

REVIEW

Immunogenicity and antibody persistence of diphtheria-tetanus-acellular pertussis vaccination in adolescents and adults: a systematic review of the literature showed different responses to the available vaccines

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Keywords

Immunogenicity • Antibody persistence • Diphtheria-tetanus-acellular *Bordetella pertussis* vaccination • Adolescents • Adults

Summary

Introduction. In industrialized countries, the routine use of *Bordetella pertussis* vaccines has shifted the burden of *Bordetella pertussis* disease from children to infants, adolescents and adults, leading to the necessity for booster doses.

Materials and methods. We prepared a review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) with the aims of: a) describing the immunogenicity of the main available vaccines for adolescents and adults; b) describing antibody persistence after immunization with the main vaccines available in childhood and adults and, also, possible co-administration; and c) identifying the gold standard for adolescent and adult immunizations.

Results. We identified 6906 records. After removing duplicate

records, we included 12 RCT (Randomized Controlled Trial) (people aged 11-73): 7 of these studies had only 1 control group, 4 had 2 control groups and 1 had 5 control groups; moreover, of the 12 studies included, only 2 regarded co-administration, while all concerned immunogenicity. Nine of the 12 studies had a Jadad score above 3 points, and 10 out of 12 met the criteria of Cochrane Back Review Group Criteria List for Methodological Quality Assessment.

Discussion and conclusion. We found a limited number of good-quality RCTs investigating our object. The 5-component vaccines, although containing a lower dose of antigen, proved more effective than the 1-component vaccine. Evidence supports the use of 5-component vaccines for booster sessions in adolescence and adulthood.

Introduction

In industrialized countries, the routine use of *Bordetella pertussis* vaccines has shifted the burden of *Bordetella pertussis* disease from children to infants, adolescents and adults [1]. Although this disease is not generally as severe in adolescents and adults as in infants, it nevertheless has a heavy impact on morbidity and mortality; furthermore, these older age-groups are often the reservoir of infection for infants [2]. As the incidence of *Bordetella pertussis* in adults and older individuals has been seen to be increasing, reduced-dose acellular *Bordetella pertussis* vaccines combined with diphtheria and tetanus toxoids (Tdap) are required. The goals of Tdap booster doses are to protect older vaccinees, reduce the circulation of the bacterium, and thereby protect young infants [3].

Responses to immunization vary according to the different vaccines used and the immunization and infection history of vaccinees; in the scientific literature, immunity is evaluated through the assay of IgG anti-pertussis toxin (IgG anti-PT) antibodies by means of the ELISA method [4].

The following vaccines are currently available: Tdap5 vaccine, produced by Sanofi Pasteur [5], which is an adsorbed combination vaccine containing purified

diphtheria and tetanus toxoids and five purified components of *Bordetella pertussis*; Tdap3, which contains purified diphtheria and tetanus toxoids and 3 purified components of *Bordetella pertussis* and is produced by Glaxo-Smith Kline [6]; and Tdap1, which is a combined adsorbed tetanus, low-dose diphtheria and monocomponent ap vaccine produced by Statens Serum Institut [7]. The aims of the present study were: a) to describe the immunogenicity of the main available vaccines for adolescents and adults; b) to describe antibody persistence in adults after immunization with the main vaccines available and, also the possible co-administration of these vaccines.

Materials and methods

In accordance with PRISMA guidelines [8], we searched the main scientific libraries (PubMed including MEDLINE, Web of Science and Embase) for randomised controlled trials, cohort studies, or longitudinal studies reporting the immunogenicity and persistence of antibodies against diphtheria tetanus pertussis, for articles indexed up to the date of the search, with no language restrictions. Table I shows the keywords search strategy for one data-

base, Web of Science. Studies were included if they investigated vaccine-induced immunity in healthy individuals who received a DTPa and Tdpa vaccine, including different dosages and time-points of vaccine administration. Studies featuring child or maternal immunity, those with only one arm, and those that were not randomized were excluded. We excluded all case studies/reports, letter to editors, review papers, personal opinions and any other type of study with inconsistent data or which did not report original data. We also conducted hand searches of the reference lists of included studies and related reviews. We exported all studies retrieved from the electronic searches for deduplication and screening. Two review authors (CG and RS) independently screened the titles and abstracts to identify potentially eligible studies, and any disagreements between the two authors were resolved by discussion and consensus. We obtained the full texts of all potentially eligible studies. Two authors (RS and CG) independently screened the full texts and identified included studies, resolving discrepancies through discussion and consensus.

DATA EXTRACTION

Two independent reviewers (CG and RS) identified potentially relevant articles and collected the following data: first author’s last name; year of publication; study design; total number of participants; age range; gender; exclusion criteria and study arms with number of vaccinated participants in each arm.

EVALUATION OF STUDY QUALITY

Two reviewers (CG, RS) independently assessed the quality of individual studies included in the systematic review. The Jadad scale for reporting randomised controlled trials (RCTs) was employed [9]. This assigns an overall score of the methodological quality of a study from zero to five. We also evaluated the studies according to the Cochrane risk of bias tool for randomized controlled trials [10]. The domains assessed are: randomization method, allocation concealed, similar baseline, patient-blinded, provider-blinded, assessor-blinded, co-intervention avoided, acceptable compliance, acceptable drop-out rate, timing of outcome assessment similar and intention-to-treat analysis. The studies were included also with low quality scores, but it was taken into account when describing the results.

Results

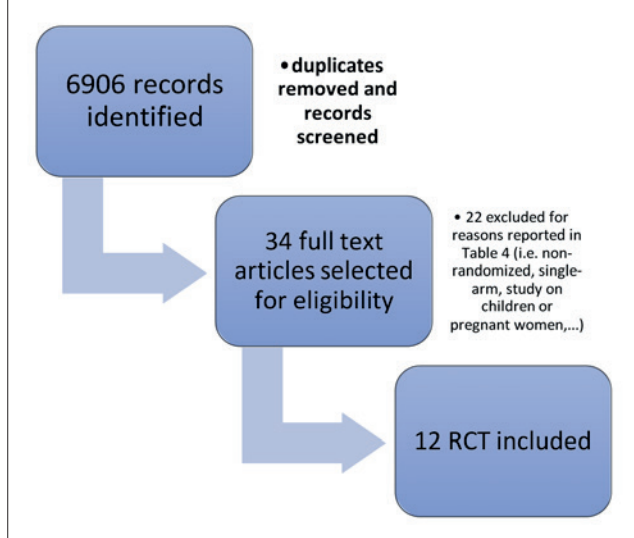
Of 6906 records identified; after removing duplicate records, we selected 34 for full text review (Fig. 1) and, finally, 12 were discussed (Tab. II). The composition of included vaccines was reported in Table III.

Description of studies

STUDY DESIGN AND POPULATION

All the studies included were randomized trails. Their characteristics are summarized in Table II. Twelve RCT

Fig. 1. PRISMA flow diagram showing the study research and selection process.



were included in our review; of these, 7 had only 1 control group, 4 had 2 control groups and 1 had 5 control groups; moreover, of the 12 studies included, only 2 regarded co-administration [12, 14], while all were about immunogenicity [11-22]. The studies were conducted among people aged 11-73 years: Tdap1 in subjects aged 14-55; Tdap3 (GSK) in subjects aged 18-73; dTap3 (BNT) in those aged 18-35; and Tdap5 in those aged 11-72. The composition of the vaccines is reported in Table I.

Four studies were conducted in Europe [11, 12, 20, 21], one in Asia [19], one in America [22], seven studies were multi-centre [13, 14, 17, 18, 20, 22], and four were conducted in more than one country [15, 17, 18, 20]. Disease background or exclusion criteria of the studies included were: a history of significant medical illness; the presence of any progressive or severe neurological disorder, seizure disorder or Guillain-Barre syndrome; immunodeficiency; administration of any diphtheria or tetanus or pertussis vaccine prior to enrolment in the study or history of allergy to any vaccine component; pregnancy or breastfeeding. For details, see Supplementary Table I.

