in each group at each vaccination dose** Serological assay: **ELISA (IgG anti-PT, anti-FHA, anti-PRN**) - ELISA >= 4-fold increase, cutoff at >= 5EU/ml for seroconversion - Geometric mean concentrations (GMC) post-immunization (data extracted from table) **Reactogenicity:** Parents reported adverse events in a standardized diary Timing of assessment: within 8 days after each vaccine dose (local reactions), 30 days (unsolicited adverse events and SAE) - Results from data figures (except temperature data in text) - Incidence expressed in % of subjects (all doses combined, reaction observed at least once) - Pain; Redness; Rectal temperature ≥38.0°C; Irritability/fussiness; Drowsiness; Loss of appetite; Local swelling; Drowsiness/prevented activity; Not eating at all. - aP vs. HepB at birth

	Clinical effectiveness: no data reported

Bias	**Reviewers' judgment**	**Support for judgment**
Inclusion bias	Low risk	Criteria for inclusion/exclusion was clearly stated
Random sequence generation (selection bias)	Unclear or moderate risk	Randomized study, but method not reported
Allocation concealment (selection bias)	Low risk	Study was double blinded, Vaccines and assays were prepared externally
Blinding of participants (performance bias)	Low risk	Participants were blinded
Blinding of outcome assessment (detection bias)	Unclear or moderate risk	Not reported

Knuf 2010 *(with Knuf 2008)*

Methods	Site: Germany, Booster (12-23 months post-primary); July 2004 – April 2006 (primary series) Design: Double-blinded, controlled RCT Follow-up: 1 month post-booster
Participants	Included: 12 – 23 months, completed primary series Excluded: Already received booster (n=25); subjects dropped out of primary study (n=11); lost to follow-up (n=1); parents/guardians refused further blood sampling or vaccinations (n=6)
Interventions	**Primary DTaP series (booster, 12-23mo), with vs. without birth dose (primary)** Vaccines : Booster: DTaP-HBV-IPV/Hib – 2, 4, 6 month doses (GlaxoSmithKline), both groups Primary: 1. Experimental group – Received aP birth dose (primary): GlaxoSmithKline), 3-component: PT(25µg), FHA(25µg), PRN(8µg) 2. Control group – Received Hep B at birth (primary) Dose schedule: Experimental group: 11-18 months (N=31) : 1 dose Control group: 11-18 months (N=35) : 1 dose
Outcomes	**Immunogenicity** : Timing of assessment: at 11 – 18 months, 1 month post-booster - Mean age at booster was 13.7 months

- Immunogenicity was performed on the according-to-protocol (ATP) sub-cohort: **Experimental group**: Pre-boost (N=16), 1mo post-boost (N=19); **Control group**: Pre-boost (N=18), 1mo post-boost (N=15)
- APA cohort: All subjects who had complied with the vaccination schedule defined in the protocol and with available serological data.
- **Group numbers fluctuate for serological data in each group at each vaccination dose**

Serological assay: **ELISA (IgG anti-PT, anti-FHA, anti-PRN**)

- ELISA >= 4-fold increase, cutoff at >= 5EU/ml for seroconversion
- Geometric mean concentrations (GMC) post-immunization (data extracted from table)

Reactogenicity:

Parents reported adverse events in a standardized diary

Timing of assessment: within 8 days after each vaccine dose (local reactions), 30 days (unsolicited adverse events and SAE)

- Incidence expressed in % of subjects (data from chart)
- Pain; Redness; Rectal temperature ≥38.0°C; Irritability/fussiness; Drowsiness; Loss of appetite; Local swelling
- System intensity graded on 3-point scale: "Grade 3" = Fever >39.5°C; Crying when limb is moved/spontaneously painful; Diameter of >50mm in swelling/redness; crying or irritability without comfort/prevent normal activity; Drowsiness/prevented activity; Not eating at all.

Results from data figures

Clinical effectiveness: no data reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Low risk	All subjects who participated in primary series could participate in booster series
Random sequence generation (selection bias)	Unclear risk	Randomization remained the same as during primary series, but method not stated
Allocation concealment (selection bias)	Low risk	Vaccines and assays were prepared externally
Blinding of participants (performance bias)	Unclear risk	Participants were blinded during primary series, but not stated if they remained blinded for booster
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated if laboratory results were blinded
Selective reporting	Unclear risk	Protocol not available

Li R.C., 2011 (I)

Methods	Site: China time not specified Design: RCT (no details on randomization or blinding) Follow-up: 1 month post third dose (9% and 3% drop-out)
Participants	Included: healthy infants aged 60-74 days, full-term Excluded: immunodeficiency/suppression, history of seizures, bleeding disorder, fever on day of inclusion…
Interventions	**Primary DTaP series: 3,4,5 mo vs. 2,3,4 mo** Vaccines : **Pentavalent DTaP (with IPV, Hib): Sanofi Pasteur 2-component (PT, FHA)** Dose schedule 1. Group 1: 3,4,5-mo-schedule (N=263) 2. Group 2: 2,3,4-mo-schedule (N=263)
Outcomes	**Immunogenicity** : Timing of assessment: 1 month post 3rd dose (age 6 and 5 mo, respectively) Serological assay: **ELISA (IgG anti-PT, anti-FHA**) - Seroconversion defined as IgG ≥ 4-fold increase - Geometric mean titers (GMT) pre- and post-immunization **Reactogenicity:** Parents' diary during 7 days (or 8 days?) following vaccination - Incidence expressed in % of subjects (any dose) - Tenderness (any); erythema (>3cm); swelling (>3cm); Any - Axillary temperature ≥37.1°C; abnormal crying (>3h); irritability Clinical effectiveness: no data reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Low risk	Usual exclusion criteria
Random sequence generation (selection bias)	Unclear risk	No details reported
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants (performance bias)	Low / high risk	Unblinded trial : low risk for serology, high for reactogenicity
Blinding of outcome assessment (detection bias)	Unclear risk	Unblinded; potentially a problem for serology

Selective reporting	Moderate risk	Authors include vaccine manufacturer, but trial registration

Li R.C., 2011 (II)

Methods	Site: China time not specified Design: RCT (no details on randomization or blinding) Follow-up: 1 month post booster dose (9% and 3% drop-out)
Participants	Included: participants of previous trial (Li 2011, I) (N=719, 98.3%) Excluded: compliance with booster protocol
Interventions	**Booster dose DTaP at 18-20 mo, after primary series: 3,4,5 mo vs. 2,3,4 mo** Vaccines : **Pentavalent DTaP (with IPV, Hib): Sanofi Pasteur 2-component (PT, FHA)** Dose schedule 1. Group 1: 3,4,5-mo-schedule (N=251) 2. Group 2: 2,3,4-mo-schedule (N=233)
Outcomes	**Immunogenicity** : Timing of assessment: 1 month post booster dose (age 19-21mo) Serological assay: **ELISA (IgG anti-PT, anti-FHA**) - Seroconversion defined as IgG ≥ 4-fold increase - Geometric mean titers (GMT) pre- and post-immunization **Reactogenicity:** Parents' diary during 7 days (or 8 days?) following vaccination - Incidence expressed in % of subjects (any dose) - Tenderness (any); erythema (>3cm); swelling (>3cm); Any - Axillary temperature ≥37.1°C; abnormal crying (>3h); irritability Clinical effectiveness: no data reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Low risk	Usual exclusion criteria
Random sequence generation (selection bias)	Unclear risk	No details reported
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants (performance bias)	Unclear risk	No details reported (possibly low risk for serology, high for reactogenicity)

Blinding of outcome assessment (detection bias)	Unclear risk	No details reported
Selective reporting	Moderate risk	Authors include vaccine manufacturer, but trial registration

Liese J., 1997

Methods	Site: Germany, 1993 - 1995 Design: age-matched case-control study within population of children seen in 64 pediatric practices (a part being part of a cohort study) Information from medical records or from contact with family
Participants	Cases (N=241): **Pertussis cases aged <2 years,** Up to 4 controls per case (N=949): sampling from cohort or practice registries, birth date +/- 30 days.
Exposure	**Primary series (2,4,6 mo) of DTaP, vs. no vaccination** Vaccine: DTaP (Pasteur Mérieux Connaught: 2-component, PT and FHA)
Outcomes	**Clinical effectiveness** : **Similar to old WHO definition :** o Paroxysmal cough ≥21 days with either culture confirmation of *B. pertussis* or household contact with laboratory-confirmed pertussis case Alternative (not-per-protocol): o ≥21 days of coughing, with either culture confirmation of *B. pertussis* or household contact with laboratory-confirmed pertussis case - Crude and multiply-adjusted VE Immunogenicity and reactogenicity: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Moderate risk	Parent's choice for vaccination, but adjusting for family characteristics
Missing data on exposure	Low risk	High exhaustiveness of vaccine information
Performance bias	Unclear risk	No details reported
Exposure assessment bias	Moderate risk	Clinical charts
Selective reporting	Unclear or low risk	Probably all results reported, but other case definitions?

Miller E., 1997

Methods	Site: UK, 1988-94 Design: Synopsis of two parallel group double-blind RCT evaluating wP vs. aP, each using two different schedules The two trials are presented as using an identical protocol
Participants	Included: Children attending clinics for primary vaccination, partents accepting randomization to wP or aP (2 vaccine types can be evaluated for schedule impact) Excluded: history of pertussis, neurological disorder or serious chronic disease 4.2% drop-out
Interventions	**DTaP accelerated vs. long schedule** Vaccines : DTaP (1) Porton: 3-component (PT, FHA, Agg2,3); (2) Mérieux: 2-component (PT, FHA) Dose schedule: Group 1: **2,3,4 mo** (N=94 and 74 for vaccines 1 and 2) (mean age 8, 13, 18 weeks) Group 2: **3,5,9 mo** (N=88 and 89 for vaccines 1 and 2) (mean age 14, 22, 38 weeks)
Outcomes	**Immunogenicity** : Timing of assessment: **6 weeks and 12-18 mo** (subgroup) **after 3rd dose** Serological assay: **ELISA [IgG anti-PT, anti-FHA and fimbrial antigens** (agglutinogens) 2 and 3] - GMT (95% CI) post-vaccination - Prevalence of detectable antibody **Reactogenicity:** Study diary kept by parents, study nurse visits - % of children with symptoms within 24h at any of three doses: - Rectal temp ≥ 38.0°C (group 1) / ≥100.4°F (group 2), local redness ≥2.5cm, local swelling ≥ 2.5cm; ≥3 systemic symptoms (disturbed feeding, sleeping; unusual crying) Clinical effectiveness: no data presented

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Unclear or moderate risk	Probability or factors deciding whether to be included into one or the other trial not reported; bias if this probability is differential between schedules
Attrition bias	Moderate risk	4.2%, similar in both trials Follow-up serology at 12-18 mo in <50%, reason for loss not specified
Performance bias	Low or unclear risk	No event reported
Detection bias	Low risk	Immunogenicity evaluation Larger intervals could have impacted reporting probability of

	High risk	reactions
Selective reporting	Low risk	Large range of outcomes presented

Olin P., 1998

Olin P., 1997 (trial II)

Methods	Site: Sweden, 1993-96 Design: Secondary open cohort analysis of a multisite trial comparing vaccines; one site used a different schedule. Follow-up until October 1996 (min. age 28 mo), by laboratory reporting and nurse interview
Participants	Included: Children attending Child Health Centres in 22 of 24 Swedish counties (N=83,000) Excluded: no details provided Attrition rate not provided
Interventions	**DTaP in accelerated vs. long schedule** Vaccines : within schedules, participants were equally randomized to three DTaP vaccines 2-component (SKB): PT, FHA; 3-component (Chiron): PT, FHA, PRN; 5-component (Connaught): PT, FHA, PRN, Fim2/3 Dose schedule: Group 1: **2,4,6 mo** (N=227 for serology) - Malmö County Group 2: **3,5,12 mo** (N=201 for serology) - other counties Included 10,194 children in 2,4,6 schedule (75% wP = appr. 7646) and 72,698 children in 3,5,12 schedule (75% wP = appr. 54524)
Outcomes	**Immunogenicity** : Timing of assessment: age 7 mo and 1 mo after 3rd dose Serological assay: **ELISA (IgG anti-PT, -FHA, -Fim2/3, -PRN)** - GM (95% CI) post-vaccination by group **Clinical effectiveness**: prospective assessment and monitoring, notification by laboratories of culture confirmation of B. pertussis. Nurse interview for symptoms. **Old WHO definition**: paroxysmal cough ≥21d with culture confirmation **Laboratory-confirmed**: any cough with culture confirmation - Vaccine effectiveness and incidence rate per group - Follow-up until minimum age 28 mo Alternative definitions as **CDC confirmed case** - (culture-confirmation and cough of any duration) - Case number and incidence rate (person-months) after age 5/6 months per schedule - => calculation of person-time and of VE

	Reactogenicity: no data presented

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Moderate risk	Comparison of county populations (participating in trial) in two counties ; no information on comparability of population Reports different pertussis incidence in county groups
Attrition bias	Unclear risk	Not reported
Performance bias	Low risk	Nested within a monitored clinical trial
Detection bias	Moderate risk	Outcome assessment following standardized procedures, but not blinded (serology probably not)
Selective reporting	Low risk	Reports both VE and immunogenicity, secondary analysis Study team includes vaccine manufacturer

Scheifele DW., 2005

Methods	Site: Canada, 2000-01 Design: RCT (open-label) Follow-up: 1 month post booster (10% attrition)
Participants	Included: healthy infants aged 12 months, following 3 primary doses of same vaccine before age 8 mo Excluded: history of pertussis; neurological disorder, chronic disorder; immunodeficiency/suppression, fourth dose of included antigens
Interventions	**Booster DTaP at 15, 16, 17 or 18 mo** Vaccines : **Pentavalent DTaP (with IPV, Hib): Sanofi Pasteur 2-component (PT, FHA, FIM2,3, PRN)** Dose schedule Group 1: age 15 mo (N=445) Group 2: age 16 mo (N=449) Group 3: age 17 mo (N=450) Group 4: age 18 mo (N=438)
Outcomes	**Immunogenicity** : Timing of assessment: 1 month post booster Serological assay: **ELISA (IgG anti-PT, anti-FHA, anti-FIM2,3, anti-PRN**) - Seroconversion defined as IgG $\geq$ 4-fold increase, at 15+16 vs. 17+18 mo

- Geometric mean titers (GMT) pre- and post-immunization

Reactogenicity:

Parents' diary during 8 days following vaccination

- Incidence expressed in % of subjects
- Tenderness (any/severe); redness (>5mm, >50mm); swelling (5mm; >50mm)
- Axillary temperature (≥38.0°C, ≥39.5°C); vomiting, diarrhea, crying , fussiness, anorexia, rash (any, severe)

Clinical effectiveness: no data reported

Risk of Bias	Reviewer judgment	Support for judgment
Inclusion bias	Low risk	Usual exclusion criteria
Random sequence generation (selection bias)	Unclear risk	No details reported
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants (performance bias)	Moderate risk	Unblinded trial : low risk for serology, higher for reactogenicity
Blinding of outcome assessment (detection bias)	Unclear risk	Unblinded; potentially a problem for serology
Selective reporting	Unclear or moderate risk	Authors include vaccine manufacturer

