Systematic Review Report

Topic: Safety from randomized controlled trials and observational studies of pertussis vaccines

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August 10, 2014

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1 Glossary

AE	Adverse events
aP	acellular Pertussis
CI	Confidence interval
DT	Diphtheria-Tetanus
DTP	Diphtheria-Tetanus- Pertussis
M-H	Mantel-Haenszel
N/A	Not Applicable
RCT	Randomized Controlled Trial
wP	whole-cell Pertussis

2 Summary of main findings

2.1 Absolute reactogenicity

Does administration of any aP pertussis vaccine affect reactogenicity compared to administration of any wP pertussis vaccine?*				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting score		2 RCTs, 1 observational study[1]	3
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[3]	-1
		Imprecision	Serious[4]	-1
		Publication bias	Not apparent	0
	Factors increasing confidence	Strength of association	Not demonstrated	N/A
		Dose-response	Not demonstrated	N/A
		Mitigated bias and confounding	Not demonstrated	N/A
	Final numerical score of quality of evidence			0
Summary of findings	**Statement on quality of evidence**			We have very little confidence in the evidence about the effects of any aP pertussis vaccine compared to any wP pertussis vaccine on reactogenicity.
	Conclusion			Administration of any aP pertussis vaccine may reduce the risk of reactogenicity outcomes compared to administration of any wP pertussis vaccine.*

* Administration together with diphtheria and tetanus vaccines.
[1] Starting score of 3 due to inclusion of two RCTs as well as one observational study.
[2] Two of the included studies were of moderate to high risk of bias.
[3] All studies were carried out in Europe.
[4] There were only three studies.

Does administration of any aP or wP pertussis vaccine affect reactogenicity compared to administration of no pertussis vaccine?*				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting score		4RCTs, 1 observational study[1]	3
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[3]	-1
		Imprecision	None serious	0
		Publication bias	Not apparent	0
	Factors increasing confidence	Strength of association	Not demonstrated	N/A
		Dose-response	Not demonstrated	N/A
		Mitigated bias and confounding	Not demonstrated	N/A
	Final numerical score of quality of evidence			1
Summary of findings	**Statement on quality of evidence**			We have very little confidence in the evidence about the effects of any pertussis vaccine compared to no pertussis vaccine on reactogenicity.

	Conclusion	Administration of no pertussis vaccine may reduce the risk of reactogenicity outcomes compared to administration of any aP or wP pertussis vaccine.*

* Administration together with diphtheria and tetanus vaccines.
[1] Starting score of 3 due to inclusion of four RCTs as well as one observational study.
[2] Two of the included studies were of moderate to high risk of bias.
[3] The studies were carried out only in Europe or the USA.

Does administration of any aP pertussis vaccine affect reactogenicity compared to administration of no pertussis vaccine?*				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting score		2 RCTs	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	Serious[1]	-1
		Indirectness	Serious[2]	-1
		Imprecision	Serious[3]	-1
		Publication bias	Not apparent	0
	Factors increasing confidence	Strength of association	Not demonstrated	N/A
		Dose-response	Not demonstrated	N/A
		Mitigated bias and confounding	Not demonstrated	N/A
	Final numerical score of quality of evidence			1
Summary of findings	**Statement on quality of evidence**			We have very little confidence in the evidence about the effects on reactogenicity of aP pertussis vaccines.
	Conclusion			There may be little or no difference in reactogenicity outcomes for children administered aP pertussis vaccine, compared to those that are not.*

* Administration together with diphtheria and tetanus vaccines.
[1] Inconsistent directions of effect.
[2] The studies were carried out only in Europe.
[3] There were only two studies.

Does administration of any wP perussis vaccine affect reactogenicity compared to administration of no pertussis vaccine?*				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting score		4 RCT, 1 observational study[1]	3
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[3]	-1
		Imprecision	None serious	0
		Publication bias	Not apparent	0
	Factors increasing confidence	Strength of association	Not demonstrated	N/A
		Dose-response	Not demonstrated	N/A
		Mitigated bias and confounding	Not demonstrated	N/A
	Final numerical score of quality of evidence			1
mary of findi	**Statement on quality of evidence**			We have very little confidence in the evidence about the effects of wP pertussis vaccines on reactogenicity.

	Conclusion	Administration of no pertussis vaccine may reduce the risk of reactogenicity outcomes compared to administration of any wP pertussis vaccine.*

* Administration together with diphtheria and tetanus vaccines.
[1] Starting score of 3 due to inclusion of four RCTs as well as one observational study.
[2] Two of the included studies were of moderate to high risk of bias.
[3] The studies were carried out only in Europe or the USA.

2.2 Schedules

Does administration of an accelerated aP perussis vaccine schedule affect reactogenicity compared to a long schedule?*				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting score		3 RCTs, 2 observational studies[1]	3
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	Not apparent	0
	Factors increasing confidence	Strength of association	Not demonstrated	N/A
		Dose-response	Not demonstrated	N/A
		Mitigated bias and confounding	Not demonstrated	N/A
	Final numerical score of quality of evidence			2
Summary of findings	**Statement on quality of evidence**			Our confidence in the evidence about the effects of an accelerated aP pertussis vaccination schedule on reactogenicity is limited.
	Conclusion			An accelerated aP pertussis vaccination schedule may reduce the risk of some reactogenicity outcomes.*

* Administration together with diphtheria and tetanus vaccines.
[1] Starting score of 3 due to inclusion of three RCTs as well as two observational studies.
[2] Three of the included studies were of moderate to high risk of bias.

Does administration of an accelerated wP perussis vaccine schedule affect reactogenicity compared to a long schedule?*				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting score		2 observational studies	2
	Factors decreasing confidence	Limitation in study design	Serious[1]	0
		Inconsistency	Serious[2]	-1
		Indirectness	Serious[3]	-1
		Imprecision	Serious[4]	-1
		Publication bias	Not apparent	0
	Factors increasing confidence	Strength of association	Not demonstrated	N/A
		Dose-response	Not demonstrated	N/A
		Mitigated bias and confounding	Not demonstrated	N/A
	Final numerical score of quality of evidence			0

Summary of findings	**Statement on quality of evidence**	We have very little confidence in the evidence about the effects of an accelerated wP pertussis vaccination schedule on reactogenicity.
	Conclusion	An accelerated wP pertussis vaccination schedule may reduce the risk of some reactogenicity outcomes.*

* Administration together with diphtheria and tetanus vaccines.
[1] Addressed by starting score of 2.
[2] Inconsistent directions of effect.
[3] The studies were carried out only in Europe.
[4] There were only two studies.

Does administration of a birth dose with the wP perussis vaccine schedule affect reactogenicity compared to a schedule with no birth dose?*				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting score		1 RCT	4
	Factors decreasing confidence	Limitation in study design	Serious[1]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[2]	-1
		Imprecision	Serious[3]	-1
		Publication bias	Not apparent	0
	Factors increasing confidence	Strength of association	Not demonstrated	N/A
		Dose-response	Not demonstrated	N/A
		Mitigated bias and confounding	Not demonstrated	N/A
	Final numerical score of quality of evidence			1
Summary of findings	**Statement on quality of evidence**			We have very little confidence in the evidence about the effect on reactogenicity of a wP pertussis vaccination schedule that includes a birth dose.
	Conclusion			There is insufficient evidence to draw a conclusion about the effects of administering a birth dose of wP pertussis vaccine on reactogenicity outcomes.*

* Administration together with diphtheria and tetanus vaccines.
[1] Unclear or moderate risk of bias.
[2] The study was carried out only in the USA.
[3] There was only one study with 4 events and 20 participants.

3 Analyses: Absolute reactogenicity of pertussis vaccines

3.1 Any DTaP vaccine compared to any DTwP vaccine

Three studies evaluated reactogenicity for DTaP compared to DTwP vaccines. Greco 1996 was an RCT conducted in Italy of low risk of bias that administered DTaP Chiron (3c), DTaP SKB (3c), or DTwP doses at 2, 4 and 6 months. Gustafsson 1996 was an RCT conducted in Sweden of moderate risk of bias that administered DTaP Connaught (5c), DTaP SKB (2c), or DTwP doses at 2, 4, and 6 months. Miller 1997 was a cohort analysis of two trials conducted in the UK with moderate to high risk of bias that administered DTaP Porton (3c), DTaP Mérieux (2d), or DTwP doses at 2, 3, and 4 months or at 3, 5, and 9 months. Greco 1996 and Gustafsson 1996 also administered a DT vaccine arm not included in this comparison.

Table 1: Characteristics of studies contributing to the any DTaP vs. any DTwP vaccines comparison

Study Country	Design	Status	Schedules	
Greco 1996(1)* Italy	RCT	Included Low risk of bias	DTaP Chiron (3c) or DTaP SKB (3c) at 2, 4, and 6 months	DTwP at 2, 4, and 6 months
Gustafsson 1996(2) Sweden	RCT	Included Moderate risk of bias	DTaP Connaught (5c) or DTaP SKB (2c) at 2, 4, and 6 months	DTwP at 2, 4, and 6 months
Miller 1997(3) UK	cohort analysis of two trials	Included moderate to high risk of bias	DTaP Porton (3c) or DTaP Mérieux (2d) at 2, 3, and 4 months or at 3, 5, and 9 months	DTwP at 2, 3, and 4 months or at 3, 5, and 9 months

* Reported vaccine doses (as opposed to participants) as denominator

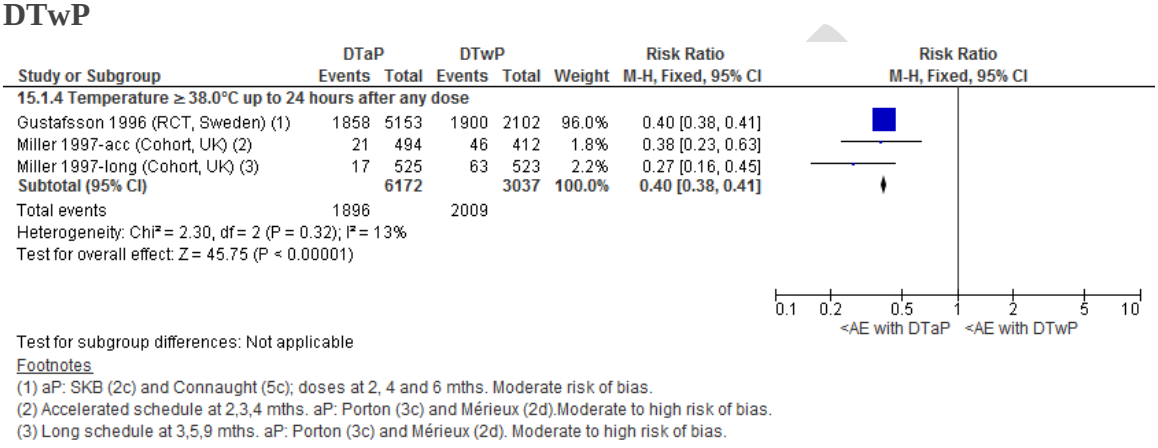
The studies reported on Temperature ≥38.0°C, Persistent crying, Hypotonic, hyporesponsive episode, Local pain/tenderness, Erythema/redness, Swelling/nodule, Seizures, and Any systemic symptoms. Mostly, the risk of adverse events was significantly lower for children vaccinated with any DTaP vaccine compared to those vaccinated with any DTwP vaccine. However, for Seizures and for some timepoints for Erythema/redness, there were no statistically significant differences.

Temperature ≥38.0°C

An RCT and a cohort analysis of two RCTs found that there is a 60% lower risk of Temperature ≥38.0°C after any dose of DTaP compared to DTwP (RR 0.40, 95% CI 0.38 to 0.41, I^2=13%;

9209 participants). An RCT found that there is a lower risk of Temperature ≥38.0°C after dose 1 (RR 0.11, 95% CI 0.10 to 0.12; 7255 participants), dose 2 (RR 0.25, 95% CI 0.23 to 0.26; 7151 participants) and dose 3 (RR 0.35, 95% CI 0.33 to 0.37; 7086 participants) of DTaP compared to DTwP. An RCT, which reported doses instead of participants, found that there is a 86% lower risk of Temperature ≥38.0°C after any dose of DTaP compared to DTwP (RR 0.14, 95% CI 0.14 to 0.15; 40994 doses).

Figure 1. Meta-analysis of Temperature ≥38°C reactogenicity for DTaP compared to DTwP



Test for subgroup differences: Not applicable

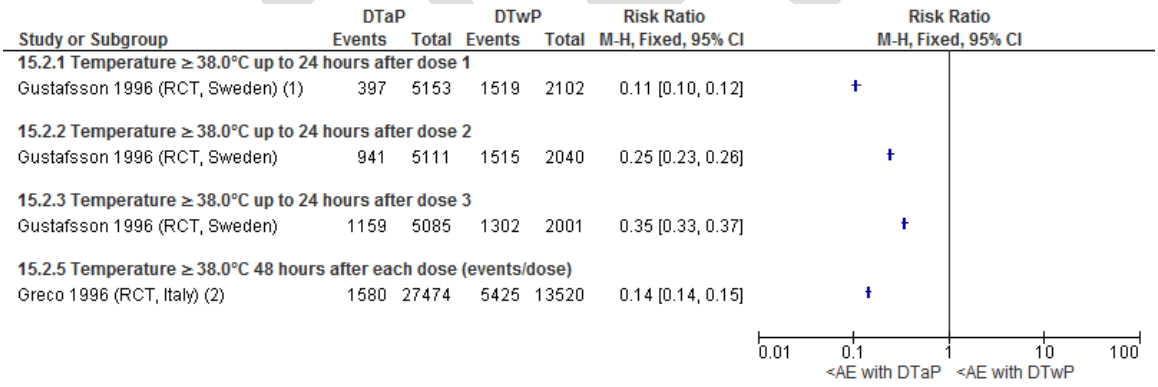
Footnotes

(1) aP: SKB (2c) and Connaught (5c); doses at 2, 4 and 6 mths. Moderate risk of bias.

(2) Accelerated schedule at 2,3,4 mths. aP: Porton (3c) and Mérieux (2d).Moderate to high risk of bias.

(3) Long schedule at 3,5,9 mths. aP: Porton (3c) and Mérieux (2d). Moderate to high risk of bias.

Figure 2. Single studies analyses of Temperature ≥38°C reactogenicity for DTaP compared to DTwP



Footnotes

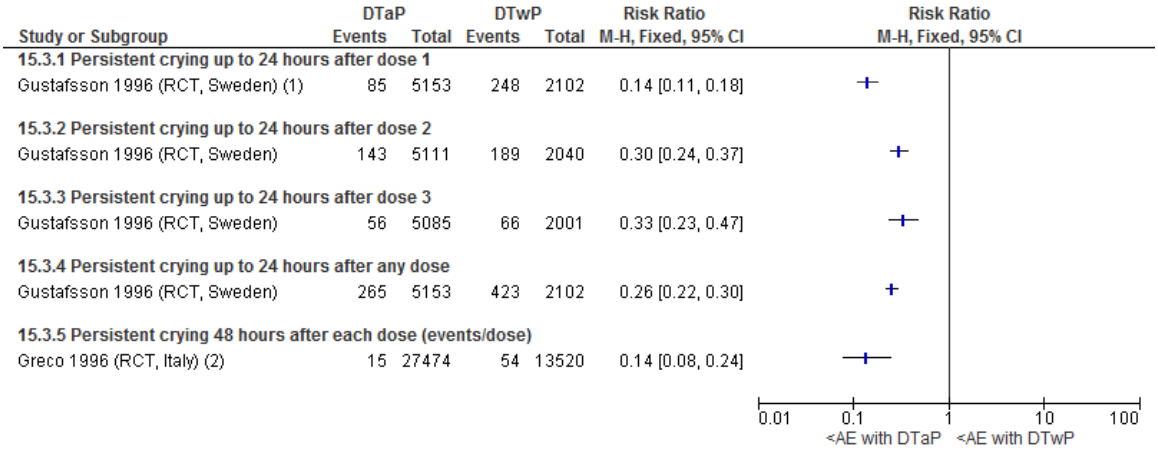
(1) aP: SKB (2c) and Connaught (5c); doses at 2, 4 and 6 mths. Moderate risk of bias.

(2) aP: Chiron (3c) and SKB (3c); doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Persistent crying

An RCT found that there is a lower risk of Persistent crying after dose 1 (RR 0.14, 95% CI 0.11 to 0.18; 7255 participants), dose 2 (RR 0.30, 95% CI 0.24 to 0.37; 7151 participants), dose 3 (RR 0.33, 95% CI 0.23 to 0.47; 7086 participants) and after any dose (RR 0.26, 95% CI 0.22 to 0.30; 7255 participants) of DTaP compared to DTwP. An RCT, which reported doses instead of participants, found that there is a 86% lower risk of Persistent crying after any dose of DTaP compared to DTwP (RR 0.14, 95% CI 0.08 to 0.24; 40994 doses).

Figure 3. Persistent crying reactogenicity for DTaP compared to DTwP

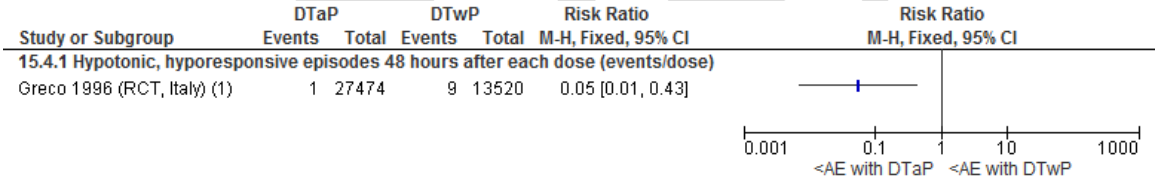


Footnotes
(1) Persistent crying ≥1h. aP: SKB (2c) and Connaught (5c); doses at 2, 4 and 6 mths. Moderate risk of bias.
(2) Persistent crying ≥3h. aP: Chiron (3c) and SKB (3c); doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Hypotonic, hyporesponsive episode

An RCT, which reported doses instead of participants, found that there is a 95% lower risk of Hypotonic, hyporesponsive episode after any dose of DTaP compared to DTwP (RR 0.05, 95% CI 0.01 to 0.43; 40994 doses).

Figure 4. Hypotonic, hyporesponsive episode reactogenicity for DTaP compared to DTwP

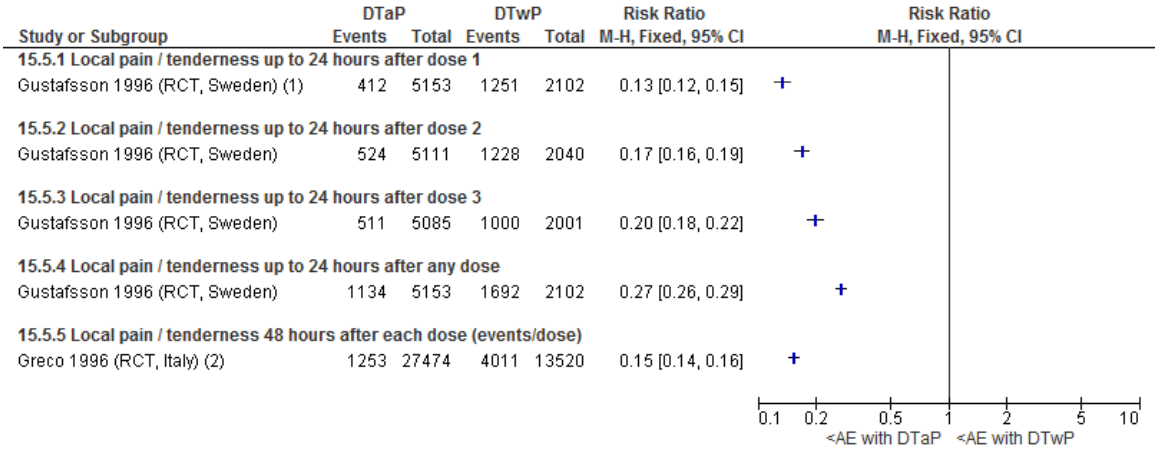


Footnotes
(1) aP: Chiron (3c) and SKB (3c); doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Local pain/tenderness

An RCT found that there is a lower risk of Local pain/tenderness after dose 1 (RR 0.13, 95% CI 0.12 to 0.15; 7255 participants), dose 2 (RR 0.17, 95% CI 0.16 to 0.19; 7151 participants), dose 3 (RR 0.20, 95% CI 0.18 to 0.22; 7086 participants) and after any dose (RR 0.27, 95% CI 0.26 to 0.29; 7255 participants) of DTaP compared to DTwP. An RCT, which reported doses instead of participants, found that there is a 85% lower risk of Local pain/tenderness after any dose of DTaP compared to DTwP (RR 0.15, 95% CI 0.14 to 0.16; 40994 doses).

Figure 5. Local pain/tenderness reactogenicity for DTaP compared to DTwP

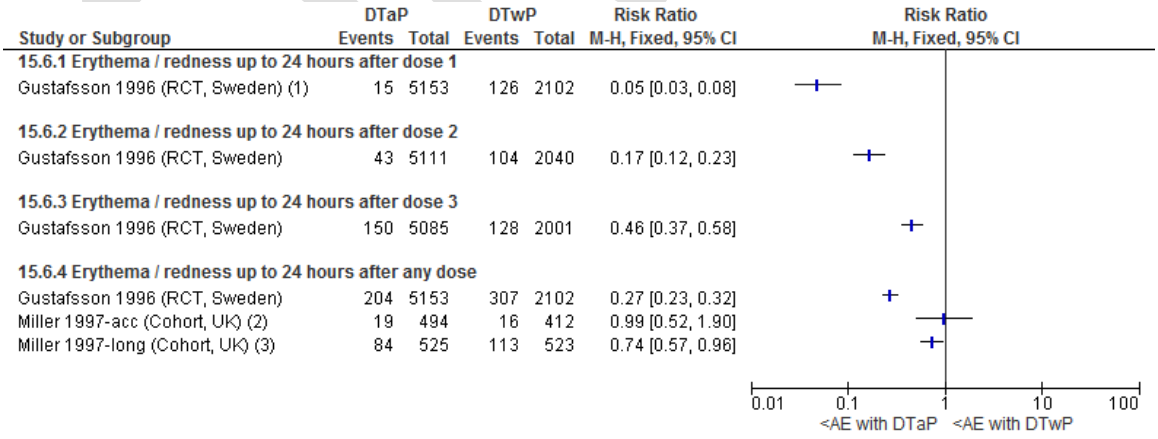


Footnotes
(1) aP: SKB (2c) and Connaught (5c); doses at 2, 4 and 6 mths. Moderate risk of bias.
(2) aP: Chiron (3c) and SKB (3c); doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Erythema/redness

An RCT found that there is a lower risk of Erythema/redness after dose 1 (RR 0.05, 95% CI 0.03 to 0.08; 7255 participants), dose 2 (RR 0.17, 95% CI 0.12 to 0.23; 7151 participants), dose 3 (RR 0.46, 95% CI 0.37 to 0.58; 7086 participants), and after any dose (RR 0.27, 95% CI 0.23 to 0.32; 7255 participants) of DTaP compared to DTwP. The long schedule of a cohort analysis of two RCTs found that there is a lower risk of Erythema/redness after any dose of DTaP compared to DTwP (RR 0.74, 95% CI 0.57 to 0.96; 906 participants), whereas no significant difference was found for the accelerated schedule of DTaP compared to DTwP (1048 participants) of the same study. The measurements of Erythema/redness after any dose could not be pooled due to very high heterogeneity (I^2=96%).

Figure 6. Erythema/redness reactogenicity for DTaP compared to DTwP

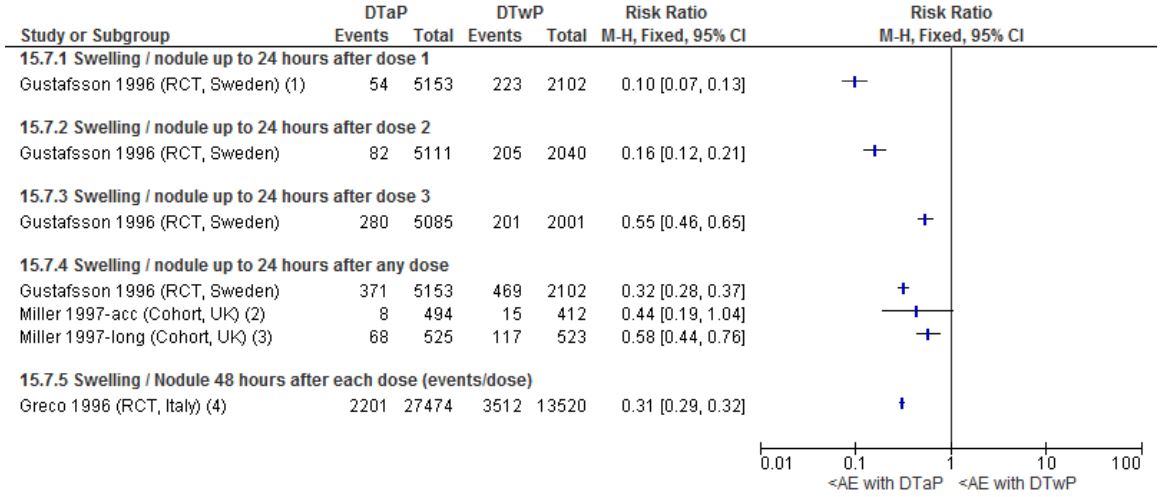


Footnotes
(1) Redness ≥2cm. aP: SKB (2c) and Connaught (5c); doses at 2, 4 and 6 mths. Moderate risk of bias.
(2) Accelerated schedule at 2,3,4 mths. aP: Porton (3c) and Mérieux (2d). Moderate to high risk of bias.
(3) Long schedule at 3,5,9 mths. aP: Porton (3c) and Mérieux (2d). Moderate to high risk of bias.

Swelling/nodule

An RCT found that there is a lower risk of Swelling/nodule after dose 1 (RR 0.10, 95% CI 0.07 to 0.13; 7255 participants), dose 2 (RR 0.16, 95% CI 0.12 to 0.21; 7151 participants), dose 3 (RR 0.55, 95% CI 0.46 to 0.65; 7086 participants), and after any dose (RR 0.32, 95% CI 0.28 to 0.37; 7255 participants) of DTaP compared to DTwP. The long schedule of a cohort analysis of two RCTs found that there is a lower risk of Swelling/nodule after any dose of DTaP compared to DTwP (RR 0.58, 95% CI 0.44 to 0.76; 906 participants), whereas no significant difference was found for the accelerated schedule of DTaP compared to DTwP (1048 participants) of the same study. The measurements of Swelling/nodule after any dose could not be pooled due to very high heterogeneity (I^2=86%). An RCT, which reported doses instead of participants, found that there is a 69% lower risk of Swelling/nodule after any dose of DTaP compared to DTwP (RR 0.31, 95% CI 0.29 to 0.32; 40994 doses).

Figure 7. Swelling/nodule reactogenicity for DTaP compared to DTwP

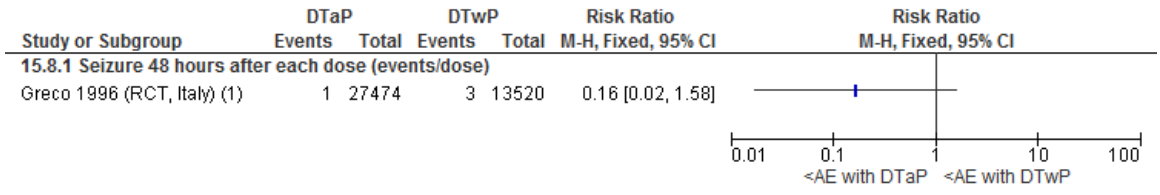


Footnotes
(1) Nodule ≥2cm. aP: SKB (2c) and Connaught (5c); doses at 2, 4 and 6 mths. Moderate risk of bias.
(2) Accelerated schedule at 2,3,4 mths. aP: Porton (3c) and Mérieux (2d). Moderate to high risk of bias.
(3) Long schedule at 3,5,9 mths. aP: Porton (3c) and Mérieux (2d). Moderate to high risk of bias.
(4) aP: Chiron (3c) and SKB (3c); doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Seizures

No statistically significant difference was found between DTaP compared to DTwP vaccines for Seizures.

Figure 8. Seizures reactogenicity for DTaP compared to DTwP

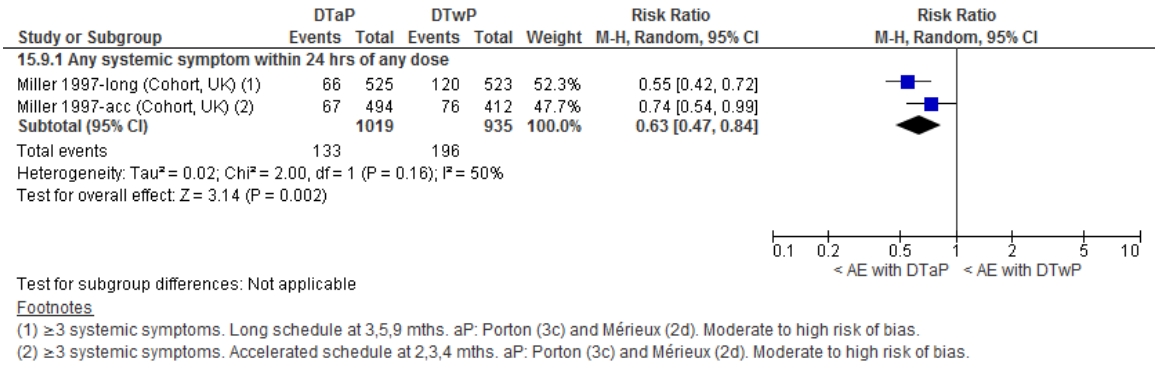


Footnotes
(1) aP: Chiron (3c) and SKB (3c); doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Any systemic symptoms

A cohort analysis of two RCTs found that there is a 37% lower risk of Any systemic symptoms after any dose of DTaP compared to DTwP (RR 0.63, 95% CI 0.47 to 0.84; 1954 participants). Random effects model was used due to high heterogeneity (I^2=50%; with fixed effects model: RR 0.62, 95% CI 0.51 to 0.76).

Figure 9. Any systemic symptoms reactogenicity for DTaP compared to DTwP



3.2 Any DTP vaccine compared to DT vaccine (pertussis vaccine vs. no pertussis vaccine)

Five studies evaluated reactogenicity for DTP versus DT vaccines. Greco 1996 was an RCT conducted in Italy of low risk of bias that administered DTaP Chiron (3c), DTaP SKB (3c), DTwP, or DT doses at 2, 4 and 6 months. Gustafsson 1996 was an RCT conducted in Sweden of moderate risk of bias that administered DTaP SKB (2c), DTaP Connaught (5c), DTwP, or DT doses at 2, 4, and 6 months. Pollock 1984 was a cohort study conducted in the UK of high risk of bias that administered DTwP, DTwP plain, or DT doses at 3, 4.5-6 and 8-12 months. Barkin 1985 was a double-blind RCT conducted in the USA of unclear risk of bias that administered DTwP and DT doses at 2, 4 and 6 months. It should be noted that Barkin 1985 does not fit with this protocol as it does not report differences between the two schedules. Cody 1981 was a double-blind RCT conducted in the USA of unclear risk of bias that administered DTwP and DT. It should be noted that Cody 1981 does not fit with this protocol as it does not report by vaccine schedule.

Table 2. Characteristics of studies contributing to the any DTP vs. DT vaccines comparison

Study Country	Design	Status	Schedules	
Greco 1996(1)* Italy	RCT	Included Low risk of bias	DTaP Chiron (3c), DTaP SKB (3c), or DTwP at 2, 4, and 6 months	DT at 2, 4, and 6 months
Gustafsson 1996(2) Sweden	RCT	Included Moderate risk of bias	DTaP SKB (2c), DTaP Connaught (5c), or DTwP at 2, 4, and 6 months	DT at 2, 4, and 6 months

Study Country	Design	Status	Schedules	
Pollock 1984(4) UK	Cohort	Included High risk of bias	DTwP and DTwP plain at 3, 4.5-6, and 8-12 months	DT at 3, 4.5-6, and 8-12 months
Barkin 1985(5)* USA	RCT	Additional study Not per protocol: Reports no difference between two schedules	DTwP – DTwP – DT at 2, 4, and 6 months	DTwP – DT – DTwP at 2, 4, and 6 months
			DTwP doses were compared to DT doses across schedules	
Cody 1981(6)* USA	RCT	Additional study Not per protocol: Does not report by vaccination schedule	DTwP with no application of a specific vaccination schedule	DT with no application of a specific vaccination schedule

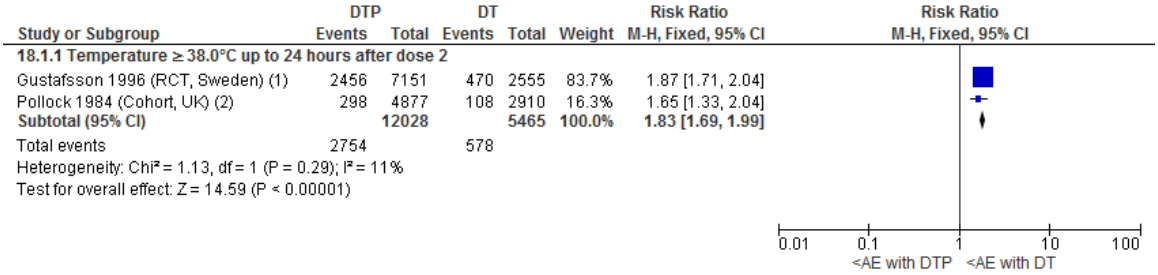
* Reported vaccine doses (as opposed to participants) as denominator

The studies reported on Temperature ≥38.0°C, Persistent crying, Local pain/tenderness, Erythema/redness, Swelling/nodule, Hypotonic, hypo-responsive episodes, Seizure, Crying more than usual, Crying/screaming, Acute behavioural changes, Use of antipyretics, Any reaction, and Local reactions. Mostly, the risk of adverse events was significantly lower for children vaccinated with DT vaccine compared to DTP vaccines, however, for Seizures and Hypotonic, hyporesponsive episodes and for some timepoints for Persistent crying, there were no statistically significant differences.

