



SYSTEMATIC REVIEW

# Systematic review of immunogenicity and duration of immunity of currently licensed pertussis wP vaccines in children

[version 1; peer review: 2 approved with reservations]

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## Abstract

**Background:** Currently recommended whole cell pertussis (wP) vaccination schedule for children includes a 3-dose primary schedule, and at least one booster dose. When estimating the impact of additional strategies to reduce pertussis burden through modelling, duration of immunity conferred by childhood immunization is among the parameters models are most sensitive to. We aim to assess the duration of immunity of currently available wP vaccines in children and the additional protection conferred by booster doses.

**Methods:** We conducted a systematic review of published studies of current commercially available vaccines indexed in Medline, Embase, Web of Science, Lilacs, SciELO and Central until September 2021. We included clinical trials, observational longitudinal, and cross-sectional studies. Citation screening, data extraction, and risk of bias and methodological quality assessment were done in duplicate by independent reviewers, following the study protocol registered in PROSPERO. Studies were included if they reported primary data on the protection, immunity, or duration of immunity conferred by  $\geq 3$  doses of wP vaccine in healthy children, without restriction to time or location of the study. Outcomes included clinical events or serological evidence of protection.

**Results:** We included 12 studies conducted from 2007-2020 with heterogeneous methodological quality. Studies report on 5 of the 18

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currently available wP vaccines in use. After primary immunization, geometric mean concentration (GMC) of anti-pertussis toxin ranged from 9.1 EU/mL (95% confidence intervals [CI]: 8.1-10.2) to 50.9 (95%CI: 45.9-56.4). Prior to the 1st booster, GMC titers were low ranging from 4.7 to 10 EU/mL, and after the 1st booster averaged around 42 EU/mL.

**Conclusions:** The limited available evidence on immunogenicity of currently available wP vaccines reinforces the need for booster doses and suggests that the duration of wP immunity is short, probably <5 years. This is important information for vaccination policy makers, investigators and modelers.

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### Keywords

systematic review, immunogenicity, pertussis vaccine, whole-cell, children, duration of protection

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## Introduction

Pertussis (whooping cough), a respiratory infectious disease caused by *Bordetella pertussis*, and characterized by mild fever, runny nose, and paroxysmal coughing. It is most severe in infants, where the burden of disease is greatest<sup>1</sup>. Pertussis vaccines have been available globally for decades through national immunization programs<sup>2</sup>. Two types of pertussis vaccines are available: whole-cell (wP) vaccines composed of killed *B. pertussis*, and acellular (aP) vaccines based on purified *B. pertussis* antigens. Pertussis antigens are generally combined in a trivalent formulation with diphtheria and tetanus toxoids (DTP), and often, in addition, with *Haemophilus influenzae* type B (Hib) and hepatitis B virus (HepBV) antigens as tetravalent or pentavalent vaccines. Although aP have replaced wP vaccines in high-income countries, most middle/low-income countries use wP in their childhood vaccine schedules. Globally, vaccine schedules vary significantly. While the majority of low/middle income countries in the Western-Pacific, African and South-East Asian regions use the six-, 10- and 14-week schedule without a booster, Latin American countries use a two-, four- and six-month schedule with boosters at 18 or/and 60 months of age<sup>3,4</sup>. More than 100 countries among the 194 monitored by the World Health Organization (WHO) use vaccines that include wP for routine childhood immunization<sup>5</sup>.

With pertussis outbreaks being reported by many countries in the last decade<sup>6-8</sup>, additional prevention strategies have been suggested, including maternal immunization, adolescent immunization, and vaccination of close contacts to infants too young to be vaccinated (strategy *cocooning*). In order to guide decision making, studies modeling the impact and cost-effectiveness of these strategies have been published<sup>9</sup>. The duration of immunity and protection conferred by childhood wP immunization, one of the parameters to which models are most sensitive, is not known, particularly for wP vaccines currently in use in the world<sup>2</sup>. In addition, it is still unclear what additional protection is provided by the varying number of booster doses.

Given the importance of understanding the duration of protection from a three-dose primary series, the objective of the present study was to identify, summarize and critically appraise the current evidence on the duration of immunity of currently available wP vaccines in children, for public health purposes and for modelling studies. We also assessed the additional protection conferred by fourth and fifth doses (booster doses), when compared to the three-dose primary series. A review at this time is particularly needed because, in recent years, original manufacturers of wP vaccines have withdrawn from the market and been replaced by new emerging-market manufacturers<sup>10,11</sup>. Thus, much of the evidence in the literature, which evaluated older products, is no longer relevant.

## Methods

### Study design

We first conducted a search to identify currently available wP vaccines and their manufacturers, then conducted a systematic search for published articles that assessed the duration

of immunity and effect of boosters of currently available vaccines. The study protocol was registered in PROSPERO (registration number [CRD42018107309](https://doi.org/10.1186/1745-6215-107309)). We planned and developed the review following the Cochrane Handbook for Systematic Reviews of Interventions<sup>12</sup>. We followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations for reporting<sup>13,14</sup>.

The review question, developed in accordance with the elements of the acronym PICO (Population, Intervention, Comparator and Outcomes), is presented in [Box 1](#).

### Box 1. The PICO statement

- P – Healthy children vaccinated with wP, under 6 years old, of both sexes.
- I – Currently available wP vaccine in 3+0, 3+1 or 3+2 dosing schedules.
- C – No comparator; children vaccinated with aP; or children vaccinated with different wP dosing schedules.
- O – Any outcomes of clinical efficacy or effectiveness, or immunogenicity markers

### Currently available wP vaccines

As there is no single structured source of information on wP vaccines currently in use, we first obtained the 2019 list of wP vaccines pre-qualified by the World Health Organization (WHO)<sup>15</sup>, which listed five wP vaccine manufacturers. Vaccines from these manufacturers are likely to be used by developing countries as they are commercially available through vaccine procurement funds such as United Nations Children's Fund (UNICEF) and the Pan American Health Organization (PAHO)'s Revolving Fund<sup>4</sup>. We then obtained the 2018 list of wP vaccine manufacturers from the "Developing Countries Vaccine Manufacturing Network" (DCVMN) from WHO<sup>4</sup>, which lists 13 manufacturers of wP vaccine, only three of which were also included in WHO's pre-qualified list. The remaining 10 wP manufacturers likely produce wP vaccines for domestic use by National Immunization Programs, which are thus not commercialized or exported. Finally, we used a January 2018 Global Vaccine Market study commissioned by WHO<sup>16</sup>, which presents a map of global producers of vaccines that contain diphtheria and tetanus components. Producers that were not on the previous lists (WHO pre-qualified and DCVMN) and could be producers of wP were identified from the map and further verified through internet searches on the websites of each producer. Three more manufacturers were identified from this source.

### Inclusion and exclusion criteria

We included all studies reporting primary data, in which the protection, immunity or duration of immunity conferred by a currently available wP vaccine was assessed. In keeping with the goals of the review, only studies in which immunological markers in a group of individuals were assessed over time after the primary series, or which compared three doses with four or five doses, were included.

Randomized controlled trials (RCTs) and observational studies were included. We categorized observational studies as case-control, cohort (including controlled and uncontrolled cohort studies), and cross-sectional study designs. To be eligible for review, studies had to target healthy children of either sex who had received wP vaccination by the age of six years, and also evaluate a primary schedule of three doses administered by six months of age and/or any additional booster doses. Eligible studies could have compared children vaccinated with wP to unvaccinated children, to children vaccinated with aP, to children vaccinated with different wP dosing schedules, or have no comparator.

The outcomes measured in the study could be clinical efficacy/effectiveness or immunogenicity levels, including seroconversion (% of individuals who seroconverted at a given threshold value), antibody levels (reported as described by the authors as geometric mean antibody concentrations/titers (GMC/GMT)), and/or serological measurements of antibody levels over time. Immunologic markers included anti-pertussis toxin (PT), anti-pertussis fimbriae (anti-PF), anti-pertussis agglutinating antibody (anti-Agg), and anti-filamentous hemagglutinin (anti-FHA).

Studies were excluded if they: assessed children with underlying disease; used fractionated vaccine doses; evaluated only acellular pertussis (aP) vaccine; evaluated only 1 or 2 doses; or had only one immunogenicity assessment after the 3rd primary dose, without any later assessment to evaluate the decay of antibody titers. We also excluded ecological and modeling studies, letters to the editor, recommendations, guidelines, and reviews.