The risk of bias in the studies included is summarized in Table IV.

We excluded 22 studies [23-44] from our analysis because they did not meet any inclusion criteria (Supplementary Tab. I).

Seroconversion, antibody persistence and adverse events in adolescents and adults

The 12 RCT included in our analysis are described below.

Carlsson et al. [11] reported the results of a non-blind RCT (see risk of bias in Tab. III) with two vaccines, a

Tab. I. Research strategy.

Adults [^]	TS = ((Diphtheria Tetanus Pertussis Vaccine or Vaccine, Diphtheria-Tetanus-Pertussis or DTWP Vaccine or Vaccine, DTWP or DPT Vaccine or Vaccine, DPT or DTP Vaccine or Vaccine, DTP or Di-Te-Per Vaccine or Di Te Per Vaccine or Vaccine, Di-Te-Per or Diphtheria-Pertussis-Tetanus Vaccine or Diphtheria Pertussis Tetanus Vaccine or Vaccine, Diphtheria-Pertussis-Tetanus) and (Case-Control Study or Studies, Case-Control or Study, Case-Control or Case-Comparison Studies or Case Comparison Studies or Case-Comparison Study or Studies, Case-Comparison or Study, Case-Comparison or Case-Compeer Studies or Studies, Case-Compeer or Case-Referrent Studies or Case Referrent Studies or Case-Referrent Study or Studies, Case-Referrent or Study, Case-Referrent or Case-Referent Studies or Case Referent Studies or Case-Referent Study or Studies, Case-Referent or Study, Case-Referent or Case-Base Studies or Case Base Studies or Studies, Case-Base or Case Control Studies or Case Control Study or Studies, Case Control or Study, Case Control or Nested Case-Control Studies or Case-Control Studies, Nested or Case-Control Study, Nested or Nested Case Control Studies or Nested Case-Control Study or Studies, Nested Case-Control or Study, Nested Case-Control or Matched Case-Control Studies or Case-Control Studies, Matched or Case-Control Study, Matched or Matched Case Control Studies or Matched Case-Control Study or Studies, Matched Case-Control or Study, Matched Case-Control or Cohort Study or Studies, Cohort or Study, Cohort or Concurrent Studies or Studies, Concurrent or Concurrent Study or Study, Concurrent or Closed Cohort Studies or Cohort Studies, Closed or Closed Cohort Study or Cohort Study, Closed or Study, Closed Cohort or Studies, Closed Cohort or Analysis, Cohort or Cohort Analysis or Analyses, Cohort or Cohort Analyses or Historical Cohort Studies or Cohort Study, Historical or Historical Cohort Study or Study, Historical Cohort or Cohort Studies, Historical or Studies, Historical Cohort or Incidence Studies or Incidence Study or Studies, Incidence or Study, Incidence or Vaccinations or Immunization, Active or Active Immunization or Active Immunizations or Immunizations, Active or Intervention Study or randomized controlled trial or Clinical Trial, Phase 4) NOT ("ANIMALS" NOT "humans").
Adolescents	TS = ((Diphtheria Tetanus Pertussis Vaccine or Vaccine, Diphtheria-Tetanus-Pertussis or DTWP Vaccine or Vaccine, DTWP or DPT Vaccine or Vaccine, DPT or DTP Vaccine or Vaccine, DTP or Di-Te-Per Vaccine or Di Te Per Vaccine or Vaccine, Di-Te-Per or Diphtheria-Pertussis-Tetanus Vaccine or Diphtheria Pertussis Tetanus Vaccine or Vaccine, Diphtheria-Pertussis-Tetanus) and (Case-Control Study or Studies, Case-Control or Study, Case-Control or Case-Comparison Studies or Case Comparison Studies or Case-Comparison Study or Studies, Case-Comparison or Study, Case-Comparison or Case-Compeer Studies or Studies, Case-Compeer or Case-Referrent Studies or Case Referrent Studies or Case-Referrent Study or Studies, Case-Referrent or Study, Case-Referrent or Case-Referent Studies or Case Referent Studies or Case-Referent Study or Studies, Case-Referent or Study, Case-Referent or Case-Base Studies or Case Base Studies or Studies, Case-Base or Case Control Studies or Case Control Study or Studies, Case Control or Study, Case Control or Nested Case-Control Studies or Case-Control Studies, Nested or Case-Control Study, Nested or Nested Case Control Studies or Nested Case-Control Study or Studies, Nested Case-Control or Study, Nested Case-Control or Matched Case-Control Studies or Case-Control Studies, Matched or Case-Control Study, Matched or Matched Case Control Studies or Matched Case-Control Study or Studies, Matched Case-Control or Study, Matched Case-Control or Cohort Study or Studies, Cohort or Study, Cohort or Concurrent Studies or Studies, Concurrent or Concurrent Study or Study, Concurrent or Closed Cohort Studies or Cohort Studies, Closed or Closed Cohort Study or Cohort Study, Closed or Study, Closed Cohort or Studies, Closed Cohort or Analysis, Cohort or Cohort Analysis or Analyses, Cohort or Cohort Analyses or Historical Cohort Studies or Cohort Study, Historical or Historical Cohort Study or Study, Historical Cohort or Cohort Studies, Historical or Studies, Historical Cohort or Incidence Studies or Incidence Study or Studies, Incidence or Study, Incidence or Vaccinations or Immunization, Active or Active Immunization or Active Immunizations or Immunizations, Active or Intervention Study or randomized controlled trial or Clinical Trial, Phase 4) NOT ("ANIMALS" NOT "humans") and (Adolescence, Adolescents, Adolescents, Female - Adolescents, Male Teenagers, Teens and Youth).

[^]In accordance with guidelines, no age restriction was used; to avoid limiting search results, we did not use the word "adult" to screen references.

Tdap5 and Tdap1 [5, 7]. Briefly, children born in 1994 were invited to participate in booster studies of immunogenicity and reactogenicity on two separate occasions: a booster study of the DTaP5 vaccine in 1999 at age 5 years, and a second one with the same Tdap5 and a monocomponent (Tdap1) vaccine in 2009 at age 14-15 years [11]. Both studies used an open, randomized, parallel-group multicentre study design with blinded seroanalyses. The lower and upper limits of anti-PT after Tdap5 and Tdap1 were similar; regarding reactogenicity, fever, moderate or severe headache and moderate to severe swelling ≥ 2.5 at the injection site were reported more often after Tdap1 than Tdap5 (RR 2, 1.4 and 1.5, respectively). Embree et al. [12] evaluated sierological assays (pre-vaccination, at 1 month, and 3-5-10 years after immunization) and co-administration (see co-administration section for description). At 1-month post-vaccination, the seroprotection rates

were comparable between the groups and remained high for up to 10 years post-vaccination for diphtheria, tetanus and poliomyelitis, but subsequently returned to pre-vaccination levels. Anti-pertussis Geometric Mean Titers (GMTs) declined over time: anti-PT displayed the lowest percentage of participants with detectable antibodies after 10 years (74.1%) while the percentages of the other three antigens were higher. No serious adverse events were reported. Halperin et al. [13] showed that the proportion of participants displaying a booster response to Tdap5 vaccination was similar in the naïve group and the repeat-dose group, demonstrating that a second dose of a five-pertussis-component Tdap in adults was safe and immunogenic in comparison with adults in the naïve group. A solicited adverse event was reported by just over 92% of recipients of Tdap and there were no differences in rates of any adverse events.

Tab. II. Studies included in systematic review.