Temperature ≥38°C

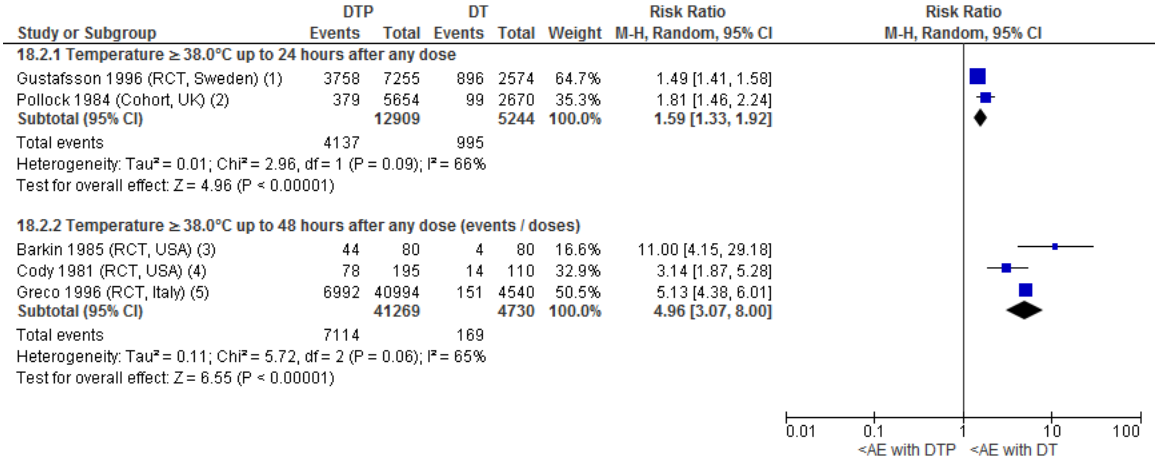
An RCT and a cohort study found that there is a lower risk of Temperature ≥38°C after DT dose 2 (RR 1.83, 95% CI 1.69 to 1.99; 17493 participants), and after any DT dose (RR 1.59, 95% CI 1.33 to 1.92; 18153 participants; random effects model due to high heterogeneity (I^2=66%), with fixed effects model: RR 1.52, 95% CI 1.43 to 1.60), compared to DTP. Three RCTs that measured does as opposed to participants, also found that there is a lower risk of Temperature ≥38°C after any DT dose compared to DTP (RR 4.96, 95% CI 3.07 to 8.00; 45999 doses; random effects model due to high heterogeneity (I^2=65%), with fixed effects model: RR 5.09, 95% CI 4.38 to 5.91). An RCT, found that there is a lower risk of Temperature ≥38°C after DT dose 1 (RR 3.47, 95% CI 3.02 to 3.99; 9829 participants) and 3 (RR 1.57, 95% CI 1.45 to 1.70; 9624 participants), compared to DTP. A cohort study also found that there is a lower risk of Temperature ≥38°C after DT dose 1 (RR 1.90, 95% CI 1.56 to 2.32; 8676 participants) and 3 (RR 2.39, 95% CI 1.90 to 3.00; 5732 participants), compared to DTP. These were not pooled due to very high heterogeneity ($I^2 \geq 91\%$).

Figure 10. Meta analyses of Temperature ≥38.0°C reactogenicity for any DTP vaccine compared to DT vaccine



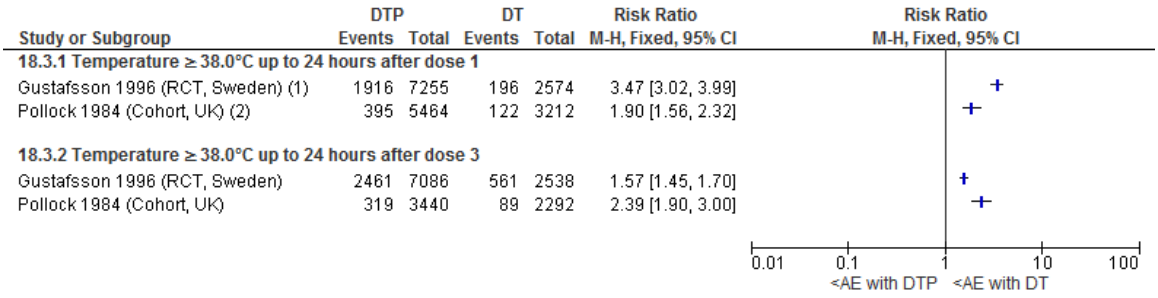
Footnotes
(1) DTwP, DTaP Connaught (5c) and SKB (2c) vs. DT. Doses at 2, 4 and 6 mths. Measured within 24 hours of dose. Moderate risk of bias.
(2) Feverishness,12 hours post dose. DTwP and DTwP plain vs. DT, doses at 3, 4.5-6, 8-12 months. High risk of bias.

Figure 11. Random effects meta analyses of Temperature ≥38.0°C reactogenicity for any DTP vaccine compared to DT vaccine



Footnotes
(1) DTwP, DTaP Connaught (5c) and SKB (2c) vs. DT. Doses at 2, 4 and 6 mths. Measured within 24 hours of dose. Moderate risk of bias.
(2) Feverishness,12 hours post dose. DTwP and DTwP plain vs. DT, doses at 3, 4.5-6, 8-12 months. High risk of bias.
(3) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Reports no difference between two schedules.
(4) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Does not report by vaccination schedule
(5) DTwP, DTaP Chiron (3c) and SKB (3c) vs. DT. Doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Figure 12. Single study outcome measures of Temperature ≥38.0°C reactogenicity for any DTP vaccine compared to DT vaccine

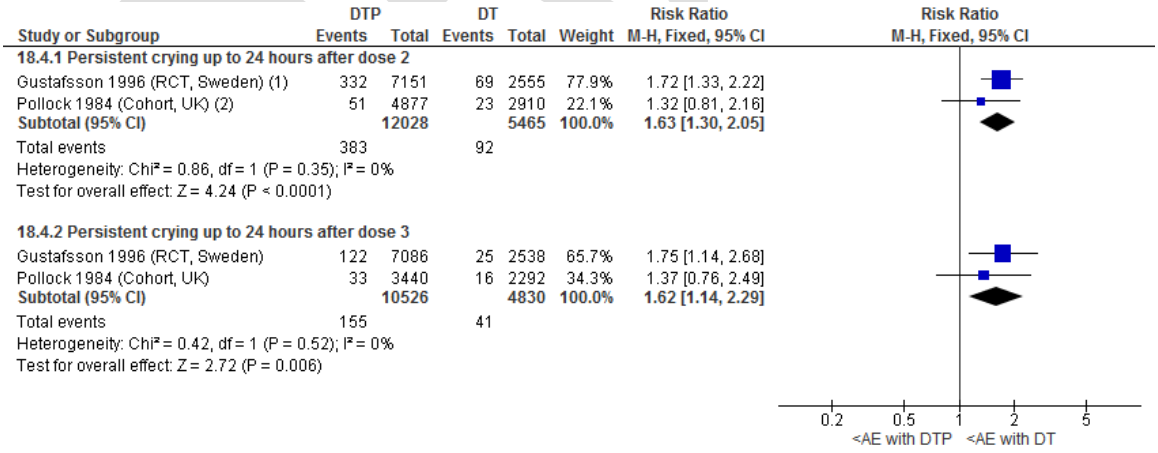


Footnotes
(1) DTwP, DTaP Connaught (5c) and SKB (2c) vs. DT. Doses at 2, 4 and 6 mths. Measured within 24 hours of dose. Moderate risk of bias.
(2) Feverishness,12 hours post dose. DTwP and DTwP plain vs. DT, doses at 3, 4.5-6, 8-12 months. High risk of bias.

Persistent crying

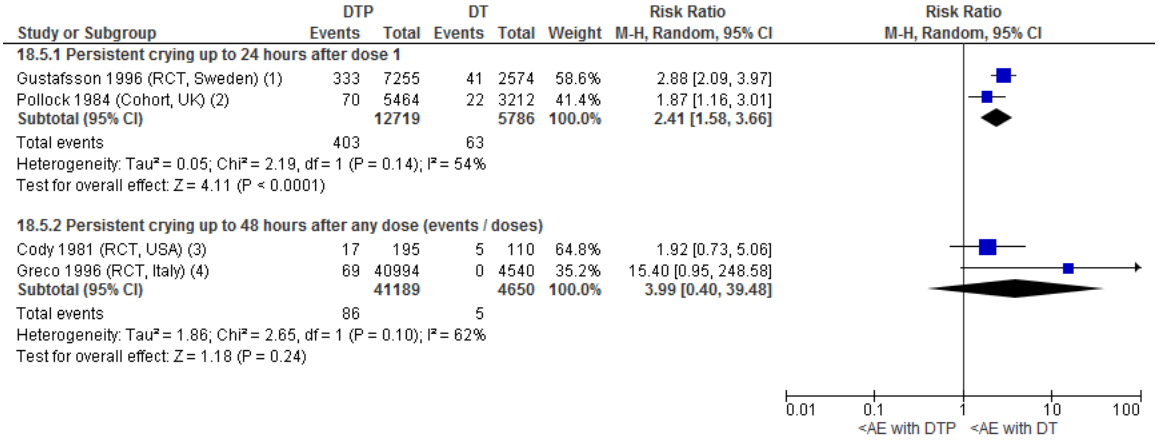
An RCT and a cohort study found that there is a lower risk of Persistent crying after DT doses 1 (RR 2.41, 95% CI 1.58 to 3.66; 18505 participants; random effects model due to high heterogeneity (I^2=54%), with fixed effects model: RR 2.56, 95% CI 1.96 to 3.35), 2 (RR 1.63, 95% CI 1.30 to 2.05; 17493 participants), and 3 (RR 1.62, 95% CI 1.14 to 2.29; 15356 participants), compared to DTP. An RCT found that there is a lower risk of Persistent crying after any DT dose (RR 1.94, 95% CI 1.61 to 2.33; 9829 participants), compared to DTP doses. Two RCTs that measured doses as opposed to participants, found no statistically significant difference in Persistent crying between DTP and DT (a random effects model was used due to high heterogeneity (I^2=62%); with a fixed effects model the pooled estimate becomes significant with a lower risk for DT: RR 3.58, 95% CI 1.39 to 9.22, 45839 doses).

Figure 13. Meta analyses of Persistent crying reactogenicity for any DTP vaccine compared to DT vaccine



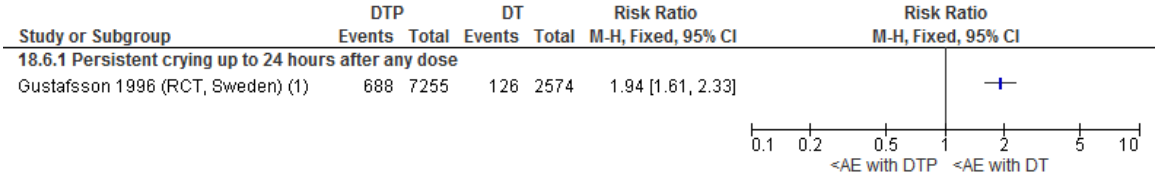
Footnotes
(1) DTwP, DTaP Connaught (5c) and SKB (2c) vs. DT, doses at 2, 4 and 6 mths. Persistent crying ≥1h measured within 24 hours of dose. Moderate risk...
(2) Persistent crying >5h, 12 hours post-dose. DTwP and DTwP plain vs. DT, doses at 3, 4.5-6, 8-12 months. High risk of bias.

Figure 14. Random effects meta analyses of Persistent crying reactogenicity for any DTP vaccine compared to DT vaccine



Footnotes
(1) DTwP, DTaP Connaught (5c) and SKB (2c) vs. DT, doses at 2, 4 and 6 mths. Persistent crying ≥1h measured within 24 hours of dose. Moderate risk of...
(2) Persistent crying >5h, 12 hours post-dose. DTwP and DTwP plain vs. DT, doses at 3, 4.5-6, 8-12 months. High risk of bias.
(3) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Does not report by vaccination schedule
(4) DTwP, DTaP Chiron (3c) and SKB (3c) vs. DT. Doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Figure 15. Single study outcome measures of Persistent crying reactogenicity for any DTP vaccine compared to DT vaccine

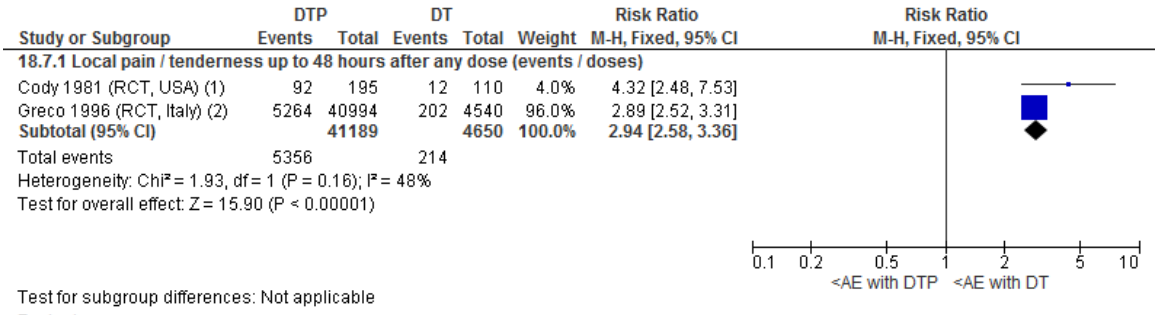


Footnotes
(1) DTwP, DTaP Connaught (5c) and SKB (2c) vs. DT, doses at 2, 4 and 6 mths. Persistent crying ≥1h. Moderate risk of bias.

Local pain/tenderness

Two RCTs found that there is a lower risk of Local pain/tenderness after DT doses compared to DTP (RR 2.94, 95% CI 2.58 to 3.36; 45839 doses). An RCT also found that there is a lower risk of Local pain/tenderness after DT doses 1 (RR 2.73, 95% CI 2.39 to 3.12; 9829 participants), 2 (RR 2.38, 95% CI 2.11 to 2.69; 9706 participants), 3 (RR 2.13, 95% CI 1.88 to 2.41; 9624 participants), and after any DT dose (RR 1.76, 95% CI 1.62 to 1.90; 9829 participants), compared to after DTP doses.

Figure 16. Meta analyses of Local pain/tenderness reactogenicity for any DTP vaccine compared to DT vaccine



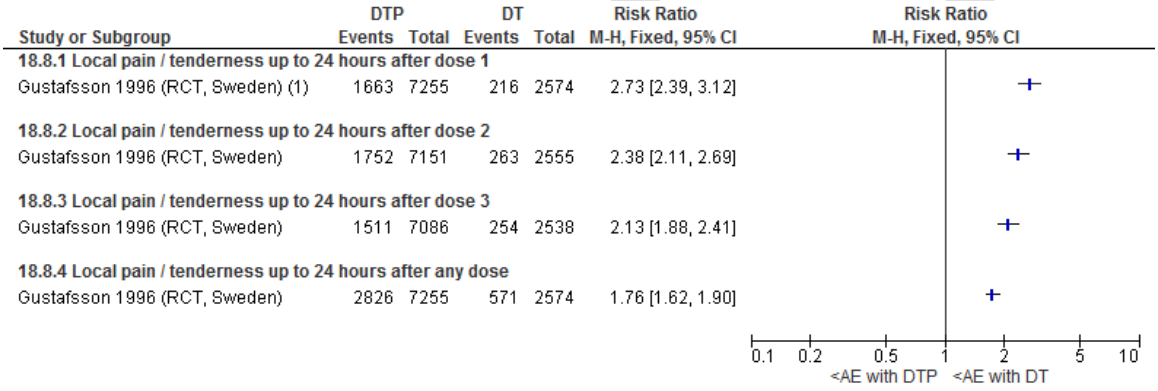
Test for subgroup differences: Not applicable

Footnotes

(1) DTwP vs. DT. Pain. N reported as doses, not participants. Not per protocol: Does not report by vaccination schedule

(2) DTwP, DTaP Chiron (3c) and SKB (3c) vs. DT, doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Figure 17. Single study outcome measures of Local pain/tenderness reactogenicity for any DTP vaccine compared to DT vaccine



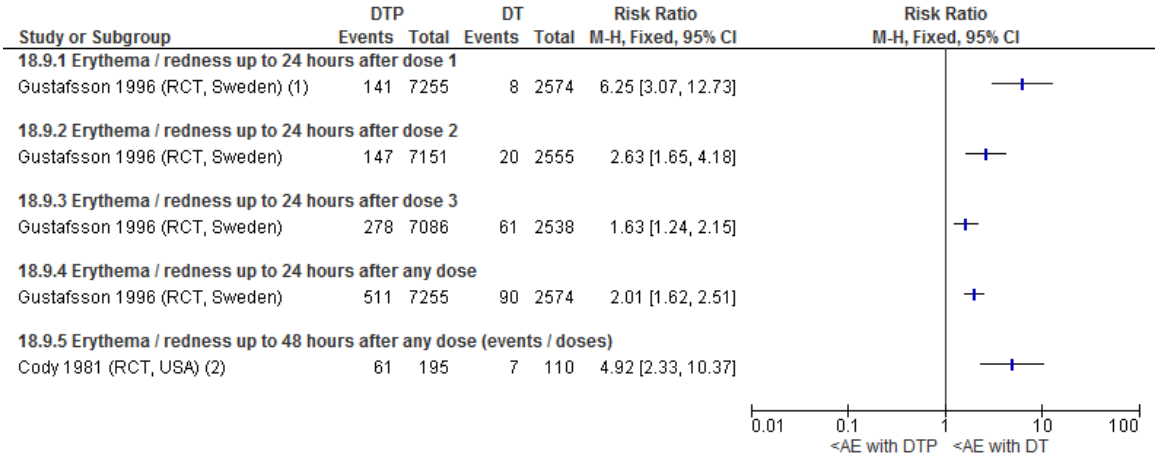
Footnotes

(1) DTwP, DTaP Connaught (5c) and SKB (2c) vs. DT, doses at 2, 4 and 6 mths. Measured within 24 hours of dose. Moderate risk of bias.

Erythema/redness

An RCT also found that there is a lower risk of Erythema/redness after DT doses 1 (RR 6.25, 95% CI 3.07 to 12.73; 9829 participants), 2 (RR 2.63, 95% CI 1.65 to 4.18; 9706 participants), 3 (RR 1.63, 95% CI 1.24 to 2.15; 9624 participants), and after any DT dose (RR 2.01, 95% CI 1.62 to 2.51; 9829 participants), compared to after DTP doses. Another RCT that measured doses as opposed to participants, and was subsequently not pooled with the other study, also found that there is a lower risk of Erythema/redness after any DT dose compared to DTP (RR 4.92, 95% CI 2.33 to 10.37; 305 doses).

Figure 18. Erythema/redness reactogenicity for any DTP vaccine compared to DT vaccine

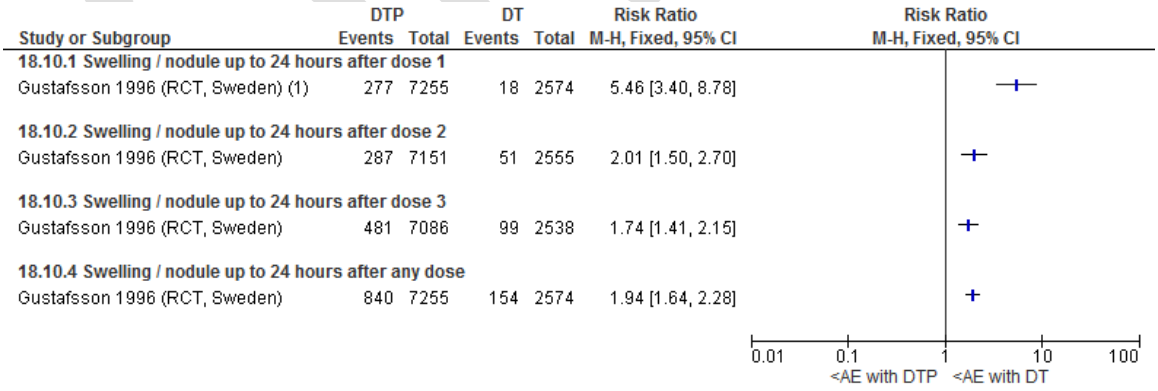


Footnotes
(1) DTwP, DTaP Connaught (5c) and SKB (2c) vs. DT, doses at 2, 4 and 6 mths. Redness ≥2 cm measured within 24 hours of dose....
(2) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Does not report by vaccination schedule

Swelling/nodule

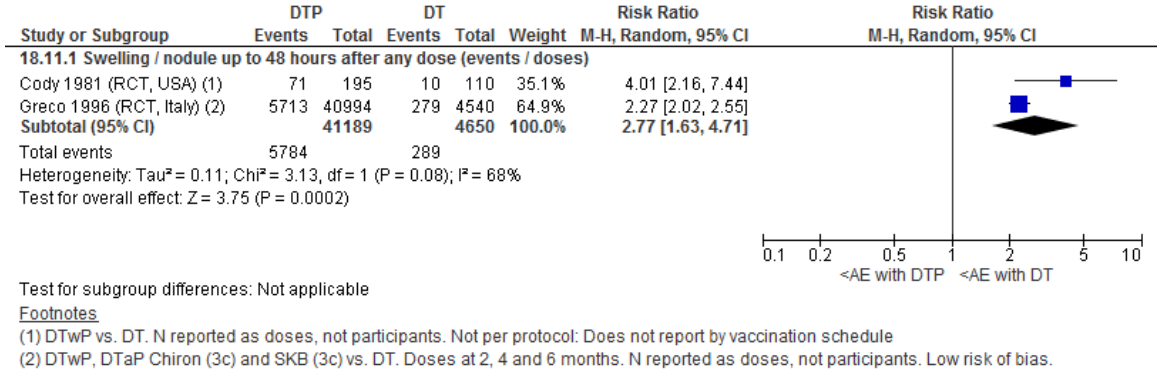
An RCT found that there is a lower risk of Swelling/nodule after DT doses 1 (RR 5.46, 95% CI 3.40 to 8.78; 9829 participants), 2 (RR 2.01, 95% CI 1.50 to 2.70; 9706 participants), 3 (RR 1.74, 95% CI 1.41 to 2.15; 9624 participants), and after any DT dose (RR 1.94, 95% CI 1.64 to 2.28; 9829 participants), compared to after DTP doses. Two RCTs that measured doses as opposed to participants, and was subsequently not pooled with the other study, found that there is a lower risk of Swelling/nodule after DT doses compared to DTP (RR 2.77, 95% CI 1.63 to 4.71; 45839 doses; random effects model due to high heterogeneity (I^2=68%), with fixed effects model: RR 2.31, 95% CI 2.06 to 2.59).

Figure 19. Single study outcome measures of Swelling/nodule reactogenicity for any DTP vaccine compared to DT vaccine



Footnotes
(1) DTwP, DTaP Connaught (5c) and SKB (2c) vs. DT. Doses at 2, 4 and 6 mths. Nodule ≥2 cm measured within 24 hours of dose. Moderate...

Figure 20. Meta-analyses of Swelling/nodule reactogenicity for any DTP vaccine compared to DT vaccine



Footnotes

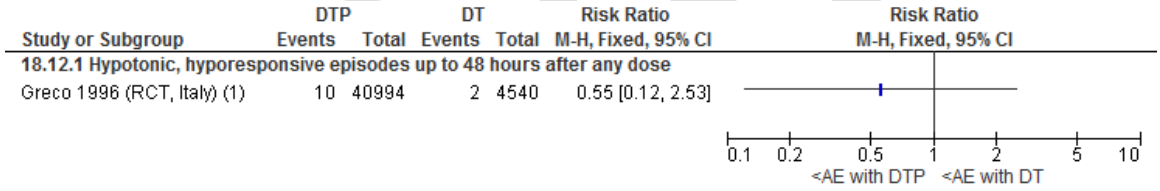
(1) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Does not report by vaccination schedule

(2) DTwP, DTaP Chiron (3c) and SKB (3c) vs. DT. Doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Hypotonic, hypo-responsive episodes

An RCT found no statistically significant difference between any DTP vaccine compared to DT vaccine for Hypotonic, hypo-responsive episodes up to 48 hours after any dose.

Figure 21. Hypotonic, hypo-responsive episodes reactogenicity for any DTP vaccine compared to DT vaccine



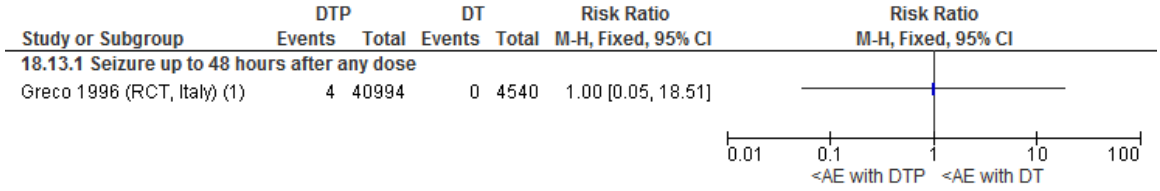
Footnotes

(1) DTwP, DTaP Chiron (3c) and SKB (3c) vs. DT. Doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Seizures

An RCT found no statistically significant difference between any DTP vaccine compared to DT vaccine for Seizures up to 48 hours after any dose.

Figure 22. Seizures reactogenicity for any DTP vaccine compared to DT vaccine



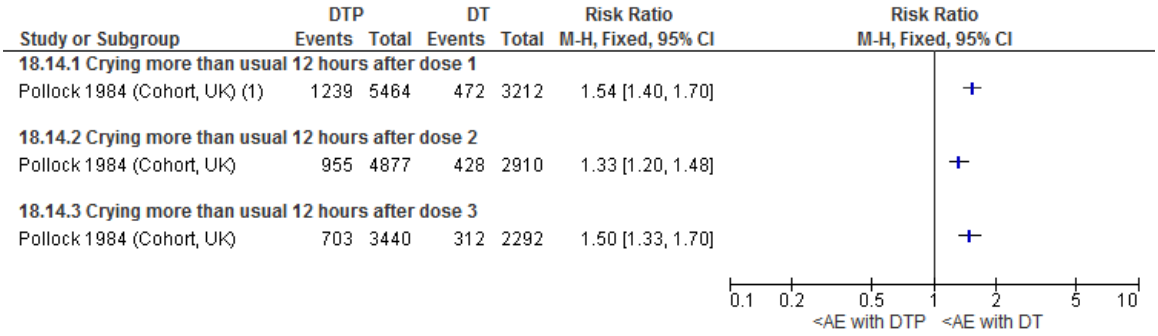
Footnotes

(1) DTwP, DTaP Chiron (3c) and SKB (3c) vs. DT. Doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Crying more than usual

A cohort study found that there is a lower risk of Crying more than usual after DT doses 1 (RR 1.54, 95% CI 1.40 to 1.70; 8676 participants), 2 (RR 1.33, 95% CI 1.20 to 1.48; 7787 participants), and 3 (RR 1.50, 95% CI 1.33 to 1.70; 5732 participants), compared to after DTP doses.

Figure 23. Crying more than usual reactogenicity for any DTP vaccine compared to DT vaccine

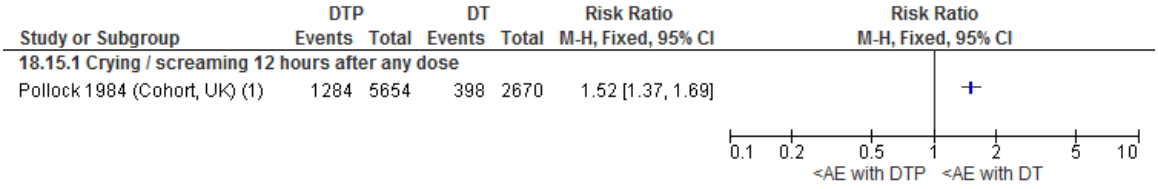


Footnotes
(1) DTwP and DTwP plain vs. DT, doses at 3, 4.5-6, 8-12 months. Measured 12 hours post-dose. High risk of bias.

Crying/screaming

A cohort study found that there is a lower risk of Crying/screaming 12 hours after any DT dose, compared to after any DTP dose (RR 1.52, 95% CI 1.37 to 1.69; 8324 participants).

Figure 24. Crying/screaming reactogenicity for any DTP vaccine compared to DT vaccine

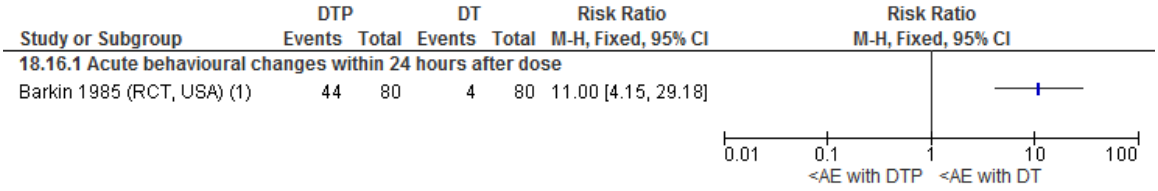


Footnotes
(1) DTwP and DTwP plain vs. DT, doses at 3, 4.5-6, 8-12 months. Measured 12 hours post-dose. High risk of bias.

Acute behavioural changes

An RCT found that there is a lower risk of Acute behavioural changes 24 hours after DT dose, compared to after DTP dose (RR 11.00, 95% CI 4.15 to 29.18; 160 doses).

Figure 25. Acute behavioural changes reactogenicity for any DTP vaccine compared to DT vaccine

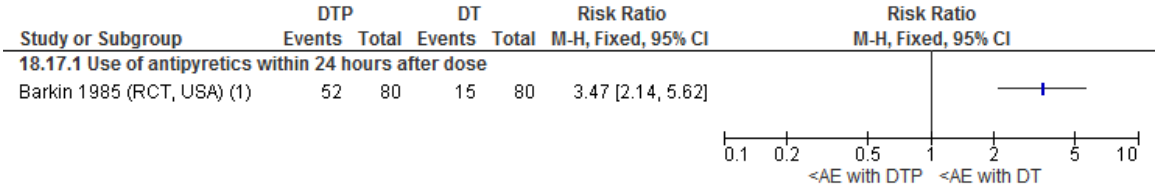


Footnotes
(1) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Reports no difference between two schedules.

Use of antipyretics

An RCT found that there is a lower risk of Use of antipyretics 24 hours after DT dose, compared to after DTP dose (RR 3.47, 95% CI 2.14 to 5.62; 160 doses).

Figure 26. Use of antipyretics reactogenicity for any DTP vaccine compared to DT vaccine

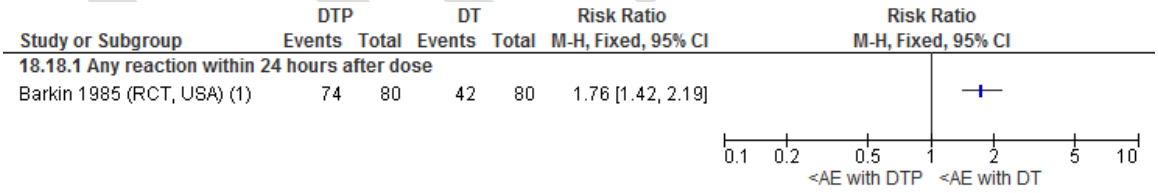


Footnotes
(1) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Reports no difference between two schedules.

Any reaction

An RCT found that there is a lower risk of Any reaction 24 hours after DT dose, compared to after DTP dose (RR 1.76, 95% CI 1.42 to 2.19; 160 doses).

Figure 27. Any reaction reactogenicity for any DTP vaccine compared to DT vaccine

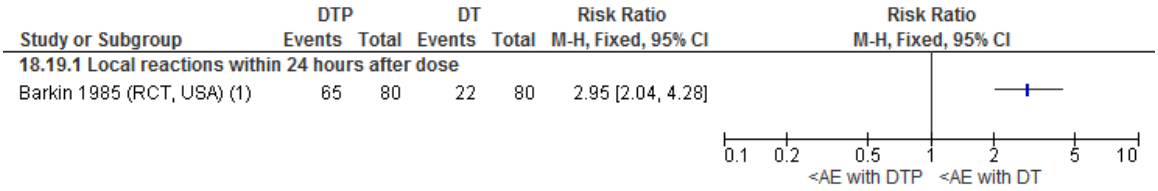


Footnotes
(1) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Reports no difference between two schedules.

Local reactions

An RCT found that there is a lower risk of Local reactions 24 hours after DT dose, compared to after DTP dose (RR 2.95, 95% CI 2.04 to 4.28; 160 doses).

Figure 28. Local reactions reactogenicity for any DTP vaccine compared to DT vaccine



Footnotes
(1) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Reports no difference between two schedules.

3.3 Any DTaP vaccine compared to DT vaccine (aP pertussis vaccines vs. no pertussis vaccine)

Two studies evaluated reactogenicity for DTaP vaccines versus DT vaccines. Gustafsson 1996 was an RCT conducted in Sweden of moderate risk of bias that administered DTaP SKB (2c), DTaP Connaught (5c), and DT doses at 2, 4, and 6 months. Greco 1996 was an RCT conducted in Italy of low risk of bias that administered DTaP Chiron (3c), DTaP SKB (3c), and DT doses at 2, 4, and 6 months.