### Literature search

Electronic searches were conducted in Medline (PubMed), Embase, Web of Science, Lilacs, and Central. A complementary search was conducted in the electronic library SciELO. Additionally, reference lists of selected articles and reviews were screened. No date, location, or language limits were placed on the searches which included publications between 30 April, 2019 and updated in September 21, 2021. Search strategies for each database are presented in Supplementary Table 1 (*Extended data*<sup>14</sup>).

### Study selection

The procedure for screening and selecting studies was carried out in two phases. In the first phase, three reviewers (AB, MQ and GP) independently screened all titles and abstracts for duplication and inclusion criteria. Then, screened articles were categorized as potentially eligible, unclear, or excluded. Citations on which the reviewers disagreed were discussed or assessed by a fourth reviewer (CT). In the second phase, two reviewers (AB and MQ) independently screened studies obtained for full reading to confirm that they met the eligibility criteria.

### Data collection

Data extraction, done by two independent reviewers, using abstraction forms developed for this review with Microsoft

Excel (Microsoft Inc.), included country, funding source, study design, intervention details (vaccine and manufacturer, vaccination schedule, age of administration of each dose), study setting and period, measure of outcome including case definition and diagnostic criteria, baseline information on study population, methods for data analysis, and main results. Results extracted included descriptive study characterization, clinical results (absolute numbers or rates of pertussis cases), and serological results considering any anti-pertussis antibody type, including percentage of individuals who seroconverted and/or antibody GMT/GMC. Finally, information on pertussis vaccines and schedules in use in the country where each study was conducted was also obtained in WHO-reported immunization schedules by vaccine, by country<sup>17</sup>.

### Quality assessment

The methodological quality of studies was assessed using: a) the revised Cochrane tool for assessing risk of bias in randomized trials (Cochrane Risk of Bias tool)<sup>18</sup>, b) the Quality Assessment Tool for cohort or case-control, non-randomized trials studies with: The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I)<sup>19</sup>, and c) the Critical Appraisal tools for use in Systematic Reviews Checklist for Analytical Cross Sectional Studies from Joanna Briggs Institute<sup>20</sup>. For the latter, considering the eight items in the checklist, we categorized the studies as presenting low risk (when scoring 7 or 8), moderate risk (scoring 6 or 5), or high risk (scoring 4 or lower).

Two authors performed the methodological assessments independently, and disagreements between reviewers were assessed and sources of divergence discussed until agreement was reached. When disagreement was not resolved, a third reviewer was used as an arbitrator.

### Data analysis

We conducted descriptive analyses of manufacturers and vaccines identified and of published study characteristics including design, country, study period, population, vaccine and schedule used, endpoints considered, number of children enrolled and assessed, and study follow-up period.

For studies reporting immunological outcomes, we originally planned to conduct a meta-analysis to pool results from similar studies presenting antibody titers or seroconversion rates at similar points in time in relation to primary series and each additional booster dose. The meta-analysis was precluded; however, as the included studies were very heterogeneous in terms of the immunological markers and indicators considered, points in time in which they were assessed, and study designs. Thus, we have restricted our findings to a qualitative descriptive synthesis of the results reported by each study.

Results are presented by type of outcome. For efficacy or effectiveness, for studies with clinical endpoints, the main measure of interest is the vaccine's effect in reducing pertussis, reported as number of events in each study group and absolute risk between vaccinated and unvaccinated as calculated by the review authors. For immunogenicity studies, results are

presented either as GMT or GMC of anti-PT, anti-FHA, and/or as percent of individuals who seroconverted given a threshold as reported in the original study. All results are presented by dose of vaccine and timing of measurement of immune response, considering point in time after the primary vaccine series.

## Results

### Vaccines currently in use

In total, we identified 18 manufacturers producing the currently available wP vaccines (Table 1). Seven are located in India, and no other country reports more than one manufacturer; with South Korea being the only high-income country represented. Five of these manufacturers are in WHO's pre-qualification list – four in India and one in South Korea. Although the WHO list included wP vaccine Quinvaxem, produced by Janssen Vaccines Corp. since 2011, the manufacturer discontinued its production in 2017 and the latest expiry date of batches supplied was December 2019. As this vaccine is currently no longer in use, we did not include it in our analysis.

### Articles identified for the systematic review

A total of 2,648 non-duplicate references were identified, and, after screening based on titles and abstracts (first phase), 517 were retained for further assessment. Although the searches were done without language restriction, seven articles had to be excluded because they were written in languages not read by the authors (two Chinese<sup>21,22</sup>, two German<sup>23,24</sup>, one Russian<sup>25</sup> and two in Uzbek<sup>26,27</sup>). After full texts were assessed (second phase), a total of 12 studies<sup>28–39</sup> met the inclusion criteria. We present the complete PRISMA flow diagram in Figure 1. The complete list of excluded articles and reasons for exclusion is available upon request.

### Study characteristics

The included 12 studies report on research conducted in 2007–2020. They evaluated 13 vaccines from only six of the 18 vaccine manufacturers we identified as producing vaccines currently in use. The majority of the included studies (n=8) presented data from vaccines manufactured by Serum Institute of India Ltd (Table 2, Supplementary Table 2, Extended data<sup>14</sup>). Study designs included three RCT<sup>28,29,32</sup>, two uncontrolled prospective cohort<sup>33,34</sup>, and seven cross-sectional studies<sup>30,31,35–39</sup>. The studies were conducted in seven countries, none of which had introduced maternal pertussis vaccination at the time of study completion (Table 2).

Detailed characteristics of the included studies are presented in Table 3. Only two studies assessed clinical outcomes<sup>35,36</sup>, whereas the other studies assessed immunogenicity levels as main study outcomes. For studies that presented individual data over time (all except cross-sectional studies), most had a follow-up time of only one month after a given vaccine dose. Two of the RCT<sup>28,29</sup> assessed the first booster dose (equivalent to fourth dose), reporting immunogenicity levels one month later. Three studies<sup>34,35,39</sup> assessed children who received a second booster dose (equivalent to fifth dose).

### Methodological assessment of studies

Methodological quality assessment of the included studies and reasons for judgement are presented in Supplementary Tables 3, 4 and 5 in the Extended data<sup>14</sup>. The quality of the 12 included studies varied significantly.

The two uncontrolled prospective cohort studies had serious<sup>33</sup> or critical<sup>34</sup> quality issues on Robins-I quality assessment tool (Supplementary Table 3, Extended data<sup>14</sup>). Of the seven cross-sectional studies, two studies reporting clinical outcomes were assessed as of moderate overall quality<sup>35,36</sup>. Cross-sectional studies reporting immunogenicity outcomes had heterogeneous quality assessments, with one of high risk<sup>37</sup>, three moderate risk<sup>31,38,39</sup>, and two low risk<sup>30</sup> based on the Joanna Briggs' Institute checklist (Supplementary Table 4, Extended data<sup>14</sup>). The 3 randomized controlled trials all had an overall high risk of bias (Supplementary Table 5, Extended data<sup>14</sup>).

### Study results

All the RCTs and uncontrolled prospective cohort studies had short follow-up periods<sup>28,29,32–34</sup>, with a maximum of six weeks post-completion of the primary schedule (third wP dose). Five<sup>30,31,37–39</sup> cross-sectional studies included children of older ages (six years of age and older), and only one of these<sup>39</sup> evaluated children of 72 months of age who received a second booster dose (Table 3).

We report study results separately for the 10 studies that reported immunogenicity outcomes and the two that reported clinical outcomes (Table 4, panels A and B, respectively). For studies reporting on immunogenicity outcomes, GMC levels (EU/mL; 95% confidence interval [CI] or mean  $\pm$  standard deviation [SD]), and seroconversion percentages (and 95% CI) at each timepoint are described in Table 4 (Panel A). One study<sup>33</sup> evaluated two independent cohorts of individuals separately: although both cohorts received the same wP vaccine as the first booster dose, each cohort received a different vaccine in the primary series. We thus report results for these two cohorts separately, resulting in 13 sets of results in total.

We analyzed outcomes at five separate time points: up to 30 days post-third dose (primary series); pre-fourth dose/first booster (usually measured at 15–18 months); up to 30 days post-fourth dose; pre-fifth dose/second booster (usually measured at four–six years of age); and post-fifth dose, as depicted in Table 5.

