Duration of Pertussis Immunity After DTaP Immunization: A Meta-analysis

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abstract

BACKGROUND AND OBJECTIVES: Pertussis incidence is increasing, possibly due to the introduction of acellular vaccines, which may have decreased the durability of immune response. We sought to evaluate and compare the duration of protective immunity conferred by a childhood immunization series with 3 or 5 doses of diphtheria-tetanus-acellular pertussis (DTaP).

METHODS: We searched Medline and Embase for articles published before October 10, 2013. Included studies contained a measure of long-term immunity to pertussis after 3 or 5 doses of DTaP. Twelve articles were eligible for inclusion; 11 of these were included in the meta-analysis. We assessed study quality and used meta-regression models to evaluate the relationship between the odds of pertussis and time since last dose of DTaP and to estimate the probability of vaccine failure through time.

RESULTS: We found no significant difference between the annual odds of pertussis for the 3- versus 5-dose DTaP regimens. For every additional year after the last dose of DTaP, the odds of pertussis increased by 1.33 times (95% confidence interval: 1.23–1.43). Assuming 85% vaccine efficacy, we estimated that 10% of children vaccinated with DTaP would be immune to pertussis 8.5 years after the last dose. Limitations included the statistical model extrapolated from data and the different study designs included, most of which were observational study designs.

CONCLUSIONS: Although acellular pertussis vaccines are considered safer, the adoption of these vaccines may necessitate earlier booster vaccination and repeated boosting strategies to achieve necessary "herd effects" to control the spread of pertussis.

REVIEW ARTICLE

Pertussis, a highly contagious upper respiratory infection caused by *Bordetella pertussis*, is a poorly controlled vaccine-preventable disease in Canada, despite relatively high vaccine coverage rates.[1,2] Disease incidence is highest in infants, with mortality rates greatest in infants younger than 3 months[3]; however, the burden of disease among adolescents and adults has recently increased considerably.[3] Although this increase has been attributed to a multitude of factors, including aging of undervaccinated cohorts[4] and more sensitive laboratory testing methods,[5] recent reports have suggested that waning immunity of vaccinated individuals may also contribute to the resurgence of pertussis.[6–10]

Vaccination against pertussis was introduced in Canada in 1943[1] and was associated with a marked decline in the incidence of pertussis.[3] However, small outbreaks of pertussis continued to persist with predictable seasonality.[4] In 1997–1998, an acellular preparation of pertussis vaccine (diphtheria-tetanus-acellular pertussis [DTaP]) was introduced in Canada. This combination vaccine was associated with fewer side effects and had a better safety profile than the previously used diphtheria-tetanus-whole cell pertussis (DTwP) vaccine.[11,12] There are currently 2 types of acellular preparations licensed for use. The children's preparation, DTaP, contains high concentrations of antigens for diphtheria, tetanus, and acellular pertussis while the adolescent/adult formulation, Tdap, contains high concentrations of antigens for tetanus, but lower concentrations of antigens for diphtheria and acellular pertussis.[1] Recommendations in Canada call for DTaP immunizations at 2, 4, and 6 months and between 12 and 23 months of age. A childhood booster vaccine (of either DTaP or Tdap) is recommended between ages 4 and 6.[1,13] Additional boosters for adolescents and adults are recommended between ages 14 and 16

and once again as an adult.[1,14] Although a similar 5-dose DTaP vaccine series is used in Canada and the United States, globally there are a wide variety of DTaP vaccination schedules that are recommended. In many European countries, a 3-dose DTaP vaccine series is offered, often in conjunction with a booster vaccine for school-aged children aged 4 to 9 years.[15] The 3-dose schedule typically recommends vaccination at 2, 3, and 4 months; 2, 4, and 6 months; or 3, 5, and 11 months of age.[15] However, despite widespread implementation of these different immunization programs and associated levels of uptake, pertussis persists.

A previous review by Wendelboe et al[16] summarized several studies relating to the duration of protective immunity conferred by natural infection with pertussis, with DTwP, and with DTaP. However, this study was published in 2005, well before the existence of much of the current literature. In addition, the review did not include a meta-analysis of the key results. Thus, we believe there is a critical need for a systematic literature review and meta-analysis to evaluate the weight of evidence about waning pertussis immunity from available studies, and to synthesize this evidence.

Understanding waning immunity and its impact on the disease burden of pertussis in different age groups is critical to designing vaccination programs to control the spread of pertussis in the community. Although ethical issues surround the feasibility of a randomized controlled trial to

evaluate vaccine-induced waning immunity, decisions still need to be made on optimal vaccine strategies, and systematic review and meta-analysis provide a mechanism whereby such decisions can be informed by the best available data. Our objectives were to (1) synthesize the current literature surrounding waning immunity to pertussis after vaccination with 3 and 5 childhood doses of DTaP and (2) estimate the duration of protective immunity to pertussis after 3 and 5 doses of DTaP using meta-analytic techniques.