First author's last name	Year of publication	Study design	Total n. of participants	Age range	Gender	Arm 1	Arm 2
Carlsson	2015	RCT	230	14-15	Both	114 (Tdap5)	113 (Tdap1)
Embree	2015	RCT	236	11-14	Both	144 (Tdap5 -Polio) HepB 1 month later	132 (Tdap5-Polio) HepB concurrently
Halperin	2012	RCT	769	20-72	Both	407 (Naive Tdap)	362 (Repeat dose group Tdap5)
McNeil	2007	RCT	720	19-64	Both	359 (Tdap5 concomitant administration with flu)	361 (Tdap5 sequential administration with flu)
Halperin	2000	RCT	1207	12-60	Both	Adolescents [^] Adults ^{^^}	Adolescents [^] Adults ^{^^}
Halperin (Vaccine)	2000	RCT	749	12-55	Both	151* (Td)	449* (Tdap5)
Halperin	2019	RCT	1330	18-65	Both	1002 (Tdap5)	328 (Td)
Sirivichayakul	2017	RCT	60	18-35	Both	20 [°] (Tdap5)	20 [°] BNA'S Tdap3
Van der Wielen	2000	RCT	299	18-73	Both	96 [§] (Tdap3)	98 [§] (Td)
Thierry-Carstensen	2012	RCT	802	18-55	Both	401 (Tdap1)	401 (Td)
Jahnmatz	2014	RCT	230	14-15	Both	Tdap1	Tdap5
Pichichero	2005	RCT	4480	11-64	Both	3053 (Tdap5) [§]	1427 (Td) [§]

Note: [^] Adolescent cohort 1: Td-IPV at visit 1 and aP at visit 2; cohort 2: Tdap-IPV
^{^^} Adults: cohort 1: Td at visit 1 and aP at visit 2; cohort 2: Tdap at visit 1 and IPV at visit 2; cohort 3: Tdap at visit 1 and aP at visit 2; cohort 4: Tdap-IPV.
^{*} Cohort 3: n = 149 aP (5 components)
[°] Cohort 3: n = 20 BNA's aP (3 components)
[§] cohort 3: n = 96 aP (3 components)
[§] Adolescent cohort 1: n = 1232 Tdap5; cohort 2 :n = 821Td
Adults: cohort 1:n = 1821 Tdap5; cohort 2:n=606 Td

Tab. III. Composition of dTpa vaccines analyzed.

Antigen	dTpa (1) AJ Vaccines	dTpa (3) GSK	dTpa (5) Sanofi Pasteur	dTpa (3) Bionet
Diphtheria toxoid	Not less than 2 UI	Not less than 2 UI	Not less than 2 UI	Not less than 2 UI
Tetanus toxoid (TT)	Not less than 20 UI	Not less than 20 UI	Not less than 20 UI	Not less than 20 UI
Pertussis toxoid (PT)	20 µg	8 µg	2,5 µg	5 µg
Filamentous hemagglutinin (FHA)	---	8 µg	5 µg	5 µg
Pertactin (PRN)	---	2,5 µg	3 µg	2.5 µg
Fimbriae type 2/3	---	---	5 µg	-

McNeil et al. [14] performed a study on the concomitant administration of Tdap and trivalent inactivated influenza vaccines or influenza vaccine followed (in 4-6 weeks) by Tdap. For this purpose, they enrolled 720 healthy subjects aged 19-64 years. Regarding diphtheria and tetanus, seroprotection rates and post-vaccination GMTs were non-inferior in the concomitant administration group compared with the sequential administra-

tion group. A trend towards lower antibody responses to *Bordetella pertussis* antigens PT, FHA and FIM was observed after concomitant administration, and in the case of PRN, this difference failed the non-inferiority criteria. Halperin et al. [15] performed an RCT to evaluate the safety of and antibody response to a single dose of an adult formulation of a Tdap5 and inactivated poliovirus vaccine (Tdap-IPV) in adolescents and adults, and

Tab. IV. Risk of bias in included studies.

First author's name and year	Jadad score	Cochrane [^]
Carlsson, 2015 [11]	3	6/10
Embree, 2015 [12]	3	7/10
Halperin, 2012 [13]	1	4/10
McNeil, 2007 [14]	3	7/10
Halperin, 2000 [15]	5	9/10
Jahnmatz, 2014 [16]	1	4/10
Halperin, 2000 [17]	5	9/10
Halperin, 2019 [18]	3	6/10
Sirivichayakul, 2017 [19]	3	9/10
Van der Wielen, 2000 [20]	5	7/10
Thierry-Carstensen, 2012 [21]	2	6/10
Pichichero, 2005 [22]	5	9/10

[^]We reported the number of domains fitted by the study (ten domains were analyzed: randomization method, allocation concealed, similar baseline, patient blinded, provider blinded, assessor blinded, co-intervention avoided, acceptable compliance, acceptable drop-out rate, timing of outcome assessment similar and intention-to-treat analysis).

to assess the response to a second dose of the acellular pertussis vaccine in a subset of the adults. The antibody response against *Bordetella Pertussis* antigens was vigorous in all groups, although adults given the Tdap-IPV vaccine had lower antibody titers against filamentous hemagglutinin, pertactin, diphtheria and tetanus toxins than those given Tdap vaccine. Similarly, adolescents given Tdap-IPV had lower antibody titers against *Bordetella pertussis* toxin, filamentous hemagglutinin, fimbriae and agglutinins than those given Td-IPV and aP alone. A second dose of acellular *Bordetella pertussis* vaccine was not associated with increased adverse events in adults, but raised antibody titers above the level achieved by a single dose only against pertussis toxin.

Jahnmatz et al. [16] described a study on 230 adolescents (aged 14-15 years) in an open-label, randomized multicenter study without a control group and with blinded analysis. Both vaccine groups had significant increases in *Bordetella pertussis* toxin-specific serum IgG levels, and the 5-component group had significant increases in filamentous hemagglutinin- and pertactin-specific memory B-cell and serum IgG levels; these were not seen in the 1-component group, as expected.

Halperin et al. [17] measured antibody levels before and one month after immunization and investigated adverse events (at 24 h, 72 h and 8 to 10 days). They did not find statistically significant differences in tetanus and diphtheria antitoxin levels between recipients of Td and Tdap, and the antibody response against *Bordetella Pertussis* antigens was vigorous in all groups. Adverse events were reported with similar frequency among the three vaccine groups. Moderate pain at the injection site was reported less frequently in the aP group than the Tdap group (RR = 0.4) and chills were reported less frequently after Td than after Tdap (RR = 0.4).

Halperin et al. [18] found a robust antibody response to each *Bordetella pertussis* antigen in the Tdap-vaccinated group, while post-vaccination geometric mean concentrations of tetanus and diphtheria antibodies were similar in the Tdap and Td groups with seroprotection rates

> 99%. A solicited adverse event was reported by 87.7% of Tdap and 88.0% of Td vaccine recipients. No significant differences in the rates of local and systemic reactions between the vaccine groups were found.

Sirivichayakul et al. [19] enrolled only 60 subjects in 3 cohorts randomized to receive one of the vaccines in study, as reported in the Table II. Safety follow-up was performed for one month, while immunogenicity was assessed at the baseline and at 7 and 28 days after vaccination. One month after vaccination, seroresponse rates of anti-PT, anti-FHA and anti-PRN IgG antibodies exceeded 78% in all vaccine groups. Although the authors concluded that, in this clinical study, PTgen-based Bio-Net's aP and Tdap vaccines showed similar tolerability and safety profiles to those of Tdap5, the sample size was very small and moreover, follow-up was too short.