Schmitt H-J., 1996

Methods	Site: six areas of Germany, 1992-94 Design: Household contact cohort within the study area of a aP/wP vaccine trial Notification by physicians to study team; study monitor performing weekly follow-up of household in blinded fashion during 28 to 56 days Not clear which clinical signs triggered pernasal swabbing in contacts
Participants	Household members (N=360) of primary cases (defined by typical clinics and culture- or serology confirmation); household needed to have at least on contact aged 6- to 47-mo; mean (range) was 27.6 mo (6-47 mo) in unvaccinated and 18.6 mo (6-43 mo) in vaccinated contacts.
Exposure	**Primary series (3,4,5 mo) of DTaP, vs. no vaccination** Vaccine: DTaP (SKB: 2-compondent, PT and FHA) Vaccine status assessed by physician at enrollment

Outcomes	**Clinical effectiveness** : **Old WHO definition :** o Paroxysmal cough ≥21 days with either culture confirmation of *B. pertussis* or household contact with laboratory-confirmed pertussis case Alternative (not-per-protocol): o ≥21 days of spasmodic coughing, irrespectively of confirmation - Crude VE (evaluates possible confounding by covariable) Immunogenicity and reactogenicity: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Moderate risk	Non randomized, but no apparent confounding by characteristics
Attrition bias	Unclear risk	No-drop-out reported
Performance bias	Low risk	No event reported
Detection bias	Low risk	Blinded follow-up
Selective reporting	Unclear risk	Protocol not available, but investigators possibly convinced about value of pertussis vaccination

Schmitt-Grohé S., 1997

⇨ **Überall MA., 1997**

Methods	Site: Germany, 1990s Design: double-blind group RCT, **but relevant comparison to the unrandomised DT group** Follow-up: during 72 h
Participants	Included: Healthy unvaccinated infants (2-4 months) Excluded: not reported (different reference), but probably usual
Interventions	**Primary and booster aP : vs. nihil** Vaccine: DTaP (Lederle, 4-component: PT, FHA, PRN, Fim-2) and DP (Lederle) Group 1: DTaP at 2-4 mo, two further doses in 6-weeks intervals, plus booster at 15-18 mo (N=4064) Group 2: DT 2-4, one further dose in 6-weeks interval, plus booster at 15-18 mo (N=1635)
Outcomes	**Reactogenicity:** During 72 hours following vaccination, using a diary card for parents Comparable time points are at dose 1 (age 2-4 mo), dose 2 (3.5 – 5.5 mo) and at booster (age 15-18 mo) Immunogenicity and clinical effectiveness: not reported

Risk of Bias	Reviewer judgment	Support for judgment
Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Low risk	Criteria not specified (see Heininger), but probably usual criteria
Attrition bias	Moderate risk	6% (randomized DTaP) and 11% (open DT group) drop-out
Performance bias	Unclear risk	No details reported
Detection bias	Moderate risk	Non-blinded comparison group
Selective reporting	Low risk	Part of several articles on same study

Simodon F., 1997

Methods	Site: rural town in Senegal, 1990-1994 Design: cohort study, conducted within a vaccine trial population No control for confounders (only comparison of characteristics)
Participants	Included: Children exposed to household contacts with confirmed pertussis: 197 children vaccinated at 2,4,6 mo with DTaP in the context of a vaccine trial, and 17 unvaccinated children of same population not enrolled (age not specified, but similar). Surveillance of the entire population <15 yrs during four years (2587 compounds)
Exposure	**Primary series (2,4,6 mo) of DTwP vs. no vaccination** **Vaccine:** DTaP (Pasteur Mérieux: 2-component, PT and FHA)
Outcomes	**Clinical effectiveness** : Case identification by physician after weekly screening by fieldworkers **Old WHO definition of confirmed cases** : - ≥21 days of paroxysmal cough, with positive culture or serology, or epi link Alternative definitions as - ≥21 days of paroxysmal cough, with positive culture or serology, or epi link confirmed by PCR - ≥21 days of any cough, with positive culture or serology, or epi link [confirmed by PCR] Serological confirmation based on two-fold increase in anti-PT or anti-FHA IgG - VE based case contact analysis or from proportional hazard analysis Immunogenicity and reactogenicity: not reported
Bias	**Reviewers'** **Support for judgment**

	judgment	
Selection bias	High risk	Inclusion of vaccinated from children participating in a vaccine trial comparing two vaccines, who became household contact; unvaccinated controls included from eligible children of same population that were not enrolled in trial (no reason provided) and became household contact. Authors report that characteristics between groups were compared and that contact to case was different between groups. No controlling for confounders, no other information to support absence of bias.
Attrition bias	Unclear	Controls not reported since study start, so unclear whether unvaccinated less likely to be included by time of household case of pertussis (competing risks, etc.)
Performance bias	Low risk	Low risk, but no details reported on duration of follow-up of children; proportional hazard analysis accounts from variation of risk in population due to epidemics etc.
Detection bias	Moderate risk	Case detection by active weekly screening by field workers in entire population; no blinding of field workers reported with regard to participation in trial (and thus vaccination), therefore some risk
Selective reporting	Unclear or low risk	Probably all results reported

Simodon F., 1999

Methods	Site: rural town in Senegal, 1996 Design: parallel group RCT Follow-up: one month after 3rd dose; 29% drop-out
Participants	Included: Healthy unvaccinated infants (1-2 months) Excluded: severe disease, fever, cachexia
Interventions	**Primary DTaP series: 2,3,4 mo vs. 2,4,6 mo** Vaccine: DTaP (Pasteur Mérieux Connaught, 2-component: PT and FHA) Group 1: 2,3,4 mo (N=130) Group 2: 2,4,6 mo (N=130)
Outcomes	**Immunogenicity** : Timing of assessment: at first and one month after 3rd dose Serological assay: **ELISA (IgG anti-PT, anti-FHA,** PT-neutralising antibody (CHO) - GMT pre- and post-immunization - % with seroresponse : >4-fold rise in IgG **Reactogenicity:** not reported by schedule. Clinical effectiveness: see Simodon 1997
	Reviewer

Risk of Bias	judgment	Support for judgment
Inclusion bias	Low risk	Criteria for inclusion/exclusion as usual in trials
Random sequence generation (selection bias)	Unclear risk	Randomized study, but method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants (performance bias)	Unclear or moderate risk	Not reported whether blinded; only moderate risk of bias, as immunogenicity evaluation; high drop-out, not reported whether differential
Blinding of outcome assessment (detection bias)	Unclear or moderate risk	Not reported, immunogenicity evaluation
Selective reporting	Unclear risk	Protocol not available

Stehr K., 1998

Methods	Site: Germany, 1991-94 Design: Cohort (RCT with open control arm for no vaccine) Follow-up during up to 3 yrs
Participants	Included: Healthy unvaccinated children 2- to 4-month-old (N=15,601) Per protocol follow-up in 93% of both groups.
Interventions	**Primary series (3, 4.5, 6 mo and 15-18mo): comparison DTwP vs. DT** Vaccines : 1. DTaP (Wyeth-Lederle: 4-component, PT, FHA, PRN, Fim2) 2. DT (control group; given at 3, 4.5, 15-18 mo) Number enrolled and evaluated: 4273 (vaccine group) , 1739 (control group)
Outcomes	**Clinical efficacy:** Passive and active case ascertainment (bi-weekly phone calls); case incidence for follow up from 14 days after 3rd dose (vaccine group) or 61 days after 2nd dose (control group); **Modified WHO definition of confirmed cases:** - ≥21 days of paroxysmal cough (=cough with paroxysm, whooping or posttussive vomiting), with positive culture or serology, or epi link - Several alternative definitions (variations of laboratory confirmation) - Incidence rates (person days) per group and vaccine efficacy Immunogenicity and reactogenicity : not reported

Risk of Bias	Reviewer judgment	Support for judgment
Selection bias	High risk	Assignment according to parents' preference for or against pertussis vaccination

Attrition bias	Low risk	Similar drop-out in both groups
Performance bias	Low risk	No particular event reported
Detection bias	Moderate risk	Unblinded study for vaccine/no vaccine, could have led to differential diagnostic
Selective reporting	Low risk	Extensive presentation and discussion of alternative outcomes

Storsaeter J., 1992

⇨ **RCT Anonymous, 1988**

Methods	Site: Sweden, 1986-87 Design: RCT with follow-up after household contact Surveillance: mean 16 mo from 1 mo after 2nd dose)
Participants	Included: unvaccinated children aged 6 to 11 mo Excluded: (=> Anon. 1988) chronic disease, pervious pertussis 152 children with household contact
Interventions	**Primary series: aP vs. nihil** Vaccines : 1. aP (JNIH-7: 1-component, PT) (N=26) 2. aP (JNIH-6: 2-component, PT, FHA) (N=19) 3. placebo (N=16) Dose schedule: **3 doses at 2-mo interval, initiation at age 6-11 mo**
Outcomes	**Clinical efficacy:** Clinical surveillance after household case; culture-confirmation - **old WHO definition**: ≥21d of coughing spasms and culture confirmation - **CDC confirmed case**: culture plus any coughing - **2010 WHO clinical case**: ≥14d of coughing spasms - **Suspected case**: ≥14d of coughing spasms Alternative definitions (any cough, any duration) - N cases per group and VE Immunogenicity and reactogenicity: not reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Low risk	Usual inclusion criteria
Random sequence generation (selection bias)	Low risk	Randomized study, but method not reported

Allocation concealment (selection bias)	Low risk	Not reported
Blinding of participants (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Double-blind
Selective reporting	Low risk	Several outcomes assessed

Taranger J., 2000

Methods	Site: Sweden, 1992-1997 Design: Cohort study Follow-up: until age 48 mo
Participants	Inclusion: criteria not indicated, recruitment in child health centers in six districts Exclusion: health problems, loss to follow-up, pertussis infection
Intervention	**Primary series of DTaP with booster: 3 vs. 2 primary doses** Vaccines : DTaP (North American Vaccine, USA: 1-component, PT) **Dose schedule**: Group 1: 2,4,6+15-mo-schedule (N=118); Group 2: 3,5+12-mo-schedule (N=103);
Outcomes	**Immunogenicity** : Timing of assessment: 1 mo post last primary, at booster, 1 mo post booster and at 48+ mo Serological assay: **ELISA (IgG anti-PT)** - Geometric mean titers (units/ml) pre- and post-immunization **Clinical effectiveness**: - **Old WHO definition**: Paroxysmal cough of ≥21 days between last vaccination and fourth birthday, "verified" by culture or serology - Number of cases and cumulative incidence by group **Reactogenicity:** assessed by diary - % by group and dose - Fever (different T°C cut-offs) during 48h following vaccination - Local reactions during 7d following vaccination

Risk of bias	**Reviewer judgment**	**Support for judgment**
Selection bias	High risk	The two groups were from different districts, the different schedules were not compared in these various districts.
Attrition bias	Low risk	Only about 1.8% loss to follow-up
Confounding	Moderate	The children received different vaccines with different concentrations of toxoids.

Performance bias	Low risk	No likely indications of performance bias, as samples were sent to laboratory.
Detection bias	Low risk	No likely indication of detection bias
Selective reporting	Unclear risk	Protocol was not included

Tomoda T., 1997

Methods	Site: Japan, date not given Design: Cohort Follow-up during up to 3 yrs
Participants	Included: Healthy children aged 21 months, after primary vaccination with 2 (accidental omission) or 3 doses (standard), 12 months earlier (N=45) Follow-up up to 10 years after booster (included here: 3 years)
Interventions	**Primary series DTaP and booster at 12 mo: comparison 3 primary vs. 2 primary doses** Vaccines : DTaP (Takeda: 2-component, PT and FHA) Group 1 : 2 doses (j0-w4) and booster after 12 mo: N=26 Group 2 : 3 doses (j0-w4-w8) and booster after 12 mo: N=19
Outcomes	**Immunogenicity** : Timing of assessment: 4 weeks and 1-3 years after booster vaccination Serological assay: **ELISA (IgG anti-PT, anti-FHA,** - Mean pre- and post-immunization titers (SD) Reactogenicity and **c**linical effectiveness: not reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Selection bias	Unclear or moderate risk	No details provided on reason for missing 3rd dose in 2-dose group (moderate risk for immunogenicity evaluation)
Attrition bias	Unclear risk	Long-term follow-up sample larger than post-booster sample => problem?
Performance bias	Low risk	No particular event reported
Detection bias	Unclear or moderate risk	Not clear whether blinded serology
Selective reporting	Unclear or low risk	Presentation of various outcomes, protocol not available

Wood N., 2010

Methods	Site: Australia, February 2005 – March 2007 Design: randomized, non-blinded control trial Follow up: 8 months post-birth dose
Participants	Included: Healthy full-term newborn infants (0-5 days old)(N=76) Excluded: Not <36 week gestation; not enrolled with 120 hours after birth; complications during pregnancy; mothers seropositive for Hepatitis B; administration of immunoglobulins or blood products before first dose; severe illness at birth; any confirmed immunosuppressive or immunodeficient condition in parent or child.
Interventions	**Primary DTaP series (2,4,6 mo), birth dose + 1 mo vs. birth dose vs without birth dose** Vaccines : 1. aP stand alone – birth dose, 1month (GlaxoSmithKline), 3-component: PT(25μg), FHA(25μg), PRN(8μg) 2. Hep B – birth dose (GlaxoSmithKline), Control group 3. DTaP-HBV-IPV/Hib – 2, 4, 6 month doses (GlaxoSmithKline), All groups Dose schedule: Group 1: 0,1,2,4,6 mo: 5 doses, interval 1-2-2-2 mo Group 2: 0,2,4,6 mo: 4 doses, interval 2-2-2 mo Control group: 2,4,6 mo: 3 doses, interval 2-2 mo
Outcomes	**Immunogenicity** Timing of assessment: **0, 2, 4, 6, 8 mo** Serological assay: **ELISA (IgG-PT, IgG-FHA, IgG-PRN**) - Blood sample at birth (baseline) came from the mothers in order to reduce number of withdrawals taken Seroconversion criteria: antibody concentration ≥ 4x MLD (minimum level of detection = 5 EU/ml) and ≥ 4-fold increase from pre-vaccination - GMC post-immunization: See external tables **Reactogenicity:** Parents reported adverse events in a standardized diary for 7 days Timing of assessment: 3 and 6 hours post-vaccination and at bedtime; 2 month total follow-up - Only local swelling or redness >10mm was reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Low risk	Usual crriteria for inclusion/exclusion stated
Random sequence generation (selection bias)	Unclear or moderate risk	Randomization method not reported

Allocation concealment (selection bias)	Moderate risk	Vaccines and assays were prepared externally
Blinding of participants (performance bias)	Low risk	Serologcial evaluation => little impact
Blinding of outcome assessment (detection bias)	Low risk	Serological testing blinded
Selective reporting	Unclear risk	Protocol not available

Zepp F., 2007

Methods	Site: Germany, 2000s Design: open RCT Surveillance: one month after booster; 4 days after vaccination (=extracted)
Participants	Included: children aged 12-23 mo, after 3-dose primary schedule Excluded: usual criteria
Interventions	**Booster: aP vs. nihil at age 12-23 mo** Vaccines : 1. DTaP-HBV-IPV/Hib GSK7: 3-component, PT, FHA, PRN) (N=150) 2. MMR-Varicella (GSK) (N=150)
Outcomes	**Reactogenicity:** Symptoms within 4 days after vaccination, using a diary card Immunogenicity: relevant data not presented Clinical efficacy: not reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Low risk	Usual inclusion criteria
Random sequence generation (selection bias)	Unclear risk	Randomization procedure not specified
Allocation concealment (selection bias)	Unclear risk	Randomization procedure not specified
Blinding of participants (performance bias)	Moderate risk	Non-blinded RCT
Blinding of outcome assessment (detection bias)	Low risk	Non-blinded RCT
Selective reporting	Unclear risk	Possible