METHODS

Search Criteria

A literature search was conducted by using both Medline and Embase databases. In consultation with a research librarian at the University of Toronto, the search strategy consisted of key words and medical subject headings. Similar terms and synonyms were combined with an "OR" operator, and these distinct components were linked together with an "AND" operator. Search terms included "whooping cough," "pertussis," "diphtheria-tetanus-acellular pertussis vaccine," "time-factors," "follow-up studies," "drug efficacy," "outcome assessment," and "treatment duration." The search strategies were carried out without limits on October 10, 2013. The unique search strategies for each database can be found in Table 1. To ensure completeness, the reference lists of the included studies

TABLE 1 Search Strategies Used in the 2 Different Databases

Database	Search Terms
Medline	"exp Whooping Cough/ep, im, pc [Epidemiology, Immunology, Prevention & Control]" AND "exp Child/ OR exp Adolescent/" AND "exp Follow-Up Studies/ OR exp Time Factors/ OR exp Immunization Schedule/" AND "exp Diphtheria-Tetanus-Pertussis Vaccine/ad, im, st [Administration & dosage, Immunology, Standards] OR exp Diphtheria-Tetanus-acellular Pertussis Vaccines/ad, im, st [Administration & Dosage, Immunology, Standards] OR exp Pertussis Vaccine/ad, im [Administration& Dosage]"
Embase	"exp pertussis/dt, ep, pc [Drug Therapy, Epidemiology, Prevention]" AND "exp diphtheria pertussis tetanus vaccine/dt [Drug Therapy] OR exp pertussis vaccine/dt [Drug Therapy" AND "exp drug efficacy/ OR exp follow up/ OR exp risk assessment/ or exp outcome assessment/ or exp treatment duration/" AND "child/ OR adolescent"

were searched to identify any studies that had not been captured by the original literature search.

Study Selection

Relevancy Screen

We reviewed the titles and abstracts of the retrieved articles to assess for relevancy. All primary research articles, not including modeling studies, that assessed a measure of long-term immunity (>18 months of follow-up) were included. Studies in which pertussis immunity was not an outcome, studies about diphtheria-tetanus toxoids-pertussis (DTP) or DTwP, studies about strategies to improve vaccine uptake, and studies about adverse events after vaccination were excluded at this stage. Abstracts published in languages other than English were translated by using Google Translate to assess relevancy.[17] Agreement between the 2 reviewers was assessed by using the κ statistic, and where discrepancies on the study inclusion criteria existed, they were resolved by discussion and consensus.

Full-Text Review

The full texts of the studies screened for inclusion were read and included in the review if they met the predefined full-text inclusion criteria. Specifically, studies that used either 3 or 5 childhood doses of DTaP and that included a measure of time since vaccination were included. To ensure completeness of the literature search, the references of the included studies were scanned and relevant articles were included in the systematic review.

Quality Assessment

A modified version of the Downs and Black critical appraisal tool for randomized and nonrandomized studies was used to evaluate the quality of the included studies.[18] This validated and widely used instrument contains 27 questions pertaining to reporting, external validity, internal

validity (bias and confounding), and power.[18,19] Each question was scored as a 0 or 1, except for 1 question (reporting of confounders), which was scored from 0 to 2. For the purpose of this study, the instrument was modified by removing the question about power because the different study designs each have their own sample size requirement. One author (A.M.) analyzed the quality of the included studies. Study quality categories were assigned on the basis of the following modified Downs and Black scores: excellent (25–27), good (19–24), fair (14–18), and poor (≤13).

Data Abstraction

Data from the relevant articles were abstracted to calculate odds ratios and SEs comparing the odds of pertussis for each year since the last dose of DTaP, where available. One year after the last dose of DTaP was

chosen as the referent because the majority of articles presented the results this way. When available, measures of association and SEs were taken directly from the articles, and where tabular data existed, measures of association and corresponding SEs were calculated manually. In 1 case, the referent data were obtained from a previously published article from the same research study.[20] When the odds ratios were presented by using a continuous predictor of time since last dose of DTaP, the logistic model was extrapolated to calculate odds ratios and SEs for each year. Risk ratios for the serologic studies were calculated by comparing the risk of vaccine failure at the given time period with the risk of vaccine failure 1 year post–vaccine administration (assumed to be 18.8% for the 5-dose series and 17.7% for the 3-dose series, as per previous studies of the same cohorts of subjects[21,22]). Risk
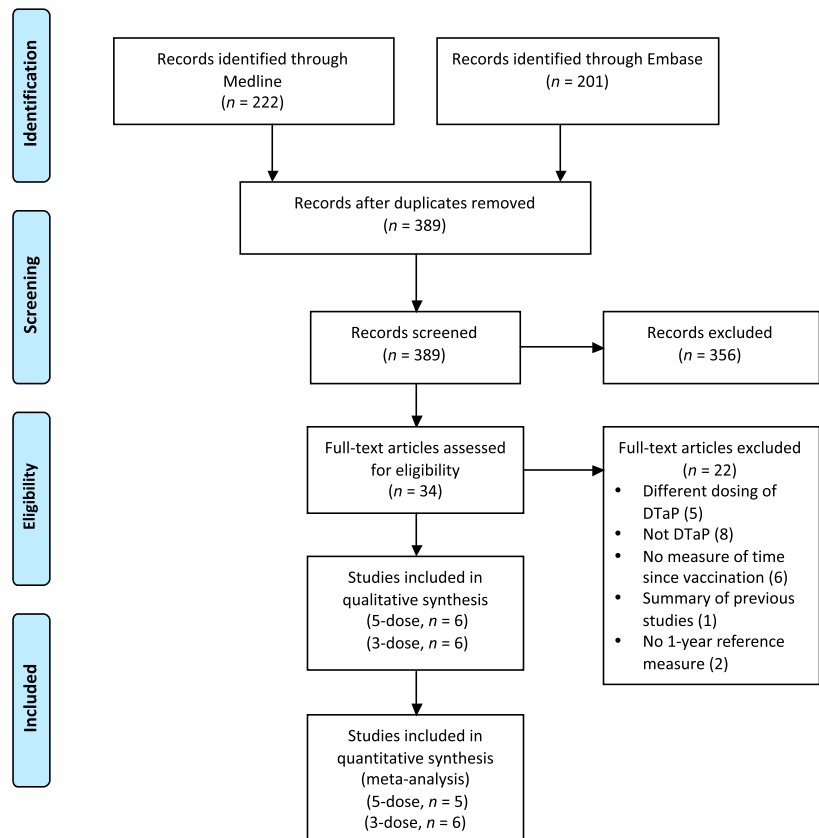
FIGURE 1
Flowchart of studies included in the review and meta-analysis.