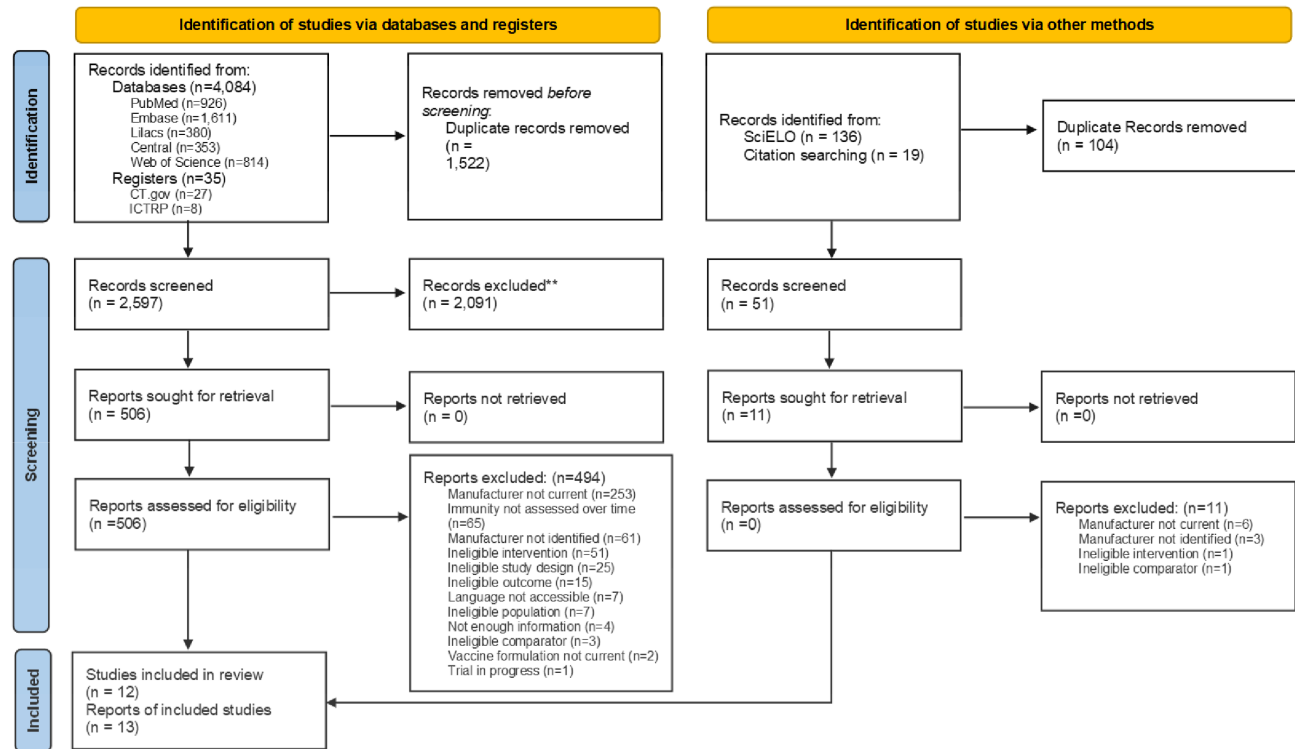
The data show that immunogenicity levels, reported as mean GMT, were low right before the fourth (first booster) with all studies reporting levels below 11 EU/mL<sup>33,37,39</sup>, with three reporting values reaching above 40 EU/mL one month after the fourth-dose studies<sup>29,33</sup> (Figure 2). Similarly, low levels of GMT were reported prior to the fifth dose<sup>34,37–39</sup>, with the single study evaluating pre and post-fifth dose reporting levels of 8.4 EU/mL prior, and 30.2 EU/mL 30 days post booster<sup>34</sup>.

**Table 1. Currently available wP vaccines as of 2019.**

Vaccine manufacturer	Commercial name	Country of origin (Source of information)	Vaccine Composition	Other vaccine components
The Bio Farma- PT (Persero)	DTP-HB-Hib (Pentabio)	Indonesia (WHO-PQ)	Each 0.5 ml dose contained: 20 Lf purified diphtheria toxoid, 7.5 Lf purified tetanus 12 OU inactivated whole-cell B. pertussis	0.10% thiomersal
Biological E. Limited (GPO)	TRIPVAC HB and ComBE Five	India (WHO-PQ, DCVMN)	Each 0.5 ml dose contained: 25 Lf(>30IU) purified diphtheria toxoid, 8.8 Lf(>60IU) purified tetanus 16I OU inactivated whole-cell B. pertussis, 12.5 Mg rHBsAg 10 Mg H. influenzae type b (PRP)	0.10% Thiomersal, Aluminium (Al) <1.25 mg
LG Chem Ltd	Eupenta™ Inj., Euforvac-Hib™ Inj.	South Korea (WHO-PQ, DCVMN)	Each dose contained: Diphtheria Toxoid 15 Lf Tetanus Toxoid 10 Lf Inactivated w-B. pertussis>4 IU HBsAg 10 mcg H. influenzae type b conjugated to Tetanus Toxoid 30-50 mcg	Aluminium (Al) 0.39 mg, Thiomersal as preservative 0.10% mg/dose
Panacea Biotec Ltd.	EasySix, Easyfive-TT and Easyfour-TT, Ecovac4	India (WHO-PQ, DCVMN)	Each dose of 0.5 ml contained: Diphtheria Toxoid* 20 Lf (30 IU) Tetanus Toxoid* 7.5 Lf (60 IU) Inactivated w-B. pertussis* 12 OU (4 IU) HBsAg 10 mcg H. influenzae type b (PRP) conjugated to Tetanus Toxoid 10 mcg	Aluminium (Al) 0.25 mg, Thiomersal as preservative 0.025 mg/dose
Shantha Biotechnics Private Limited (A Sanofi Company)	Shan-5	India (WHO-PQ)	Each dose vaccine contained: diphtheria toxoid (≥30 IU), tetanus toxoid (≥60 IU), whole cell Bordetella pertussis (≥4 IU), HBV surface antigen (10 mcg), Hib polysaccharide conjugated with tetanus toxoid (10 mcg)	Adsorbed on Aluminium Phosphate (0.625 mg) as adjuvant, Thiomersal as preservative (0.050 mg) along with sodium chloride (4.5 mg) and the volume was made 0.5 mL with water for injection
Serum Institute of India (SII) Pvt. Ltd.	Pentavalent, Quadravax and Q-Vac	India (WHO-PQ, DCVMN)	Each dose Pentavalent contained: a combination vaccine containing the diphtheric and tetanic toxoids, inactivated cells of B. pertussis bacteria, a conjugated polysaccharide of Haemophilus influenzae B type, and the surface antigen of Hepatitis-B virus Each dose Quadravax contains: Diphtheria Toxoid 25 Lf ( 30 IU) Tetanus Toxoid 5 Lf ( 40 IU) B. pertussis 16 OU ( 4 IU) Purified Capsular Polysaccharide (PRP) 10 mcg	Adsorbed on Aluminium Phosphate, Al 1.25 mg Preservative: Thiomersal 0.005%