Van der Wielen et al. [20] evaluated responses to a Tdap3 vaccine. In all groups, severe reactions were infrequent and no serious adverse events were reported during the study; the incidence of local and systemic reactions following the administration of Tdap or Td vaccine was comparable. One month after vaccination, a similar percentage of subjects in the Tdap and Td groups had anti-diphtheria, anti-tetanus, anti-FHA and anti-PRN antibodies, while the anti-PT vaccine response rates were 96.8 and 100.0%, respectively, for Tdap3 and aP.

Thierry-Carstensen et al. [21] showed antibody responses (anti-PT) in adults aged 18-55 years in 92% of cases. The frequencies of solicited local adverse reactions were low and comparable between Tdap and Td vaccinees. In the Tdap group, 30.7% reported pain, 4.2% swelling and 2.0% erythema at the injection site. The most frequent solicited general symptoms were headache (20.4%), fatigue (17.0%) and myalgia (10.0%).

Pichichero et al. [22] showed that Tdap5 elicited robust immune responses to *Bordetella pertussis*, tetanus, and diphtheria antigens in adolescents and adults, while exhibiting an overall safety profile similar to that of a licensed Td vaccine; these data support the potential routine use of this Tdap vaccine in adolescents and adults. Indeed, 94% of Tdap recipients had protective antibody concentrations of at least 0.1 IU/mL against diphtheria and tetanus. Geometric mean antibody titers against the five antigens of *Bordetella pertussis* used exceeded (by 2.1 to 5.4 times) levels in infants following immunization with DTaP at 2, 4 and 6 months. The safety profile was similar in the Tdap and Td groups.

Co-administration

Two studies [12, 14] evaluated the co-administration of dTap5 with flu and with hepatitis B vaccines in adolescents and adults.

In the study by Embree et al. [12], no clinically relevant interference was observed on co-administration of Tdap5-IPV and HepB. Participants achieved seroprotective levels against tetanus (100%) and diphtheria (98.6% of group 1 and 100% of group 2). The *Bordetella pertussis* antibody seroresponses 1 month after Tdap-IPV vac-

cination were comparable in groups 1 and 2, as measured by 4-fold increases in PT, FHA, FIM and PRN. McNeil [14] did not observe clinically relevant between-group differences (Tdap5 with flu or Tdap5 followed 1 month later by flu) in terms of safety; injection-site pain was the most commonly reported adverse event (66.6% concomitant administration group vs 60.8% sequential administration group), showing the possibility of concomitant administration.

In our analysis, we identified several studies on the co-administration of reduced-antigen content vaccines indicated for boosters in adults (Tdap3 and Tdap5), while no evidence emerged to support the co-administration of the Tdap1 vaccine with others one (such as HBV, etc.).

Discussion and conclusion

In our systematic review, we observed that all vaccines were immunogenic but, as expected, the contents and concentrations of antigens influenced the responses.

In the study by Jahnmatz et al. [15], the authors found that the 1-component vaccine induced higher levels of PT-specific memory B cells than the 5-component vaccine, which could be explained by the higher concentration of antigen in the 1-component vaccine.

The 5-component vaccine, on the other hand, produced broader responses, with increases in both FHA- and PRN-specific memory B cells. Furthermore, this vaccine also elicited PT antibodies [11-18, 22, 31, 32].

It is important to establish the optimal antigen contents and concentrations to include in a booster dose, as we have shown here that these factors influence the extent of the vaccine response.

Regarding the immunogenicity and tolerability studies of Tdap vaccines, the authors of the Halperin studies [31] amply demonstrated that, on administering a booster dose of Tdap vaccine in adult subjects five years after the first vaccination, 100% and 95% of participants had protective levels of antibodies against tetanus and diphtheria, respectively). Furthermore, with regard to *Bordetella pertussis*, a post-vaccination antibody threshold of ≥ 50 IU/mL was seen in 82.1% (pertussis toxoid), 96.7% (filamentous haemagglutinin), 95.6% (pertactin) and 99.8% (fimbriae); this showed that a second dose of Tdap vaccine was immunogenic in adolescents and adults and was well tolerated (in fact, adverse events were slightly more frequent than after the initial dose) [31]. In the immunogenicity, reactogenicity and safety study by Asatryan et al. [32], one month after the administration of a single dose of Tdap vaccine all subjects (> 99.0%) enrolled were seroprotected against diphtheria and tetanus, and > 96.0% of the participants were seropositive for *Bordetella pertussis* antibodies. Furthermore, only one serious adverse event occurred, and this was not causally related to the vaccine under study.

With regard to the persistence of antibodies at 3, 5 and 10 years, there is a lack of long-term studies on the efficacy of the 1-component Tdap vaccine; such studies on

the 3-component and 5-component Tdap vaccines are, however, available [11-22].

Below, we report the results of two robust follow-up studies: the first one evaluated antibody persistence after a single dose of Tdap vaccine (tetanus, diphtheria and acellular *Bordetella pertussis* 5-component vaccine) in a follow-up study of 3 RCTs [43] involving both adolescents and adults; this study amply demonstrated the presence of protective antibodies against diphtheria (99%) and tetanus antitoxin (100%). Seropositivity for one or more *Bordetella pertussis* antigens also persisted for 10 years in most of the subjects enrolled, and antibody levels remained high in nearly all adults. The second study, a follow-up study of 1 RCT, was conducted 1, 3, 5 and 10 years after immunization [44]; almost all adolescents and 91% of adults had diphtheria antibody levels > 0.01 IU/mL before receiving Tdap or Td vaccines. One month after vaccination, nearly all adolescents and 94% of adults in both study groups had diphtheria antibody levels > 0.1 IU/mL; this percentage decreased slightly to 95% at 5 and 10 years. Almost all adolescents and adults always had high levels of tetanus antibodies during the entire follow-up period. GMC antibodies against each *Bordetella pertussis* antigen contained in the Tdap vaccine decreased 1 month after vaccination but remained higher than baseline levels at all follow-up times, with the exception of anti-PT after 5 and 10 years, which declined to near pre-vaccination levels in both adolescents and adults. The persistence of pertussis antibodies in adolescents followed a similar pattern to that observed in adults.

Therefore, the robustness of the data on antibody persistence in adults who receive vaccines with reduced antigen concentration is evident from the analysis of the present studies. This evidence is provided by RCTs and their related follow-up studies, which constitute an essential tool for monitoring the decay rate of antigens over time. However, we found a lack of follow-up studies on the persistence of antibodies against diphtheria-tetanus and *Bordetella pertussis* with regard to the 1-component Tdpa vaccine.

Thus, according to the follow-up studies conducted to date on adults, it can be concluded that there are substantial differences regarding the possibility of administering booster doses in the different age-groups; this finding must guide the regulatory authorities.

On the basis of the RCTs included in our analysis and of the indications for use reported in each "Summary of Product Characteristics", we briefly analyzed the age limits at which the vaccines can be administered. Indeed, the 1-component Tdpa vaccine is authorized for use in subjects aged up to 55 years (however, the short period of follow-up prevented the evaluation of long-term response) [16]. By contrast, studies on the persistence of antibodies elicited by the 3-component and 5-component Tdpa vaccines [11-22] have involved subjects up to 76 and 79 years of age, respectively. Moreover, the CDC recommends these vaccines for all subjects over 65 years of age [45].

In our analysis, we identified several studies, both in

children and in adults [12,14], involving the co-administration of reduced-antigen content vaccines indicated for boosters in adults (Tdap3 and Tdap5) with other vaccines, such as hepatitis B, influenza, pneumococcal, meningococcal vaccines and HPV vaccines; however, there is a lack of evidence to support the co-administration of the Tdap1 vaccine with others one. Furthermore, vaccines with reduced antigen content display adequate immunogenicity, as demonstrated by non-inferiority studies, without yielding a clinically significant increase in reactogenicity [12, 14, 46-48].