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TABLE 2 Characteristics of Included Studies

Study, year (source)	Location	Study Design	Data Source(s)	Study Period	Study Population	Vaccine Schedule	Loss of Immunity "Case Definition"	Control Selection	Statistical Technique	Covariates
Tartof et al, 2013 (9)	Minnesota/ Oregon	Cohort	National Notifiable Diseases Surveillance System and Immunization Information Systems	2000–2010	Children born between 1998 and 2003 with 5 recorded doses of DTaP with last between ages 4 and 6	2, 4, 6, and 15–18 mo, 4–6 y	Confirmed cases as Council of State and Territorial Epidemiologists	Age-specific populations of Minnesota and Oregon	Log binomial model of calculated incidence rates	Examined age at receipt of fifth dose but found no difference
Klein et al, 2012 (10)	Northern California	Case-control	Kaiser Permanente Northern California databases	January 2006–June 2011	Kaiser Permanente Northern California members born after 1999 without Tdap or any pertussis vaccine between fifth dose and PCR test date	2, 4, 6, and 15–18 mo, 4–6 y	PCR positive for pertussis and PCR negative for parapertussis	PCR negative for pertussis and PCR negative for parapertussis	Conditional logistic regression (conditioned on calendar time)	Age (4 to <7, 7 to <10, and 10 to 12), gender, medical clinic, race/ ethnicity
Misegades et al, 2012 (47)	California	Case-control	Reports to local health departments and medical records	2010–December 2010	Children aged 4 to 10 from 15 California counties (Alameda, Del Norte, El Dorado, Fresno, Madera, Marin, Merced, Orange, Riverside, San Diego, San Luis Obispo, Santa Clara, Santa Cruz, Sonoma, and Stanislaus)	2, 4, 6, and 15–18 mo, 4–6 y	Probable and confirmed cases as defined by Council of State and Territorial Epidemiologists, suspected cases as defined by the California Department of Public Health	3 controls per case, selected through reporting clinicians	Logistic regression accounting for clustering by county and physician	Gender, age at enrollment, and age at fifth dose were assessed as potential confounders, but none found to be
Witt et al, 2012 (59)	Marin County, California	Retrospective cohort	Kaiser Permanente electronic medical records	March 2010–October 2010	Children and adolescent members of Kaiser Permanente Medical Center in San Rafael, California	2, 4, 6, and 15–18 mo, 4–6 y of age	PCR positive for pertussis	Kaiser Permanente Medical Center population as a whole	Stratification (vaccine effectiveness via screening method)	None
Zinke et al, 2010 (61)	Germany	Serologic follow-up study of RCT	ATP cohort from earlier RCT, Study B (Zinke et al, 2009[70])	July 2006–December 2006	Healthy German children between 7 and 9 y of age who had been immunized with DTPa-HBV-IPV-Hib vaccine in previous RCT	3, 4, 5, and 12–18 mo of age, 4–6 y of age	Anti-PT ≥5 EL U/mL	NA	Seropositivity rates	None
Zepp et al, 2007 (60)	Germany	Double-blind crossover Study	ATP cohort from earlier RCT (Knuf et al, 2006[69])	Not specified	German adolescents who were enrolled and complied with the protocol of a previous RCT who had available immunogenicity data	3, 4, 5, and 12–18 mo of age, 4–6 y of age	Anti-PT ≥5 EL U/mL	Crossover design	Seropositivity rates	None

TABLE 2 Continued

Study, year (source)	Location	Study Design	Data Source(s)	Study Period	Study Population	Vaccine Schedule	Loss of Immunity "Case Definition"	Control Selection	Statistical Technique	Covariates
Gustafsson et al, 2006 (41)	Sweden (except Gothenburg and area)	Surveillance study	Swedish Institute for Infectious Disease Control, Statistics Sweden, clinical chart review	October 1997–September 2004	Swedish children	3, 5, and 12 mo of age	Culture or PCR confirmed pertussis, regardless of symptoms	NA	Incidence rates	None
Lacombe et al, 2004 (44)	Niakhar, Senegal	Follow-up of previous RCT	Patients previously enrolled in RCT (Simondon et al, 1997[71])	Patients enrolled 1990–1995	Newborn infants enrolled in original RCT	2, 4, and 6 mo of age	Cough lasting >20 d with bacteriologic or serologic confirmation or link to documented case	NA	Logistic regression	Intensity of exposure, birth rank, height-for-age index at 7 mo
Olin et al, 2003 (51)	Sweden (except Gothenburg and area)	Surveillance study	Swedish Institute for Infectious Disease Control, Statistics Sweden, clinical chart review	October 1997–September 2000	Swedish children born between January 1996 and September 2000	3, 5, and 12 mo of age	Culture- or PCR-confirmed pertussis, regardless of symptoms	NA	Incidence rates	None
Esposito et al, 2002 (39)	Italy	Serum antibody study	Patients enrolled in clinic at University of Bologna	December 1999	Healthy Italian children 5 and 6 y old who were born premature and given 3 doses of DTaP as an infant	3, 5, and 11 mo of age	Positive ELISA (EU/mL) for anti-PT, cutoff value not specified	NA	Seropositivity rates	None
Salmaso, et al 2001 (55)	Piemonte, Veneto, Friuli-Venezia Giulia, and Puglia, Italy	Follow-up of previous RCT	Patients remaining under surveillance at stage 3 of RCT (Greco et al, 1996[20])	October 1995–October 1998	Newborn infants enrolled in original RCT	2, 4, and 6 mo of age	Laboratory-confirmed pertussis infection and spasmodic cough lasting ≥14 d or cough lasting ≥21 d	NA	Vaccine efficacy using person-time incidence density	None
Esposito, et al 2001 (38)	Italy	Serum antibody study	Patients enrolled in clinics at the University of Palermo and the University of Bologna	December 1999–January 2000	Healthy Italian children 5 and 6 y old either given 3 doses of DTaP as an infant or had clinical pertussis as an infant	3, 5, and 11 mo of age	Positive ELISA (EU/mL) for anti-PT, cutoff value not specified	NA	Seropositivity rates	None