Vaccine manufacturer	Commercial name	Country of origin ( Source of information)	Vaccine Composition	Other vaccine components
Bharat Biotech International Limited	ComVac3, ComVac 4-HB and ComVac5	India (DCVMN)	Each dose contained: Com Vac 3:Diphtheria Toxoid 20 - 25 Lf Tetanus Toxoid 5.0 - 7.5 Lf B. Pertussis whole cell inactivated 15 OU - 20 OU Comvac4: add Hepatitis B Surface Antigen (rDNA)10mcg ComVac5 Diphtheria Toxoid $\geq 20$ Lf to $\leq 30$ Lf ( $\geq 30$ IU) Tetanus Toxoid $\geq 5$ Lf to $\leq 25$ Lf ( $\geq 60$ IU) B. pertussis (Whole Cell Inactivated) $\geq 4$ IU Hepatitis B surface Antigen (HBsAg) $\geq 10\mu\text{g}$ Hib PRP-TT Conjugate $\geq 10\mu\text{g}$	Comvac3 and 4: Aluminium (Al) 0.3 mg Thiomersal I.P. (as Preservative) 0.0 25 mg Com Vac5: Aluminium (Al) 0.3mg
Bio Manguinhos	DTPHib	Brazil (DCVMN)	Not reported	Not reported
BulBIO	Diftetkok / Diftetkok	Bulgaria (GVM)	Each dose contained: Vaccinum diphtheria, tetani and pertussis adsorbatum	Not reported
DTP vaccine-Vaccera	DTP vaccine	Egypt (DCVMN)	Not reported	Not reported
Finlay Intitute	DTP vax	Cuba (DCVMN)	Each 0.5 ml dose contained: 25 Lf purified diphtheria toxoid, 10 Lf purified tetanus 16 OU inactivated whole-cell B. pertussis	Thiomersal, 0.05 mg Aluminium 1 mg
HLL Biotech Limited	PENTAHIL	India (DCVMN)	Each dose contained: Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA) and Haemophilus Type b Conjugate Vaccine (Adsorbed) I.P.	
Indian Immunological	Vantar-5 e Abhay TAG	India (DCVMN)	Each dose of 0.5 mL contained: Diphtheria toxoid: $\geq 30$ IU ( $\geq 20$ Lf to $\leq 30$ Lf) Tetanus toxoid: $\geq 60$ IU ( $\geq 5$ Lf to $\leq 25$ Lf) Inactivated whole cell B. pertussis: $\geq 4$ IU HBsAg (rDNA): $\geq 10\mu\text{g}$ Hib Polysaccharide covalently bound to TT (PRP-TT): $\geq 10\mu\text{g}$	Al content (as AlPO4 gel): $\leq 1.25$ mg Thiomersal (as preservative): $\leq 0.01\%$ w/v
Instituto Rafael Rangel Caracas	Triple DPT	Venezuela (GVM)	Not reported	Not reported
Institute of vaccine e medical biologicals-IVAC	DTP vaccine	Vietnam (DCVMN)	Each 0.5 ml dose contained $\geq 30$ IU purified diphtheria toxoid, $\geq 60$ IU purified tetanus toxoid, $\geq 4$ IU inactivated whole-cell B. pertussis suspension, 10 $\mu\text{g}$ Hib oligosaccharide conjugated to approximately 25 $\mu\text{g}$	Thiomersal, 0.05 mg Aluminium 3 mg
Torlak	Alidpete - T	Serbia (GVM)	Each dose vaccine contained: Concentrated and purified diphtheria toxoid (not less than 30 IU); concentrated and purified tetanus toxoid (not less than 40 IU) and Bordetella pertussis, inactivated (not less than 4 IU).	Aluminium Phosphate (up to 2.0mg), Thiomersal 0.050mg sodium chloride, 4.5 mg sodium hydroxide, sodium hydrogen carbonate and water for injection
Microgen	wDTP	Russia (DCVMN)	Each dose of 0.5 ml DTWP contained: 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid, 4 IU inactivated Bordetella pertussis bacterial cells,	0.25–0.55mg aluminium hydroxide and 0.05 mg/ml merthiolate.
Razi Vaccine & Serum Research Institute	Trivalent DTP; Razi-DTWP	Iran (DCVMN)(GVM)	Each dose of a 0.5 ml of Razi-DTWP vaccine contained 15 Lf diphtheria toxoid, 10 Lf tetanus toxoid, 16 IU inactivated Bordetella pertussis bacterial cells	0.3 to 0.6 mg aluminium phosphate (metal ion) and 0.01% merthiolate

Note. WHO-PQ: World Health Organization's list of pre-qualified vaccines. DCVMN: Developing Countries Vaccine Manufacturing Network. GVM: Global Vaccine Market study.



\*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).  
 \*\*If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org>.

**Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.**

When looking at seroconversion rates (Figure 3), higher (over 75%) seroconversion was observed after completion of the three-dose primary regimen, after the first booster<sup>28,29,33</sup>, and after the second booster<sup>34</sup>. The only two studies that reported low levels of seroconversion rates post-fourth dose<sup>30,31</sup> are those that evaluated seroconversion post second booster later in time (at least one year after the booster), at three-five years of age<sup>30</sup>, and one to two years after the booster<sup>31</sup>.

The results viewed in combination suggest that immunogenicity may wane substantially after the primary series and between booster doses.

How immunogenicity correlates with clinical outcomes is not totally clear. In the two cross-sectional studies reporting clinical outcomes (Table 4, Panel B), infection rate of PCR-confirmed pertussis in children was heterogeneous, with 7.6% (6/79) post-third dose and 8.8% (8/91) post-fourth reported by Bailon *et al.*<sup>35</sup>, and 37.5% (3/8) post-3rd dose and 50% (7/14) post-fourth reported by Dumaidi *et al.*<sup>36</sup>.

## Discussion

We conducted a systematic review of the published literature on the effectiveness of whole-cell pertussis (wP) vaccines currently used in childhood vaccination programs to address two related issues: the duration of immunity conferred by currently available wP vaccines and the efficacy of booster doses. These issues are especially important as much of the evidence in the literature evaluated older and no longer available vaccines. Many traditional manufacturers have withdrawn from the market and new vaccines from emerging-market manufacturers of wP vaccines have entered in their place<sup>11,40</sup>.

We identified 18 manufacturers that provide wP vaccines currently in use and 12 studies that evaluated the efficacy of some of those vaccines. The first important result to highlight is that there is thus no published information about many of the vaccines currently in use worldwide.

Current pre-qualification and registration requirements request only that pre-licensure studies of combination vaccines

**Table 2. Summary characteristics of the studies included in the Systematic Review.**

Characteristic	Number of studies n (%)
Manufacturer*	
Bio Farma - PT	1 (8)
Microgen Company	1 (8)
Panacea Biotec	1 (8)
Razi Vaccine & Serum Research Institute	1 (8)
Serum Institute of India Ltd	8 (67)
Shantha Biotechnics	1 (8)
Study design	
Randomized Clinical Trial	3 (25)
Cross-sectional	7 (58)
Uncontrolled Prospective Cohort	2 (17)
Publication Year	
2007	1 (8)
2008	1 (8)
2011	1 (8)
2012	1 (8)
2013	1 (8)
2016	2 (17)
2017	1 (8)
2018	1 (8)
2019	2 (17)
2020	1 (8)
Outcome	
Clinical	2 (17)
Immunological	10 (83)
Country of study	
India	4 (34)
Iran	3 (25)
Palestine	1 (8)
Peru	1 (8)
Russia	1 (8)
Tunisia	1 (8)
Turkey	1 (8)

\* Sharma H, 2013<sup>33</sup> assessed 2 different vaccine manufacturers

demonstrate non-inferiority to existing vaccines over a short follow-up period (usually 30 days). Longer-term studies of the duration of immunity are not required by licensing authorities and are no longer routinely conducted<sup>3</sup>. For the vaccine products for which we identified published studies included in this review, many did not directly address duration of immunity, due to the current pre-qualification and registration requirements described above<sup>3</sup>. We attempted to glean some information about duration of immunity by examining the pattern of outcomes just before and after booster doses. Serological measures indicated low immunity just before administration of booster doses, and high immunity in the 30 days after they were administered, suggesting that the duration of immunity after the three-dose primary series may not be long, perhaps only a few years. This conclusion is, however, only suggestive because of the short follow-up periods in these studies, and the fact that the majority of them presented with high or moderate risk of bias.

It has been thought for some time that anti-pertussis antibody levels rapidly wane over time<sup>41</sup> and the pattern in these 12 studies supports this hypothesis, as demonstrated by high GMC and seroconversion rates observed shortly after vaccination, but lowering levels over time. Three published meta-analyses reported on the clinical efficacy and effectiveness of wP and aP vaccines, reaching similar conclusions<sup>42-44</sup>. Fulton *et al.* conducted a meta-analysis to evaluate the clinical efficacy or effectiveness over three years of childhood vaccination of a primary series of then-available vaccine formulations (wP and aP), reporting an overall effectiveness of 94% for both aP and wP vaccines. The protective effect was lower for aP when compared to wP vaccines<sup>42</sup>. McGirr *et al.* evaluated and compared the duration of protective immunity from childhood immunization series with three or five doses of then-available diphtheria-tetanus-acellular pertussis (DTaP) vaccines<sup>44</sup>. McGirr estimated that protection from aP vaccines dropped to only 10% after 8.5 years of the last dose received. A recently systematic review of Wilkinson *et al.*<sup>45</sup> evaluated the effectiveness and duration of protection from both aP and wP, concluding that pertussis vaccines confer protection in the short term against disease, with protection waning rapidly for aP vaccine. This review included 22 studies reporting on wP vaccine and reported an overall effectiveness against disease of 79% (I<sup>2</sup>=93%) in meta-analysis. However, this study included many vaccines no longer available, and as opposed to our study, did not limit the analyses to vaccines currently in use.