Table set 4. Characteristics and criticial appraisal of additional studies not per protocol

Blennow M., 1988

Blennow M., 1989

Methods	Site: Sweden after 1984 Design: parallel group open RCT; this publication is on the booster response, comparing the two primary schedules from the initial trial Follow up: 2 weeks after booster vaccination at age 2 years
Participants	Included: Children included in a Phase II study (N=231) [*see Blennow et al. Pediatrics 1988*] Excluded: children who did not respond to primary immunization (had been given an early booster)
Interventions	**Booster vaccination aP at age 2 yrs, after primary series DTaP comparing primary 2 doses vs. 3 doses** Booster vaccine : 2-component aP with PT and FHA (JNIH) Group 1: 2 primary doses of aP (N=102) (schedules were 6-8 mo, 6-7 mo or 7-8 mo; N=40 each) Group 2: 3 doses aP (schedule 6-7-8 mo)(N=109)
Outcomes	**Immunogenicity**: Timing of assessment: **before and 2 weeks after booster at 2 years** Serological assay: **PT-neutralising** antibodies (CHO assay) => additional information - GMT pre- and post-immunization Reactogenicity not reported by schedule group, clinical efficacy not reported

Mortimer EA., 1990

Methods	Site: Japan, 1980s Design: Cohort study among household contacts
Participants	Inclusion: >2y-old children with 2-4 doses of aP vaccine (cohort analysis, partly among trial population) Exclusion: health problems, loss to follow-up, pertussis infection
Intervention	**Primary series of DTaP with booster vs. no vaccination** Vaccines : DTaP (Takeda, FHA, PT, Fim; + *outer membrane protein*) **Dose schedule**: 3 + 1 doses starting age 2 yrs
Outcomes	**Clinical effectiveness**: - **Cases of clinical pertussis (including mild) among household contacts of partially laboratory-confirmed primary cases** Immunogenicity and reactogenicity**:** not reported

-

Risk of bias	Reviewer judgment	Support for judgment
Selection bias	High risk	Inclusion criteria not stated
Attrition bias	Low risk	Not clear
Confounding	Moderate to high risk	Not clear how vaccine decision was made
Performance bias	Unclear risk	unclear
Detection bias	Low risk	Possibly differential case ascertainment between groups
Selective reporting	Unclear risk	Protocol was not included

Table 5a-A: Included studies on primary vaccination schedule impact on vaccine effectiveness/efficacy

Accelerated vs. long schedule								
Old WHO definition (⩾21 d paroxysmal cough with culture confirmation)					N cases	Incidence per mio person days	**RR (95%-CI)**	**Relative VE (%) (95% CI)**
Olin 1998, 97 Sweden	Follow-up to age >13 mo	**SKB (2c)** 2,4,6 vs. 3,5,12 mo	From 1st dose	Group 1: 2,4,6 mo Group 2: 3,5,12 mo	9 99	6.91 10.91	1 1.58 (0.78-3.06)	36.7 (-28.2 – 67.3) 1
Cohort analysis			From 9 mo post 1st dose	Group 1: 2,4,6 mo Group 2: 3,5,12 mo	3 28	4.87 44.79	1 0.98 (0.28-3.15)	-2.0 (-257 – 68.3) 1
Moderate risk	Follow-up to age >28mo	**Chiron (3c)**	From 1st dose	Group 1: 2,4,6 mo Group 2: 3,5,12 mo	9 66	3.76 3.89	1 1.04 (0.52-2.04	3.8 (-92.3 – 51.0) 1
			From 9 mo post 1st dose	Group 1: 2,4,6 mo Group 2: 3,5,12 mo	6 24	3.51 1.99	1 0.57 (0.23-1.37)	-75.4 (-335 – 27.0) 1
	Follow-up to age >28mo	**Connaught (5c)**	From 1st dose	Group 1: 2,4,6 mo Group 2: 3,5,12 mo	10 50	4.15 2.94	1 0.71 (0.36-1.38)	-40.8 (-178 – 27.5) 1
			From 9 mo post 1st dose	Group 1: 2,4,6 mo Group 2: 3,5,12 mo	8 18	4.64 1.49	1 0.32 (0.14-0.73)	-212 (-614 – -73.0) 1
Laboratory-confirmed cases (any cough with culture confirmation)								
	Follow-up to age >13 mo	**SKB (2c)**	From 1st dose	Group 1: 2,4,6 mo Group 2: 3,5,12 mo	16 145	12.29 15.98	1 1.30 (0.76-2.13)	23.1 (-31.6- 53.1) 1
			From 9 mo post 1st dose	Group 1: 2,4,6 mo Group 2: 3,5,12 mo	6 41	9.74 9.77	1 1.00 (0.41-2.26)	0 (-144 – 55.8) 1
	Follow-up to age >28mo	**Chiron (3c)**	From 1st dose	Group 1: 2,4,6 mo Group 2: 3,5,12 mo	19 116	7.93 6.84	1 0.86 (0.53-1.39)	-16.3 (-88.7 – 28.1) 1
			From 9 mo post 1st dose	Group 1: 2,4,6 mo Group 2: 3,5,12 mo	14 54	8.18 4.48	1 0.55 (0.30-0.97)	-81.8 (-233 – -3.1) 1
	Follow-up to age >28mo	**Connaught (5c)**	From 1st dose	Group 1: 2,4,6 mo Group 2: 3,5,12 mo	13 79	5.39 4.65	1 0.86 (0.47-1.53)	-16.3 (-113 – 34.6) 1
			From 9 mo post 1st dose	Group 1: 2,4,6 mo Group 2: 3,5,12 mo	10 32	5.81 2.65	1 0.46 (0.22-2.57)	-117 (355 – 61.1) 1
Included 10,194 children in 2,4,6 schedule (75% aP = appr. 7646) and 72,698 children in 3,5,12 schedule (75% aP = appr. 54524)								

3 vs. 2 primary doses (plus booster)							
Old WHO definition (⩾21 d paroxysmal cough with culture confirmation)					N cases	Incidence per 100 person yrs	**Relative VE (%) (95% CI)**
Taranger 2000 Sweden	Cohort analysis Moderate risk	**North American Vaccine (1c)** 2,4,6 + 15 vs. 3,5+12 mo	From Last dose to fourth birthday	Group 1: 2,4,6, 15 mo Group 2: 3,5, 12 mo	2 5	0.6 1.6	62.5 (*not significant*)

Table 5b-A: Included studies on primary vaccination, schedule impact on immunogenicity

Publication and country	Design Risk of Bias	Vaccines, schedules evaluated	Timing of assessment	Comparison groups	Proportion seroconverted or seropositive (%)		GMT (95%-CI) post-vaccination	
2,3,4 vs 2,4,6 mo					**anti-PT (>4-fold rise) [probably ≥4-fold]**		**IgG anti-PT**	**IgG anti-FHA**
Simondon, 1999 Senegal	RCT Unclear to moderate risk	**Pasteur Mérieux (2c)** 2,3,4 mo vs. 2,4,6 mo	One month post 3rd dose	Group 1 : 2,3,4 mo (N=37) Group 2 : 2,4,6 mo (N=44)	100% 97.7%		82.6 (72.0 – 94.7) 91.9 (81.6 – 103)	244 (205 – 289) 258 (224 – 297)
3,4,5 vs 2,3,4 mo					**Proportion (%, 95% CI) seroconverted (≥4-fold rise)**		**GMT (95%-CI) post-vaccination**	
					IgG anti-PT	**IgG anti-FHA**	**IgG anti-PT (EU/ml)**	**IgG anti-FHA (EU/ml)**
Li, 2011 (I) China	RCT Unclear or low risk	**Sanofi Pasteur (2c)** 3,4,5 mo vs. 2,3,4 mo	One month post 3rd dose	Group 1 : 3,4,5 mo (N=239) Group 2 : 2,3,4 mo (N=257)	98.0 (95.4 – 99.4) 100 (98.5 – 100)	99.6 (97.6 – 100) 100 (98.4 – 100)	101.5 (96.3 – 107.0) 98.4 (93.7 – 103.4)	103.6 (97.9 – 109.5) 92.9 (87.8 – 98.3)
Li, 2011 (II) China	RCT Unclear or low risk	**Sanofi Pasteur (2c)** DTaP booster given at 18-20 mo, by primary groups	One month post booster	Group 1 : 3,4,5 mo (N=232) Group 2 : 2,3,4 mo (N=250)	95.2 (90.0 – 96.6) 97.6 (93.8 – 98.6)	85.5 (79.0 – 88.8) 89.9 (84.7 – 92.8)	198.1 (185.4 – 211.6) 194.4 (182.8 – 206.8)	137.9 (130.0 – 146.3) 131.5 (124.0 – 139.5)

					GMT (range) of IgG post-vaccination			
3,4,5 vs 2,4,6 mo					**anti-FHA**		**anti-PT**	
Just, 1991 Switzerland, Turkey	Synopsis of two trials High risk	**SKB (2c) lot 1** 3,4,5 mo vs. 2,4,6 mo	One month after third dose	Group 1 (CH): 3,4,5 mo (N=33) Group 2 (TK): 2,4,6 mo (N=36)	93.9 (<5 – 84) 142.5 (35 – 1224)		43.3 (8 – 512) 47.9 (8 – 128)	
					% seroconversion (IgG ≥4-fold rise): Belgium/Turkey combined		**GMT (95% CI) of IgG**	
					anti-FHA	anti-PT	anti-FHA	anti-PT
Hoppenbrouwers, 1999 Belgium and Turkey	RCT Low risk	**Pasteur Mérieux (2c)** 3,4,5 vs 2,4,6 mo	One month after 3rd dose	Group 1: 3,4,5 mo (N=135) Group 2: 2,4,6 mo (N=137)	95.8/100 98.0/98.6	100/97.3 90.4/97.3	202.5 (181.4 – 226.2) 186.5 (167.4 – 207.7)	79.3 (72.3 – 87.1) 85.2 (77.8 – 93.3)
					GMT (95% CI) of IgG			
3,5,7 vs 2,4,6 mo					**anti-FHA**	**anti-PT**	**anti-PRN**	
Kamiya, 1992 Japan	Cohort Moderate risk	**Takeda (4c)** 3,5,7+19 vs. 2,4,6+20 mo	2 months post 2nd dose	Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	41.2 (37.2 – 45.7) 53.6 (45.4 – 63.3)	34.3 (30.4 – 38.5) 36.9 (30.0 – 45.4)	52.9 (43.6 – 64.3) 54.3 (42.5 – 69.3)	
			1 month post 3rd dose	Group 1: 3,5,7 mo (N=73) Group 2: 2,4,6 mo (N=43)	69.5 (61.8 – 78.1) 76.6 (65.1 – 90.0)	45.1 (40.3 – 50.4) 43.0 (35.4 – 52.4)	138.0 (115.8 - 164.5) 98 (79.5 - 120.8)	
			12 months post 3rd dose (age 19 or 18 mo)	Group 1: 3,5,7 mo (N=75) Group 2: 2,4,6 mo (N=42)	17.8 (14.9 – 21.1) 15.2 (11.6 – 19.8)	11.7 (9.8 – 14.0) 11.5 (8.7 – 15.2)	23.5 (18.4 – 29.8) 19.1 (13.6 – 26.6)	
			1 month post booster (age 20 or 19 mo)	Group 1: 3,5,7 mo (N=74) Group 2: 2,4,6 mo (N=42)	138.9 (121.5 – 158.7) 118.4 (100.9 – 139.1)	59.0 (52.2 – 66.8) 47.8 (40.1 – 56.9)	348.8 (298.0 – 408.4) 226.2 (189.3 – 270.3)	

Accelerated vs. long schedule					Proportion with detectable antibodies (%)			GMT (95%-CI) post-vaccination		
					Anti-FHA	Anti-PT	Anti-Fim2/3	Anti-FHA	Anti-PT	Anti-Fim2/3
Miller, 1997 UK	Cohort analysis of two trials	**Porton (3c)** 2,3,4 mo vs. 3,5,9 mo	6 weeks after 3rd dose	Group 1: 2,3,4 mo (N=83) Group 2: 3,5,9 mo (N=83)	83 (100%) 83 (100%)	83 (100%) 82 (99%)	83 (100%) 83 (100%)	2897 (2376-3533) 4688 (3844-5718)	3199 (2695-3797) 4345 (3390-5569)	53456 (45032-63457) 53333 (44726-63597)
			12-18 mo after 3rd dose	Group 1: 2,3,4 mo (N=48) Group 2: 3,5,9 mo (N=30)	48 (100%) 29 (97%)	48 (100%) 30 (100%)	48 (100%) 30 (100%)	1016 (754-1368) 1648 (1026-2647)	352 (277-440) 920 (601-1406)	2471 (1843-3314) 7396 (5875-9310)
		Mérieux (2c) 2,3,4 mo vs. 3,5,9 mo	6 weeks after 3rd dose	Group 1: 2,3,4 mo (N=87) Group 2: 3,5,9 mo (N=66)	87 (100%) 64 (97%)	87 (100%) 65 (98%)	87 (100%) 62 (94%)	19187 (16458-22369) 24547 (17817-33819)	6486 (5489-7665) 4385 (3375-5697)	55 (43-70) 908 (570-1445)
			12-18 mo after 3rd dose	Group 1: 2,3,4 mo (N=48) Group 2: 3,5,9 mo (N=34)	48 (100%) 27 (79%)	48 (100%) 34 (100%)	44 (92%) 15 (44%)	3854 (2662-5581) 3388 (2372-4830)	837 (610-1148) 299 (155-579)	148 (106-205) 108 (140-289)

2 vs. 3 doses					**Mean (SD) titers (EU/ml) of IgG anti-FHA**		**Mean (SD) titers (EU/ml) of IgG anti-PT**	
Tomoda, 1997 Japan	Cohort Unclear or moderate risk	**Takeda (2c)** 2d (j0-m1) vs. 3d (j0-m1-m2) Both groups with booster at about 21 mo	One month after booster	Group 1: 2 doses (N=26) Group 2: 3 doses (N=19) (data extracted from graph)	30 40 (data range overlapping)		20 20	
2+1 vs 3+1			1-3 years after booster	Group 1: 2 doses (N=31) Group 2: 3 doses (N=29)	27.2 (30.6) 33.7 (29.7)		23.1 (25.0) 26.1 (20.0)	
					Proportion (%) with IgG ≥ 4 (≥32; ≥256)		**GMC (U/ml)**	
					anti-FHA	**anti-PT**	**anti- FHA**	**anti - PT**
Carlson, 1998 Sweden	RCT Low risk	**Pasteur Mérieux (2c)** 3,5 +12 mo vs. 2,4,6 +13 mo	1 mo after primary vaccination (2 or 3 doses)	Group 1: 2 primary doses (N=111) Group 2: 3 primary doses (N=116)	100 (85; 3.6) 100 (98; 16)	100 (76; 0) 100 (91; 3.4)	48.5 75.1	73.8 49.2 ?
			7 mo after primary vaccination	Group 1: 2 primary doses (N=110) Group 2: 3 primary doses (N=115)	98 (34; 4.5) 100 (57; 8.7)	94 (17. 1.8) 95 (27; 0)	24.5 43.7	14.8 19.7
			1 mo post booster	Group 1: 2 primary doses (N=111) Group 2: 3 primary doses (N=111)	100 (100; 48) 100 (100; 46)	100 (99; 14) 100 (100; 7)	262.1 256.0	145.0 134.4
							GMT anti-FHA	**GMT anti-PT**
Biritwum, 1984 Ghana	RCT Unclear risk	**JNIH (1c)** 2 vs. 3 monthly doses	Age 3mo to 3 yrs Assessed 4 weeks after 2 and 3rd dose	Group 1: 2 doses (N=12/32) Group 2: 3 doses (N=23/77)			99 (68 – 143) 123 (95 – 159)	65 (42 – 99) 62 (49 – 79)