Table 3. Characteristics of studies contributing to the DTaP vs. DT vaccines comparison

Study Country	Design	Status	Schedules	
Gustafsson 1996(2) Sweden	RCT	Included Moderate risk of bias	DTaP SKB (2c) and DTaP Connaught (5c) at 2, 4, and 6 months	DT at 2, 4, and 6 months
Greco 1996(1)* Italy	RCT	Included Low risk of bias	DTaP Chiron (3c) and DTaP SKB (3c) at 2, 4 and 6 months	DT at 2, 4, and 6 months

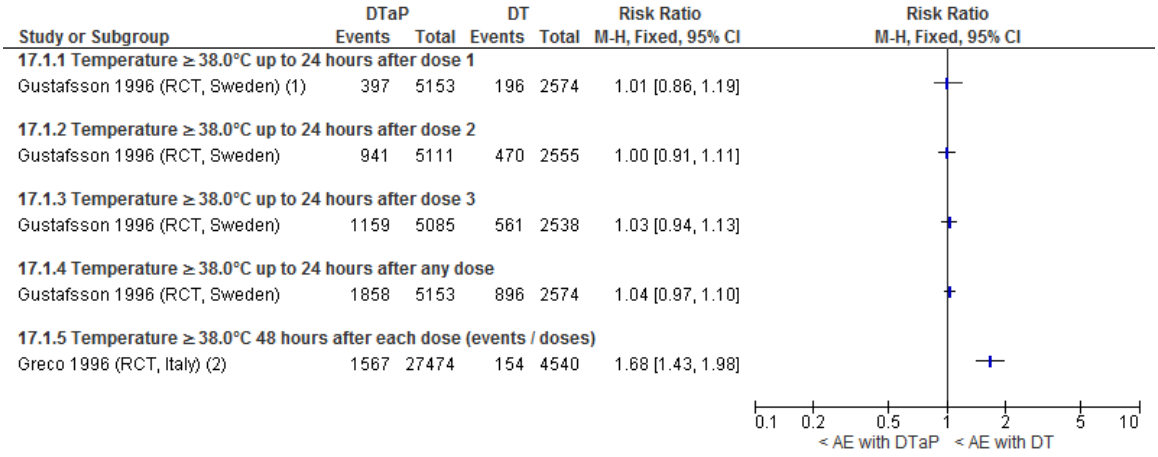
* Reported vaccine doses (as opposed to participants) as denominator

The studies reported on Temperature ≥38.0°C, Persistent crying, Hypotonic, hyporesponsive episodes, Local pain/tenderness, Erythema/redness, Swelling/nodule, and Seizures. Mostly, there were no significant differences in reactogenicity between DTaP vaccines and DT vaccine. However, for some timepoints for Temperature ≥38°C and Swelling/nodule the risk of adverse events was lower with DT vaccine, and for Hypotonic, hyporesponsive episode the risk of adverse events was lower with DTaP vaccines.

Temperature ≥38°C

One RCT found that there is a lower risk of Temperature ≥38°C after any DT dose compared to any DTaP vaccines dose (RR 1.68, 95% CI 1.43 to 1.98; 32014 doses). Another RCT found no statistically significant differences between DTaP vaccines compared to DT vaccine.

Figure 29. Temperature ≥38°C reactogenicity for DTaP vaccines compared to DT vaccine

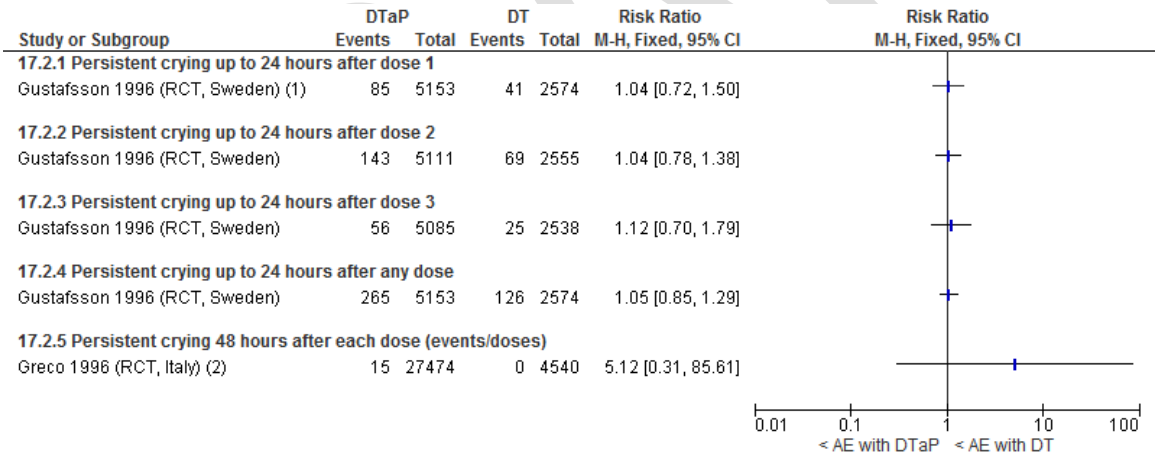


Footnotes
(1) DTaP Connaught (5c) or SKB (2c) vs. DT, doses at 2, 4 and 6 mths. Moderate risk of bias.
(2) DTaP Chiron (3c) or SKB (3c) vs. DT, doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Persistent crying

No statistically significant differences were found between DTaP vaccines compared to DT vaccine for Persistent crying.

Figure 30. Persistent crying reactogenicity for DTaP vaccines compared to DT vaccine

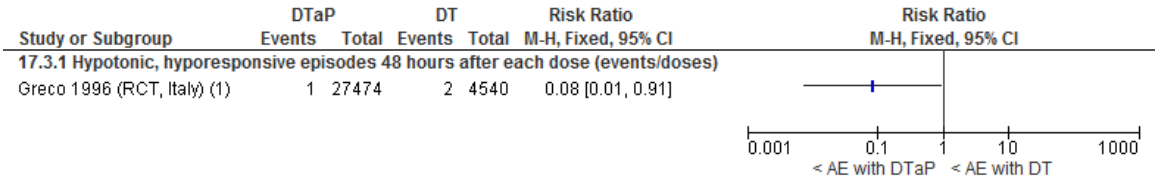


Footnotes
(1) Persistent crying ≥1h. DTaP Connaught (5c) or SKB (2c) vs. DT, doses at 2, 4 and 6 mths. Moderate risk of bias.
(2) Persistent crying ≥3h. DTaP Chiron (3c) or SKB (3c) vs. DT, doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of...

Hypotonic, hyporesponsive episode

One RCT found that there is a lower risk of Hypotonic, hyporesponsive episode after any DTaP dose compared to any DT dose (RR 0.08, 95% CI 0.01 to 0.91; 32014 doses).

Figure 31. Hypotonic, hyporesponsive episode reactogenicity for DTaP vaccines compared to DT vaccine



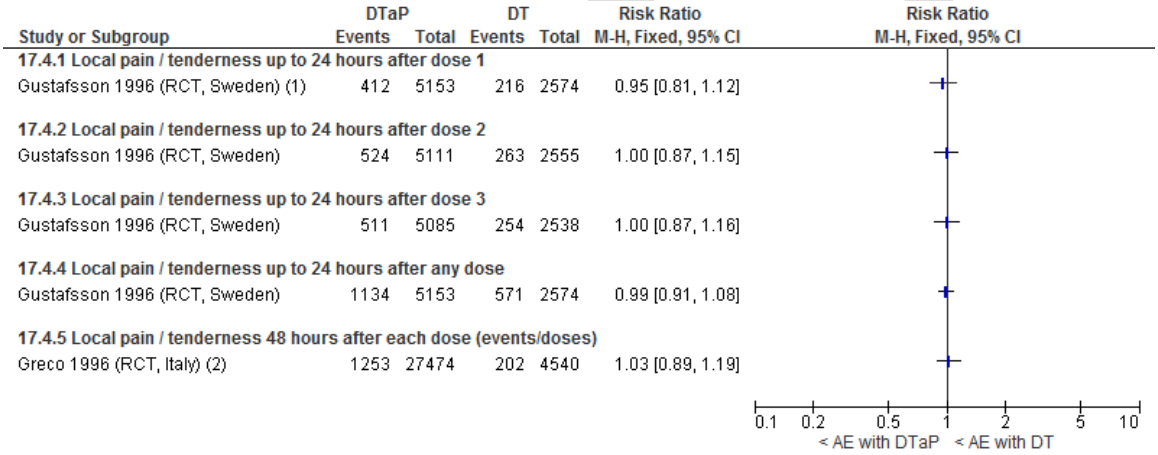
Footnotes

(1) DTaP Chiron (3c) or SKB (3c) vs. DT, doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Local pain/tenderness

No statistically significant differences were found between DTaP vaccines compared to DT vaccine for Local pain/tenderness.

Figure 32. Local pain/tenderness reactogenicity for DTaP vaccines compared to DT vaccine



Footnotes

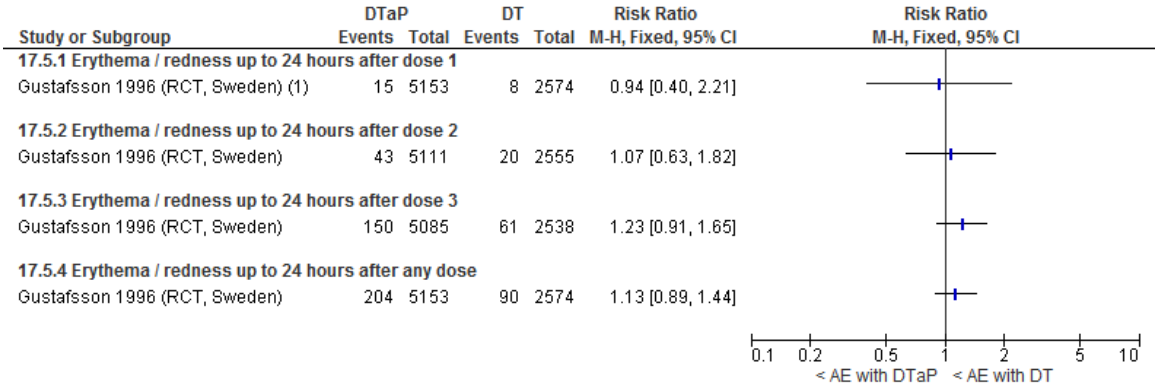
(1) DTaP Connaught (5c) or SKB (2c) vs. DT, doses at 2, 4 and 6 mths. Moderate risk of bias.

(2) DTaP Chiron (3c) or SKB (3c) vs. DT, doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Erythema/redness

No statistically significant differences were found between DTaP vaccines compared to DT vaccine for Erythema/redness.

Figure 33. Erythema/redness reactogenicity for DTaP vaccines compared to DT vaccine

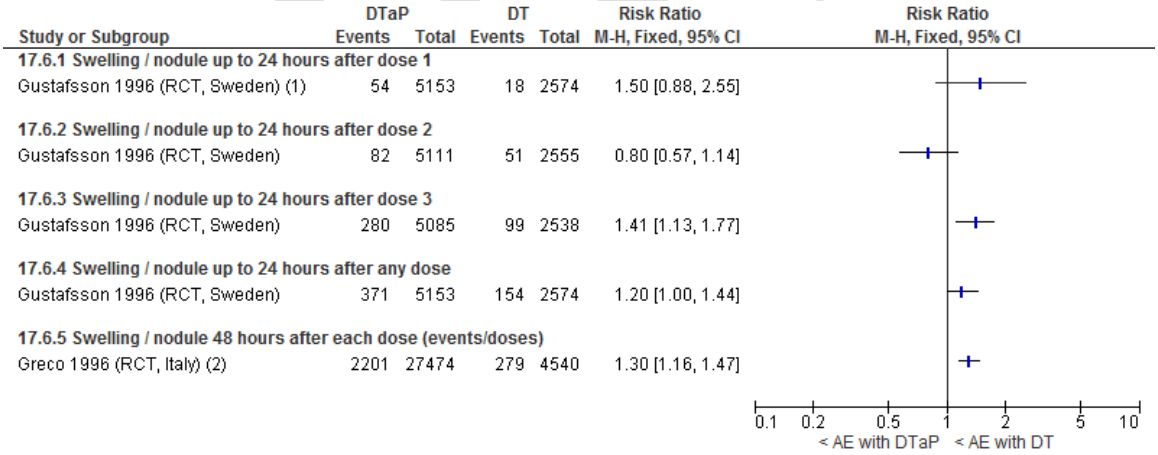


Footnotes
(1) Redness ≥2cm. DTaP Connaught (5c) or SKB (2c) vs. DT, doses at 2, 4 and 6 mths. Moderate risk of bias.

Swelling/nodule

One RCT found that there is a lower risk of Swelling/nodule after DT dose 3 (RR 1.41, 95% CI 1.13 to 1.77; 7623 participants), and after any DT dose (RR 1.20, 95% CI 1.00 to 1.44; 7727 participants) compared to DTaP vaccines doses. Another RCT that reported on doses as opposed to participants also found that there is a lower risk of Swelling/nodule after any DT dose (RR 1.30, 95% CI 1.16 to 1.47; 32014 doses) compared to after DTaP vaccines doses. An RCT found no statistically significant differences between DTaP vaccines compared to DT vaccine after doses 1 and 2 for Swelling/nodule.

Figure 34. Swelling/nodule reactogenicity for DTaP vaccines compared to DT vaccine

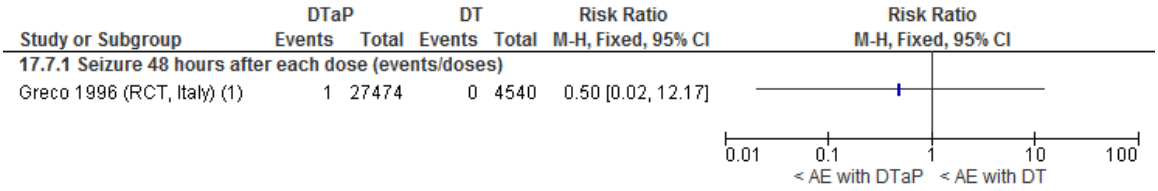


Footnotes
(1) Nodule ≥2cm. DTaP Connaught (5c) or SKB (2c) vs. DT, doses at 2, 4 and 6 mths. Moderate risk of bias.
(2) DTaP Chiron (3c) or SKB (3c) vs. DT, doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Seizures

No statistically significant difference was found between DTaP vaccines compared to DT vaccine for Seizures.

Figure 35. Seizures reactogenicity for DTaP vaccines compared to DT vaccine



Footnotes
(1) DTaP Chiron (3c) or SKB (3c) vs. DT, doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

3.4 Any DTwP vaccine compared to DT vaccine (wP pertussis vaccines vs. no pertussis vaccine)

Five studies evaluated reactogenicity for DTwP versus DT pertussis vaccines. Greco 1996 was an RCT conducted in Italy of low risk of bias that administered DTwP doses at 2, 4 and 6 months. Gustafsson 1996 was an RCT conducted in Sweden of moderate risk of bias that administered DTwP doses at 2, 4, and 6 months. Pollock 1984 was a cohort study conducted in the UK of high risk of bias that administered DTwP and DTwP plain doses at 3, 4.5-6 and 8-12 months. Barkin 1985 was a double-blind RCT conducted in the USA of unclear risk of bias that administered DTwP doses at 2, 4 and 6 months. It should be noted that Barkin 1985 does not fit with this protocol as it does not report differences between the two schedules. Cody 1981 was a double-blind RCT conducted in the USA of unclear risk of bias that administered DTwP. It should be noted that Cody 1981 does not fit with this protocol as it does not report by vaccine schedule.

Table 4. Characteristics of studies contributing to the any DTwP vs. DT vaccines comparison

Study Country	Design	Status	Schedules	
Greco 1996(1)* Italy	RCT	Included Low risk of bias	DTwP at 2, 4, and 6 months	DT at 2, 4, and 6 months
Gustafsson 1996(2) Sweden	RCT	Included Moderate risk of bias	DTwP at 2, 4, and 6 months	DT at 2, 4, and 6 months
Pollock 1984(4) UK	Cohort	Included High risk of bias	DTwP and DTwP plain at 3, 4.5-6, and 8-12 months	DT at 3, 4.5-6, and 8-12 months
Barkin 1985(5)* USA	RCT	Additional study Not per protocol: Reports no difference between two schedules	DTwP – DTwP – DT at 2, 4, and 6 months	DTwP – DT – DTwP at 2, 4, and 6 months
			DTwP doses were compared to DT doses across schedules	
Cody 1981(6)* USA	RCT	Additional study Not per protocol: Does	DTwP with no application of a	DT with no application of a

Study Country	Design	Status	Schedules	
		not report by vaccination schedule	specific vaccination schedule	specific vaccination schedule

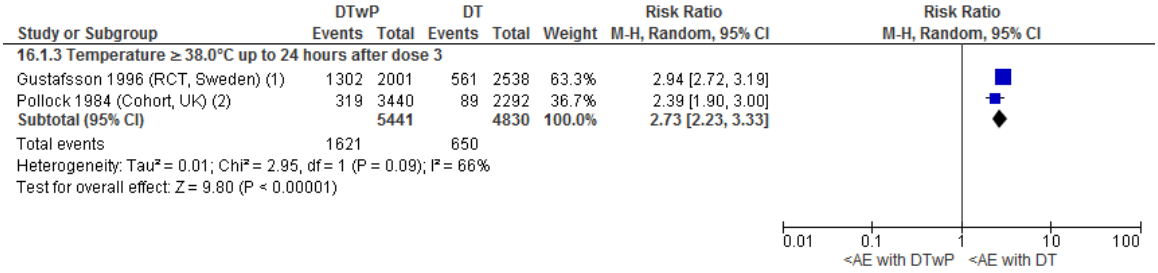
* Reported vaccine doses (as opposed to participants) as denominator

The studies reported on Temperature ≥38.0°C, Persistent crying, Local pain/tenderness, Erythema/redness, Swelling/nodule, Hypotonic, hypo-responsive episodes, Seizure, Crying more than usual, Crying/screaming, Acute behavioural changes, Use of antipyretics, Any reaction, and Local reactions. Mostly, the risk of adverse events was lower for children after vaccination with DT vaccine without pertussis vaccine compared to DTwP vaccines that include whole-cell pertussis vaccine, however, for Seizures and Hypotonic, hyporesponsive episodes and for some timepoints for Persistent crying, there were no statistically significant differences.

Temperature ≥38°C

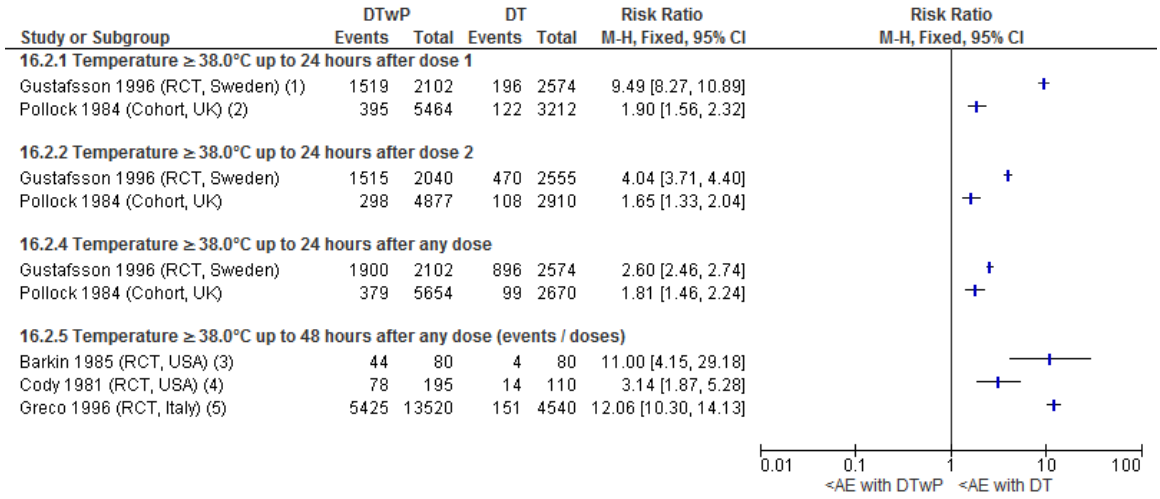
An RCT and a cohort study found that there is a lower risk of Temperature ≥38°C after DT dose 3 compared to DTwP and DTwP plain doses (RR 2.73, 95% CI 2.23 to 3.33; 10271 participants). A random effects model was used due to high heterogeneity (I^2 = 66%; with fixed effects model: RR 2.85, 95% CI 2.64 to 3.07). Studies were not pooled for the remaining outcome measures due to very high heterogeneity (I^2 ≥ 91%). An RCT found that there is a lower risk of Temperature ≥38°C after DT doses 1 (RR 9.49, 95% CI 8.27 to 10.89; 4676 participants) and 2 (RR 4.05, 95% CI 3.71 to 4.40; 4595 participants) and after any DT dose (RR 2.60, 95% CI 2.46 to 2.74; 2998 participants), compared to after DTwP doses. A cohort study also found that there is a lower risk of Temperature ≥38°C after DT doses 1 (RR 1.90, 95% CI 1.56 to 2.32; 8676 participants) and 2 (RR 1.65, 95% CI 1.33 to 2.04; 7787 participants) and after any DT dose (RR 1.81, 95% CI 1.46 to 2.24; 8324 participants), compared to after DTwP and DTwP plain doses. Three RCTs that measured doses as opposed to participants, also found that there is a lower risk of Temperature ≥38°C after any DT dose (RR 11.00, 95% CI 4.15 to 29.18, 160 doses; RR 3.14, 95% CI 1.87 to 5.28, 305 doses; and RR 12.06, 95% CI 10.30 to 14.13, 18060 doses), compared to after DTwP doses.

Figure 36. Meta analyses of Temperature ≥38.0°C reactogenicity for DTwP vaccines compared to DT vaccine



Footnotes
(1) DTwP vs. DT, doses at 2, 4 and 6 mths. Measured within 24 hours of dose. Moderate risk of bias.
(2) Feverishness,12 hours post dose. DTwP or DTwP plain vs. DT, doses at 3, 4.5-6, 8-12 months. High risk of bias.

Figure 37. Single study outcome measures of Temperature ≥38.0°C reactogenicity for DTwP vaccines compared to DT vaccine

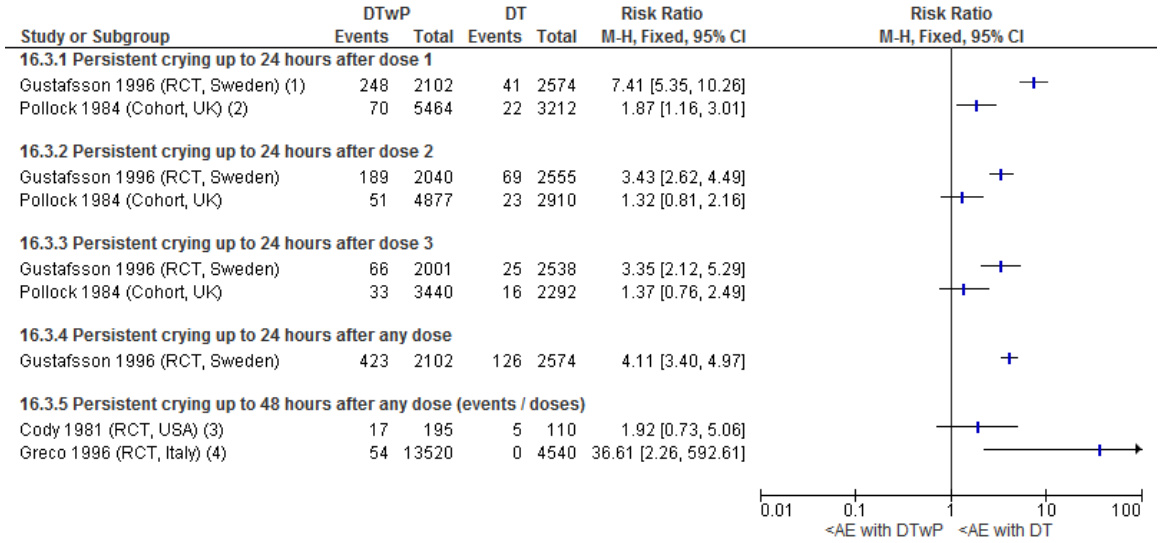


Footnotes
(1) DTwP vs. DT, doses at 2, 4 and 6 mths. Measured within 24 hours of dose. Moderate risk of bias.
(2) Feverishness,12 hours post dose. DTwP or DTwP plain vs. DT, doses at 3, 4.5-6, 8-12 months. High risk of bias.
(3) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Reports no difference between two schedules.
(4) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Does not report by vaccination schedule
(5) DTwP vs. DT, doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Persistent crying

An RCT (RR 7.41, 95% CI 5.35 to 10.26; 4676 participants) and a cohort study (RR 1.87, 95% CI 1.16 to 3.01; 8676 participants) found that there is a lower risk of Persistent crying after DT dose 1, compared to DTwP and DTwP plain doses, but results were not pooled due to very high heterogeneity (I^2=95%). An RCT found that there is a lower risk of Persistent crying after DT doses 2 (RR 3.43, 95% CI 2.62 to 4.49; 4595 participants), 3 (RR 3.35, 95% CI 2.12 to 5.29; 4539 participants), and after any DT dose (RR 4.11, 95% CI 3.40 to 4.97; 4676 participants), compared to DTwP doses. An RCT found that there is a lower risk of Persistent crying after any DT dose (RR 36.61, 95% CI 2.26 to 592.61; 18060 doses), compared to DTwP doses. A cohort study did not find any statistically significant differences for Persistent crying between DTwP and DT after dose 2 or 3, and an RCT did not find any statistically significant differences for Persistent crying between DTwP and DT after any dose. The studies were not pooled due to very high heterogeneity (I^2 > 82%).

Figure 38. Persistent crying reactogenicity for DTwP vaccines compared to DT vaccine

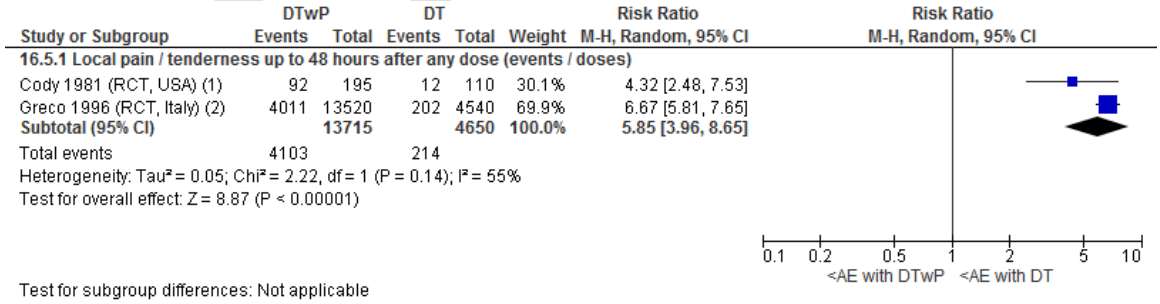


Footnotes
(1) DTwP vs. DT, doses at 2, 4 and 6 mths. Persistent crying ≥1h measured within 24 hours of dose. Moderate risk of bias.
(2) Persistent crying >5h, 12 hours post-dose. DTwP or DTwP plain vs. DT, doses at 3, 4.5-6, 8-12 months. High risk of bias.
(3) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Does not report by vaccination schedule
(4) DTwP vs. DT, doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Local pain/tenderness

An RCT found that there is a lower risk of Local pain/tenderness after DT doses 1, 2, 3, and after any DT dose, compared to after DTwP doses, with a RR range of 3.63 to 7.09 and a 95% CI range of 3.37 to 8.10 after different doses. Two RCTs that measured doses as opposed to participants, and was subsequently not pooled with the other study, found that there is a lower risk of Local pain/tenderness after DT doses compared to DTwP (RR 5.85, 95% CI 3.96 to 8.65; 18365 doses). Local pain/tenderness up to 48 hours after any dose was analysed with a random effects model due to high heterogeneity (I^2=55%, with a fixed effects model: RR 6.55, 95% CI 5.74 to 7.49).

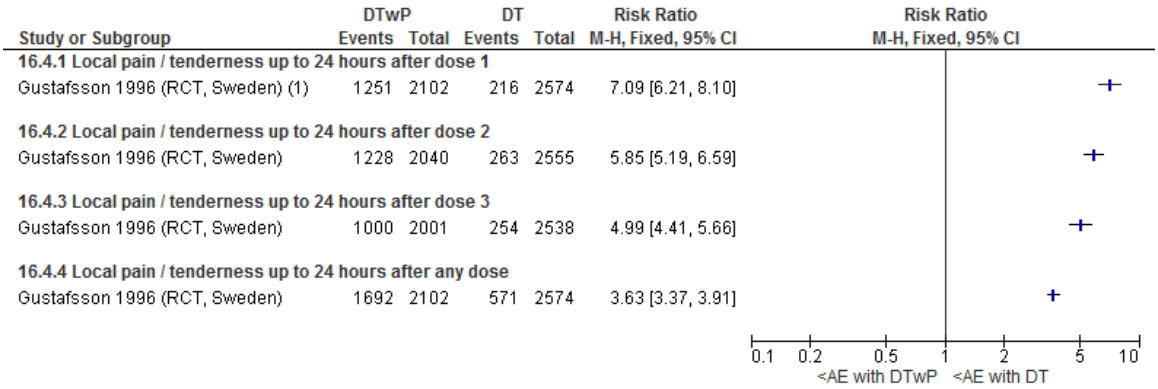
Figure 39. Meta analyses of Local pain/tenderness reactogenicity for DTwP vaccines compared to DT vaccine



Test for subgroup differences: Not applicable

Footnotes
(1) DTwP vs. DT. Pain. N reported as doses, not participants. Not per protocol: Does not report by vaccination schedule
(2) DTwP vs. DT. Doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Figure 40. Single study outcome measures of Local pain/tenderness reactogenicity for DTwP vaccines compared to DT vaccine

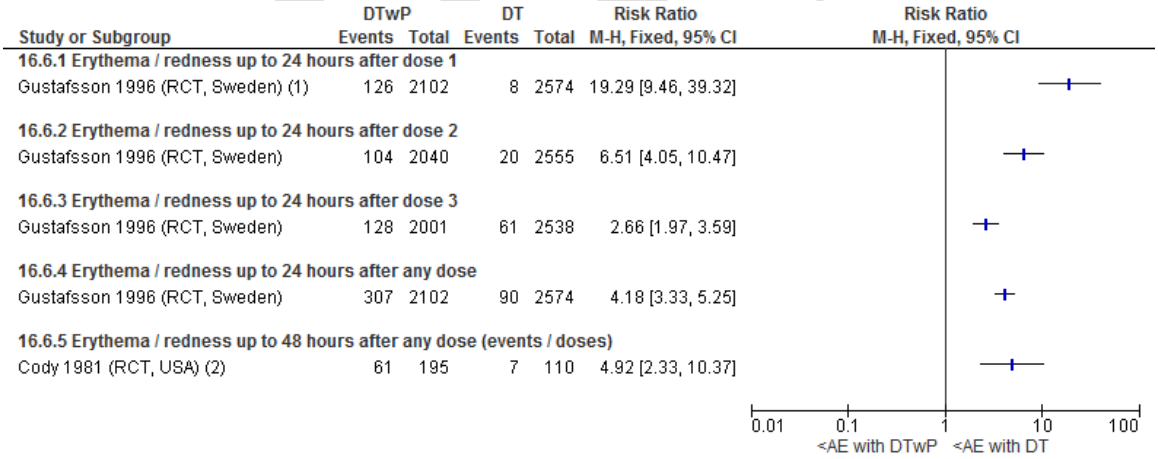


Footnotes
(1) DTwP vs. DT, doses at 2, 4 and 6 mths. Measured within 24 hours of dose. Moderate risk of bias.

Erythema/redness

An RCT found that there is a lower risk of Erythema/redness after DT doses 1, 2, 3, and after any DT dose, compared to after DTwP doses, with a RR range of 2.66 to 19.29 and a 95% CI range of 1.97 to 39.32 after different doses. Another RCT that measured doses as opposed to participants, and was subsequently not pooled with the other study, also found that there is a lower risk of Erythema/redness after DT doses compared to DTwP (RR 4.92, 95% CI 2.33 to 10.37; 305 doses).

Figure 41. Erythema/redness reactogenicity for DTwP compared to DT vaccine



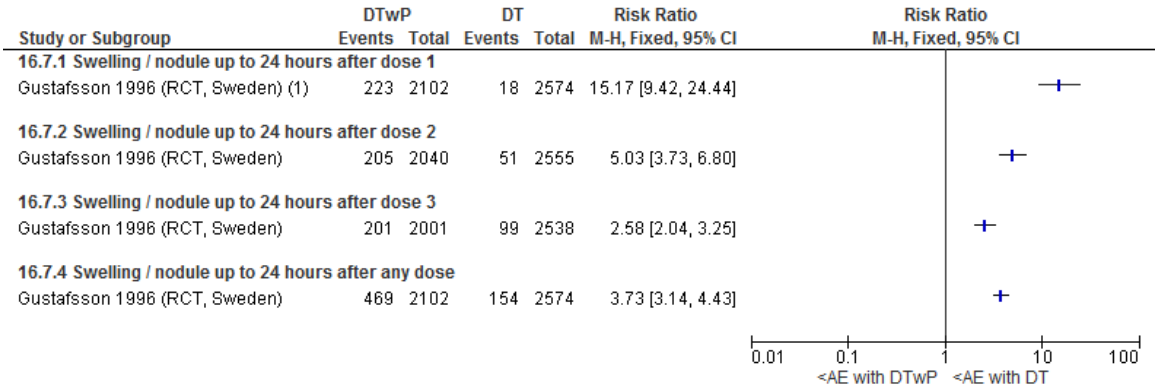
Footnotes
(1) DTwP vs. DT, doses at 2, 4 and 6 mths. Redness ≥2 cm measured within 24 hours of dose. Moderate risk of bias.
(2) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Does not report by vaccination schedule

Swelling/nodule

An RCT found that there is a lower risk of Swelling/nodule after DT doses 1, 2, 3, and after any DT dose, compared to after DTwP doses, with a RR range of 2.58 to 15.17 and a 95% CI range of 2.04 to 24.44 after different doses. Two RCTs that measured doses as opposed to participants, and was subsequently not pooled with the other study, found that there is a lower risk of

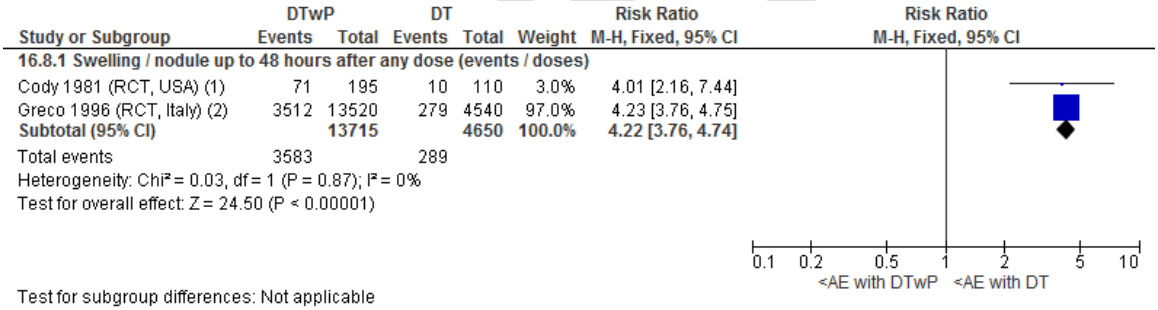
Swelling/nodule after DT doses compared to DTwP (RR 4.22, 95% CI 3.76 to 4.74; 18365 doses).

