Comparative efficacy/effectiveness of schedules in infant immunisation against pertussis, diphtheria and tetanus: Systematic review and meta-analysis.

Part 2: Whole-cell pertussis vaccine

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Introduction

Methods

Results

Study selection

Results of individual studies

Primary vaccination

Number of doses: Two vs. three doses

Only one of the included studies evaluated the effect of the number of primary doses on any of the three outcomes (**Table 8b-A**). A cohort analysis from a clinical trial [Olin 1998] reported that at age 7 mo, a 2,4,6-mo had provided ≥2-fold higher antibody titers (four pertussis antigens) than a 3,5-mo schedule (differences statistically significant).

This study also compared vaccine effectiveness between a 2,4,6-mo- vs. a 3,5,12-mo schedule, starting with the first dose (follow-up to at least 28 months of age), thus providing some *not-per-protocol* evidence on 2 vs. 3 doses (**Table 8a-A**). According to the old WHO case definition, the schedule giving 3 doses before age 6 mo, had a relative vaccine effectiveness of 29.6% (not significant) starting with the 1st dose and of -31.6 (not significant) from 9 mo after the 1st dose (age 11 or 12 mo). Taken together, this suggests that there is some clinical benefit from the third primary dose during the first year of life, possibly with a vaccine effectiveness around 60% (rVE@1st – rVEpost9m = 30% - -32% = 62%).

Indirect *not-per-protocol* evidence also comes from several included studies evaluating absolute effectiveness of vaccination with different numbers of received doses (**Table 5**). This includes RCT [Gustafsson 1996 and Greco 1996], cohorts [Onorato 1992], case control studies [Bisgard 2005, Izuireta 1996] and surveillance data analysed using the screening method [Guris 1997], as well as several not-per-protocol studies [Broome 1981, Brink 1982, Campbell 2012, Walker 1981]. These studies varied by case definitions, age ranges evaluated (most at least up to age 3 years) and vaccine schedules used (majority 2,4,6-mo schedule), but the general picture emerged that absolute vaccine effectiveness is <50% if vaccination implies 1 or 1-2 doses, higher with 2 doses (50-85%), with some further increase if 3 or ≥3 doses were received (range 35%-95%). One case control study among children <7 months showed negative VE at 1 or 2 doses and moderate positive VE with complete adherence to the 2,4,6-mo schedule [Izurieta 1996].

Further not-per-protocol evidence on the difference between 2 and 3 primary doses was available from seven serological studies, all using agglutination or microagglutination techniques, and one study on reactogenicity (**Table 8b-B and 8c-B**). Two doses usually were given in a larger interval, and one month after the last dose (usually at a comparable age), three doses led to higher antibody titers or higher seroprevalence [Laurell 1957, Bhandari 1981, Muller 1984, Barkin 1985 I and II, Swartz 1985]. Comparable seroprevalence was found one month after the final dose by a small RCT [Wilkins 1971], and one small cohort found lower levels after 3 vs. 2 doses after a booster in 6-16mo interval [Wilkins 1987]. One cohort found that at the time of a booster dose (age 10/12 mo) and over the following two

years, the group of children with 2 primary dose (2, 3.5 mo) had up to two-fold lower GMT than children with 3 primary doses (2,4,6 mo) [Swartz 1985]. However, no difference was observed in the seroprevalence of titers ≥1:10.

Some indirect *not-per-protocole* evidence on reactogenicity is avaible from a small unblinded trial, where local reactions occurred most frequently after the second (compared to first or third dose) and fever most frequently after the third dose [Bhandari 1981].

Two studies evaluated the effect of a birth dose (*see below*).

Different ages of vaccination initiation

One included synopsis of two trials compared a 3,4,5-mo with a 2,4,6-mo schedule [Just 1991] and found (insignificantly) higher anti-FHA GMT in the 2,4,6-mo schedule (**Table 8b-B**). Although this may evaluate the effect of first primary dose at 3 vs. 2 mo, it may mainly evaluate length of intervals between the doses.

Additional *not-per-protocol* evidence is available from two studies, one using microagglutination technique and the other comparing schedules with different vaccines (**Table 8b-B**). A cohort study evaluated agglutinin seroprevalence after different ages of first doses (4-11 wk, 12-19 wk, 20+ wk) and found consistently higher levels with later initiation one month later [Wilkins 1987]. While after two months, this difference was no longer clear-cut, the following second dose appeared to have greater immunogenic effect in the group with later initiation. An RCT comparing schedules with different vaccine products (DTwP by Pasteur Mérieux Connaught vs. DTwP-HBV by GSK) found substantially and significantly higher GMC of IgG (not specified) in a 1.5,3,5-mo schedule than a 3,4,5-mo schedule, with little difference in seroprevalence of "protective" titers [Wong 2008]. At age 12 months, the relation was inverted, however without any significant difference.

One small RCT provided per-protocol and *not-per-protocol* evidence on the effect of an additional birth dose [Baraff 1984 / Burstyn 1983]. At age 4 months, children with a birth dose in addition to the 2,4,6-mo schedule had the same anti-FHA IgG mean concentration as children without a birth dose, and no consistent difference was observed at following assessments at age 6 and 9 months (**Table 8b-A**). Combining all doses, children with a birth dose had a marginally increased risk of local reactions than children receiving only the 2,4,6-mo schedule (**Table 8c-B**).

Interval

One synopsis of two trials compared a 3,4,5-mo with a 2,4,6-mo schedule in two countries [Just 1991] and found (insignificantly) higher anti-FHA GMT in the 2,4,6-mo schedule (**Table 8b-B**). The difference may mainly be the effect of longer intervals, but a country effect cannot be ruled out (2,4,6 in Turkey, vs. Switzerland).

Three *not-per-protocol* studies using microagglutination techniques evaluated the impact of interval length in 2- and 3-dose schedules (**Table 8b-B**). A interval difference of 4 or 8 weeks in a 2-dose schedule did not impact on antibody titers or seroprevalence, while delaying the 3rd dose by 5 months produced higher mean antbody titer (not significant in a small RCT among preterm babies born at 23-25 weeks gestational age) [Conway 1993].

Accelerated vs. long schedules

Evidence comparing a 3+0 (accelerated) to a 2+1 (long) schedule came from one effectiveness study (**Table 8a-A**) and three serological studies (**Table 8b-A**), summarized in a GRADE table (**Table 3**). In

a study comparing two counties using different schedules in the context of a vaccine trial, children in the county with an accelerated 2,4,6-mo schedule had 30% and 10%, respectively, less risk of disease, depending on the case definition (old WHO or laboratory-confirmed cases based on any cough), compared to a long 3,5,12-mo schedule in other counties [Olin 1998]. This estimated was obtained including cases from the first dose of vaccine to at least age 28 months, and did not achieve statistical significance. Taking into account only cases occurring 9 months after the first dose (age 11 or 12 mo), the children in the county with the accelerated schedule had a 20%-30% higher risk (no statistical significance).

One cohort study found slightly higher GMT against FHA (difference significant) and PT in a group vaccinated with a long vs. an accelerated schedule [Olin 1998]. Two synopses of unrelated but comparable cohorts found that GMT against FHA, PT and Fim2/3 were similar in groups with accelerated or long schedules, at one month or up to 18 months after the third dose [Miller 1997, Booy 1992]. The prevalence of "protective" titers was not different between groups [Miller 1997].

Additional *not-per-protocol* evidence comes from two cohort studies, one comparing two unrelated cohorts [Miller 1995] and comparing two similar cohorts but using a radio-immune assay [Ramsay 1993 II] (**Table 8b-B**). The results show slightly higher mean titers of anti-FHA IgG, and substantially higher mean titers of anti-PT IgG at up to 12 months after the 3rd dose.

Absolute effectiveness

Evidence comparing primary wP vaccination to no vaccination was available from 17 studies evaluating vaccine efficacy/effectiveness (3 of which were randomized trials) (**Table 9a-A**), three randomized trials evaluating immunogenicity (**Table 9b-A**) and three randomized trials plus one observational study evaluating reactogenicity (**Table 9c-A**).

Additional *not-per-protocol* information was available from 6 studies evaluating vaccine effectiveness and one randomized trial evaluating vaccine efficacy (all seven studies used not-per-protocol case definitions), 3 randomized trials and one observation study evaluating immunogenicity (all not-per-protocol due to specific serological methods that cannot be combined among each other and are not considered standard today) and 1 randomized trial evaluating reactogenicity.

Absolute effectiveness/efficacy

Studies on absolute wP effectiveness/efficacy were heterogeneous with regard to vaccination schedule or pertussis case definition used (**Figure 4, Table 9a-A)**. Several studies were household contact studies, including household members of confirmed pertussis cases, such that all observed cases fulfilled the "epilink" criterion and the case definition by default had increased specificity. As the epilink criterion is included in several confirmed case definitions included in this review per protocol, the houshold contact studies are not presented separately, but according to the general case definition used.

Six studies used the old WHO case definition (patient with ≥ 21 days paroxysmal cough, confirmed as pertussis by culture, serology, or with epidemiologic link to a culture-confirmed case). Four of them evaluated a 2,4,6-mo schedule: two randomized trials compared DTwP to DT [Gustafsson 1996; Greco 1996] with a follow-up to age 3-4 years, one non-randomized household contact study compared DTwP to no vaccination with a follow-up to age 4 years [Simodon 1997] and one case control study [Liese 1997]. The trials both found low vaccine efficacy between 34% and 48% (with little variation depending on whether follow-up started after the 1st or 3rd dose), the confidence intervals reaching overall from 12% to 58%. By contrast, the houshold contact study found an VE of 92% (81% – 97%) and the case control study of 96% (71%-100%).

A cohort study using a 3,4.5-6,15-18-mo schedule for DTwP compared to DT (in a slightly different schedule) found a VE of 93% (89% – 96%) [Stehr 1998]. A similar study evaluated a 3,4,5-mo schedules and found a VE of 98% (83% – 100%).

The trial reported by Greco (1996) was the only study using the 2010 WHO definition, and estimated a VE of 32% (10% - 48%) following the 3rd dose of a 2,4,6-schedule.

Two case control studies used the CDC definition of confirmed cases or clinical cases with laboratory confirmation using a 2,4,6-mo (+12-18mo) schedule, with different results. In a case control study including children <7 years of age during a community outbreak, VE of up-to-date vaccination was 30% (-140% – 80%) [Izurieta 1996]. By contrast, Bisgard (2005) reported, for children aged 6-59 months, an VE of 3 or 4 doses of 96% (87 – 98%) and 97% (92 – 99%), respectively.

A household contact study during a 2,4,6-mo (+12-18mo) schedule, using a definition that corresponds to both the 2010 WHO definition fo clinical cases and the CDC of confirmed cases, found a VE of 85% (59 – 94%) among 1- to 4-year-old children [Onorato 1992].

An evaluation using the screening method during a 2,4,6-mo (+12-18mo) schedule among children aged 7 to 47 months found a VE of 79% (74 – 83%) and 90% (88 – 92%), respectively, for 3 and ≥4 doses [Guris 1997].

Five studies reported on VE based on physician diagnosis, irrespectively of laboratory confirmation or other criteria. These studies usually did not use a vaccination schedule with clearly specified ages of injections, rather indication of intervals. One older randomized trial [Anonymous 1951] evaluated 3 doses of wP (5 different vaccine types were evaluated) given in monthly intervals to children aged 6 to 18 months and followed over 23 to 30 months. The control group received an "anti-catarrhal vaccine". The overall VE across vaccine types was 79% (75-82%), and ranged among children with home exposure between 73% and 84%, without any clear trend by age.

Two cohort studies in infants and toddlers found comparable VE of 88% (75-94%) [Laurell 1957] and 85% (80-89%) [Kendrick 1939], using 3 doses of wP in 4-6 weeks intervals, and four doses in weekly intervals, respectively. Kendrick (1939) also presented VE for household contact children only, and found a lower VE of 61% (47-71%).

Another UK-based study on household contacts of pertussis cases included children up to age 4 years, after 3 doses of wP (possibly the 3,5,10 month schedule used at that time) or without vaccination, and found a low VE of 24% (11-36%) [PHLSWC 1969].

Bassili (1976) estimated VE from surveillance data using the screening method and found a VE of 72% (64-79%) among children under five years of age, which gradually decreased by age group (from ∞ among <1 years and 89% amon 2-<3 years to 52% among 4-<5 years. The vaccination schedule was not specified by likely was the 3,5,10 month-scheduled used in the UK at that time.

Figure 4 summarizes these results of included studies with regard to sources of heterogeneity. To the exception of one older RCT (reporting issues with randomization and blinding), RCTs yielded low VE, whereas all observational studies (to two exceptions) yielded high VE. This could in principal could be explained by selection bias (factors associated with vaccine refusal are risk factors for disease). However, vaccine types were particular in the two low-VE RCTs (adsorbed wP produced by Connaught US).

The two observational studies with low VE estimates were conducted among children <7 mo and <5 years, respectively [Izurieta 1996 and PHLSWC 1969]; the case control study had extremly wide confidence intervals making conclusion difficult [Izurieta 1996].

Figure 5 summarizes these results of not-per-protocol studies with regard to study design.

Table 10 summarises evidence that in principal could inform a network comparison between a 2,4,6-mo-schedule and a 3,4.5-6, 15-18 mo –schedule. However, given the differential quality of the available studies (no RCT data are available for the long schedule), meaningful interpretation may not be possible.

Additional information is available from seven *not-per-protocol* studies, which could not be assigned to any case definition described in the protocol (**Table 9a-B**).

High VE of 93% (72-98%) was reported from an unblinded randomized trial [Blennow 1988] using a 2,3,4-mo schedule and a follow-up up to 23 months, and a definition of coughing for ≥4 weeks. Using a defintion of laboratory confirmed cases irrespective of symptoms, VE was lower at 71% (37-86%). High VE of 93% (86-99%) was also reported by Simodon (1997) using the old WHO with PCR diagnosis of the contact case, and 2,4,6-month schedule. Estimated based on other case defintions (≥21 days of cough with different degrees of laboratory confirmation), however, yielded VE as low as 55% (38-68%). Walker (1981) reported from a case-control study using 3 doses among chilredren age 6 months to 5 years a VE of 95% (91-97%). VE in the higher range was also reported by Stehr (1998) from a cohrt using a schedule of 3, 4.5-6 and 15-18 months, using ≥7 days of cough and anti-PT serological confirmation. Brink (1982) reported a VE of 81% (66-89%) from a houshold contact cohort, after a vaccination schedue of 2,4,6 months and using data from the national reporting system (CDC), without describing details about the case definition.

Low VE between 20% and 59% were described by a PHLSWC report (1982), probably using a 3,5,10-month schedule in a houshold contact study including any suspected cases (any cough of any duration) and children up to age 6 years. Using the same case definition, Onorato (1992) found a VE of 63% (43 – 76%) for ≥3 doses in the US schedule (probably 2,4,6 mo + 12-18mo).

Using a similar case definition (which requierd paroxysmal cough) and the US schedule, Broome (1981) estimated that 3-5 doses of wP (given until age 5 years had a VE of 55% (8-79%). Onorato (1992) found for this definition a VE of 78% (44 – 91%).

Table 5 summarizes results from included and not-per-protocol studies reporting on absolute vaccine effectiveness by effective number of doses received. Some vaccine effectiveness is demonstrated from one single dose on, and is almost consistently high from 3 doses on. Four studies evaluate 2 doses: among the two included studies, one very imprecise case control study presents absence of effectiveness among infants <7 mo, the other, a houshold contact cohort, a VE of 50%. Two observational *not-per-protocol* studies report VE of 60% and 85%

Immunogenicity

Three publications reported randomized trials evaluating the absolute immunogenicity of a 2,4,6-month schedule (**Table 9b-A**). Giuliano (1998) and Greco (1996) probably presented overlapping data. Their data showed that one month after the 3rd dose, anti-FHA and anti-PRN GMC were about 5 fold higher in the vaccinated than the unvaccinated group (difference statistically significant), while there was not substantial or significant difference with regard to anti-PT GMC or PT-neutralizing antibody GMT (not per protocol). 15 months after the 3rd dose, minor (1.5-fold), statistically significant differences persisted for anti-FHA and anti-PRN GMC.

In the trial by Gustafsson (1997), one month after the 3rd dose, the proportion of participants with IgG concentrations ≥1 unit/ml were 1.5-fold (anti-PT) to 6-fold higher (anti-FHA, anti-PRN, anti-Fim2/3) in the vaccinated compared to the unvaccinated group. Median IgG concentrations were substantially

higher (10 to 13 units/ml for anti-FHA, anti-PRN and anti-Fim2/3 antibody) in the vaccinated than in the unvaccinated group (<1 unit/ml).

Additional information on absolute immunogenicity of schedule with 2 doses in 3-month interval given from age 9 to 36 months on (**Table 9b-B**). Titers as measured with a micromethod (not per protocol) were at least 60% higher one month after the 2nd dose compared to three groups vaccinated with other vaccines, and the proportion of aprticipants with ≥4-fold increase was at least 3-fold.

Reactogenicity

Absolute reactogenicity of wP has been evaluated by three randomized trials, all using a 2,4,6-month schedule. Gustaffson (1996) reported risk of reactions within 24h after each dose and any dose, comparing DTwP to DT. Greco (1996) reported reactions within 48h hours after any dose, comparing DTwP to DT. Long (1990) reported risk of reactions within 48h after the third dose , comparing DTwP at the third injection compared to placebo. Fever with T°≥38.0°C was overall about 12-times more likely with wP, with a decreasing trend by doses (fold increase of ris, 9.5 to 2.9). The comparison to placebo naturally incurred a higher relative risk of fever at the third injection (7-fold). Similar patterns were seen for persisting crying (where Greco 1996 evaluated very long persistance ≥3h and did not find any reaction in the DT group), local pain or tenderness, local redness or local swelling/nodule.

Additional evidence comes from two studies. One compared risk of reaction following DTwP vs. DT injections, given in a 2,4-month or a 2,6-month schedule (Barkin 1985), and found 11-fold increased risk of febrile response and acute behavioral changes, whild local reactions were 3-fold more likely. Cody (1981) reported that within 48h after vaccination DTwP injection yielded 2 to 5-fold increased risk of fever, crying, pain, local redness or local swelling.

Booster vaccination

Booster schedule effect

One RCT compared reactogencity of booster given at different ages after a 3-dose primary series before age 7 months [Scheifele 1999]. Moderate or severe local reactions were substantially more frequent after boosters at age 15 or 18 months compared to age 12 months, but no large differences were observed for all local reactions combined or systemic reactions (**Table 10c-A**).

Additional evidence was available from two *not-per-protocol* studies **(Table 10b-B)**. One observational study reported on immunogenicity without providing details on the preceding primary vaccination schedule (two groups receiving 2 or 3 doses were combined) [Wilkins 1987]. The proportion of children with a ≥4-fold pre-post booster increase of agglutinin titers at 1-2 months after the booster was higher with an interval of 6-9 months to the last primary dose (73%) and lowest with an interval of ≥16 months (63%).

By contrast, an RCT using microassay for agglutinin measurement [Scheifele 1999] found that after a booster dose at age 18 months (after a not further specified 3-dose primary series before age 7 months), titers were substantially higher (GMT 1126) compared to a booster at age 12 (872) or 15 months (539) (the latter difference was statistically significant). However, the prevalence of titers ≥1:64 was similar in all three groups.

Absolute booster effectiveness

Evidence on absolute vaccine effectiveness of booster vaccination was available from one included and two *not-per-protocol* studies (**Tables 11a-A and b-B**). The included study estimated the vaccine efficacy of booster vaccination (no detail on timing provided) after three primary doses in an household contact study [PHLSWC 1973]. The outcome definition was pertussis diagnosis by a physician, independently from laboratory confirmation. The effectiveness was estimated as negative, with a wide confidence interval [-31% (95% CI -72 to 23%)]. The main bias in this study (vaccine status assessment probably after occurrence of secondary cases) would have overestimated vaccine effectiveness, but treatment bias towards the null may be present in this observational study.

The two additional studies evaluated immunogenicity. Conway (1993) found in a small randomized trial among children born preterm (32-35 weeks) vaccinated at 3,4,5-mo, that mean "pertussis antibody units" (likely combining several antigens) were 3.5-fold higher one month after a booster at 18 months than without. Miller (1995) compared two cohorts of children vaccinated at 3,5,10 months, without reporting on their comparability. Six months after a booster at age 4.5 years, GMT anti-FHA were >10-fold and GMT anti-PT were >7-fold higher in the booster group compared to children without such booster.

Result summary and GRADE evidence profiles

Tables 3 and 4 present GRADE evidence profiles for by objectives addressed by at least two studies with a comparable outcome (accelerated vs. long schedule; absolute effect of an accelerated and a long schedule). The following summarizes the overall retrieved evidence:

Objective a. (effect of the number of doses on the outcomes) was addressed by one included study comparing 2 vs. 3 primary doses on immunogenicity [Olin 1998], yielding a low level of evidence (limitations: cohort study, indirectness: no correlate of protection, imprecision: wide confidence intervals including the Null). The results suggest that at age 7 mo, antibody titers are ≥2-fold higher after 3 compared to 2 primary doses.

Appropriate *not-per-protocol studies* support the lower antibody titers after 2 compared to 3 doses soon after the primary series. The serological differences may not persist during the second year of life and may not concern seroprevalence of protective titers. Indirect evidence suggests that lower antibody titers with 2 compared to 3 doses translate into some higher risk of disease during the first year of life, but not afterwards.

Objective b. (effect of age at initiation of vaccination on the outcomes) was addressed by one study on a birth dose, and one on two later schedules. At very low level of evidence, a birth dose prior to a 2,4,6-mo schedule did not provide higher antibody titers at ages 4 through 9 months, and not substantial differences were seen in reactogenicity (not-per-protocol).

Furthermore, at very low level of evidence (limitation, indirectness) one study suggested that a 2,4,6-mo schedule provided higher antibody titers than a 3,4,5-mo schedule, but the difference may be due to longer intervals. Additional evidence is inconsistent, but shows only little differences between 3-dose schedules during the first 6 months of life.

Objective c. (effect of length of interval on the outcomes) was addressed by two included studies at very low level of evidence.

One study compared clinical effectiveness between an accelerated and a long schedule. At very low level of evidence (cohort design comparing counties, imprecision), the results suggest that an accelerated schedule protects children better compared to a long schedule during the first year or life, but not afterwards. This is supported by the three included observational serological studies (very low level of evidence: limitations and indirectness) (**Table 3**).

One study suggests that longer intervals between primary doses (2- vs. 1-mo) yield only marginally higher titers. Additional evidence supports this and suggests that a substantially longer interval of several months may produce a greater increase in titers.

Objective d. (effect of any vaccination on the outcomes) was addressed by in total 19 studies. Level of evidence was low or very low for clinical effectiveness, mainly due to the relative lack of randomized trials, and heterogeneity and only partially explained inconsistency between trials. Across the great variety of outcome definitions and schedules evaluated, most studies converged to a high absolute VE of three wP doses (>80%). Additional *not-per-protocol* evidence tends to support this.

Estimates of low absolute VE (<50%) may be invalid due to anecdotally questionable vaccine lot quality and high imprecision, or not comparable due to focus on infants <7 mo. However, treatment bias cannot be excluded, as all high estimates come from observation studies or trials reporting difficulties in randomization and blinding.

Objective e. (effect of booster schedule on the outcomes) was addressed with low level of evidence by one study on reactogenicity, suggesting that booster vaccination at age 15 or 18 months (after a 3-dose primary series before age 7 months), was associated with higher risk of moderate or severe local reactions, but not any local reaction or systemic reactions, compared to boosting at age 12 months.

Not-per-protocol evidence is inconsistent and suggests that an interval of 6-9 months to primary vaccination may be more immunogenic than longer intervals, while boosting at 18 months, is more immunogenic than at 12 or 15 months (after a 3-dose primary series before age 7 months).

Objective f. (effect of any booster vaccination on the outcomes) was addressed by one cohort among house hold contacts with overall very low level evidence (limitations, imprecision). The result suggests a booster in addition to primary doses did not provide additional protection (VE was negative but insignificant). Additional evidence documents substantially higher antibody titers one or >3 years after accelerated or long primary vaccination.

Discussion [to be developed]

Summary of findings

- ❖ Some evidence available for all questions on wP primary (all outcomes) or booster schedules
- ❖ Only one observational study evaluated schedule impact on clinical effectiveness

The available evidence suggests that

- ➢ Two versus three primary doses result in substantially lower titers after primary series *(GRADE 2),* but insufficient evidence on
  - persistence of difference during 2nd year
  - possibly higher disease risk during 1st, but not 2nd year of life
- ➢ An accelerated 3+0 schedule protects children better during the 1st year than a long 2+1 schedule, but not afterwards. Age of initiation of a 3-dose primary series does not substantially impact on resulting antitoxin titer levels *(GRADE 1),*
- ➢ A birth dose (in addition to a three-dose primary series) does not provide higher titers *(GRADE 1),*
- ➢ 2,4,6 mo provides higher titers than 3,4,5 mo, but no substantial difference between 1- and 2-mo intervals *(GRADE 1)*
- ➢ Across the great variety of outcome definitions and schedules evaluated, studies converge to an absolute VE of >80% after three wP doses *(GRADE 1-2),* vaccine and design quality may play a role in heterogeneity,
- ➢ Booster vaccination at 15 or 18 months of age is somewhat more reactogenic than 12 months *(GRADE 2),*
- ➢ Booster vaccination during the second year of life after a 3-dose primary series did not improve clinical protection for household contacts *(GRADE 1).*

Quality of evidence

Further evidence needed – implications for further research:

Implications for decision making

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Figures and Tables

Table set 10. Data from included and additional studies evaluating **booster vaccination schedule impact** on relevant outcomes

Tables 10a-A: Included studies on booster vaccination, schedule impact on vaccine effectiveness/efficacy – no studies identified

Tables 10a-B: Additional studies - Booster vaccination, schedule impact on vaccine effectiveness/efficacy – no studies identified

Tables 10b-A: Included studies on booster vaccination, schedule impact on immunogenicity – no studies identified

Tables 10b-B: Additional studies - Booster vaccination, schedule impact on immunogenicity

Tables 10c-A: Included studies on booster vaccination, schedule impact on reactogenicity

Tables 10c-B: Additional studies - Booster vaccination, schedule impact on reactogenicity – no studies identified

Table set 11. Data from included and additional studies evaluating **booster vaccination absolute impact** on relevant outcomes

Tables 11a-A: Included studies on booster vaccination, absolute vaccine effectiveness/efficacy

Tables 11a-B: Additional studies - Booster vaccination, absolute vaccine effectiveness/efficacy – no studies identified

Tables 11b-A: Included studies on booster vaccination, absolute immunogenicity – no studies identified

Tables 11b-B: Additional studies - Booster vaccination, absolute immunogenicity

Tables 11c-A: Included studies on booster vaccination, absolute reactogenicity – no studies identified

Tables 11c-B: Additional studies - Booster vaccination, absolute reactogenicity – no studies identified

Appendix 1. Search terms

Appendix 2. Synopsis of inclusion of references from landmark reviews on pertussis vaccines

Figure 1. Flow chart of reference screening

* Articles contributing exclusively not-per-protocol evidence. In addition, some included studies provide not-per-protocol evidence.