Duration of immunity is key to establishing optimal vaccination strategies and one of the parameters to which dynamic models of pertussis are most sensitive. Models have used values varying from 10 to 75 years to represent the duration of immunity from wP<sup>46</sup>. This wide range of assumptions clearly show a lack of consensus with regards to this estimate, likely resulting from a lack of good evidence in the literature. Though models can explore a wide range of assumptions and thus suggest how this uncertainty may impact the study findings, it nevertheless highlights how the projection of the consequences of vaccination strategies is impaired by lack of robust evidence on the duration of immunity.

**Table 3. Main characteristics of the studies included in the Systematic Review.**

Study, year	Study design	Country	Study period	Population	Doses (vaccine schedule)	Main outcome assessed	WP vaccine (manufacturer, combination)	Number of children enrolled	Children assessed at end of study	Time of follow-up (months)
Sharma HJ, 2011 <sup>29</sup>	Randomized Clinical Trial	India	2006–2008	Healthy infants aged 6–8 weeks at the time of first immunization	4, NI*	Serological, anti-pertussis toxin (PT)	Serum Institute of India Ltd., DTWP-HepB-Hib	373	304	1m after booster
Gandhi DJ, 2016 <sup>28</sup>	Randomized Clinical Trial	India	2012	Healthy toddlers aged 15–18 months based upon their primary immunization profile	4, NI	Serological, anti-pertussis toxin (PT)	Shantha Biotechnics Private Limited, DTWP-HepB-Hib	15	15	1m after booster
Susarla SK, 2019 <sup>32</sup>	Randomized Clinical Trial	India	2016	Infants aged 6–8 weeks with a history of being born after normal gestational period (36–42 weeks) with a birth weight $\geq$ 2.5 kg and having received birth dose of Hepatitis B vaccine	3(6-10-14w primary series)	anti-pertussis antibody levels	Serum Institute of India Ltd, Primary series: DTWP-HepB-Hib	405	387	4–6 weeks after third dose of vaccination
Zarei S, 2007 <sup>34</sup>	Uncontrolled Prospective Cohort	Iran	2006	Healthy 4–6 years old children, who had received four doses of DTWP vaccine according to the national vaccination schedule	5 (2-4-6 primary series and boosters at 18 and 48–72mo)	Serological, anti-pertussis toxin (PT)	Razi Vaccine & Serum Research Institute, Razi-DTWP	350	337	1m after booster
Sharma H, 2013 <sup>33</sup>	Uncontrolled Prospective Cohort	India	NI	Children aged 15–18 months who had completed their primary immunization schedule	4 (6-10-14wk primary series and booster at 15–18mo)	Serological, anti-pertussis toxin (PT)	Primary series: Serum Institute of India Ltd, DTWP-HepB-Hib / Booster: Serum Institute of India Ltd, DTWP-Hib	121	118	1m after booster
							Primary series: Panacea Biotec, DTWP-HepB-Hib / Booster: Serum Institute of India Ltd, DTWP-Hib	108	106	1m after booster
Cevik, M, 2008 <sup>36</sup>	Cross-sectional	Turkey	2006	Healthy 4–24 years individuals who had received four doses of DTWP vaccine according to the national vaccination schedule	4 (2-4-6 primary series and booster at 18mo)	Serological, anti-pertussis toxin (PT) + filamentous haemagglutinin (FHA)	Serum Institute of India Ltd	550	550	NA

Study, year	Study design	Country	Study period	Population	Doses (vaccine schedule)	Main outcome assessed	WP vaccine (manufacturer, combination)	Number of children enrolled	Children assessed at end of study	Time of follow-up (months)
Dashti AS, 2012 <sup>39</sup>	Cross-sectional	Iran	NI	Healthy children aged 2, 4, 6, 12, 18 and 72 months with a valid vaccination record (card), referring to centers for DTWP vaccination	5 (2-4-6 primary series and boosters at 18-72mo)	Serological, anti-pertussis toxin (PT)	Serum Institute of India Ltd., DTWP	725	284**	NA
Bailon, H, 2016 <sup>35</sup>	Cross-sectional	Peru	2012	Patients of all ages hospitalized or receiving care due to suspected pertussis, or contacts of suspected cases of pertussis	5 (2-4-6 primary series and boosters at 18 and 48mo)	Clinical	Serum Institute of India Ltd., DTWP-Hib-HepB / Booster: DTWP	840	191 PCR positive (649 PCR negative)	NA
Khramtsov P, 2017 <sup>37</sup>	Cross-sectional	Perm, Russia	NI	Children aged of 2 weeks to 17 years vaccinated according to the National immunization schedule	4 (3-4-5-6mo primary series and booster at 18mo)	Serological, anti-pertussis toxin (PT)	Microgen Company, DTWP	135	135	NA
Dumaidi K, 2018 <sup>36</sup>	Cross-sectional	Palestine	2004-2008	Infants and children hospitalized with clinically suspected pertussis	4 (2-4-6mo primary series and booster at 12mo)	Clinical	Primary series: Serum Institute of India Ltd, DTWP-HepB-Hib / Booster: Bio farma, DTWP	267	130 PCR positive (137 PCR negative)	NA
Fraj I, 2019 <sup>30</sup>	Cross-sectional	Tunisia	2018	Children aged 3-18 years, not having current respiratory infection and visiting the Hospital for check-up.	4 (2, 3 and 6 mo primary series and booster at 18mo)	Serological, anti-pertussis toxin (PT)	Serum Institute of India Ltd, Primary series: DTWP-HepB-Hib/ Booster: DTWP	304	304	NA
Noel, 2020 <sup>31</sup>	Cross-sectional	Iran	2016-2017	Children at 3 to 15 years, having completed pertussis primary immunization (3 first injections) and with detailed information about history of pertussis immunization in schools	4 (2, 4 and 6 mo primary series and booster at 18mo)	Serological, anti-pertussis toxin (PT)	Serum Institute of India Ltd, Primary series: DTWP-HepB-Hib/ Booster: DTWP	1047	1047	NA

DTWP: Diphtheria, Tetanus, whole-cell Pertussis

Hib: Haemophilus influenzae type b

HepB: Hepatitis B

NA: Not applicable

NI: No information

\*we only considered children aged 4-6 in the study

\*\*estimated by the authors

**Table 4. Main results from the studies included in the Systematic Review, by study outcome.**

Study, Year	IgG cutoff value considered (EU/ml)	Baseline/ time of evaluation	Time 1 after primary immunization			Time 2 after primary immunization			Time 3 after primary immunization				
			GMC (EU/mL; 95%CI or mean ± SD)	Number of individuals assessed	Seroconversion N (%; 95%CI)	Follow up/ time of evaluation	GMC (EU/mL; 95%CI or mean ± SD)	Number of individuals assessed	Seroconversion N (%; 95%CI)	Follow up/ time of evaluation	GMC (EU/mL; 95%CI or mean ± SD)	Number of individuals assessed	Seroconversion N (%; 95%CI)
<b>Randomized Clinical Trial</b>													
Sharma HJ, 2011 <sup>29</sup>	22	1 mo post-3rd dose	50.87 <sup>§</sup> (45.88 - 56.38)	152	146* (96.06; 91.61-98.54)	1 mo post-1 <sup>st</sup> booster	42.40 (31.40 - 57.25)	52	43* (82.7; 69.67 - 91.77)	NA	NA	NA	NA
Gandhi DJ, 2016 <sup>30</sup>	>11 NTU	1 mo post-1 <sup>st</sup> booster	21.8 NTU	10	8 (80; 44.4 - 97.5)	NA	NA	NA	NA	NA	NA	NA	NA
Susaria SK, 2019 <sup>32</sup>	any rise in titre post vaccination in comparison with pre vaccination	4-6 wk post-3 <sup>rd</sup> dose	9.06 (8.09 - 10.16)	257	238 (92.61, 89-96)	NA	NA	NA	NA	NA	NA	NA	NA
<b>Uncontrolled Prospective Cohort</b>													
Zarei S, 2007 <sup>34</sup>	16	pre-2nd booster (children aged 4-6y)	8.41 <sup>§</sup> (NI)	337	85* (25.2; NI)	2-4 wk post- 2nd booster	30.2 <sup>§</sup> (NI)	337	237* (70.3; NI)	NA	NA	NA	NA
Sharma H, 2013 <sup>33</sup>	> 22	pre-1st booster (children aged 15-18mo)	9 (NI)	118	64* (53.8; NI)	1 mo post-1st booster (children aged 15-18mo)	42.08 (NI)	118	93* (78.8; NI)	NA	NA	NA	NA
<b>Cross-sectional</b>													
Cevik, M, 2008 <sup>38</sup>	>24	post-1 <sup>st</sup> booster (children aged 4-6y)	15.38 <sup>§</sup> (0.5-48.9)	87	33 (38; NI)	Children aged 7-12y	67.85 <sup>§</sup> (21.4-127.2)	162	119 (73.4; NI)	Children aged 13-18y	81.61 <sup>§</sup> (40.32-134.08)	156	132 (84; NI)
Dashti AS, 2012 <sup>39</sup>	up to mean 2SD	12 mo of age (post primary series)	8.58 ± 1.08	72* <sup>§</sup>	NI	18 mo of age (pre 1 <sup>st</sup> booster)	7.35 (1.11)	85* <sup>§</sup>	NI	72mo of age (pre 2nd booster)	14.4 ± 1.06	127* <sup>§</sup>	NI
Khramtsov P, 2017 <sup>137</sup>	≥ 100 IU/ml	6-18 mo of age	4.7 <sup>§</sup> (1.1-8.4)	15	NI	1-1.5y after 1st booster (children aged 2.5-3y)	3.2 (0.8-5.6)	28	NI	5-6 y after 1st booster (children aged 6-7y)	3.5 <sup>§</sup> (1.4 - 8.5)	27	NI