Figure 42. Single study outcome measures of Swelling/nodule reactogenicity for DTwP vaccines compared to DT vaccine



Footnotes
(1) DTwP vs. DT, doses at 2, 4 and 6 mths. Nodule ≥2 cm measured within 24 hours of dose. Moderate risk of bias.

Figure 43. Meta-analyses of Swelling/nodule reactogenicity for DTwP vaccines compared to DT vaccine



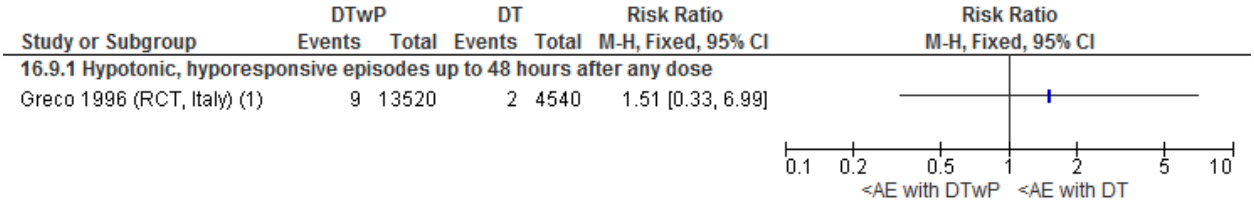
Test for subgroup differences: Not applicable

Footnotes
(1) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Does not report by vaccination schedule
(2) DTwP vs. DT, doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Hypotonic, hypo-responsive episodes

An RCT found no statistically significant difference between DTwP compared to DT vaccines for Hypotonic, hypo-responsive episodes up to 48 hours after any dose.

Figure 44. Hypotonic, hypo-responsive episodes reactogenicity for DTwP vaccines compared to DT vaccine



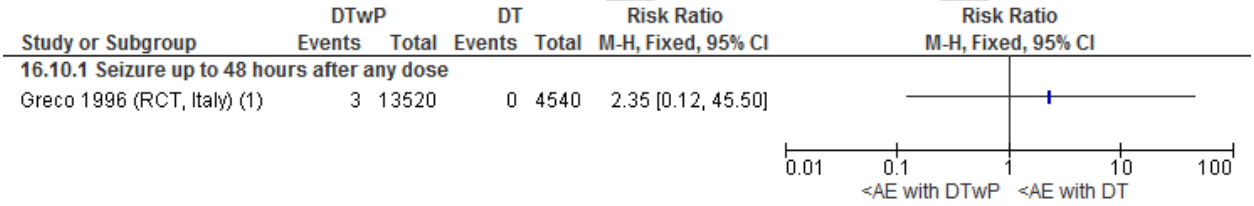
Footnotes

(1) DTwP vs. DT, doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Seizures

An RCT found no statistically significant difference between DTwP compared to DT vaccines for Seizures up to 48 hours after any dose.

Figure 45. Seizures reactogenicity for DTwP vaccines compared to DT vaccine



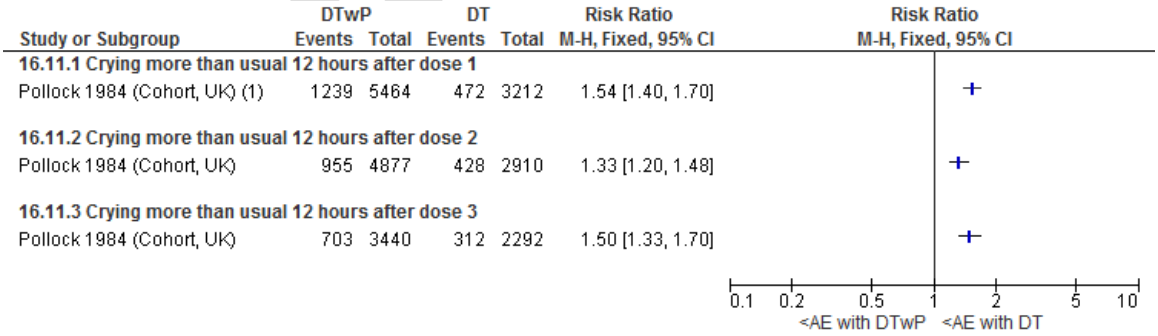
Footnotes

(1) DTwP vs. DT, doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Crying more than usual

A cohort study found that there is a lower risk of Crying more than usual after DT doses 1 (RR 1.54, 95% CI 1.40 to 1.70; 8676 participants), 2 (RR 1.33, 95% CI 1.20 to 1.48; 7787 participants), and 3 (RR 1.50, 95% CI 1.33 to 1.70; 5732 participants), compared to after DTwP or DTwP plain doses.

Figure 46. Crying more than usual reactogenicity for DTwP vaccines compared to DT vaccine



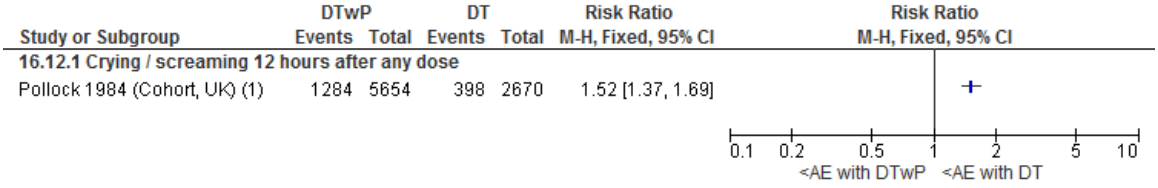
Footnotes

(1) DTwP or DTwP plain vaccines vs. DT vaccine, doses at 3, 4.5-6, 8-12 months. Measured 12 hours post-dose. High risk of bias.

Crying/screaming

A cohort study found that there is a lower risk of Crying/screaming 12 hours after any DT dose, compared to after any DTwP or DTwP plain dose (RR 1.52, 95% CI 1.37 to 1.69; 8324 participants).

Figure 47. Crying/screaming reactogenicity for DTwP vaccines compared to DT vaccine



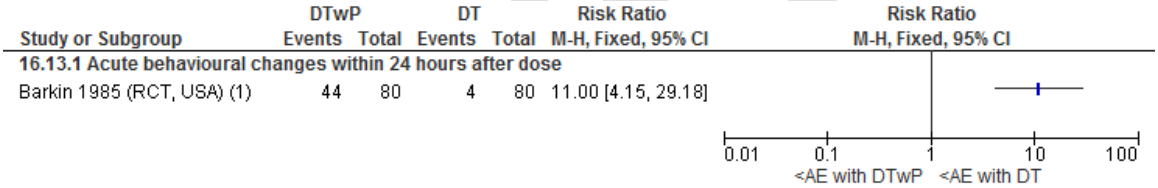
Footnotes

(1) DTwP or DTwP plain vaccines vs. DT vaccine, doses at 3, 4.5-6, 8-12 months. Measured 12 hours post-dose. High risk of bias.

Acute behavioural changes

An RCT found that there is a lower risk of Acute behavioural changes 24 hours after DT dose, compared to after DTwP dose (RR 11.00, 95% CI 4.15 to 29.18; 160 doses).

Figure 48. Acute behavioural changes reactogenicity for DTwP vaccines compared to DT vaccine



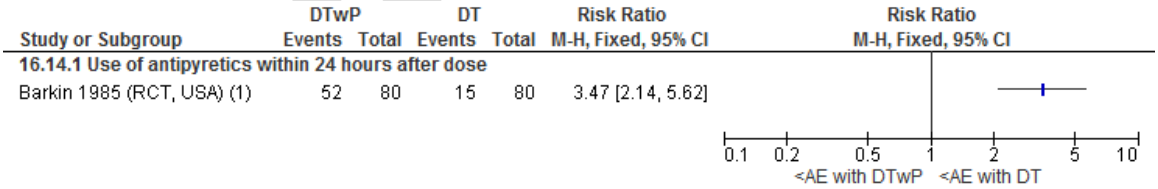
Footnotes

(1) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Reports no difference between two schedules.

Use of antipyretics

An RCT found that there is a lower risk of Use of antipyretics 24 hours after DT dose, compared to after DTwP dose (RR 3.47, 95% CI 2.14 to 5.62; 160 doses).

Figure 49. Use of antipyretics reactogenicity for DTwP vaccines compared to DT vaccine



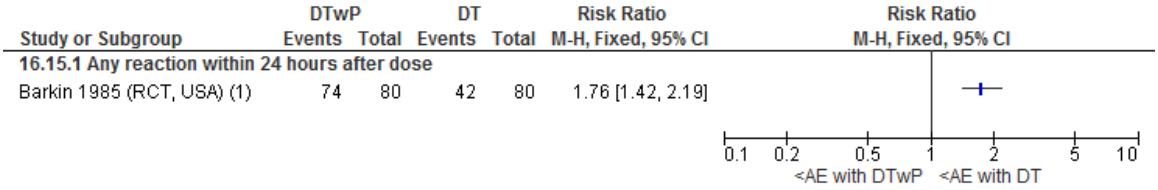
Footnotes

(1) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Reports no difference between two schedules.

Any reaction

An RCT found that there is a lower risk of Any reaction 24 hours after DT dose, compared to after DTwP dose (RR 1.76, 95% CI 1.42 to 2.19; 160 doses).

Figure 50. Any reaction reactogenicity for DTwP vaccines compared to DT vaccine

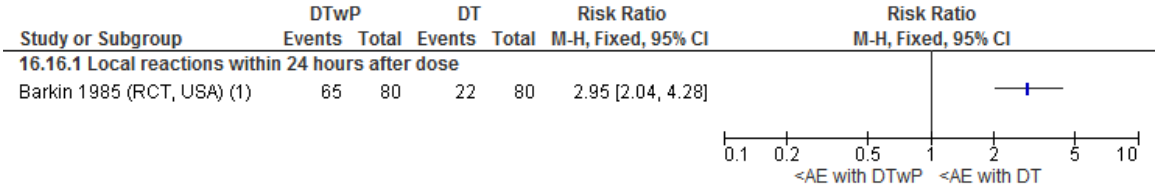


Footnotes
(1) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Reports no difference between two schedules.

Local reactions

An RCT found that there is a lower risk of Local reactions 24 hours after DT dose, compared to after DTwP dose (RR 2.95, 95% CI 2.04 to 4.28; 160 doses).

Figure 51. Local reactions reactogenicity for DTwP vaccines compared to DT vaccine



Footnotes
(1) DTwP vs. DT. N reported as doses, not participants. Not per protocol: Reports no difference between two schedules.

3.5 DTaP 2c vaccine compared to DT vaccine

One study evaluated reactogenicity for DTaP 2c versus DT vaccines. Gustafsson 1996 was an RCT conducted in Sweden of moderate risk of bias that administered DTaP SKB (2c) doses at 2, 4, and 6 months compared to DT doses at 2, 4, and 6 months. The study also had a DTaP 5c vaccine arm not included in this comparison.

Table 5. Characteristics of studies contributing to the DTaP 2c vs. DT vaccines comparison

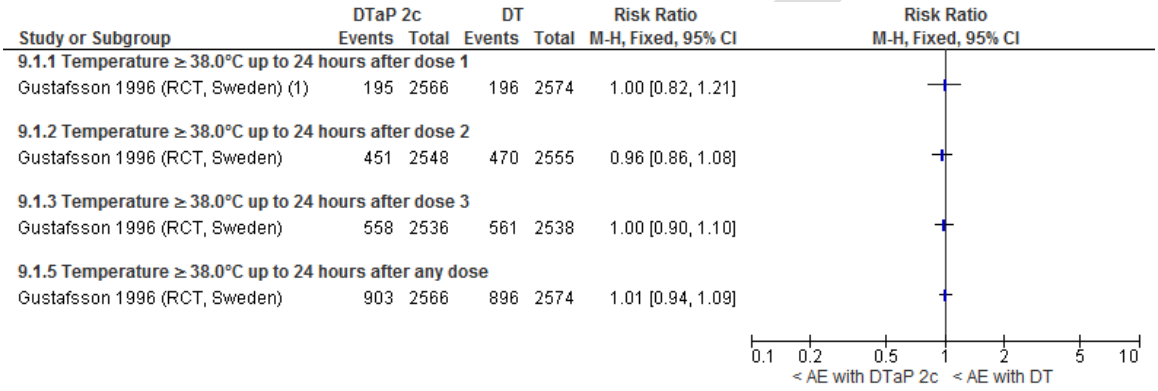
Study Country	Design	Status	Schedules	
Gustafsson 1996(2) Sweden	RCT	Included Moderate risk of bias	DTaP SKB (2c) at 2, 4, and 6 months	DT at 2, 4, and 6 months

The study reported on Temperature ≥38.0°C, Persistent crying, Local pain/tenderness, Erythema/redness, and Swelling/nodule. There were no significant differences in reactogenicity between DTaP 2c and DT vaccines.

Temperature ≥38°C

No statistically significant differences were found between DTaP 2c compared to DT vaccines for Temperature ≥38.0°C.

Figure 52. Temperature ≥38°C reactogenicity for DTaP 2c compared to DT



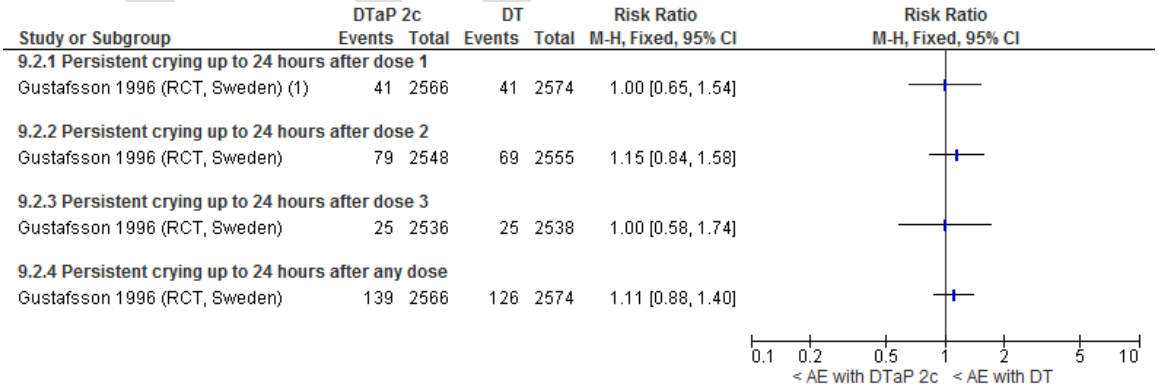
Footnotes
(1) SKB (2c), doses at 2, 4 and 6 mths. Moderate risk of bias.

DT= diphtheria-tetanus

Persistent crying

No statistically significant differences were found between DTaP 2c compared to DT vaccines for Persistent crying.

Figure 53. Persistent crying reactogenicity for DTaP 2c compared to DT



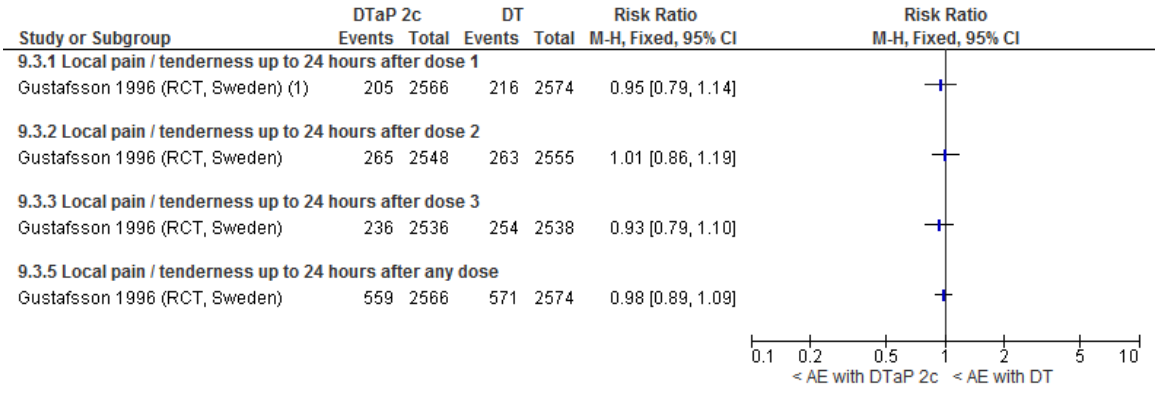
Footnotes
(1) Persistent crying ≥1h. SKB (2c), doses at 2, 4 and 6 mths. Moderate risk of bias.

DT= diphtheria-tetanus

Local pain/tenderness

No statistically significant differences were found between DTaP 2c compared to DT vaccines for Local pain/tenderness.

Figure 54. Local pain/tenderness reactogenicity for DTaP 2c compared to DT



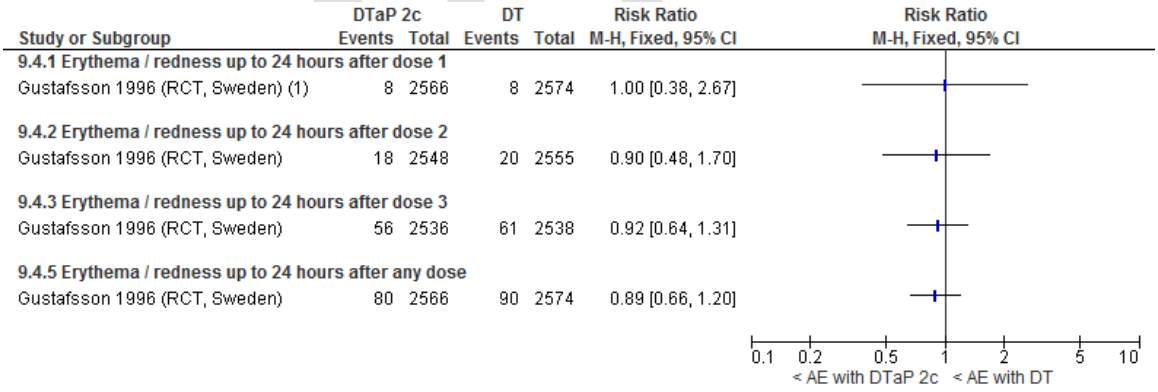
Footnotes
(1) SKB (2c), doses at 2, 4 and 6 mths. Moderate risk of bias.

DT= diphtheria-tetanus

Erythema/redness

No statistically significant differences were found between DTaP 2c compared to DT vaccines for Erythema/redness.

Figure 55. Erythema/redness reactogenicity for DTaP 2c compared to DT



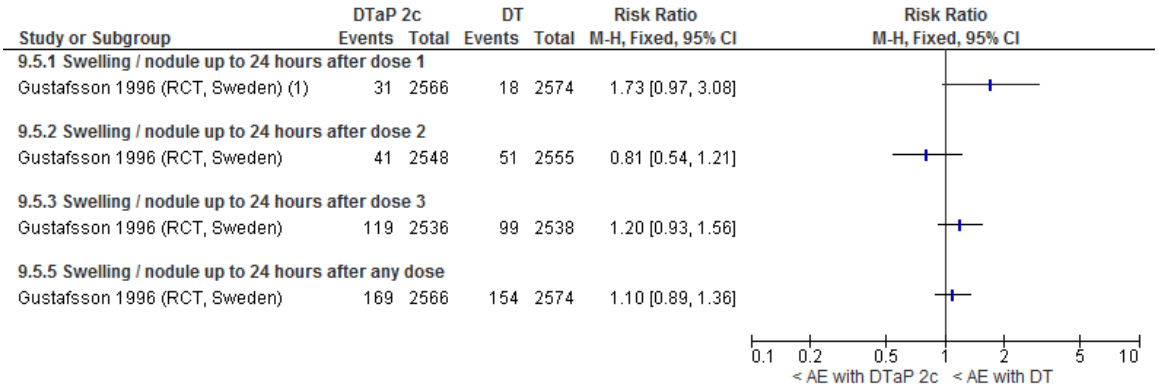
Footnotes
(1) Redness ≥2cm. SKB (2c), doses at 2, 4 and 6 mths. Moderate risk of bias.

DT= diphtheria-tetanus

Swelling/nodule

No statistically significant differences were found between DTaP 2c compared to DT vaccines for Swelling/nodule.

Figure 56. Swelling/nodule reactogenicity for DTaP 2c compared to DT



Footnotes
(1) Nodule ≥2cm. SKB (2c), doses at 2, 4 and 6 mths. Moderate risk of bias.

DT= diphtheria-tetanus

3.6 DTaP 5c vaccine compared to DT vaccine

One study evaluated reactogenicity for DTaP 5c versus DT vaccines. Gustafsson 1996 was an RCT conducted in Sweden of moderate risk of bias that administered DTaP Connaught (5c) doses at 2, 4, and 6 months compared to DT doses at 2, 4, and 6 months. The study also had a DTaP 2c vaccine arm not included in this comparison.

Table 6. Characteristics of studies contributing to the DTaP 5c vs. DT comparison

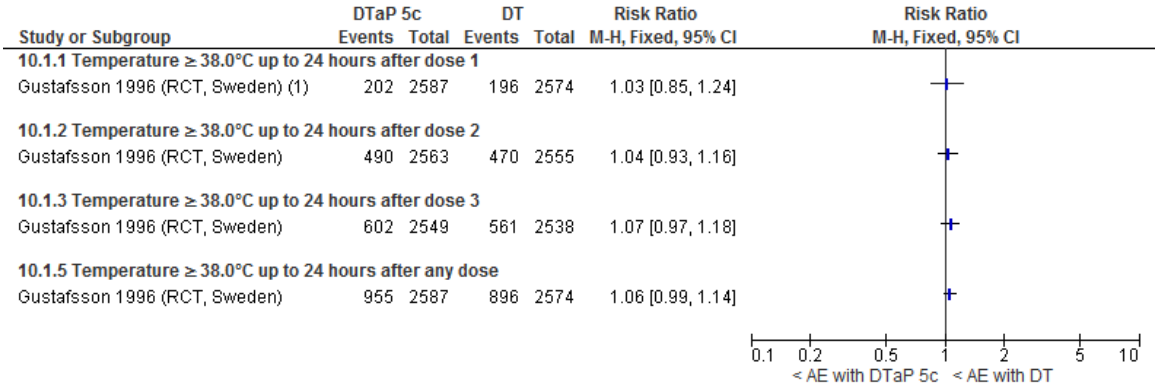
Study Country	Design	Status	Schedules	
Gustafsson 1996(2) Sweden	RCT	Included Moderate risk of bias	DTaP Connaught (5c) at 2, 4, and 6 months	DT at 2, 4, and 6 months

The study reported on Temperature ≥38.0°C, Persistent crying, Local pain/tenderness, Erythema/redness, and Swelling/nodule. Mostly, there were no significant differences in reactogenicity between DTaP 5c and DT vaccines, however, when there were, there was a lower risk of adverse events with DT vaccine.

Temperature ≥38°C

No statistically significant differences were found between DTaP 5c compared to DT vaccines for Temperature ≥38.0°C.

Figure 57. Temperature ≥38°C reactogenicity for DTaP 5c compared to DT



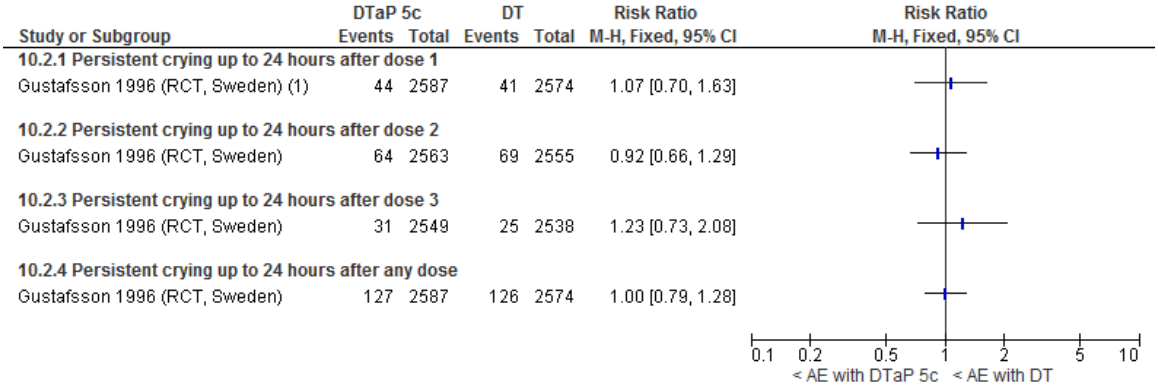
Footnotes
(1) Connaught (5c), doses at 2, 4 and 6 mths. Moderate risk of bias.

DT= diphtheria-tetanus

Persistent crying

No statistically significant differences were found between DTaP 5c compared to DT vaccines for Persistent crying.

Figure 58. Persistent crying reactogenicity for DTaP 5c compared to DT



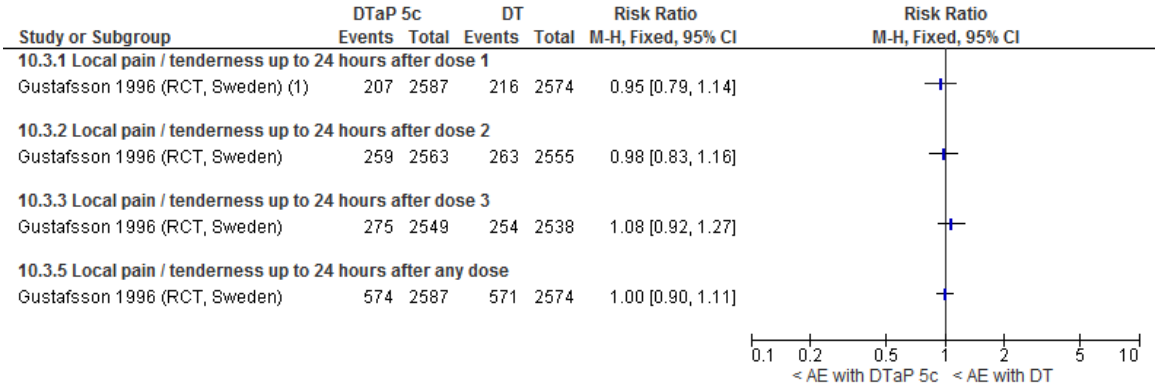
Footnotes
(1) Connaught (5c), doses at 2, 4 and 6 mths. Moderate risk of bias.

DT= diphtheria-tetanus

Local pain/tenderness

No statistically significant differences were found between DTaP 5c compared to DT vaccines for Local pain/tenderness.

Figure 59. Local pain/tenderness reactogenicity for DTaP 5c compared to DT



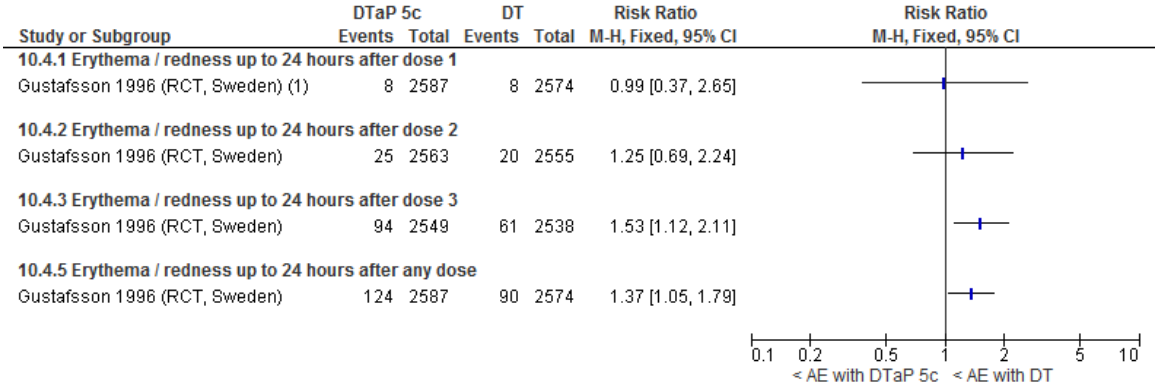
Footnotes
(1) Connaught (5c), doses at 2, 4 and 6 mths. Moderate risk of bias.

DT= diphtheria-tetanus

Erythema/redness

The RCT found that there is a lower risk of redness ≥2cm up to 24 hours after any DT dose (RR 1.37, 95% CI 1.05 to 1.79; 5161 participants) and also a lower risk after DT dose 3 (RR 1.53, 95% CI 1.12 to 2.11; 5087 participants), compared to DTaP 5c. No statistically significant differences were found between DTaP 5c compared to DT vaccines after dose 1 or 2 for erythema/redness.

Figure 60. Erythema/redness reactogenicity for DTaP 5c compared to DT



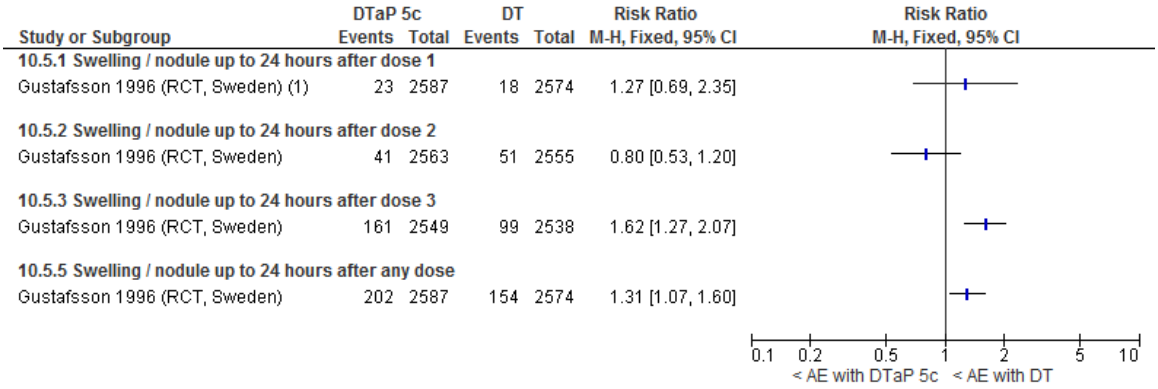
Footnotes
(1) Redness ≥2cm. Connaught (5c), doses at 2, 4 and 6 mths. Moderate risk of bias.

DT= diphtheria-tetanus

Swelling/nodule

The RCT found that there is a lower risk of nodule ≥2cm up to 24 hours after any DT dose (RR 1.31, 95% CI 1.07 to 1.60; 5161 participants) and also a lower risk after DT dose 3 (RR 1.62, 95% CI 1.27 to 2.07; 5087 participants), compared to DTaP 5c. No statistically significant differences were found between DTaP 5c compared to DT vaccines after dose 1 or 2.

Figure 61. Swelling/nodule reactogenicity for DTaP 5c compared to DT



Footnotes
(1) Nodule ≥2cm. Connaught (5c), doses at 2, 4 and 6 mths. Moderate risk of bias.

DT= diphtheria-tetanus

3.7 DTaP chi vaccine compared to DT vaccine

One study evaluated reactogenicity for DTaP chi versus DT vaccines. Greco 1996 was an RCT conducted in Italy of low risk of bias that administered DTaP Chiron (3c) doses at 2, 4, and 6 months compared to DT doses at 2, 4, and 6 months. The study also had a DTaP SKB (3c) vaccine arm not included in this comparison.

Table 7. Characteristics of studies contributing to the DTaP chi vs. DT vaccines comparison

Study Country	Design	Status	Schedules	
Greco 1996(1)* Italy	RCT	Included Low risk of bias	DTaP Chiron (3c) at 2, 4 and 6 months	DT at 2, 4, and 6 months

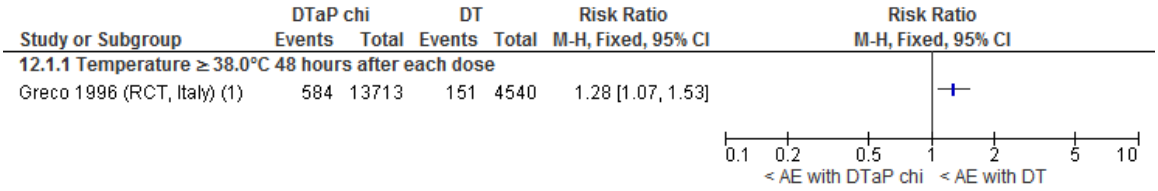
* Reported vaccine doses (as opposed to participants) as denominator

The study reported on Temperature ≥38.0°C, Persistent crying, Hypotonic, hyporesponsive episode, Local pain/tenderness, Swelling/nodule, and Seizure. The risk of Temperature ≥38.0°C and Swelling/nodule were significantly lower after DT vaccine administration compared to DTaP chi vaccine. For Persistent crying, Hypotonic, hyporesponsive episode and Local pain/tenderness there were no significant differences in reactogenicity between the two vaccines. No seizures were reported.

Temperature ≥38.0°C

The RCT found that there is a lower risk of Temperature ≥38.0°C up to 48 hours after DT doses (RR 1.28, 95% CI 1.07 to 1.53; 18253 doses), compared to DTaP chi doses.