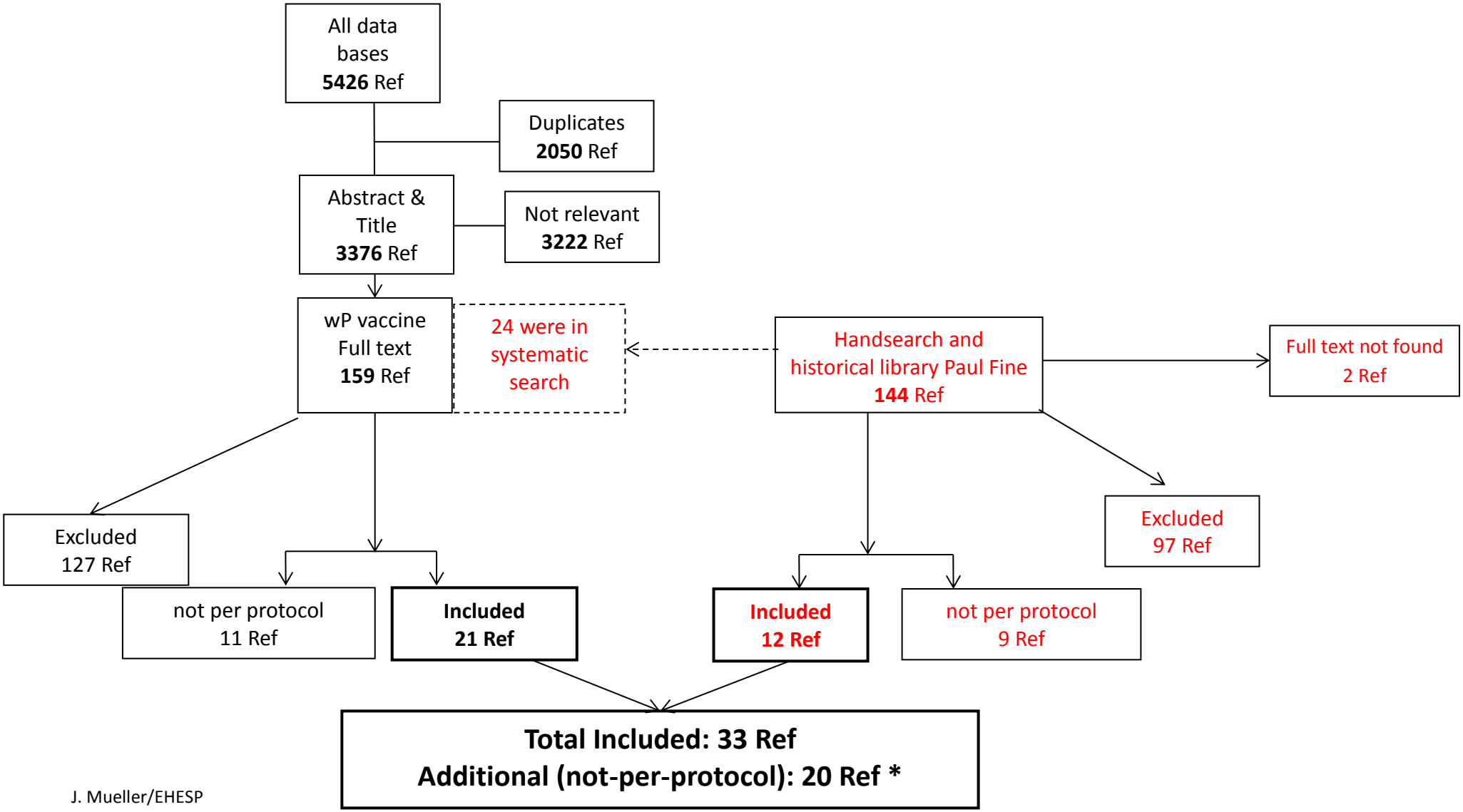


Figure 2. Overview of type of evidence available from included studies

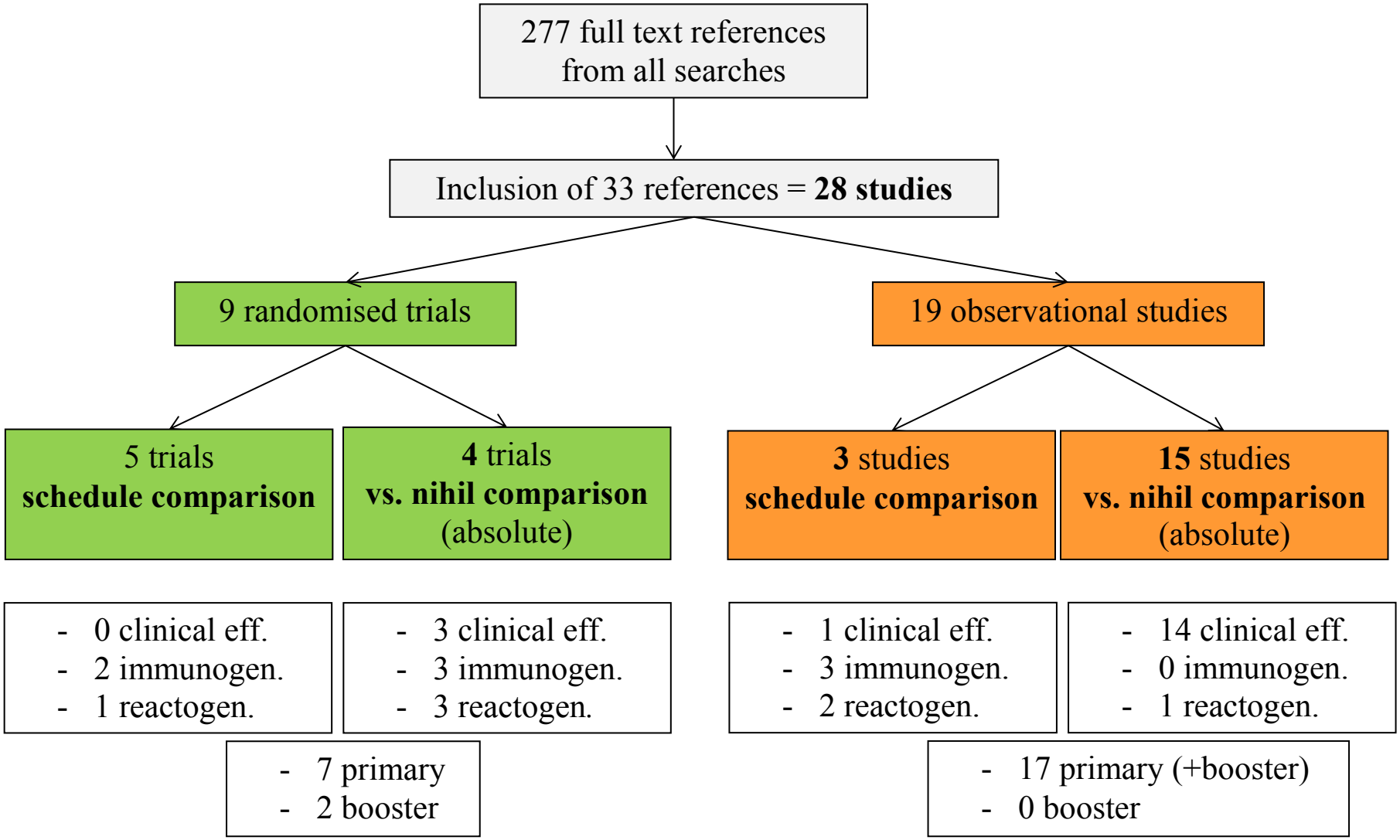


Figure 3. Overview of type of additional evidence available from not-per-protocol studies
* studies may include different types of evaluation

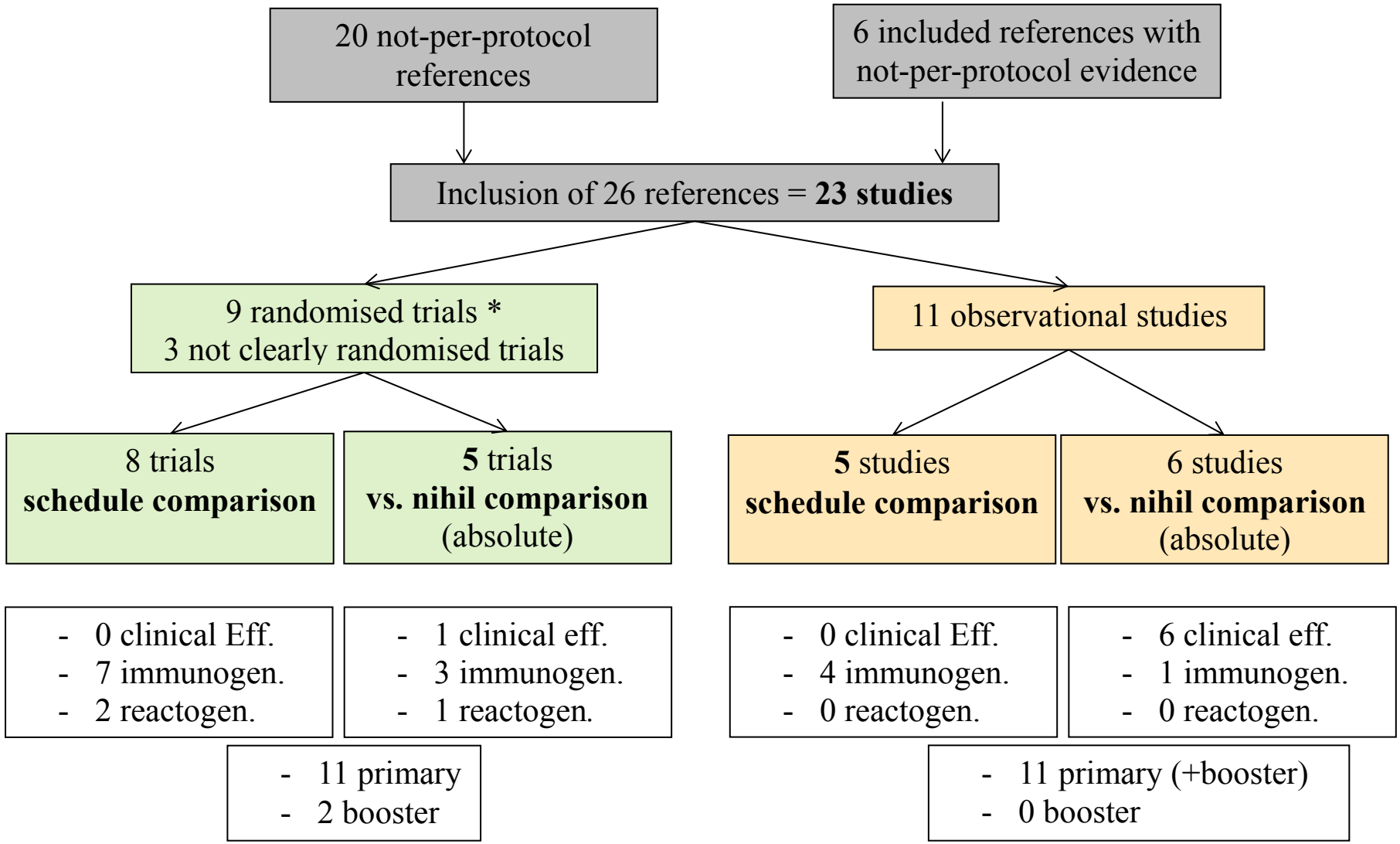


Table 1. Included studies on wP vaccination impact

Author	Design	Primary /booster	Comparison	Schedule	VE	Imgen.	Reactogen.
Anonymous 1951	RCT	primary	vs. nihil	3d monthly	X		
Baraff 1984 (Burstyn 1983)	RCT	primary	schedule	0,2,4,6 vs. 2,4,6 mo		X	
Barkin 1995 (II)	RCT	primary	schedule	2 vs. 3 d, 2 d in 2- or 4-mo interval			X
Bassili 1976	screening method	primary	vs. nihil	(3,5,10 mo*)	X		
Bisgard 2005	CC	primary, (primary+booster)	vs. nihil	2,4,6 mo + 12-18 mo	X		
Booy 1992	RCT	primary	schedule	3,5,9 vs 2,3,4 mo		X	
Giuliano 1998, Greco 1996	RCT	primary	vs. nihil	2,4,6 mo	X	X	X
Guris 1997	screening method	primary (primary+booster)	vs. nihil	2,4,6 mo + 12-18 mo	X		
Gustafsson 1996 (Olin 1997)	RCT	primary	vs. nihil	2,4,6 mo	X	X	X
Izurieta 1996	CC	primary	vs. nihil	2,4,6 mo	X		
Jenkinson 1988	cohort	primary	vs. nihil	3,5,13 mo	X		
Just 1991	cohort	primary	schedule	3,4,5 vs. 2,4,6 mo		X	
Kendrick 1939	cohort (HH)	primary	vs. nihil	4d monthly	X		
Laurell 1957	cohort	primary	vs. nihil	3d (monthly?)	X		
Liese 1997	CC	primary	vs. nihil	2,4,6 mo	X		
Long 1990	RCT	primary	schedule	2,4,6 vs. 2,4 mo+placebo			X

Miller 1995	RCT	**booster**	vs. nihil	booster vs. nihil		X	X
Miller 1997	cohort	primary	schedule	2,3,4 vs. 3,5,9 mo		X	X
Olin 1998 (Olin 1997)	cohort	primary	schedule	2,4,6 vs. 3,5,12 mo	X	X	
Onorato 1992	cohort (HH)	primary+booster	vs. nihil	(2,4,6 mo + 12-18 mo)	X		
PHLS 1969 (PHLS 1973)	cohort (HH)	primary+booster	vs. nihil	(3d monthly?) +/- booster	X		
Pollock 1984	cohort	primary	vs. nihil	3,5,10 mo*			X
Ramsay 1992	cohort	primary	schedule	2,3,4 vs. 3,5,10 mo*			X
Ramsay 1993 (I)	screening	primary	vs. nihil	3,5,10 mo*	X		
Scheifele 1999	RCT	booster	schedule	12, 15 or 18 mo			X
Schmitt 1996	cohort (HH)	primary	vs. nihil	3,4,5 mo	X		
Simodon 1997	cohort (HH)	primary	vs. nihil	2,4,6 mo	X		
Stehr 1998	cohort	primary	vs. nihil	3d 6-wk interval	X		

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

*actual schedule is 3, 4.5-5.5, 8.5-11 mo

Primary+booster: study compares primary vaccination schedules including after a booster dose

Table 2. Additional studies on wP vaccination impact, *not- per-protocol*

Author	Design	Primary	Comparison	Schedule	VE	Imgen.	Reactogen.
***Baraff 1984 (Burstyn*)**	RCT	primary	schedule	0,2,4,6 vs 2,4,6 mo			X
Barkin 1985 (I *and II)*	RCT	primary	schedule	2,4 vs 2,6 mo ; 2 vs. 3 d		X	X
Bhandari 1981	RCT	primary	schedule	2 vs. 3 d		X	
Blennow 1988	RCT	primary	vs. nihil	2,3,4 mo	X		
Brink 1982	cohort (HH)	primary+booster	vs. nihil	2,3,4 mo	X		
Broome 1981	cohort (HH)	primary+booster	vs. nihil	(2,4,6 mo + 12-18 mo)	X		
Campbell 2012	screening	primary	vs. nihil	2,3,4 mo	X		
Conway 1993	RCT	primary booster	schedule vs. nihil	3,4,5 vs 3,4,10 mo		X	
Cody 1981 (Mortimer)	RCT (rand ?)	primary	vs. nihil	3-4 d			X
Laurell 1957	cohort	primary	schedule	2 vs. 3 d		X	
Mangary-Angara 1978	(R)CT	primary	vs. nihil	2 d (6-mo interval)		X	
McBean 1978	RCT	primary	vs. nihil	3d 3-mo interval		X	
Miller 1995	cohort synopsis	primary	schedule	2,3,4 vs 3,5,10 mo*		X	
Muller 1984	CT	primary	schedule	2 vs. 3 d, 3-mo interval		X	
PHLSWG 1982	cohort (HH)	primary	vs. nihil	3d from 3-6 mo on	X		
Ramsay 1993 (II)	cohort synopsis	primary	schedule	2,3,4 vs. 3,5,10 mo *		X	
Swartz 1985	cohort	primary	schedule	2,3,10.5 vs. 2,4,5,12 mo		X	
Scheifele 1999	RCT	booster	schedule	12, 15 or 18 mo		X	

Walker 1981	CC	primary	vs. nihil	3 vs. 0, 1-2 vs. 0	X		
White 1996	screening method	primary	vs. nihil	2,3,4 mo	X		
Wilkins 1971	RCT	primary	schedule	2 vs. 3d, interval 2nd dose		X	
Wilkins 1987	cohort	primary	schedule	age first dose, interval		X	
Wong 2008	RCT	primary	schedule	1.5,3,5 vs 3,4,5 mo		X	X

Abbreviations: VE, vaccine effectiveness/efficacy; RCT, Randomized clinical trial; HH household; d, doses; mo, months; w, weeks; CC, case control study
*actual schedule is 3, 4.5-5.5, 8.5-11 mo

References in italic are included per protocol and provide additional not-per-protocol evidence.

Primary+booster: study compares primary vaccination schedules including after a booster dose

Table 3. GRADE evidence profile: primary wP vaccination, accelerated (2, 3, 4 mo) vs. long (3, 5, 9-10 mo) schedule

Quality assessment						Summary of finding	Final Grade: quality of evidence
Number of studies by design	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Ratio 2,3,4 / 3,5,9-10 mo Min – Max.**	**1-4**
Clinical effectiveness							
Old WHO definition							
From 1st dose							
1 cohort	Moderate	-	Low	Low to moderate	Unclear	VE 29.6% (95% CI, -1.0 – 58.3)	1
From 9 mo after 1st dose							
1 cohort	Moderate	-	low	Low to moderate	Unclear	VE -31.6% (95% CI, -355 – 61.1)	1
Immunogenicity							
GMT @ (1mo-6 wks) post 3rd (anti-FHA)							
2 synopses of two cohorts	Moderate to high	High	High *	Moderate	Unclear	0.71 – 1.29	1
GMT @ (1mo-6 wks) post 3rd (anti-PT)							
2 synopses of two cohorts	Moderate to high	High	High *	Moderate	Unclear	0.37 – 3.54	1
GMT @ (1mo-6 wks) post 3rd (anti-Fim2/3)							
3 synopses of two cohorts	Moderate to high	High	High *	Moderate	Unclear	0.71 – 1.19	1
GMT @ 12-18 mo post 3rd (anti-FHA)							
2 synopses of two cohorts	Moderate to high	High	High *	Moderate	Unclear	0.88 – 1.17	1
GMT @ 12-18 mo post 3rd (anti-PT)							
1 synopsis of two cohorts	Moderate to high	-	High *	Moderate	Unclear	1.03	1
GMT @ 12-18 mo post 3rd (anti-Fim2/3)							
1 synopsis of two cohorts	Moderate to high	-	High *	Moderate	Unclear	0.65	1
% seropositive 6 wks post 3rd (anti-FHA)							
1 synopsis of two	Moderate to high	-	High *	Moderate	Unclear	0.91	1

cohorts							
% seropositive 6 wks post 3rd (anti-PT)							
1 synopsis of two cohorts	Moderate to high	-	High *	Moderate	Unclear	1.01	1
% seropositive 6 wks post 3rd (anti-Fim2/3)							
1 synopsis of two cohorts	Moderate to high	-	High *	Moderate	Unclear	1.00	1
% seropositive 12-18 mo post 3rd (anti-FHA)							
1 synopsis of two cohorts	Moderate to high	-	High *	Moderate	Unclear	1.23	1
% seropositive 12-18 mo post 3rd (anti-PT)							
1 synopsis of two cohorts	Moderate to high	-	High *	Moderate	Unclear	1.00	1
% seropositive 12-18 mo post 3rd (anti-Fim2/3)							
1 synopsis of two cohorts	Moderate to high	-	High *	Moderate	Unclear	1.00	1
Reactogenicity, any dose within 2 days							
T° equivalent ≥37.7-38.0°C							
2 synopses of two cohorts	High	Moderate	Low	Moderate	Unclear	0.44 – 0.96	1
Erythema/redness							
2 synopses of two cohorts	High	High	Low	Moderate	Unclear	0.18 – 1.38	1
Local swelling ≥2.5 cm							
2 synopses of two cohorts	High	High	Low	Moderate	Unclear	0.16 – 2.29	1
≥3 systemic symptoms							
1 synopsis of two cohorts	High	-	Low	Moderate	Unclear	0.8	1
≥3 symptoms							
1 synopsis of two cohorts	High	-	Low	Moderate	Unclear	1.08 – 0.79 – 0.67 (by order of dose)	1

* High indirectness, as no correlate of protection exists

T°, rectal temperature; GMT, geometric mean titre

Included studies:

RCT: Booy 1992, Miller 1995; Cohort: Olin 1998; Cohort synopsis: Miller 1997, Ramsay 1992, Ramsay 1993 (I)

Table 4. GRADE evidence profile: primary wP vaccination, absolute effect of 2,4,6 mo schedule, combined with absolute effect of 3,4.5-6, 15-18 mo

Quality assessment						Summary of finding	Final Grade: quality of evidence
Number of studies by design	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Absolute VE Min.-max. (95%CI if only one study)**	**1-4**
Clinical effectiveness: old WHO definition (+/- epilink)							
2, 4, 6 mo (from 3rd dose on)							
2 RCT	Low	low	low	low	unclear	36% – 48% *	4 *
1 cohort HH	Moderate to high	-	low	moderate	unclear	92% (81 – 97%)	1
1 CC study (adjusting)	Moderate	-	low	high	unclear	96% (71 – 100%)	1
3,4.5-6, 15-18 mo (from 2nd dose on)							
1 cohort study	Moderate	-	low	moderate	unclear	93% (89 - 96%)	1

* VE potentially not generalizable, as influenced by vaccine lot

RCT, randomized clinical trial; cohort HH, cohort among household contacts; CC, case control;
Included studies:
RCT: Gustafsson, Greco
Cohort HH: Simodon
Cohort: Brink
Case control: Izurieta

Figure 4. Overview of absolute vaccine efficacy/effectiveness estimates from included studies, by potential factors of heterogeneity (design; case definition; schedule)

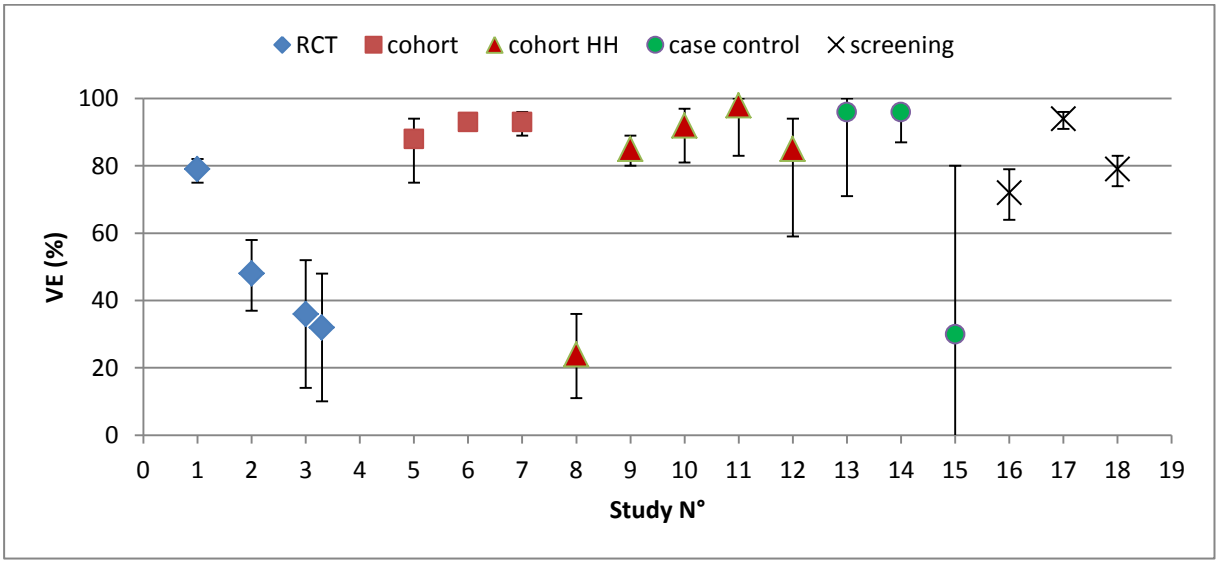
N°	Study	Design	Schedule	Age	Case definition	Vaccine
1	Anonymous	RCT	2+1 (UK long)	<30m	Old clinical	PL vs AD, We vs Gx
2	Gustafsson	RCT	246 m	<3y	Old WHO	AD-Co
3	Greco	RCT	246 m	<2y	Old WHO	AD-Co
3.3	Greco	RCT	246 m	<2y	2010 WHO	AD-Co
5	Laurell	cohort	2+1 (UK long)	<5y	Old clinical	AD
6	Jenkinson	cohort	2+1 (UK long)	1-4y	Old clinical	PL-UK?
7	Stehr	cohort	2+1 (UK long)	<3y	Old WHO	AD-Wy
8	PHLSWC	cohort HH	2+1 (UK long)	<5y	Old clinical	PL-UK?
9	Kendrick	cohort HH	≤4d US	<4y	Old clinical	PL?
10	Simodon	cohort HH	246 m	<4y	Old WHO	AD-Mé
11	Schmitt	cohort HH	345 m	<4y	Old WHO	Be
12	Onorato	cohort HH	up to date ≥3d US	<5y	CDC conf / old WHO	AD
13	Liese	case control	246 m	<2y	Old WHO	Be
14	Bisgard	case control	246m	<5y	CDC conf/clin+lab	AD-Co + AD-Wy
15	Izurieta	case control	up to date ≥3d US	<7m	CDC conf/clin+lab	AD?
16	Bassili	screening	2+1 (UK long)	<5y	Old clinical	PL-UK?
17	Ramsay	screening	2+1 (UK long)	<5y	Old clinical	We
18	Guris	screening	246 m	<4y	CDC culture	AD

RCT, randomized clinical trial; cohort HH, cohort study among household contacts

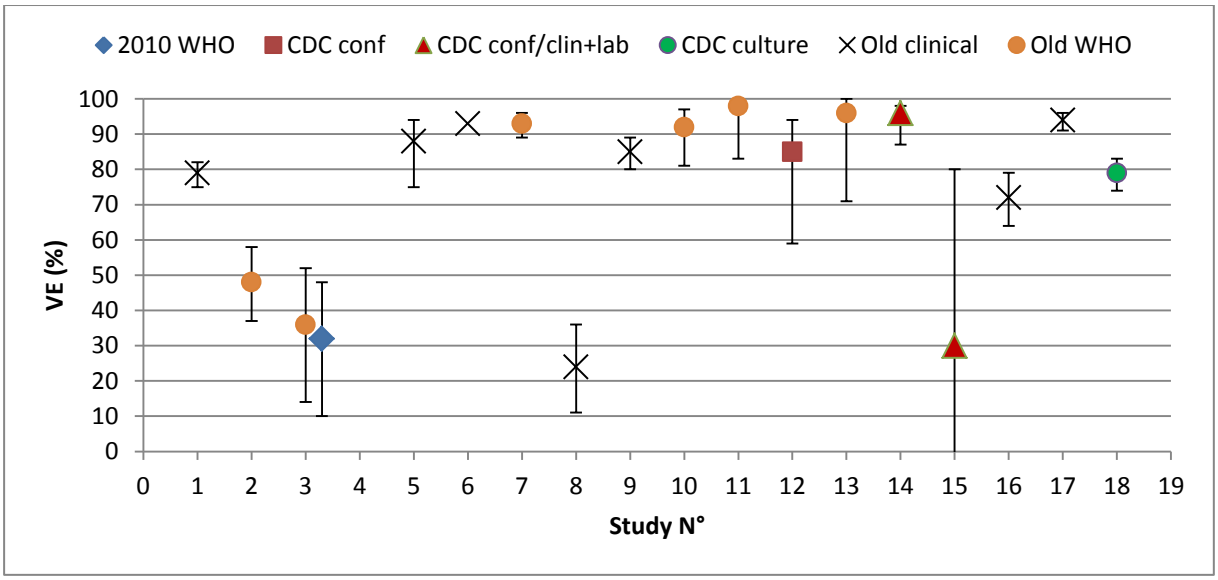
AD, adsorbed; PL, plain; Co, Connaught; Mé, Mérieux; Wy, Wyeth; Be, Behringwerke; Gx, Glaxo; We, Wellcome

- ⇨ Anonymous (1951) was a randomized trial but reported issues with randomization and blinding
- ⇨ Apart from age, most studies did not treat potential confounding variables by matching, adjustment, or just by commenting on the groups' comparability.