Publication and country	Design Risk of bias	Schedules evaluated	Timing of assessment	Comparison groups	GMT (EU/ml) (95% CI)		
Accelerated vs. long schedule 3 vs 2 doses					**Anti-FHA**	**Anti-PT**	**Anti-PRN**
Giammanco 1998 Italy	Cohort study Unclear or moderate risk	2,3,6 vs. 3,5,11 mo	1 month after 3rd dose	Group 1: 2,4,6 mo (N=172) Group 2: 3,5,11 mo (N=196)	153 (136-172) 232 (212-252)	56.1 (50.3-62.6) 65.3 (58.5-73.0)	240 (214-269) 372 (330-418)
			Age 7 or 6 mo	Group 1: 2,4,6 mo (N=172) Group 2: 3,5 mo (N=196)	153 (136-172) 85.8 (76.4-96.3)	56.1 (50.3-62.6) 31.8 (28.6-35.3)	240 (214-269) 113 (98.3-131)
NB: Seroprevalence of titer ≥5 EU/ml at one month after 3rd dose was 100% in both groups and for all antigens							

					GMT (95% CI) post-immunization			
Accelerated vs. long schedule					**Anti-FHA**	**Anti-PT**	**Anti-Fim2/3**	**Anti-PRN**
Olin 1998 Sweden	Cohort analysis Moderate risk	**SKB (2c)** 2,4,6 vs. 3,5,12 mo	1 mo after 3rd dose	Group 1: 2,4,6 mo (N=67) Group 2: 3,5,12 mo (N=60)	105 (89-125) 168 (136-208)	61 (51-74) 68 (58-80)	<1 <1	<1 <1
		Chiron (3c)		Group 1: 2,4,6 mo (N=80) Group 2: 3,5,12 mo (N=56)	19 (16-24) 21 (16-26)	150 (132-171) 151 (127-180)	<1 <1	123 (102-149) 166 (130-211)
		Connaught (5c)		Group 1: 2,4,6 mo (N=80) Group 2: 3,5,12 mo (N=58)	57 (49-66) 77 (64-92)	52 (45-60) 54 (45-65)	352 (273-454) 390 (296-516)	134 (111-163) 212 (169-266)
2 vs. 3 doses								

		SKB (2c) 2,4,6 vs. 3,5,12 mo	Age 7 mo	Group 1: 2,4,6 mo (N=67) Group 2: 3,5 mo (N=65)	105 (89-125) 70 (56-88)	61 (51-74) 38 (31-46)	<1 <1	<1 <1
		Chiron (3c)		Group 1: 2,4,6 mo (N=80) Group 2: 3,5 mo (N=71)	19 (16-24) 10 (8-12)	150 (132-171) 116 (97-138)	<1 <1	123 (102-149) 51 (39-66)
		Connaught (5c)		Group 1: 2,4,6 mo (N=80) Group 2: 3,5 mo (N=75)	57 (49-66) 44 (36-54)	52 (45-60) 27 (23-32)	352 (273-454) 103 (73-146)	134 (111-163) 31 (22-42)

Publication and country	**Design Risk of bias**	**Schedules evaluated**	**Timing of assessment**	**Comparison groups**	**IgG anti-PT (IU/ml)**		
2 vs. 3 doses, plus booster					**GMC**	**% ≥1**	**% ≥10**
Taranger 2000 Sweden	Cohort, unclear or moderate risk	3-5 +12 vs. 2-4-6 +15 mo	1 month after primary vaccination (6 and 7 mo)	Group 1: 3,5 mo (N=103) Group 2: 2,4,6 mo (N = 116)	81 109	100 100	100 100
			At booster (12 and 15 mo)	Group 1: 3,5 mo (N=102) Group 2: 2,4,6 mo (N = 112)	14 10	97 96	70 54
			1 mo post booster (13 and 16 mo)	Group 1: 3,5 mo (N=101) Group 2: 2,4,6 mo (N=112)	146 154	100 100	100 100
			Age 48 mo +	Group 1: 3,5 mo (N=54) Group 2: 2,4,6 mo (N = 74)	7.2 5.5	97 96	46 25

Publication and country	Design Risk of bias	Schedules evaluated	Timing of assessment	Comparison groups	Anti-FHA		Anti-PT	
Early vs late initiation of 3 doses		**Children with negative pre-immunization titers**			GMT (EU/ml) (95%-CI)	% sero-conversion (≥10, 20, 40)	GMT (EU/ml) (95%-CI)	% sero-conversion (≥10, 20, 40)
Kimura 1991 Japan	Cohort Unclear or high risk	Initiation @ 3-8 mo vs. 9-23 mo 3 doses at 6-10-wk interval Booster 12-18 mo post primary in both groups	Baseline	3-8 months (N=16) 9-23months (N=22)	2.7 (2.4-3.0) 2.2 (1.9-2.6)	-	1.4 (1.3-1.5) 1.1 (1.0-1.2)	-
			Before 3rd dose	3-8 months (N=16) 9-23months (N=22)	49.3 (43.0-56.7) 61.0 (50.0-74.4)	100, 93, 61 98, 96, 73	51.0 (43.8-59.4) 54.4 (45.8-64.5)	99, 94, 66 100, 98, 69
			1 mo after 3rd dose	3-8 months (N=16) 9-23months (N=22)	110.3 (96.9-125.5) 114.9 (96.9-136-.1)	100, 100, 100 100, 98, 96	74.5 (66.6-83.4) 74.6 (63.9-87.1)	100, 98, 88 100, 100, 95
			Before booster	3-8 months (N=45) 9-23months (N=21)	20.9 (17.6 - 24.9) 32.2 (24.6-42.1)	86, 52, 20 93, 79, 46	13.1 (11.3-15.2) 18.8 (14.3-24.7)	72, 29, 6 79, 43, 11
			1 mo after booster	3-8 months (N=45) 9-23months (N=21)	149.5 (126.5-176.7) 274.2 (210.7-357.0)	100, 100, 96 100, 100, 100	67.8 (58.4-78.8) 105.4 (77.9-142.6)	99, 96, 80 100, 96, 93
		Among children vaccinated at 3-8 mo, children with negative pre-immunization titers, by age at first dose			**GMT (EU/ml) (95%-CI)**			
			Baseline	3 mo (N=≥30) 4-5 mo (N=≥23) 6-8 mo (N=≥26)	2.8 (2.2-3.4) 2.7 (2.1-3.4) 2.7 (2.3-3.2)		1.6 (1.4-1.9) 1.4 (1.1-1.7) 1.2 (1.1-1.4)	
			Before 3rd dose	3 mo (N=≥30) 4-5 mo (N=≥23) 6-8 mo (N=≥26)	50.1 (37.9-66.2) 46.5 (35.4-61.0) 50.6 (41.6-61.6)		48.8 (35.7-66.9) 53.1 (42.5-66.4) 51.7 (40.6-65.9)	
			1 mo after 3rd dose	3 mo (N=≥30) 4-5 mo (N=≥23) 6-8 mo (N=≥26))	97.1 (77.2-123.6) 115.4 (89.1-149.4) 118.9 (97.0-145.8)		69.6 (56.8 (85.3) 77.4 (62.6-95.7) 77.3 (64.0-93.2)	

			Before booster	3 mo (N=≥30) 4-5 mo (N=≥23) 6-8 mo (N=≥26)	20.5 (15.3-27.5) 21.3 (15.7-29.1) 21.1 (15.1-29.5)	11.5 (9.1-14.4) 13.1 (10.0-17.2) 15.5 (11.4-21.0)
			1 mo after booster	3 mo (N=≥30) 4-5 mo (N=≥23) 6-8 mo (N=≥26)	116.4 (88.5-152.9) 165.7 (116.8-235.0) 182.5 (140.7-236.6)	51.6 (40.8-64.2) 70.4 (54.3-91.3) 90.1 (68.8-118.0)
		Children with positive pre-immunization titers			**GMT (EU/ml) (95%-CI)**	
			Baseline	3-8 months (N=≥25) 9-23months (N=≥11)	10.2 (7.9-13.1) 12.5 (8.7-18.1)	5.3 (3.8-7.5) 2.3 (1.0-5.2)
			Before 3rd dose	3-8 months (N=≥25) 9-23months (N=≥11)	63.0 (54.5-72.8) 150.5 (90.9-249.2)	56.6 (47.3-67.9) 48.7 (27.5-86.2)
			1 mo after 3rd dose	3-8 months (N=≥25) 9-23months (N=≥11)	108.7 (88.9-132.8) 223.6 (150.6-332.0)	77.5 (65.2-91.9) 107.5 (64.3-197.6)
			Before booster	3-8 months (N=≥25) 9-23months (N=≥11)	24.6 (18.1-33.3) 34.5 (20.7-57.5)	18.7 (13.8-25.3) 16.6 (9.3-29.5)
			1 mo after booster	3-8 months (N=≥25) 9-23months (N=≥11)	162.1 (127.5-206.0) 242.6 (174.1-337.3)	62.7 (50.3-78.3) 149.4 (65.3-341.9)
Data for agglutination titers => not per protocol						

Tables 5b-B: Additional studies - Primary vaccination, schedule impact on immunogenicity

Publication and country	Design Risk of Bias	Vaccines, schedules evaluated	Timing of assessment	Comparison groups	Proportion seroconverted) (>4-fold rise)	GMT (95%-CI) post-vaccination
2,3,4 vs 2,4,6 mo					**PT neutralizing titers (CHO)**	
Simodon, 1999 Senegal	RCT Unclear to moderate risk	**Pasteur Mérieux (2c)** 2,3,4 mo vs. 2,4,6 mo	One month post 3rd dose	Group 1 : 2,3,4 mo (N=47) Group 2 : 2,4,6 mo (N=47)	96% 97.9%	42.9 (36.7 – 50.1) 73.2 (61.5 – 87.1)
Not per-protocol: PT neutralizing tites (CHO)						

Publication and country	Design Risk of Bias	Vaccines, schedules evaluated	Timing of assessment	Comparison groups	GMT (range) post-vaccination
2 vs. 3 doses					**PT neutralizing titers (CHO)**
Blennow, 1989 Sweden	RCT (see Blennow, Pediatrics 1988)	**JNIH (2c)** 2 doses (6-7; 7-8 or 6-8 mo) vs. 3 doses (6-7-8 mo) Both groups with booster at age 2 yrs	Before booster	Group 1 : 2 doses (N=102) Group 2 : 3 doses (N=109)	24 (<2 – 512) 25 (<2 – 256)
			2 weeks after booster	Group 1 : 2 doses (N=97) Group 2 : 3 doses (N=108)	586 (64 – 16384) 597 (64 – 4096)
Not per-protocol: PT neutralizing tites (CHO), children without immune response after primary vaccination were excluded					

2 vs. 3 doses					**Proportion (%) with titer ≥ 4 (≥32; ≥256)** of PT-neutralising antibody	**GMT (U/ml)** of PT-neutralising antibody
Carlson, 1998 Sweden	RCT Low risk	Pasteur Mérieux (2c) 3,5 +12 mo vs. 2,4,6 +13 mo	1 mo after primary vaccination (2 or 3 doses)	Group 1: 2 primary doses (N=35) Group 2: 3 primary doses (N=41)	100 (74; 0) 100 (95; 4.9)	38.2 53.1
			7 mo after primary vaccination	Group 1: 2 primary doses (N=35) Group 2: 3 primary doses (N=41)	63 (20; 2.9) 98 (24; 2.4)	9.4 12.4
			1 mo post booster	Group 1: 2 primary doses (N=35) Group 2: 3 primary doses (N=41)	100 (100; 86) 100 (100; 46)	271.7 164.9
Not per protocol: PT-neutralizing antibody (CHO assay)						

3,5,7 vs 2,4,6 mo					GMT (95% CI) of agglutinogens
Kamiya, 1992 Japan	Cohort Moderate risk	**Takeda (4c)** 3,5,7+19 vs. 2,4,6+20 mo	2 months post 2nd dose	Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	23.1 (19.1 – 28.0) 24.8 (18.0 – 34.3)
			1 month post 3rd dose	Group 1: 3,5,7 mo (N=73) Group 2: 2,4,6 mo (N=43)	44.4 (35.9 – 54.9) 35.4 (24.6 – 51.1)
			12 months post 3rd dose (age 19 or 18 mo)	Group 1: 3,5,7 mo (N=75) Group 2: 2,4,6 mo (N=42)	10.3 (8.5 – 12.5) 10.0 (7.4 – 13.5)
			1 month post booster (age 20 or 19 mo)	Group 1: 3,5,7 mo (N=74) Group 2: 2,4,6 mo (N=42)	74.9 (61.9 – 90.7) 64.5 (46.4 – 89.7)
Not per protocol: microagglutination assay for agglutinating antibodies; IgG anti-LPF					

Table 5c-A: Included studies on primary vaccination, schedule impact on reactogenicity

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Details	Comparison groups	Risk (%)	Relative Risk
Various schedules							
Rectal T°≥38.0°C							
Miller, 1997 UK	Cohort analysis of two trials Moderate to high risk	**Porton (3c)** 2,3,4 mo vs. 3,5,9 mo	Within 24h, any dose	Rectal T°≥100.4°F Rectal T°≥38.0°C	Group 1: 2,3,4 mo (N=278) Group 2: 3,5,9 mo (N=262)	5.3 3.0	1.77
		Mérieux (2d) 2,3,4 mo vs. 3,5,9 mo	Within 24h, any dose	Rectal T°≥100.4°F Rectal T°≥38.0°C	Group 1: 2,3,4 mo (N=216) Group 2: 3,5,9 mo (N=263)	3.1 3.5	0.89
Giammanco 1998 Italy	Cohort study Unclear or moderate risk	2,3,6 vs. 3,5,11 mo	Within 8 days, any dose	Rectal T°≥38.0°C	Group 1: 2,4,6 mo (N=172) Group 2: 3,5,11 mo (N=196)	8.5 9.0 Per dose	0.94
Li, 2011(I) China	RCT Unclear or low risk	**Sanofi Pasteur (2c)** 2,3,4 mo vs. 3,4,5 mo	Within 7 days, any dose	Axillary T°≥37.1°C	Group 1: 2,3,4 mo (N=777) Group 2: 3,4,5 mo (N=721)	28.7 32.3	0.89
Li, 2011 (II) China	RCT Unclear or low risk	**Sanofi Pasteur (2c)** DTaP booster given at 18-20 mo, by primary groups	Within 7 days, any dose	Axillary T°≥37.1°C	Group 1: 2,3,4 mo (N=251) Group 2: 3,4,5 mo (N=233)	32.7 37.8	0.87