ATP, According to Protocol; DTPa-HBV-IPV-Hib, ; EL, ELISA units; ELISA, enzyme-linked immunosorbent assay; EU, ELISA units; NA, not applicable; anti-PT, pertussis antitoxin; RCT, randomized controlled trial.

ratios and incident rate ratios were assumed to approximate odds ratios according to the rare disease assumption.[23] These odds ratios and corresponding SEs were entered manually into a spreadsheet for analysis.

Statistical Analysis

All data analysis and statistical modeling were performed by using the *metafor* package in R Statistical Software.[24,25] Publication bias was assessed by using funnel plots with asymmetry between the measures of association and SEs quantified by using Egger's test.[26] Random-effects models using the DerSimonian-Laird estimator were used to pool the results between the included studies once heterogeneity, as assessed by using Higgins' I^2 statistic, among the outcomes was considered.[27,28] A meta-regression model using the DerSimonian-Laird estimator was fit to the data to evaluate the relationship between the odds ratio of pertussis and time since last DTaP vaccination.[27] To evaluate the importance of the number of doses and the type of pertussis "diagnosis" (ie, clinical versus serologic), we included these variables in the meta-regression model and evaluated the change in the estimate of the main effect. Using a range of vaccine efficacy estimates from the United States and Canada we were able to anchor the probability of vaccine failure for the first year since DTaP series completion.[1,29,30] We assumed that the probability of vaccine failure followed an exponential distribution, where the probability of immunity at some time t was $P(I)_t = VE(exp[-\lambda t])$, with VE being the efficacy of vaccination during the initial period after series completion, and λ representing the rate of vaccine failure. Under this scheme, the mean duration of immunity among those who initially respond to the vaccine is $1/\lambda$. With the rare disease assumption, the predicted odds ratios from the meta-regression were assumed to approximate risk ratios, allowing for the creation of functions of probability of vaccine failure through time.

RESULTS

Included Studies in Review

Of the 389 potentially relevant articles identified through the literature search, 33[9,10,31–61] underwent full-text review. Agreement between the independent reviewers with respect to the title/abstract scan was fair (κ = 0.61). Six[9,10,47,59–61] of these studies fit the 5-dose eligibility criterion to be included in this review and 6 studies[38,39,41,44,51,55] met the 3-dose criterion (Fig 1). None of the articles published in languages other than English met inclusion criteria. No additional articles were identified through hand-searches of reference lists.

Of the included studies, 2 were case-control studies,[10,47] 2 were cohort studies,[9,59] 3 were follow-up studies from previously conducted randomized controlled trials,[44,55,61] 2 were surveillance studies,[41,51] 2 were serum antibody studies,[38,39] and 1 was a double-blind crossover study[60] (Table 2). Despite searching without limits on publication dates, the included studies with 5 doses of DTaP were all published between 2010 and 2013 and the included studies with 3 doses of DTaP were all published between 2001 and 2006. The majority of the 5-dose included studies were conducted in the United States (California,[10,47,59] Minnesota,[9] and Oregon[9]), with the remaining 5-dose studies conducted in cities across Germany.[60,61] Almost all of the 3-dose studies were conducted in Europe (Italy[38,39,55] and Sweden[41,51]), although 1 study was conducted in Senegal.[44]

The studies included in the analysis differed in terms of defining loss of immunity. The clinical studies compared the incidence of pertussis for every year since the vaccine was administered with the use of various case definitions of pertussis. Two of

TABLE 3 Quality Assessment of the Included Studies

Downs and Black Criteria	Possible Points	Esposito et al, 2001 (38)	Esposito et al, 2002 (39)	Gustafsson et al (41)	Klein et al (10)	Lacombe et al (44)	Misegades et al (48)	Olin et al (51)	Salmaso et al (55)	Tartof et al (9)	Witt et al (59)	Zepp et al (60)	Zinke et al (61)
Reporting	11	8	7	6	10	10	9	5	7	6	4	4	7
External validity	3	1	1	3	2	2	1	3	1	1	3	1	1
Internal validity													
Bias	7	6	5	4	5	4	4	3	4	5	5	5	3
Confounding	6	3	3	3	4	5	3	3	3	4	3	4	2
Total	27	18	16	16	21	21	17	14	15	16	15	14	13
Quality rating		Fair	Fair	Fair	Good	Good	Fair	Fair	Fair	Fair	Fair	Fair	Poor

the studies used polymerase chain reaction (PCR) laboratory methods only,[10,59] 2 of the studies used culture or PCR methods regardless of symptoms,[41,51] 1 used a cough lasting >20 days with bacteriologic or serologic confirmation or link to a documented case,[44] and 1 used laboratory confirmed pertussis infection and spasmodic cough lasting ≥14 days or cough lasting ≥21 days.[55] The remaining 2 studies used the Council of State and Territorial Epidemiologists–confirmed case definition[9] and the confirmed/probable case definition in conjunction with the suspected case definition from the California Department of Public Health.[47]