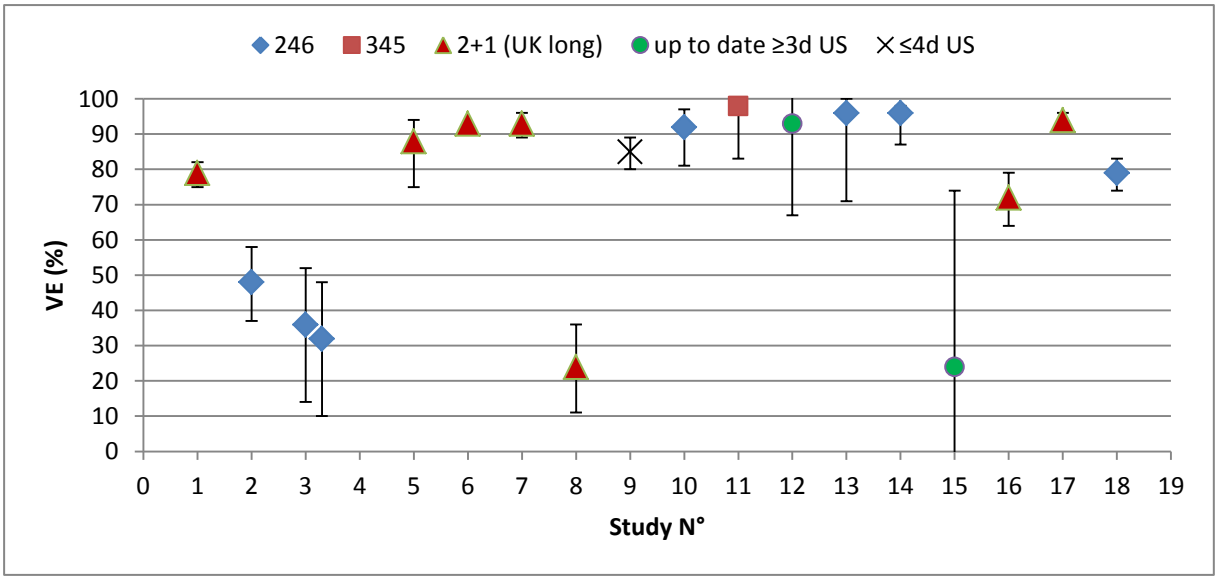
a) By study design



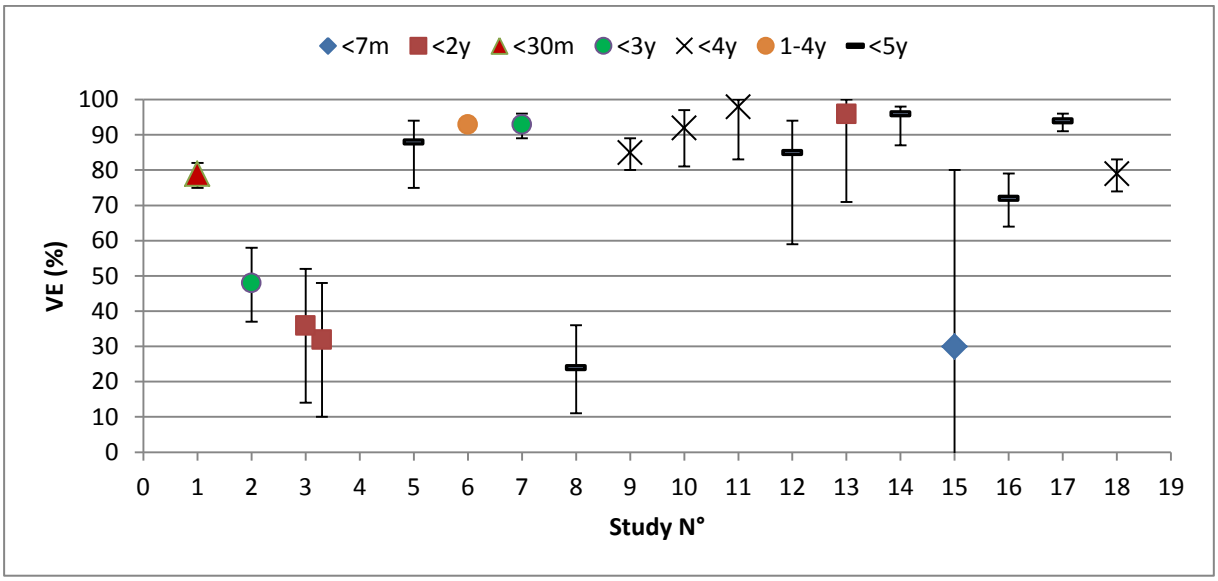
b) By case definition



c) By schedule



d) By age of included cases



d) By vaccine type

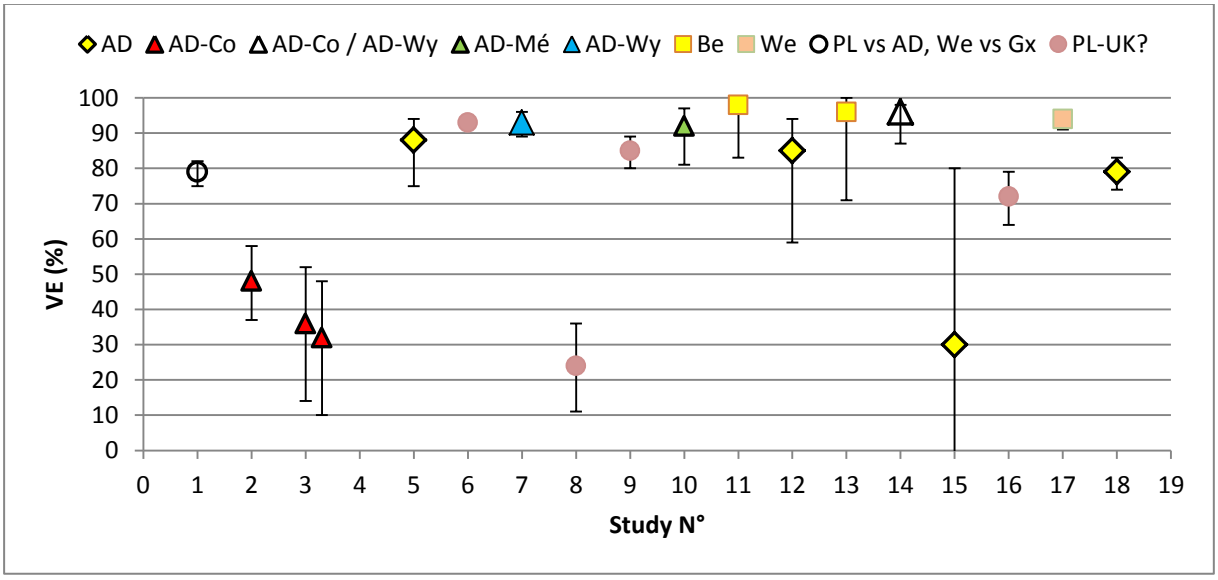
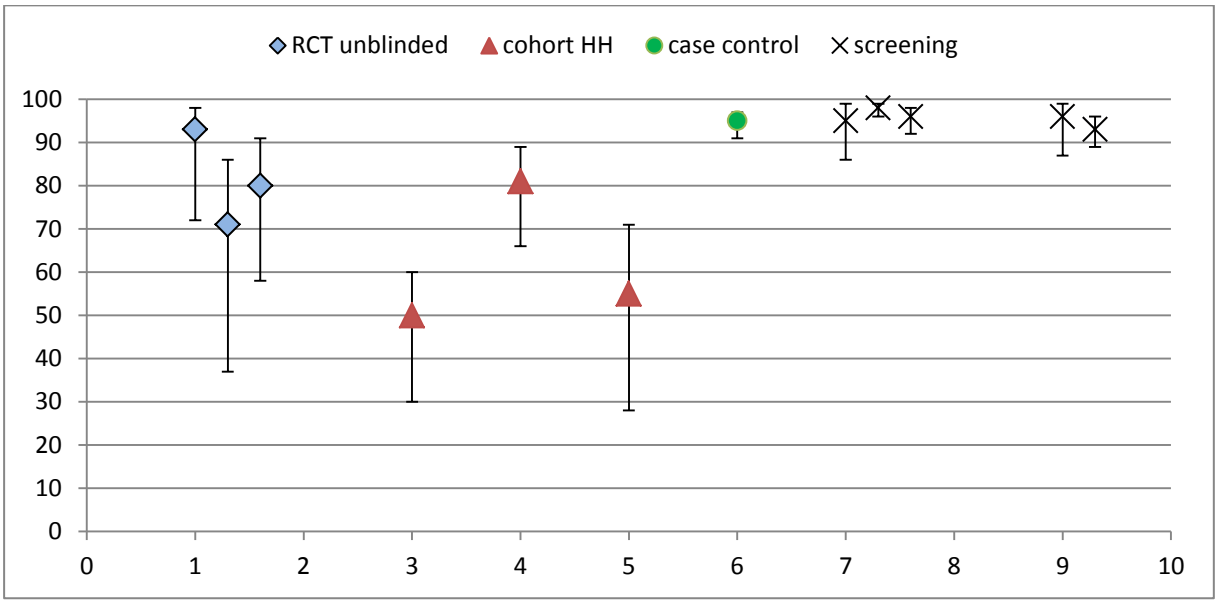


Figure 5. Overview of absolute vaccine efficacy/effectiveness estimates from not-per-protocol studies, by study design



N°	Study	Design	Schedule	Case definition	Age	Country
1	Blennow	RCT unblinded	234 m	cough 4w	≤ 24m	UK
1.3	Blennow	RCT unblinded	234 m	lab conf	≤ 24m	UK
1.6	Blennow	RCT unblinded	234 m	lab conf or cough 4w	≤ 24m	UK
3	PHLSWG 82	cohort HH	2+1 (UK long)	any cough	≤ 6 y	UK
4	Brink	cohort HH	246 m	US reporting	?	US
5	Broome	cohort HH	246 (+2b)	clinical +/- lab	1-5 y	US
6	Walker	case control	2+1 (UK long)	clinical +/- lab	up to 5 y	UK
7	Campbell	screening	234 m	lab conf	9wk - 6m	UK
7.3	Campbell	screening	234 m	lab conf	12-39m	UK
7.6	Campbell	screening	234 m	lab conf	40-59m	UK
9	White	screening	234 m	lab conf	6-11 m	UK
9.3	White	screening	234 m	lab conf	1-4y	UK

RCT, randomized clinical trial; cohort HH, cohort study among household contacts

Table 5. Overview of studies showing estimates of absolute vaccine effectiveness/efficacy for less than 3 doses

Reference	Schedule	Age	Case definition	Dose comparison	VE (CI)
Onorato, 1992	probably 2,4,6 mo + 12-18 mo	Age 1 to 4 years	CDC conf or 2010 WHO definition	1 vs. 0	36
Izurieta, 1996	0 to 3 doses, given at 2,4,6 months (+booster at 12-18 mo)	<7mo	CDC conf/clin+lab	1 vs. 0	- 60 (-350 – 40)
Gustafsson, 1996	2,4,6 mo	<3 y	Old WHO	1 vs. 0	48.3 (37.3-57.3)
Greco, 1996	2,4,6 mo	<2 y	Old WHO	1 vs. 0	34.0 (12.8-49.8)
Campbell 2012	2,3,4 mo	Age 9 wk - <6 mo	lab conf	1 vs. 0	62 (53 – 69)
Broome 1981	Up to 5 doses until age 5 years (probably 2,4,6 mo + 12-18 mo)	0-<1 yrs	clinical +/- lab	1-2 vs. 0	15.6 (-55.5 – 54.2)
Broome 1981	Up to 5 doses until age 5 years (probably 2,4,6 mo + 12-18 mo)	Age 1-5 yr	clinical +/- lab	1-2 vs. 0	55.6 (7.7 – 78.6)
Walker 1981	3 doses, probably 2,4,6 mo + 12-18 mo	Age 6 mo to 5 years	clinical +/- lab	1-2 vs. 0	32.9 (-68.7 – 70.6)
Onorato, 1992	probably 2,4,6 mo + 12-18 mo	Age 1 to 4 years	CDC conf or 2010 WHO definition	2 vs. 0	49
Izurieta, 1996	0 to 3 doses, given at 2, 4, 6 months (+booster at 12-18 mo)	<7mo	CDC conf/clin+lab	2 vs. 0	-20 (-700 – 20)
Brink 1982	2,4,6 mo + 12-18 mo	0-4 yrs	US reporting	2 vs. 0	59.4 (16.7 – 80.2)
Campbell 2012	2,3,4 mo	Age 9 wk - <6 mo	lab conf	2 vs. 0	85 (77 – 91)
Guris, 1997	2,4,6 mo + 12-18 mo	Age 7-47 mo	clinical +/- lab	3 vs. 0	82 (79 – 85)
Guris, 1997	2,4,6 mo + 12-18 mo	Age 7-47 mo	CDC culture	3 vs. 0	79 (74 – 83)

Onorato, 1992	probably 2,4,6 mo + 12-18 mo	Age 1 to 4 years	CDC conf or 2010 WHO definition	3 vs. 0	83
Gustafsson, 1996	2,4,6 mo	<3 y	Old WHO	3 vs. 0	48.3 (37.0-57.6)
Bisgard, 2005	2,4,6 mo (+12-18 mo)	Age 6-59 months	CDC conf/clin+lab	3 vs. 0	95.5 (87.3 – 98.4)
Greco, 1996	2,4,6 mo	<2 y	Old WHO	3 vs. 0	36.1 (14.2-52.1)
Brink 1982	2,4,6 mo + 12-18 mo	0-4 yrs	US reporting	3 vs. 0	38.4 (-46.7 – 74.1)
Walker 1981	3 doses, probably 2, 4, 6 mo + 12-18 mo	Age 6 mo to 5 years	clinical +/- lab	3 vs. 0	94.6 (91.0 – 96.7)
Campbell 2012	2,3,4 mo	Age 9 wk - <6 mo	lab conf	3 vs. 0	95 (86 – 99)
Onorato, 1992	probably 2,4,6 mo + 12-18 mo	Age 1 to 4 years	CDC conf or 2010 WHO definition	≥3 vs. 0	85 (59 – 94)
Brink 1982	2,4,6 mo + 12-18 mo	0-4 yrs	US reporting	≥3 vs. 0	80.6 (65.9 – 88.9)
Broome	Up to 5 doses until age 5 years (probably 2, 4, 6 mo + 12-18 mo)	Age 1-5 yr	clinical +/- lab	3-5 vs. 0	54.6 (28.2 – 71.2)
Bisgard, 2005	2,4,6 mo (+12-18 mo)	Age 6-59 months	CDC conf/clin+lab	4 vs. 0	96.7 (91.9 – 98.7)
Guris, 1997	2,4,6 mo + 12-18 mo	Age 7-47 mo	clinical +/- lab	≥4 vs. 0	92 (90 – 93)
Onorato, 1992	probably 2,4,6 mo + 12-18 mo	Age 1 to 4 years	CDC conf or 2010 WHO definition	≥4 vs. 0	83
Guris, 1997	2,4,6 mo + 12-18 mo	Age 7-47 mo	CDC culture	≥4 vs. 0	90 (88 – 92)

Included study	Not-per-protocol study

Table set 6. Characteristics and criticial appraisal of studies included per protocol

Anonymous (MRC), 1951

Methods	Site: UK, 1946-50 Design: parallel group double-blind RCT Follow up: average 27 months after dose 1 (range 23-30 months)
Participants	Included: Healthy unvaccinated children 6- to 18-mo-old (N=8927) Excluded: contraindications for further doses., illness, removal from area Vaccinated with 3 doses: 7558 children (85% of randomized)
Interventions	**Primary series (3 doses at 1-mo interval): comparison wP vs. other vaccine** Vaccines : 1. wP (5 different types; dose of organism between 60 and 112 x 10^9) 2. "anti-catarrhal vaccine" containing killed suspensions of *St. aureus*, *S. pneumoniae*, *Corynebacterium*, *N. catarrhalis* (control group) Number vaccinated with 3 doses: 3801 (group 1), 3757 (control group)
Outcomes	**Clinical efficacy:** Observation from 3rd dose on, monthly visits by study nurse. **Case definition not detailed: appears to be based on clinical suspicion with or without on nasopharyngeal swabs. Definition apparently used by other studies => included "per protocol"** - Incidence rates (person months) per group and vaccine type - Risk per group for home exposure cases, stratified by age Immunogenicity and reactogenicity: not reported

Risk of Bias	Reviewer judgment	Support for judgment
Inclusion bias	Low risk	No particular information
Random sequence generation (selection bias)	Low or moderate risk	Randomization list provided externally, but open list to fill-in prospectively
Allocation concealment (selection bias)	Low or moderate risk	Randomization list provided externally, but open list to fill-in prospectively
Blinding of participants (performance bias)	Moderate risk	Double-blind, authors report problems with apparent labelling on trial card during first phase of trial
Blinding of outcome assessment (detection bias)	Moderate to high risk	Not clear whether study nurse or other staff saw trial card
Selective reporting	Unclear risk	Protocol not available

Baraff L.J., 1984 (Burstyn D.G., 1983)

Methods	Site: USA, 1979 Design: parallel group RCT Follow-up until age 9 months
Participants	Included: Healthy full-term newborn infants Excluded: not reported
Interventions	**Primary DTwP series (2,4,6 mo), with vs. without birth dose** Vaccines : DTwP (Wyeth Laboratories) Dose schedule: Group 1: 0,2,4,6 mo (N=45) : 4 doses, interval 2-2-2 mo Control group: 2,4,6 mo (N=46) : 3 doses, interval 2-2 mo
Outcomes	**Immunogenicity** : Timing of assessment: at 4, 6 and 9 months Serological assay: **ELISA (IgG anti-FHA)**, only subgroup of 10 (birth dose) and 13 (control) infants - Mean IgG concentrations (units) post-immunization (data extracted from text) **Reactogenicity:** During 48h following vaccination, standardized questionnaire filled-in by parents; results only in text; not clear whether any dose or at specific dose Clinical effectiveness: no data reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Low risk	
Random sequence generation (selection bias)	Unclear or moderate risk	Randomization based on clinical chart number, not clear whether potential risk
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants (performance bias)	Moderate risk	No blinding, but immunogenicity study less exposed to bias
Blinding of outcome assessment (detection bias)	Moderate risk	Laboratory testing not blinded?
Selective reporting	Unclear risk	Protocol not available

Barkin R.M., 1985 (Develop Biol Standard)

See Table set 4.

Bassili W.R., 1976

Methods	Site: Central Glasgow/UK, 1974 during a pertussis outbreak Design: Analysis of routine administrative data (immunization coverage) and hospital and immunization records of cases; analysis basically in form of *screening method*; methods of data collection for birth cohorts not further explained.
Participants	Children of birth cohorts 1967 – 1974 in Glasgow (only cohort 1969 included, <5 yrs at time of study). 483 cases identified
Exposure	**Primary series with 3 doses of wP (not specified: possibly 3,5,10 mo, schedule in UK after 1968), comparison to unvaccinated** Vaccine: wP (including serotype 1,3)
Outcomes	**Clinical effectiveness** : Case identification by health professional (not further specified) during 1974; **Definition likely similar to MRC report (Anonymous 1951)** : clinical suspicion and culture confirmation from swabs in some cases - Vaccine effectiveness (protection rate) Immunogenicity and reactogenicity: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Not applicable	Screening method, ecological analysis
Attrition bias	Not applicable	Unlikely with screening method
Performance bias	High risk	Study validity depends on quality of vaccine coverage estimates and of surveillance
Detection bias	Unclear risk	Unclear, as not known whether immunization coverage data of comparable validity as case immunization status comparable, eg, if both based on family physician charts filled-out upon immunization)
Selective reporting	Moderate risk	Author could be not neutral to study question, possible that results more in favor of vaccination have not been included in report.

Bisgard K., 2005

Methods	Site: Four US states (Ohio, Colorado, Idaho, Minnesota), 1998-2001 ; Design: age- and area-matched case-control study

	Telephone contact with parents and care providers (vaccination status)
Participants	Cases (N=184): Confirmed **pertussis cases aged 6-59 months,** reported to local public health officials. 5 controls per case (N=893): sampling from birth registry: children from same region or zip-code are, born the same day.
Exposure	**Primary series (2,4,6 mo) of DTwP, vs. no vaccination** Primary series and booster -12-18 mo) of DTwP, vs. no vaccination Comparison groups: 0 doses of wP
Outcomes	**Clinical effectiveness** : **CDC definition of confirmed cases :** o Cough ≥1 day with culture confirmation of *B. pertussis* o illness with ≥14 days of cough with paroxysm, whooping or posttussive vomiting and PCR confirmation or epilink with lab-confirmed case - Odds ratio by immunization status Immunogenicity and reactogenicity: not reported

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

Booy R., 1992

Methods	Site: Oxford/UK, 1988 and 1990 Design: Synopsis of two cohort studies, one observed 1988 (old long schedule), the other 1990 (new accelerated schedule); no information on comparability of the two cohorts; but methods appear to be similar

Participants	Included/exclusion criteria: no details presented
Interventions	**DTwP accelerated vs. long schedule** Vaccines : DTwP (Wellcome) Dose schedule: Group 1: **2,3,4 mo** (N=103) Group 2: **3,5,9 mo** (N=107)
Outcomes	**Immunogenicity** : Timing of assessment: at one month after third dose Serological assay: **ELISA (IgG anti-FHA, anti-PT, anti-Fim2/3)** - GMT of IgG titers post-immunization Clinical effectiveness and reactogenicity: no data presented

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Moderate risk	According to national schedules
Attrition bias	Low risk	5% drop-out, similar in both groups
Performance bias	Low risk	No event reported
Detection bias	Low risk	Immunogenicity study; no element for differential laboratory performance
Selective reporting	Low to moderate risk	Possible, as only few data presented?