Figure 62. Temperature ≥38.0°C reactogenicity for DTaP chi compared to DT



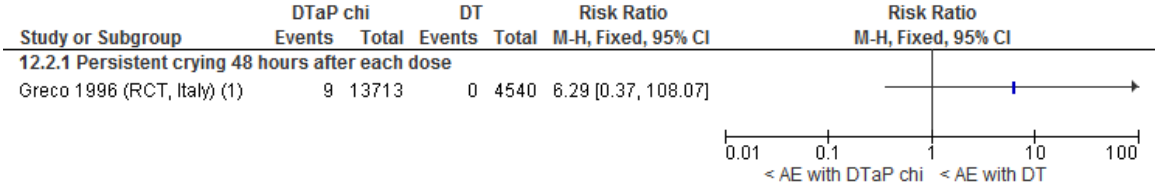
Footnotes
(1) Chiron (3c), doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DT= diphtheria-tetanus

Persistent crying

No statistically significant difference was found between DTaP chi compared to DT vaccines for Persistent crying.

Figure 63. Persistent crying reactogenicity for DTaP chi compared to DT



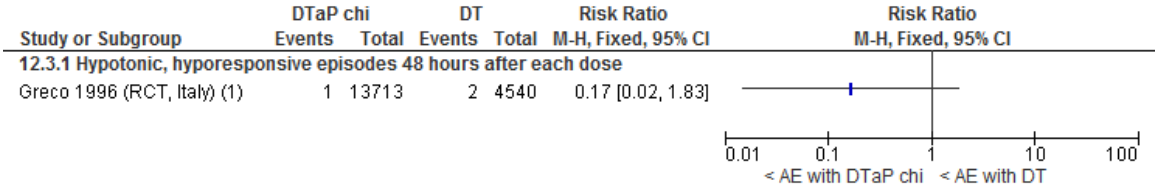
Footnotes
(1) Persistent crying ≥3h. Chiron (3c). N reported as doses, not participants. Low risk of bias.

DT= diphtheria-tetanus

Hypotonic, hyporesponsive episode

No statistically significant difference was found between DTaP chi compared to DT vaccines for Hypotonic, hyporesponsive episode.

Figure 64. Hypotonic, hyporesponsive episode reactogenicity for DTaP chi compared to DT



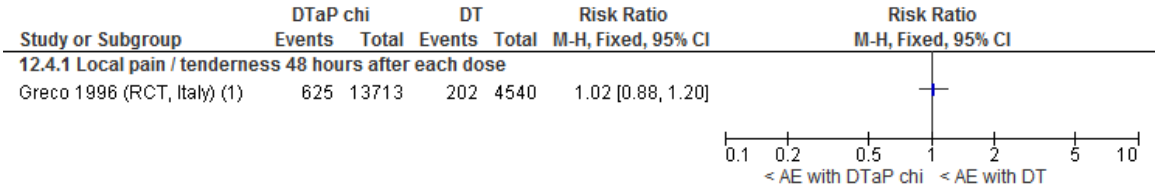
Footnotes
(1) Chiron (3c), doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DT= diphtheria-tetanus

Local pain/tenderness

No statistically significant difference was found between DTaP chi compared to DT vaccines for Local pain/tenderness.

Figure 65. Local pain/tenderness reactogenicity for DTaP chi compared to DT



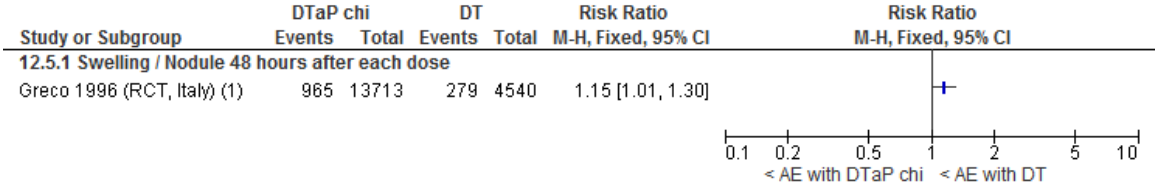
Footnotes
(1) Chiron (3c), doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DT= diphtheria-tetanus

Swelling/nodule

The RCT found that there is a lower risk of swelling/nodule up to 48 hours after DT doses (RR 1.15, 95% CI 1.01 to 1.30; 18253 doses), compared to DTaP chi doses.

Figure 66. Swelling/nodule reactogenicity for DTaP chi compared to DT



Footnotes
(1) Chiron (3c), doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DT= diphtheria-tetanus

Seizures

No seizures were reported for DTaP chi or DT vaccines during the included RCT.

3.8 DTaP skb vaccine compared to DT vaccine

One study evaluated reactogenicity for DTaP skb versus DT vaccines. Greco 1996 was an RCT conducted in Italy of low risk of bias that administered DTaP SKB (3c) doses at 2, 4, and 6 months compared to DT doses at 2, 4, and 6 months. The study also had a DTaP Chiron (3c) vaccine arm not included in this comparison.

Table 8. Characteristics of studies contributing to the DTaP SKB vs. DT vaccines comparison

Study Country	Design	Status	Schedules	
Greco 1996(1)* Italy	RCT	Included Low risk of bias	DTaP SKB (3c) at 2, 4 and 6 months	DT at 2, 4, and 6 months

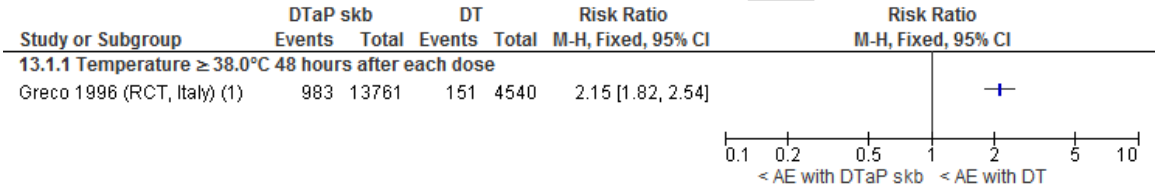
* Reported vaccine doses (as opposed to participants) as denominator

The study reported on Temperature ≥38.0°C, Persistent crying, Hypotonic, hyporesponsive episode, Local pain/tenderness, Swelling/nodule, and Seizure. The risk of Temperature ≥38.0°C and Swelling/nodule were significantly lower after DT vaccine administration compared to DTaP skb vaccine. For the other reactogenicity outcomes the study reported on, there were no significant differences between the two vaccines.

Temperature ≥38.0°C

The RCT found that there is a lower risk of Temperature ≥38.0°C up to 48 hours after DT doses (RR 2.15, 95% CI 1.82 to 2.54; 18301 doses), compared to DTaP skb doses.

Figure 67. Temperature ≥38.0°C reactogenicity for DTaP skb compared to DT



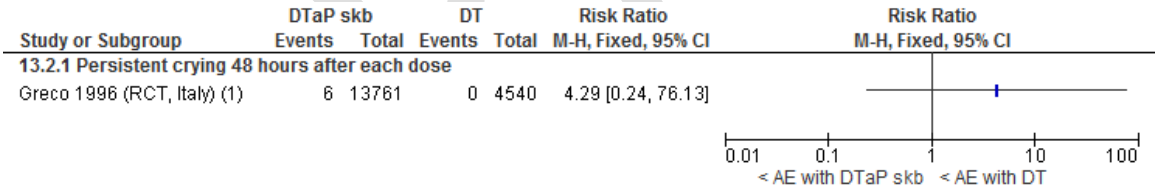
Footnotes
(1) SKB (3c), doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DT= diphtheria-tetanus

Persistent crying

No statistically significant difference was found between DTaP skb compared to DT vaccines for Persistent crying.

Figure 68. Persistent crying reactogenicity for DTaP skb compared to DT



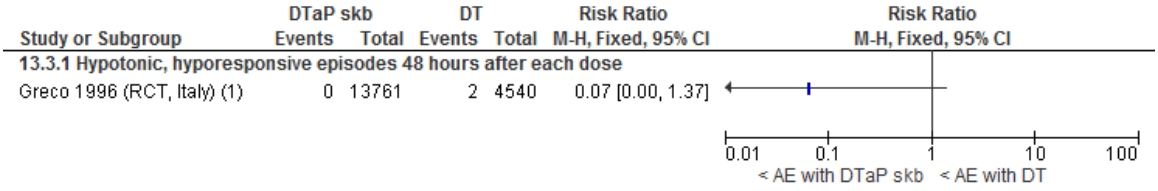
Footnotes
(1) Persistent crying ≥3h. SKB (3c). Doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DT= diphtheria-tetanus

Hypotonic, hyporesponsive episodes

No statistically significant difference was found between DTaP skb compared to DT vaccines for Hypotonic, hyporesponsive episodes.

Figure 69. Hypotonic, hyporesponsive episodes reactogenicity for DTaP skb compared to DT



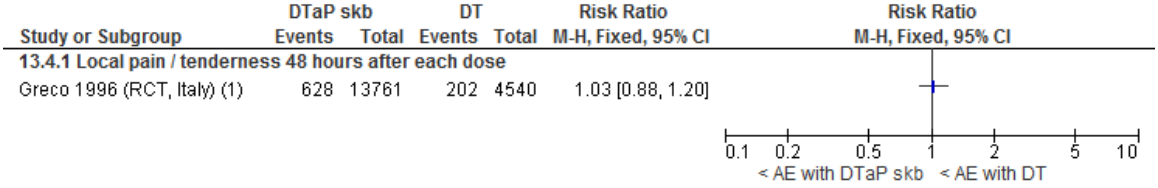
Footnotes
(1) SKB (3c). Doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DT= diphtheria-tetanus

Local pain/tenderness

No statistically significant difference was found between DTaP skb compared to DT vaccines for Local pain/tenderness.

Figure 70. Local pain/tenderness reactogenicity for DTaP skb compared to DT



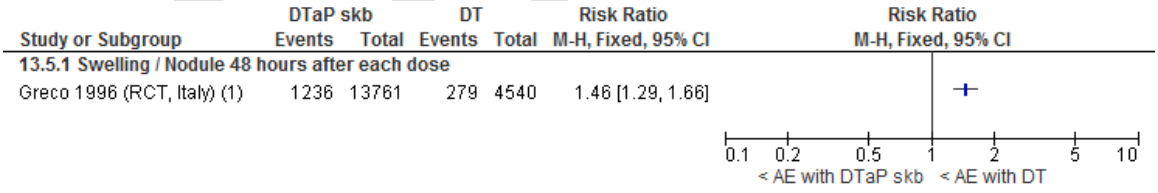
Footnotes
(1) SKB (3c), doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DT= diphtheria-tetanus

Swelling/nodule

The RCT found that there is a lower risk of Swelling/nodule up to 48 hours after DT doses (RR 1.46, 95% CI 1.29 to 1.66; 18301 doses), compared to DTaP skb doses.

Figure 71. Swelling/nodule reactogenicity for DTaP skb compared to DT



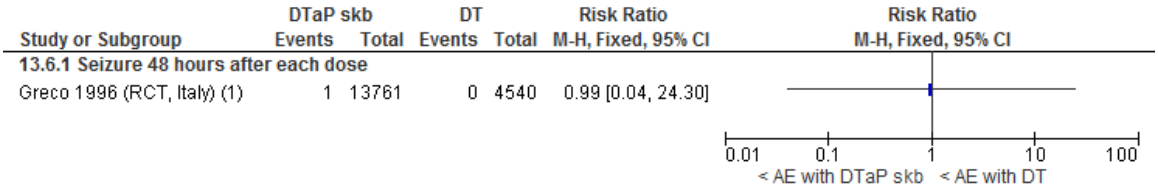
Footnotes
(1) SKB (3c), doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DT= diphtheria-tetanus

Seizures

No statistically significant difference was found between DTaP skb compared to DT vaccines for Seizures.

Figure 72. Seizures reactogenicity for DTaP skb compared to DT



Footnotes
(1) SKB (3c). Doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DT= diphtheria-tetanus

3.9 DTwP vaccine compared to DT vaccine

Five studies evaluated reactogenicity for DTwP versus DT vaccines. Greco 1996 was an RCT conducted in Italy of low risk of bias that administered doses at 2, 4 and 6 months. Gustafsson 1996 was an RCT conducted in Sweden of moderate risk of bias that administered doses at 2, 4, and 6 months. Pollock 1984 was a cohort study conducted in the UK of high risk of bias that administered doses at 3, 4.5-6 and 8-12 months. This study also had a DTwP plain vaccine arm. Barkin 1985 was a double-blind RCT conducted in the USA of unclear risk of bias that administered doses at 2, 4 and 6 months. It should be noted that Barkin 1985 does not fit with this protocol as it does not report differences between the two schedules. Cody 1981 was a double-blind RCT conducted in the USA of unclear risk of bias. It should be noted that Cody 1981 does not fit with this protocol as it does not report by vaccine schedule.

Table 9. Characteristics of studies contributing to the DTwP vs. DT comparison

Study Country	Design	Status	Schedules	
Greco 1996(1)* Italy	RCT	Included Low risk of bias	DTwP at 2, 4, and 6 months	DT at 2, 4, and 6 months
Gustafsson 1996(2) Sweden	RCT	Included Moderate risk of bias	DTwP at 2, 4, and 6 months	DT at 2, 4, and 6 months
Pollock 1984(4) UK	Cohort	Included High risk of bias	DTwP at 3, 4.5-6, and 8-12 months	DT at 3, 4.5-6, and 8-12 months
Barkin 1985(5)* USA	RCT	Additional study Not per protocol: Reports no difference between two schedules	DTwP – DTwP – DT at 2, 4, and 6 months	DTwP – DT – DTwP at 2, 4, and 6 months
			DTwP doses were compared to DT doses across schedules	
Cody 1981(6)* USA	RCT	Additional study Not per protocol: Does not report by vaccination schedule	DTwP with no application of a specific vaccination schedule	DT with no application of a specific vaccination schedule

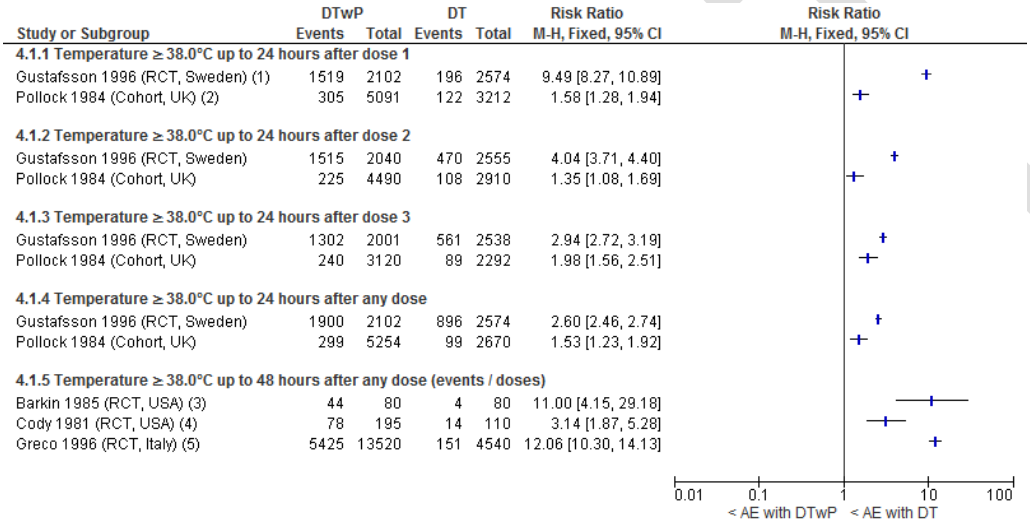
* Reported vaccine doses (as opposed to participants) as denominator

The studies reported on Temperature ≥38.0°C, Persistent crying, Local pain/tenderness, Erythema/redness, Swelling/nodule, Hypotonic, hypo-responsive episodes, Seizure, Crying more than usual, Crying/screaming, Acute behavioural changes, Use of antipyretics, Any reaction, and Local reactions. Mostly, the risk of adverse events was lower with DT vaccine compared to DTwP vaccine, however, in some instances there were no statistically significant differences between DTwP and DT.

Temperature ≥38°C

All five studies found that there is a lower risk of Temperature ≥38.0°C after DT doses, compared to DTwP doses, with a RR range of 1.35-12.06 and a 95% CI range of 1.08 to 29.18 after different doses. The studies were not pooled due to very high heterogeneity (I^2 > 90%).

Figure 73. Temperature ≥38.0°C reactogenicity for DTwP compared to DT vaccines



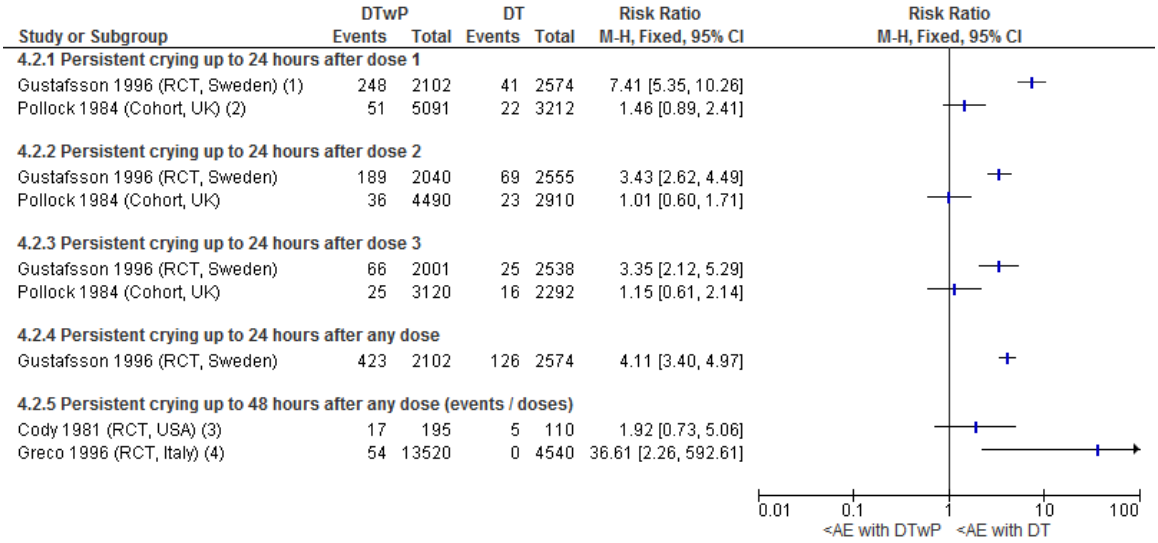
Footnotes
(1) Doses at 2, 4 and 6 mths. Measured within 24 hours of dose. Moderate risk of bias.
(2) Doses at 3, 4.5-6, 8-12 months. Feverishness,12 hours post dose. High risk of bias.
(3) N reported as doses, not participants. Not per protocol: Reports no difference between two schedules.
(4) N reported as doses, not participants. Not per protocol: Does not report by vaccination schedule
(5) Doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Persistent crying

An RCT found that there is a lower risk of Persistent crying after DT doses 1, 2, 3, and after any DT dose, compared to DTwP doses, with a RR range of 3.35 to 7.41 and a 95% CI range of 2.12 to 10.26 after different doses. A cohort study and two RCTs did not find any statistically significant differences for Persistent crying between DTwP and DT vaccines. The studies were not pooled due to very high heterogeneity (I^2 > 85%).

Figure 74. Persistent crying reactogenicity for DTwP compared to DT vaccines



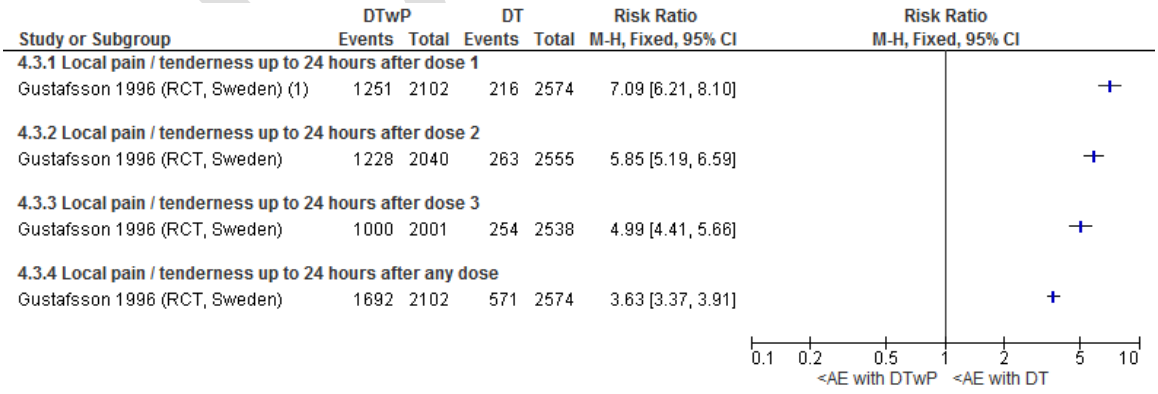
Footnotes
(1) Doses at 2, 4 and 6 mths. Persistent crying ≥ 1h measured within 24 hours of dose. Moderate risk of bias.
(2) Doses at 3, 4.5-6, 8-12 months. Persistent crying >5h, 12 hours post-dose. High risk of bias.
(3) N reported as doses, not participants. Not per protocol: Does not report by vaccination schedule
(4) Doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Local pain/tenderness

An RCT found that there is a lower risk of Local pain/tenderness after DT doses 1, 2, 3, and after any DT dose, compared to after DTwP doses, with a RR range of 3.63 to 7.09 and a 95% CI range of 3.37 to 8.10 after different doses. Two RCTs that measured doses as opposed to participants and could not be pooled with the other study, found that there is a lower risk of Local pain/tenderness after DT doses compared to DTwP (RR 5.85, 95% CI 3.96 to 8.65; 18365 doses). Local pain/tenderness up to 48 hours after any dose was analysed with a random effects model due to high heterogeneity (I^2=55%, with a fixed effects model: RR 6.55, 95% CI 5.74 to 7.49).

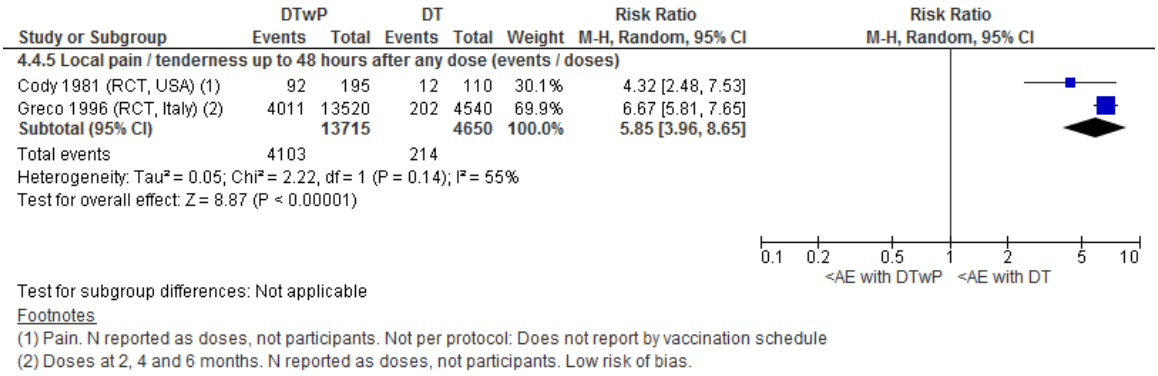
Figure 75. Single study outcome measures of Local pain/tenderness reactogenicity for DTwP compared to DT vaccines



Footnotes
(1) Doses at 2, 4 and 6 mths. Measured within 24 hours of dose. Moderate risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Figure 76. Meta-analyses of Local pain/tenderness reactogenicity for DTwP compared to DT vaccines



Test for subgroup differences: Not applicable

Footnotes

(1) Pain. N reported as doses, not participants. Not per protocol: Does not report by vaccination schedule

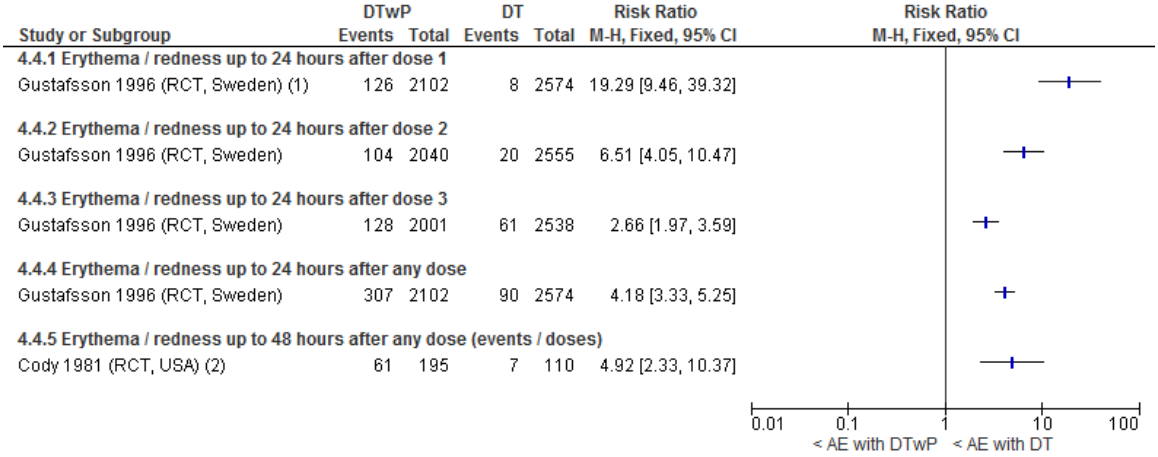
(2) Doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Erythema/redness

An RCT found that there is a lower risk of Erythema/redness after DT doses 1, 2, 3, and after any DT dose, compared to after DTwP doses, with a RR range of 2.66 to 19.29 and a 95% CI range of 1.97 to 39.32 after different doses. Another RCT that measured doses as opposed to participants and could not be pooled with the other study, also found that there is a lower risk of Erythema/redness after DT doses compared to DTwP (RR 4.92, 95% CI 2.33 to 10.37; 305 doses).

Figure 77. Erythema/redness reactogenicity for DTwP compared to DT vaccines



Footnotes

(1) Doses at 2, 4 and 6 mths. Redness ≥2 cm measured within 24 hours of dose. Moderate risk of bias.

(2) N reported as doses, not participants. Not per protocol: Does not report by vaccination schedule

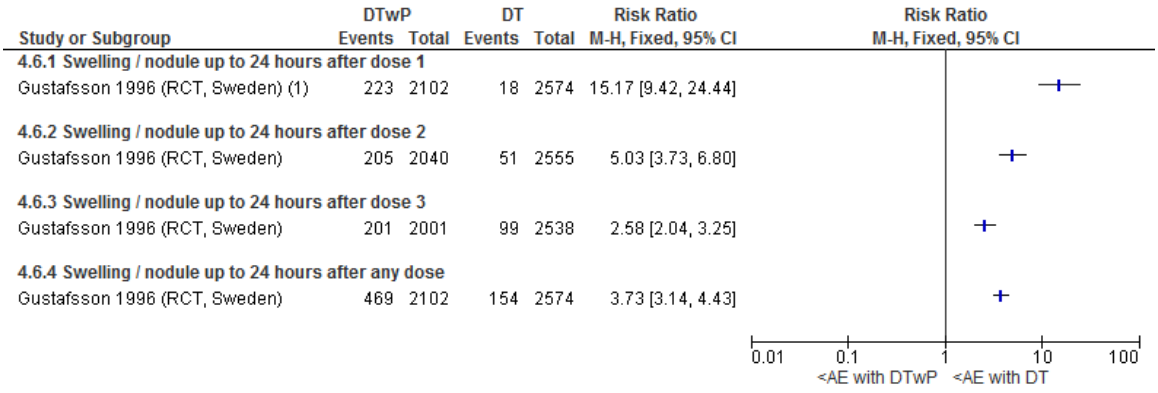
DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Swelling/nodule

An RCT found that there is a lower risk of Swelling/nodule after DT doses 1, 2, 3, and after any DT dose, compared to after DTwP doses, with a RR range of 2.58 to 15.17 and a 95% CI range of 2.04 to 24.44 after different doses. Two RCTs that measured doses as opposed to participants

and could not be pooled with the other study, found that there is a lower risk of Swelling/nodule after DT doses compared to DTwP (RR 4.22, 95% CI 3.76 to 4.74; 18365 doses).

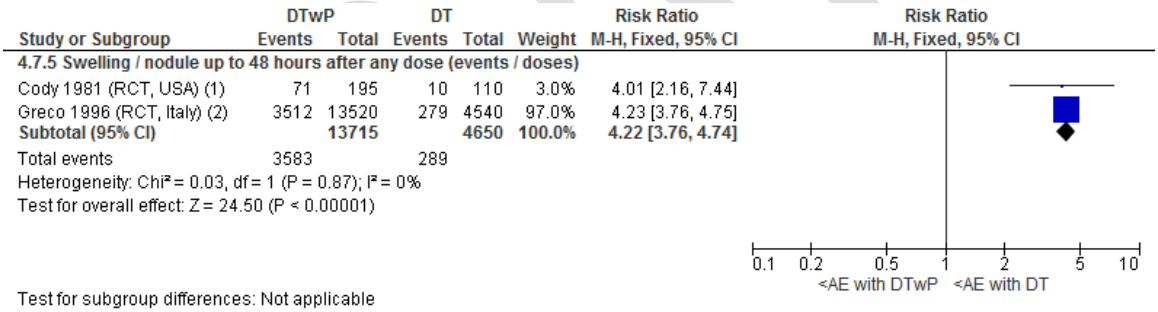
Figure 78. Single studies analysis of Swelling/nodule reactogenicity for DTwP compared to DT vaccines



Footnotes
(1) Doses at 2, 4 and 6 mths. Nodule ≥2 cm measured within 24 hours of dose. Moderate risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Figure 79. Meta-analyses of Swelling/nodule reactogenicity for DTwP compared to DT vaccines



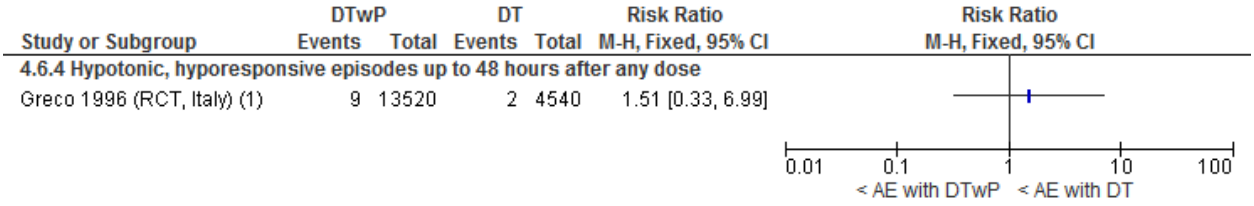
Footnotes
(1) N reported as doses, not participants. Not per protocol: Does not report by vaccination schedule
(2) Doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Hypotonic, hypo-responsive episodes

An RCT found no statistically significant difference between DTwP compared to DT vaccines for Hypotonic, hypo-responsive episodes up to 48 hours after any dose.

Figure 80. Hypotonic, hypo-responsive episodes reactogenicity for DTwP compared to DT vaccines



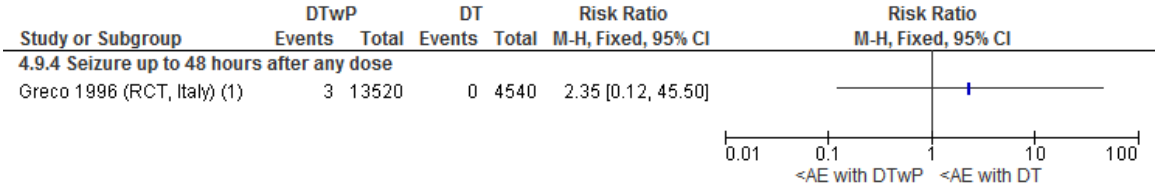
Footnotes
(1) Doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Seizures

An RCT found no statistically significant difference between DTwP compared to DT vaccines for Seizures up to 48 hours after any dose.

Figure 81. Seizures reactogenicity for DTwP compared to DT vaccines



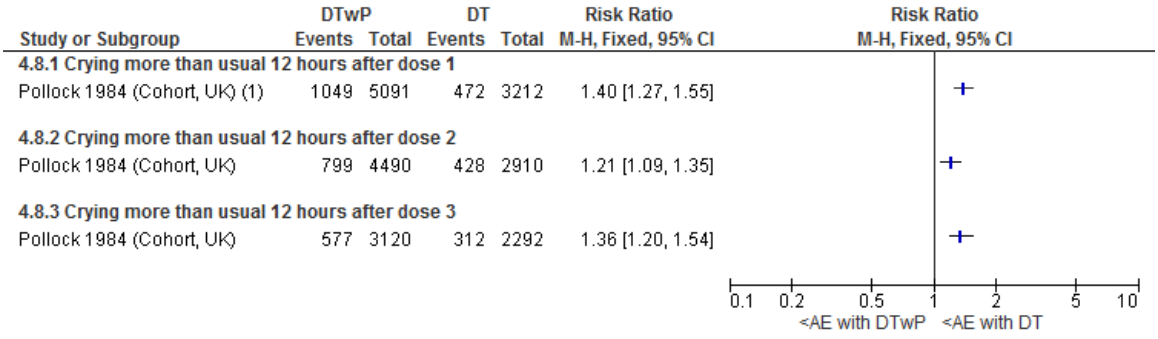
Footnotes
(1) Doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Crying more than usual

A cohort study found that there is a lower risk of Crying more than usual after DT doses 1, 2, and 3, compared to after DTwP doses, with a RR range of 1.21 to 1.40 and a 95% CI range of 1.09 to 1.55 after different doses.