Carlson, 1998 Sweden	RCT Moderate risk	**Pasteur Mérieux (2c)** 3,5 +12 mo vs. 2,4,6 +13 mo	Within 3 days After first vaccination	Rectal T°≥38.0°C	Group 1: age 3 mo (N=113) Group 2: age 2 mo (N=118)	9.7 3.4	2.85
			After second vaccination		Group 1: 3,5 mo (N=112) Group 2: 2,4 mo (N=117)	15.2 12.0	1.27
			After booster		Group 1: 2 primary doses (N=112) Group 2: 3 primary doses (N=116)	29.3 25.0	1.17
Taranger 2000 Sweden	Cohort, unclear or moderate risk	3-5 +12 vs. 2-4-6 +15 mo	Within 24 h after last primary vaccination (6 and 7 mo)	Rectal T°≥38.0°C	Group 1: 3,5 mo (N=103) Group 2: 2,4,6 mo (N = 116)	23 26	0.88
			Within 24 h post booster (12 and 15 mo)		Group 1: 3,5 mo (N=102) Group 2: 2,4,6 mo (N = 115)	35 25	1.4
Hoppenbrouwers, 1999 Belgium and Turkey	RCT Low risk	**Pasteur Mérieux (2c)** 3,4,5 vs 2,4,6 mo	Within 72h, post 1st dose	Rectal T°≥38.0°C	Group 1: 3,4,5 mo (N=49/78) Group 2: 2,4,6 mo (N=54/77) Belgium/Turkey	18.4/5.1 18.5/9.1	0.99/0.56
			Within 72h, post 2st dose		Group 1: 3,4,5 mo (N=49/78) Group 2: 2,4,6 mo (N=53/76) Belgium/Turkey	12.2/5.1 9.4/10.5	1.30/0.49
			Within 72h, post 3st dose		Group 1: 3,4,5 mo (N=49/76) Group 2: 2,4,6 mo (N=53/76) Belgium/Turkey	8.2/6.6 18.9/6.6	0.43/1
Kamiya, 1992 Japan	Cohort Moderate risk	**Takeda (4c)** 3,5,7+19 vs. 2,4,6+20 mo	Within 24 h post 1st dose	Axillary T°≥37.5°C	Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	7.7 11.6	0.66
			Within 24 h post 2nd dose		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	5.1 7.0	0.73

			Within 24 h post 3rd dose		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	4.0 11.6	0.34
			Within 24 h post booster		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	4.1 4.8	0.85
Erythema / redness ≥2.5cm							
Miller, 1997 UK	Cohort analysis of two trials Moderate to high risk	**Porton (3c)** 2,3,4 mo vs. 3,5,9 mo	Within 24h, any dose		Group 1: 2,3,4 mo (N=278) Group 2: 3,5,9 mo (N=262)	5.0 20.9	0.24
		Mérieux (2d) 2,3,4 mo vs. 3,5,9 mo	Within 24h, any dose		Group 1: 2,3,4 mo (N=216) Group 2: 3,5,9 mo (N=263)	2.3 11.1	0.21
Giammanco 1998 **Italy**	Cohort study Unclear or moderate risk	2,3,6 vs. 3,5,11 mo	Within 8 days, any dose	Erythema > 2 cm	Group 1: 2,4,6 mo (N=172) Group 2: 3,5,11 mo (N=196)	0.5 1.3 Per dose	0.38
Li, 2011(I) China	RCT Unclear or low risk	**Sanofi Pasteur (2c)** 2,3,4 mo vs. 3,4,5 mo	Within 7 days, any dose	Erythema >3cm	Group 1: 2,3,4 mo (N=777) Group 2: 3,4,5 mo (N=721)	0.4 1.0	0.40
Li, 2011 (II) China	RCT Unclear or low risk	**Sanofi Pasteur (2c)** DTaP booster given at 18-20 mo, by primary groups	Within 7 days, any dose	Erythema >3cm	Group 1: 2,3,4 mo (N=251) Group 2: 3,4,5 mo (N=233)	8.8 6.9	1.28
Carlson, 1998 Sweden	RCT Moderate risk	**Pasteur Mérieux (2c)** 3,5 +12 mo vs. 2,4,6 +13 mo	Within 3 days After first vaccination	Redness ≥2 cm	Group 1: age 3 mo (N=113) Group 2: age 2 mo (N=118)	0.9 0.8	1.13

			After second vaccination		Group 1: 3,5 mo (N=112) Group 2: 2,4 mo (N=117)	4.5 0.9	5.0
			After booster		Group 1: 2 primary doses (N=112) Group 2: 3 primary doses (N=116)	13.4 9.5	1.41
Taranger 2000 Sweden	Cohort, unclear or moderate risk	3-5 +12 vs. 2-4-6 +15 mo	Within 24 h after last primary vaccination (6 and 7 mo)	Redness ≥2 cm	Group 1: 3,5 mo (N=103) Group 2: 2,4,6 mo (N = 116)	15 20	0.75
			Within 24 h post booster (12 and 15 mo)		Group 1: 3,5 mo (N=102) Group 2: 2,4,6 mo (N = 115)	41 26	1.58
Kamiya, 1992 Japan	Cohort Moderate risk	**Takeda (4c)** 3,5,7+19 vs. 2,4,6+20 mo	Within 24 h post 1st dose	Any redness	Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	20.5 23.3	0.88
			Within 24 h post 2nd dose		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	29.5 41.9	0.70
			Within 24 h post 3rd dose		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	42.7 65.1	0.66
			Within 24 h post booster		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	48.7 56.1	0.87
Local swelling ≥2.5cm							
Miller, 1997 UK	Cohort analysis of two trials Moderate to high risk	**Porton (3c)** 2,3,4 mo vs. 3,5,9 mo	Within 24h, any dose		Group 1: 2,3,4 mo (N=278) Group 2: 3,5,9 mo (N=262)	2.3 18.7	0.16

		Mérieux (2d) 2,3,4 mo vs. 3,5,9 mo	Within 24h, any dose		Group 1: 2,3,4 mo (N=216) Group 2: 3,5,9 mo (N=263)	0.8 7.4	0.11
Giammanco 1998 Italy	Cohort study Unclear or moderate risk	2,3,6 vs. 3,5,11 mo	Within 8 days, any dose	Swelling > 2 cm	Group 1: 2,4,6 mo (N=172) Group 2: 3,5,11 mo (N=196)	0.3 1.5 Per dose	0.2
Li, 2011(I) China	RCT Unclear or low risk	**Sanofi Pasteur (2c)** 2,3,4 mo vs. 3,4,5 mo	Within 7 days, any dose	Swelling >3cm	Group 1: 2,3,4 mo (N=777) Group 2: 3,4,5 mo (N=721)	0.9 0.1	9.00
Li, 2011 (II) China	RCT Unclear or low risk	**Sanofi Pasteur (2c)** DTaP booster given at 18-20 mo, by primary groups	Within 7 days, any dose	Swelling >3cm	Group 1: 2,3,4 mo (N=251) Group 2: 3,4,5 mo (N=233)	6.8 6.0	1.13
Carlson, 1998 Sweden	RCT Moderate risk	**Pasteur Mérieux (2c)** 3,5 +12 mo vs. 2,4,6 +13 mo	Within 3 days After first vaccination	Swelling ≥2 cm	Group 1: age 3 mo (N=113) Group 2: age 2 mo (N=118)	1.8 3.4	0.53
			After second vaccination		Group 1: 3,5 mo (N=112) Group 2: 2,4 mo (N=117)	8.6 3.6	0.42
			After booster		Group 1: 2 primary doses (N=112) Group 2: 3 primary doses (N=116)	12.5 10.3	1.21
Taranger 2000 Sweden	Cohort, unclear or moderate risk	3-5 +12 vs. 2-4-6 +15 mo	Within 24 h after last primary vaccination (6 and 7 mo)	Swelling ≥2 cm	Group 1: 3,5 mo (N=103) Group 2: 2,4,6 mo (N = 116)	11 17	0.65

			Within 24 h post booster (12 and 15 mo)		Group 1: 3,5 mo (N=102) Group 2: 2,4,6 mo (N = 115)	30 21	1.43
Kamiya, 1992 Japan	Cohort Moderate risk	**Takeda (4c)** 3,5,7+19 vs. 2,4,6+20 mo	Within 24 h post 1st dose	Any swelling	Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	6.4 9.3	0.69
			Within 24 h post 2nd dose		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	19.2 20.9	0.92
			Within 24 h post 3rd dose		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	33.3 37.2	0.90
			Within 24 h post booster		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	43.2 46.3	0.93
Tenderness/pain							
Li, 2011(I) China	RCT Unclear or low risk	**Sanofi Pasteur (2c)** 2,3,4 mo vs. 3,4,5 mo	Within 7 days, any dose	Any degree of tenderness	Group 1: 2,3,4 mo (N=777) Group 2: 3,4,5 mo (N=721)	26.4 25.0	1.06
Li, 2011 (II) China	RCT Unclear or low risk	**Sanofi Pasteur (2c)** DTaP booster given at 18-20 mo, by primary groups	Within 7 days, any dose	Any degree of tenderness	Group 1: 2,3,4 mo (N=251) Group 2: 3,4,5 mo (N=233)	0.0 0.0	-
Kamiya, 1992 Japan	Cohort Moderate risk	**Takeda (4c)** 3,5,7+19 vs. 2,4,6+20 mo	Within 24 h post 1st dose	Any degree of tenderness	Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	0.0 4.7	- ∞
			Within 24 h post 2nd dose		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	1.3 9.3	0.14

			Within 24 h post 3rd dose		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	1.3 9.3	0.14
			Within 24 h post booster		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	15.1 10.0	1.51
Giammanco 1998 **Italy**	Cohort study Unclear or moderate risk	2,3,6 vs. 3,5,11 mo	Within 8 days, any dose	Any degree of tenderness	Group 1: 2,4,6 mo (N=172) Group 2: 3,5,11 mo (N=196)	9.8 10.7 Per dose	0.92
Any systemic symptoms							
Miller, 1997 UK	Cohort analysis of two trials Moderate to high risk	**Porton (3c)** 2,3,4 mo vs. 3,5,9 mo	Within 24h, any dose	≥3 systemic symptoms	Group 1: 2,3,4 mo (N=278) Group 2: 3,5,9 mo (N=262)	14.5 9.0	0.80
		Mérieux (2d) 2,3,4 mo vs. 3,5,9 mo	Within 24h, any dose		Group 1: 2,3,4 mo (N=216) Group 2: 3,5,9 mo (N=263)	12.5 16.2	0.77
Li, 2011(I) China	RCT Unclear or low risk	**Sanofi Pasteur (2c)** 2,3,4 mo vs. 3,4,5 mo	Within 7 days, any dose	Any systemic reaction	Group 1: 2,3,4 mo (N=777) Group 2: 3,4,5 mo (N=721)	52.6 51.2	1.03
Li, 2011 (II) China	RCT Unclear or low risk	**Sanofi Pasteur (2c)** DTaP booster given at 18-20 mo, by primary groups	Within 7 days, any dose	Any systemic reaction	Group 1: 2,3,4 mo (N=251) Group 2: 3,4,5 mo (N=233)	1.2 1.7	0.71
Hoppenbrouwers, 1999 Belgium and Turkey	RCT Low risk	**Pasteur Mérieux (2c)** 3,4,5 vs 2,4,6 mo	Within 72h, post 1st dose	Any systemic reaction	Group 1: 3,4,5 mo (N=49/78) Group 2: 2,4,6 mo (N=54/77) Belgium/Turkey	46.9/12.8 61.1/18.2	0.77/0.70

			Within 72h, post 2st dose		Group 1: 3,4,5 mo (N=49/78) Group 2: 2,4,6 mo (N=53/76) Belgium/Turkey	24.5/11.5 30.2/14.5	0.81/0.79
			Within 72h, post 3st dose		Group 1: 3,4,5 mo (N=49/76) Group 2: 2,4,6 mo (N=53/76) Belgium/Turkey	10.2/10.5 26.4/7.9	0.39/1.33
Kamiya, 1992 Japan	Cohort Moderate risk	**Takeda (4c)** 3,5,7+19 vs. 2,4,6+20 mo	Within 24 h post 1st dose	Any systemic reaction	Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	32.1 44.2	0.73
			Within 24 h post 2nd dose		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	26.9 30.2	0.89
			Within 24 h post 3rd dose		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	21.3 20.9	1.02
			Within 24 h post booster		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	19.2 26.2	0.73
Persistent crying							
Li, 2011(I) China	RCT Unclear or low risk	**Sanofi Pasteur (2c)** 2,3,4 mo vs. 3,4,5 mo	Within 7 days, any dose	>3h	Group 1: 2,3,4 mo (N=777) Group 2: 3,4,5 mo (N=721)	0.4 0.0	∞
Giammanco 1998 **Italy**	Cohort study Unclear or moderate risk	2,3,6 vs. 3,5,11 mo	Within 8 days, any dose	Unusual crying > 3h	Group 1: 2,4,6 mo (N=172) Group 2: 3,5,11 mo (N=196)	14.1 10.5 Per dose	1.34
Irritability							
Li, 2011(I) China	RCT Unclear or low risk	**Sanofi Pasteur (2c)** 2,3,4 mo vs. 3,4,5 mo	Within 7 days, any dose	Any degree	Group 1: 2,3,4 mo (N=777) Group 2: 3,4,5 mo (N=721)	0.5 0.1	5.00

Li, 2011 (II) China	RCT Unclear or low risk	**Sanofi Pasteur (2c)** DTaP booster given at 18-20 mo, by primary groups	Within 7 days, any dose	Any degree	Group 1: 2,3,4 mo (N=251) Group 2: 3,4,5 mo (N=233)	0.4 0.0	∞
Hoppenbrouwers, 1999 Belgium and Turkey	RCT Low risk	**Pasteur Mérieux (2c)** 3,4,5 vs 2,4,6 mo	Within 72h, post 1st dose		Group 1: 3,4,5 mo (N=49/78) Group 2: 2,4,6 mo (N=54/77) Belgium/Turkey	24.5/6.4 38.9/9.1	0.63/0.70
			Within 72h, post 2st dose		Group 1: 3,4,5 mo (N=49/78) Group 2: 2,4,6 mo (N=53/76) Belgium/Turkey	14.3/5.1 17.0/7.9	2.80/0.65
			Within 72h, post 3st dose		Group 1: 3,4,5 mo (N=49/76) Group 2: 2,4,6 mo (N=53/76) Belgium/Turkey	6.1/5.3 7.5/1.3	0.81/4.08
Kamiya, 1992 Japan	Cohort Moderate risk	**Takeda (4c)** 3,5,7+19 vs. 2,4,6+20 mo	Within 24 h post 1st dose	Fretfulness	Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	10.3 18.6	0.55
			Within 24 h post 2nd dose		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	14.1 9.3	1.52
			Within 24 h post 3rd dose		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	10.7 14.0	0.76
			Within 24 h post booster		Group 1: 3,5,7 mo (N=78) Group 2: 2,4,6 mo (N=43)	9.6 14.3	0.67

Table 6a-A: Included studies on primary vaccination, absolute vaccine effectiveness/efficacy