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

Methods	Site: Italy 1992-93 Design: parallel group double-blind RCT Follow up: 15 months after dose 3 (age 21 months)
Participants	Included: Healthy unvaccinated children < 2 months-old Excluded: contraindications for further doses Only 1572 participants from a larger efficacy trial participated in the immunogenicity study (children whose parents consented to the collection of capillary blood)
Interventions	**Primary series (2,4,6 mo): DTwP vs. DT comparison** Vaccines : 1. DTwP (Cannaught Laboratories) 2. DT (control group)

	Dose schedule: **2, 4, 6 months** Number randomized: 4680 (group 1), 1561 (control group)
Outcomes	**Immunogenicity** : Timing of assessment: **1 month** (mean 34.4 days, range 15-95 days) and **15 months** (mean 15.5mo, range 6.3-22.5 mo) **post-third dose** Serological assay: **ELISA (IgG-PT, IgG-FHA, IgG-PRN**) PT-neutralizing antibodies (CHO assay) => additional informatino Seropositivity criteria: antibody concentration ≥ 4x MLD [minimum level of detection = 8 EU/ml for PT and FHA, 12 EU/ml for PRN; ≥ 160 neutralizing titer] - Percentage seropositive post-immunization - GMC post-immunization Clinical effectiveness and reactogenicity: no data presented (see Greco 1996

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

Greco D., 1996

Methods	Site: Italy 1992-93 Design: parallel group double-blind RCT Follow up: average 17 months after dose 3 (mean 17.2 mo; age 23 months)
Participants	Included: Healthy unvaccinated children 6-12 week-old (N=15,601) Excluded: contraindications for further doses. Follow-up of 14,832 children (95% of randomized); subsample of 10% for immunogenicity
Interventions	**Primary series (2,4,6 mo): DTwP vs. DT** Vaccines :

	1. DTwP (Connaught) 2. DT (control group) Dose schedule: **2, 4, 6 months** Number randomized (vaccinated with at least 1 dose): 4348 (group 1) , 1555 (control group)
Outcomes	**Clinical efficacy:** Passive and active case ascertainment; case incidence adjusted for follow up from the day of first dose or 30 days after 3rd dose (intention to treat); **Confirmed pertussis cases: illness with ≥21 paroxysmal cough and evidence of *B. pertussis* infection or positive diagnostic serologic test**. Alternative definitions (cough - paroxysmal cough; duration varying 7 to 60 days) - Incidence rates (person days) per group and N doses (3 or ≥1) - Relative risk and vaccine efficacy **Immunogenicity** : *(see also Giuliano 1998)* Timing of assessment: **pre-vaccination and 1 month (?) post-third dose** Serological assay: **ELISA (IgG-PT, IgG-FHA, IgG-PRN**) PT-neutralizing antibodies (CHO assay) => additional information Seroconversion criteria: antibody concentration ≥ 4x MLD (minimum level of detection = 8 EU/ml for PT and FHA, 12 EU/ml for PRN; ≥ 160 neutralizing titer) and ≥ 4-fold increase from pre-vaccination - Percentage seroconverted - GMC post-immunization **Reactogenicity:** Parents reported adverse events in a standardized diary Timing of assessment: within 2 days after each vaccine dose - Incidence expressed as rate per 1000 doses - Irritability; Rectal temperature ≥38.0°C, ≥40.0°C; Persistent crying ≥3h; Hypotonic, hypo- responsive episodes; Seizures - Local swelling; local tenderness;

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Low risk	No unusual exclusion criterion
Random sequence generation (selection bias)	Low risk	Randomization list provided externally
Allocation concealment (selection bias)	Low risk	Randomisation material and vaccines prepared externally

Blinding of participants (performance bias)	Low risk	Regular clinical personnel prepared and administered the vaccine. Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Neither parents nor investigators knew the infants' vaccine assignment.
Selective reporting	Unclear risk	Protocol not available

Guris D., 1997

Methods	Site: USA, 1992-94 Design: Analysis of NHIS survey data and CDC case reporting systems ; *screening method*
Participants	Children aged 7 – 47 months
Exposure	**Primary series with 3 (or ≥4) doses of wP (2,4,6 months + 12-18 mo), comparison to unvaccinated** Vaccine: DTwP
Outcomes	**Clinical effectiveness** : **CDC definition of culture-confirmed cases :** o Cough ≥1 day with culture confirmation of *B. pertussis* - Vaccine effectiveness Immunogenicity and reactogenicity: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Not applicable	Screening method, but no possibility to infer on causality with this method
Attrition bias	Not applicable	Unlikely with screening method
Performance bias	Moderate risk	Probably good quality of NHIS vaccine coverage estimates and of surveillance, but by principal of limited validity
Detection bias	Unclear risk	Unclear, as not known whether immunization coverage data of comparable validity as case immunization status comparable, eg, if both based on family physician charts filled-out upon immunization)
Selective reporting	Unclear risk	

Gustafsson L., 1996

Methods	Site: Sweden 1992-95 Design: parallel group double-blind RCT Follow-up: up to 3 years (average 21 to 23.5 months post dose 3), by nurse show also

	enrolled and vaccinated infants Cox proportional hazard model
Participants	Included: 9829 healthy unvaccinated children < 2 months-old Excluded: contraindications for further doses, pertussis diagnosis Loss to follow-up after complete vaccination : 205
	Primary series (2,4,6 mo): DTwP vs. DT Vaccines : 1. DTwP (Cannaught Laboratories, Swiftwater, Pa.) 2. DT (Control group, Swedish National Bacteriological Lab, Stockholm) Dose schedule: 2, 4, 6 months Number randomized: 2566 (group 1), 2574 (group 2)
Outcomes	**Clinical effectiveness**: Passive and active case assessment (parent report, telephone call by nurses every 6-8 wks); case incidence adjusted for follow up from the day of first dose (intention to treat **Old WHO definition of confirmed cases** with ≥ 21 days of paroxysmal cough plus culture or serology positive, or epi link with confirmed case. Serological confirmation based on two-fold increase in anti-PT or anti-FHA IgG or IgA (FHA culture/PCR negative for *B. parapertussis).* - Incidence rate (per person year) and vaccine efficacy, starting post 3rd dose or post 1st dose **Immunogenicity (provides additional, not per protocol evidence)** : Evaluated in one study site only Timing of assessment: **1 month post-third dose**; high pre-vaccination maternal antibody concentration => not reported Serological assay: **ELISA (IgG anti-PT, anti-FHA, anti-PRN, anti-Fim2/3**) - Percentage ≥1 units/ml post-immunization (limit of detection, estimated from figure) - Median concentration post-immunization (estimated from figure) - => classed as additional information **Reactogenicity**: Active ascertainment of adverse events during day 1-14 after vaccination (structured questionnaire by telephone) *Timing of assessment:* within one day post dose 1, 2, and 3 - Percentage of children with symptom within one day after each dose, and any dose - Rectal temperature ≥38.0°C; Persistent crying ≥ 1h; - Local nodule ≥ 2cm; local tenderness; redness ≥2cm;

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

Izurieta H. S., 1996

Methods	Site: One pediatric hospital in Chicago, USA, 1993 during a pertussis outbreak Design: matched case-control study Telephone interviews with standardized questionnaire
Participants	Cases (N=39): **Pertussis cases < 7 months** of age with cough onset between 15 June and 15 Sept 1993 reported by infection control staff members at Children's Memorial Hospital (Chicago). 2-4 controls per case (N=92): infants from same zip-code are, who had an appointment during study period at the child clinic associated with the same hospital, no cough ≥7 days during preceding month, **matched by age** (4 weeks).
Exposure	**Primary series (2,4,6 mo) of DTwP, vs. no vaccination** Comparison groups: 0 dose (reference), 1 dose, 2 doses, up to date for age, delayed immunization.

Outcomes	**Clinical effectiveness** : Case identification by health professional (not further specified) during three months; **CDC definition of clinical case with laboratory confirmation, or confirmed cases (no mention of epi-link)**: o illness with ≥14 days of cough with paroxysm, whooping or posttussive vomiting o or positive culture for *B. pertussis* and cough of any duration - Odds ratio by immunization status Immunogenicity and reactogenicity: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias (with regard to case and controls)	Moderate risk	Cases and controls identified during same period at same institution (diagnosed cases vs. children with scheduled appointment and exclusion of recent history of cough) Age-matched inclusion and analysis
Missing data on exposure	Unclear risk	Details not reported
Performance bias	Unclear risk	Details not reported (vaccination campaign?)
Exposure assessment bias	Moderate risk	Assessment by telephone interview with care giver. Verification in subset (convenience sample) showed that in 6 out of 8 cases immunization dates reported by caregivers were accurate.
Selective reporting	Unclear or low risk	Probably all results reported

Jenkinson D., 1988

Methods	Site: Keyworth general medicine practice, UK, 1977-87 Design: Open cohort analysis
Participants	Included/exclusion criteria: no details presented , children cared for in the practice
Interventions	**DTwP long schedule vs. no vaccination** Vaccines : DTwP (not specified) Dose schedule: 3,5,12 mo
Outcomes	**Clinical effectiveness :** Timing of assessment: by year, up to age 4 years Case definition: **Clinically suspected case (≥3 weeks paroxysmal coughing)** - Incidence by age group in vaccinated and unvaccinated Immunogenicity and reactogenicity: no data presented

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Moderate to high risk	Not clear which factors impacted on decision for vaccination
Attrition bias	Low risk	Low, as annual calculation
Performance bias	Low risk	No particular details reported
Detection bias	Moderate to high risk	Possibly differential likelihood of diagnosis according to vaccination status (GP)
Selective reporting	moderate risk	Possible, as only few data presented

Just M., 1991

Methods	Site: Switzerland and Turkey, 1989-90 Design: Synopsis of two parallel group double-blind RCT evaluating wP vs. 2 aP vaccines, the two trials using a different schedules. The two trials are presented as using an identical protocol. Follow-up by appointments for vaccination or blood sampling
Participants	Included: Children (total N=313) at age for primary vaccination (2 or 3 months), no details on setting of enrollment Excluded: no details provided 70%-72% follow-up for immunogenicity, 83% for reactogenicity
Interventions	**DTwP 1-mo vs. 2-mo intervals** Vaccines : DTwP (Behringwerke) Dose schedule: Group 1: **3,4,5 mo** (N=37) - Switzerland Group 2: **2,4,6 mo** (N=40) - Turkey
Outcomes	**Immunogenicity** : Timing of assessment: **one month after 3rd dose** Serological assay: **ELISA (IgG anti-FHA)** and **neutralization test anti-PT** *(not per protocol)* - GMT (range) pre- and post-vaccination by country group **Reactogenicity:** Study diary kept by parents, revised at visit; comparison between Switzerland and Turkey does not appear appropriate for this outcome - % of children with symptoms 7 days by serial dose and at any of three doses: - Any local or general symptom, any local reaction (redness, swelling, pain),

	pain, swelling, rectal temp ≥ 38.0°C, severe general symptoms (restlessness, unusual crying) Clinical effectiveness: no data presented

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

Kendrick P., 1939

Methods	Site: USA, 1934-37 Design: Cohort study with follow-up over up to 4 years, by nurses' visits every 3-4, later every 2 months, and review of Public Health reports of pertussis cases.
Participants	Included: "White" children aged 8 months to <6 years (later <5 years). Vaccinated: presenting at city immunization clinics for wP vaccination. Controls: randomly selected from lists of unvaccinated children (established during a coverage survey) Second analysis among the children who are household contacts of cases (not clear whether only laboratory-confirmed primary cases were considered)
Interventions	**Primary vaccination with wP vs. no vaccination** Vaccines : wP with $10*10^9$ organisms per ml, doses of 1 to 3 ml per vaccination Dose schedule: 4 weekly doses, starting anytime between 8 mo and 4 (5) years
Outcomes	**Clinical effectiveness**: Case definition **close to the CDC definition of clinical or confirmed cases**. In addition to moderate or severe cases, the following clinical ratings are included: o "Very light": 7 days of any cough, with either epilink to confirmed case or culture confirmation o "Light": Occasional attacks of cough with whooping or vomiting, usually up to 4 weeks duration (no minimal duration given) Incidence rate (per person-years) - Attack rate among household contacts

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Moderate risk	Self-selection for vaccination; authors report comparable risk of the two groups for measles or scarlatine fever, thus considered moderate risk of bias
Attrition bias	Moderate risk	14% of controls eventually got wP, otherwise comparable drop-out
Performance bias	Moderate risk	Changes in protocol (inclusion age; interval of follow-up visits)
Detection bias	High risk	No blinded evaluation
Selective reporting	Low risk	Several outcomes presented

Laurell G., 1957 (Rabo)

Methods	Site: Sweden 1951-52 and following Design: cohort study, vaccine assignment not explained Follow-up during up to 5 yrs (0.2% loss to follow-up) Groups of same age, fair concordance of sex, living conditions (family and housing), no control for confounding
Participants	Included: 604 children, aged <0.5 yr (around 60% of total) to > 1 yr (10%) Inclusion and exclusion criteria not detailed
Exposure	**Primary series (3 doses): DTwP vs. no vaccination** Vaccine schedule: Number of doses: 3 doses ; 24% of DTwP group received 4th dose Interval between doses: 4-6 wks Vaccine: not specified Group 1 (3 doses): 315 children, group 2 (no vaccination): 289 children
Outcomes	**Clinical effectiveness** : Case identification by the only pediatrician in study town **Clinical case definition, criteria not defined:** "Certain" pertussis case (as assessed by pediatrician), excluding "probable or possible" cases. **Study performed to compare with British MRC data, so probably used same clinical criteria** - Incidence rate (person-months) and VE per group Immunogenicity and reactogenicity: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Unclear or low risk	No details provided, apart from relatively good accordance of age and living conditions between groups

Attrition bias	Low risk	High follow-up
Performance bias	Unclear risk	No details reported; 24% of vaccinees received 4th dose
Detection bias	High risk	Evaluation carries on severe cases without any clear definition; investigator was only pediatrician in town vaccinating and making diagnostic.
Selective reporting	Low risk	Probably all results reported

Liese J., 1997

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

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Moderate risk	Parent's choice for vaccination, but adjusting for family characteristics
Missing data on exposure	Low risk	High exhaustiveness of vaccine information
Performance bias	Unclear risk	No details reported
Exposure assessment bias	Moderate risk	Clinical charts

Selective reporting	Unclear or low risk	Probably all results reported, but other case definitions?

Long S. 1990

Methods	Site: Philadelphia/USA, 1984-85 Design: parallel group double-blind RCT Follow up: up to age 18 months
Participants	Included: Healthy unvaccinated children 2-months-old (N=1771) Excluded: usual. Follow-up of 538 children as planned; after 20 months, the DMSB then recommended stopping the study (immunogenicity inferior in 3-dose compared to 4-dose arm) => catch-up dose for group with placebo at 6 months.(Deforest A, abstract 1987). Paper reports data on reactions at 6 months in 451 children.
Interventions	**Primary series DTwP (3 doses vs. 2 doses + placebo)** Vaccine: DTwP (Wyeth); Placebo: sterile saline Comparison: DTwP (Group 1) or placebo (group 2) @ age 6 months Vaccine **schedule: 2, 4, 6 mo** Number receiving the 3 injections: 233 (group 1), 218 (control group)
Outcomes	**Reactogenicity:** Active and passive assessment of adverse reactions (telephone interview by nurses or parents reported using standardized observation material) Timing of assessment: within 48 hours after each vaccine dose - Incidence expressed as events per children at 6th dose (%) - Rectal temperature ≥38.3°C; Persistent crying (prolonged); - Local swelling >1.27 cm; local tenderness; redness; Clinical efficacy and immunogenicity : no data reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Unclear risk	Only first third enrollments finished the study as planned, not clear whether specific characteristics
Random sequence generation (selection bias)	Unclear risk	Details not reported
Allocation concealment (selection bias)	Low risk	Syringes with vaccine and placebo prepared for the 6 months dose were taped to prevent viewing and were distributed in individual coded packages for each subject.

Blinding of participants (performance bias)	Low risk	Regular clinical personnel prepared and administered the vaccine. Neither parents nor investigators knew the infants' vaccine assignment.
Blinding of outcome assessment (detection bias)	Low risk	After every injection a study nurse who was unaware of the vaccine group assignment at 6 months telephoned each family between 24 and 48 hours after injection to assess reactions
Selective reporting	Unclear risk	Protocol not available

Miller E., 1995 (booster)

Methods	Site: UK, 1991-93 Design: parallel group double-blind RCT
Participants	Included: **Children previously vaccinated with DTwP at 3,5,10 mo** Excluded: contra-indication to pertussis vaccine
Interventions	**Booster @ 4.5 yr : DTwP vs. DT** Vaccines : DTwP (Wellcome) Dose schedule: Group 1: 3,5,10 mo + 4.5 yr (N=74): 4 doses Control group: 3,5,10 mo (N=77): 3 doses
Outcomes	**Immunogenicity** : Timing of assessment: 6 weeks after booster dose Serological assay: **ELISA (IgG anti-PT, anti-FHA)** - GMT (95% CI) post-booster **Reactogenicity:** Study diary kept by parents, active follow-up - Oral temp ≥100°F, local redness >2cm, local swelling > 2cm - % of children with symptoms within 48h Clinical effectiveness: no data reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Unclear risk	No details reported
Random sequence generation (selection bias)	Unclear risk	No details reported
Allocation concealment (selection bias)	Unclear risk	No details reported

Blinding of participants (performance bias)	Low risk	Double-blind, placebo controlled
Blinding of outcome assessment (detection bias)	Low risk	Double-blind, placebo controlled
Selective reporting	Unclear risk	Protocol not available

Miller E., 1997

Methods	Site: UK, 1988-94 Design: Synopsis of two parallel group double-blind RCT evaluating wP vs. aP, each using two different schedules The two trials are presented as using an identical protocol
Participants	Included: Children attending clinics for primary vaccination, partents accepting randomization to wP or aP (various vaccine types) Excluded: history of pertussis, neurological disorder or serious chronic disease 4.2% drop-out
Interventions	**DTwP accelerated vs. long schedule** Vaccines : DTwP (Wellcome) Dose schedule: Group 1: **2,3,4 mo** (N=139) (mean age 8, 13, 18 weeks) Group 2: **3,5,9 mo** (N=179) (mean age 14, 22, 38 weeks)
Outcomes	**Immunogenicity** : Timing of assessment: **6 weeks and 12-18 mo** (subgroup) **after 3rd dose** Serological assay: **ELISA [IgG anti-PT, anti-FHA and fimbrial antigens** (agglutinogens) 2 and 3] - GMT (95% CI) post-vaccination - Prevalence of detectable antibody **Reactogenicity:** Study diary kept by parents, study nurse visits - % of children with symptoms within 24h at any of three doses: - Rectal temp ≥ 38.0°C (group 1) / ≥100.4°F (group 2), local redness ≥2.5cm, local swelling ≥ 2.5cm; ≥3 systemic symptoms (disturbed feeding, sleeping; unusual crying) Clinical effectiveness: no data presented
Bias	**Reviewers' judgment** **Support for judgment**

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

Olin P., 1997 (trial II) => full report in Olin P., 1998

Olin P., 1998

Methods	Site: Sweden, 1993-96 Design: Secondary open cohort analysis of a multisite trial comparing vaccines; one site used a different schedule. Follow-up until October 1996 (min. age 28 mo), by laboratory reporting and nurse interview
Participants	Included: Children attending Child Health Centres in 22 of 24 Swedish counties (N=83,000) Excluded: no details provided Attrition rate not provided
Interventions	**DTwP in accelerated vs. long schedule** Vaccines : DTwP (Wellcome) Dose schedule: Group 1: **2,4,6 mo** (N=2510; N=80 for serology) - Malmö County Group 2: **3,5,12 mo** (N=17929; N=75 for serology) - other counties
Outcomes	**Immunogenicity** : Timing of assessment: age 7 mo and 1 mo after 3rd dose Serological assay: **ELISA (IgG anti-PT, -FHA, -Fim2/3, -PRN)** - GM (95% CI) post-vaccination by group **Clinical effectiveness** : prospective assessment and monitoring, Notification by laboratories of culture confirmation of B. pertussis. Nurse interview for symptoms. **Old WHO definition**: paroxysmal cough ≥21d with culture confirmation

	Laboratory-confirmed: any cough with culture confirmation - Vaccine effectiveness and incidence rate per group - Follow-up until minimum age 28 mo Alternative definitions as **CDC confirmed case** - (culture-confirmation and cough of any duration) - Case number and incidence rate (person-months) after age 5/6 months per schedule - => calculation of person-time and of VE **Reactogenicity:** no data presented

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

Onorato IM, 1992

Methods	Site: USA1984-86 Design: Surveillance in 3 urban areas of the US: suspected case reporting with consequent laboratory confirmation (swap) VE analysis including only secondary cases after household exposition
Participants	Children who are **household contacts of a lab-confirmed pertussis case**, 1-4 years of age, and who developed no symptoms during one week after primary case illness
Exposure	**Primary series with ≥3 doses of wP (2,4,6 months + 12-18 mo), comparison to unvaccinated** (not reported in article; US schedule at that time) Vaccine: DTwP
Outcomes	**Clinical effectiveness** : **2010 WHO clinical case definition**: cough ≥14d + paroxysms, whoop or vomiting, *data are equivalent to*: **CDC confirmed case definition**: cough ≥14d + paroxysms, whoop or vomiting and epilink to culture-confirmed case Other definitions evaluated (duration of cough with/without paroxysm; without

	laboratory confirmation of primary case) - Vaccine effectiveness - By number of doses only reported for household case +/- lab confirmation Immunogenicity and reactogenicity: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Low risk	All household contacts were to be included
Attrition bias	Unclear risk	Short follow-up period after household primary case, attrition likely not high
Performance bias	Low risk	No particular event reported
Detection bias	Unclear to high risk	Not reported at which time vaccination status was assessed (at beginning or end of follow-up)
Selective reporting	Unclear or low risk	Public agency with theoretically neutral position

Public Health Laboratory Service Whooping-cough Committee and Working Party (PHLSWCP), 1973 and **Preliminary report 1969**

Methods	Site: UK 1966-67 Design: Surveillance in 33 areas of UK, based on reporting of suspected cases by general practitioner and culture analysis of NP swabs VE analysis including only secondary cases after household exposition
Participants	Children who are household contacts of a confirmed pertussis case, <11 years of age, and who developed no symptoms during one week after primary case illness Data presented separately for age 0-4 yrs
Exposure	**Primary series with 3 doses of wP** (not specified: possibly 3 doses in 1-mo internal = UK before 1968)**, vs. unvaccinated** **Primary only vs. primary plus booster** Vaccine: wP (Glaxo, Bourroughs Wellcome [incl. antigen 3], or others) Fully vaccinated = at least 3 doses
Outcomes	**Clinical effectiveness** : Case definition: **Clinical suspicion** based on paroxysmal cough, with or without vomiting or whooping. **Definition likely similar to MRC report (Anonymous 1951)** - Attack rate and VE fully versus not vaccinated - Attack rate and VE fully vaccinated plus booster vs. no booster Immunogenicity and reactogenicity: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Low risk	All household contact were to be included

Attrition bias	Unclear risk	Short follow-up period after household primary case, attrition likely not high
Performance bias	Low risk	No particular event reported
Detection bias	High risk	Vaccination status recorded after three weeks of primary case detection, so likely cases had already illness; this could have prevented from detection bias, but may have biased the assessment of vaccination status
Selective reporting	Low risk	Publicly commanded investigation, selective reporting unlikely

Pollock T.M., 1984

Methods	Site: UK, 1978-81 Design: Cohort study (not clear how vaccines were assigned) Follow-up by standard questionnaires and nurse contact
Participants	Included: Children attending clinics for routine immunisation, Excluded: no criteria reported 10% drop-out overall
Interventions	**Primary vaccination, DTwP vs. DT** Vaccines : adsorbed wP (in DTwP) and DT (Lister, Wellcome and Duncan Flockhart) a third group received plain wP in the DTwP Dose schedule: Group 1: **adsorbed DTwP** (N=5091) Group 2: **DT** (N=3212) Group 3: plain DTwP (N=371)
Outcomes	**Reactogenicity:** Study diary kept by parents, study nurse visits - % of children with symptoms within 12h by serial number of doses: o Feverishness, local reactions (>=2.8 cm), crying more than usual, persistence crying for >5h, screaming attacks - % of children with symptoms within 12h after any dose o Crying/screaming, feverishness Clinical effectiveness and immunogenicity: no data presented

	Reviewers' judgment	**Support for judgment**
Selection bias	Unclear (high) risk	Procedure to assign vaccine type not described
Attrition bias	Moderate risk	10% drop-out
Performance bias	Low or unclear risk	No event reported

Detection bias	High risk	Non-blinded study
Selective reporting	Moderate risk	Fairly large range of outcomes presented

Ramsay MEB, 1992

Methods	Site: UK, Design: Synopsis of two cohorts, one observed 1986-87 (long), the other 1989-90 (accelerated); the two cohorts are presented as using an identical protocol and diary. Participants characteristics are comparable (age, sex, breast feeding: 81% vs. 75%)
Participants	Included: Children attending clinics for primary vaccination; parents accepting inclusion in 2,3,4mo cohort (which was a new schedule, soon to be introduced in the population)
Interventions	**DTwP accelerated vs. long schedule** Vaccines : DTwP (Wellcome) Dose schedule: Group 1: **2,3,4 mo** (N=107) Group 2: **3, 4.5-5, 8.5-11 mo** (N=115)
Outcomes	**Reactogenicity:** Diary kept by parents with telephone contact by nurse - % of children with symptoms on second evening after each of three doses: - Axillary temp ≥ 37.2°C, local redness ≥2.5cm, local swelling ≥ 2.5cm; ≥3 symptoms (disturbed feeding, sleeping; unusual crying) Clinical effectiveness and immunogenicity: no data presented

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Moderate risk	Parents assenting, but to the future national routine schedule of 2,3,4 mo
Attrition bias	High risk	19% drop-out from analysis in accelerated schedule group; not reported for long schedule group
Performance bias	Low risk	No event reported
Detection bias	Moderate risk	Possible, but both nurses participated in follow-up
Selective reporting	Moderate risk	Some specific outcomes of reactogenicity may have been unreported (to assure the public about the vaccine)

Ramsay M.E.B., 1993 (I)

Methods	Site: UK, 1989 Design: Analysis of notification data (physician questionnaire) and national vaccine coverage data ; VE estimated by *screening method*, by epidemic and non-

	epidemic period (during 1989)
Participants	Children age 1-4 yrs abd 5-9 yrs, 12765 cases identified
Exposure	**Primary series with 3 doses of wP (3,5,10 mo) comparison to unvaccinated** Vaccine: wP
Outcomes	**Clinical effectiveness** : **Clinical case** with ≥21 days of paroxysmal cough; and divers other not-per-protocol definitions - Vaccine effectiveness Immunogenicity and reactogenicity: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Not applicable High risk of bias	Screening method, ecological analysis
Attrition bias	Not applicable	Unlikely with screening method
Performance bias	High risk	Study validity depends on quality of vaccine coverage estimates and of surveillance
Detection bias	Unclear risk	Unclear, as not known whether immunization coverage data of comparable validity as case immunization status comparable, eg, if both based on family physician charts filled-out upon immunization)
Selective reporting	Moderate risk	Author could be not neutral to study question, possible that results more in favor of vaccination have not been included in report.

Scheifele D.W., 1999

Methods	Site : Canada, 1990 Design: RCT Follow-up: until 4-6 weeks after booster
Participants	Included : healthy participants of a previous trial on DPT-IPV-PRP-T vaccine (N=257) Excluded: contradiction, laboratory-confirmed target infection, blood products, immune impairment
Interventions	**Booster immunization: DTwP at differents ages** Vaccines : DTwP (PENTA™, Pasteur Mérieux) Booster at 12, 15 or 18 mo after a primary series finished before age 7 mo
Outcomes	***Immunogenicity (NPP)*** *:* Timing of assessment: 4-6 wks after booster

	Serological assay: microassay for measurement of agglutinin measurement - GMC (95%-CI) at pre- and post-booster - Prevalence antitoxin ≥1:64 **Reactogenicity:** assessed one day after vaccination, by parents' diary Local (redness, swelling, tenderness) and general (irritability, temperature ≥38.0°C and ≥39.0°C) Clinical efficacy not evaluated.

