**Distribution Agreement**

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Timothy Roice Fulton Date

Protective effect of pertussis vaccine and the impact of waning protection:

a systematic review and meta-analysis

By

T. Roice Fulton

Master of Public Health Candidate

Hubert Department of Global Health & Department of Epidemiology

_____ [Chair‘s signature]

[Saad B. Omer, MBBS, MPH, PhD]

Committee Chair

# Protective effect of pertussis vaccine and the impact of waning protection: a systematic review and meta-analysis

By

T. Roice Fulton

B.S.

University of North Carolina at Chapel Hill

2005

Faculty Thesis Advisor: Saad B. Omer, MBBS, MPH, PhD

An abstract of

A thesis submitted to the Faculty of the Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of Master of Public Health

in Global Health and Epidemiology

2014

## Abstract

Protective effect of pertussis vaccine and the impact of waning protection:

a systematic review and meta-analysis

By T. Roice Fulton

**Background**
Pertussis accounted for an estimated 195,000 deaths worldwide in 2012. A variety of vaccine formulations have been brought to market, with the more recent acellular (aP) formulations demonstrating similar efficacy to whole-cell (wP) vaccine while exhibiting less reactogenicity than the older whole-cell formulations.

Several recent studies bear new data on the real-world effectiveness of acellular vaccines in multiple contexts. Further, recent experiences with pertussis outbreaks worldwide suggest that the protective effect of acellular vaccine may significantly decline in the years following the final dose administered.

This review aims to estimate the overall effectiveness and waning protective effect of pertussis vaccines on the market for use in the Lives Saved Tool (LiST), which allows assessment of the impact of interventions against child morbidity and mortality in low-income countries.

**Data sources & review methods**
We conducted a systematic review of published efficacy and effectiveness trials of pertussis vaccines, searching PubMed, the Cochrane Library, Web of Science, EMBASE, and the World Health Organization (WHO) Regional Databases. Study descriptors and outcome measures for qualifying articles were abstracted into standardized tables, and each study was assigned a grade for quality of evidence. We performed a meta-analysis on acellular and whole-cell vaccine trials and observational studies to determine an overall effect size for vaccines currently on the market, and applied the Child Health Epidemiology Reference Group (CHERG) Rules for Evidence Review to estimate the effect of the vaccines on severe pertussis morbidity.

**Results**
We identified eighteen studies for inclusion in the review. Twelve studies assessed the efficacy or effectiveness of pertussis vaccines currently on the market against the incidence of pertussis in children under six. Nine studies explored the long-term protective effect of acellular and/or whole-cell vaccine.

We performed meta-analyses stratifying studies by type of vaccine and efficacy/effectiveness. These provided an overall effect size of 84% (95% confidence interval: 81-87%) for acellular vaccine efficacy studies and 94% (88-97%) for whole-cell vaccine effectiveness studies. No studies were identified that explored pertussis-specific mortality, but all studies indicated a significant reduction in incidence of pertussis in fully-vaccinated children under six.

All studies exploring long-term protective effect of pertussis vaccine in children over six indicated either a progressive decrease in vaccine effectiveness (VE) or an increase in pertussis incidence or risk in the years following the final dose. The study demonstrating the highest quality of evidence showed an average annual increase of 42% in the odds of acquiring pertussis after the fifth and final dose of acellular pertussis.

**Conclusion**
Whole-cell and acellular pertussis vaccines currently on market are effective against severe pertussis morbidity. However, effectiveness wanes steadily after the administration of the final dose for acellular vaccines in particular, requiring the thoughtful implementation of vaccination schedules and programs that yield sustained protection in low-income countries.

# Protective effect of pertussis vaccine and the impact of waning protection: a systematic review and meta-analysis

By

T. Roice Fulton

B.S.

University of North Carolina at Chapel Hill

2005

Faculty Thesis Advisor: Saad B. Omer, MBBS, MPH, PhD

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of Master of Public Health

in Global Health and Epidemiology

2014

**TABLE OF CONTENTS**

ACKNOWLEDGEMENTS ..... 2
STUDENT CONTRIBUTION ..... 3
ABSTRACT ..... 5
Background ..... 5
Data sources & review methods ..... 5
Results ..... 6
Conclusion ..... 7
INTRODUCTION ..... 8
Description of the condition ..... 8
Description of the intervention ..... 9
Importance of this review ..... 11
Objectives ..... 14
METHODS ..... 14
Criteria for considering studies for this review ..... 14
Search methodology ..... 20
Data collection and analysis ..... 21
RESULTS ..... 27
Description of studies ..... 27
Effects of interventions ..... 29
DISCUSSION ..... 37
Summary of main results ..... 37
Overall completeness and applicability of evidence ..... 39
Quality of evidence ..... 40
Risk of bias in included studies/in the review process ..... 42
Conclusions and future directions ..... 45
SUPPLEMENTARY DATA ..... 47
FUNDING ..... 47
CONFLICTS OF INTEREST ..... 47

**ACKNOWLEDGEMENTS**

"The mind is not a vessel to be filled, but a fire to be kindled."