Publication and country	Design Risk of bias	Vaccine, Schedule used	Timing of assessment	Comparison groups				
Old WHO definition: ≥21 days of paroxysmal cough with evidence of *B. pertussis* infection (culture, serology)					**N Cases**	**Denominator**	**Rate**	**VE % (95%-CI)**
Gustafsson, 1996 Sweden	RCT Low risk	**SKB (2c)** 2, 4, 6 mo	From day of 3rd doses	Group 1:DTaP Group 3: DT	159 371	4946.4 4786.2 person- yrs	32 78 (per 100 p-mo)	58.9 (50.9 – 65.9)
		Connaught (5c)		Group 2:DTaP Group 3: DT	59 371	5083.4 4786.2 person- yrs	1.2 7.8	85.2 (80.6 – 88.8)
		SKB (2c)	From day of 1st dose	Group 1:DTaP Group 3: DT	165 385	5756.5 5603.1 person- yrs	2.9 7.8	58.8 (50.5 – 65.7)
		Connaught (5c)		Group 2:DTaP Group 3: DT	65 385	5916.5 5603.1 person- yrs	1.1 7.8	84.3 (79.6 – 88.0)
Note: Serological confirmation: two-fold increase of IgG anti-PT of anti-FHA								
Greco, 1996 Italy	RCT Low risk	**SKB (3c)** 2, 4, 6 mo	From 30 days post 3rd dose	Group 1: DTaP Group 3: DT	37 74	2,354,321 758,646 person-days	0.56 3.5 (per 100 p-yrs)	83.9 (75.8 – 89.4)
		Chiron (3c)		Group 2: DTaP Group 3: DT	36 74	2,342,952 758,646 person-days	0.55 3.5	84.2 (76.2 – 89.7)

		SKB (3c)	From day of 1st dose	Group 1: DTaP Group 3: DT	46 81	3,099,438 1,010,145	0.54 2.9	81.5 (73.1 – 87.4)
		Chiron (3c)		Group 2: DTaP Group 3: DT	41 81	3,089,325 1,010,145	0.48 2.9	83.5 (75.6 – 88.9)
Salmaso, 1998 Italy	Cohort (unblinded after RCT) Moderate risk	**SKB (3c)** 2, 4, 6 mo	Age 24-33 mo	Group 1: DTaP Group 3: DT	36 29			77.7 (62.3 – 86.7)
		Chiron (3c)		Group 1: DTaP Group 3: DT	18 29			88.8 (79.1 – 94.1)
Salmaso, 2001 Italy	Cohort (unblinded after RCT) Moderate risk	**SKB (3c)** 2, 4, 6 mo	Age ca. 2.8 – 3.8 mo	Group 1: DTaP Group 3: DT				83 (48 – 93)
		Chiron (3c)	Age ca. 2.8 – 3.8 mo	Group 1: DTaP Group 3: DT				81 (46 – 93)
			Age ca. 3.9 - 4.8 mo	Group 1: DTaP Group 3: DT				87 (65 – 95)
			Age ca. 3.9 - 4.8 mo	Group 1: DTaP Group 3: DT				89 (69 – 96)
					Cases (%)	**Total (%)**	**VE % (95%-CI)**	
Simodon, 1997 Senegal	HH contact cohort Moderate to high risk	**Pasteur Mérieux (2c)** 2, 4, 6 mo	Surveillance in population during up to 4 years, HH contacts	Group 1: DTaP Group 2: no vaccination	24 8	197 17	74 (51 – 86)	
Note: Serological confirmation: two-fold increase of IgG anti-PT of anti-FHA			RR from proportional hazard model	Group 1: DTaP Group 2: no vaccination			79 (58 – 89)	

					N Cases	Rate per 100 p-yrs	VE % (95%-CI)
Stehr, 1998 Germany	Cohort Moderate risk	**Wyeth (4c)** 3, 4.5-6, 15-18 mo	Surveillance from 6 mo of age during up to 3 years	Group 1: DTaP Group 2: DT	45 91	0.5 3.0	83 (76 – 88)
Note: Definition modified for translation of term "paroxysmal"; serological confirmation: significant increase of IgG or IgA concentrations against anti-PT, anti-FHA or anti-Fim							
Liese, 1997 Germany	Case control Moderate risk	**Pasteur Mérieux Connaught (2c)** 2, 4, 6 mo	Children aged <2 years	Group 1: DTaP Group 2: no aP vaccination		Adjusted VE	93 (63 – 99)
Schmitt, 1996 Germany	HH contact cohort Moderate risk	**SKB (2c)** 3,4,5 mo	Not detailed, probably <4 yrs	Group 1: 3 doses of DTaP Group 2: 0 doses of aP			88.7 (76.6 – 94.6)
Storsaeter, 1990 Sweden (with Anon. 1988)	RCT Low risk	**JNIH-6 (2c) and JNIH-7 (1c)** 2 doses d0 – m2-3 @ 5-11mo	30 days post 2nd dose Follow-up over 17-19mo post 1st dose	Group 1: *NA* Group 2: JNIH-7 (N=1403) Group 3: Placebo (923)	8 34	Cumul. incidence 0.0064 0.0381	83 (63 – 92)
Storsaeter 1992 Sweden (with Anon. 1988)	RCT Household study Low risk	**JNIH-7 (1c) and JNIH-6 (2c)** 3 d (2-mo interval, starting 6-11 mo)	Overall follow-up from 1 mo after 2nd dose during mean 16 mo	Group 1: JNIH-7 (N=26) Group 2: placebo (N=16)	3 9		79 (32 – 95)

				Group 1: JNIH--(N=19) Group 2: placebo (N=16)	5 3		53 (-23 – 83)
Trollfors, 1995 Sweden	RCT Low risk	**Amvax (1c)** 3,5,12 mo	Follow-up to age 30 mo 30 days post 3rd dose	Group 1: DTaP (N=1724) Group 2: DT (N=1726)	72 240		71 (63 – 78)
			30 days post 2nd dose to 30 days post 3rd dose	Group 1: DTaP (N=1724) Group 2: DT (N=1726)	14 31		55 (12 – 78)
Trollfors 1997, Sweden	RCT, cases after HH contact Low risk	**Amvax (1c)** 3,5,12 mo	30 days post 3rd dose	Group 1: DTaP (N=82) Group 2: DT (N=60)	19 52		73 (61 – 83)
			30 days post 2nd dose	Group 1: DTaP (N=21) Group 2: DT (N=25)	2 11		78 (29 – 96)
Taranger, 1997 Sweden	Cohort after RCT unblinding	**Amvax (1c)** 3,5,12 mo	Follow-up from age 30 to age 36 mo	Group 1: DTaP (N=1724) Group 2: DT (N=1726)	29 110		77 (65 – 85)

Publication and country	Design Risk of bias	Schedule used	Timing of assessment	Comparison groups	N Cases	Person-days	VE % (95%-CI)
2010 WHO definition: ≥14 days of paroxysmal cough with evidence of *B. pertussis* infection (culture, serology, PCR)							
Greco, 1996 Italy	RCT Low risk	**SKB (3c)** 2, 4, 6 mo	30 days post 3rd dose	Group 1: DTaP Group 3: DT	55 82	2,354,321 758,646	78.4 (69.2 – 84.9)
		Chiron (3c)		Group 2: DTaP Group 3: DT	49 82	2,342,952 758,646	80.6 (72.1 – 86.7)
Storsaeter 1992 Sweden (with Anon. 1988)	RCT Household study Low risk	**JNIH-7 (1c) and JNIH-6 (2c)** 3 d (2-mo interval, starting 6-11 mo)	Overall follow-up from 1 mo after 2nd dose during mean 16 mo	Group 1: JNIH-7 (N=26) Group 2: placebo (N=16)	3 13		86 (60 – 95)
				Group 1: JNIH-6 (N=19) Group 2: placebo (N=16)	6 13		61 (19 – 78)

Publication and country	Design Risk of bias	Vaccine, Schedule used	Timing of assessment	Comparison groups	Vaccination status		
CDC definition of confirmed case or of clinical case with laboratory confirmation					**Cases (%)**	**Controls (%)**	**VE % (95%-CI)**
Bisgard, 2005 USA	Case-control study (matching for age and residence) Moderate risk	**4 different types of aP vaccines (1-4c)** 2,4,6 mo (+12-18 mo)	Age 6-59 months	Reference: 0 dose Exposure : 3 doses DTaP	not reported 34 (72)	not reported 210 (71)	95.4 (88.7 – 98.2)
				Reference: 0 dose Exposure : 4 doses DTaP	not reported 20 (32)	not reported 126 (25)	96.7 (90.8 – 98.8)

Publication and country	Design Risk of bias	Vaccine, Schedule used	Timing of assessment	Comparison groups	N Cases	Cumulative incidence (%)	VE % (95%-CI)
CDC definition of confirmed case (culture plus any cough)							
Anon., 1988 Sweden	RCT Low risk	**JNIH-6 (2c) and JNIH-7 (1c)** 2 doses d0 – m2-3 @ 5-11mo	30 days post 2nd dose Follow-up over 17-19mo post 1st dose	Group 1: JNIH-6 (N=1419) Group 2: JNIH-7 (N=1428) Group 3: Placebo (954)	18 27 40	1.4 2.0 4.5	69 (47 – 82) 54 (26 – 72)
Storsaeter 1992 Sweden (with Anon. 1988)	RCT Household study Low risk	**JNIH-7 (1c) and JNIH-6 (2c)** 3 d (2-mo interval, starting 6-11 mo)	Overall follow-up from 1 mo after 2nd dose during mean 16 mo	Group 1: JNIH-7 (N=26) Group 2: placebo (N=16)	7 13		67 (32-80)
				Group 1: JNIH-6 (N=19) Group 2: placebo (N=16)	10 13		35 (-14 – 57)

Tables 6a-B: Additional studies - Primary vaccination, absolute vaccine effectiveness/efficacy

Publication and country	Design Risk of bias	Vaccine, Schedule used	Comparison groups	Alternative case definitions	Analysis	VE % (95%-CI)
Simodon, 1997 Senegal	Household contact cohort High risk	**Pasteur Mérieux (2c)** 2, 4, 6 months	Group 1: DTaP Group 2: no vaccination	Old WHO definition with PCR diagnostic of epilink	Case-contact analysis	85 (66 – 93)
				≥21 days of cough with evidence of *B. pertussis* infection (culture, serology)	Case-contact analysis	31 (7 – 49)
				≥21 days of cough with evidence of *B. pertussis* infection (culture, serology)	RR from proportional hazard model	48 (18 – 66)
				≥21 days of cough with evidence of *B. pertussis* infection (culture, serology) with PCR diagnostic of epi link	Case-contact analysis	53 (23 – 71)
Not per protocol: Case definition no allowing grouping with other studies Note: Serological confirmation: two-fold increase of IgG anti-PT of anti-FHA						

Publication and country	Design Risk of bias	Vaccine, Schedule used	Timing of assessment	Comparison groups	Alternative case definitions	VE % (95%-CI)
Trollfors, 1988 Sweden	RCT Low risk	**Amvax (1c)** 3,5,12 mo	Follow-up to age 30 mo, 30 days post 3rd dose	Group 1: DTaP (N=1724) Group 2: DT (N=1726)	Göteborg definition of confirmed case (1 major, 2 minor criteria)	
					≥21 days of paroxysmal cough	77 (69 – 83)
					≥21 days of cough	69 (60 – 77)
					≥7 days of cough	62 (51 – 70)

Trollfors 1997, Sweden	RCT, cases after HH contact Low risk	**Amvax (1c)** 3,5,12 mo	30 days post 3rd dose	Group 1: DTaP (N=82) Group 2: DT (N=60)	≥7 days of cough	51 (38 – 63)
			30 days post 2nd dose	Group 1: DTaP (N=21) Group 2: DT (N=25)		8 (-65 – 52)
Taranger, 1997 Sweden	Cohort after RCT unblinding	**Amvax (1c)** 3,5,12 mo	Follow-up from age 30 to age 36 mo	Group 1: DTaP (N=1724) Group 2: DT (N=1726)	≥21 days of paroxysmal cough	80 (69 – 87)
					≥21 days of cough	76 (64 – 85)
					≥7 days of cough	73 (60 – 82)
Not per protocol: Case definition no allowing grouping with other studies Note: Serological confirmation: convalescence sample IgG anti-PT of anti-FHA ≥6000						

Publication and country	**Design Risk of bias**	**Schedule use**	**Timing of assessment**	**Comparison groups**	**N Cases**	**Rate per 100 p-yrs**	**VE % (95%-CI)**
Stehr, 1998 Germany	Cohort, Moderate risk	**Wyeth (4c)** 3, 4.5-6, 15-18 mo	Surveillance from 6 mo of age during up to 3 years				
≥14 days of paroxysmal cough, due to *B. pertussis* or *B. parapertussis* Note: Serological confirmation: significant increase of IgG or IgA concentrations against any of the four pertussis antigens				Group 1: DTaP Group 2: DT	65 104	0.7 3.5	79 (71 – 84)
≥7 days of paroxysmal cough (mild or typical pertussis), due to *B. pertussis* (excluding *B. parapertussis*) Note: Serological confirmation: significant increase of IgG or IgA concentrations against anti-PT				Group 1: DTaP Group 2: DT	85 103	1.0 3.4	72 (62 – 79)
≥7 days of paroxysmal cough (mild or typical pertussis), due to *B. pertussis* or *B. parapertussis* Note: Serological confirmation: significant increase of IgG or IgA concentrations against any of the four pertussis antigens				Group 1: DTaP Group 2: DT	139 130	1.6 4.4	63 (53 – 71)

Publication and country	Design Risk of bias	Vaccine, Schedule used	Timing of assessment	Comparison groups			VE % (95% CI)
≥21 days of cough with culture confirmation of *B. pertussis* infection (culture, serology) or epi-link with laboratory-confirmed household case							
Liese, 1997 Germany	Case control Moderate risk	**Pasteur Mérieux Connaught (2c)** 2, 4, 6 mo	Children aged <2 years	Group 1: DTaP Group 2: no aP vaccination		Adjusted VE	80 (63 – 89)

Publication and country	Design Risk of bias	Vaccine, Schedule used	Timing of assessment	Comparison groups	VE (%) (95%-CI)
Laboratory confirmed epi-link, clinically suspected cases with ⩾21 days of spasmodic cough					
Schmitt, 1996 Germany	HH contact cohort Moderate risk	**SKB (2c)** 3,4,5 mo	Not detailed, probably <4 yrs	Group 1: 3 doses of DTaP Group 2: 0 doses of aP	82.7 (70.8 – 89.7)

Publication and country	Design Risk of bias	Vaccine, Schedule used	Timing of assessment	Comparison groups	N Cases	VE (%) (95%-CI)
Laboratory confirmed (culture, serological), irrespective of symptoms						
Campbell, 2012 UK	Screening method High risk	**?, (5c)** 2,3,4 mo Booster given exceptionally	Age 12-39 mo	≥3 doses vs. 0 doses aP	19 cases, of which 11 were vaccinated	96.6 (90.2 – 98.7)