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Low risk	Usual inclusion and exclusion criteria
Random sequence generation (selection bias)	Low risk	Details reported, quality procedures
Allocation concealment (selection bias)	Low risk	Details reported, quality procedures
Blinding of participants (performance bias)	Low risk	Serological evaluation, probably low risk
Blinding of outcome assessment (detection bias)	Unclear risk	Not clear whether serological assessment blinded
Selective reporting	Unclear risk	Protocol not available. Manufacturers among authors

Schmitt H-J., 1996

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

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

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

Simodon F., 1997

Methods	Site: rural town in Senegal, 1990-1994 Design: cohort study, conducted within a vaccine trial population No control for confounders (only comparison of characteristics)
Participants	Included: Children exposed to household contacts with confirmed pertussis: 190 children vaccinated at 2,4,6 mo with DTwP in the context of a vaccine trial, and 17 unvaccinated children of same population not enrolled (age not specified, but similar). Surveillance of the entire population <15 yrs during four years (2587 compounds)
Exposure	**Primary series (2,4,6 mo) of DTwP vs. no vaccination** **Vaccine:** DTwP (Pasteur Mérieux)
Outcomes	**Clinical effectiveness** : Case identification by physician after weekly screening by fieldworkers **Old WHO definition of confirmed cases** : - ≥21 days of paroxysmal cough, with positive culture or serology, or epi link Alternative definitions as - ≥21 days of paroxysmal cough, with positive culture or serology, or epi link confirmed by PCR

	- ≥21 days of any cough, with positive culture or serology, or epi link [confirmed by PCR] Serological confirmation based on two-fold increase in anti-PT or anti-FHA IgG - VE based case contact analysis or from proportional hazard analysis Immunogenicity and reactogenicity: not reported

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

Stehr K., 1998

Methods	Site: Germany, 1991-94 Design: Cohort (RCT with open control arm for no vaccine) Follow-up during up to 3 yrs
Participants	Included: Healthy unvaccinated children 2- to 4-month-old (N=15,601) Per protocol follow-up in 93% of both groups.
Interventions	**Primary series (3, 4.5, 6 mo and 15-18mo): comparison DTwP vs. DT** Vaccines : 1. DTwP (Wyeth-Lederle) 2. DT (control group; given at 3, 4.5, 15-18 mo) Number enrolled and evaluated: 4259 (vaccine group) , 1739 (control group)

Outcomes	**Clinical efficacy:** Passive and active case ascertainment (bi-weekly phone calls); case incidence for follow up from 14 days after 3rd dose (vaccine group) or 61 days after 2nd dose (control group); **Modified WHO definition of confirmed cases:** - ≥21 days of paroxysmal cough (=cough with paroxysm, whooping or posttussive vomiting), with positive culture or serology, or epi link - Several alternative definitions (variations of laboratory confirmation) - Incidence rates (person days) per group and vaccine efficacy Immunogenicity and reactogenicity : not reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Selection bias	High risk	Assignment according to parents' preference for or against pertussis vaccination
Attrition bias	Low risk	Similar drop-out in both groups
Performance bias	Low risk	No particular event reported
Detection bias	Moderate risk	Unblinded study for vaccine/no vaccine, could have led to differential diagnostic
Selective reporting	Low risk	Extensive presentation and discussion of alternative outcomes

Table set 7. Characteristics and criticial appraisal of additional studies not per protocol

Barkin R.M., 1985 (Pediatric Infect Dis)

Barkin R.M., 1985 (Develop Biol Standard)

Methods	Site: Five pediatric practices, Colorado, early 1980? Design: parallel group double-blind RCT (random number table) Follow up: 24h after 3rd dose, no drop-out Comparison with external cohort
Participants	Included: Infants <2 mo of age coming to pediatric practice, no details provided (N=40) Excluded: no criteria specified
Interventions	**Primary series (2,4,6 months): schedule comparison wP vs. no wP** Schedule : Group 1: DTwP – DT – DTwP (2 doses, 4-mo interval; N=20) Group 2: DTwP – DTwP – DT (2 doses, 2-mo interval; N=20) "External cohort" : DTwP - DTwP – DTwP (3 doses, 2-mo interval; N=39) Vaccines : 1. DTwP (Connaught) 2. DT (Connaught) Number vaccinated with 3 doses: 20 (DTwP group), 20 (control group)
Outcomes	**Immunogenicity** *Timing of assessment*: 1-2 months after the last wP administration (age 5-6 or 7-8 months) Microagglutionation technique - GMT (SEM) by group **Reactogenicity:** Parents' reporting form and phone contact at 24h after vaccination *Timing of assessment*: within 24h after injection - Risk for reaction by dose - Risk for reaction by vaccine type (all doses combined) Clinical efficacy: not reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**

Inclusion bias	High risk	Private practice, no further information provided
Random sequence generation (selection bias)	Moderate risk (High risk)	Random number table No randomization for external cohort
Allocation concealment (selection bias)	High risk	No concealment
Blinding of participants (performance bias)	Low risk	Double-blind (DT controlled)
Blinding of outcome assessment (detection bias)	Low risk (High risk)	Double-blind Unblinded for external cohort
Selective reporting	Unclear risk	Protocol not available, manufacturer among authors

Bhandari 1981

Methods	Site: India, before 1981 Design: parallel group non-blinded RCT (random sampling table) Follow up: until 1 month after last dose
Participants	Included: children aged 3 months to 5 yrs (N=200) Excluded: contradiction to vaccination (such as allergic diathesis or CNS disease) Complete follow-up: 162 children (81% of randomized)
Interventions	**Primary series: 3 doses at 1-mo interval vs. 2 doses at 2-mo interval** Vaccines : DTwP (Central Research Institute, Kasauli, India) Age at initiation: 3 months to 5 years
Outcomes	**Immunogenicity:** *Timing of assessment:* one month after last dose Agglutination method. - Proportion with titers ≥1:320 (putatively protective) or ≥1:1280 **Reactogenicity**: Reported by serial number of dose (any1st dose, any 2nd dose, 3rd dose) No details how assessment was made or during which period after vaccination.

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Low risk	Usual inclusion and exclusion criteria; socio-economic setting not further described (malnutrition)

Random sequence generation (selection bias)	Moderate risk	Randomisation with random sampling table
Allocation concealment (selection bias)	Moderate risk	Randomisation with random sampling table
Blinding of participants (performance bias)	Low to moderate risk	Non-blinded study; relevant mainly for reactogenicity
Blinding of outcome assessment (detection bias)	Unclear risk	Non-blinded study; not clear whether serology done blinded
Selective reporting	Unclear risk	Protocol not available

Blennow M., 1988

Methods	Site: Sweden, 1982-85 Design: parallel group non-blinded RCT (group assignment by date of birth: odds/even days) Follow up between age 6 and 23 months, regular visits (every 2-4 months) with nurses documenting symptoms
Participants	Included: Healthy unvaccinated children <2-mo-old (N=1177) (effective age: 1.2-7.3 mo) Excluded: not specified Vaccinated with 3 doses: 525 children (93% of randomized)
Interventions	**Primary series of wP (2,3,4 mo; 3 monthly doses) vs. no vaccination** Vaccines : wP not specified Number vaccinated with 3 doses: 525 children (93% of randomized), 615 controls
Outcomes	**Clinical efficacy:** Observation from 3rd dose on; participants report forms and review of laboratory registries (exhaustive for study population) Case definition: o laboratory-confirmed cases (culture, serology) irrespectively of symptoms [serology: significant rise in ELISA titers of FHA or PT, or toxin neutralization test] o typical symptoms (coughing for ≥4 weeks, whoops, cough with vomiting) and diagnosis by physician or epilink with whooping cough o the combination of both (OR) - Attack proportion per group and VE per age group - Risk per group for home exposure cases, stratified by age Immunogenicity and reactogenicity: not reported

Risk of Bias	Reviewer judgment	Support for judgment
Inclusion bias	Unclear risk	No exclusion criteria specified
Random sequence generation (selection bias)	Moderate risk	Assignment based on odd or even birthday date
Allocation concealment (selection bias)	NA	
Blinding of participants (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding
Selective reporting	Low risk	Unlikely

Brink E.W., 1982

Methods	Site: USA 1979-81 Design: Analysis of data from the Pertussis Case Household Report by the CDC (for 5% of all reported cases) and the Pertussis Sporadic Case Reports Surveillance System VE analysis including only secondary cases after household exposition
Participants	Household contacts of primary cases
Exposure	**Primary series with ≥3 doses of wP (2,4,6 months + 12-18 mo), comparison to unvaccinated** (not reported in article; US schedule at that time) Vaccine: DTwP
Outcomes	**Clinical effectiveness** : **Epi-link and CDC reporting** : not specified, but probably clinical suspicion with or without laboratory confirmation - Secondary attack rate by number of vaccine doses and age Immunogenicity and reactogenicity: not reported

Bias	Reviewers' judgment	Support for judgment
Selection bias	Low risk	Only 5% of case households included; no controlling for confounders
Attrition bias	Unclear risk	No details on follow-up provided
Performance bias	Unclear risk	No particular event reported
Detection bias	Unclear to high risk	Not reported at which time vaccination status was assessed (at beginning or end of follow-up)
Selective reporting	Unclear or low risk	Public agency with theoretically neutral position

Broome C., 1981

Methods	Site: USA, 1977; urban population around a municipal hospital during an pertussis outbreak Design: Prospective surveillance of household members of pertussis cases, by telephone follow-up VE analysis including only secondary cases after household exposure	
Participants	Children <15 years of age **living in the household of a laboratory-confirmed** pertussis case, seen in the municipal hospital or its outpatient clinic	
Exposure	**Primary and booster: wP vs. no wP** schedule not specified: of schedule USA before 1977, not detailed Vaccine: not specified **3-5 doses vs. 1-2 doses vs. no vaccination**	
Outcomes	**Clinical effectiveness** : Case definition: Clinical suspicion based on **paroxysmal cough (any duration)** with or without laboratory confirmation, with **epi-link with laboratory-confirmed case**. Symptoms commencing 7-28 days after primary case illness (definition similar, but not identical to current CDC definition of confirmed cases: epi-link and ≥14 days of paroxysmal cough) - Attack proportion and VE by age group	
Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Low risk	Vaccination status recorded probably at beginning of exposure period, so bias unlikely. No control for confounders
Attrition bias	Low risk	Unlikely, as only short follow-up period after household exposure
Performance bias	Low risk	No particular event reported
Detection bias	High risk	Parents or investigators calling could preferentially document coughing in unvaccinated children.
Reporting bias	Low risk	Publicly commanded investigation, selective reporting unlikely

Campbell H., 2012

Methods	Site: UK, 1998-2009 Design: Analysis of notification data, death registrations, laboratoryies, hospital episode statistics; and national coverage data ; VE estimated by *screening method*
Participants	Children age 12-59 mo (up to 16 y), 193 cases identified
Exposure	**Primary series with 3 doses of wP (2,3,4 mo) comparison to unvaccinated** Vaccine: wP

Outcomes	**Clinical effectiveness** : **Laboratory-confirmed case: culture/PCR/serology, irrespective of clinical symptoms** - Vaccine effectiveness by age group (12-39 mo; 40 – 59 mo) [definition does not include serology]; - VE by number of doses [definition includes serology] Immunogenicity and reactogenicity: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Not applicable High risk of bias	Screening method, ecological analysis
Attrition bias	Not applicable	Unlikely with screening method
Performance bias	High risk	Study validity depends on quality of vaccine coverage estimates and of surveillance
Detection bias	Unclear risk	Unvaccinated children may have higher probability to be laboratory-diagnosed
Selective reporting	unclear risk	Unclear

Cody C.L., 1981

Methods	Site: USA, 1978-79 Design: cohort study, blinded for participants; no randomization mentioned No control for confounders (only comparison of characteristics)
Participants	Included: Children aged 0 to 6 years scheduled for DTP vaccination
Exposure	**Primary series 3 doses** (schedule varied between including physicians) **Vaccine:** DTwP adsorbed (Wyeth)
Outcomes	Reactogenicity: Parents' questionnaire, assessment within 48h of vaccination Fever, crying and local reactions Clinical effectiveness and immunogenicity: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	High risk	Assignment by physician
Attrition bias	Unclear	No details reported
Performance bias	Low risk	No particular event reported

Detection bias	Low risk	Blinded parents
Selective reporting	Unclear or low risk	Probably all results reported

Conway S., 1993

Methods	Site: UK 1986-7 Design: parallel group double-blind RCT Follow up: 15 months after dose 3 (age 21 months)
Participants	Included: **69 preterm infants:** <32 wks (N=32); 32-35 wks (N=37) Excluded: not specified Only 1572 participants from a larger efficacy trial participated in the immunogenicity study (children whose parents consented to the collection of capillary blood)
Interventions	**Primary DTwP series: third dose early after 1 mo or late after 6 mo** **Booster DTwP: effect of booster 18 mo vs. no booster** Vaccines : DTwP (not specified) Dose schedule: A: 3,4,5 mo (N=22) : 3 doses, interval 1-1 mo B: 3,4,10 mo (N=21) : 3 doses, interval 1-6 mo C: 3,4,5,18 mo (N=26) : 4 doses, interval 1-1-13 mo
Outcomes	**Immunogenicity** : Timing of assessment: 1 month after 3rd dose; at 19th mo of age; at 4-5 yrs of age Serological assay: antibody IgG anti-PT, anti-FHA and agglutinogens 2 and 3, reported as Pertussis Antibody Units (PAU /ml) - **Mean antibody titers post immunization** Clinical effectiveness and reactogenicity: no data presented

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Unclear risk	Not reported
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants (performance bias)	Unclear risk	Not reported

Blinding of outcome assessment (detection bias)	Unclear risk	Not reported

Laurell G., 1957 (Laurell)

Methods	Site: Sweden 1953-56 Design: cohort study, vaccine assignment not explained No exploration or control of confounders
Participants	Included: 325 children, inclusion and exclusion criteria not detailed
Exposure	**Primary series of DTwP, schedule with 3 doses compared to 2 doses** Schedules not specified : 3 doses "usual schedule", which appears to be in intervals of 4-6 weeks (see Rabo) and to end by 6 months; Vaccine not specified Group 1 (3 doses): 325 children, group 2 (2 doses) 41 children
Outcomes	**Immunogenicity:** Timing of assessment: 3-6 weeks after last dose (during 8th month of life) Agglutination testing, methods not further specified - **Median agglutination titer per group (extracted from figure)** **Clinical effectiveness and reactogenicity**: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Unclear risk	No details provided on assignment
Attrition bias	Unclear	No details reported
Performance bias	Low risk	Participants and parents not blinded, not relevant in serological evaluation?
Detection bias	Unclear risk	Not clear whether blinded testing
Selective reporting	Unclear or low risk	Probably all results reported

Mangay-Angara A., 1978

Methods	Site : Philippines, 1970s Design: Clinical trial, participants were "allotted" to groups Follow-up: until one month after the 3rd dose
Participants	Included : Healthy infants 3-8 months of age with no symptoms of intestinal disease, respiratory infection or fever (N=522)

	Excluded : not specified
Interventions	**Primary series: 2 doses DTwP vs. D** Vaccines : DTwP (adsorbed; N=177) vs. D (N=174) (Alabang Institute, Manila) Dose schedule: 2 doses in 6-mo interval, starting 3-8 months A third group was vaccinated with a Dutch DTwP vaccine.
Outcomes	**Immunogenicity**: Timing of assessment: 40 days after 2nd dose Serological assay: **micro-agglutination reaction** - GMT at 40 days post 2nd dose Reactogenicity: mean temperature by group, not taken into account Clinical efficacy not evaluated.

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Low risk	Usual exclusion criteria, but no details on study population
Random sequence generation (selection bias)	Unclear risk	No details reported
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants (performance bias)	Unclear risk	No details reported (possibly low risk for serology)
Blinding of outcome assessment (detection bias)	Unclear risk	No details reported
Selective reporting	Unclear risk	Protocol not available.

McBean A.M., 1978

Methods	Site: Cameroun, 1970s Design: parallel group RCT (4 groups, primary objective was evaluation of measles vaccination; three doses of DTP given, but evaluation only after 2nd dose) Follow up until 1 month post 2nd dose
Participants	Included: children 9- to 36-mo-old (N=168) Excluded: no criteria specified Vaccinated with 3 doses: 7558 children (85% of randomized)
Interventions	**Primary series (2 doses at 3-mo interval): comparison wP vs. nihil** Vaccines:

	1. DTwP (Wyeth) (N=91) 2. controls receive placebo or measles vaccine (N=277)
Outcomes	**Immunogenicity:** 3 months post 1st dose, 1 month post 2nd dose. Micromethod for agglutinin titers - Median titers - ≥ 4-fold risk after 2nd dose Clinical efficacy and reactogenicity: not reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	Unclear risk	No information provided
Random sequence generation (selection bias)	Low risk	Consecutive enrolment, previous group assignment of numbers
Allocation concealment (selection bias)	Moderate risk	Not clear whether list open or concealed
Blinding of participants (performance bias)	Low risk	Placebo- or measles controlled
Blinding of outcome assessment (detection bias)	Unclear or moderate risk	Not clear whether blinded serological testing
Selective reporting	Unclear risk	Protocol not available

Miller E., 1995 (primary schedule)

Methods	Site: North Hertfodshire/UK, 1988 and 93 Design: Synopsis of comparable cohorts: no details provided
Participants	Not reported
Interventions	**Primary DTwP series, usual long vs. accelerated schedule** Vaccines : not reported Dose schedule: Group 1: 3,5,10 mo (N=155): 4 doses, interval 2-5 mo Group 2: 2,3,4 mo (N=91): 3 doses, interval 1-1mo
Outcomes	**Immunogenicity** : Timing of assessment: post 3rd dose Serological assay: ELISA (IgG anti-PT, anti-FHA) - **GMT (95% CI) post-vaccination** Clinical effectiveness and reactogenicity: no data presented

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	High risk	Historical cohorts from two different trials, no details or controlling reported
Attrition bias	Unclear risk	No details reported
Performance bias	Unclear and low risk	No particular event reported
Detection bias	Moderate risk	Not clear whether serological studies performed in blinded fashion
Selective reporting	Unclear or low risk	Probably all results reported

Muller A.S., 1984

Methods	Site: rural Kenya, 1975-1981 Design: parallel group CT (assignment by serial inclusion number) Follow up: up to 54 months after last dose; weekly household visits by fieldworker; symptoms and diagnosis by physician (and NP swabs and serum until 1977); 100-103 children followed-up for serology
Participants	Included: Healthy children without DTwP vaccination; age 3-6 months (N=1165) Excluded: previous DTwP
Interventions	**Primary series, schedule comparison: 3 doses vs. 2 doses wP** Vaccines : DTwP (RIVN), Salk injectable polio vaccine (not specified) Group 1: DTwP – DTwP – DTwP (N=50) Group 2: DTwP - polio – DTwP (N=54) Vaccination administered during 3-monthly mass campaigns
Outcomes	**Clinical efficacy:** - Difficult to evaluated, as based on probability score of pertussis event, does not compared between groups **Immunogenicity** *Timing of assessment*: 1 mo, 24-30 mo, 39-42 mo and 51-54 mo after last wP dose Microtechnique agglutination testing - Median titre - % without demonstrable titre Reactogenicity: not reported
	Reviewer

Risk of Bias	judgment	Support for judgment
Inclusion bias	High risk	No particular information
Random sequence generation (selection bias)	Moderate risk	Assignment based on serial inclusion number
Allocation concealment (selection bias)	Moderate risk	Assignment based on serial inclusion number
Blinding of participants (performance bias)	Low risk	Not reported whether parents aware of group, but likely; but serological evaluation
Blinding of outcome assessment (detection bias)	Low risk	Staff likely aware of group, but serological evaluation
Selective reporting	Unclear risk	Protocol not available

Public Health Laboratory Service Whooping-cough Committee and Working Party (PHLSWCP), 1982

Methods	Site: UK 1978-80 Design: Surveillance in 21 areas of UK, based on reporting of suspected cases by general practitioner and culture analysis of NP swabs VE analysis including only secondary cases after household exposition
Participants	Children who are **household contacts of a confirmed pertussis** case, <6 years of age, and who developed no symptoms during one week after primary case illness
Exposure	**Primary series (3 doses starting 3-6 mo): DTwP vs. no vaccination** **Booster vs. no booster (after primary series)** (schedule not specified: possibly 3,5,10 = UK after 1968) Vaccine: not specified Fully vaccinated = at least 3 doses
Outcomes	**Clinical effectiveness** : **Case definition: <u>Clinical suspicion based on</u> <u>any cough of any duration</u>**. - Attack rate and VE fully versus not vaccinated **Immunogenicity and reactogenicity**: not reported

Bias	Reviewers' judgment	Support for judgment
Selection bias	High risk	Physicians could notify preferentially unvaccinated children. No control for confounders
Missing data on exposure	Unclear risk	Percentage of missing vaccination status among household contacts is not reported

Performance bias	Low risk	No particular event reported
Exposure assessment bias	High risk	Vaccination status recorded after three weeks of primary case detection, so likely cases had already illness; this could have biased exposure assessment
Reporting bias	Low risk	Publicly commanded investigation, selective reporting unlikely

Ramsay M.A.B., 1993 (II)

Methods	Site: UK, 1988 – 1990 Design: Synopsis of three studies: 1. cohort 1989-90 in Colchester: 2,3,4 mo (N=57); follow-up 6-8 weeks post third dose (46% drop-out for pertussis serology) 2. cohort 1989-91 in three districts with delayed schedules change: 3, 4.5-5, 8.5-11 mo (N=50); follow-up 6-8 weeks post third dose (16% drop-out for pertussis serology) 3. cohort 1988-89 in North Hertfordshire : 3, 4.5-5, 8.5-11 mo (N=32); follow-up 12 months post third dose; the timing of assessment is delayed compared to the other cohorts (18 vs. 11 months), thus this cohort was not included in the review
Participants	Included: Children schedules for primary vaccination, attending general practices or clinics Excluded: not specified
Interventions	**DTwP accelerated vs. long schedule** Vaccines : DTwP (Wellcome) Dose schedule: Group 1: **2,3,4 mo** (N=31) Group 2: **3, 4.5-5, 8.5-11 mo** (N=42)
Outcomes	**Immunogenicity** : Timing of assessment: 12 months after 3rd dose And 6-8 weeks after third dose (accelerated schedule only) Serological assay: **anti-FHA (solid phase RIA)** ("good correlation with ELISA") - GMC (95% CI) post-vaccination Clinical effectiveness and reactogenicity: no data presented

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Unclear risk	Risk could be low as far as assignment followed national recommendations, not individual choice; but no data presented

Attrition bias	Moderate risk	Considerable drop-out, particularly in group 1; differential impact on serology may be small
Performance bias	Unclear risk	No event reported
Detection bias	Low risk	Immunogenicity evaluation
Selective reporting	Moderate risk	Secondary evaluation of existing data

Swartz TA., 1985

Methods	Site: Israel, 1979-82 Design: comparison of two infant cohorts (not clear how recruited) ; follow-up until age 3 years No report or control for confounders
Participants	Included: Children vaccinated with DTP or DTP-IPV (total N=171)
Exposure	**Primary series DTwP 2+1 vs. 3+1 schedule** **Vaccine:** DTwP adsorbed (Mérieux) Dose schedules: Group 1: 2,3.5,10 mo (N=79) Group 2: 2,4,6,12 mo (N=92)
Outcomes	**Immunogenicity** : Timing of assessment: at booster (10.5 vs. 12 mo), 1 yr post booster, 2 yr post booster; 1 mo post 2nd / post 3rd not taken into account Serological assay: **seroagglutination microtitration technique** - Proportion with agglutinin titer ≥1:10 - GMT post-vaccination Clinical effectiveness and reactogenicity: no data presented

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	High risk	Assignment by physician
Attrition bias	Unclear	No details reported
Performance bias	Low risk	No particular event reported
Detection bias	Low risk	Blinded parents
Selective reporting	Unclear or low risk	Probably all results reported

Walker E., J Infect 1981

Methods	Site: Glasgow 1969 – 1980 (includes 3 epidemic periods) Design: case control analysis of surveillance data Review of clinical charts from all hospitals in Glasgow (discharge diagnosis of whooping cough)
Participants	Cases (N=387): **Pertussis cases** Controls (N=312): measles cases (probably hospitalisations in the same hospitals).
Exposure	**wP vaccination (3 doses, 1-2 doses vs. no vaccination)** Schedule not specified, probably three monthly doses (UK until xx)
Outcomes	**Clinical effectiveness** : **Included as pertussis case, if paroxysmal cough and at least one of the following** - whoop and duration of ≥21days - whoop and pronounced lymphocytosis (≥12.0*10^9/l among <12 mo; 9.0*10^9/l among ≥12 mo) - positive pernasal swab for *B. pertussis* (routinely taken) - fourfold risking tire of antibodies to *B. pertussis* (method not specified) Presents number of cases and controls by vaccination status - Calculation of OR and VE Immunogenicity and reactogenicity: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias (with regard to case and controls)	Unclear or high risk	No information on selection of measles cases; potentially reduced prevalence of vaccination, thus underestimating VE
Missing data on exposure	High risk	7% of cases and 45% of controls without vaccine status
Exposure assessment bias		
Performance bias	Unclear risk	No details reported
Selective reporting	Low risk	Secondary analysis of existing data

White JM., 1996

Methods	Site: UK, 1994 Design: Analysis of case reports from various national surveillance systems and national vaccine coverage surveys ; *screening method*
Participants	Children aged up to 14 years

Exposure	**Primary series with 2,3,4 mo vs. nihil** [analysis probably carries only on the period after change to accelerated schedule, although not clearly stated] Vaccine: DTwP (not specified)
Outcomes	**Clinical effectiveness** : **Laboratory-confirmed cases :** Culture confirmation of *B. pertussis*, clinical inclusion not specified - Vaccine effectiveness 3 vs. 0 d in age group 6-11 mo and 1-4 yrs - Coverage not given for partial vaccination => cannot calculate partial VE Immunogenicity and reactogenicity: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Not applicable	Screening method, but no possibility to infer on causality with this method
Attrition bias	Not applicable	Unlikely with screening method
Performance bias	High risk	Probably good quality of national vaccine coverage estimates and of surveillance, but by principal of limited validity
Detection bias	High risk	Culture-confirmation more likely in unvaccinated children
Selective reporting	Moderate risk	Possibly exhaustive analysis surveillance data

Wilkins J., 1971

Methods	Site: Los Angeles, 1964-68 Design: parallel group double-blind RCT Follow up: 21-45 days after final dose
Participants	Included: Healthy infants (N=563), first dose at age 6 weeks – 5 months; only subgroups "A" and "C" relevant for this review Excluded: not reported; no details on randomization reported
Interventions	**Primary series,** **Schedule comparison: 3 doses at 1-mo interval vs. 2 doses at 2-mo interval** Vaccines : 0.5 ml wP (NIH) Age at initiation: 6 weeks to 5 months Effective number of sera available: 3 doses (N=106 of 166); 2 doses (N=88 of 172) Additional analysis by **effective interval between 1st and 2nd dose (<30 d - ≥90 d)** among children with two 0.5ml doses. Not clear whether this analysis includes only group "A" (N=166 randomized) or also others.
Outcomes	**Immunogenicity:**

	Timing of assessment: 21-45 days after final dose Quantitative agglutination technique - **Percentage of children with titers ≥1:40 or ≥1:80 (putatively protective)** Efficacy or reactogenicity: not reported

