ERRATA CORRIGE

The original version of this article unfortunately contained some mistakes. These errors were corrected.

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Review

Immunogenicity and antibody persistence of diphteria-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 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 6,906 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) safe and efficacy 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; c) identifying the gold standard for adolescent and adult immunizations.

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 database, 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

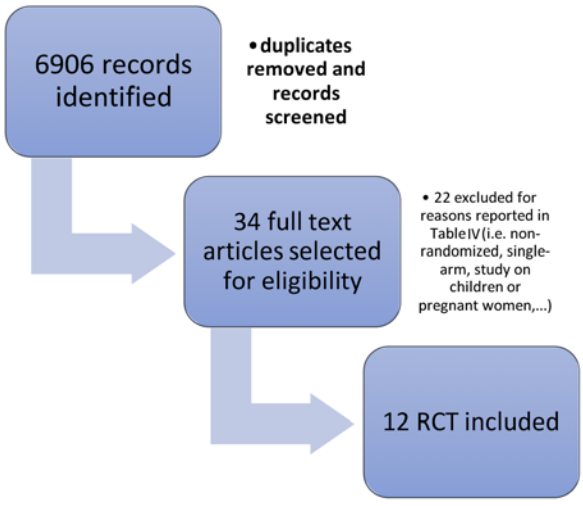
All the studies included were randomized trails. Their characteristics are summarized in Table II. Twelve RCT were included in our review; of these, 7 had only 1 control group, 4 had 2 control groups and 1 had 5 control groups; moreover, of the 12 studies included, only 2 regarded co-administration [12, 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 presnce 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;

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.

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



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 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

Tab. II. Studies included in systematic review.

Reference	Year of publication	Study design	Total n. of participants	Age range	Gender	Arm 1	Arm 2
Carlsson [11]	2015	RCT	230	14-15	Both	114 (Tdap5)	113 (Tdap1)
Embree [12]	2015	RCT	236	11-14	Both	144 (Tdap5 -Polio) HepB 1 month later	132 (Tdap5-Polio) HepB concurrently
Halperin [13]	2012	RCT	769	20-72	Both	407 (Naive Tdap)	362 (Repeat dose group Tdap5)
McNeil [14]	2007	RCT	720	19-64	Both	359 (Tdap5 concomitant administration with flu)	361 (Tdap5 sequential administration with flu)
Halperin [15]	2000	RCT	1,207	12-60	Both	Adolescents^ Adults^^	Adolescents^ Adults^^
Jahnmatz [16]	2014	RCT	230	14-15	Both	Tdap1	Tdap5
Halperin [17]	2000	RCT	749	12-55	Both	151* (Td)	449* (TdaP5)
Halperin [18]	2019	RCT	1,330	18-65	Both	1002 (Tdap5)	328 (Td)
Sirivichayakul [19]	2017	RCT	60	18-35	Both	20° (Tdap5)	20° BNA'S Tdap3
Van der Wielen [20]	2000	RCT	299	18-73	Both	96$ (Tdap3)	98$ (Td)
Thierry-Carstensen [21]	2012	RCT	802	18-55	Both	401 (Tdap1)	401 (Td)
Pichichero [22]	2005	RCT	4,480	11-64	Both	3053 (Tdap5)§	1427 (Td)§

^ 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 = 1,232 TdaP5; cohort 2: n = 821 Td.
Adults: cohort 1: n = 1,821 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 (DT)	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	-

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

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).

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.

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 administration 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 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 toxoids 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 BioNet'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, adverse reactions were infrequent and no serious ones 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 vaccination 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, flu, 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 receivingTdap 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 Tdpa 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 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.

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

Reference	Disease background and exclusion criteria
Carlsson [11]	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 [12]	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 [13]	a. Pregnant or nursing b. Allergic to Tdap vaccine or any of its constituents or to latex
McNeil [14]	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 [15]	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
Jahnmatz [16]	a. Clinical or bacteriological diagnosis of pertussis
Halperin [17]	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 [18]	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 [19]	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 [20]	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 [21]	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 [22]	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 [23]	Single-arm study evaluating the antibody response induced after booster vaccination and infection
Gustafsson, 1996 [24]	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 [25]	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 [26]	Observational study of reactivity of acellular pertussis vaccine in 4-year-olds
Hanvatananukul, 2020 [27]	Cross-sectional study to determine the seroprevalence of antibodies against DTP among Thai adolescents
Afari, 1996 [28]	RCT study of acellular DTP in southern Ghana on children under 5 years of age and women of fertile age
Halperin, 1995 [29]	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 [30]	RCT study on pregnant and non-pregnant women
Halperin, 2011 [31]	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 [32]	Phase III, open-label, non-randomized study
Cherry, 2010 [33]	Described other study performed in the 1980s and 1990s
Collins, 2004 [34]	RCT on immunogenicity and reactivity of two combined low-dose DTaP vaccines in children aged 3-3.5 years
Hori, 2016 [35]	RCT of two dtap vaccines in Ghana in 89 infants
Knuf, 2004 [36]	A controlled open-labelled double-blind trial with Biken acellular pertussis vaccine
Langley, 2005 [37]	RCT on children 4-6 years old
Schmitt, 1996 [38]	Blinded prospective follow-up of immunized children
Pichichero, 1996 [39]	RCT on 190 infants
Meyer, 2008 [40]	RCT on immunogenicity and reactivity in 4- to 6-year-old children
Trollfors, 2006 [41]	Open study on 502 10-year-old children
Tiru, 2000 [42]	Post hoc analysis
Tomovici, 2012 [43]	Follow-up study of 3 RCT
Pool, 2018 [44]	Follow-up of an RCT at 1, 3, 5 and 10 years post-vaccination