The serologic studies compared the number of individuals who had levels of immunologic markers above a certain threshold for every year since the vaccine was administered. Two of the studies explicitly defined seropositivity as anti-PT (≥5 EL U/mL),[60,61] whereas 2 defined seropositivity as positivity by using an enzyme-linked

immunosorbent assay without a clear description of cutoff.[38,39] These varying clinical and serologic case definitions of pertussis likely contributed to the observed heterogeneity between the studies (Table 2).

Quality Assessment

The included studies had a diverse range of quality. Two studies were assessed as "good" quality,[10,44] 9 studies were assessed as "fair" quality,[9,38,39,41,47,51,55,59,60] and 1 study was assessed as "poor" quality[61] (Table 3). Of the 4 categories assessed with the modified Downs and Black rating scale, reporting showed the biggest variability in scores. Most commonly, studies scored poorly because of undefined study aims, vague or no description of the study participant characteristics, and no mention of participants lost to follow-up.

Included Studies in Meta-analysis

One study[59] was excluded from the meta-analysis because of

contamination of the measure of association. The study participants were classified as being up-to-date for age of immunization according to the US Centers for Disease Control and Prevention Guidelines but were grouped into age categories of 2 to 7 years of age, 8 to 12 years of age, and 13 to 18 years of age. Because the Centers for Disease Control and Prevention recommends a booster immunization at 10 to 12 years of age, some of the participants in the 8- to 12-year age category and most of the participants in the 13- to 18-year age category would have had the adolescent booster vaccine already. The authors highlighted this as a potential reason for the lower attack rates of pertussis in the older age groups. To ensure comparability of the estimates, the results from this study were removed from the meta-analysis.