A further problem noted in our review is the paucity of studies evaluating long-term immunogenicity and long-term persistence of antibodies elicited by the 1-component Tdap vaccine.

When a new treatment is studied, it is important to perform well-designed clinical trials; in particular, randomization, blindness, research duration and sample size calculation are key features to evaluate [49]. In our review, we noted some shortcomings in this area (as shown by bias evaluation) with regard to studies on the 1-component Tdap vaccine [11, 21].

In conclusion, we can confirm that few RCTs with a low risk of bias are currently available to guide us in choosing the best vaccine. However, the broadest antibody response is elicited by the 3- or 5-component vaccines; the presence of antibody persistence, as demonstrated by the studies analyzed in this review, should prompt public health authorities to choose a vaccine with multiple *Bordetella pertussis* components (Tdap3 or Tdap5).

Although there is a lower content of *Bordetella pertussis* toxin in 2 out of 3 of the vaccines described, several studies support their use as vaccines during booster sessions in adolescence and/or in adults, and those with more components are generally considered more effective than a vaccine/Pa that contains only PT or even FHA [50]. Finally, as changes in circulating *Bordetella Pertussis* strains may affect vaccine efficacy, the incidence and transmission of *Bordetella pertussis* deserve to be closely monitored. In conclusion, although 3-component and 5-component vaccines contain a lower dose of antigen, they are more effective than 1-component vaccines in the prevention of diphtheria-tetanus and *Bordetella pertussis*, owing to the persistence of the antibodies elicited and the feasibility of their co-administration. The robustness of the data and the analytical tests support the use of vaccines with reduced antigen concentration for decennial booster sessions in adolescence and adulthood.

The Tdap vaccine remains of fundamental importance throughout life. Not only does it protect children through the “cocoon strategy” and immunize them in their early years, it also protects subjects who are at risk because of their working conditions or chronic diseases. Moreover, it can effectively be administered to all people every 10 years, given the demonstrated need for booster doses [51]. Finally, in order to protect infants in the postpartum period, the immunization of pregnant women is of paramount importance and is recommended in the third trimester of each gestation, regardless of

the woman’s vaccination history and the time that has elapsed since the previous gestation [52]. However, if women are not vaccinated during pregnancy, administration of the dTpa vaccine remains important. Indeed, the Advisory Committee on Immunization Practices recommends that all adolescents and adults who have, or who anticipate having, close contact with an infant younger than 12 months (siblings, parents, grandparents, child care providers and health care workers), and who have not previously undergone vaccination with the Tdap vaccine, should receive a single dose of Tdap at least 2 weeks before coming into close contact with an infant [53].

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Conflict of interest statement

The authors declare no conflict of interest.

Author's contribution

All authors carried out a systematic review to identify all scientific publications. Screening was carried out independently by the two authors (RS, CG). Any disagreement about eligibility between reviewers was resolved by discussion. The two authors extracted data from included papers using a data extraction form reviewed by each other. The two reviewers (CG and RS) identified potentially relevant articles, collected the data and independently assessed the quality of individual studies included.

References

- [1] Gabutti G, Rota MC. Pertussis: a review of disease epidemiology worldwide and in Italy. *Int J Environ Res Public Health* 2012;9:4626-38. <https://doi.org/10.3390/ijerph9124626>
- [2] Kilgore PE, Salim AM, Zervos MJ, Schmitt HJ. Pertussis: microbiology, disease, treatment, and prevention. *Clin Microbiol Rev* 2016;29:449-86. <https://doi.org/10.1128/CMR.00083-15>. PMID: 27029594; PMCID: PMC4861987.
- [3] Mink CM, Yeh SH. Pertussis in adolescents and its prevention using Tdap vaccination. *Adolesc Med State Art Rev* 2010;21:220-35, viii. PMID: 21047026.
- [4] Dalby T, Petersen JW, Harboe ZB, Krogfelt KA. Antibody responses to pertussis toxin display different kinetics after clinical *Bordetella pertussis* infection than after vaccination with an acellular pertussis vaccine. *J Med Microbiol* 2010;59(Pt 9):1029-36. <https://doi.org/10.1099/jmm.0.020826-0>. Epub 2010 May 27. PMID: 20508003.
- [5] Triaxis. Package leaflet: information for the user. Agenzia italiana del farmaco (Italian Medicines Agency). Available at https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_005532_039760_FI.pdf&retry=0&sys=m0b113. Last access on 23.10.2020