Panel A: Results from studies presenting immunogenicity levels												
Study, Year	IgG cutoff value considered (EU/ml)	Baseline/ time of evaluation	GMC (EU/ml; 95%CI or mean ± SD)	Number of individuals assessed	Seroconversion N (%; 95%CI)	Follow up/ time of evaluation	GMC (EU/ml; 95%CI or mean ± SD)	Number of individuals assessed	Seroconversion N (%; 95%CI)	Follow up/ time of evaluation	GMC (EU/ml; 95%CI or mean ± SD)	Number of individuals assessed
Fraj I, 2019 <sup>30</sup>	≥ 40 IU/ml	post-1st booster 3-5 years	11±3.3	55	12 (21.8;10.9–32.7)	NA	NA	NA	NA	NA	NA	NA
Noel, 2020 <sup>31</sup>	≥ 40 IU/ml	post-1st booster 1-2 years after	NI	42	1 (2.4, NI)	NA	NA	NA	NA	NA	NA	NA
Panel B: Results from the studies presenting clinical outcomes												
Study	Study, year	Case definition	Laboratorial technique	N of PCR positive individuals (after 3 doses)	N of PCR negative individuals (after 3 doses)	N of PCR positive individuals (after 4 doses)	N of PCR negative individuals (after 4 doses)	N of PCR positive individuals (after 5 doses)	N of PCR negative individuals (after 5 doses)			
Cross-sectional	Bailon, H, 2016 <sup>35</sup>	Laboratory confirmed cases	Real-time PCR	6	73	8	83	0	29			
	Dumaldi K, 2018 <sup>36</sup>	Laboratory confirmed cases	Real-time PCR	3	5	7	7	NA	NA			

EU: Elisa units; GMC: Geometric Mean Concentration; GMT: Geometric Mean Titer; NI: Not informed; NA: Not applicable; Anti-PT: anti-pertussis; AB: Antibody; CI: confidence interval; RP: Prevalence Ratio; mo: months, wk: weeks;

\* Estimated by the reviewers

‡ Results reported as Geometric Mean Titer, IU/mL

† This study reports serological evaluation in 4 points in time, 3 of which are reported in the table. Results for time 4 after primary immunization (19–24 years of age) = GMT median 77.31 EU/mL (interquartile range 30–263.12).

‡ Median and interquartile range reported

† This study reports serological evaluation in 5 points in time, 3 of which are reported in the table. Results for time 4 after primary immunization (10–11 y after booster) = GMC 33.9 EU/mL (95%CI 10.3–57.5); 23 assessed. Results for time 5 after primary immunization (15–16 y after booster) = GMC 22.3 EU/mL (95%CI 6.6–38.1); 22 assessed.

**Table 5.** Timepoints assessed and outcomes reported by studies reporting on immunogenicity.

Study, Year	Post 3rd dose (end of primary series)		Prior to 4th dose/1st booster		Post 4th dose/1st booster		4-6 years of age (before 5th dose/2nd booster)		Post 5th dose% (after 2nd booster)	
	GMT	Seroconversion	GMT	Seroconversion	GMT	Seroconversion	GMT	Seroconversion	GMT	Seroconversion
Sharma, 2013a <sup>a,33</sup>			X <sup>&amp;</sup>	X	X <sup>&amp;</sup>	X				
Sharma, 2013b <sup>a,33</sup>			X <sup>&amp;</sup>	X	X <sup>&amp;</sup>	X				
Gandhi, 2016 <sup>28</sup>					X <sup>&amp;</sup>	X				
Zarei, 2007 <sup>34</sup>							X <sup>&amp;</sup>	X	X <sup>&amp;</sup>	X
Sharma, 2011 <sup>29</sup>	X	X			X	X				
Cevik, 2008 <sup>38</sup>							X	X		
Khramtsov, 2017 <sup>37</sup>			X (at 6-18m)	NI	X (at 2.5-3 yrs)	NI	X (at 6-7 yrs)			
Dashti, 2012 <sup>39</sup>	X (at 12m)	NI	X				X (at 6 yrs)			
Fraj I, 2019 <sup>30</sup>					X	X (at 3-5 yrs of age)				
Susarla SK, 2019 <sup>32</sup>	X	X								
Noel, 2020 <sup>31</sup>						X (1-2yrs after)				

<sup>a</sup> Sharma H. *et al.* (2013)<sup>33</sup> assessed 2 cohorts of children. We thus report on each cohort individually.

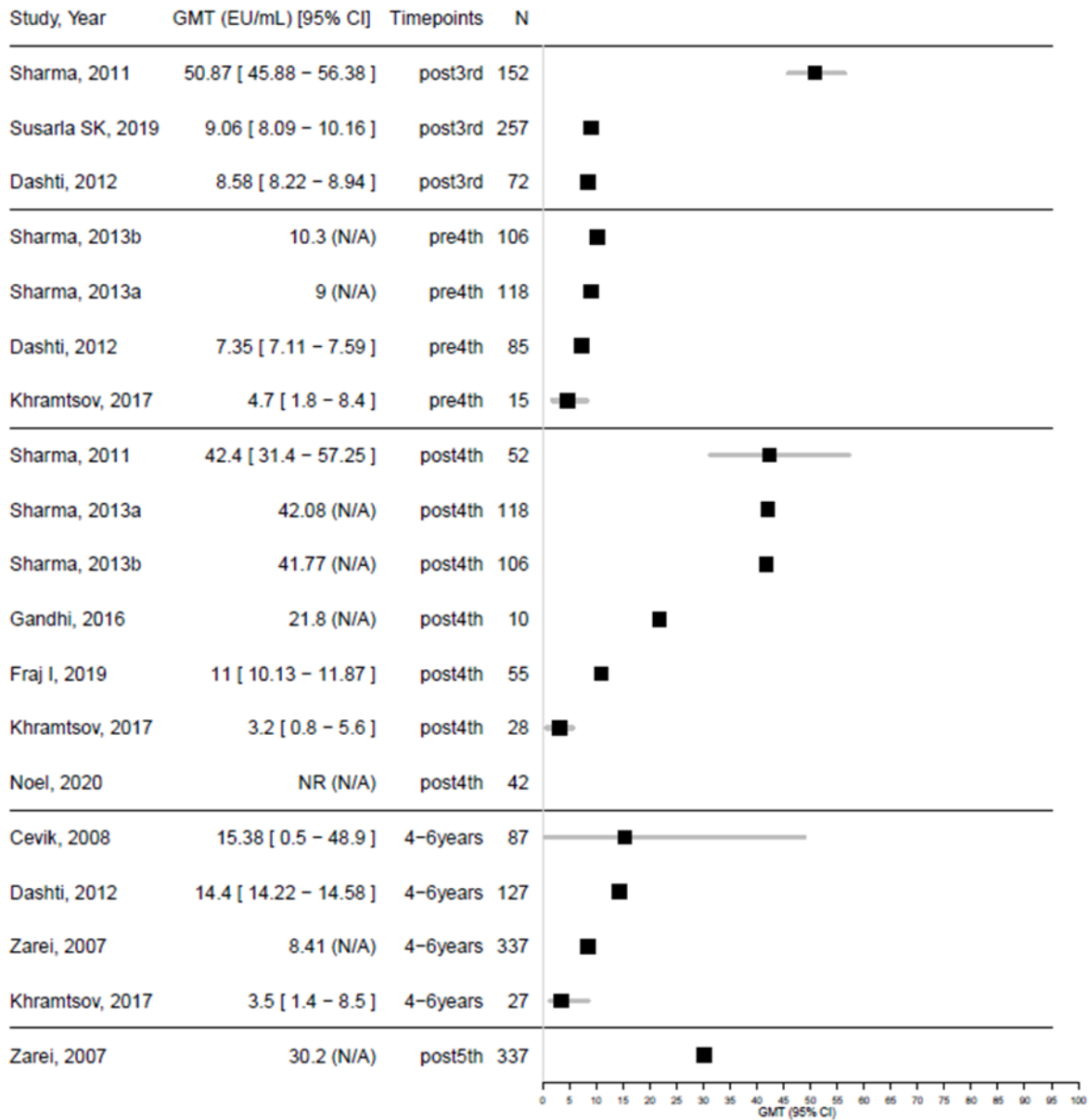
<sup>&</sup> GMT measures available but no SD or 95%CI.