The study by Klein et al[10] contained 2 control groups (PCR-negative controls and matched controls) and used them to calculate 2 different
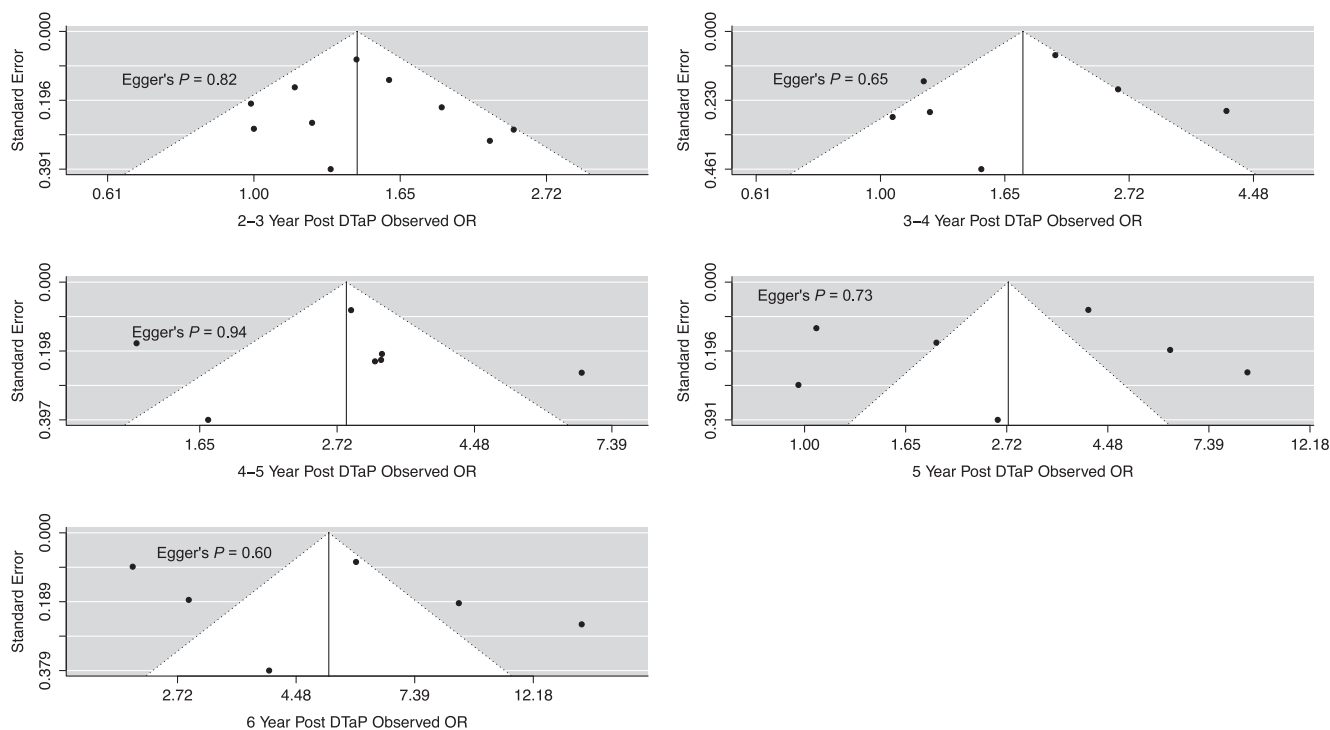
FIGURE 2
Funnel plots and P values from Egger's test evaluating the risk of publication bias for the odds ratios of pertussis for years 2 to 6 after the last dose of DTaP. OR, odds ratio.
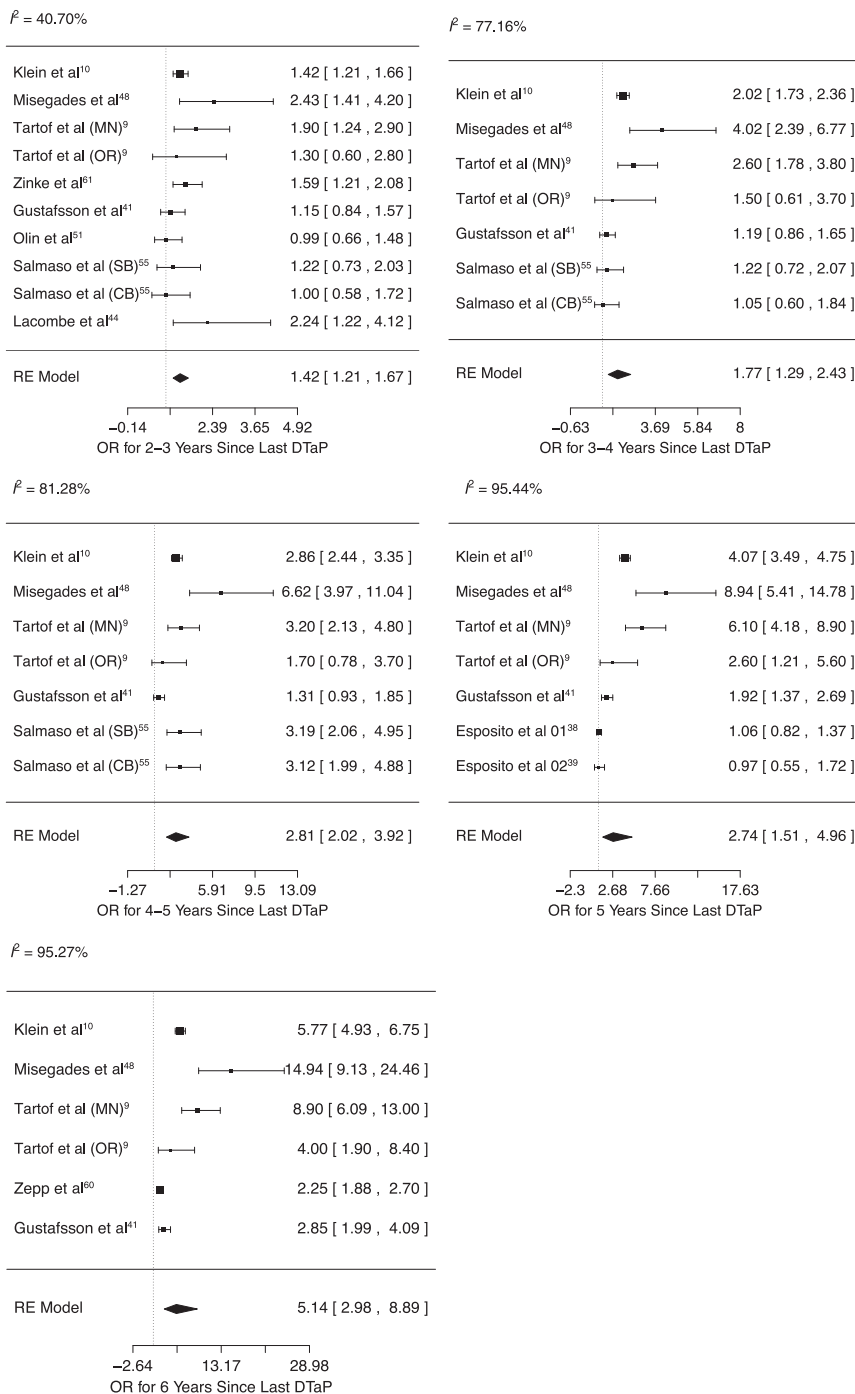
FIGURE 3
Forest plots showing the pooled odds ratios of pertussis for years 2 to 6 versus year 1 after the last dose of DTaP. Pooled odds ratios were calculated by using random-effects models with the DerSimonian-Laird estimator. CB, Chiron-Biocine vaccine; I^2, Higgins' I^2 measure of heterogeneity; MN, Minnesota; (OR), Oregon; OR, odds ratio; RE, random effects model; SB, SmithKline Beecham.

odds ratios for pertussis. Because the 2 control groups were compared with the same case group, we used only the estimates for the PCR-negative controls because the authors believed

this measure contained the least amount of bias. The study by Tartof et al[9] contained 2 distinct study populations (Minnesota and Oregon) with separate measures of

association. Similarly, the study by Salmaso et al[55] contained 2 study populations: 1 that was vaccinated with a DTaP vaccine made by SmithKline Beecham and the other that was vaccinated with a DTaP vaccine made by Chiron-Biocine. As such, we included both sets of results from each of these studies in the analysis, for a total of 13 distinct estimates.

Meta-analysis Results

Publication Bias

There was no evidence of publication bias for any of the years since the last DTaP vaccine, with all funnel plots showing symmetry between the measure of association and the SE according to Egger's test (Fig 2).