Publication and country	Design Risk of bias	Vaccine, Schedule used	Timing of assessment	Comparison groups		
Laboratory confirmed (culture, serological), with cough of various duration						
Salmaso, 1998 Italy	Cohort (unblinded after RCT) Moderate risk	**SKB (3c)** 2, 4, 6 mo	24-33 mo of life Cough duration >7 days	Group 1: DTaP Group 3: DT	58 35	70.2 (53.3 – 80.7)
		Chiron (3c)		Group 1: DTaP Group 3: DT	37 35	80.9 (68.8 – 88.3)
		SKB (3c)	Cough duration ≥14 days	Group 1: DTaP Group 3: DT	55 35	71.7 (55.5 – 81.8)
		Chiron (3c)		Group 1: DTaP Group 3: DT	32 35	83.5 (72.6 – 90.1)
		SKB (3c)	Cough duration ≥21 days	Group 1: DTaP Group 3: DT	48 33	73.8 (57.9 – 83.5)
		Chiron (3c)		Group 1: DTaP Group 3: DT	27 33	85.2 (74.7 – 91.5)
Laboratory confirmed (culture, serological), with cough of various duration						
Salmaso, 1998 Italy	Cohort (unblinded after RCT) Moderate risk	**SKB (3c)** 2, 4, 6 mo	Cough duration ≥7 days Age ca. 2.8 – 3.8 yr	Group 1: DTaP Group 3: DT		
		Chiron (3c)		Group 1: DTaP Group 3: DT		
		SKB (3c)	Age ca. 3.9 – 4.8 yr	Group 1: DTaP Group 3: DT		
		Chiron (3c)		Group 1: DTaP Group 3: DT		
		SKB (3c) 2, 4, 6 mo	≥14 d spasmodic or ≥14 d any cough Age ca. 2.8 – 3.8 yr	Group 1: DTaP Group 3: DT		
		Chiron (3c)		Group 1: DTaP Group 3: DT		

		SKB (3c)	Age ca. 3.9 – 4.8 yr	Group 1: DTaP Group 3: DT		
		Chiron (3c)		Group 1: DTaP Group 3: DT		

Publication and country	**Design Risk of bias**	**Vaccine, Schedule used**	**Timing of assessment**	**Comparison groups**	**Source**	**VE (%) (95%-CI)**
Notification/hospital diagnostic keys, most but not all cases with laboratory confirmation						
Hviid, 2004 Denmark	Cohort Adjusted for some variables	**aP** 3,5,12 mo	Age 0-1 yrs	1 doses vs. 0 doses aP 2 doses vs. 0 doses aP 3 doses vs. 0 doses aP	Non-hospitalisation	35 (1 – 57) 59 (34 – 75) 78 (59 – 88)
				1 doses vs. 0 doses aP 2 doses vs. 0 doses aP 3 doses vs. 0 doses aP	Hospitalisation	37 (13 – 54) 72 (52 – 83) 93 (78 – 98)

Table 6b-A: Included studies on primary vaccination, absolute immunogenicity

Publication and country	Design Risk of Bias	Vaccine, Schedule used	Timing of assessment	Comparison groups	anti-FHA	anti-PT	anti-PRN	anti-FHA	anti-PT	anti-PRN
2, 4, 6 months					**Proportion seropositive (%)**			**GMC (95%-CI) Post-vaccination (EU/ml)**		
Giuliano, 1998 Italy *[overlap with participants of Greco 1996]*	RCT Low risk	**Connaught (3c)** **SKB (3c)** 2, 4, 6 mo	1 mo after 3rd dose (age 7 mo)	Group 1: CO-DTaP (N=486)	99.4	99.8	99.8	52.6 (49.1 – 56.3)	94.3 (88.8 – 100.3)	136.6 (127.0 – 146.8)
				Group 2: SKB-DTaP (N=476)	100	98.9	99.6	146.9 (138.3 – 156.1)	51.3 (47.9 – 54.9)	274.2 (253.6 – 296.7)
				Group 3: DT (N=161)	--	--	--	1.5 (1.3 – 1.6)	1.0 (1.0 – 1.1)	1.6 (1.6 – 1.7)
			15 mo after 3rd dose (age 21 mo)	Group 1: CO-DTaP (N=403)	29.0	31.5	42.2	4.7 (4.2 – 5.4)	4.5 (4.0 – 5.0)	9.9 (8.9 – 11.1)
				Group 2: SKB-DTaP (N=389)	64.0	17.7	68.5	11.4 (10.2 – 12.8)	2.7 (2.4 – 3.0)	17.9 (16.1 – 20.1)
				Group 3: DT (N=127)	--	--	--	1.2 (1.0-1.3)	1.1 (1.0-1.2)	1.6 (1.5-1.7)
					Proportion seroconverted (%)					
Greco, 1996 Italy	RCT Low risk	**SKB (3c)** 2, 4, 6 mo	(Pre-vaccination and) 1 month (?) post 3rd dose	Group 1: DTaP	85.1	94.5	96.6	147.0 (138 – 156.2)	51.3 (47.9 – 54.9)	274.2 (253.6 – 296.7)
				Group 3: DT [N=1572 in four study groups]	--	--	--	1.5 (1.3-1.6)	1.0 (1.0-1.1)	1.6 (1.6-1.7)
		Chiron (3c)		Group 2: DTaP	60.5	96.7	95.9	52.6 (49.1 – 56.3)	94.4 (88.8 – 100.3)	136.6 (127.0 – 146.8)
				Group 3: DT [N=1572 in four study groups]	--	--	--	1.5 (1.3-1.6)	1.0 (1.0-1.1)	1.6 (1.6-1.7)

					Proportion with IgG ≥ 1 unit /ml (%)				Median IgG concentration (units/ml)			
					anti-FHA	**anti-PT**	**anti-PRN**	**anti-Fim2/3**	**anti-FHA**	**anti-PT**	**anti-PRN**	**anti-Fim2/3**
Gustafsson, 1997 Sweden	RCT Low risk	**SKB (2c) and Connaught (5c)** 2, 4, 6 mo	1 mo after 3rd dose (age 7 mo)	Group 1: DTaP 2c (N=186)	100	100	15	35	200	65	2	2.5
				Group 2: DTaP 5c (N=178)	100	100	100	100	40	50	200	400
				Group 3: DT (N=181)	48	42	15	35	<1	<1	<1	<1

Tables 6b-B: Additional studies - Primary vaccination, absolute immunogenicity

Publication and country	Design Risk of Bias	Schedule used	Timing of assessment	Comparison groups	PT-neutralizing antibody Seropositive (%)	PT-neutralizing antibody GMT (95%-CI) post-vaccination
2, 4, 6 months						
Giuliano, 1998 Italy *[overlap with participants of Greco 1996]*	RCT Low risk	**Connaught (3c)** **SKB (3c)** 2, 4, 6 mo	1 mo after 3rd dose (age 7 mo)	Group 1: CO-DTaP (N=251) Group 2: SKB-DTaP (N=239) Group 3: DT (N=81)	100 80.3 --	787.6 (718 – 863.5) 223 (203.7 – 259.7) 22.0 (20.2-23.9)
			15 mo after 3rd dose (age 21 mo)	Group 1: CO-DTaP (N=208) Group 2: SKB-DTaP (N=190) Group 3: DT (N=60)	58.2 31.1 --	148.7 (124.7 – 177.4) 67.9 (56.0 – 82.3) 21.2 (18.8-23.7)
Greco, 1996 Italy	RCT Low risk	**SKB (3c)** 2, 4, 6 mo	(Prevaccination and) 1 month (?) post 3rd dose	Group 1: DTaP Group 3: DT [N=1572 in four study groups]	67.8 --	230.0 (203.7 – 259.7) 22.0 (20.2-23.9)
		Chiron (3c)		Group 2: DTaP Group 3: DT [N=1572 in four study groups]	93.6 --	787.6 (718.2 – 863.5) 22.0 (20.2-23.9)
Not per protocol: Measurement of neutralizing antibody titre						

Table 6c-A: Included studies on primary vaccination, absolute reactogenicity

Publication and country	Design Risk of Bias	Vaccine, Schedule used	Timing of assessment	Comparison groups	N Events	Denominator	Risk (% or per N doses)	Relative Risk (95%-CI)
Temperature ≥38.0°C								
Gustafsson, 1996 **Sweden**	RCT Moderate bias	**SKB (2c) and Connaught (5c)** 2, 4, 6 mo	Within 24 hours post-dose 1	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2566 children 2587 2574 children	7.6 7.8 7.6	
			Within 24 hours post-dose 2	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2548 children 2563 2555 children	17.7 19.1 18.4	
			Within 24 hours post-dose 3	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2536 children 2549 2538 children	22.0 23.6 22.1	
			Within 24 hours after any dose	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2566 children 2587 2574 children	35.2 36.9 34.8	
Greco, 1996 Italy	RCT Low risk	**SKB (3c) and Chiron (3c)** 2, 4, 6 months	48 hours after each dose	Group 1: DTaP skb Group 2: DTaP chi Group 3: DT	983 584 151	13,761 doses 13,713 4540 doses	7.2 4.3 3.4	
							%	
Schmitt-Grohé and Überall, 1997 Germany	Cohort Moderate risk	Lederle (4c) 2-4 mo, 3.5-5.5 mo (aP also at 5-7 mo)	Within 72h post 1st dose	Group 1: DTaP (N=4064) Group 2: DT (N=1635)			7 11	

			Within 72h post 2nd dose	Group 1: DTaP (N=4041) Group 2: DT (N=1588)			13 17	
		Booster at 12-15 mo	Within 72h post booster	Group 1: DTaP (N=3809) Group 2: DT (N=1448)			28 26	
Persistent crying								
Gustafsson , 1996 Sweden ≥1h	RCT Moderate bias	**SKB (2c) and Connaught (5c)** 2, 4, 6 mo	Within 24 hours post-dose 1	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2566 children 2587 2574 children	1.6 1.7 1.6	
			Within 24 hours post-dose 2	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2548 children 2563 2555 children	3.1 2.5 2.7	
			Within 24 hours post-dose 3	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2536 children 2549 2538 children	1.0 1.2 1.0	
			Within 24 hours after any dose	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2566 children 2587 2574 children	5.4 4.9 4.9	
Greco, 1996 Italy ≥3h	RCT Low risk	**SKB (3c) and Chiron (3c)** 2, 4, 6 months	48 hours after each dose	Group 1: DTaP skb Group 1: DTaP chi Group 3: DT	6 9 --	13,761 doses 13,713 4540 doses	0.04 0.07 --	

Schmitt-Grohé and Überall, 1997 Germany	Cohort Moderate risk	Lederle (4c) 2-4 mo, 3.5-5.5 mo (aP also at 5-7 mo)	Within 72h post 1st dose	Group 1: DTaP (N=4064) Group 2: DT (N=1635)			0.2 0.2	
			Within 72h post 2nd dose	Group 1: DTaP (N=4041) Group 2: DT (N=1588)			0.2 0.4	
		Booster at 12-15 mo	Within 72h post booster	Group 1: DTaP (N=3809) Group 2: DT (N=1448)			0.2 0.3	
Seizure								
Greco, 1996 Italy	RCT Low risk	**SKB (3c) and Chiron (3c)** 2, 4, 6 months	48 hours after each dose	Group 1: DTaP skb Group 1: DTaP chi Group 3: DT	1 -- --	13,761 doses 13,713 4540 doses	0.007 -- --	
Schmitt-Grohé and Überall, 1997 Germany	Cohort Moderate risk	Lederle (4c) 2-4 mo, 3.5-5.5 mo (aP also at 5-7 mo)	Within 72h post 1st dose	Group 1: DTaP (N=4064) Group 2: DT (N=1635)			0 0	
			Within 72h post 2nd dose	Group 1: DTaP (N=4041) Group 2: DT (N=1588)			0 0	
		Booster at 12-15 mo	Within 72h post booster	Group 1: DTaP (N=3809) Group 2: DT (N=1448)			0 0	
Hypotonic, hyporesponsive episodes								
Greco, 1996 Italy	RCT Low risk	**SKB (3c) and Chiron (3c)** 2, 4, 6 months	48 hours after each dose	Group 1: DTaP skb Group 1: DTaP chi Group 3: DT	-- 1 2	13,761 doses 13,713 4540 doses	-- 0.007 0.04	

Local Pain/ Tenderness								
Gustafsson, 1996 Sweden	RCT Moderate bias	**SKB (2c) and Connaught (5c)** 2, 4, 6 mo	Within 24 hours post-dose 1	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2566 children 2587 2574 children	8.0 8.0 8.4	
			Within 24 hours post-dose 2	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2548 children 2563 2555 children	10.4 10.1 10.3	
			Within 24 hours post-dose 3	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2536 children 2549 2538 children	9.3 10.8 10.0	
			Within 24 hours after any dose	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2566 children 2587 2574 children	21.8 22.2 22.2	
Greco, 1996 Italy	RCT Low risk	**SKB (3c) and Chiron (3c)** 2, 4, 6 months	48 hours after each dose	Group 1: DTaP skb Group 1: DTaP chi Group 3: DT	628 625 202	13,761 doses 13,713 4540 doses	4.6 4.6 4.5	
Redness								
Gustafsson, 1996 Sweden Redness ⩾2 cm	RCT Moderate bias	**SKB (2c) and Connaught (5c)** 2, 4, 6 mo	Within 24 hours post-dose 1	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2566 children 2587 2574 children	0.3 0.3 0.3	
			Within 24 hours post-	Group 1: DTaP 2c Group 2: DTaP 5c		2548 children 2563	0.7 1.0	

			dose 2	Group 3: DT		2555 children	0.8	
			Within 24 hours post-dose 3	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2536 children 2549 2538 children	2.2 3.7 2.4	
			Within 24 hours after any dose	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2566 children 2587 2574 children	3.1 4.8 3.5	
Schmitt-Grohé and Überall, 1997 Germany	Cohort Moderate risk	Lederle (4c) 2-4 mo, 3.5-5.5 mo (aP also at 5-7 mo)	Within 72h post 1st dose	Group 1: DTaP (N=4064) Group 2: DT (N=1635)			2 4	
			Within 72h post 2nd dose	Group 1: DTaP (N=4041) Group 2: DT (N=1588)			3 6	
		Booster at 12-15 mo	Within 72h post booster	Group 1: DTaP (N=3809) Group 2: DT (N=1448)			10 14	
Swelling/Nodule								
Greco, 1996 Italy	RCT Low risk	**SKB (3c) and Chiron (3c)** 2, 4, 6 months	48 hours after each dose	Group 1: DTaP skb Group 1: DTaP chi Group 3: DT	1236 965 279	13,761 doses 13,713 4540 doses	9.0 7.0 6.1	
Gustafsson, 1996 Sweden Nodule ⩾2 cm	RCT Moderate bias	**SKB (2c) and Connaught (5c)** 2, 4, 6 mo	Within 24 hours post-dose 1	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2566 children 2587 2574 children	1.2 0.9 0.7	
			Within 24 hours post-dose 2	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2548 children 2563 2555 children	1.6 1.6 2.0	
			Within 24 hours post-	Group 1: DTaP 2c Group 2: DTaP 5c		2536 children 2549	4.7 6.3	

			dose 3	Group 3: DT		2538 children	3.9	
			Within 24 hours after any dose	Group 1: DTaP 2c Group 2: DTaP 5c Group 3: DT		2566 children 2587 2574 children	6.6 7.8 6.0	
Schmitt-Grohé and Überall, 1997 Germany	Cohort Moderate risk	Lederle (4c) 2-4 mo, 3.5-5.5 mo (aP also at 5-7 mo)	Within 72h post 1st dose	Group 1: DTaP (N=4064) Group 2: DT (N=1635)			2 5	
			Within 72h post 2nd dose	Group 1: DTaP (N=4041) Group 2: DT (N=1588)			4 8	
		Booster at 12-15 mo	Within 72h post booster	Group 1: DTaP (N=3809) Group 2: DT (N=1448)			9 14	