NI: Not informed

Accurate estimates are more challenging to identify for pertussis vaccines as there is no established immunological correlation between protection against pertussis<sup>47</sup> and immunogenicity data, which is the outcome reported in 10 of the 12 studies included in our analysis. Different wP vaccines may have different antigenic content, leading to variations in post-vaccination immune response. However, as pointed out by the WHO's Strategic Advisory Group of Experts (WHO SAGE) working group on pertussis vaccine, patterns of immune response may contribute insights on vaccine effectiveness<sup>48</sup>, and despite the lack of serological correlates for protection, the United Kingdom Medical Research Council suggested a correlation between high agglutinin titers and clinical protection<sup>49</sup>. Furthermore, epidemiological observations also suggest that the protection of pertussis vaccine is high only for a limited period and

falls gradually with time after immunization<sup>3</sup>. Our study of currently available wP vaccines corroborates those observations.

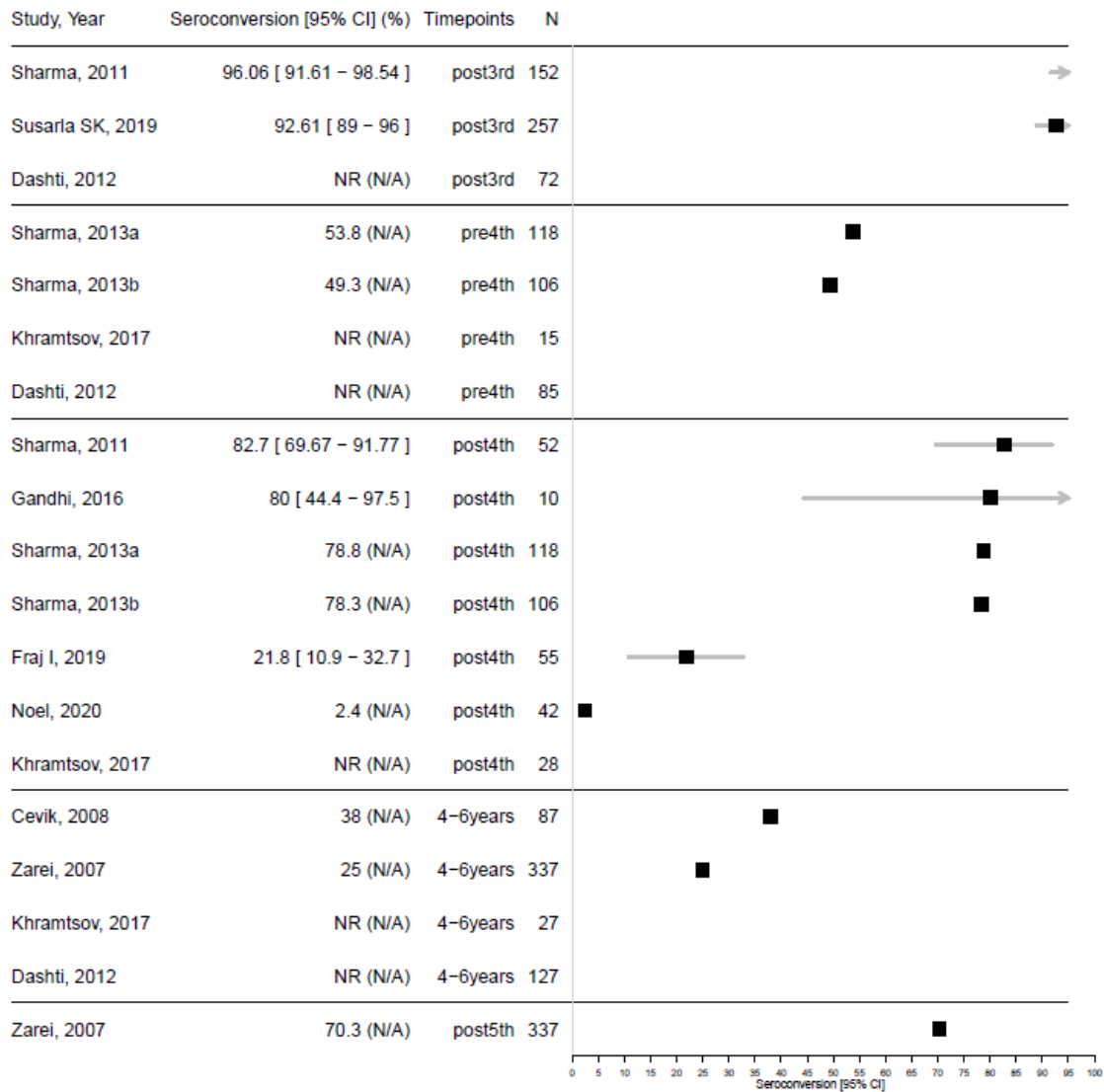
Our study has several limitations. First, identifying all currently available vaccines was difficult because of the market changes over time and the merging and incorporation of vaccine manufacturers globally in this period<sup>49</sup>. Second, due to current licensure and pre-qualification requirements, most studies were not randomized clinical trials nor prospective cohorts of immunized children, but rather cross-sectional or immunogenicity studies, the former with no follow-up and the latter with very short follow-up. In cross-sectional studies, groups of children at various ages are assessed at one timepoint; interpretation of antibody titers and their relation to vaccine doses is difficult since natural infection also influences antibody titers.



**Figure 2.** Forest plot presenting immunogenicity study results for different timepoints assessed and outcome reported, including Geometric Mean Titers (GMT).

Taken together, our results and the limitations highlighted above suggest that the way current wP vaccines are assessed hinders the adequate evaluation of the duration of immunity and protection over time. The scant evidence available from this and other studies suggests that the immunity conferred by currently available wP vaccines may be relatively short, perhaps only a few years, but that suggestion is based on studies of short duration and poor design that used an unreliable measure

of immunity. Considering that wP vaccine formulations are widely used globally, to protect millions of children each year, careful consideration and planning needs to be given to alternative approaches for monitoring duration of immunity and for developing reliable correlates of protection. Thus for researchers, alternative strategies for evaluating the duration of wP protection and immunity are needed; they may involve developing new ways of using epidemiological observation studies



**Figure 3. Forest plot presenting immunogenicity study results for different timepoints assessed and outcome reported, including % seroconversion.**

and surveillance systems to track pertussis outbreaks, guide vaccination efforts, and promote the development of vaccines with more durable effects.

**Data availability**

**Underlying data**

All data underlying the results are available as part of the article and no additional source data are required.