Figure 82. Crying more than usual reactogenicity for DTwP compared to DT vaccines



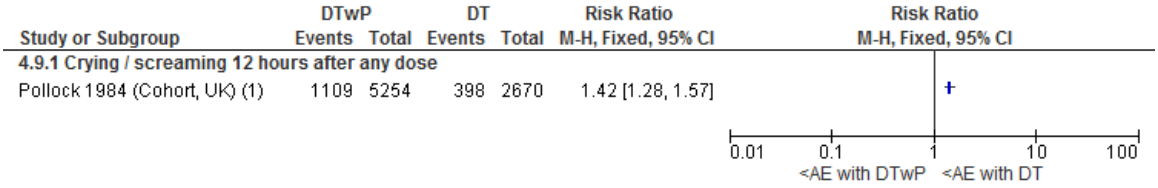
Footnotes
(1) Doses at 3, 4.5-6, 8-12 months. Measured 12 hours post-dose. High risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Crying/screaming

A cohort study found that there is a lower risk of Crying/screaming 12 hours after any DT dose, compared to after any DTwP dose (RR 1.42, 95% CI 1.28 to 1.57; 3779 participants).

Figure 83. Crying/screaming reactogenicity for DTwP compared to DT vaccines



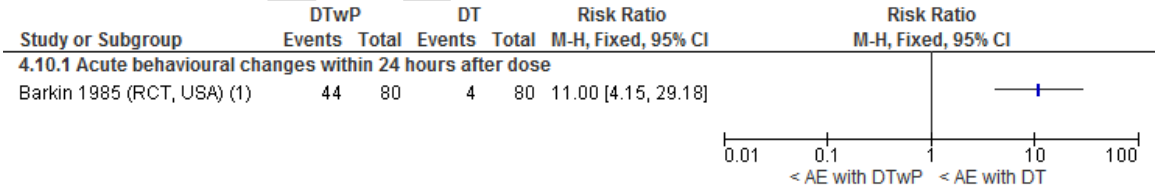
Footnotes
(1) Doses at 3, 4.5-6, 8-12 months. Measured 12 hours post-dose. High risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Acute behavioural changes

An RCT found that there is a lower risk of Acute behavioural changes 24 hours after DT dose, compared to after DTwP dose (RR 11.00, 95% CI 4.15 to 29.18; 160 participants).

Figure 84. Acute behavioural changes reactogenicity for DTwP compared to DT vaccines



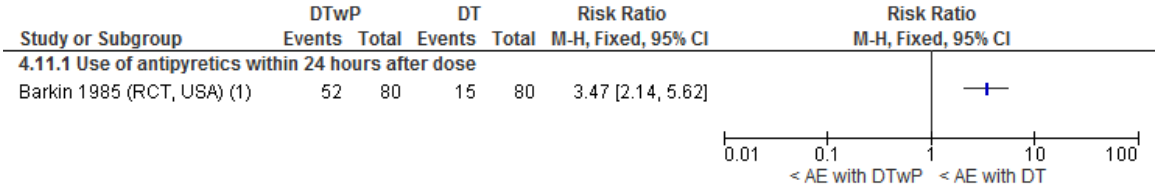
Footnotes
(1) N reported as doses, not participants. Not per protocol: Reports no difference between two schedules.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Use of antipyretics

An RCT found that there is a lower risk of Use of antipyretics 24 hours after DT dose, compared to after DTwP dose (RR 3.47, 95% CI 2.14 to 5.62; 160 participants).

Figure 85. Use of antipyretics reactogenicity for DTwP compared to DT vaccines



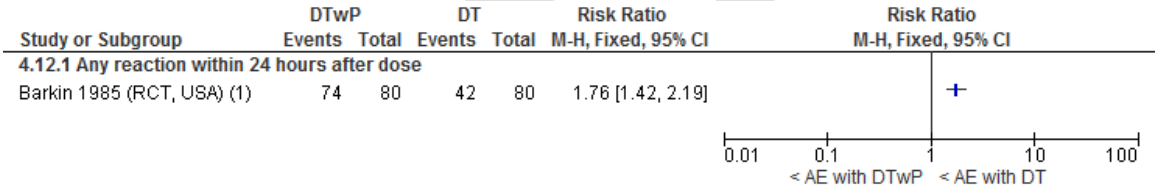
Footnotes
(1) N reported as doses, not participants. Not per protocol: Reports no difference between two schedules.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Any reaction

An RCT found that there is a lower risk of Any reaction 24 hours after DT dose, compared to after DTwP dose (RR 1.76, 95% CI 1.42 to 2.19; 160 participants).

Figure 86. Any reaction reactogenicity for DTwP compared to DT vaccines



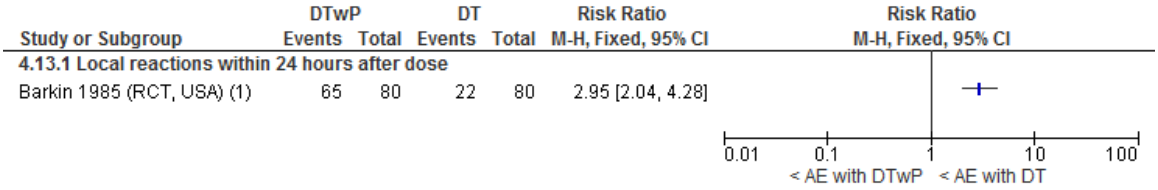
Footnotes
(1) N reported as doses, not participants. Not per protocol: Reports no difference between two schedules.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Local reactions

An RCT found that there is a lower risk of Local reactions 24 hours after DT dose, compared to after DTwP dose (RR 2.95, 95% CI 2.04 to 4.28; 160 participants).

Figure 87. Local reactions reactogenicity for DTwP compared to DT vaccines



Footnotes
(1) N reported as doses, not participants. Not per protocol: Reports no difference between two schedules.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

3.10 DTwP plain vaccine compared to DT vaccine

One study evaluated reactogenicity for DTwP plain versus DT vaccines. Pollock 1984 was a cohort study conducted in the UK with high risk of bias that administered the vaccines at 3, 4.5-6 and 8-12 months. This study also had a DTwP vaccine arm.

Table 10. Characteristics of studies contributing to the DTwP plain vs. DT vaccines comparison

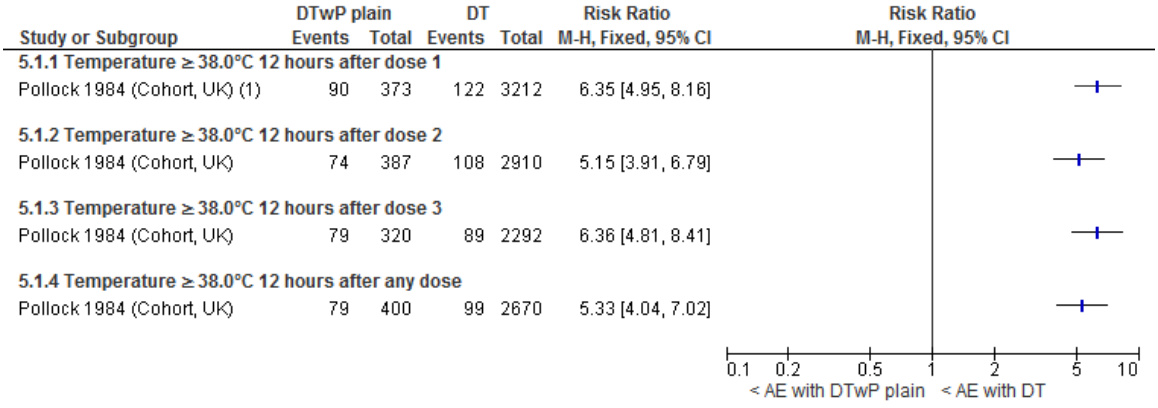
Study Country	Design	Status	Schedules	
Pollock 1984(4) UK	Cohort	Included High risk of bias	DTwP plain at 3, 4.5-6, and 8-12 months	DT at 3, 4.5-6, and 8-12 months

The study reported on Temperature ≥38.0°C, Persistent crying, Crying more than usual, and Crying/screaming. The study found that a lower risk of these adverse events after DT vaccine administration compared to DTwP plain.

Temperature ≥38°C

The RCT found that there is a lower risk of Temperature ≥38.0°C up to 12 hours after DT dose 1, 2, 3, or any dose administration, compared to after DTwP plain administration, with a RR range of 5.15 to 6.36 and a 95% CI range of 3.91 to 8.41 after different doses.

Figure 88. Temperature ≥38°C reactogenicity for DTwP plain compared to DT vaccines



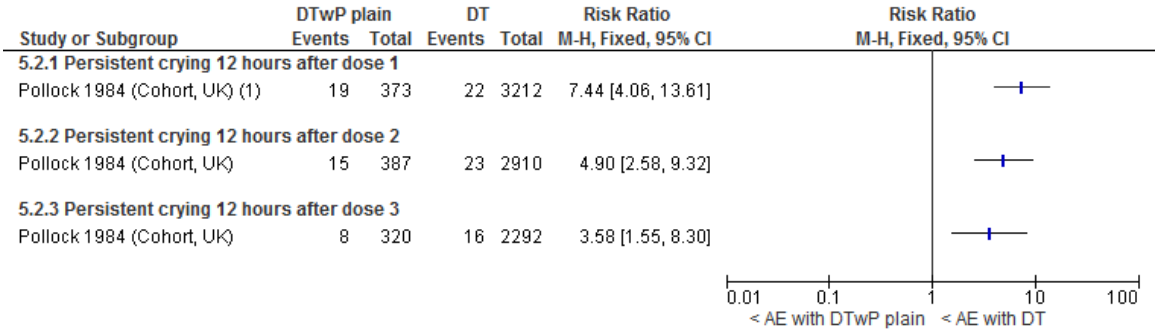
Footnotes
(1) Doses at 3, 4.5-6, 8-12 months. Feverishness,12 hours post dose. High risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Persistent crying

The RCT found that there is a lower risk of Persistent crying up to 12 hours after DT dose 1, 2, or 3, compared to after DTwP plain administration, with a RR range of 3.58 to 7.44 and a 95% CI range of 1.55 to 13.61 after different doses.

Figure 89. Persistent crying reactogenicity for DTwP plain compared to DT vaccines



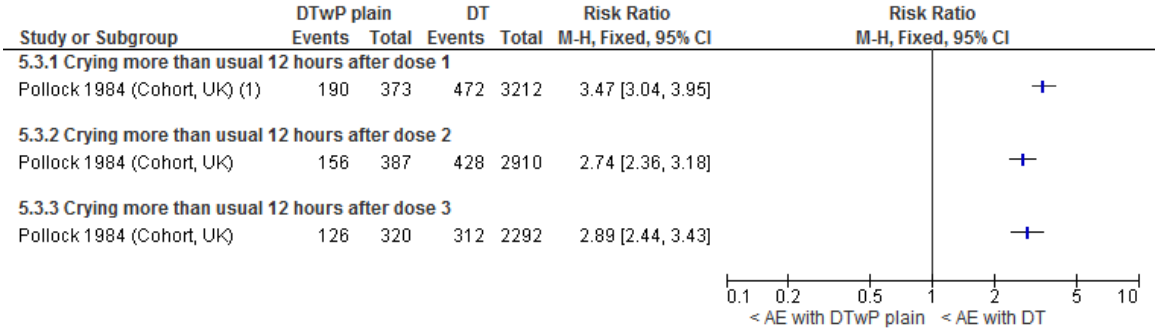
Footnotes
(1) Doses at 3, 4.5-6, 8-12 months. Persistent crying >5h, 12 hours post-dose. High risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Crying more than usual

The RCT found that there is a lower risk of Crying more than usual up to 12 hours after DT dose 1, 2, or 3, compared to after DTwP plain administration, with a RR range of 2.74 to 3.47 and a 95% CI range of 2.36 to 3.95 after different doses.

Figure 90. Crying more than usual reactogenicity for DTwP plain compared to DT vaccines



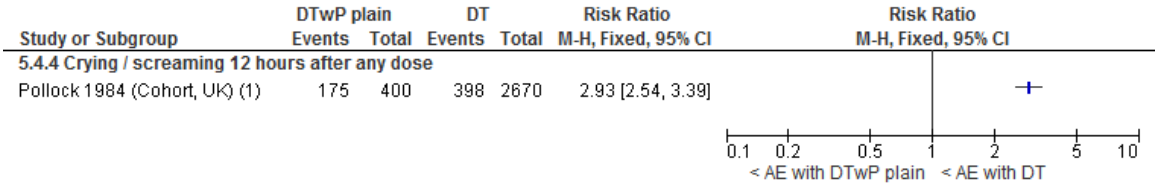
Footnotes
(1) Doses at 3, 4.5-6, 8-12 months. High risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

Crying/screaming

The RCT found that there is a lower risk of Crying/screaming up to 12 hours after any DT dose, compared to after DTwP plain administration (RR 2.93, 95% CI 2.54 to3.39; 3070 participants).

Figure 91. Crying/screaming reactogenicity for DTwP plain compared to DT vaccines



Footnotes
(1) Doses at 3, 4.5-6, 8-12 months. High risk of bias

DTwP= diphtheria-tetanus-whole-cell pertussis; DT= diphtheria-tetanus

3.11 DTaP skb vaccine compared to DTaP chi vaccine

One study evaluated reactogenicity for DTaP skb versus DTaP chi vaccines. Greco 1996 was an RCT conducted in Italy of low risk of bias that administered DTaP SKB (3c) doses at 2, 4, and 6 months compared to DTaP Chiron (3c) doses at 2, 4, and 6 months. The study also had a DT vaccine arm not included in this comparison.

Table 11. Characteristics of studies contributing to the DTaP skb vs. DTaP chi vaccines comparison

Study Country	Design	Status	Schedules	
Greco 1996(1)* Italy	RCT	Included Low risk of bias	DTaP SKB (3c) at 2, 4 and 6 months	DTaP Chiron (3c) at 2, 4, and 6 months

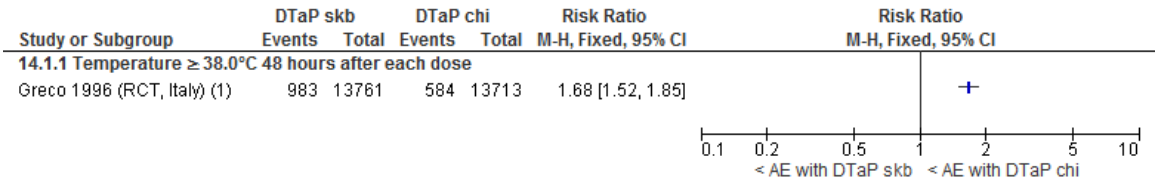
* Reported vaccine doses (as opposed to participants) as denominator

The study reported on Temperature ≥38.0°C, Persistent crying, Hypotonic, hyporesponsive episode, Local pain/tenderness, Swelling/nodule, and Seizure. The risk of Temperature ≥38.0°C and Swelling/nodule were significantly lower after DTaP chi vaccine administration compared to DTaP skb vaccine. For the other reactogenicity outcomes the study reported on, there were no significant differences between the two vaccines.

Temperature ≥38.0°C

The RCT found that there is a lower risk of Temperature ≥38.0°C up to 48 hours after DTaP chi doses compared to DTaP skb doses (RR 1.68, 95% CI 1.52 to 1.85; 27474 doses).

Figure 92. Temperature ≥38.0°C reactogenicity for DTaP skb compared to DTaP chi

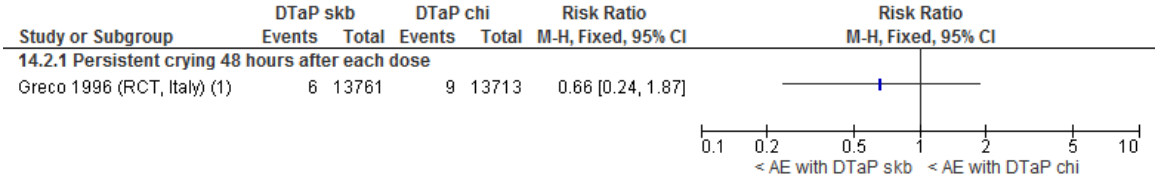


Footnotes
(1) Chiron (3c) and SKB (3c), doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Persistent crying

No statistically significant difference was found between DTaP skb compared to DTaP chi vaccines for Persistent crying.

Figure 93. Persistent crying reactogenicity for DTaP skb compared to DTaP chi



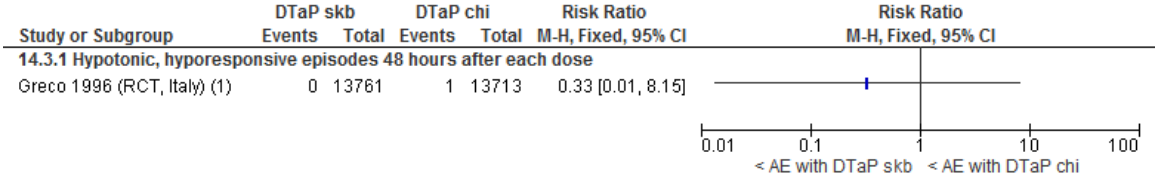
Footnotes

(1) Persistent crying ≥3h. Chiron (3c) and SKB (3c), doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Hypotonic, hyporesponsive episodes

No statistically significant difference was found between DTaP skb compared to DTaP chi vaccines for Hypotonic, hyporesponsive episodes.

Figure 94. Hypotonic, hyporesponsive episodes reactogenicity for DTaP skb compared to DTaP chi



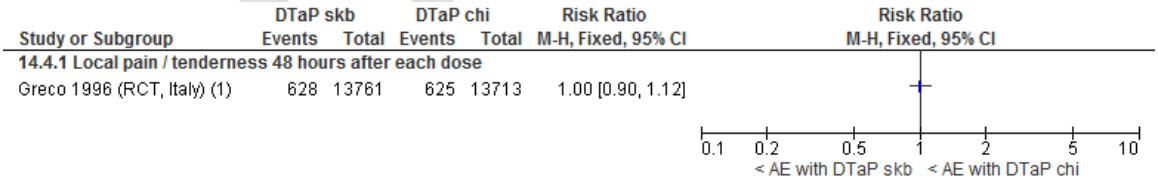
Footnotes

(1) Chiron (3c) and SKB (3c), doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Local pain/tenderness

No statistically significant difference was found between DTaP skb compared to DTaP chi vaccines for Local pain/tenderness.

Figure 95. Local pain/tenderness reactogenicity for DTaP skb compared to DTaP chi



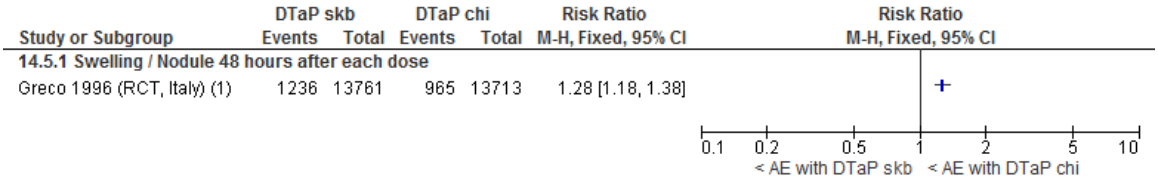
Footnotes

(1) Chiron (3c) and SKB (3c), doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Swelling/nodule

The RCT found that there is a lower risk of Swelling/nodule up to 48 hours after DTaP chi doses compared to DTaP skb doses (RR 1.28, 95% CI 1.18 to 1.38; 27474 doses).

Figure 96. Swelling/nodule reactogenicity for DTaP skb compared to DTaP chi

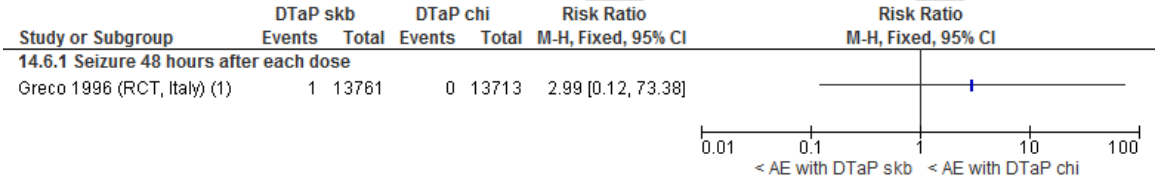


Footnotes
(1) Chiron (3c) and SKB (3c), doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

Seizures

No statistically significant difference was found between DTaP skb compared to DTaP chi vaccines for Seizures.

Figure 97. Seizures reactogenicity for DTaP skb compared to DTaP chi



Footnotes
(1) Chiron (3c) and SKB (3c), doses at 2, 4 and 6 months. N reported as doses, not participants. Low risk of bias.

3.12 DTaP 2c vaccine compared to DTaP 5c vaccine

One study evaluated reactogenicity for DTaP 2c versus DTaP 5c vaccines. Gustafsson 1996 was an RCT conducted in Sweden of moderate risk of bias that administered DTaP SKB (2c) doses at 2, 4, and 6 months compared to DTaP Connaught (5c) doses at 2, 4, and 6 months. The study also had a DT vaccine arm not included in this comparison.

Table 12. Characteristics of studies contributing to the DTaP 2c vs. DTaP 5c vaccines comparison

Study Country	Design	Status	Schedules	
Gustafsson 1996(2) Sweden	RCT	Included Moderate risk of bias	DTaP SKB (2c) at 2, 4, and 6 months	DTaP Connaught (5c) at 2, 4, and 6 months

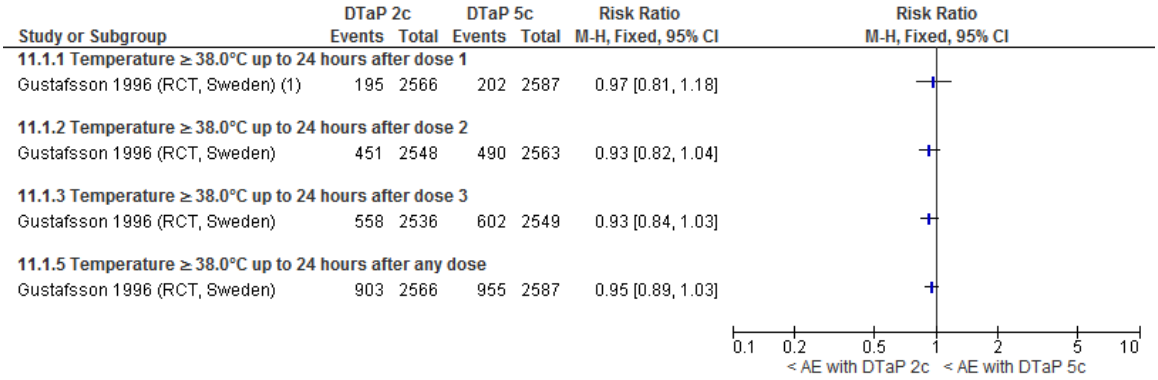
The study reported on Temperature ≥38.0°C, Persistent crying, Local pain/tenderness, Erythema/redness, and Swelling/nodule. Mostly, there were no significant differences in

reactogenicity between DTaP 2c and DTaP 5c vaccines, however, when there were, there was a lower risk of adverse events with DTaP 2c vaccine.

Temperature ≥38°C

No statistically significant differences were found between DTaP 2c compared to DTaP 5c vaccines for Temperature ≥38.0°C.

Figure 98. Temperature ≥38°C reactogenicity for DTaP 2c compared to DTaP 5c

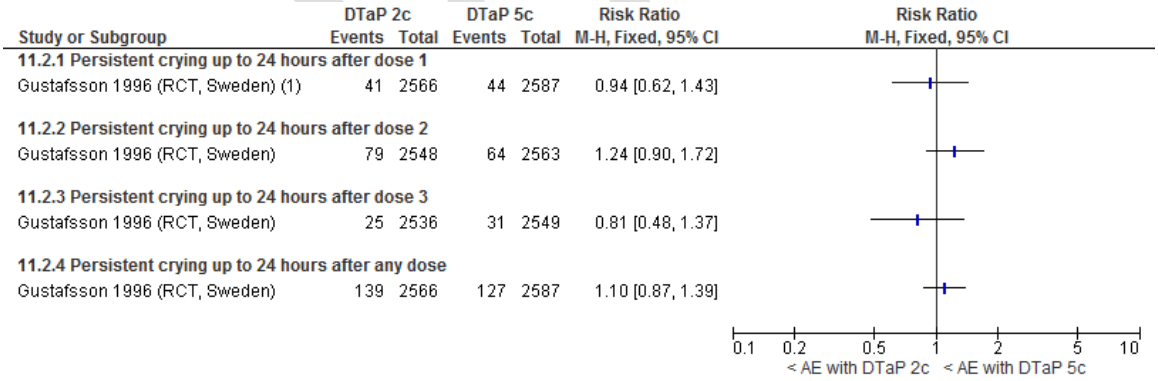


Footnotes
(1) SKB (2c) and Connaught (5c), doses at 2, 4 and 6 mths. Moderate risk of bias.

Persistent crying

No statistically significant differences were found between DTaP 2c compared to DTaP 5c vaccines for Persistent crying.

Figure 99. Persistent crying reactogenicity for DTaP 2c compared to DTaP 5c

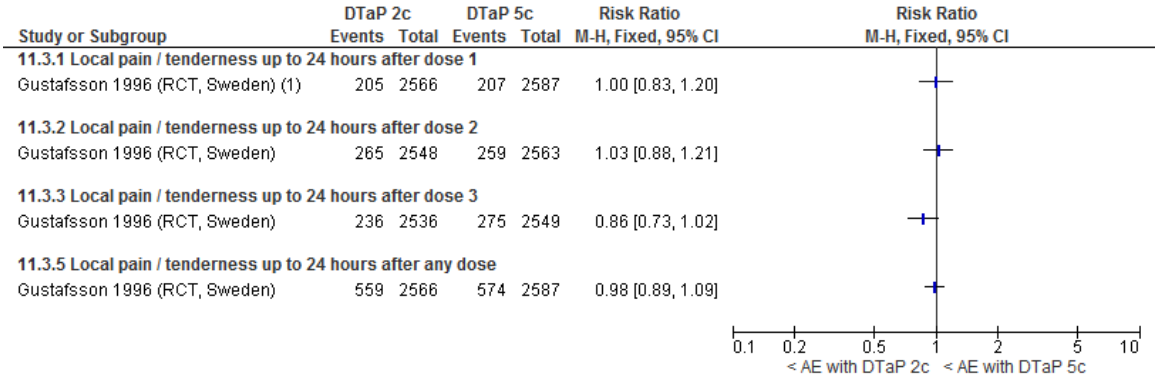


Footnotes
(1) SKB (2c) and Connaught (5c), doses at 2, 4 and 6 mths. Moderate risk of bias.

Local pain/tenderness

No statistically significant differences were found between DTaP 2c compared to DTaP 5c vaccines for Local pain/tenderness.

Figure 100. Local pain/tenderness reactogenicity for DTaP 2c compared to DTaP 5c

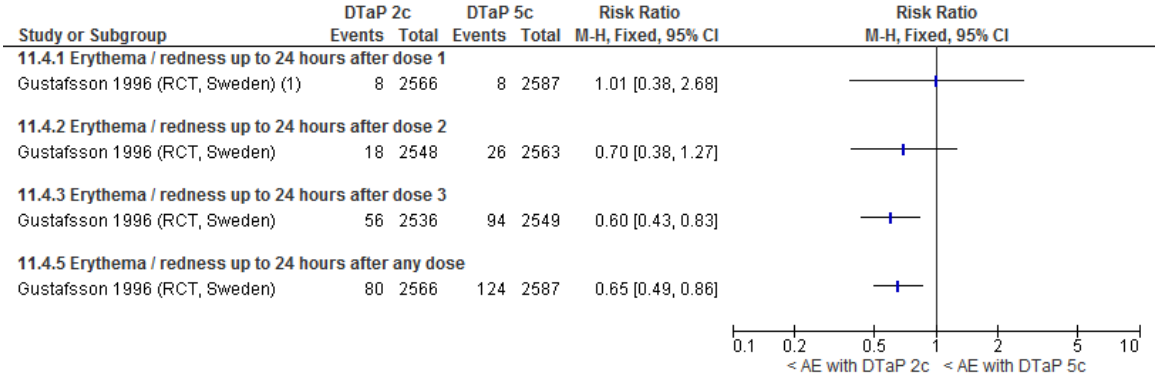


Footnotes
(1) SKB (2c) and Connaught (5c), doses at 2, 4 and 6 mths. Moderate risk of bias.

Erythema/redness

The RCT found that there is a 35% lower risk of redness ≥2cm up to 24 hours after any DTaP 2c dose (RR 0.65, 95% CI 0.49 to 0.86; 5153 participants) and a 40% lower risk after DTaP 2c dose 3 (RR 0.60, 95% CI 0.43 to 0.83; 4085 participants), compared to DTaP 5c. No statistically significant differences were found between DTaP 2c compared to DTaP 5c vaccines after dose 1 or 2 for erythema/redness.

Figure 101. Erythema/redness reactogenicity for DTaP 2c compared to DTaP 5c

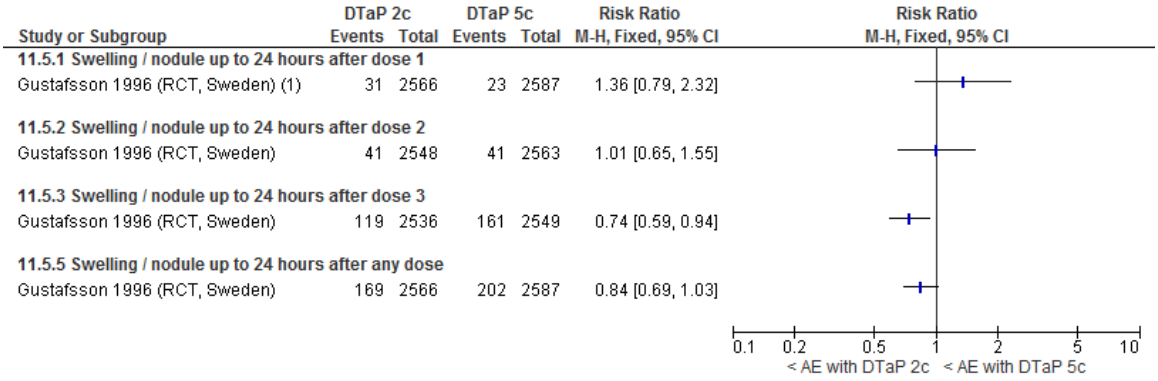


Footnotes
(1) Redness ≥2cm. SKB (2c) and Connaught (5c), doses at 2, 4 and 6 mths. Moderate risk of bias.

Swelling/nodule

The RCT found that there is a 26% lower risk of nodule ≥2cm up to 24 hours after DTaP 2c dose 3 (RR 0.74, 95% CI 0.59 to 0.94; 4085 participants), compared to DTaP 5c. No statistically significant differences were found between DTaP 2c compared to DTaP 5c vaccines after dose 1, 2, or after any dose for swelling/nodule.

Figure 102. Swelling/nodule reactogenicity for DTaP 2c compared to DTaP 5c



Footnotes
(1) Nodule ≥2cm. SKB (2c) and Connaught (5c), doses at 2, 4 and 6 mths. Moderate risk of bias.

3.13 DTwP vaccine compared to DTwP plain vaccine

One study evaluated reactogenicity for DTwP versus DTwP plain vaccines. Pollock 1984 was a cohort study conducted in the UK of high risk of bias that administered doses at 3, 4.5-6 and 8-12 months. This study also had a DT vaccine arm.

Table 13. Characteristics of studies contributing to the DTwP vs. DTwP plain vaccines comparison

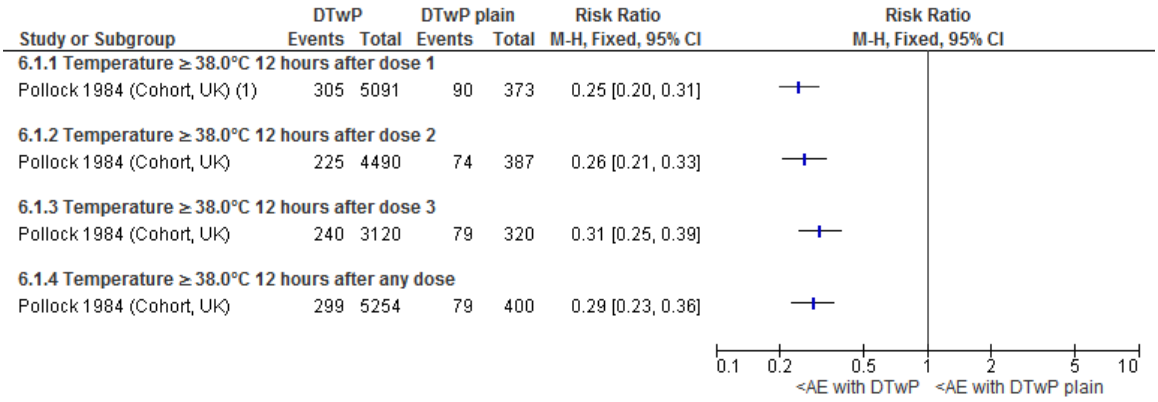
Study Country	Design	Status	Schedules	
Pollock 1984(4) UK	Cohort	Included High risk of bias	DTwP at 3, 4.5-6, and 8-12 months	DTwP plain at 3, 4.5-6, and 8-12 months

The study reported on Temperature ≥38.0°C, Persistent crying, Crying more than usual, and Crying/screaming. The study found a lower risk of these adverse events after DTwP vaccine administration compared to DTwP plain.

Temperature ≥38.0°C

The RCT found that there is a lower risk of Temperature ≥38.0°C up to 12 hours after DTwP dose 1, 2, 3, or any dose administration, compared to after DTwP plain administration, with a RR range of 0.25 to 0.31 and a 95% CI range of 0.20 to 0.39 after different doses.