- [6] Boostrix. Package leaflet: information for the user. Agenzia italiana del farmaco (Italian Medicines Agency). Available at https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_000200_034813_Fl.pdf&retry=0&sys=m0b113. Last access on 23.10.2020
- [7] Tribaccine. Package leaflet: information for the user. Agenzia italiana del farmaco (Italian Medicines Agency). Available at https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_004314_042607_Fl.pdf&retry=0&sys=m0b113. Last access on 23.10.2020
- [8] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009;62(10):e1-34. <https://doi.org/10.1016/j.jclinepi.2009.06.006>
- [9] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17(1):1-12. PMID: 8721797
- [10] Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions* version 5.1.0. Available at: www.cochrane-handbook.org.
- [11] Carlsson RM, Gustafsson L, Hallander HO, Ljungman M, Olin P, Gothefors L, Nilsson L, Netterlid E. Two consecutive randomized controlled pertussis booster trials in children initially vaccinated in infancy with an acellular vaccine: The first with a five-component Tdap vaccine to 5-year olds and the second with five- or monocomponent Tdap vaccines at age 14-15 years. *Vaccine* 2015;33:3717-25. <https://doi.org/10.1016/j.vaccine.2015.05.079>
- [12] Embree J, Law B, Voloshen T, Tomovici A. Immunogenicity, safety, and antibody persistence at 3, 5, and 10 years postvaccination in adolescents randomized to booster immunization with a combined tetanus, diphtheria, 5-component acellular pertussis, and inactivated poliomyelitis vaccine administered with a hepatitis B virus vaccine concurrently or 1 month apart. *Clin Vaccine Immuno*. 2015;22:282-90. <https://doi.org/10.1128/0014-8177.00682-14>
- [13] Halperin SA, Scheifele D, De Serres G, Noya F, Meekison W, Zickler P, Larrivéé L, Langley JM, McNeil SA, Dobson S, Jordanov E, Thakur M, Decker MD, Johnson DR. Immune responses in adults to revaccination with a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine 10 years after a previous dose. *Vaccine* 2012;30:974-82. <https://doi.org/10.1016/j.vaccine.2011.11.035>
- [14] McNeil SA, Noya F, Dionne M, Predy G, Meekison W, Ojah C, Ferro S, Mills EL, Langley JM, Halperin SA. Comparison of the safety and immunogenicity of concomitant and sequential administration of an adult formulation tetanus and diphtheria toxoids adsorbed combined with acellular pertussis (Tdap) vaccine and trivalent inactivated influenza vaccine in adults. *Vaccine* 2007;25:3464-74. <https://doi.org/10.1016/j.vaccine.2006.12.047>
- [15] Halperin SA, Smith B, Russell M, Scheifele D, Mills E, Hasselback P, Pim C, Meekison W, Parker R, Lavigne P, Barreto L. Adult formulation of a five component acellular pertussis vaccine combined with diphtheria and tetanus toxoids and inactivated poliovirus vaccine is safe and immunogenic in adolescents and adults. *Pediatr Infect Dis J*. 2000;19:276-83. <https://doi.org/10.1097/00006454-200004000-00003>
- [16] Jahnmatz M, Ljungman M, Netterlid E, Jenmalm MC, Nilsson L, Thorstensson R. Pertussis-specific memory B-cell and humoral IgG responses in adolescents after a fifth consecutive dose of acellular pertussis vaccine. *Clin Vaccine Immunol* 2014;21:1301-8. <https://doi.org/10.1128/0014-8177.00280-14>
- [17] Halperin SA, Smith B, Russell M, Hasselback P, Guasparini R, Skowronski D, Meekison W, Parker R, Lavigne P, Barreto L. An adult formulation of a five-component acellular pertussis vaccine combined with diphtheria and tetanus toxoids is safe and immunogenic in adolescents and adults. *Vaccine* 2000;18:1312-9. [https://doi.org/10.1016/s0264-410x\(99\)00415-6](https://doi.org/10.1016/s0264-410x(99)00415-6)
- [18] Halperin SA, Donovan C, Marshall GS, Pool V, Decker MD, Johnson DR, Greenberg DP; Tdap Booster Investigators. Randomized controlled trial of the safety and immunogenicity of revaccination with tetanus-diphtheria-acellular pertussis vaccine (Tdap) in adults 10 years after a previous dose. *J Pediatric Infect Dis Soc* 2019;8:105-14. <https://doi.org/10.1093/jpids/pix113>
- [19] Sivichayakul C, Chanthavanich P, Limkittikul K, Siegrist CA, Wijagkanalan W, Chinwangso P, Petre J, Hong Thai P, Chauhan M, Viviani S. Safety and immunogenicity of a combined Tetanus, Diphtheria, recombinant acellular Pertussis vaccine (Tdap) in healthy Thai adults. *Hum Vaccin Immunother* 2017;13:136-43. <https://doi.org/10.1080/21645515.2016.1234555>
- [20] Van der Wielen M, Van Damme P, Joossens E, François G, Meurice F, Ramalho A. A randomised controlled trial with a diphtheria-tetanus-acellular pertussis (Tdap) vaccine in adults. *Vaccine* 2000;18:2075-82. [https://doi.org/10.1016/s0264-410x\(99\)00568-x](https://doi.org/10.1016/s0264-410x(99)00568-x)
- [21] Thierry-Carstensen B, Dalby T, Stevner MA, Robbins JB, Schneerson R, Trollfors B. Experience with monocomponent acellular pertussis combination vaccines for infants, children, adolescents and adults—a review of safety, immunogenicity, efficacy and effectiveness studies and 15 years of field experience. *Vaccine* 2013;31:5178-91. <https://doi.org/10.1016/j.vaccine.2013.08.034>
- [22] Pichichero ME, Rennels MB, Edwards KM, Blatter MM, Marshall GS, Bologna M, Wang E, Mills E. Combined tetanus, diphtheria, and 5-component pertussis vaccine for use in adolescents and adults. *JAMA* 2005;293:3003-11. <https://doi.org/10.1001/jama.293.24.3003>. Epub 2005 Jun 2. Erratum in: *JAMA* 2005 Dec 28;294(24):3092. PMID: 15933223.
- [23] Barkoff AM, Gröndahl-Yli-Hannuksela K, Vuononvirta J, Mertsola J, Kallonen T, He Q. Differences in avidity of IgG antibodies to pertussis toxin after acellular pertussis booster vaccination and natural infection. *Vaccine* 2012;30:6897-902. <https://doi.org/10.1016/j.vaccine.2012.09.003>. Epub 2012 Sep 13. PMID: 22981763.
- [24] Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. *N Engl J Med* 1996;334:349-55. <https://doi.org/10.1056/NEJM199602083340602>. Erratum in: *N Engl J Med* 1996 May 2;334(18):1207.
- [25] Ohfuji S, Okada K, Nakano T, Ito H, Hara M, Kuroki H, Hirota Y. Effectiveness of acellular pertussis vaccine in a routine immunization program: a multicenter, case-control study in Japan. *Vaccine* 2015;33:1027-32. <https://doi.org/10.1016/j.vaccine.2015.01.008>
- [26] Keijzer-Veen MG, Holty-van der Wekken L, Juttman RE, de Groot R, Rümke HC. Reactogenicity of acellular pertussis vaccine in 4-year-olds in The Netherlands. *Vaccine* 2004;22:3256-7. <https://doi.org/10.1016/j.vaccine.2004.03.010>
- [27] Pourakbari B, Moradi B, Mirzaee F, Mahmoudi S, Teymuri M, Mamishi S. Seroprevalence of antibodies to diphtheria, tetanus and pertussis among healthy adolescents and adults in Iran. *Roum Arch Microbiol Immunol* 2013;72:250-4. PMID: 24923108.
- [28] Afari EA, Kamiya Y, Nkrumah FK, Dunyo SK, Akpedonu P, Kamiya H, Fukai F. Randomized controlled trial of acellular diphtheria, pertussis and tetanus vaccines in southern Ghana. *Ann Trop Paediatr* 1996;16:39-48. <https://doi.org/10.1080/02724936.1996.11747802>. PMID: 8787364.
- [29] Halperin SA, Mills E, Barreto L, Pim C, Eastwood BJ. Acellular pertussis vaccine as a booster dose for seventeen- to nineteen-month-old children immunized with either whole