**Extended data**

Harvard Dataverse: Systematic review of immunogenicity and duration of immunity of currently licensed wP vaccines in

children – Supplementary Files. <https://doi.org/10.7910/DVN/XFRXGA><sup>14</sup>

This project contains the following extended data files:

- Figure 1- PRISMA 2020 flow diagram.
- Figure 2.png
- Figure 3.png
- Supplementary Table 1. Databases searched, electronic search strategy, and dates last searched by database.docx

- Supplementary Table 2. Whole-Cell Pertussis vaccines (manufacturer, commercial name and country of origin) included in the Systematic Review.docx
- Supplementary Table 3.docx
- Supplementary Table 4.docx
- Supplementary Table 5.docx

## Reporting guidelines

Harvard Dataverse: PRISMA flowchart and checklist for 'Systematic review of immunogenicity and duration of

immunity of currently licensed wP vaccines in children'. <https://doi.org/10.7910/DVN/XFRXGA><sup>14</sup>

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CCO 1.0 Public domain dedication).

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## Open Peer Review

Current Peer Review Status: ? ?

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### Version 1

Reviewer Report 02 June 2023

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**Matthieu Domenech de Cellès** 

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In this study, the authors conduct a systematic review to assess the immunogenicity and duration of protection conferred by currently available whole-cell pertussis (wP) vaccines in children. A total of 12 studies are identified (10 studies reporting immunological outcomes and 2 studies clinical outcomes), which cover 5 out of the 18 currently available wP vaccines. Based on the limited evidence identified in the review, the authors suggest that “[...] the duration of wP immunity is short, probably <5 years.”

This is an interesting and rigorous study, which adheres to the latest guidelines for systematic reviews (including pre-registration of the study protocol, tools like ROBINS-I for quality assessment, and PRISMA recommendations for reporting). However, as the authors themselves acknowledge, the evidence garnered from the review is very limited, with only 12 studies identified, all with short monitoring time post-vaccination. Among those, 10 studies report only serological outcomes, but the absence of definite correlates of protection for pertussis makes their results essentially irrelevant. The two other studies report more relevant clinical outcomes but were not designed to assess waning immunity and do not report estimates of waning vaccine effectiveness. All in all, considering the study’s main objective to assess the duration of wP protection, the evidence presented is too weak to draw any conclusion, and the authors’ suggestion that wP vaccines confer short-term protection (maybe <5 years) is widely speculative. Moreover, I think this suggestion is not only baseless but also contradicted by a strong body of epidemiological evidence - see my more specific comments below.

#### Major comments:

1. As explained above, the evidence garnered from the review is too limited to draw any conclusion about the duration of wP protection. I would recommend that the authors revise the title, the abstract, and the text to more clearly acknowledge this fact.
2. Related to the previous comment, the authors’ suggestion that wP vaccines might confer only short-term protection is contradicted by epidemiological evidence in many locations. How could these vaccines confer <5 years of protection, given the documented massive

impact of wP vaccines worldwide, for example in the US (Rohani *et al.*, 2011<sup>1</sup>), Sweden (Rohani *et al.*, 2010<sup>2</sup>), England (Rohani *et al.*, 2000<sup>3</sup>), Thailand (Blackwood *et al.*, 2013<sup>4</sup>), and many other locations (Broutin *et al.*, 2010<sup>5</sup>)? In keeping with these observations, modeling studies have estimated a long duration of wP protection (Blackwood *et al.*, 2013<sup>4</sup>, Gambhir *et al.*, 2015<sup>6</sup> and Domenech de Cellès *et al.*, 2018<sup>7</sup>). Admittedly, the effectiveness of wP vaccines is heterogeneous, with more limited protection demonstrated in countries like Canada and the Netherlands. Yet the authors' blanket statement at the end of the abstract is baseless and ignores a large part of the literature.

3. It would be useful to clarify how the present study compares with previous reviews and meta-analyses, and in particular why it includes fewer studies (and none with VE estimates over time since vaccination). For example, the authors discuss the review by Wilkinson *et al.* (2022<sup>8</sup>), which includes one study of the duration of wP protection (Lopalco *et al.*, 2015<sup>9</sup>). Wilkinson *et al.* (2022<sup>8</sup>) report the results of the latter study as follows: (Results section): "[...] VE declined from 93% (65–99%) three years post-vaccination to 80% (10–96%) by 7–9 years post-vaccination [20]." Why was this study not included? Similarly, in a recent meta-analysis of acellular pertussis vaccine effectiveness (not cited in the present study), the authors identified a study of wP vaccines (Lacombe *et al.*, 2004<sup>10</sup>) Please clarify.

#### Minor comments

- In Figure 1, please remove the instructions marked by \* below the figures.
- In the discussion, the authors report the results from a meta-analysis, purporting to show that only 10% of children remain immune to pertussis 8.5 years after the last aP vaccination (McGirr *et al.*, 2015<sup>11</sup>). Please note that another meta-analysis (Chit *et al.*, 2018<sup>12</sup>) arrived at widely different estimates, with initial effectiveness of 3-dose aP of 91%, then declining by 9.6% every year. These estimates translate into a fraction of children still protected 8.5 years after the last aP vaccination of 0.91(1-0.096)<sup>8.538%</sup>, much higher than that in (McGirr *et al.*, 2015<sup>11</sup>). As explained in (Chit *et al.*, 2018<sup>12</sup>) and further demonstrated in a modeling study (Domenech de Cellès *et al.*, 2019<sup>13</sup>), the difference may be explained by confusion between relative and absolute VE in earlier epidemiological studies of aP vaccines (Klein *et al.*, 2012<sup>14</sup>).

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**Are the rationale for, and objectives of, the Systematic Review clearly stated?**

Yes

**Are sufficient details of the methods and analysis provided to allow replication by others?**

Yes

**Is the statistical analysis and its interpretation appropriate?**

Partly

**Are the conclusions drawn adequately supported by the results presented in the review?**

Partly

**Competing Interests:** I received consulting fees from GSK for discussions about pertussis vaccines. I confirm that this potential conflict of interest did not affect my ability to write an objective and unbiased review of the article.

**Reviewer Expertise:** Infectious disease epidemiology

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Reviewer Report 31 May 2023

<https://doi.org/10.21956/gatesopenres.14945.r32961>

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In this systematic review, the authors aimed to assess the duration of immunity of currently available whole-cell pertussis (wP) vaccines in children. In addition, the authors looked to synthesize available evidence on the protection conferred by booster doses of the wP vaccines. Findings from the 12 included studies suggest that sero-conversion is high (>75%) shortly (~1 month) after completing the primary 3-dose series, as well as after the 3+1 and the 3+2 booster series. However, immunogenicity may wane after the primary series and between booster vaccinations. Overall, the manuscript is well written and easy to follow, save for minor grammatical and typographical errors. The following comments need to be addressed:

**Introduction:**

- Pg 3: "Pertussis (whooping cough), a respiratory infectious disease caused by *Bordetella pertussis*, and characterized by mild fever, runny nose, and paroxysmal coughing." This sentence should be reviewed for better clarity.

**Literature search:**

- Pg 4: It is noted that the initial search was conducted in April 2019 and then updated in September 2021. The authors are encouraged to update the search and include any relevant evidence emerging in the past year. Updated search strategies depicting the most recent search date should be provided in Supplementary Table 1.

**Study selection:**

- Pg 4: The authors should clarify if a reference manager or review manager was used during the literature screening process.

**Articles identified for the systematic review:**

- Pg 5: "...two Chinese<sup>21,22</sup>, two German<sup>23,24</sup>, **onw** Russian<sup>25</sup> and two in..." Replace "onw" with "one".
- Pg 5: Figure 1. In relation to Figure 1 which is presented on page 8, the authors should carefully review the PRISMA for ease of clarity. Kindly remove all Asterix provided in the PRISMA template which may not be relevant for this review. The authors should provide an indication of the origin of the *13 reports of the included studies*. It is noted under the "*Identification of studies via other methods*" that n=11 were sought for retrieval, however n=0

were assessed for eligibility?

**Discussion:**

- Pg 9: "A recently systematic review of Wilkinson et al.<sup>45</sup> evaluated the effectiveness..." - the authors should rephrase for better clarity.
- Pg 9: "However, this study included many..." - are the authors still referring to the Wilkinson *et al.* review?

The findings from this review on the duration of immunity conferred by widely used wP vaccines have not been explicitly compared with published evidence on that conferred by acellular pertussis (aP) vaccines.

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**

Yes

**Are sufficient details of the methods and analysis provided to allow replication by others?**

Partly

**Is the statistical analysis and its interpretation appropriate?**

Yes

**Are the conclusions drawn adequately supported by the results presented in the review?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Vaccinology, public health, epidemiology

**We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.**

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