Pooled Effects

Summary measures of association along with the observed Higgins' I^2 measure of heterogeneity for every year since the last dose of DTaP are shown in Fig 3. The pooled odds ratios of pertussis were found to increase with the time since the last dose of DTaP, suggesting considerable waning immunity. Between-study heterogeneity was also found to increase for every year since the last dose of DTaP, with year 2 showing moderate heterogeneity and years 3 to 6 showing substantial heterogeneity (Fig 4). This increasing heterogeneity in effect estimates as the time since last DTaP vaccine increases is likely due to a compounding effect of the heterogeneity in the study designs.

Meta-regression

The results from the final meta-regression model suggest that the odds of pertussis for every year since the last dose of DTaP was estimated to increase by a multiple of 1.33 (95% confidence interval: 1.23–1.43) (Table 4, Fig 5). Because the odds ratio associated with the years since last DTaP variable did not change appreciably when the number of doses variable was included, there is
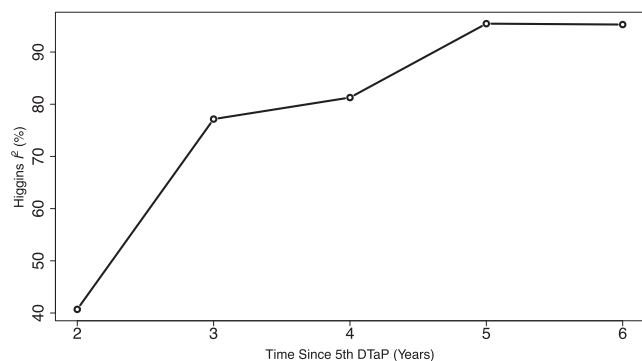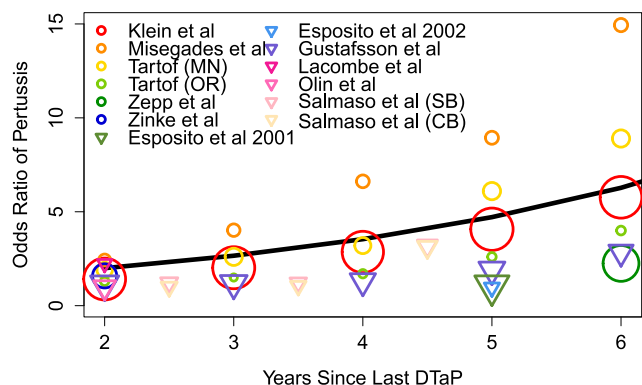
FIGURE 4
Relationship between heterogeneity between studies (as measured with Higgins' I^2) and time since last DTaP. Higgins' I^2 is a measure of the total variation between studies due to heterogeneity.[28]

TABLE 4 β Coefficients and Corresponding SEs for the 3 Different Meta-regression Models

	Intercept	Years Since Last DTaP	5 Doses	Serologic Study
Model 1	0.321 (0.14)	0.289 (0.06)		
Model 2	−0.053 (0.14)	0.26 (0.05)	0.719 (0.14)	
Model 3	−0.003 (0.11)	0.2862 (0.04)	0.695 (0.11)	−0.728 (0.16)

SEs are shown in parentheses. β coefficients represent the log of the odds ratio for every unit increase in the predictor variable.

FIGURE 5
Odds ratios of pertussis for each year since the last dose of DTaP. The circles, inversely weighted by study variability, represent the odds ratios calculated from each of the studies examining 5 doses of DTaP, whereas the inverted triangles represent the odds ratios from the studies examining 3 doses of DTaP included in the meta-analysis. The black line represents the fitted meta-regression curve accounting for the effects of time. In this meta-regression curve, dose type was assumed to be constant at 5 doses and the diagnosis type was assumed to be constant at "clinical." MN, Minnesota; OR, Oregon.

evidence to suggest that the duration of protective immunity from DTaP is the same for those given 3 or 5 doses of the vaccine (Table 4). Similarly, when the definition of loss of immunity variable was included, the odds ratio again did not change appreciably, suggesting that the duration of protective immunity from DTaP is the same for the studies measuring clinical markers of

pertussis and those measuring serologic markers (Table 4). However, the addition of these variables changes the absolute risk of pertussis, with a higher risk of pertussis in the studies examining the 5-dose vaccine series and a lower risk of pertussis in the studies that used serologic outcomes (Table 4).

Using the above estimated odds ratio of 1.33, we created curves of the

predicted probability of vaccine failure through time (Fig 6). From this analysis, the average duration of vaccine protection from DTaP is ~3 years, assuming 85% vaccine efficacy. With this loss of protection, we predict that only 10% of the children vaccinated with DTaP would be protected by 8.5 years after the last dose, but this could be higher or lower with alternate assumptions regarding vaccine efficacy.

DISCUSSION

Understanding the duration of protective immunity conferred by a vaccine is critical to the development of immunization guidelines and programs. To our knowledge, this is the first systematic review and meta-analysis of the duration of protective immunity to pertussis after routine childhood immunization with DTaP. Our findings suggest that the odds of pertussis increase by 1.33 times (95% confidence interval: 1.23–1.43) for every additional year since the last dose of DTaP. With this loss of protection, we predict that only 10% of the children vaccinated with DTaP would be protected by 8.5 years after the last dose, assuming an initial vaccine efficacy of 85%.[1,30]