- cell or acellular pertussis vaccine at two, four and six months of age. *Pediatr Infect Dis J* 1995;14:792-7. <https://doi.org/10.1097/00006454-199509000-00012>. PMID: 8559630.
- [30] Fortner KB, Swamy GK, Broder KR, Jimenez-Truque N, Zhu Y, Moro PL, Liang J, Walter EB, Heine RP, Moody MA, Yoder S, Edwards KM. Reactogenicity and immunogenicity of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant and nonpregnant women. *Vaccine* 2018;36:6354-60. <https://doi.org/10.1016/j.vaccine.2018.07.012>
- [31] Halperin SA, McNeil S, Langley J, Blatter M, Dionne M, Embree J, Johnson R, Latiolais T, Meekison W, Noya F, Senders S, Zickler P, Johnson DR. Tolerability and antibody response in adolescents and adults revaccinated with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed (Tdap) 4-5 years after a previous dose. *Vaccine* 2011;29:8459-65. <https://doi.org/10.1016/j.vaccine.2011.07.068>
- [32] Asatryan A, Meyer N, Scherbakov M, Romanenko V, Osipova I, Galustyan A, Shamsheva O, Latysheva T, Myasnikova T, Baudson N, Dodet M, Xavier S, Harrington L, Kuznetsova A, Campora L, Van den Steen P. Immunogenicity, safety, and reactogenicity of combined reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine administered as a booster vaccine dose in healthy Russian participants: a phase III, open-label study. *Hum Vaccin Immunother* 2020;1-8. <https://doi.org/10.1080/21645515.2020.1796423>
- [33] Cherry JD, Heininger U, Richards DM, Storsaeter J, Gustafsson L, Ljungman M, Hallander HO. Antibody response patterns to *Bordetella pertussis* antigens in vaccinated (primed) and unvaccinated (unprimed) young children with pertussis. *Clin Vaccine Immunol* 2010;17:741-7. <https://doi.org/10.1128/CVI.00469-09>
- [34] Collins CL, Salt P, McCarthy N, Chantler T, Lane L, Hemme F, Diggle L, Buttery J, Kitchin NR, Moxon ER, Pollard AJ. Immunogenicity and safety of a low-dose diphtheria, tetanus and acellular pertussis combination vaccine with either inactivated or oral polio vaccine as a pre-school booster in UK children. *Vaccine* 2004;22(31-32):4262-9. <https://doi.org/10.1016/j.vaccine.2004.04.027>
- [35] Hori H, Afari EA, Akanmori BD, Kamiya Y, Sakatoku H, Nkrumah FK, Kamiya H, Chazono M, Fukai K. A randomized controlled trial of two acellular pertussis-diphtheria-tetanus vaccines in primary immunization in Ghana: antibody responses and adverse reactions. *Ann Trop Paediatr* 1994;14:91-6. <https://doi.org/10.1080/02724936.1994.11747699>
- [36] Knuf M, Zepp F, Meyer C, Grzegowski E, Wolter J, Riffelmann M, Wirsing von König CH. Immunogenicity of a single dose of reduced-antigen acellular pertussis vaccine in a non-vaccinated adolescent population. *Vaccine* 2006;24:2043-8. <https://doi.org/10.1016/j.vaccine.2005.11.024>
- [37] Langley JM, Predy G, Guasparini R, Law B, Diaz-Mitoma F, Whittitt P, Tapiero B, Dionne M, Tomovici A, Mills E, Halperin SA. An adolescent-adult formulation tetanus and diphtheria toxoids adsorbed combined with acellular pertussis vaccine has comparable immunogenicity but less reactogenicity in children 4-6 years of age than a pediatric formulation acellular pertussis vaccine and diphtheria and tetanus toxoids adsorbed combined with inactivated poliomyelitis vaccine. *Vaccine* 2007;25:1121-5. <https://doi.org/10.1016/j.vaccine.2006.09.053>
- [38] Schmitt HJ, von König CH, Neiss A, Bogaerts H, Bock HL, Schulte-Wissermann H, Gahr M, Schult R, Folkens JU, Rauh W, Clemens R. Efficacy of acellular pertussis vaccine in early childhood after household exposure. *JAMA* 1996;275:37-41.
- [39] Pichichero ME, Green JL, Francis AB, Marsocci SM, Murphy AM, Buscarino C. Antibody response and reactions to completion of a four-dose series with a two- or three-component acellular pertussis vaccine compared to whole cell pertussis vaccine. *Scand J Infect Dis* 1996;28:159-63. <https://doi.org/10.3109/00365549609049068>
- [40] Meyer CU, Habermehl P, Knuf M, Hoet B, Wolter J, Zepp F. Immunogenicity and reactogenicity of acellular pertussis booster vaccines in children: standard pediatric versus a reduced-antigen content formulation. *Hum Vaccin* 2008;4:203-9. <https://doi.org/10.4161/hv.4.3.5290>
- [41] Trollfors B, Knutsson N, Taranger J, Mark A, Bergfors E, Sundh V, Lagergård T. Diphtheria, tetanus and pertussis antibodies in 10-year-old children before and after a booster dose of three toxoids: implications for the timing of a booster dose. *Eur J Pediatr* 2006;165:14-8. <https://doi.org/10.1007/s00431-005-1763-3>
- [42] Tiru M, Hallander HO, Gustafsson L, Storsaeter J, Olin P. Diphtheria antitoxin response to DTP vaccines used in Swedish pertussis vaccine trials, persistence and projection for timing of booster. *Vaccine* 2000;18:2295-306. [https://doi.org/10.1016/s0264-410x\(99\)00539-3](https://doi.org/10.1016/s0264-410x(99)00539-3)
- [43] Tomovici A, Barreto L, Zickler P, Meekison W, Noya F, Voloshen T, Lavigne P. Humoral immunity 10 years after booster immunization with an adolescent and adult formulation combined tetanus, diphtheria, and 5-component acellular pertussis vaccine. *Vaccine* 2012;30:2647-53. <https://doi.org/10.1016/j.vaccine.2012.02.013>
- [44] Pool V, Tomovici A, Johnson DR, Greenberg DP, Decker MD. Humoral immunity 10 years after booster immunization with an adolescent and adult formulation combined tetanus, diphtheria, and 5-component acellular pertussis vaccine in the USA. *Vaccine* 2018;36:2282-7. <https://doi.org/10.1016/j.vaccine.2018.03.029>
- [45] Center of Disease Control (CDC). Safety information. Diphtheria, Tetanus, and Pertussis Vaccines. Available on <https://www.cdc.gov/vaccinesafety/vaccines/dtap-tdap-vaccine.html#:~:text=CDC%20recommends%3A,or%20Td%20every%2010%20years>. Last access on 29 October 20.
- [46] Muse D, Christensen S, Bhuyan P, Absalon J, Eiden JJ, Jones TR, York LJ, Jansen KU, O'Neill RE, Harris SL, Perez JL. A phase 2, randomized, active-controlled, observer-blinded study to assess the immunogenicity, tolerability and safety of bivalent rLP2086, a meningococcal serogroup b vaccine, coadministered with tetanus, diphtheria and acellular pertussis vaccine and serogroup A, C, Y and W-135 meningococcal conjugate vaccine in healthy US adolescents. *Pediatr Infect Dis J* 2016;35:673-82. <https://doi.org/10.1097/INF.0000000000001124>. PMID: 26974889.
- [47] Tashani M, Alfelali M, Barasheed O, Alqahtani AS, Heron L, Wong M, Rashid H, Findlow H, Borrow R, Booy R. Effect of Tdap upon antibody response to meningococcal polysaccharide when administered before, with or after the quadrivalent meningococcal TT-conjugate vaccine (coadministered with the 13-valent pneumococcal CRM197-conjugate vaccine) in adult Hajj pilgrims: a randomised controlled trial. *Vaccine* 2018;36:4375-82. <https://doi.org/10.1016/j.vaccine.2018.04.033>. Epub 2018 Jun 5. PMID: 29880243.
- [48] Schilling A, Parra MM, Gutierrez M, Restrepo J, Ucros S, Herrera T, Engel E, Huicho L, Shew M, Maansson R, Caldwell N, Luxembourg A, Ter Meulen AS. Coadministration of a 9-Valent human papillomavirus vaccine with meningococcal and Tdap Vaccines. *Pediatrics* 2015;136:e563-72. <https://doi.org/10.1542/peds.2014-4199>. Epub 2015 Aug 3. PMID: 26240207.
- [49] Zhong B. How to calculate sample size in randomized controlled trial? *J Thorac Dis* 2009;1:51-4. PMID: 22263004; PMCID: PMC3256489.
- [50] Poolman JT, Hallander HO. Acellular pertussis vaccines and the role of pertactin and fimbriae. *Expert Rev Vaccines* 2007;6:47-56. <https://doi.org/10.1586/14760584.6.1.47>.
- [51] Zepp F, Heininger U, Mertsola J, Bernatowska E, Guiso N, Roord J, Tozzi AE, Van Damme P. Rationale for pertussis booster vaccination throughout life in Europe. *Lancet Infect Dis* 2011;11:557-70. [https://doi.org/10.1016/S1473-3099\(11\)70007-X](https://doi.org/10.1016/S1473-3099(11)70007-X)
- [52] Murphy TV, Slade BA, Broder KR, Kretsinger K, Tiwari T, Joyce PM, et al. Prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants:

recommendations of the Advisory Committee on Immunization Practices (ACIP). Centers for Disease Control and Prevention (CDC) [published erratum appears in MMWR Morb Mortal Wkly Rep 2008;57:723]. MMWR Recomm Rep 2008;57(RR-4):1-51.

[53] Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women - Advisory Committee on Immunization Practices (ACIP), 2012. Centers for Disease Control and Prevention (CDC). MMWR Morb Mortal Wkly Rep 2013;62:131-5.

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Supplementary Tab. I. Disease background and exclusion criteria of included study.