Figure 103. Temperature ≥38.0°C reactogenicity for DTwP compared to DTwP plain vaccine



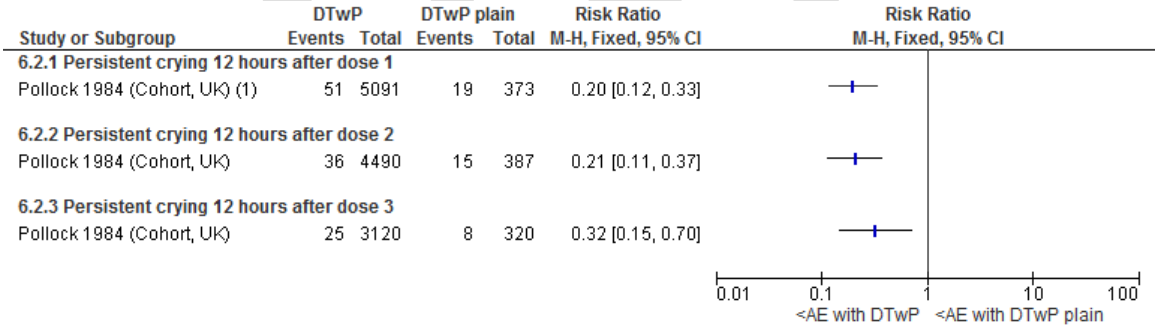
Footnotes
(1) Doses at 3, 4.5-6, 8-12 months. Feverishness,12 hours post dose. High risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis

Persistent crying

The RCT found that there is a lower risk of Persistent crying up to 12 hours after DTwP dose 1, 2, or 3, compared to after DTwP plain administration, with a RR range of 0.20 to 0.32 and a 95% CI range of 0.11 to 0.70 after different doses.

Figure 104. Persistent crying reactogenicity for DTwP compared to DTwP plain vaccine



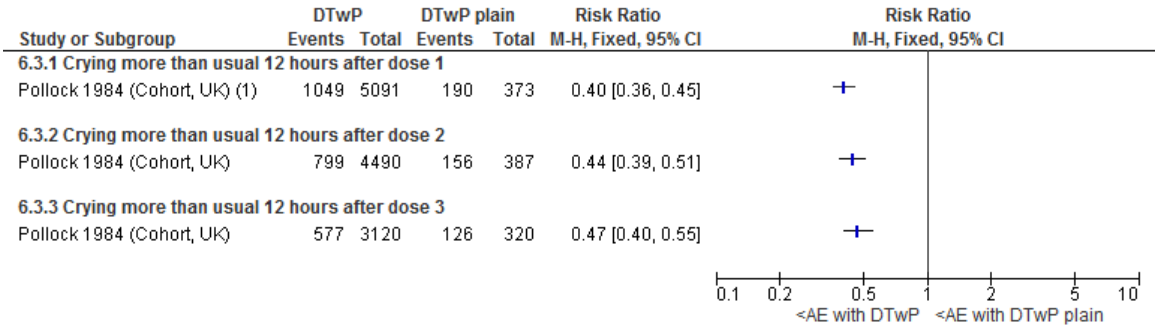
Footnotes
(1) Doses at 3, 4.5-6, 8-12 months. Persistent crying >5h, 12 hours post-dose. High risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis

Crying more than usual

The RCT found that there is a lower risk of Crying more than usual up to 12 hours after DTwP dose 1, 2, or 3, compared to after DTwP plain administration, with a RR range of 0.40 to 0.47 and a 95% CI range of 0.36 to 0.55 after different doses.

Figure 105. Crying more than usual reactogenicity for DTwP compared to DTwP plain vaccine



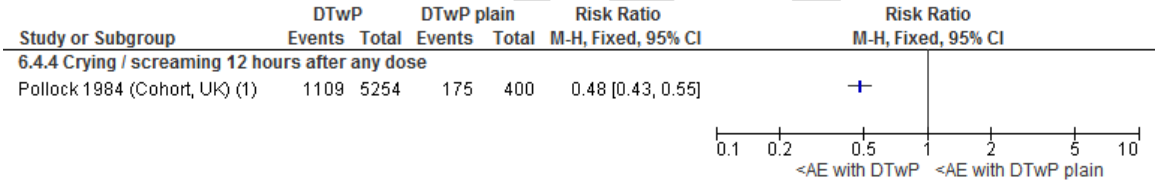
Footnotes
(1) Doses at 3, 4.5-6, 8-12 months. High risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis

Crying/screaming

The RCT found that there is a 52% lower risk of Crying/screaming up to 12 hours after any DTwP dose, compared to after DTwP plain administration (RR 0.48, 95% CI 0.43 to 0.55; 5654 participants).

Figure 106. Crying/screaming reactogenicity for DTwP compared to DTwP plain vaccine



Footnotes
(1) Doses at 3, 4.5-6, 8-12 months. High risk of bias.

DTwP= diphtheria-tetanus-whole-cell pertussis

4 Analyses: Pertussis vaccines schedules impact on reactogenicity

4.1 DTaP accelerated schedule compared to DTaP long schedule

Five studies evaluated reactogenicity in children that received DTaP vaccine on an accelerated versus long schedule. Miller 1997 was a cohort analysis of two trials conducted in the UK with moderate to high risk of bias that administered doses at 2, 3 and 4 months compared to 3, 5 and 9 months. Li 2011 was an RCT conducted in China with unclear or low risk of bias that administered doses at 2, 3 and 4 months compared to 3, 4 and 5 months, and a booster at 18-20 months. Carlson 1998 was an RCT conducted in Sweden with moderate risk of bias that administered doses at 3, 5 + 12 months compared to 2, 4, 6 + 13 months. Hoppenbrouwers 1999 was an RCT conducted in Belgium and Turkey with low risk of bias that administered doses at 3, 4 and 5 months compared to 2, 4 and 6 months. Kamiya 1992 was a cohort study conducted in Japan with moderate risk of bias that administered doses at 3, 5, 7 + 19 months compared to 2, 4, 6 + 20 months.

Table 14. Characteristics of studies contributing to the accelerated vs. long DTaP schedules comparison

Study Country	Design	Status	Schedules	
			Accelerated	Long
Miller 1997(3)* UK	cohort analysis of two trials	Included moderate to high risk of bias	DTaP Porton (3c) or Mérieux (2d) at 2, 3, and 4 months	DTaP Porton (3c) or Mérieux (2d) at 3, 5, and 9 months
Li 2011(7, 8)** China	RCT	Included unclear or low risk of bias	DTaP Sanofi Pasteur (2c) at 2,3,4 + 18-20 months	DTaP Sanofi Pasteur (2c) at 3,4,5 + 18-20 months
Carlson 1998(9) Sweden	RCT	Included moderate risk of bias	DTaP Pasteur Mérieux (2c) at 3,5 +12 months	DTaP Pasteur Mérieux (2c) at 2,4,6 +13 months
Hoppenbrouwers 1999(10)*** Belgium, Turkey	RCT	Included low risk of bias	DTaP Pasteur Mérieux (2c) at 3,4,5 months	DTaP Pasteur Mérieux (2c) at 2,4,6 months
Kamiya 1992(11) Japan	Cohort	Included Moderate risk of bias	DTaP Takeda (4c) at 3,5,7+19 months	DTaP Takeda (4c) at 2,4,6+20 months

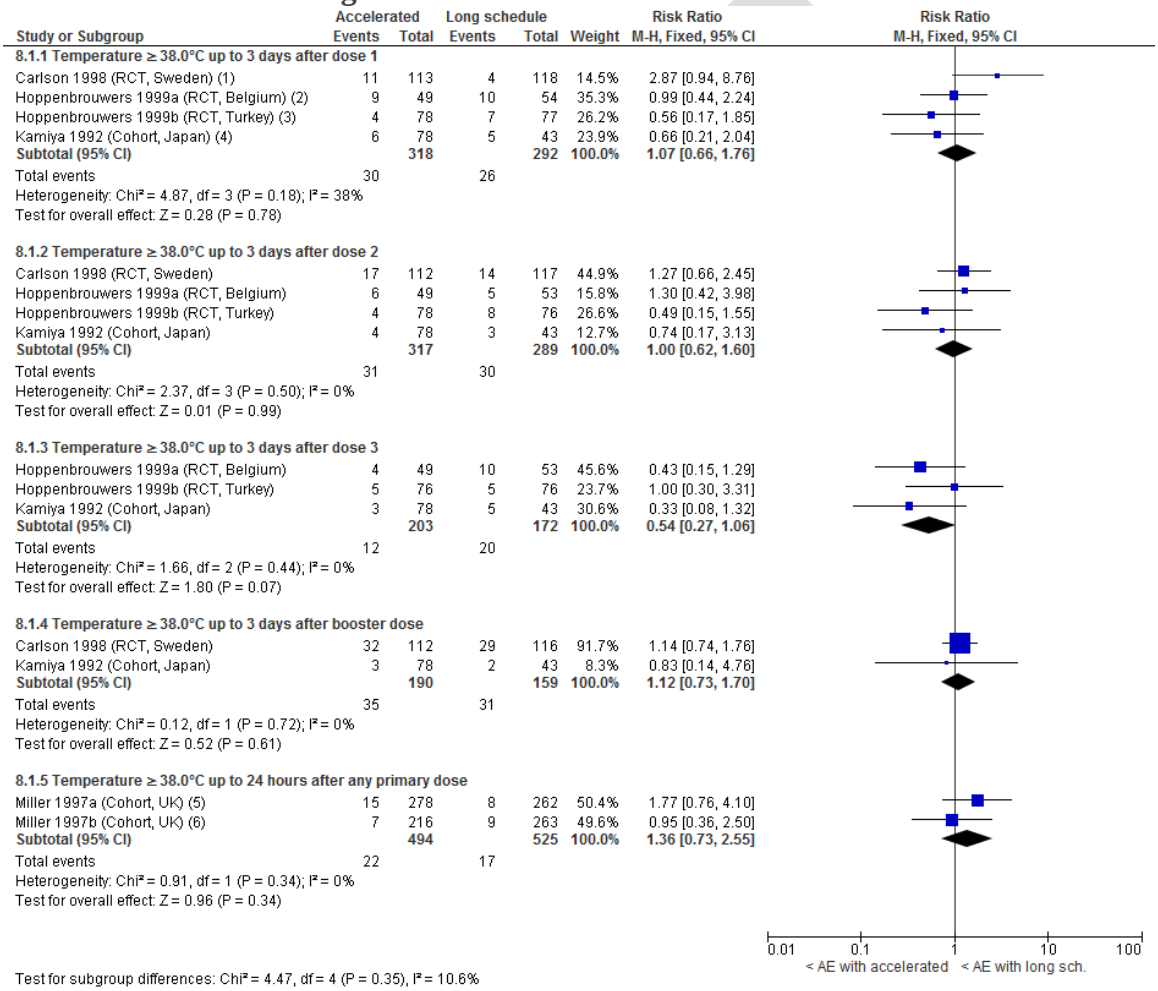
* participants were analysed in two groups: those that received Porton (3c) and those that received Mérieux (2d)
** outcome measures were reported in two separate publications: after primary vaccination and after booster dose
*** participants were analysed in two groups: those in Belgium and those in Turkey

The studies reported on Temperature ≥38.0°C, Erythema/redness, Swelling/nodule, Tenderness/pain, Any systemic symptoms, Persistent crying and Irritability. Mostly, there were no significant differences in reactogenicity between the accelerated and longer schedules, however, for some of the timepoints for Erythema/redness, Swelling/nodule, Any systemic symptoms, and Irritability there was a lower risk of adverse events with the accelerated schedule.

Temperature ≥38.0°C

No statistically significant differences were found between accelerated compared to longer DTaP schedules for Temperature ≥38.0°C.

Figure 107. Meta-analyses of Temperature ≥38°C reactogenicity outcome measures for DTaP accelerated vs. long schedules

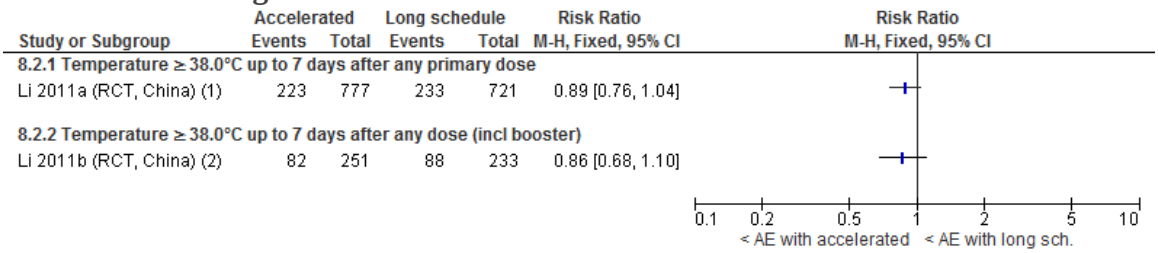


Test for subgroup differences: Chi² = 4.47, df = 4 (P = 0.35), I² = 10.6%

Footnotes

(1) Pasteur Mérieux (2c) 3,5 +12 vs. 2,4,6 +13 mths. Measured within 3 days of dose. Moderate risk of bias.
(2) Pasteur Mérieux (2c) 3,4,5 vs 2,4,6 mths. Measured within 72 hours of dose. Low risk of bias.
(3) Pasteur Mérieux (2c) 3,4,5 vs 2,4,6 mths. Measured within 72 hours of dose. Low risk of bias.
(4) Takeda (4c) 3,5,7+19 vs. 2,4,6+20 mths. Axillary temperature ≥37.5°C measured within 24 hours of dose. Moderate risk of bias.
(5) Porton (3c) 2,3,4 vs 3,5,9 mths. Measured within 24 hours of dose. Moderate to high risk of bias.
(6) Mérieux (2d) 2,3,4 vs 3,5,9 mths. Measured within 24 hours of dose. Moderate to high risk of bias.

Figure 108. Single study outcome measures of Temperature ≥38°C reactogenicity for DTaP accelerated vs. long schedules

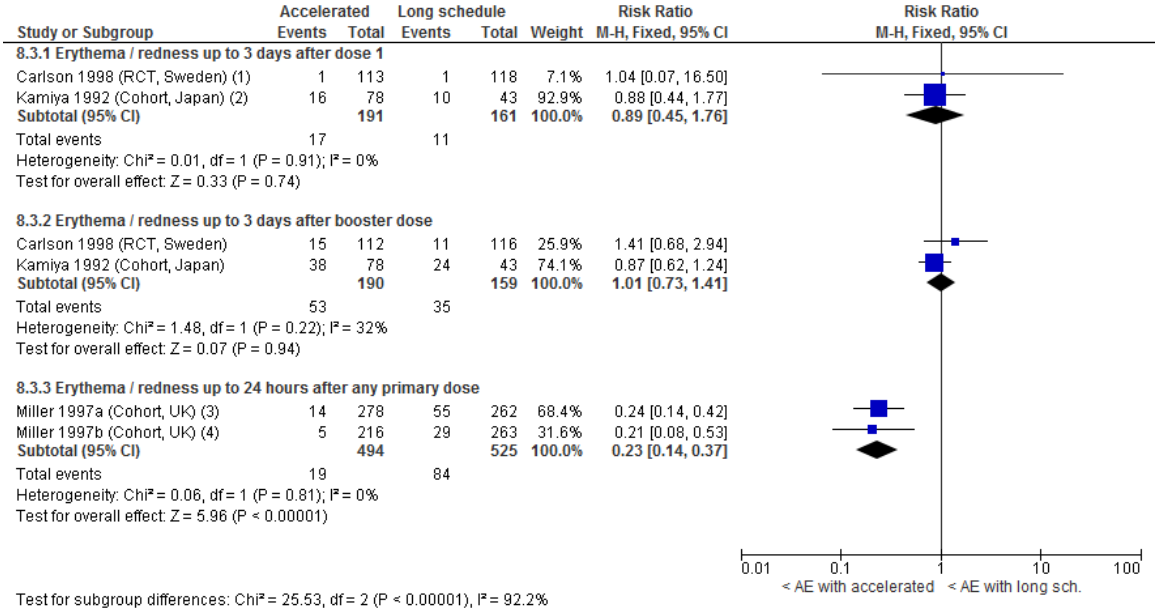


Footnotes
(1) Sanofi Pasteur (2c) 2,3,4 vs 3,4,5 mths. Axillary temperature ≥37.1°C measured within 7 days of dose. Unclear or low risk of bias.
(2) Sanofi Pasteur (2c) 2,3,4 vs 3,4,5 mths + booster at 18-20 mths. Axillary temperature ≥37.1°C measured within 7 days of dose. Unclear or...

Erythema/redness

Two cohort studies found that there is a 67% lower risk of erythema/redness up to 24 hours after any primary schedule dose (excluding booster dose) with an accelerated compared to a long schedule (RR 0.23, 95% CI 0.14 to 0.37; 1019 participants). Another cohort study found that there is a 35% lower risk of erythema/redness up to 24 hours after dose 3 with an accelerated compared to a long schedule (RR 0.65, 95% CI 0.46 to 0.91; 121 participants). After dose 1, 2, booster, or after any dose, no statistically significant differences in erythema/redness between accelerated compared to longer schedules of DTaP vaccines were found. Erythema/redness up to 3 days after dose 2 was analysed with a random effects model due to high heterogeneity (I^2=71%, with a fixed effects model there was also no statistically significant difference between accelerated and long schedule).

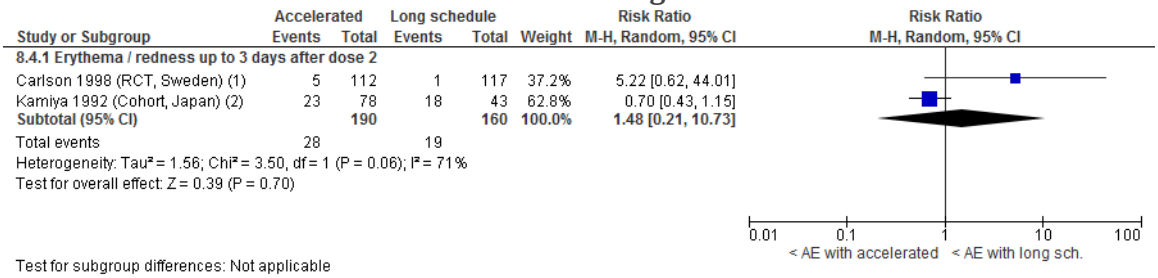
Figure 109. Meta-analyses of Erythema/redness reactogenicity outcome measures for DTaP accelerated vs. long schedules



Test for subgroup differences: Chi² = 25.53, df = 2 (P < 0.00001), I² = 92.2%

Footnotes
(1) Pasteur Mérieux (2c) 3,5 +12 vs. 2,4,6 +13 mths. Redness ≥2 cm measured within 3 days of dose. Moderate risk of bias.
(2) Takeda (4c) 3,5,7+19 vs. 2,4,6+20 mths. Any redness measured within 24 hours of dose. Moderate risk of bias.
(3) Porton (3c) 2,3,4 vs 3,5,9 mths. Erythema / redness ≥2.5cm, measured within 24 hours of dose. Moderate to high risk of bias.
(4) Mérieux (2d) 2,3,4 vs 3,5,9 mths. Erythema / redness ≥2.5cm, measured within 24 hours of dose. Moderate to high risk of bias.

Figure 110. Random effects model meta-analyses of Erythema/redness reactogenicity outcome measures for DTaP accelerated vs. long schedules



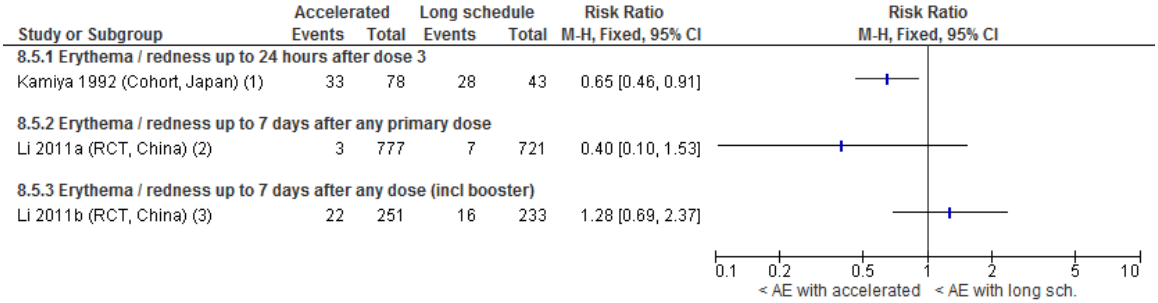
Test for subgroup differences: Not applicable

Footnotes

(1) Pasteur Mérieux (2c) 3,5 +12 vs. 2,4,6 +13 mths. Redness ≥2 cm measured within 3 days of dose. Moderate risk of bias.

(2) Takeda (4c) 3,5,7+19 vs. 2,4,6+20 mths. Any redness measured within 24 hours of dose. Moderate risk of bias.

Figure 111. Single study outcome measures of Erythema/redness reactogenicity for DTaP accelerated vs. long schedules



Footnotes

(1) Takeda (4c) 3,5,7+19 vs. 2,4,6+20 mths. Any redness measured within 24 hours of dose. Moderate risk of bias.

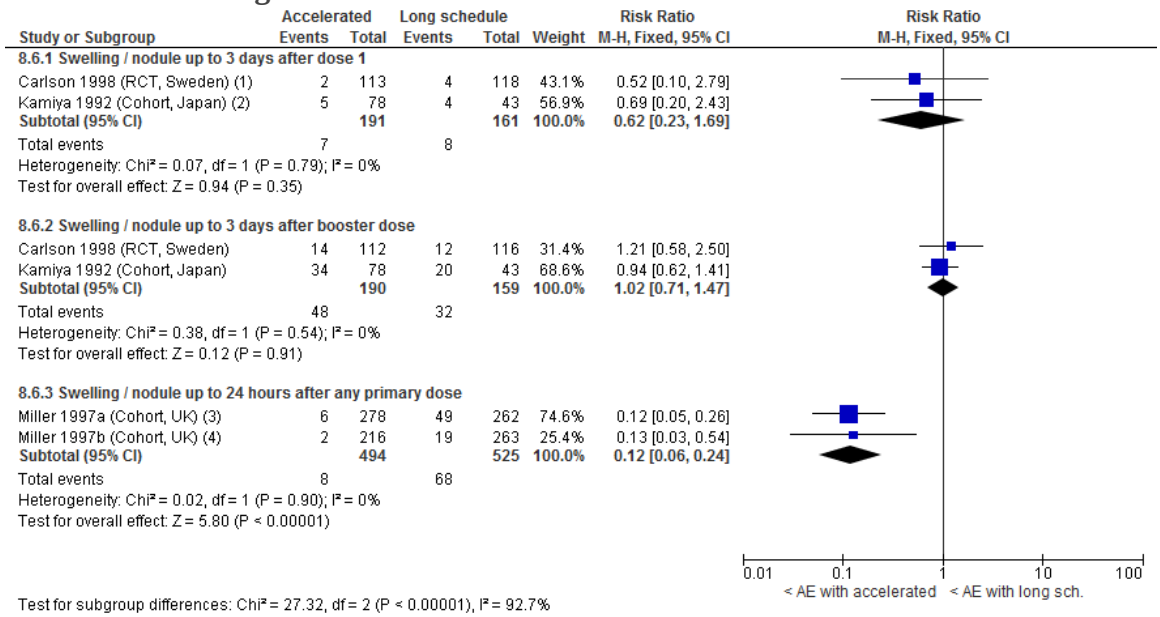
(2) Sanofi Pasteur (2c) 2,3,4 vs 3,4,5 mths. Erythema >3cm measured within 7 days of dose. Unclear or low risk of bias.

(3) Sanofi Pasteur (2c) 2,3,4 vs 3,4,5 mths + booster at 18-20 mths. Erythema >3cm measured within 7 days of dose. Unclear or low risk of bias.

Swelling/nodule

Two cohort studies found that there is a 67% lower risk of swelling/nodule up to 24 hours after any primary schedule dose (excluding booster dose) with an accelerated compared to a long schedule (RR 0.12, 95% CI 0.06 to 0.24; 1019 participants). After dose 1, 2, 3, booster, or after any dose, no statistically significant differences in swelling/nodule between accelerated compared to longer schedules of DTaP vaccines were found. Swelling/nodule up to 3 days after dose 2 was analysed with a random effects model due to high heterogeneity (I^2=57%, with a fixed effects model there was also no statistically significant difference between accelerated and long schedule).

Figure 112. Meta-analyses of Swelling/nodule reactogenicity outcome measures for DTaP accelerated vs. long schedules

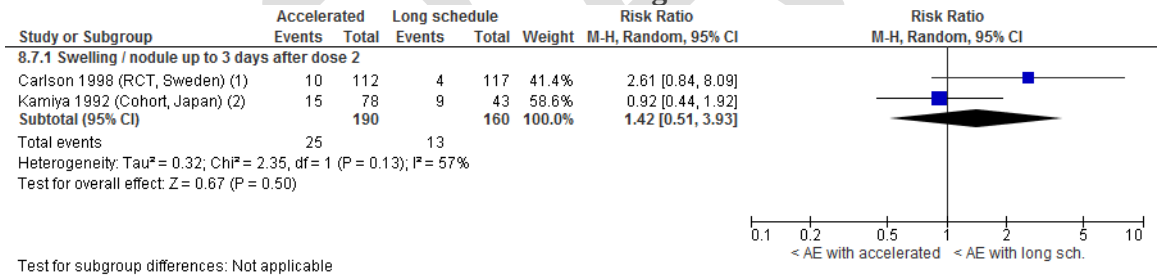


Test for subgroup differences: Chi² = 27.32, df = 2 (P < 0.00001), I² = 92.7%

Footnotes

(1) Pasteur Mérieux (2c) 3,5 +12 vs. 2,4,6 +13 mths. Swelling ≥2 cm measured within 3 days of dose. Moderate risk of bias.
(2) Takeda (4c) 3,5,7+19 vs. 2,4,6+20 mths. Any swelling measured within 24 hours of dose. Moderate risk of bias.
(3) Porton (3c) 2,3,4 vs 3,5,9 mths. Local swelling ≥2.5cm, measured within 24 hours of dose. Moderate to high risk of bias.
(4) Mérieux (2d) 2,3,4 vs 3,5,9 mths. Local swelling ≥2.5cm, measured within 24 hours of dose. Moderate to high risk of bias.

Figure 113. Random effects model meta-analyses of Swelling/nodule reactogenicity outcome measures for DTaP accelerated vs. long schedules

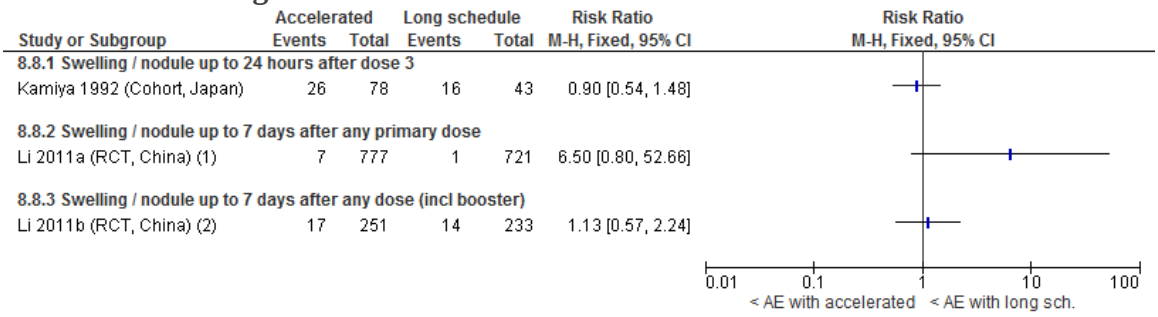


Test for subgroup differences: Not applicable

Footnotes

(1) Pasteur Mérieux (2c) 3,5 +12 vs. 2,4,6 +13 mths. Swelling ≥2 cm measured within 3 days of dose. Moderate risk of bias.
(2) Takeda (4c) 3,5,7+19 vs. 2,4,6+20 mths. Any swelling measured within 24 hours of dose. Moderate risk of bias.

Figure 114. Single study outcome measures of Swelling/nodule reactogenicity for DTaP accelerated vs. long schedules

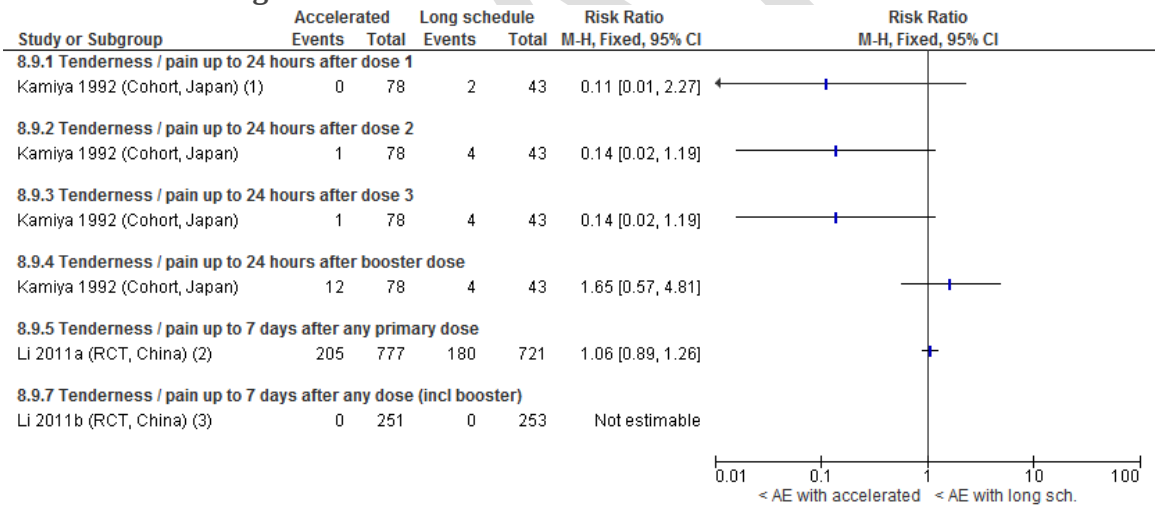


Footnotes
(1) Sanofi Pasteur (2c) 2,3,4 vs 3,4,5 mths. Swelling >3cm measured within 7 days of dose. Unclear or low risk of bias.
(2) Sanofi Pasteur (2c) 2,3,4 vs 3,4,5 mths + booster at 18-20 mths. Swelling >3cm measured within 7 days of dose. Unclear or low risk of bias.

Local pain/tenderness

No statistically significant differences were found between accelerated compared to longer schedules of DTaP vaccines for Tenderness/pain.

Figure 115. Single study outcome measures of Tenderness/pain reactogenicity for DTaP accelerated vs. long schedules



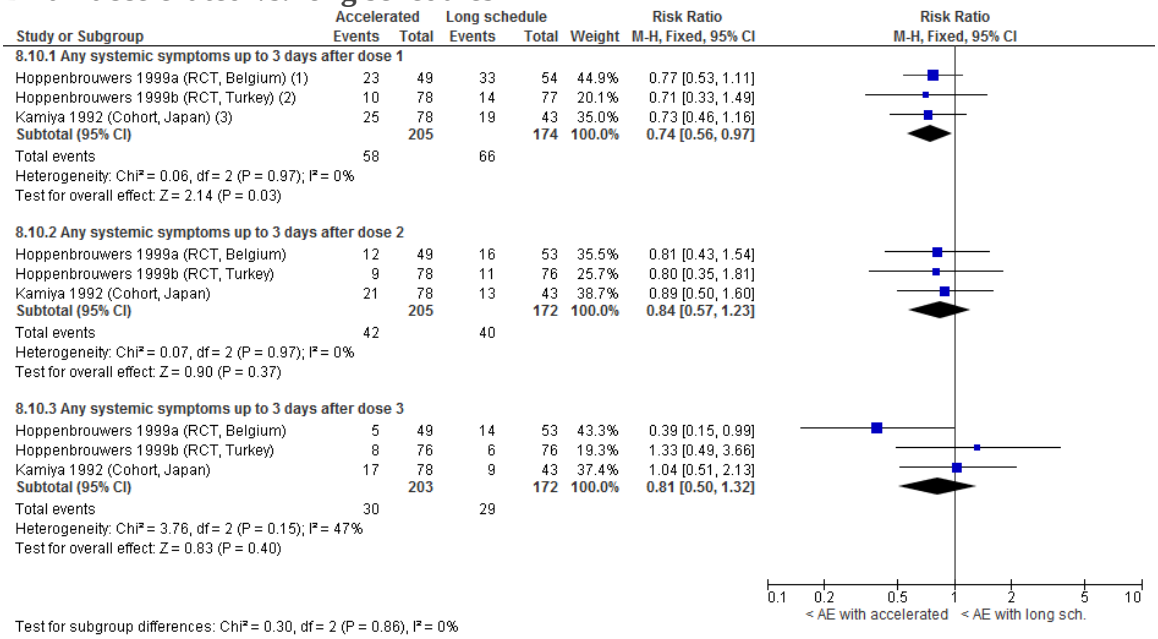
Footnotes
(1) Takeda (4c) 3,5,7+19 vs. 2,4,6+20 mths. Any degree of tenderness measured within 24 hours of dose. Moderate risk of bias.
(2) Sanofi Pasteur (2c) 2,3,4 vs 3,4,5 mths. Any degree of tenderness measured within 7 days of dose. Unclear or low risk of bias.
(3) Sanofi Pasteur (2c) 2,3,4 vs 3,4,5 mths + booster at 18-20 mths. Any degree of tenderness measured within 7 days of dose. Unclear or low risk of...

Any systemic symptoms

An RCT and a cohort study found that there is a 26% lower risk of any systemic symptoms up to 3 days after dose 1 with an accelerated compared to a longer schedule (RR 0.74, 95% CI 0.56 to 0.97; 379 participants). After dose 2, 3, booster, or after any dose, no statistically significant differences in systemic symptoms between accelerated compared to longer schedules of DTaP vaccines were found. Any systemic symptoms up to 24 hours after any primary schedule dose (excluding booster) was analysed with a random effects model due to high heterogeneity

(I^2=79%, with a fixed effects model there was also no statistically significant difference between accelerated and long schedule).