Risk of Bias	**Reviewer judgment**	**Support for judgment**
Inclusion bias	High risk	Criteria not reported; high drop-out without reporting of reasons
Random sequence generation (selection bias)	Unclear risk	No details of randomization reported
Allocation concealment (selection bias)	Unclear risk	No details of randomization reported
Blinding of participants (performance bias)	Low risk	No placebo use, no details on blinding reported; serological evaluation
Blinding of outcome assessment (detection bias)	Unclear risk	No details reported
Selective reporting	Unclear risk	Protocol not available

Wilkins J., 1987

Methods	Site: Los Angeles, 1964-74 Design: cohort follow-up by regular visits after final and booster dose (>16 months)
Participants	Included: Children aged 4weeks to 8 months attending the a "growth and development clinic" (no details reported). Participants overlapping with randomized trial (Wilkins 1971).
Exposure	**Primary series of DTwP (**not clear whether children were assigned to specific schedules or whether the effective intervals and timings within a common theoretical schedule were evaluated) **Vaccine:** DTwP (Eli Lilly or Wyeth)
Outcomes	**Immunogenicity:** Quantitative agglutination technique - **Percentage of children (without detectable titers prevaccination) with post-vaccination titers ≥1:40 or ≥1:80 (putatively protective)** 1 and 2 months after first dose, by age at first dose 1 month post second dose, by interval between doses and by age at first dose - **≥4-fold increase pre-post booster** 1 month after booster, comparing 2- and 3-dose schedule; and by interval before booster

	Efficacy or reactogenicity: not reported

Bias	**Reviewers' judgment**	**Support for judgment**
Selection bias	Unclear risk	No details reported, part of the children participated in a randomized trial
Attrition bias	Unclear risk	No details reported
Performance bias	Unclear risk	No details reported
Detection bias	Low or unclear risk	Serological study ; unclear whether analyses were blinded
Selective reporting	Unclear risk	Unlikely, as results do not suggest any strong pre-test hypothesis

Author: Wong SL., 2008

Methods	Site: Malaysia 2000-2002 Design: 78nblended RCT Follow-up: until age 12 months
Participants	Included: healthy term infants in two not further specified study centers Excluded: immunosuppressive disorder or congenital defect; previous disease or vaccination against study diseases, allergy against vaccines…
Intervention	**Primary series: 3 doses starting age 1.5 mo vs 3 mo** Schedule: Group 1: 1.5,3,5 mo vs. Group 2: 3,4,5 mo Vaccines: Group 1: DTwP-HepB (Tritanrix-HepB, GSK) mixed with Hib; Group 2: DTwP (D.T.COQ, Pasteur Mérieux Connaught) with HepB and Hib in separate injections
Outcomes	**Immunogenicity :** - Timing of assessment: age 6 and 12 months (1 and 7 months after last dose) - Serological assay: anti-whole cell *B. pertussis* ELISA with cut-off set at 15 EL.U/ml **Reactogenicity:**

- Parents' questionnaire, assessment within 4 days following vaccination
- % of doses with local and systemic reactions (comparison between two products given in two different schedules) (extraction from graph)

Vaccine efficacy not assessed

Risk of Bias	Reviewer judgment	Support for judgment
Inclusion bias	Low risk	Usual inclusion/exclusion criteria
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not indicated.
Allocation concealment (selection bias)	Unclear risk	Method is not disclosed
Blinding of participants (performance bias)	moderate risk	Non-blinded trial; immunogenicity outcome only at moderate risk of bias
Blinding of outcome assessment (detection bias)	Unclear risk	Not mentioned whether blinded serology
Selective reporting	Unclear risk	Protocol not disclosed

Table set 8. Data from included and additional studies evaluating primary vaccination schedule impact on relevant outcomes

Table 8a-A: Included studies on primary vaccination schedule impact on vaccine effectiveness/efficacy

Accelerated vs. long schedule								
Old WHO definition (⩾21 d paroxysmal cough with culture confirmation)					N cases	Incidence per mio person days	**RR (95%-CI)**	**VE (%) (95% CI)**
Olin 1998 Sweden	Cohort analysis Moderate risk Follow-up to min. age 28 mo	3,5,12 vs. 2,4,6 vs. mo	From 1st dose Up to age >28mo	Group 1: 2,4,6 mo (N=2549) Group 2: 3,5,12 mo (N=18,175)	4 40	1.66 2.35	1 1.42 (0.50 – 2.40	29.6 (-1 – 58.3) 1
			From 9 mo post 1st dose Up to age >28mo	Group 1: 2,4,6 mo (N=2549) Group 2: 3,5,12 mo (N=18,175)	3 16	1.74 1.32	1 0.76 (0.22 – 2.57)	-31.6 (-355 – 61.1) 1
Laboratory-confirmed cases (any cough with culture confirmation)								
			From 1st dose Up to age >28mo	Group 1: 2,4,6 mo (N=2549) Group 2: 3,5,12 mo (N=18,175)	8 63	3.32 3.71	1 1.12 (0.53 – 2.30)	10.7 (-88.7 – 56.5) 1
			From 9 mo post 1st dose Up to age >28mo	Group 1: 2,4,6 mo (N=2549) Group 2: 3,5,12 mo (N=18,175)	4 23	2.32 1.90	1 0.82 (0.28 – 2.33)	-22.0 (-257 – 57.1) 1
Included 10,194 children in 2,4,6 schedule (25% wP = appr. 2549) and 72,698 children in 3,5,12 schedule (25% wP = appr. 18,175)								

Table 8b-A: Included studies on primary vaccination, schedule impact on immunogenicity

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Comparison groups					
Birth dose vs. no birth dose								**Mean concentration of IgG ELISA anti-FHA (units) ***	
Baraff, 1984 USA	RCT Unclear or moderate risk	0,2,4,6 mo vs. 2,4,6 mo	At 4 mo	Group 1: Birth dose (N=10) Group 2: no birth dose (N=13)				60 60	
			At 6 mo	Group 1: Birth dose (N=10) Group 2: no birth dose (N=13)				75 65	
			At 9 mo	Group 1: Birth dose (N=10) Group 2: no birth dose (N=13)				80 95	
								* data extracted from graph	
3,4,5 vs 2,4,6 mo								**GMT (range) of IgG anti-FHA post vaccination**	
Just, 1991 Switzerland, Turkey	Synopsis of two trials High risk	3,4,5 mo vs. 2,4,6 mo	One month after third dose	Group 1 (CH): 3,4,5 mo (N=37) Group (TK): 2,4,6 mo (N=40)				19.1 (<5 – 155) 31.1 (<5 – 493)	
Accelerated vs. long schedule					**Proportion seroconverted or seropositive (%)**			**GMT (95%-CI) post-vaccination**	
					Anti-FHA	**Anti-PT**	**Anti-Fim2/3**	**Anti-FHA**	**Anti-PT**	**Anti-Fim2/3**

Miller, 1997 UK	Cohort analysis of two trials Moderate risk	2,3,4 mo vs. 3,5,9 mo	6 weeks after 3rd dose	Group 1: 2,3,4 mo (N=133) Group 2: 3,5,9 mo (N=154)	120 (90%) 153 (99%)	133 (100%) 153 (99%)	133 (100%) 154 (100%)	5,164 (4,253-6,270) 4,008 (3,500-4,589)	1,439 (1,169-1,770) 407 (310-534)	27,925 (22,284-34,995) 23,388 (19,263-28,397)
			12-18 mo after 3rd dose	Group 1: 2,3,4 mo (N=64) Group 2: 3,5,9 mo (N=70)	59 (92%) 53 (75%)	64 (100%) 64 (100%)	64 (100%) 64 (100%)	1,224 (917-1,634) 1,042 (750-1,449)	185 (142-241) 179 (14-281)	2,636 (2,075-3,348) 4,055 (2,606-6,310)
								GMT (IU/ml)		
								Anti-FHA	**Anti-PT**	**Anti-Fim2/3**
Booy, 1992 UK	Synopsis of two cohort studies Moderate risk	2,3,4 mo vs. 3,5,9 mo	One month post 3rd dose	Group 1: 2,3,4 mo (N=98) Group 2: 3,5,9 mo (N=103)				6,200 (1,200 – 30,900) 7,600 (1,100 – 53,700)	850 (32 – 22,400) 710 (24 – 20,900)	38,900 (4,500 – 339,000) 40,700 (3,200 – 513,000)
					GMT (95% CI) post-immunization					
Accelerated vs. long schedule					**Anti-FHA**	**Anti-PT**		**Anti-Fim2/3**		**Anti-PRN**
Olin 1998 Sweden	Cohort analysis Moderate risk	2,4,6 vs. 3,5,12 mo	1 mo after 3rd dose	Group 1: 2,4,6 mo (N=80) Group 2: 3,5,12 mo (N=63)	34 (28-41) 59 (46-75)	10 (7-14) 13 (9-18)		677 (556-825) 658 (472-917)		150 (120-187) 147 (114-191)
2 vs. 3 doses										
		2,4,6 mo vs. 3,5.	Age 7 mo	Group 1: 2,4,6 mo (N=80) Group 2: 3,5 mo (N=75)	34 (28-41) 17 (14-21)	10 (7-14) 5 (3-7)		677 (556-825) 198 (41-276)		150 (120-187) 49 (38-63)

Tables 8b-B: Additional studies – Primary vaccination, schedule impact on immunogenicity

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Comparison groups	Median titer post-vaccination (50% according to cumulative curve)
2 vs. 3 doses					
Laurell, 1957 (Laurell) Sweden	Cohort Unclear risk	A: 2 doses (no detail) B: 3 doses in intervals 4-6 weeks	One month after last dose (age 7 mo)	A: 2 doses B: 3 doses	320 – 640 640 – 1280
Not per protocol: Agglutinin testing, no further details on method					

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Comparison groups	Proportion with "putatively protective titers" ⩾ 1:320 (%)	Proportion with titers ⩾1:1280 (%)
2 vs. 3 doses						
Bhandari, 1981 India	RCT Low risk	A: 2 doses in 2-mo interval B: 3 doses in 1-mo interval Children aged 3 mo to 5 yrs	1 mo after last dose (=3 mo after first dose)	A : 2 doses (N=80) B : 3 doses (N=82)	100 100	3.75 12.30
Not per protocol: Agglutination method. DTwP produced at Indian laboratory (Central Research Institute), containing $16*10^9$ organisms per dose.						

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Comparison groups	Proportion with demonstrable titer (%)	Ratio	Median titre
2 vs. 3 doses							
Muller, 1984 Kenya	Unblinded RCT Moderate risk (84nblended84ion based on study number)	A: 2 doses in 6-mo interval B: 3 doses in 3-mo interval Children aged ≥3 mo to <6 mo, vaccinated in mass campaigns (rounds)	1 mo after last dose (=7 mo after first dose)	A : 2 doses (N=49) B : 3 doses (N=54)	39/49 (80%) 48/54 (89%)	0.90	1 :96 1 :96
			24-30 mo after last dose	A : 2 doses (N=48) B : 3 doses (N=48)	10/48 (21%) 25/48 (52%)	0.40	1:8 1:28
			39-42 mo after last dose	A : 2 doses (N=50) B : 3 doses (N=50)	8/50 (16%) 30/50 (60%)	0.27	1:8 1:32
			51-54 mo after last dose	A : 2 doses (N=50) B : 3 doses (N=50)	18/50 (36%) 32/50 (64%)	0.56	1:4 1:16
Not per protocol: Microtechnique agglutination testing DTwP produced at RIV, Netherlands							

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Comparison groups	Proportion titers ≥1:40	Proportion with "putatively protective titers" (≥1:80)
2 vs. 3 doses						
Wilkins 1971 USA	RCT Unvaccinated infants (4-8 mo of age)	2 doses at 2-mo interval vs. 3 doses at 1-mo interval (only 0.5 ml doses considered)	21 to 45 days after final dose	A : 2 doses ¨DTP B : 3 doses DTP	104/106 (98.1%) 80/88 (90.9%)	61/88 (69%) 78/106 (74%)

		Short or long interval between 1st and 2nd dose	21 to 45 days after second dose	A (N=166): <30 days B (N=96): 30-59 days C (N=172): 60-89 days D (N=56): ≥90 days	46/57 (81%) 67/80 (84%) 52/59 (88%) 16/16 (100%)	20/57 (35%) 40/80 (50%) 41/59 (69%) 12/16 (75%)
Not per protocol : Quantitative agglutination technique Presented are only schedules with equal dosage per injection; DTP with 9 to 22 units per ml						

Publication and country	**Design Risk of Bias**	**Schedules evaluated**	**Timing of assessment**	**Comparison groups**	**GMT (SEM) post-vaccination (units/ml)**
2 doses at short or long interval 2 vs. 3 doses					
Barkin, 1985 USA (I and II)	Double-blind RCT	Short interval 2,4 mo vs. long interval 2,6 mo	Age 5-6 mo (1-2 mo after 2nd dose)	Group 1: DTwP – DTwP – DT (N=20) Group 2: DTwP – DT – DTwP (N=20) External cohort: DTwP – DTwP – DTwP (N=39)	4.30 (0.32) 2.95 (0.43) 5.10 (0.23)
	(and comparison with comparable cohort)	2 doses vs. 3 doses at 2,4,6 mo	Age 7-8 mo (1-2 mo after 3rd dose)	Group 1: DTwP – DTwP – DT (N=20) Group 2: DTwP – DT – DTwP (N=20) External cohort: DTwP – DTwP – DTwP (N=39)	3.70 (0.40) 5.30 (0.40) 7.51 (0.35)
Not per protocol: Micro-agglutination testing **For 2 vs. 3 doses: comparison between cohorts from "comparable" study; no detail given. (Cf. Barkin 1984, randomized trial on reduced doses, similar protocol)**					

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Comparison groups	GMT (range) of anti-PT neutralizing antibody post vaccination
Later 1-mo vs. earlier 2-month intervals					
Just, 1991 Switzerland, Turkey	Synopsis of two trials High risk	3,4,5 mo vs. 2,4,6 mo	One month after third dose	Group 1 (CH): 3,4,5 mo (N=37) Group (TK): 2,4,6 mo (N=40)	69.0 (<4 – 1024) 44.1 (<4 – 256)
Not per protocol: neutralizing effect of serum antibody on CHO cells					

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Comparison groups	IgG anti-PT GMT (95% CI)	IgG anti-FHA GMT (95% CI)
Accelerated vs. long schedule						
Miller, 1995 UK	Synopsis of two cohorts High risk	A: 2,3,4 mo B: 3,5,10 mo	Post 3rd dose	A: 2,3,4 mo B: 3,5,10 mo	574 (454 – 726) 1538 (1273-1859)	4027 (3393 – 4781) 5675 (4846 – 6647)
Not per protocol: Synopsis of two cohorts (from two trials), no details on trials reported						

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Comparison groups	GMT (95%-CI) post-vaccination
Accelerated vs. long schedule				87	**FHA antibody (arbitrary units/ml)**
Ramsay, 1993 (II) UK	Comparison of two comparable cohorts	2,3,4 mo vs. 3,4.5-5, 8.5-11mo	After 12 months after 3rd dose	Group 1: accelerated (N=14), median age 20 mo (range 17-24) Group 2: long schedule (N=25), mean age 22 mo (range 20-26)	0.014 (0.008 – 0.026) 0.016 (0.011 – 0.023)
		2,3,4 mo By actual age of first dose	6-8 months after 3rd dose (median age 7 mo, range 6-9)	Group 1: 8 - <10 wks Group 2: 10 - <12 wks Group 3: 12 - <16 wks	0.033 (0.019 – 0.058) 0.088 (0.046 – 0.137) 0.028 (0.013 – 0.063)
Not per protocol: Solid-phase RIA (but mentions "good correlation with ELISA") **Samples not taken at same age or interval after 3rd dose. Data from a third cohort was not included at all, as assessment at 18 vs. 11 mo of age in groups.**					

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Comparison groups	Mean antibody titer (SD) (PAU/ml)
Early (5mo) vs late third dose (10mo)					
Conway 1993 UK	RCT Unclear risk Preterm babies 32-35 gestational week	A/B: 3,4,5 mo C: 3,4,10 mo *B: see booster*	One month after 3rd dose	A/B: last interval 1 mo (N=11 and 14) C: last interval 6 mo (N=10)	21.74 (7.57) and 30.39 (44.33) 44.91 (40.28)
			Age 19 mo	A: last interval 1 mo (N=6) C: last interval 6 mo (N=10)	7.13 (4.52) 11.19 (8.05)
Not per protocol: Unit of reporting: Pertussis antibody units, all antigens combined					

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Comparison groups	Proportion titers ≥1:40	Proportion with putatively protective titers (≥1:80)
Various age at first dose, interval between doses, number of doses						
Wilkins 1987 USA	Cohort Age 4 weeks to 8 months High risk	Age at first primary dose	One month post 1st dose	A: 4-11 wks B: 12-19 wks C: 20+ wks	3/36 (8.3%) 26/126 (20.6%) 13/28 (46.4%)	0/36 (0%) 1/126 (0.8%) 1/28 (3.6%)
			Two months post 1st dose	A: 4-11 wks B: 12-19 wks C: 20+ wks	4/21 (19.0%) 23/56 (41.1%) 6/22 (17.4%)	3/21 (14.3%) 2/56 (3.6%) 0/22 (0%)
		Interval 1st – 2nd dose	One month post 2nd dose	First dose at 4-11 wks A: 3-7 weeks interval B: 8+ weeks interval	 28/40 (70.0%) 27/34 (79.4%)	 13/40 (32.5%) 18/34 (52.9%)
				First dose at 12-19 wks A: 3-7 weeks interval B: 8+ weeks interval	 72/78 (92.3%) 57/60 (95.0%)	 35/78 (44.9%) 42/60 (70.0%)
				First dose at 20+ wks A: 3-7 weeks interval B: 8+ weeks interval	 11/12 (91.7%) 18/18 (100%)	 6/12 (50%) 15/18 (83.3%)
					≥4-fold increase pre-post booster	
		2-dose vs 3-dose schedule (not further specified)	One month post booster dose (given 6-16+ months after last primary)	A: 2-dose schedule B: 3-dose schedule	6/20 (30.0%) 4/24 (16.7%)	
Not per protocol: Microtechnique for measuring pertussis agglutinins; not clear how 2- and 3-dose groups were assigned (cf Wilkins 1971; different dosages?) Partially purified pertussis vaccine						

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Comparison groups	GMC of IgG (IU/ml) (95% confidence interval)	Percentage with putatively protective titers (95%-CI) (%)
Various age at first dose, interval between doses						
Wong, 2008 Malaysia	RCT Low and unclear risk	1.5,3,5 vs. 3,4,5 mo	Age 6 mo (1 mo after last primary dose)	Group 1: 1.5,3,5 months (N=102) Group 2: 3,4,5 months (N=103)	110.0 (98.4 – 122.9) 63.6 (56.0 – 72.2)	100.0 (96.4 – 100.0) 98.1 (93.2 – 99.8)
			Age 12 mo (7 mo after last primary dose)	Group 1: 1.5,3,5 months (N=82) Group 2: 3,4,5 months (N=89)	13.5 (11.6 – 15.6) 17.9 (15.3 – 20.9)	47.6 (36.4 – 58.9) 62.9 (52.0 – 72.9)
Not per protocol: schedules delivered with different vaccine products (DTwP-HepB vs. DTwP) Cut-off for putatively protective titers: ⩾15 EL. U/ml						

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Comparison groups	GMT	Percentage with titers ≥1:10 (%)
2+1 vs. 3+1 schedule						
Swartz 1985 Israel	Cohort Moderate to high risk	2, 3.5, 10 vs. 2,4, 6, 12 mo	At booster (10/12 mo)	Group 1: 2,3.5,10 mo (N=79) Group 2: 2,4,6,12 mo (N=92)	138.0 256.0	97.9 100
			1 mo post booster	Group 1: 2,3.5,10 mo (N=79) Group 2: 2,4,6,12 mo (N=92)	594.5 844.5	100 100
			2 yr post booster	Group 1: 2,3.5,10 mo (N=79) Group 2: 2,4,6,12 mo (N=92)	177.5 343.0	100 100
Not per protocol: seroagglutination microtitration technique						

Table 8c-A: Included studies on primary vaccination, schedule impact on reactogenicity

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Details	Comparison groups	Risk per 100 injections (%)	Relative Risk
Accelerated vs. long schedule							
Rectal T°≥38.0°C							
Miller, 1997 UK	Cohort analysis of two trials Moderate to high risk	2,3,4 mo vs. 3,5,9 mo	Within 24h, any dose	Rectal T°≥100.4°F Rectal T°≥38.0°C	Group 1: 2,3,4 mo (N=412) Group 2: 3,5,9 mo (N=523)	11.2 12.1	0.93
Axillary T°≥37.2°C							
Ramsay, 1992 UK	Analysis of two cohorts Moderate to high risk	2,3,4 mo vs. 3, 4.5-5, 8.5-11 mo	On second evening after vaccination	Doses $1^{st} – 2^{nd} – 3^{rd}$ Doses $1^{st} – 2^{nd} – 3^{rd}$	Group 1: 2,3,4 mo (N=107) Group 2: 3,5,10 mo (N=115)	22 – 25 – 23 23 – 35 – 52	0.96 – 0.71 – 0.44
Erythema / redness ≥2.5cm							
Miller, 1997 UK	Cohort analysis of two trials Moderate to high risk	2,3,4 mo vs. 3,5,9 mo	Within 24h, any dose		Group 1: 2,3,4 mo (N=412) Group 2: 3,5,9 mo (N=523)	3.9 21.6	0.18
Ramsay, 1992 UK	Analysis of two cohorts Moderate to high risk	2,3,4 mo vs. 3, 4.5-5, 8.5-11 mo	On second evening after vaccination	Doses $1^{st} – 2^{nd} – 3^{rd}$ Doses $1^{st} – 2^{nd} – 3^{rd}$	Group 1: 2,3,4 mo (N=107) Group 2: 3,5,10 mo (N=115)	18 – 17 – 26 13 – 31 – 52	1.38 – 0.55 – 0.50

Local swelling ≥2.5cm							
Miller, 1997 UK	Cohort analysis of two trials Moderate to high risk	2,3,4 mo vs. 3,5,9 mo	Within 24h, any dose		Group 1: 2,3,4 mo (N=412) Group 2: 3,5,9 mo (N=523)	3.6 22.3	0.16
Ramsay, 1992 UK	Analysis of two cohorts Moderate to high risk	2,3,4 mo vs. 3, 4.5-5, 8.5-11 mo	On second evening after vaccination	Doses 1st – 2nd – 3rd Doses 1st – 2nd – 3rd	Group 1: 2,3,4 mo (N=107) Group 2: 3,5,10 mo (N=115)	32 – 26 – 30 14 – 27 – 50	34.0 – 0.96 – 0.60
≥3 systemic symptoms							
Miller, 1997 UK	Cohort analysis of two trials Moderate to high risk	2,3,4 mo vs. 3,5,9 mo	Within 24h, any dose		Group 1: 2,3,4 mo (N=412) Group 2: 3,5,9 mo (N=523)	18.4 22.9	0.80
≥3 symptoms							
Ramsay, 1992 UK **2 vs. 3 doses**	Analysis of two cohorts Moderate to high risk	2,3,4 mo vs. 3, 4.5-5, 8.5-11 mo	On second evening after vaccination	Doses 1st – 2nd – 3rd Doses 1st – 2nd – 3rd	Group 1: 2,3,4 mo (N=107) Group 2: 3,5,10 mo (N=115)	26 – 22 – 18 24 – 28 – 27	1.08 – 0.79 – 0.67
Barkin, 1985 **USA** **(II)**	Double-blind RCT	DTwP at 2,6 mo vs. 2,4,6 mo	Within 24 h after vaccination at 6 mo	Febrile response (>37.9°C)	Group 1: 2,6 mo (N=26) Group 2: 2,4,6 mo (N=38)	57.7 51.3	1.12
				Behavioral changes (crying)	Group 1: 2,6 mo (N=26) Group 2: 2,4,6 mo (N=38)	73.1 61.5	1.19
				Local reactions (redness, swelling, tenderness)	Group 1: 2,6 mo (N=26) Group 2: 2,4,6 mo (N=38)	76.9 71.8	1.07

2 doses in 2- vs. 4-mo interval							
		2-4-6 mo DTwP-DTwP-DT DTwP-DT-DTwP	Within 24 h after 2nd wP dose (age 4 vs. 6 mo)	Febrile response (>37.9°C)	Group 1: 2,4 mo (N=18) Group 2: 2,6 mo (N=20)	55.6 55.0	1.01
				Behavioral changes (crying)	Group 1: 2,4 mo (N=18) Group 2: 2,6 mo (N=20)	61.1 50.0	1.22
				Local reactions (redness, swelling, tenderness)	Group 1: 2,4 mo (N=18) Group 2: 2,6 mo (N=20)	83.3 80.0	1.04

Tables 8c-B: Additional studies – Primary vaccination, schedule impact on reactogenicity

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Comparison groups	Symptom	Risk (%)	Relative Risk
Birth dose vs. no birth dose							
Baraff, 1984 USA	RCT Unclear or moderate risk	0,2,4,6 mo vs. 2,4,6 mo	Any dose (?)	Group 1: birth dose (N=10) Group 2: no birth dose (N=13)	Redness, swelling or pain	18.2 16.7	1.10
Not per protocol: Only combined reactions reported							

Publication and country	Design Risk of Bias	Schedules used	Timing of assessment	Comparison groups	Symptom	Risk (%)
2 vs 3 doses						
Bhandari 1981 India	Unblinded RCT Unclear or high risk	2 doses (2-mo interval) and 3 doses (1-mo interval), combined	Not specified	Evaluation of children with reaction in both groups combined 1st doses (N=162) 2nd doses (N=162) 3rd doses (N=82)	Local reaction	 8.64 13.58 9.76
				1st doses (N=162) 2nd doses (N=162) 3rd doses (N=82)	Pyrexia	20.99 20.37 30.49
Not per protocol: Outcomes not further defined. No comparison between schedules, only by serial dose number.						

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Comparison groups	Symptom	Risk (%)
Various age at first dose, interval between doses						
Wong, 2008 Malaysia	RCT Moderate risk (94nblended)	1.5,3,5 vs. 3,4,5 mo	Within 4 days following vaccination	Group 1: 1.5,3,5 months (N=103) Group 2: 3,4,5 months (N=103)	Pain	45% 47%
				Group 1: 1.5,3,5 months (N=82) Group 2: 3,4,5 months (N=89)	Redness	30% 30%
					Swelling	25% 23%
					Drowsiness	37% 35%
					Irritability	42% 45%
					Loss of appetite	25% 35%
					Fever ≥37.5°C	47% 35%
Not per protocol: schedules delivered with different vaccine products (DTwP-HepB vs. DTwP) Data visually extracted from graph.						