First author's last name	Disease background and exclusion criteria
Carlsson	<ul style="list-style-type: none"> a. Serious chronic illness (cardiac or renal failure, failure to thrive, progressive neurological disease, uncontrolled epilepsy, infantile spasm) b. immunosuppression c. Previous culture-confirmed pertussis.
Embree	<ul style="list-style-type: none"> a. Any substantial underlying chronic disease (including malignancy; known impairment of neurological function or a seizure disorder of any etiology) b. Immunodeficiency, immunosuppression, or receipt of high-dose steroids; c. Receipt of any pertussis-, diphtheria-, tetanus-, or poliomyelitis-containing vaccines or HBV vaccine within the previous 5 years; history of physician-diagnosed or laboratory-confirmed pertussis disease within the previous 2 years; receipt of blood products or immunoglobulins within the previous 3 months; receipt of any vaccine within 2 weeks of any study vaccine administration; or daily use of non-steroidal anti-inflammatory drugs d. Known or suspected allergy to any vaccine components in the study.
Halperin	<ul style="list-style-type: none"> a. Pregnant or nursing b. Allergic to Tdap vaccine or any of its constituents or to latex
McNeil	<ul style="list-style-type: none"> a. Any significant underlying chronic disease (malignancy, neurological disease or seizure disorder requiring medication) b. Primary disease of the immune system or use of immunosuppressive therapy or daily non-steroidal anti-inflammatory therapy, c. Received any Tdap vaccines within 5 years prior to enrolment, influenza vaccine during the current year, blood products or immunoglobulins within three months of enrolment, or if they had a history of physician-diagnosed or laboratory-confirmed pertussis disease within 2 years prior to enrolment. d. Known or suspected allergy or previous adverse events to any of the vaccines or vaccine components being used in the trial e. Pregnant or breast feeding or unwilling to use effective contraception during the study
Halperin	<ul style="list-style-type: none"> a. Significant underlying chronic illness and seizure disorder b. Known or suspected diseases of the immune system or immunosuppressive therapy, receipt of a blood product in the previous 3 months, c. Receipt of any pertussis-, polio-, diphtheria- or tetanus-containing vaccine in the previous 5 year d. Allergy to a vaccine constituent, physician-diagnosed pertussis in the previous 2 years e. Pregnancy or planned pregnancy during the study period
Halperin (Vaccine)	<ul style="list-style-type: none"> a. Significant underlying chronic illness, seizure disorder b. Known or suspected diseases of the immune system or immunosuppressive therapy, receipt of a blood product in the previous 3 months c. Physician-diagnosed pertussis in the previous two years, or receipt of any pertussis-, diphtheria- or tetanus-containing vaccine in the previous 5 years d. Allergy to a vaccine constituent e. Pregnancy or planned pregnancy during the study period
Halperin	<ul style="list-style-type: none"> a. Had a chronic illness or medical condition b. Suspected congenital or acquired immunodeficiency or had received blood or blood-derived products in the previous 3 months; had received any vaccine within 30 days before receiving study vaccine (except for flu vaccine, which was allowed up to 15 days before the study vaccine) or had plans to receive another vaccine before the second study visit; had participated in another interventional clinical trial; had reported seropositivity to HIV, HBV or HCV; thrombocytopenia or a bleeding disorder that would be a contraindication for an intramuscular injection c. Received any dtp vaccine since receipt of the qualifying dose of Tdap vaccine 8 to 12 years earlier or had physician-diagnosed or laboratory-confirmed pertussis in the previous 10 years d. Hypersensitivity or previous severe reaction to a pertussis-, tetanus-, or diphtheria-containing vaccine; Guillain-Barré syndrome; moderate or severe illness at the time of vaccination e. Pregnancy or breastfeeding
Sirivichayakul	<ul style="list-style-type: none"> a. History of significant medical illness or individuals with any progressive or severe neurological disorder, seizure disorder or Guillain-Barré syndrome; b. Immunodeficiency c. Having received any Diphtheria or Tetanus or Pertussis vaccine within 5 years prior to enrolment in the present study d. History of allergy to any vaccine component or history of serious adverse event or neurological adverse event after injection with DTP vaccine e. Pregnant or breastfeeding women f. History of alcoholism and/or intravenous drug abuse

Van der Wielen	<ul style="list-style-type: none"> a. Administration of immunosuppressive/ immune-modifying drugs b. Previous vaccination against either diphtheria or tetanus within 5 years or vaccination against pertussis since childhood; a known history of diphtheria or tetanus; known exposure to diphtheria or pertussis within the previous 5 years; or a known history of non-response to diphtheria, tetanus or pertussis vaccination. c. History of allergic disease or reactions likely to be exacerbated by any component of the vaccine; or previous record, following DTP vaccination, of any serious adverse reaction or precautionary indication for DTP vaccination d. Administration of vaccines not foreseen by the protocol (one month before or after the start of the trial), of immunoglobulins and blood products (3 months prior or during the trial)
Thierry-Carstensen	<ul style="list-style-type: none"> a. Progressive neurological disease, uncontrolled epilepsy, progressive encephalopathy b. Immune deficiency or administration of immune-modulating drugs ≤ 3 months before inclusion c. Tetanus, diphtheria, or pertussis vaccination or infection ≤ 5 years before inclusion d. Known hypersensitivity to any of the vaccine components e. Pregnancy f. vaccination with any vaccine ≤ 1 month before inclusion
Pichichero	<ul style="list-style-type: none"> a. Malignancy, significant underlying disease, neurological impairment, acute respiratory illness b. Any immunodeficiency or daily use of oral nonsteroidal, anti-inflammatory drugs; receipt of blood products or immunoglobulins within 3 months c. Receipt of any DTP vaccine within 5 years; diagnosis of pertussis within 2 years d. Allergy or sensitivity to any vaccine component, including previous vaccine reactions e. Pregnancy

Supplementary Tab. II. Characteristics of excluded studies.

Study	Reason
Barkoff, 2012 [22]	Single-arm study evaluating the antibody response induced after booster vaccination and infection
Gustafsson, 1996 [23]	RCT evaluating serological response in child at 2, 4 and 6 months of age (range of age out of the aim of the study)
Ohfuji, 2015 [24]	Multicentre case-control study comparing the history of DTaP vaccination between 55 newly diagnosed pertussis cases and 90 age- and sex- matched controls.
Keijzer-Veen, 2004 [25]	Observational study of reactivity of acellular pertussis vaccine in 4-year-olds
Hanvatananukul, 2020 [26]	Cross-sectional study to determine the seroprevalence of antibodies against DTP among Thai adolescents
Afari, 1996 [27]	RCT study of acellular DTP in southern Ghana on children under 5 years of age and women of fertile age
Halperin, 1995 [28]	RCT study of acellular pertussis vaccine as a booster dose for 17- to 19-month-old children previously immunized at 2, 4 and 6 months of age
Fortner, 2018 [29]	RCT study on pregnant and non-pregnant women
Halperin, 2011 [30]	Open-label, non-randomized, multicentre study in which participants in three previous randomized, controlled trials of Tdap received a second dose of Tdap vaccine
Asatryan, 2020 [31]	Phase III, open-label, non-randomized study
Cherry, 2010 [32]	Described other study performed in the 1980s and 1990s
Collins, 2004 [33]	RCT on immunogenicity and reactivity of two combined low-dose DTaP vaccines in children aged 3-3.5 years
Hori, 2016 [34]	RCT of two dTAP vaccines in Ghana in 89 infants
Knuf, 2004 [35]	A controlled open-labelled double-blind trial with Biken acellular pertussis vaccine
Langley, 2005 [36]	RCT on children 4-6 years old
Schmitt, 1996 [37]	Blinded prospective follow-up of immunized children
Pichichero, 1996 [38]	RCT on 190 infants
Meyer, 2008 [39]	RCT on immunogenicity and reactivity in 4- to 6-year-old children
Trollfors, 2006 [40]	Open study on 502 10-year-old children
Tiru, 2000 [41]	Post hoc analysis
Tomovici, 2012 [42]	Follow-up study of 3 RCT
Pool, 2018 [43]	Follow-up of an RCT at 1, 3, 5 and 10 years post-vaccination