Figure 116. Meta-analyses of Any systemic symptoms reactogenicity outcome measures for DTaP accelerated vs. long schedules

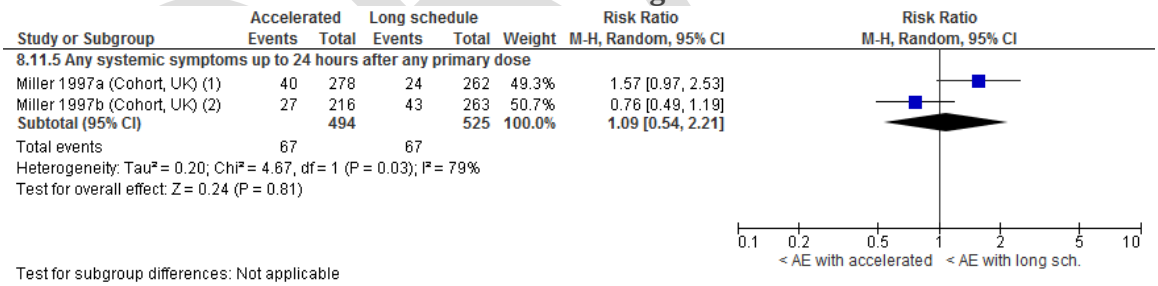


Test for subgroup differences: Chi² = 0.30, df = 2 (P = 0.86), I² = 0%

Footnotes

(1) Pasteur Mérieux (2c) 3,4,5 vs 2,4,6 mths. Any systemic reaction measured within 72 hours of dose. Low risk of bias.
(2) Pasteur Mérieux (2c) 3,4,5 vs 2,4,6 mths. Any systemic reaction measured within 72 hours of dose. Low risk of bias.
(3) Takeda (4c) 3,5,7+19 vs. 2,4,6+20 mths. Any systemic reaction measured within 24 hours of dose. Moderate risk of bias.

Figure 117. Random effects model meta-analyses of Any systemic symptoms reactogenicity outcome measures for DTaP accelerated vs. long schedules

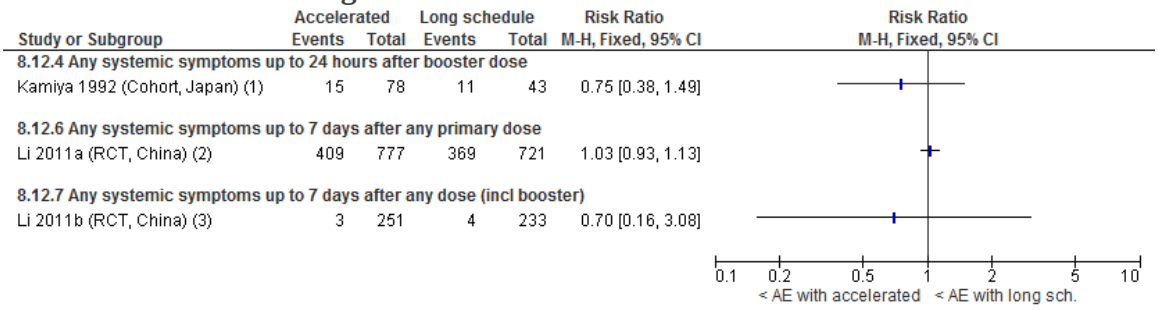


Test for subgroup differences: Not applicable

Footnotes

(1) Porton (3c) 2,3,4 vs 3,5,9 mths. ≥3 systemic symptoms measured within 24 hours of dose. Moderate to high risk of bias.
(2) Mérieux (2d) 2,3,4 vs 3,5,9 mths. ≥3 systemic symptoms measured within 24 hours of dose. Moderate to high risk of bias.

Figure 118. Single study outcome measures of Any systemic symptoms reactogenicity for DTaP accelerated vs. long schedules

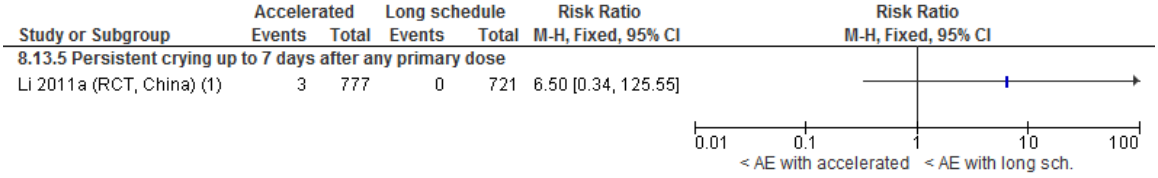


Footnotes
(1) Takeda (4c) 3,5,7+19 vs. 2,4,6+20 mths. Any systemic reaction measured within 24 hours of dose. Moderate risk of bias.
(2) Sanofi Pasteur (2c) 2,3,4 vs 3,4,5 mths. Any systemic reaction measured within 7 days of dose. Unclear or low risk of bias.
(3) Sanofi Pasteur (2c) 2,3,4 vs 3,4,5 mths + booster at 18-20 mths. Any systemic reaction measured within 7 days of dose. Unclear or low risk of bias.

Persistent crying

No statistically significant differences were found between accelerated compared to longer schedules of DTaP vaccines for persistent crying.

Figure 119. Single study outcome measures of Persistent crying reactogenicity for DTaP accelerated vs. long schedules

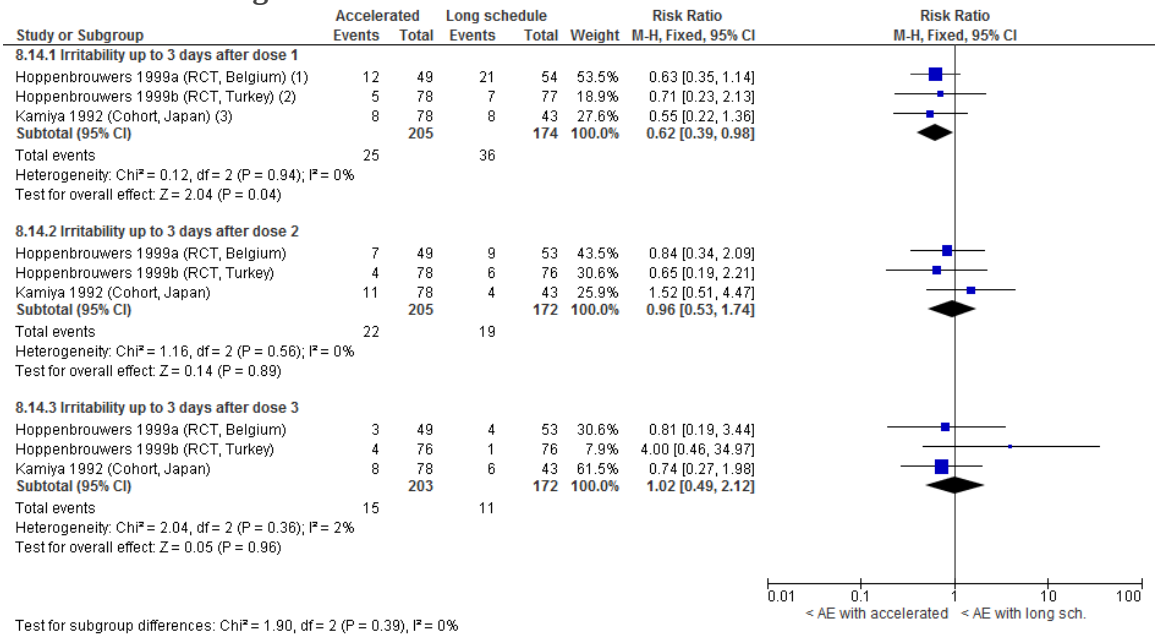


Footnotes
(1) Sanofi Pasteur (2c) 2,3,4 vs 3,4,5 mths. Persistent crying >3h measured within 7 days of dose. Unclear or low risk of bias.

Irritability

An RCT and a cohort study found that there is a 38% lower risk of irritability up to 3 days after dose 1 with an accelerated compared to a longer schedule (RR 0.62, 95% CI 0.39 to 0.98; 379 participants). After dose 2, 3, booster, or after any dose, no statistically significant differences in irritability between accelerated compared to longer schedules of DTaP vaccines were found.

Figure 120. Meta-analyses of Irritability reactogenicity outcome measures for DTaP accelerated vs. long schedules

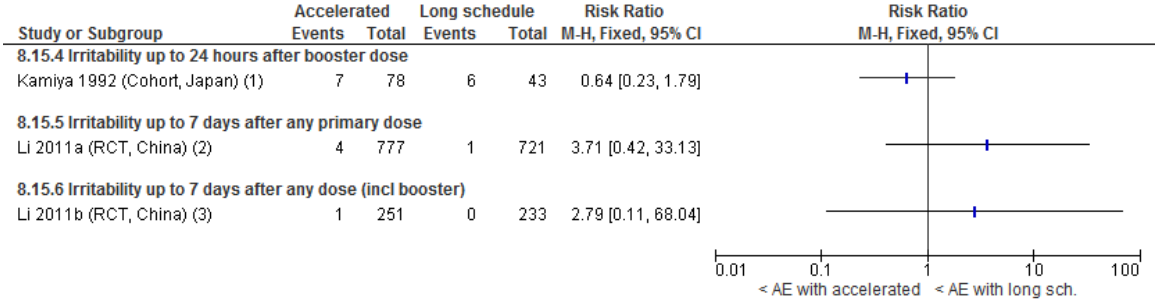


Test for subgroup differences: Chi² = 1.90, df = 2 (P = 0.39), I² = 0%

Footnotes

(1) Pasteur Mérieux (2c) 3,4,5 vs 2,4,6 mths. Measured within 72 hours of dose. Low risk of bias.
(2) Pasteur Mérieux (2c) 3,4,5 vs 2,4,6 mths. Measured within 72 hours of dose. Low risk of bias.
(3) Takeda (4c) 3,5,7+19 vs. 2,4,6+20 mths. Fretfulness measured within 24 hours of dose. Moderate risk of bias.

Figure 121. Single study outcome measures of Irritability reactogenicity for DTaP accelerated vs. long schedules



Footnotes

(1) Takeda (4c) 3,5,7+19 vs. 2,4,6+20 mths. Fretfulness measured within 24 hours of dose. Moderate risk of bias.
(2) Sanofi Pasteur (2c) 2,3,4 vs 3,4,5 mths. Any degree of irritability measured within 7 days of dose. Unclear or low risk of bias.
(3) Sanofi Pasteur (2c) 2,3,4 vs 3,4,5 mths + booster at 18-20 mths. Any degree of irritability measured within 7 days of dose. Unclear or low risk of...

DTwP accelerated schedule compared to DTwP long schedule

Two studies evaluated reactogenicity in children that received DTwP vaccination on an accelerated versus long schedule. Miller 1997 was a cohort analysis of two trials conducted in the UK with moderate to high risk of bias that compared vaccination of children at 2, 3, and 4 months versus 3, 5, and 9 months. Ramsay 1992 was an analysis of two cohorts conducted in the UK with moderate to high risk of bias that compared vaccination of children at 2, 3, and 4 months versus 3, 5, and 10 months.

Table 15. Characteristics of studies contributing to the accelerated vs. long DTwP schedules comparison

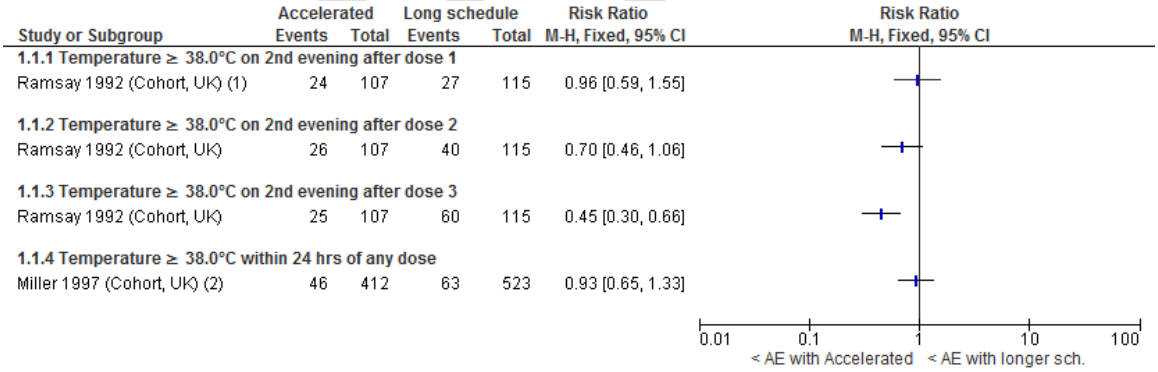
Study Country	Design	Status	Schedules	
			Accelerated	Long
Miller 1997(3) UK	cohort analysis of two trials	Included moderate to high risk of bias	DTwP at 2, 3, and 4 months	DTwP at 3, 5, and 9 months
Ramsay 1992(12) UK	analysis of two cohorts	Included moderate to high risk of bias	DTwP at 2, 3, and 4 months	DTwP at 3, 5, and 10 months

The studies reported on Temperature ≥38.0°C, Erythema/redness, Swelling/nodule, and Any systemic symptoms. Mostly, there were no significant differences in reactogenicity between the accelerated and longer schedules. However, for some of the timepoints for Temperature ≥38°C, Erythema/redness, and Swelling/nodule there was a lower risk of adverse events with the accelerated schedule, except for one timepoint for Swelling/nodule, when there was a lower risk of adverse events with the longer schedule.

Temperature ≥38°C

An RCT found that there is a 55% lower risk of Temperature ≥38.0°C after dose 3 with an accelerated compared to a long schedule (RR 0.45, 95% CI 0.30 to 0.66; 232 participants). After dose 1, 2, or after any dose, no statistically significant differences in Temperature ≥38.0°C between accelerated compared to longer schedules of DTwP vaccines were found.

Figure 122. Temperature ≥38°C reactogenicity for DTwP accelerated compared to long schedules



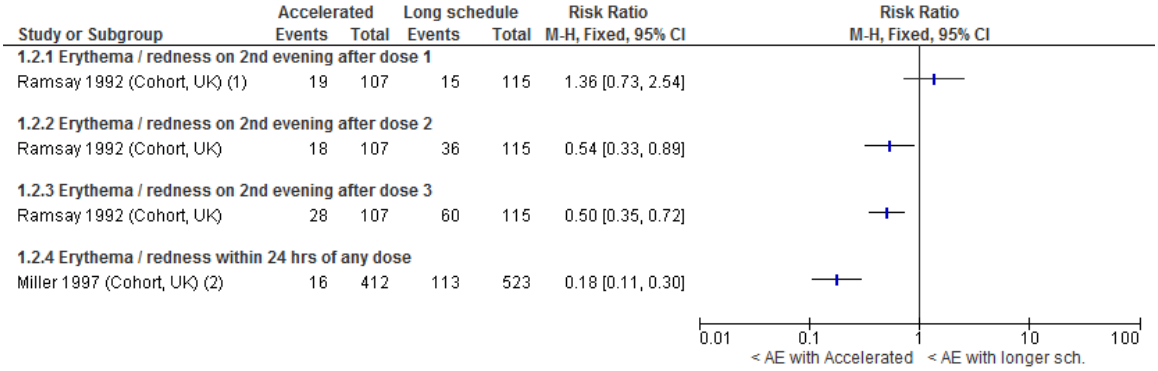
Footnotes
(1) Axillary temperature ≥ 37.2°C. Analysis of two cohorts: 2, 3, 4 mths vs. 3, 4.5-5, 8.5-11 mths. Moderate to high risk of bias.
(2) Rectal temperature ≥ 38.0°C. Cohort analysis of two trials: 2,3,4 mths vs. 3,5,9 mths. Moderate to high risk of bias.

Erythema/redness

An RCT found that with an accelerated schedule there is a 55% lower risk of Erythema/redness after dose 2 (RR 0.54, 95% CI 0.33 to 0.89; 232 participants), and a 50% lower risk after dose 3 (RR 0.50, 95% CI 0.35 to 0.72; 232 participants), compared to a longer schedule. Another RCT found that there is an 82% lower risk of Erythema/redness after any dose with an accelerated compared to a longer schedule (RR 0.18, 95% CI 0.11 to 0.30; 935 participants). After dose 1 no

statistically significant difference in Erythema/redness between accelerated compared to longer schedules of DTwP vaccines was found.

Figure 123. Erythema/redness reactogenicity for DTwP accelerated compared to long schedules

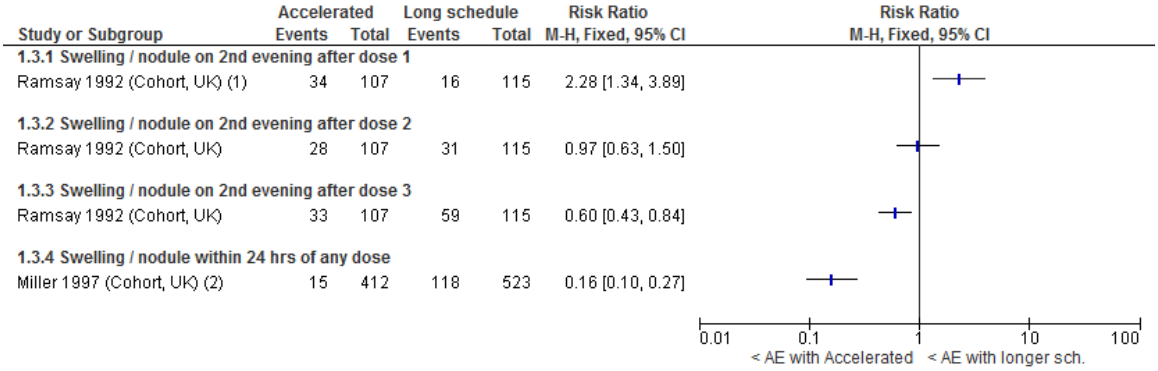


Footnotes
(1) Erythema / redness ≥2.5cm. Analysis of two cohorts: 2, 3, 4 mths vs. 3, 4.5-5, 8.5-11 mths. Moderate to high risk of bias.
(2) Erythema / redness ≥2.5cm. Cohort analysis of two trials: 2,3,4 mths vs. 3,5,9 mths. Moderate to high risk of bias.

Swelling/nodule

An RCT found that with a longer schedule there is a lower risk of Swelling/nodule after dose 1 (RR 2.28, 95% CI 1.34 to 3.89; 232 participants), compared to an accelerated schedule. The same study found that with an accelerated schedule there is a 40% lower risk after dose 3 (RR 0.60, 95% CI 0.43 to 0.84; 232 participants), compared to a longer schedule. Another RCT found that there is an 84% lower risk of Swelling/nodule after any dose with an accelerated compared to a longer schedule (RR 0.16, 95% CI 0.10 to 0.27; 935 participants). After dose 2 no statistically significant difference in Swelling/nodule between accelerated compared to longer schedules of DTwP vaccines was found.

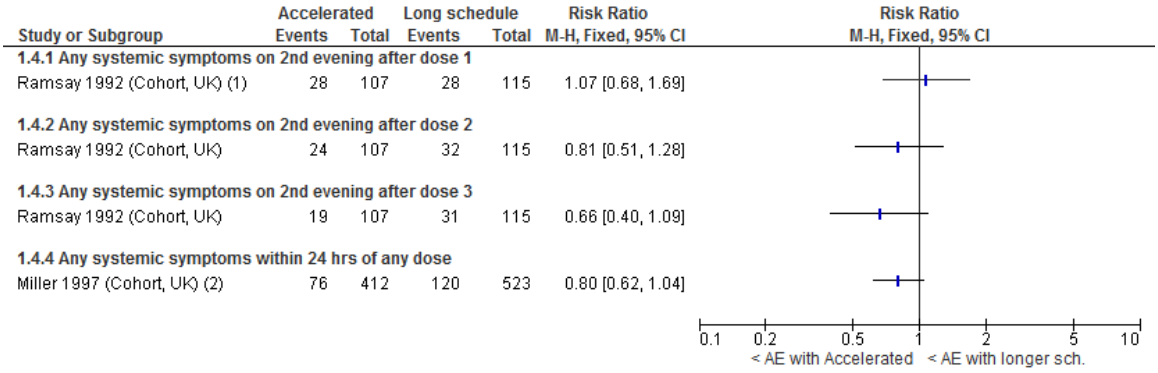
Figure 124. Swelling/nodule reactogenicity for DTwP accelerated compared to long schedules



Footnotes
(1) Local swelling ≥2.5cm. Analysis of two cohorts: 2, 3, 4 mths vs. 3, 4.5-5, 8.5-11 mths. Moderate to high risk of bias.
(2) Local swelling ≥2.5cm. Cohort analysis of two trials: 2,3,4 mths vs. 3,5,9 mths. Moderate to high risk of bias.

Any systemic symptom
No statistically significant differences in Any systemic symptoms were found between accelerated compared to longer schedules of DTwP vaccines.

Figure 125. Any systemic symptoms reactogenicity for DTwP accelerated compared to long schedules



Footnotes
(1) ≥3 symptoms. Analysis of two cohorts: 2, 3, 4 mths vs. 3, 4.5-5, 8.5-11 mths. Moderate to high risk of bias.
(2) ≥3 systemic symptoms. Cohort analysis of two trials: 2,3,4 mths vs. 3,5,9 mths. Moderate to high risk of bias.

4.2 DTwP with a birth dose compared to DTwP without a birth dose

One study evaluated reactogenicity for birth dose versus no birth dose DTwP vaccination. Baraff 1984 was an RCT conducted in the USA with unclear or moderate risk of bias that included 23 participants and compared vaccination of children at 0, 2, 4, and 6 months (birth dose) versus 2, 4, and 6 months (no birth dose).

Table 16. Characteristics of studies contributing to the birth dose vs. no birth dose DTwP schedules comparison

Study Country	Design	Status	Schedules	
Baraff 1984(13) USA	RCT	Additional study Not per protocol: Only combined reactions reported Unclear or moderate risk of bias	DTwP at 0,2, 4, and 6 months (with birth dose)	DTwP at 2, 4, and 6 months (no birth dose)

The study reported on Redness, swelling or pain as a combined outcome and found no statistically significant differences between the two schedules.

Redness, swelling or pain
No statistically significant difference in redness, swelling or pain was found between DTwP schedule with a birth dose compared to DTwP schedule without a birth dose.

Figure 126. Redness, swelling or pain reactogenicity for DTwP schedules with compared to without a birth dose

Footnotes
(1) Not per protocol: Only combined reactions reported. 0,2,4,6, mths vs. 2,4,6 mths. Timing of assessment unclear. Unclear or moderate risk of...

4.3 Different number of DTwP doses comparisons

One study evaluated reactogenicity for different number of doses of DTwP vaccine. Bhandari 1981 was an unblinded RCT conducted in India with unclear or high risk of bias that compared vaccination of children receiving 1 dose versus 2 doses, 1 dose versus 3 doses, and 2 doses versus 3 doses. It should be noted that this study did not compare schedules as per protocol, but reported serial dose number.

Table 17. Characteristics of studies contributing to different number of doses comparisons of DTwP schedules

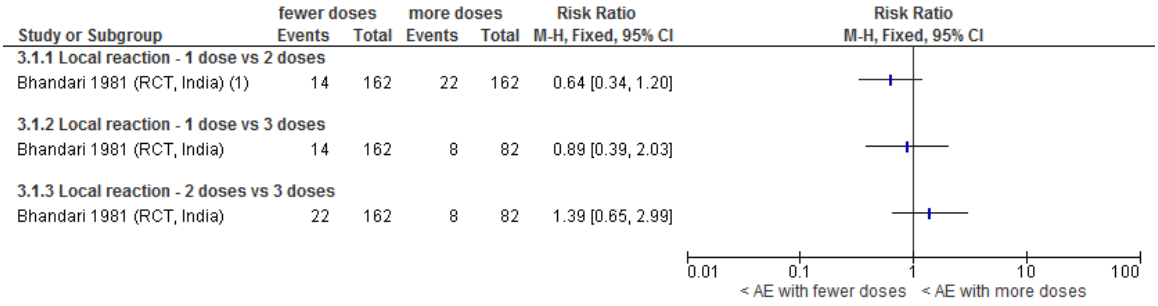
Study Country	Design	Status	Schedules
Bhandari 1981(14) India	Unblinded RCT	Additional study Not per protocol: no comparison between schedules, only by serial dose number. Unclear or high risk of bias	2 doses (2-mo interval) and 3 doses (1-mo interval) of DTwP, evaluation of children with reaction in both groups combined for 1st doses, 2nd doses, and 3rd doses.

The study reported on Local reaction and Temperature ≥38.0°C, and found no statistically significant differences between different number of doses.

Local reaction

No statistically significant difference in Local reaction was found between 1 vs. 2, 1 vs. 3, or 2 vs. 3 doses of DTwP vaccine.

Figure 127. Local reaction reactogenicity for 1 vs. 2, 1 vs. 3 and 2 vs. 3 doses of DTwP vaccine



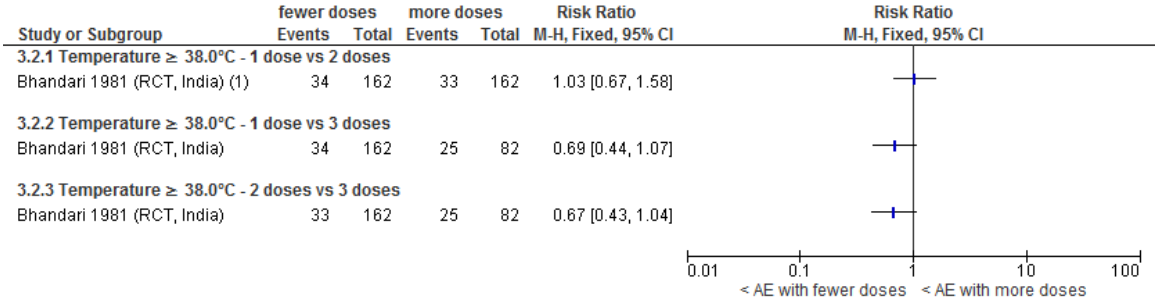
Footnotes

(1) Not per protocol: No comparison between schedules, only by serial dose number. Timing of assessment not specified. Unclear to high risk of bias.

Temperature ≥38.0°C

No statistically significant difference in Temperature ≥38.0°C was found between 1 vs. 2, 1 vs. 3, or 2 vs. 3 doses of DTwP vaccine.

Figure 128. Temperature ≥38.0°C reactogenicity for 1 vs. 2, 1 vs. 3 and 2 vs. 3 doses of DTwP vaccine



Footnotes

(1) Pyrexia. Not per protocol: No comparison between schedules, only by serial dose number. Timing of assessment not specified. Unclear to high...

4.4 DTwP schedule compared to DTwP with a 3rd dose of placebo

One study evaluated reactogenicity for DTwP vaccine schedule versus DTwP with a third dose of placebo. Long 1990 was an RCT conducted in the USA with low risk of bias that administered doses at 2, 4 and 6 months.

Table 18. Characteristics of studies contributing to the DTwP vs. 3rd dose placebo schedules comparison

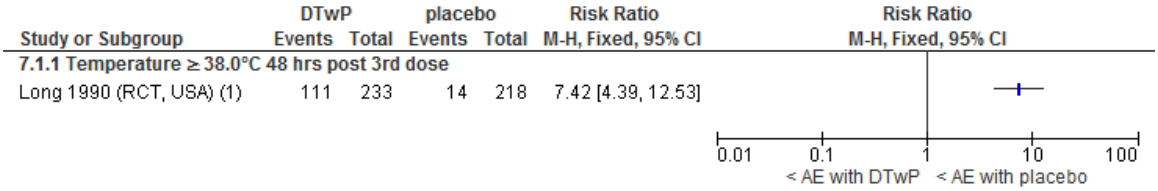
Study Country	Design	Status	Schedules	
Long 1990(15) USA	RCT	Included Low risk of bias	DTwP at 2, 4 and 6 months	DTwP at 2 and 4 months, placebo at 6 months

The study reported on Temperature ≥38.0°C, Persistent crying, Local pain/tenderness, Erythema/redness, and Swelling/nodule. The study found a lower risk of these adverse events for a third dose of placebo compared to DTwP vaccine, except for Persistent crying where no statistically significant difference was found.

Temperature ≥38°C

The RCT found that there is a lower risk of Temperature ≥38.0°C 48 hours after a 3rd dose of placebo, compared to after a 3rd dose of DTwP (RR 7.42, 95% CI 4.39 to 12.53; 451 participants).

Figure 129. Temperature ≥38.0°C reactogenicity for DTwP compared to a 3rd dose of placebo

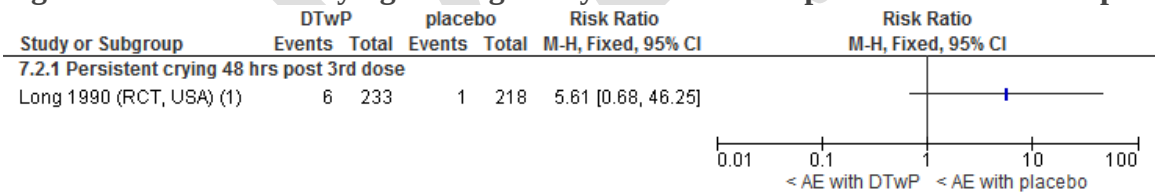


Footnotes
(1) Temperature ≥38.3°C. Doses at 2,4,6 months, at 6 months: DTwP vs. placebo. Low risk of bias.

Persistent crying

The RCT found no statistically significant difference in Persistent crying 48 hours after a 3rd dose of placebo, compared to after a 3rd dose of DTwP.

Figure 130. Persistent crying reactogenicity for DTwP compared to a 3rd dose of placebo

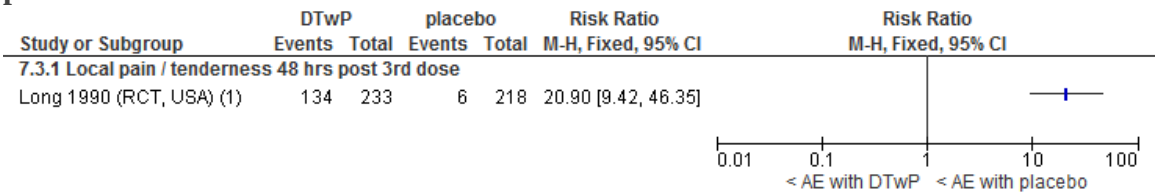


Footnotes
(1) Doses at 2,4,6 months, at 6 months: DTwP vs. placebo. Low risk of bias.

Local pain/tenderness

The RCT found that there is a lower risk of Local pain/tenderness 48 hours after a 3rd dose of placebo, compared to after a 3rd dose of DTwP (RR 20.90, 95% CI 9.42 to 46.35; 451 participants).

Figure 131. Local pain/tenderness reactogenicity for DTwP compared to a 3rd dose of placebo

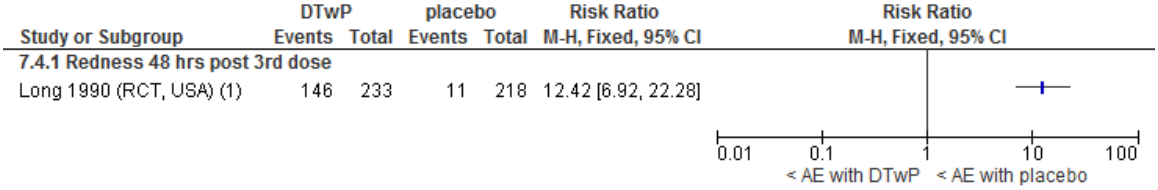


Footnotes
(1) Doses at 2,4,6 months, at 6 months: DTwP vs. placebo. Low risk of bias.

Erythema/redness

The RCT found that there is a lower risk of Redness 48 hours after a 3rd dose of placebo, compared to after a 3rd dose of DTwP (RR 12.42, 95% CI 6.92 to 22.28; 451 participants).

Figure 132. Redness reactogenicity for DTwP compared to a 3rd dose of placebo

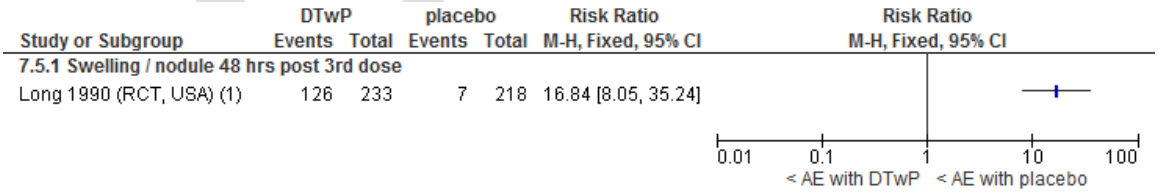


Footnotes
(1) Doses at 2,4,6 months, at 6 months: DTwP vs. placebo. Low risk of bias.

Swelling/nodule

The RCT found that there is a lower risk of Swelling/nodule 48 hours after a 3rd dose of placebo, compared to after a 3rd dose of DTwP (RR 16.84, 95% CI 8.05 to 35.24; 451 participants).

Figure 133. Swelling/nodule reactogenicity for DTwP compared to a 3rd dose of placebo



Footnotes
(1) Swelling ≥1.27 cm. Doses at 2,4,6 months, at 6 months: DTwP vs. placebo. Low risk of bias.

5 Inconsistencies between data tables and data analysed

Study	Vaccine	Comparison	Outcome	Data table	Data analysed	Comment
Carlson 1998	aP	Acc vs long	Swelling, dose 2	Acc: 8.6% of 112=9.6 Long: 3.6% of 117=4.2 RR 0.42	Acc: 10/112, long: 4/117 RR 2.61 (0.84-8.09)	In the original table the RR is for the reversed comparison, which is Long vs. Acc. It has been calculated as RR=0.036/0.086=0.42. See Figure 7
Li 2011a	aP	Acc vs long	Swelling	Acc: 0.9% of 777=6.99 Long: 0.1% of 721=0.7 RR 9.00	Acc: 7/777, long: 1/721 RR 6.50 (0.80-52.66)	This is due to rounding in RevMan. If the RR is calculated using the exact percentages for control group risk and treatment group risk, then RR=0.009/0.001=9.00. See Figure 8
Miller 1997a	aP	Acc vs long	Any systemic reaction	Acc: 14.5% of 278=40.3 Long: 9.0% of 262=23.6 RR 0.80	Acc: 40/278, long: 24/262 RR 1.57 (0.97-2.53)	We do not understand why in the original document the RR is 0.8. Based on the risks in the original document the RR should be: RR=0.145/0.09=1.61. See Figure 11

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