Table 9a-A: Included studies on primary vaccination, absolute vaccine effectiveness/efficacy

Publication and country	Design Risk of bias	Schedule used	Timing of assessment	Comparison groups				
Old WHO definition: ≥21 days of paroxysmal cough with evidence of *B. pertussis* infection (culture, serology) or epi-link					**N Cases**	**Denominator**	**Rate**	**VE % (95%-CI)**
Gustafsson, 1996 Sweden	RCT Low risk	2, 4, 6 mo	From day of 3rd doses	Group 1:DTwP Group 2: DT	148 371	3712.0 4786.2 person- yrs	4.0 7.8 (per 100 p-mo)	48.3 (37.0-57.6)
Note: Serological confirmation: two-fold increase of IgG anti-PT of anti-FHA			From day of 1st dose	Group 1: DTPwP Group 2: DT	159 385	4503.2 5603.1 person- yrs	3.5 6.9	48.3 (37.3-57.3)
Greco, 1996 Italy	RCT Low risk	2, 4, 6 mo	From 30 days post 3rd dose	Group 1: DTwP Group 2: DT	141 74	2,262,810 758,646 person-days	2.2 3.5 (per 100 p-yrs)	36.1 (14.2-52.1)
			From day of 1st dose	Group 1: DTwP Group 2: DT	162 81	3,062,822 1,010,145	1.9 2.9	34.0 (12.8-49.8)
					Cases (%)	**Total (%)**	**VE % (95%-CI)**	
Simodon, 1997 Senegal	HH contact cohort Moderate to high risk	2, 4, 6 mo	Surveillance in population during up to 4 years, HH contacts	Group 1: DTwP Group 2: no vaccination	7 8	190 17	92 (81 – 97)	
Note: Serological confirmation: two-fold increase of IgG anti-PT of anti-FHA			RR from proportional hazard model	Group 1: DTwP Group 2: no vaccination			91 (81 – 96)	

					N Cases	**Rate per 100 p-yrs**	**VE % (95%-CI)**
Stehr, 1998 Germany	Cohort Moderate risk	3, 4.5-6, 15-18 mo (DTwP)	Surveillance from 6 mo of age during up to 3 years	Group 1: DTwP Group 2: DT	18 91	0.2 3.0	93 (89 – 96)
Note: Definition modified for translation of term "paroxysmal"; serological confirmation: significant increase of IgG or IgA concentrations against anti-PT, anti-FHA or anti-Fim							
Liese, 1997 Germany	Case control Moderate risk	2, 4, 6 mo	Children aged <2 years	Group 1: DTwP Group 2: no wP vaccination		Adjusted VE	96 (71 – 100)
Schmitt, 1996 Germany	HH contact cohort Moderate risk	3,4,5 mo	Not detailed, probably <4 yrs	Group 1: 3 doses of DTwP Group 2: 0 doses of wP			97.6 (83.1 – 99.7)

Publication and country	**Design Risk of bias**	**Schedule used**	**Timing of assessment**	**Comparison groups**	**N Cases**	**Person-days**	**VE % (95%-CI)**
2010 WHO definition: ≥14 days of paroxysmal cough with evidence of *B. pertussis* infection (culture, serology, PCR)							
Greco, 1996 Italy	RCT Low risk	2, 4, 6 mo	30 days post 3rd dose	Group 1: DTwP Group 2: DT	167 82	2,262,810 758,646	31.7 (9.9 – 47.9)

Publication and country	Design Risk of bias	Schedule used	Timing of assessment	Comparison groups	N Cases	Household contacts	VE % (95%-CI)
2010 WHO definition of clinical case (≥14 days of paroxysmal cough) or CDC definition of confirmed case (⩾14 days of cough with paroxysm and epilink)							
Onorato, 1992 USA	HH contact cohort Unclear or moderate risk	not specified (probably 2, 4, 6 mo + 12-18 mo)	Age 1 to 4 years	Group 1: ≥3 doses of DTwP Group 2: 0 doses of DTwP	11 3	144 6	85 (59 – 94)
				1 vs. 0 doses (N=20 vs. 15)			36
				2 vs. 0 doses (N=21 vs. 15)			49
				3 vs. 0 doses (N=103 vs. 15)			83
				≥4 vs. 0 doses (N=188 vs. 15)			83

Publication and country	Design Risk of bias	Schedule used	Timing of assessment	Comparison groups	Vaccination status		
CDC definition of confirmed case or of clinical case with laboratory confirmation					**Cases (%)**	**Controls (%)**	**VE % (95%-CI)**
Izurieta, 1996 USA	Case control study (age-matching) High risk	0 to 3 doses, given at 2, 4, 6 months (+booster at 12-18 mo)	During outbreak, children <7 months of age	Reference : 0 dose Exposure 1 : 1 dose Exposure 2 : 2 doses Exposure A: up to date for age Exposure B: delayed immunization	22 (56) 15 (38) 2 (5) 34 (87) 5 (13)	56 (48) 33 (34) 7 (7) 85 (89) 13 (14)	- 60 (-350 – 40) -20 (-700 – 20) 30 (-140 – 80) 20 (-170 – 70)

Bisgard, 2005 USA	Case-control study (matching for age and residence) Moderate risk	2,4,6 mo (+12-18 mo)	Age 6-59 months	Reference : 0 dose Exposure : 3 doses DTwP	not reported 8 (17)	not reported 53 (18)	95.5 (87.3 – 98.4)
				Reference: 0 dose Exposure : 4 doses DTwP	not reported 25 (40)	not reported 160 (32)	96.7 (91.9 – 98.7)

Publication and country	**Design Risk of bias**	**Schedule used**	**Timing of assessment**	**Comparison groups**	**N cases**		**VE % (95%-CI)**
CDC definition of culture-confirmed case (cough of any duration/⩾1 day)							
Guris, 1997 USA	Screening method Limited validity	2, 4, 6 mo + 12-18 mo	Age 7-47 mo	3 vs. 0 doses ≥4 vs. 0 doses	362 229		79 (74 – 83) 90 (88 – 92)

Publication and country	**Design Risk of bias**	**Schedule used**	**Timing of assessment**	**Comparison groups**				
Diagnosis by physician, independently from laboratory confirmation					**N Cases**	**Person-months**	**Rate per 1000 person-mo**	**VE (%) (95%-CI)**
Anonymous, 1951 UK	RCT Moderate risk	3 doses in 1 mo-interval, age 6-18 mo	Follow-up over up to 23 to 30 months	Group 1: wP Group 2: "anti-catarrhal vaccine"	149 687	102,961 102,180		79 (75 – 82)
			10 trials grouped by vaccine type	Vaccine 1 Vaccine 2 Vaccine 3 (adsorbed) Vaccine 4 (adsorbed) Vaccine 5 unvaccinated				61 (41 – 74) 86 (78 – 92) 69 (53 – 80) 72 (63 – 79) 91 (85 – 94)

			Among children having home exposure, by age group	<5 mo 6-11 mo 12-17 mo 18-23 mo >=24 mo				84 (69 – 91) 76 (58 – 87) 82 (64 – 92) 73 (48 – 86) 75 (43 – 89)
					N Cases	**Person-months**	**Rate per 1000 person-mo**	**VE (%) (95%-CI)**
Laurell, 1957 Sweden	Cohort study High risk	3 doses (in 4-6 wk interval, infants and toddlers)	Follow-up over up to 5 years	Group 1: DTwP Group 2: no vaccination	9 55	15,898 11,964	0.6 4.6	87.7 (75.1 – 93.9)
					N Cases	**Total household contacts**	**Attack proportion**	**VE (%) (95%-CI)**
PHLSWC, 1969 UK	Household contact cohort High risk	3 doses (3,5,10 mo?)	Age <5 yrs After household exposure	Group 1: wP Group 2: not vaccinated	102 154	195 223	52.3 69.1	24.3 (11.1 – 35.5)
					N Cases	**Person-years**	**Rate per 100 person-yrs**	**VE (%) (95%-CI)**
Kendrick, 1939 USA	Cohort study High risk	Four doses in weekly interval, starting 8 mo to 4 yrs (5yrs in early phase) Old vaccine preparation	Up to 44 months	Group 1: wP Group 2: no wP	52 348	2268 2307	2.3 15.1	84.8 (79.8 – 88.6)
	Household contact study			Group 1: wP Group 2: no wP	29 143	83 160	34.9 89.4	60.9 (47.3 – 71.0)
						N Cases		**VE (%) (95%-CI)**
Bassili, 1976 UK	Similar to screening method Limited validity	Not specified (3,5,10 mo?)	Up to 5 years	Estimate based on vaccine coverage among cases and population		76	<1 yrs	∞
						51	1-<2 yrs	89 (75 – 95)

						42	2-<3 yrs	72 (48 – 85)
						46	3-<4 yrs	67 (41 – 82)
						31	4-<5 yrs	52 (3 – 76)
							All ages combined	72 (64 – 79)
Guris, 1997 USA	Screening method Limited validity	2, 4, 6 mo + 12-18 mo	Age 7-47 mo	3 vs. 0 doses ≥4 vs. 0 doses	864 772			82 (79 – 85) 92 (90 – 93)
Publication and country	Design Risk of bias	Schedule used	Timing of assessment	Comparison groups			VE (%) (95%-CI)	
Clinical case with ≥21 days of paroxysmal cough							**Non-epidemic period**	**Epidemic period**
Ramsay, 1993 (I) UK	Screening method High risk	3,5,10 (old UK)	1-4 yrs	Group 1: 3 doses wP Group 2: no wP			94 (91 – 96)	89 (85 – 92)

Publication and country	**Design** **Risk of bias**	**Schedule used**	**Timing of assessment**	**Comparison groups**	N	N cases	Incidence (per yr)	**VE (%)**
Clinical case with ≥21 days of paroxysmal cough								
Jenkinson 1988 UK	Cohort Moderate to high risk	3,5,10 (old UK)	Age 1-4 yrs	Group 1: 3 doses wP Group 2: no wP	4128 1542	35 173	0.008 0.112	92.9
			Age 1 yr	Group 1: 3 doses wP Group 2: no wP	986 45	0 35	0 0.083	100
			Age 2 yr	Group 1: 3 doses wP Group 2: no wP	993 499	3 33	0.003 0.071	96
			Age 3 yr	Group 1: 3 doses wP Group 2: no wP	1036 545	16 67	0.016 0.140	89
			Age 4 yr	Group 1: 3 doses wP Group 2: no wP	1113 453	16 38	0.015 0.092	84

Tables 9a-B: Additional studies – Primary vaccination, absolute vaccine effectiveness/efficacy

Publication and country	Design Risk of bias	Schedule used	Timing of assessment	Comparison groups	N Cases	Risk (%)	VE (%) (95%-CI)
Laboratory confirmed (culture, serological), irrespective of symptoms; or not laboratory-confirmed but <4 wks cough, whoops or vomiting, combined with physician diagnosis of pertussis our epidemiological link							
Blennow, 1988 (II) Sweden	Unblinded RCT Moderate to high	2,3,4 mo	Age 6-11 mo	Group 1: wP (N=525) Group 2: no vaccination (N=615)	2 21	0.4 3.4	88.8 (52.6 – 97.3)
			Age 12-17 mo	Group 1: wP (N=523) Group 2: no vaccination (N=594)	3 12	0.6 2.0	71.6 (0.0 – 92.3)
			Age 18-23 mo	Group 1: wP (N=520) Group 2: no vaccination (N=582)	3 14	0.6 2.4	76.0 (17.0 – 93.1)
			Total follow-up	Group 1: wP (N=525) Group 2: no vaccination (N=615)	8 47	1.5 7.6	80.1 (58.2 – 90.5)
Laboratory-confirmed cases (culture, serology), irrespective of symptoms							
				Group 1: wP (N=525) Group 2: no vaccination (N=615)	8 32	1.5 5.2	71 (37 – 86)
Coughing for ⩾4 weeks							
				Group 1: wP (N=525) Group 2: no vaccination (N=615)	2 32	6 3569	93 (72 – 98)
Not per protocol: Case definition not allowing grouping with other studies							

Publication and country	Design Risk of bias	Schedule used	Timing of assessment	Comparison groups	N Cases	VE (%) (95%-CI)
Laboratory confirmed (culture, PCR), irrespective of symptoms						
Campbell, 2012 UK	Screening method High risk	2,3,4 mo Booster given exceptionally	Age 12-39 mo	≥3 doses vs. 0 doses wP	52 cases, of which 25 were vaccinated	97.7 (95.9 – 98.7)
			Age 40-59 mo	≥3 doses vs. 0 doses wP	57 cases, of which 38 were vaccinated	95.7 (92.2 – 97.6)
	Includes		Age 9 wks - <6	1 vs. 0 doses		62 (53 – 69)

	serological diagnosis		mo			
				2 vs. 0 doses		85 (77 – 91)
				3 vs. 0 doses		95 (86 – 99)
Not per protocol: Case definition not allowing grouping with other studies						
Laboratory confirmed (culture), irrespective of symptoms						
White 1996 UK	Screening method High risk	2,3,4 mo	Age 6 – 11mo	3 vs. 0 doses wP	13 cases, of which 4 were fully vaccinated	96 (87 – 99)
			Age 1 – 4 yrs	3 vs. 0 doses wP	83 cases, of which 33 were fully vaccinated	93 (89 – 96)
Not per protocol: Case definition not allowing grouping with other studies						

Publication and country	**Design Risk of bias**	**Schedule used**	**Comparison groups**	**Alternative case definitions**	**Analysis**	**VE % (95%-CI)**
Simodon, 1997 Senegal	Household contact cohort High risk	2, 4, 6 months	Group 1: DTwP Group 2: no vaccination	Old WHO definition with PCR diagnostic of epilink	Case-contact analysis	96 (86 – 99)
				≥21 days of cough with evidence of *B. pertussis* infection (culture, serology)	Case-contact analysis	55 (38 – 68)
				≥21 days of cough with evidence of *B. pertussis* infection (culture, serology)	RR from proportional hazard model	66 (46 – 78)
				≥21 days of cough with evidence of *B. pertussis* infection (culture, serology) with PCR diagnostic of epi link	Case-contact analysis	74 (55 – 85)
Not per protocol: Case definition no allowing grouping with other studies Note: Serological confirmation: two-fold increase of IgG anti-PT of anti-FHA						

Publication and country	Design Risk of bias	Schedule used	Timing of assessment	Comparison groups			
Laboratory confirmed epi-link, clinically suspected cases (cough with paroxysm, whooping or vomiting, of any duration)					**N Cases**	**N Contacts**	**VE (%) (95%-CI)**
Broome, 1981 USA	Household contact cohort Moderate risk	Up to 5 doses until age 5 years (schedule not specified, probably 2, 4, 6 mo + 12-18 mo)	Up to 5 years after primary vaccination 7-28 days after household exposure Age 0-<1yr	Group 1: 1-2 doses wP Group 2: 0 doses wP	3 8	4 9	15.6 (-55.5 – 54.2)
			Age 1-5 yr	Group 1: 3-5 doses wP Group 2: 0 doses wP	10 5	22 5	54.6 (28.2 – 71.2)
			Age 1-5 yr	Group 1: 1-2 doses wP Group 2: 0 doses wP	4 5	9 5	55.6 (7.7 – 78.6)
Onorato, 1992 USA	HH contact cohort Unclear or moderate risk	Not specified (probably 2, 4, 6 mo + 12-18 mo)	Age 1 to 4 years	Group 1: ≥3 doses of DTwP Group 2: 0 doses of DTwP	16 3	144 6	78 (44 – 91)
Epi-link, definition not specified (national reporting system, CDC)							
Brink 1982 USA	Household contact cohort High risk	2,4,6 mo + 12-18 mo	0-4 yrs	Group 1: ≥3 doses Group 2: 0 doses	13 19	95 27	80.6 (65.9 – 88.9)
				Group 1: 2 doses Group 2: 0 doses	6 19	21 27	59.4 (16.7 – 80.2)
				Group 1: 3 doses Group 2: 2 doses	13 6	95 21	38.4 (-46.7 – 74.1)

Publication and country	Design Risk of bias	Schedule used	Timing of assessment	Comparison groups	N Cases	N Contacts	VE (%) (95%-CI)
Laboratory confirmed epi-link, clinically suspected cases (any cough of any duration)							
PHLSWC, 1982 UK	Household contact cohort High risk	3 doses starting at 3-6 mo (3,5,10 mo?)	Up to 6 years after vaccination >1 week after household exposure Age 0-<1yr	Group 1: DTwP Group 2: DT	12 34	28 56	29 (-14 – 56)
			Age 1-<2 yr	Group 1: DTwP Group 2: DT	35 316	108 399	59 (46 – 69)
			Age 2-<3 yr	Group 1: DTwP Group 2: DT	36 299	97 384	52 (38 – 63)
			Age 3-<4 yr	Group 1: DTwP Group 2: DT	34 170	108 284	47 (29 – 61)
			Age 4-<6 yr	Group 1: DTwP Group 2: DT	92 165	476 428	50 (38 – 60)
Onorato, 1992 USA	HH contact cohort Unclear or moderate risk	Not detailed (probably 2, 4, 6 mo + 12-18 mo)	Age 1 to 4 years	Group 1: ≥3 doses of DTwP Group 2: 0 doses of DTwP	44 5	144 6	63 (43 – 76)

Publication and country	Design Risk of bias	Schedule use	Timing of assessment	Comparison groups	N Cases	Rate per 100 p-yrs	VE % (95%-CI)
Stehr, 1998 Germany	Cohort, Moderate risk	3, 4.5-6, 15-18 mo (DTwP)	Surveillance from 6 mo of age during up to 3 years				
≥14 days of paroxysmal cough, due to *B. pertussis* or *B. parapertussis* Note: Serological confirmation: significant increase of IgG or IgA concentrations against any of the four pertussis antigens				Group 1: DTwP Group 2: DT	54 104	0.6 3.5	82 (75 – 87)
≥7 days of paroxysmal cough (mild or typical pertussis), due to *B. pertussis* (excluding *B. parapertussis*) Note: Serological confirmation: significant increase of IgG or IgA concentrations against anti-PT				Group 1: DTwP Group 2: DT	50 103	0.6 3.4	83 (76 – 88)
≥7 days of paroxysmal cough (mild or typical pertussis), due to *B. pertussis* or *B. parapertussis* Note: Serological confirmation: significant increase of IgG or IgA concentrations against any of the four pertussis antigens				Group 1: DTwP Group 2: DT	132 130	1.5 4.4	64 (55 – 72)

Publication and country	Design Risk of bias	Schedule used	Timing of assessment	Comparison groups	% vaccinated	VE (%) (95%-CI)
Definition combines paroxysmal cough with the following **- Duration ≥21 days with whoop** **- Whoop and lymphocytosis** **- paroxysmal cough of any duration with culture confirmation** **- paroxysmal cough of any duration with fourfold risk of antibody (type not defined)**						
Walker, 1981 UK	Case control study High risk	3 doses, schedule not known, vaccine not known	Age 6 mo to 5 years	Group 1: pertussis cases (N=327) Group 2: measles cases (N=164)	11.9% 71.3%	94.6 (91.0 – 96.7) Fully vs. unvaccinated
		1-2 doses, schedule not known		Group 1: pertussis cases (N=325) Group 2: measles cases (N=56)	11.4% 16.1%	32.9 (-68.7 – 70.6) Partially vs. unvaccinated
Not per protocol: Case definition no allowing grouping with other studies						

Publication and country	Design Risk of bias	Schedule used	Timing of assessment	Comparison groups	N Cases	Denominator	Rate	VE % (95%-CI)
≥21 days of cough with culture confirmation of *B. pertussis* infection (culture, serology) or epi-link with laboratory-confirmed household case								
Liese, 1997 Germany	Case control Moderate risk	2, 4, 6 mo	Children aged <2 years	Group 1: DTwP Group 2: no wP vaccination		Adjusted VE	95 (81 – 99)	
Not per protocol: Case definition no allowing grouping with other studies								

Table 9b-A: Included studies on primary vaccination, absolute immunogenicity

Publication and country	Design Risk of Bias	Schedule used	Timing of assessment	Comparison groups	anti-FHA	anti-PT	anti-PRN	anti-FHA	anti-PT	anti-PRN
2, 4, 6 months					**Proportion seropositive (%)**			**GMC (95%-CI) Post-vaccination (EU/ml)**		
Giuliano, 1998 Italy *[overlap with participants of Greco 1996]*	RCT Low risk	2, 4, 6 mo	1 mo after 3rd dose (age 7 mo)	Group 1: DTwP (N=449)	36.5	4.2	47.7	5.0 (4.7-5.8)	1.2 (1.1-1.3)	9.8 (8.6-11.3)
				Group 2: DT (N=161)	--	--	--	1.5 (1.3-1.6)	1.0 (1.0-1.1)	1.6 (1.6-1.7)
			15 mo after 3rd dose (age 21 mo)	Group 1: DTwP (N=332)	7.8	2.4	10.5	1.6 (1.4-1.8)	1.1 (1.1-.2)	2.3 (2.1-2.5)
				Group 2: DT (N=127)	--	--	--	1.2 (1.0-1.3)	1.1 (1.0-1.2)	1.6 (1.5-1.7)
					Proportion seroconverted (%)					
Greco, 1996 Italy	RCT Low risk	2, 4, 6 mo	(Pre-vaccination and) 1 month (?) post 3rd dose	Group 1: DTwP	13.1	4.2	37.9	5.2 (4.7-5.8)	1.2 (1.1-1.3)	9.9 (8.6-11.3)
				Group 2: DT [N=1572 in four study groups]	--	--	--	1.5 (1.3-1.6)	1.0 (1.0-1.1)	1.6 (1.6-1.7)

					Proportion with IgG ≥ 1 unit /ml (%)				Median IgG concentration (units/ml)			
					anti-FHA	anti-PT	anti-PRN	anti-Fim2/3	anti-FHA	anti-PT	anti-PRN	anti-Fim2/3
Gustafsson, 1997 Sweden	RCT Low risk	2, 4, 6 mo	1 mo after 3rd dose (age 7 mo)	Group 1: DTwP	100	60	95	78	10	1.5	13	12
				Group 2: DT [N=689 in total]	48	42	15	35	<1	<1	<1	<1

Tables 9b-B: Additional studies – Primary vaccination, absolute immunogenicity

Publication and country	Design Risk of Bias	Schedule used	Timing of assessment	Comparison groups	PT-neutralizing antibody Seropositive (%)	PT-neutralizing antibody GMT (EU/ml) (95%-CI) post-vaccination
2, 4, 6 months						
Giuliano, 1998 Italy *[overlap with participants of Greco 1996]*	RCT Low risk	2, 4, 6 mo	1 mo after 3rd dose (age 7 mo)	Group 1: DTwP (N=237) Group 2: DT (N=81)	1.7 --	23.0 (21.4-24.6) 22.0 (20.2-23.9)
			15 mo after 3rd dose (age 21 mo)	Group 1: DTwP (N=176) Group 2: DT (N=60)	0.6 --	21.4 (20.2-22.7) 21.2 (18.8-23.7)
Greco, 1996 Italy	RCT Low risk	2, 4, 6 mo	(Prevaccination and) 1 month (?) post 3rd dose	Group 1: DTwP Group 2: DT [N=1572 in four study groups]	1.7 --	23.0 (21.4-24.6) 22.0 (20.2-23.9)
Not per protocol: Measurement of neutralizing antibody titre						

Publication and country	Design Risk of Bias	Schedule used	Timing of assessment	Comparison groups	Proportion with ⩾4-fold rise in titers (%)	Median post-vaccination
2 wP doses at 3-mo interval vs. no wP						
Mc Bean, 1978 Cameroon	RCT Low risk	2 doses at 3-mo interval ; first dose at age 9-36 mo	3 mo post 1st dose	Group 1: DTwP (N=91) Groups 2-4: other non-pertussis vaccines (N=277)		207 188, 143, and 169
			1 mo post 2nd dose	Group 1: DTwP (N=91) Groups 2-4: other non-pertussis vaccines (N=277)	14.4 2.22, 2.0, 4.3	296 172, 151, and 178
Not per protocol: "Micromethod" for serological testing						

Publication and country	Design Risk of Bias	Schedule used	Timing of assessment	Comparison groups	GMT (agglutinin titer)
2 wP doses at 6-mo interval vs. no wP					
Mangay-Angara 1978 Philippines	Clinical trial with not specified allocation Unclear risk	2 doses at 6-mo interval ; first dose at age 6-8 mo	40 days post 2nd dose	Group 1: DTwP (N=115) Group 2: D (N=122)	85 <40
Not per protocol: Microagglutination for serological testing					

Table 9c-A: Included studies on primary vaccination, absolute reactogenicity

Publication and country	Design Risk of Bias	Schedule used	Timing of assessment	Comparison groups	N Events	Denominator	Risk (% or per N doses)	Relative Risk (95%-CI)
Temperature ≥38.0°C								
Gustafsson, 1996 Sweden	RCT Moderate bias	2, 4, 6 months	Within 24 hours post-dose 1	Group 1:DTwP Group 2: DT	1519 196	2102 children 2574 children	72.3 7.6	9.5 (8.3 – 10.8)
			Within 24 hours post-dose 2	Group 1:DTwP Group 2: DT	1515 470	2040 children 2555 children	74.3 18.4	4.0 (3.7 – 4.4)
			Within 24 hours post-dose 3	Group 1:DTwP Group 2: DT	1302 561	2001 children 2538 children	65.1 22.1	2.9 (2.7 – 3.2)
			Within 24 hours after any dose	Group 1:DTwP Group 2: DT	1900 896	2102 children 2574 children	90.4 34.8	2.6 (2.5 – 2.7)
Greco, 1996 Italy	RCT Low risk	2, 4, 6 months	48 hours after each dose	Group 1: DTwP Group 2: DT	5,425 151	13,520 doses 4540 doses	40.5 3.4	12.1 (10.3 – 14.1)
Long, 1990 USA ≥38.3°C	RCT Low bias	2, 4, 6 months @ 6mo: DTwP vs. placebo	48 hours post 3rd dose	Group 1: DTwP Group 2: placebo	111 14	233 children 218 children	47.6 6.5	7.4 (4.4 – 12.5)
Pollock, 1984 UK Feverishness	Cohort High bias	3,4.5-6,8-12 mo	12 hours post-dose 1	Group 1: DTwP Group 2: DT Group 3: DTwP plain		5091 3212 373 (children)	6.0 3.8 24.1	
			12 hours post-dose 2	Group 1: DTwP Group 2: DT *Group 3: DTwP plain*		4490 2910 387	5.0 3.7 19.1	