Table set 7. Data from included and additional studies evaluating booster vaccination schedule impact on relevant outcomes

Table 7b-A: Included studies on booster vaccination, schedule impact on immunogenicity

Publication and country	Design Risk of Bias	Vaccine, Schedule used	Timing of assessment	Comparison groups	anti-FHA	anti-PT	anti-FIM 2,3	anti-PRN	anti-FHA	anti-PT	anti-FIM 2,3	anti-PRN
					Proportion seroconverted (%)				GMC (95%-CI) Post-vaccination (EU/ml)			
Scheifele 2005 Canada	RCT Unclear to moderate risk	**Sanofi Pasteur (5c)** Booster at 15, 16, 17 or 18 mo	1 mo after booster	Group 1: age 15 mo (N=445)	86.8	93.5	93.5	94.3	172.67 (156.57-190.42)	251.45 (221.73-285.16)	837.67 (726.21-966.23)	187.71 (163.39-215.63)
				Group 2: age 16 mo (N=449)					182.05 (167.94-197.34)	222.77 (194.18-255.58)	726.75 (627.57-841.60)	166.33 (144.52-191.43)
				Group 3: age 17 mo (N=450)	92.5	97.8	95.6	92.8	205.45 (185.92-227.02)	267.99 (238.94-300.57)	887.05 (767.89-1024.70)	197.60 (169.98-229.72)
				Group 4: age 18 mo (N=438)					217.32 (196.92-240.20)	274.59 (242.44-310.99)	837.22 (710.67-986.31)	185.83 (158.83-217.41)
Seroconversion presented for 15+16 mo and 17+18 mo combined												

Table 7c-A: Included studies on booster vaccination, schedule impact on reactogenicity

Publication and country	Design Risk of Bias	Vaccine, Schedule used	Timing of assessment	Comparison groups	Symptom	Risk for participants (%)
Scheifele 2005 Canada	RCT Unclear to moderate risk	**Sanofi Pasteur (5c)** Booster at 15, 16, 17 or 18 mo	Within 3 days after booster	Group 1: age 15 mo (N=445) Group 2: age 16 mo (N=449) Group 3: age 17 mo (N=450) Group 4: age 18 mo (N=438)	Fever (≥38.0°C)	14.7 17.7 19.1 18.5
				Group 1: age 15 mo (N=445) Group 2: age 16 mo (N=449) Group 3: age 17 mo (N=450) Group 4: age 18 mo (N=438)	Crying > 3h	1.1 0.7 0.9 0.9
				Group 1: age 15 mo (N=445) Group 2: age 16 mo (N=449) Group 3: age 17 mo (N=450) Group 4: age 18 mo (N=438)	Redness >5cm	2.5 4.8 3.7 5.7
				Group 1: age 15 mo (N=445) Group 2: age 16 mo (N=449) Group 3: age 17 mo (N=450) Group 4: age 18 mo (N=438)	Swelling >5 cm	2.3 2.3 2.8 1.7
				Group 1: age 15 mo (N=445) Group 2: age 16 mo (N=449) Group 3: age 17 mo (N=450) Group 4: age 18 mo (N=438)	Any tenderness	2.5 3.0 2.7 3.3

Table set 8. Data from included and additional studies evaluating booster absolute vaccine impact on relevant outcomes

Table 8c-A: Included studies on booster vaccination, absolute impact on reactogenicity

Publication and country	Design Risk of Bias	Vaccine, Schedule used	Timing of assessment	Comparison groups	Symptom	Risk for participants (%)
Zepp 2007 Germany	RCT Unclear to moderate risk	**GSK (3c)** aP booster at 12-23 mo, compared to MMR-Varic	Within 4 days after booster	Group 1: aP (N=150) Group 2: MMRV (N=150)	Any pain	29.3 (22.2 – 37.3) 14.0 (8.9 – 20.6)
				Group 1: aP (N=150) Group 2: MMRV (N=150)	Redness > 2 cm	9.3 (5.2 – 15.2) 0 (0 – 2.4)
				Group 1: aP (N=150) Group 2: MMRV (N=150)	Swelling > 2 cm	9.3 (5.2 – 15.2) 0 (0 – 2.4)

Table set 9. Data from included and additional studies evaluating impact of a birth dose on relevant outcomes

Table set 9-A. Data from included and additional studies evaluating impact of a birth dose on immunogenicity

Publication and country	Design Risk of Bias	Vaccine, Schedule used	Timing of assess-ment	Comparison groups	Seroconversion (ELISA ≥4 fold) (%)			GMT (95%-CI) (U/ml)		
					anti-FHA	anti-PT	anti-PRN	anti-FHA	anti-PT	anti-PRN
Belloni 2003 Italy	RCT Low and unclear risk	DTaP (Biocine), 3c 0, 3, 5, 11 vs 3, 5, 11	At birth	Group 1: Birth (N=45) Group 2: No birth dose (N=46)	- -	- -	- -	16.6 [12.4-22.3] 23.2 [16.1-33.5]	4.5 [3.3-5.9] 5.5 [3.9-7.8]	4.6 [3.1-6.8] 4.5 [2.6-6.9]
			3 mo	Group 1: Birth (N=23) Group 2: No birth dose (N=21)	4.3 -	8.7 -	13.0 -	7.7 [5.2-11.4] 5.8 [3.5-9.4]	2.8 [1.7-4.8] 4.1 [3.4-6.8]	4.3 [2.5-7.2] 2.2 [1.4-3.6]
			5 mo	Group 1: Birth (N=17) Group 2: No birth dose (N=25)	29.4 0	41.2 14.3	70.6 14.3	20.9 [12.2-36.1] 3.6 [2.4-5.4]	19.8 [13.5-29.1] 6.2 [4.0-9.5]	26.7[12.2-58.2] 7.9 [5.3-11.9]
			6 mo	Group 1: Birth (N=23) Group 2: No birth dose (N=21)	39.5 9.5	60.9 81.0	82.6 76.2	45.8 [34.1-61.6] 12.7 [8.0-20.2]	42.5 [31.0-58.5] 59.1 [39.7-88.0]	116.1 [69.9-192.9] 49.1 [33.1-72.7]
			12 mo	Group 1: Birth (N=40) Group 2: No birth dose (N=43)	42.5 27.1	87.5 83.3	85.0 89.6	61.6 [50.5-75.3] 30.8 [21.8-43.7]	53.5 [41.9-68.4] 108.8 [87.6-135.2]	194.8 [143.7-264.0] 172.1 [129.2-229.4]

								GMT (95%-CI) (EL.U/ml)		
Wood 2010 Australia	RCT	0,1,2,4,6 vs 0,2,4,6 vs 2,4,6 mo	2 mo	Group1: Birth + 1mo Group 2: Birth Group 3: No birth dose				100 20 20	20 7 5	20 6 6
		0,1,2,4,6 vs 0,2,4,6 vs 2,4,6	4 mo	Group1: Birth + 1mo Group 2: Birth Group 3: No birth dose				200 100 20	70 30 8	60 40 10
		0,1,2,4,6 vs 0,2,4,6 vs 2,4,6	6 mo	Group1: Birth + 1mo Group 2: Birth Group 3: No birth dose				150 120 100	80 40 40	80 60 60
		0,1,2,4,6 vs 0,2,4,6 vs 2,4,6	8 mo	Group1: Birth + 1mo Group 2: Birth Group 3: No birth dose				160 130 110	80 50 50	150 100 80
Data approximated from grphic										
					% IgG ≥5 EL.U/ml			**GMT (95%-CI) (EL.U/ml)**		
Knuf 2008 Gemany	RCT (phase II)	0,2,4,6 vs 2,4,6	At birth	Group1: Birth (N=55) Group 2: No birth dose (N=57)	94.3 92	55.8 52	51.9 48	65 [55-75] 45 [35-55]	9 [8-20] 8 [6-9]	9 [7-10.1] 8.5 [6.9-10]
			3 mo	Group1: Birth Group 2: No birth dose	100 95.9	100 46.9 (P<0.05)	98 93.9	300 [250-325] 40 [35-45]	50 [40-55] 6 [5.5-6.1]	50 [47-53] 30 [25-33]

			5 mo	Group1: Birth Group 2: No birth dose	100 100	100 100	100 97.9	500 [450-525] 300 [275-325]	75 [70-80] 70 [65-75]	85 [82-90] 100 [95-120]
			7 mo	Group1: Birth Group 2: No birth dose	100 100	100 100	100 100	600 [575-625] 500 [475-525]	85 [82-87] 85 [80-87]	115 [110-120] 115 [110-118]
NB: GMT (95%-CI) extracted from graphic										
Knuf 2010 Germany	RCT	Booster (age 11-18 mo)	Pre-boost	Group1: Birth (N=29) Group 2: No birth dose (N=33)	100 100	86.2 75.8	96.6 93.9	104.5 [67.5-161.7] 63.3 [46.5-86.3]	12.7 [8.8-18.2] 9.2 [6.7-12.6]	26.2 [17.6-38.8] 24.2 [17.6-33.3]
			1 mo post booster	Group1: Birth Group 2: No birth dose	100 100	100 100	100 100	601 [451.1-800.7] 438 [339-565.8]	60.1 [45.5-79.4] 73.2 [59.8-89.5]	409.1 [312.3-535.8] 397.1 [289.1-545.4]
			% Booster response (from negative pre- or ≥2-fold)	Group1: Birth (N=29) Group 2: No birth dose (N=33)				89.7 [72.6-97.8] 97.0 [84.2-99.9]	93.1 [77.2-99.2] 97.0 [84.2-99.9]	100 [88.1-100] 100 [89.4-100]

					Seroconversion (ELISA ≥4 fold) (%)				**GMT (95%-CI) (U/ml)**			
					anti-FHA	anti-PT	anti-PRN	anti-Fim	anti-FHA	anti-PT	anti-PRN	anti-Fim
Halasa 2008 USA	RCT Low and unclear risk	DTaP (Sanofi Pasteur), 5c	2-14 days after birth	Group 1: Birth (N=25) Group 2: No birth dose (N=25)	- -	- -	- -	- -	11 [7-16] 12 [8-19]	9 [6-12] 11 [8-16]	27 [17-43] 26 [16-41]	31 [19-50] 22 [14-37]

		0,2,4,6, 17 vs 2,4,6, 17 mo	6 mo	Group1: Birth (N=22) Group2: No birth dose (N=22)	26 27	13 23	43 59	43 59	18 [12-26] 18 [12-27]	12 [9-17] 18 [13-25]	51 [32-80] 104 [64-167]	57 [35-92] 101 [35-167]
			7 mo	Group1: Birth (N=22) Group2: No birth dose dose (N=22)	30 36	17 32	52 82 (P<0.05)	57 73	25 [17-36] 26 [17-38]	17 [12-23] 27 [20-38]	161 [102-253] 442 [275-713]	113 [70-181] 264 [160-453]
			17 mo	Group1: Birth (N=22) Group2: No birth dose dose (N=20)	5 5	0 10	14 35	9 30	2 [2-4] 3 [2-4]	5 [4-7] 6 [4-9]	25 [16-39] 35 [22-58]	22 [13-36] 33 [20-56]
			18 mo	Group 1: Birth dose (N=22) Group 2: No birth dose (N=20)	27 35	9 40 (P<0.05)	64 80	55 85 (P<0.05)	21 [14-30] 33 [21-49]	12 [8-16] 29 [20-41]	176 [110-280] 508 [308-837]	149 [91-243] 447 [264-757]

Table set 9-B. Data from included and additional studies evaluating impact of a birth dose on reactogenicity

First Author. Year	Study Site	Age of Participants	Timing of assessment of outcome	Schedule evaluated	Comparison groups	Adverse events	
						%	RR [95%-CI]
Temperature ≥38°C							
Knuf M. 2008 RCT	Germany	Newborns Mean age: 2.9 days (2-5 days)	8 days post-birth dose	Birth dose vs. no birth dose	Group1: Birth dose Group2: No birth dose (Hep B)	0 0	1
	Germany	Newborns Mean age: 2.9 days (2-5 days)	8 days post-all doses		Group1: Birth dose Group2: No birth dose (Hep B)	34.5 37.3	0.92
Knuf M. 2010 RCT	Germany	11 – 18 mo (Mean age: 13.7mo)	8 days post-booster	Birth dose vs. no birth dose	Group1: Birth dose Group2: No birth dose (Hep B)	52 28	1.86
Irritability							
Knuf M. 2008 RCT	Germany	Newborns Mean age: 2.9 days (2-5 days)	8 days post-birth dose	Birth dose vs. no birth dose	Group1: Birth dose Group2: No birth dose (Hep B)	27 30	0.90
	Germany	Newborns Mean age: 2.9 days (2-5 days)	8 days post-all doses		Group1: Birth dose Group2: No birth dose (Hep B)	75 79	0.95
Knuf M. 2010 RCT	Germany	11 – 18 mo (Mean age: 13.7mo)	8 days post-booster	Birth dose vs. no birth dose	Group1: Birth dose Group2: No birth dose (Hep B)	45 46	0.98
Local Pain/ Tenderness							

Knuf M. 2008 RCT	Germany	Newborns Mean age: 2.9 days (2-5 days)	8 days post-birth dose	Birth dose vs. no birth dose	Group1: Birth dose Group2: No birth dose (Hep B)	8.0 8.2	0.98
	Germany	Newborns Mean age: 2.9 days (2-5 days)	8 days post-all doses		Group1: Birth dose Group2: No birth dose (Hep B)	20 24	0.83
Knuf M. 2010 RCT	Germany	11 – 18 mo (Mean age: 13.7mo)	8 days post-booster	Birth dose vs. no birth dose	Group1: Birth dose Group2: No birth dose (Hep B)	29 40	0.73
Redness							
Knuf M. 2008 RCT	Germany	Newborns Mean age: 2.9 days (2-5 days)	8 days post-birth dose	Birth dose vs. no birth dose	Group1: Birth dose Group2: No birth dose (Hep B)	36 38	0.90
	Germany	Newborns Mean age: 2.9 days (2-5 days)	8 days post-all doses		Group1: Birth dose Group2: No birth dose (Hep B)	58 65	0.89
Knuf M. 2010 RCT	Germany	11 – 18 mo (Mean age: 13.7mo)	8 days post-booster	Birth dose vs. no birth dose	Group1: Birth dose Group2: No birth dose (Hep B)	68 66	1.03
Swelling							
Knuf M. 2008 RCT	Germany	Newborns Mean age: 2.9 days (2-5 days)	8 days post-birth dose	Birth dose vs. no birth dose	Group1: Birth dose Group2: No birth dose (Hep B)	13 14	0.93
	Germany	Newborns Mean age: 2.9 days (2-5 days)	8 days post-all doses		Group1: Birth dose Group2: No birth dose (Hep B)	20 30	0.67
Knuf M. 2010 RCT	Germany	11 – 18 mo (Mean age: 13.7mo)	8 days post-booster	Birth dose vs. no birth dose	Group1: Birth dose Group2: No birth dose (Hep B)	44 28	1.57
Wood N. 2010 RCT	Australia	Newborns (within 5 days of birth)	7 days post- all doses	0,1,2,4,6 vs 0,2,4,6 vs 2,4,6	Group1: Birth dose + 1mo (n=4) Group 2: Birth dose (n=3) Group 3: No birth dose (n=4)	17 14 22	0.77 0.64

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