Although we found that the odds of pertussis for every year since the last dose of DTaP did not depend on the number of doses, we did find that there was a greater absolute risk of pertussis in the studies examining 5 doses of DTaP and a lower absolute risk of pertussis in the serologic studies. Because the participants in the 5-dose studies were older, on average, than the participants in the 3-dose studies, this finding may highlight the increased risk of pertussis in older age groups. Although infants <1 year remain at highest risk of pertussis, recent surveillance reports from the United States and Canada indicate that age groups with the next highest incidence of pertussis include 7- to
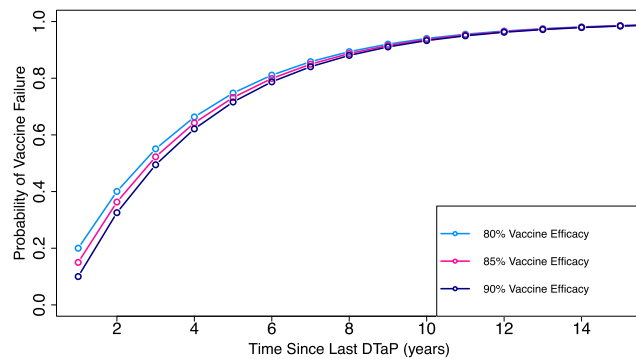
FIGURE 6
Estimated probability of vaccine failure for different levels of vaccine efficacy.

10-year-olds (United States) and 10- to 14-year-olds (Canada).[62,63] The lower absolute risk of pertussis in the studies examining serologic outcomes may be due to the sensitivity of these testing methodologies and their corresponding anti-PT (pertussis antitoxin) cutoff levels.

It is important to highlight the limitations of studies included in this review. Most studies were observational in nature,[9,10,38,39,41,47,51,59] allowing for biases and confounding to distort measures of association. Although 3 studies adjusted for potential confounders of interest (age, gender, race/ethnicity, age at fifth dose of DTaP, medical clinic; Table 2),[9,10,47] others did not, which may have contributed to over- or underestimates of the duration of protective immunity. Case-ascertainment bias could have affected individual study results: where nasopharyngeal swabs were necessary for confirmation of the case definition of pertussis,[9,10,41,44,47,51,59] physicians may have been more likely to test sicker or more medically complex patients due to the invasive nature of the procedure, which could alter estimates of effect. One of the studies specifically addressed this concern and implemented standardized procedures for collecting nasopharyngeal swabs for ongoing coughs, regardless of other clinical characteristics.[55] Serologic follow-up studies[38,39,60,61] would not be affected by this type of

case-ascertainment bias, but all serologic follow-up studies[38,39,60,61] were funded by vaccine companies producing DTaP, potentially inducing biases of another nature.

As with all systematic reviews, this study had a number of limitations. Primarily, the follow-up periods for the studies included in the meta-analysis ranged from 2 to 6 years, limiting estimates to this relatively brief period. We extrapolated meta-regression results because longer-duration studies were not identified. Although we believe this assumption was necessary, it nonetheless presents a limitation in the interpretation of the results. In addition, we found considerable between-study heterogeneity, possibly an artifact of varying case definitions, study designs, and study populations. Third, the 3- and 5-dose series each included different dosing schedules (Table 2), which may have added to the observed heterogeneity.

However, this systematic review and meta-analysis is the first of its kind to synthesize the information and provide a credible estimate on the duration of vaccine-induced immunity to pertussis. The review methods were robust and captured a wide range of studies in multiple languages and countries of publication. Although translation with the use of Google Translate is imperfect, it allowed us to determine citation relevance for non-English

studies, thereby reducing the potential for publication bias.[26] By searching multiple databases and the references of included studies, we are confident that the search captured all relevant published studies, and we found no evidence for publication bias using Egger's test and analysis of the funnel plots (Fig 2).

The results from this meta-analysis have important policy implications, mainly surrounding boosting strategies for adolescents to ensure that "herd effects" of pertussis are maintained. Although an adolescent Tdap booster is offered in Canada, it is recommended for teenagers aged 14 to 16 years,[1] which may be too late and leave those aged 10 to 14 years susceptible to pertussis. The adolescent Tdap booster is recommended for youth between 10 and 12 years of age in the United States and in many European countries,[15,64] which may represent more appropriate timing.

In addition, the results from this analysis have implications for repeated pertussis vaccinations in adults. Previous research has highlighted the importance of repeat Tdap immunization for each pregnancy.[65] It has also been suggested that a decennial booster strategy with Tdap may be an effective and cost-effective way to control the spread of pertussis among adults.[66–68] Although the risk of pertussis infection may be lower in adults, assuming waning immunity to Tdap is similar to waning immunity to DTaP, repeated booster vaccines will be necessary to maintain a population with high levels of vaccine coverage for pertussis.

Our findings also provide epidemiologists and mathematical modelers with credible data inputs for modeling studies. The weight of the evidence suggests that the average duration of protective immunity to pertussis after the fifth dose of DTaP is ~3 to 4 years, a key parameter in many studies evaluating

vaccination strategies and their economic impact. However, this estimate of the probability of vaccine failure is sensitive to the initial vaccine efficacy. The parameterization of the function can be modified to generate predictive values of duration of protection for different levels of vaccine efficacy.

In summary, we performed a systematic literature review to understand the relationship between the risk of pertussis and time since pertussis vaccination. We found evidence of waning immunity and estimated that the average duration of vaccine protection from DTaP is ~3 years, assuming 85% vaccine efficacy. With this loss of protection, we predict that only 10% of the children vaccinated with DTaP would be protected by 8.5 years after the last dose. With a preschool booster offered for children aged 4 to 6 years, our findings suggest that very few children over age 10 would be protected against pertussis, signaling the need for an earlier adolescent Tdap booster in Canada.

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