			12 hours post-dose 3	Group 1: DTwP Group 2: DT Group 3: DTwP plain		3120 2292 320	7.7 3.9 24.7	
			12 hours after any dose	Group 1: DTwP Group 2: DT Group 3: DTwP plain		5254 2670 400	5.7 3.7 19.8	
Persistent crying								
Gustafsson , 1996 Sweden ≥1h	RCT Moderate bias	2, 4, 6 months	Within 24 hours post-dose 1	Group 1:DTwP Group 2: DT	248 41	2102 children 2574 children	11.8 1.6	7.4 (5.3-10.2)
			Within 24 hours post-dose 2	Group 1:DTwP Group 2: DT	189 69	2040 children 2555 children	9.3 2.7	3.4 (2.6-4.5)
			Within 24 hours post-dose 3	Group 1:DTwP Group 2: DT	66 25	2001 children 2538 children	3.3 1.0	3.3 (2.1-5.3)
			Within 24 hours after any dose	Group 1:DTwP Group 2: DT	423 126	2102 children 2574 children	20.1 4.9	4.1 (3.4 – 5.0)
Long, 1990 USA	RCT Low bias	2, 4, 6 months @ 6mo: DTwP vs. placebo	48 hours post 3rd dose	Group 1: DTwP Group 2: placebo	6 1	233 children 218	2.6 0.5	5.6 (0.7-46.2)
Greco, 1996 Italy ≥3h	RCT Low risk	2, 4, 6 months	48 hours after each dose (crying ≥ 3h)	Group 1: DTwP Group 2: DT	54 --	13520 doses 4540 doses	4.0 --	∞
Pollock, 1984 UK Persistent crying >5h	Cohort High bias	3,4.5-6,8-12 mo	12 hours post-dose 1	Group 1: DTwP Group 2: DT *Group 3: DTwP plain*		5091 3212 373 (children)	1.0 0.7 5.1	

			12 hours post-dose 2	Group 1: DTwP Group 2: DT Group 3: DTwP plain		4490 2910 387	0.8 0.8 3.9	
			12 hours post-dose 3	Group 1: DTwP Group 2: DT Group 3: DTwP plain		3120 2292 320	0.8 0.7 2.5	
Seizure								
Greco, 1996 Italy	RCT Low risk	2, 4, 6 months	48 hours after each dose	Group 1: DTwP Group 2: DT	3 --	13,520 doses 4,540 doses	0.022 --	∞
Hypotonic, hyporesponsive episodes								
Greco, 1996 Italy	RCT Low risk	2, 4, 6 months	48 hours after each dose	Group 1: DTwP Group 2: DT	9 2	13,520 doses 4,540 doses	0.67 0.44	1.5 (0.3 – 6.7)
Local Pain/ Tenderness								
Gustafsson , 1996 Sweden	RCT Moderate bias	2, 4, 6 months	Within 24 hours post-dose 1	Group 1:DTwP Group 2: DT	1251 216	2102 children 2574 children	59.5 8.4	7.1 (6.2-8.1)
			Within 24 hours post-dose 2	Group 1:DTwP Group 2: DT	1228 263	2040 children 2555 children	60.2 10.3	5.8 (5.2-6.6)
			Within 24 hours post-dose 3	Group 1:DTwP Group 2: DT	1000 254	2001 children 2538 children	50.0 10.0	5.0 (4.4-5.6)
			Within 24 hours after any dose	Group 1:DTwP Group 2: DT	1692 571	2102 children 2574 children	80.5 22.2	3.6 (3.4 – 3.9)

Greco, 1996 Italy	RCT Low risk	2, 4, 6 months	48 hours after each dose	Group 1: DTwP Group 2: DT	4011 202	13,520 doses 4,540 doses	29.7 4.5	6.6 (5.8-7.6)
Long, 1990 USA	RCT Low bias	2, 4, 6 months @ 6mo: DTwP vs. placebo	48 hours post 3rd dose	Group 1: DTwP Group 2: placebo	134 6	233 children 218 children	57.5 2.7	20.9 (9.4 – 46.3
Redness								
Gustafsson , 1996 Sweden Redness ⩾2 cm	RCT Moderate bias	2, 4, 6 months	Within 24 hours post-dose 1	Group 1:DTwP Group 2: DT	126 8	2102 children 2574 children	6.0 0.3	19.2 (9.5-39.3)
			Within 24 hours post-dose 2	Group 1:DTwP Group 2: DT	104 20	2040 children 2555 children	5.1 0.8	6.5 (4.0-10.4)
			Within 24 hours post-dose 3	Group 1:DTwP Group 2: DT	128 61	2001 children 2538 children	6.4 2.4	2.6 (1.9-3.6)
			Within 24 hours after any dose	Group 1:DTwP Group 2: DT	307 90	2102 children 2574 children	14.6 3.5	4.2 (3.3 – 5.2)
Long, 1990 USA	RCT Low bias	2, 4, 6 months @ 6mo: DTwP vs. placebo	48 hours post 3rd dose	Group 1: DTwP Group 2: placebo	146 11	233 218	62.7 5.0	12.4 (6.9-22.3)
Swelling/Nodule								
Greco, 1996 Italy	RCT Low risk	2, 4, 6 months	Within 48 hours after each dose	Group 1: DTwP Group 2: DT	3512 279	13520 doses 4540 doses	26.0 6.1	4.2 (3.7-4.7)
Gustafsson, 1996 Sweden Nodule ⩾2 cm	RCT Moderate bias	2, 4, 6 months	Within 24 hours post-dose 1	Group 1:DTwP Group 2: DT	223 18	2102 children 2574 children	10.6 0.7	15.2 (9.4 – 24.4)

			Within 24 hours post-dose 2	Group 1:DTwP Group 2: DT	205 51	2040 children 2555 children	10.0 2.0	5.0 (3.7 – 6.8)
			Within 24 hours post-dose 3	Group 1:DTwP Group 2: DT	201 99	2001 children 2538 children	10.5 3.9	2.6 (2.0 – 3.3)
			Within 24 hours after any dose	Group 1:DTwP Group 2: DT	469 154	2102 children 2574 children	22.3 6.0	3.7 (3.1 – 4.4)
Long, 1990 USA Swelling ⩾1.27 cm	RCT Low bias	2, 4, 6 months @ 6mo: DTwP vs. placebo	48 hours post 3rd dose	Group 1: DTwP Group 2: placebo	126 7	233 218	54.1 3.2	16.8 (8.0 – 35.2)

Tables 9c-B: Additional studies – Primary vaccination, absolute reactogenicity

Publication and country	Design Risk of Bias	Schedules used	Timing of assessment	Type of reaction	Comparison groups	% of doses with reaction	Ratio
DTwP vs. DT, given in different schedules							
Barkin, 1985 USA	Double-blind RCT	2,4,6 mo Group A: DTwP – DTwP – DT (N=20) Group B: DTwP – DT – DTwP (N=20)	Within 24 h after vaccination	Any reaction	Group 1: DTwP doses (N about 80) Group 2: DT doses (N about 80)	92.1 52.5	1.8
				Febrile response	Group 1: DTwP doses Group 2: DT doses	55.3 5.0	11.1
				Acute behavioral changes	Group 1: DTwP doses Group 2: DT doses	55.3 5.0	11.1
				Antipyretics	Group 1: DTwP doses Group 2: DT doses	65.5 18.9	3.5
				Local reactions	Group 1: DTwP doses Group 2: DT doses	81.4 27.5	3.0
Not per protocol: Reports no difference between two schedules							

Publication and country	Design Risk of Bias	Schedule used	Timing of assessment	Comparison groups	N doses	Risk (%)	Ratio
Pollock, 1984 UK	Cohort High bias	3,4.5-6,8-12 mo	12 hours post-dose 1	Group 1: DTwP Group 2: DT	5091 3212	20.6 14.7	1.40

Crying more than usual				*Group 3: DTwP plain*	373 (children)	50.9	
			12 hours post-dose 2	Group 1: DTwP Group 2: DT *Group 3: DTwP plain*	4490 2910 387	17.8 14.7 40.3	1.21
			12 hours post-dose 3	Group 1: DTwP Group 2: DT *Group 3: DTwP plain*	3120 2292 320	18.5 13.6 39.4	1.36
Crying/screaming			12 hours post any dose	Group 1: DTwP Group 2: DT *Group 3: DTwP plain*	5254 2670 400	21.1 14.9 43.8	1.42

Publication and country	**Design Risk of Bias**	**Schedules used**	**Timing of assessment**	**Type of reaction**	**Comparison groups**	**% of doses with reaction**	**Ratio**
DTwP vs. DT injections, given in different schedules							
Cody, 1981 USA	Double-blind RCT	No application of a specific vaccination schedule	Within 48 h after vaccination	Temp ≥38.0°C	DTwP doses (N =195) DT doses (N=110)	39.8 12.5	3.2
				Persisting crying	DTwP doses (N =195) DT doses (N=110)	8.7 4.6	1.9
				Pain	DTwP doses (N =195) DT doses (N=110)	47.2 10.9	4.3
				Redness	DTwP doses (N =195) DT doses (N=110)	31.3 6.4	4.9
				Swelling	DTwP doses (N =195) DT doses (N=110)	36.4 9.1	4.0
Not per protocol: Does not report by vaccination schedule							

Table set 10. Data from included and additional studies evaluating booster vaccination schedule impact on relevant outcomes

Table 10b-B: Additional studies – Booster vaccination, schedule impact on immunogenicity

Publication and country	Design Risk of Bias	Schedules evaluated	Timing of assessment	Comparison groups	Proportion (%)with ≥4-fold increase pre-post booster
Interval between last primary and booster dose					
Wilkins 1987 USA	Cohort High risk	Booster interval Booster occurred after 2- or 3-dose primary schedule (groups combined)	1-2 months post booster dose	Interval final primary – booster A: 6-9 mo B: 10-12 mo C: 13-15 mo D: 16+ mo	 73.3 70.9 62.8 62.5
Not per protocol: Microtechnique for measuring pertussis agglutinins, not clear which primary schedule was used. Partially purified pertussis vaccine					

Publication and country	Design Risk of Bias	Schedule used	Timing of assessment	Comparison groups	Post-vaccination	
Age at booster					**GMC (95%-CI)**	**Proportion (%) with titer ≥1:64**
Scheifele 1999, Canada	RCT Low risk	DTwP booster after 3d-primary series, ages 12, 15 or 18 mo	4-6 wks after booster	Group 1: age 12 mo (N=86) Group 2: age 15 mo (N=85) Group 3: age 18 mo (N=82)	872 (706 – 139) 539 (427 – 680) 1126 (909 – 1397)	100% 98.8% 100%
Not per protocol: Microassay for pertussis agglutinins						

Tables 10c-A: Included studies on booster vaccination, schedule impact on reactogenicity

Publication and country	Design Risk of Bias	Schedules used	Timing of assessment	Type of reaction	Comparison groups	% of doses with reaction	Ratio (vs. Group 1)
DTwP vs. DT, given in different schedules							
Scheifele 1999, Canada	RCT Low and unclear risk	DTwP booster after 3d-primary series, ages 12, 15 or 18 mo	Within 24 h after vaccination	Peak temperature ≥38.0°C	Group 1: age 12 mo (N=78) Group 2: age 15 mo (N=78) Group 3: age 18 mo (N=75)	17.9 21.8 18.7	1.22 1.04
				Peak temperature ≥39.0°C	Group 1: age 12 mo (N=78) Group 2: age 15 mo (N=78) Group 3: age 18 mo (N=75)	1.3 2.6 4.0	2.00 3.08
				Any irritability	Group 1: age 12 mo (N=78) Group 2: age 15 mo (N=78) Group 3: age 18 mo (N=75)	79.1 78.8 81.7	1.00 1.03
				Moderate/severe irritability	Group 1: age 12 mo (N=78) Group 2: age 15 mo (N=78) Group 3: age 18 mo (N=75)	36.0 44.7 39.0	1.24 1.08
				Redness ≥5 mm	Group 1: age 12 mo (N=78) Group 2: age 15 mo (N=78) Group 3: age 18 mo (N=75)	67.4 69.4 68.5	1.03 1.02
				Redness ≥50 mm	Group 1: age 12 mo (N=78) Group 2: age 15 mo (N=78) Group 3: age 18 mo (N=75)	3.5 24.7 23.2	7.06 6.63
				Swelling ≥5 mm	Group 1: age 12 mo (N=78) Group 2: age 15 mo (N=78) Group 3: age 18 mo (N=75)	47.7 54.1 57.3	1.13 1.20
				Swelling ≥50 mm	Group 1: age 12 mo (N=78) Group 2: age 15 mo (N=78) Group 3: age 18 mo (N=75)	1.2 8.2 15.9	6.83 13.25

				Any local tenderness	Group 1: age 12 mo (N=78) Group 2: age 15 mo (N=78) Group 3: age 18 mo (N=75)	70.9 81.2 87.8	1.15 1.24
				Moderate/severe local tenderness	Group 1: age 12 mo (N=78) Group 2: age 15 mo (N=78) Group 3: age 18 mo (N=75)	29.1 44.7 41.5	1.54 1.43

Table set 11. Data from included and additional studies evaluating booster vaccination absolute impact on relevant outcomes

Table 11a-A: Included studies on booster vaccination, absolute vaccine effectiveness

Publication and country	Design Risk of bias	Schedule used	Comparison groups	Cases	Total household contacts	Attack proportion	VE (%) (95%-CI)
Booster vs. no booster							
PHLSWC, 1969 UK	Household contact cohort High risk	3 primary doses with booster	Group 1: booster Group 2: no booster	49 40	98 61	65.6 50.0	-31.2 (-71.6 – 23.4)

Tables 11b-B: Additional studies – Booster vaccination, absolute immunogenicity

Publication and country	Design Risk of Bias	Schedules used	Timing of assessment	Comparison groups	Mean antibody titer (SD) (PAU/ml)
Booster vs. no booster					
Conway 1993 UK	RCT Unclear risk Preterm babies 32-35 gestational weeks	A: 3,4,5 mo, B: 3,4,5, 18 mo	Age 19 mo	A: Booster (N=13) B: No booster (N=6)	18.31 (26.51) 7.13 (4.52)
Not per protocol: Unit of reporting: Pertussis antibody units, all antigens combined					

Publication and country	Design Risk of Bias	Schedule used	Timing of assessment	Comparison groups	Post-vaccination GMT (95% CI)	
Booster vs. no booster					**anti-FHA**	**anti-PT**
Miller 1995 UK	Synopsis of two cohorts Low risk	3,5,10 mo, booster at 4.5 yrs	6 mo after booster	Group 1: DTwP (N=74) Group 2: DT (N=77)	17,258 (13,256 – 22,021) 1318 (898 – 1935)	1614 (1277 – 2041) 248 (187 – 328)
Not per protocol: Synopsis of two cohorts (from two trials), without reporting details on comparability						

Appendix 1.

Search queries in PubMed

	Query	Items found
#87	(#53) AND #86	1825
#86	(#84) OR #85	5500726
#85	(((#73) OR #74) OR #77) OR #81	1926019
#84	(((#68) OR #69) OR #70) OR #72	4014848
#81	"case* series"[tw]	31266
#77	Case Reports [pt]	1609362
#74	((case* AND control*)[tw])	1161
#73	cohort*[tw]	293650
#72	Case-Control Studies/	624790
#70	cohort studies/	1250927
#69	Epidemiologic Studies/	1498703
#68	Epidemiological Methods/	3981368
#65	(#53) AND #64	1544
#64	(#62) NOT #63	2676437
#63	(animals [mh] NOT humans [mh])	3759657
#62	(((((((#54) OR #55) OR #56) OR #57) OR #58) OR #59) OR #60) OR #61	3121994
#61	groups [tiab]	1265127
#60	trial [tiab]	324489
#59	randomly [tiab]	193109
#58	drug therapy [sh]	1576079
#57	placebo [tiab]	146959
#56	randomized [tiab]	282417
#55	controlled clinical trial [pt]	85155
#54	randomized controlled trial [pt]	339710
#53	(#47) AND #52	4132
#52	((#49) OR #50) OR #51	1644579
#51	booster[tw]	7248
#50	month*[tw]	1017178
#49	week*[tw]	781978
#48	(#41) OR #47	23981
#47	((((#42) OR #43) OR #44) OR #45) OR #46	17805
#46	Tetanus Vaccine/	12221
#45	Diphtheria Vaccine/	7311
#44	Tetanus Toxoid/	10663
#43	Diphtheria Toxoid/	5931
#42	Pertussis Vaccine/	8163
#41	(#40) AND #39	23195

#40	((#8) OR #15) OR #22	59292
#39	(#35) OR #38	780762
#38	(#36) OR #37	772569
#37	immun*[tw]	624684
#36	vaccin*[tw]	252474
#35	((((#26) OR #31) OR #32) OR #33) OR #34	295999
#34	Immunization, Secondary/	10149
#33	Immunization Schedule/	10140
#32	Immunization/	213756
#31	Vaccination/	108937
#26	Vaccines/	181844
#22	(#18) OR #21	18138
#21	(#19) OR #20	18094
#20	Corynebacterium diphtheriae[tw]	2485
#19	Diphtheria[tw]	16993
#18	(#16) OR #17	18138
#17	Corynebacterium diphtheriae/	2533
#16	Diphtheria/	16998
#15	(#11) OR #14	24911
#14	(#12) OR #13	24887
#13	tetanus[tw]	24614
#12	Clostridium tetani[tw]	1003
#11	(#9) OR #10	24911
#10	Clostridium tetani/	1034
#9	Tetanus/	24614
#8	(#3) OR #7	28001
#7	((#4) OR #5) OR #6	28001
#6	Bordetella pertussis[tw]	5906
#5	whoop*[tw]	7367
#4	Pertuss*[tw]	25481
#3	(#1) OR #2	16369
#2	Whooping Cough/	7244
#1	Bordetella pertussis/	11311

Search queries for EMBASE

No.	Queries	Results
#58	**#56** OR **#57**	**723,499**
#57	**#44** OR **#45** OR **#49** OR **#50** OR **#51** OR **#52** OR **#54**	**430,195**
#56	**#32** OR **#35** OR **#36** OR **#37** OR **#38** OR **#40** OR **#41**	**367,017**
#55	('**cross sectional**' NEAR/1 (**study** OR **studies**)):ab,ti AND [embase]/lim	**54,981**
#54	(**epidemiologic*** NEAR/1 (**study** OR **studies**)):ab,ti AND [embase]/lim	**53,542**
#52	(**observational** NEAR/1 (**study** OR **studies**)):ab,ti AND [embase]/lim	**44,611**
#51	('**follow up**' NEAR/1 (**study** OR **studies**)):ab,ti AND [embase]/lim	**35,146**
#50	('**case control**' NEAR/1 (**study** OR **studies**)):ab,ti AND [embase]/lim	**57,451**
#49	(**cohort** NEAR/1 (**study** OR **studies**)):ab,ti AND [embase]/lim	**86,192**
#45	'**cohort analysis**'/exp AND [embase]/lim	**111,978**
#44	**#42** NOT **#43**	**139,471**
#43	'**randomized controlled trial**'/exp AND [embase]/lim	**239,204**
#42	'**prospective study**'/exp AND [embase]/lim	**156,742**
#41	'**retrospective study**'/exp AND [embase]/lim	**191,755**
#40	'**longitudinal study**'/exp AND [embase]/lim	**35,911**
#38	'**family study**'/exp AND [embase]/lim	**9,898**
#37	'**family study**' AND [embase]/lim	**12,541**
#36	'**case control study**'/exp AND [embase]/lim	**45,046**
#35	'**case control study**'/de AND [embase]/lim	**39,525**
#32	'**clinical study**'/de AND [embase]/lim	**88,635**
#31	**#13** AND **#30**	**1,394**
#30	**#24** OR **#29**	**1,026,630**
#29	**#25** OR **#26** OR **#27** OR **#28**	**275,208**
#28	'**crossover procedure**'/exp AND [embase]/lim	**30,216**
#27	'**double blind procedure**'/exp AND [embase]/lim	**94,889**
#26	'**single blind procedure**'/exp AND [embase]/lim	**12,674**
#25	'**randomized controlled trial**'/exp AND [embase]/lim	**239,204**
#24	**#14** OR **#15** OR **#16** OR **#17** OR **#18** OR **#19** OR **#20** OR **#21** OR **#22** OR **#23**	**983,774**
#23	((**singl*** OR **doubl***) NEAR/1 **blind***):ab,ti AND [embase]/lim	**133,191**
#22	**allocat***:ab,ti AND [embase]/lim	**56,171**
#21	**assign***:ab,ti AND [embase]/lim	**166,868**
#20	**volunteer***:ab,ti AND [embase]/lim	**142,943**

#19	'**cross-over**':ab,ti AND [embase]/lim	**17,800**
#18	'**cross over**':ab,ti AND [embase]/lim	**17,800**
#17	**crossover***:ab,ti AND [embase]/lim	**39,156**
#16	**factorial***:ab,ti AND [embase]/lim	**13,970**
#15	**placebo***:ab,ti AND [embase]/lim	**165,399**
#14	**random***:ab,ti AND [embase]/lim	**641,711**
#13	**#1** OR **#9** OR **#10** OR **#11** OR **#12**	**27,311**
#12	**pertuss***:ab,ti OR **whoop***:ab,ti AND [embase]/lim	**20,948**
#11	'**pertussis**'/de AND [embase]/lim	**6,766**
#10	'**bordetella pertussis**'/de AND [embase]/lim	**4,390**
#9	**#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8**	**6,095**
#8	'**diphtheria pertussis poliomyelitis tetanus haemophilus influenzae type b hepatitis b vaccine**'/de AND [embase]/lim	**315**
#7	'**diphtheria pertussis poliomyelitis tetanus hepatitis b vaccine**'/de AND [embase]/lim	**165**
#6	'**diphtheria pertussis poliomyelitis tetanus vaccine**'/de AND [embase]/lim	**391**
#5	'**diphtheria pertussis tetanus haemophilus influenzae type b hepatitis b vaccine**'/de AND [embase]/lim	**136**
#4	'**diphtheria pertussis tetanus haemophilus influenzae type b vaccine**'/de AND [embase]/lim	**475**
#3	'**diphtheria pertussis tetanus hepatitis b vaccine**'/de AND [embase]/lim	**56**
#2	'**diphtheria pertussis tetanus vaccine**'/de AND [embase]/lim	**5,329**
#1	'**pertussis vaccine**'/de AND [embase]/lim	**4,677**

Search queries in CENTRAL

ID	Search	Hits
#1	MeSH descriptor: [Whooping Cough] 1 tree(s) exploded	201
#2	MeSH descriptor: [Pertussis Vaccine] explode all trees	602
#3	MeSH descriptor: [Bordetella pertussis] explode all trees	115
#4	(#1 or #2 or #3)	651
#5	whoop* or "whooping cough":ti (Word variations have been searched)	33
#6	whoop* or "whooping cough":ab (Word variations have been searched)	35
#7	whoop* or "whooping cough":kw (Word variations have been searched)	218
#8	(#5 or #6 or #7)	245
#9	pertuss*:ti,ab,kw	912
#10	pertuss* near/2 immun*:ti,ab,kw (Word variations have been searched)	215
#11	pertuss* next vaccin*:ti,ab,kw	714
#12	pertuss* next immun*:ti,ab,kw	106
#13	(#10 or #11 or #12)	729
#14	(#9 or #13)	921
#15	(#8 or #14)	950
#16	(#4 or #15)	950

Appendix 2

Synopsis of inclusion of references in landmark reviews on absolute effectiveness of pertussis vaccines or comparative effectiveness of pertussis vaccine schedules

- Not considered: reduced doses; > 5 years
- Descriptive studies on duration of AB or protection (if not vs. nihil or between schedules)

WHO Immunization and Biologicals

wP	
Cherry 1988	No original data (review)
Halsey&Galazka 1985	No original data (review)
Baraf 1984, Burstyn 1983	Included
Provenzano 1965	No control group
Blumberg 1991	aP vs. wP
Granstrom 1985	No comparison of schedule or vs. nihil
Wilkins 1987	NPP
Funkhouser 1987	Disease risk in infants by age
Fine & Clarkson 1987	No orginal data => landmark
Wilkins 1971	NPP wP
Muller 1984	NPP wP
Bhandari 1981	NPP wP
Coursaget 1986	Data on control group not reported
Griffith 1988	No original data (review)
Jenkinson 1988	Included wP
Blennow 1988 (BMJ)	NPP aP
Barkin 1984	NPP aP
Blennow & Grandström 1989 (Pediatrics)	NPP aP
Blumberg 1991	aP vs. wP
Edwards 1991	No comparison of schedule or vs. nihil
Relyveld Nov. 1991	Age 5-14 yrs; No comparison of schedule or vs. nihil

Huovila 1982	**Full-text not yet found**
Chen 1957	No control group
Edwards 1989	No comparison of schedule or vs. nihil
Lewis 1986	No comparison of schedule or vs. nihil
Pichichero 1987	aP vs. wP
aP	
Galazka 1988	No original data (review)
Anderson 1987	**Full-text not yet found**
Blumberg 1991	aP vs. wP
Lewis 1986	No comparison of schedule or vs. nihil
Morgan 1990	aP vs. wP, 4-6 yrs
Pichichero 1987	aP vs. wP
Aoyama 1989	Update of NPP study (Aoyama 1985); age 2-8 yrs
Kimura 1991	No original data
Mortimer 1990	Included
Tomoda 1991	No comparison of schedule or vs. nihil
Aoyama 1988	Update of NPP study (Aoyama 1985); 2-8 yrs
Edwards 1989	No comparison of schedule or vs. nihil
Edwards 1991	No comparison of schedule or vs. nihil
Van Savage 1990	Comparison of vaccines, maternal antibody
Olin 1990	No original data (summary of included studies)
Blackwelder 1991	Reanalysis of included study, no new evidence
Blennow 1988 (Pediatrics)	NPP
Blennow & Grandström 1989 (Pediatrics)	NPP
Blennow & Grandström 1989 (PIDJ)	NPP
Blennow & Grandström 1990	NPP
Storsaeter 1990	Included

Jefferson 2003

41	Greco 1996	Included aP/wP
42	Gustaffson 1996	Included aP/wP
62	Stehr 1998	included aP/wP
23	Anon. MRC/Lancet 1951	Included wP
49	Miller 1995	Included wP
52	Olin 1997	Included aP/wP
70	Pollock 1984	Included wP
50	Miller 1997	Included aP/wP
64	Sun 1990	Article in Chinese; age 4-6 years
31	Blennow 1988 (BMJ)	Included aP
24	Anon. Lancet 1988	Included aP
65	Trollfors 1995	Included aP
30	**Blennow 1986 (Dev Biol stand)**	NPP aP

Pippa Scott, Rapid review

12	Nilsson 2003	allergic disease at **age 7 years**
13	Tapainen 2005	**effect of injection site** on reactogenicity and ImG
14	Trollfors 2005	effect of **co-administration of pertussis on ImmGen of DT**
17	Halasa 2008	Included aP
18	Belloni 2003	Included aP
19	Wong 2008	NPP wP
20	Knuf 2008	Included aP
21	Wilkins 1971	NPP wP
22	Bhandari 1981	NPP wP