— Plutarch

The author would like to express his gratitude to his family, for their infinite patience and steadfast support of academic pursuit; to Alex Tran and Annum Shaikh, whose kinship and encouragement through the days and months have left upon me an indelible impression; to Dr. Saad Omer, for his invaluable guidance over two years of (re-)education; to Dr. Wayne Johnson, for providing expert methodological advice in the development of this work; and to Dr. Alan Hinman, whose lifelong dedication to bettering the human condition has sparked an enduring passion for public health—both within myself, and among a generation of aspiring scholars.

## STUDENT CONTRIBUTION

This manuscript will be submitted for publication with multiple authors, to be determined but including the following: T. Roice Fulton and Saad B. Omer, MBBS, MPH, PhD. As the lead researcher on this project, T. Roice Fulton made significant contributions to the manuscript, outlined below:

Research:

1. Conducted a comprehensive search of relevant literature using defined search terms
2. Refined search terms to focus the literature search, finding 175 candidate abstracts from 3,985 original hits
3. Developed inclusion/exclusion criteria and applied to 28 final candidate articles, leaving 18 articles for inclusion

Data Extraction and Analysis:

4. Performed systematic extraction of all salient data from the 18 selected articles
5. Utilized an adapted Grading of Recommendations Assessment, Development and Adaptation (GRADE) quality assessment methodology to assess the strength of evidence for each study outcome
6. Analyzed all relevant data from the 18 included articles via review of statistical analyses and performance of meta-analyses to determine overall effect size where appropriate

Manuscript Construction:

7. Authored all sections of the manuscript, including: Abstract, Background, Methods, Results, Discussion, Conclusion, References, and Acknowledgements

8. Created or adapted all additional tables and figures for the manuscript

9. Produced revisions of the manuscript per feedback from thesis advisor

## ABSTRACT

### Background

Pertussis accounted for an estimated 195,000 deaths worldwide in 2012. A variety of vaccine formulations have been brought to market, with the more recent acellular (aP) formulations demonstrating similar efficacy to whole-cell (wP) vaccine while exhibiting less reactogenicity than the older whole-cell formulations.

Three systematic reviews, including one Cochrane review, have been conducted to assess the efficacy and effectiveness of whole-cell and the newer acellular vaccines, providing sound evidence of protection. However, several recent studies bear new data on the real-world effectiveness of acellular vaccines in multiple contexts. Further, recent experiences with pertussis outbreaks worldwide suggest that the protective effect of acellular vaccine may significantly decline in the years following the final dose administered.

This review aims to estimate the overall effectiveness and waning protective effect of pertussis vaccines on the market for use in the Lives Saved Tool (LiST), which allows assessment of the impact of interventions against child morbidity and mortality in low-income countries.

### Data sources & review methods

We conducted a systematic review of published efficacy and effectiveness trials of pertussis vaccines, searching PubMed, the Cochrane Library, Web of Science, EMBASE, and the World Health Organization (WHO) Regional Databases. Study descriptors and outcome measures for qualifying articles were abstracted into standardized tables, and each

study was assigned a grade for quality of evidence. We performed a meta-analysis on acellular and whole-cell vaccine trials and observational studies to determine an overall effect size for vaccines currently on the market, and applied the Child Health Epidemiology Reference Group (CHERG) Rules for Evidence Review to estimate the effect of the vaccines on severe pertussis morbidity.

**Results**

We identified eighteen studies for inclusion in the review. Twelve studies assessed the efficacy or effectiveness of pertussis vaccines currently on the market against the incidence of pertussis in children under six. Nine studies explored the long-term protective effect of acellular and/or whole-cell vaccine.

We performed meta-analyses stratifying studies by type of vaccine and efficacy/effectiveness. These provided an overall effect size of 84% (95% confidence interval: 81-87%) for acellular vaccine efficacy studies and 94% (88-97%) for whole-cell vaccine effectiveness studies. A meta-analysis of acellular vaccine effectiveness demonstrated high heterogeneity, thus the pooled estimate is not reported; the estimates of vaccine effectiveness ranged from 74% (51-86%) to 97% (91-99%). No studies were identified that explored pertussis-specific mortality, but all studies indicated a significant reduction in incidence of pertussis in fully-vaccinated children under six. We applied CHERG Rule 5 for generating estimated intervention effects, resulting in the recommendation of the pooled aP efficacy (84%) and wP effectiveness (94%) estimates for use in LiST.

All studies exploring long-term protective effect of pertussis vaccine in children over six indicated either a progressive decrease in vaccine effectiveness (VE) or an increase in pertussis incidence or risk in the years following the final dose. The study demonstrating the highest quality of evidence showed an average annual increase of 42% in the odds of acquiring pertussis after the fifth and final dose of acellular pertussis vaccine. Two screening studies indicated a similar, though not as severe, reduction in whole-cell vaccine effectiveness in children between the ages of 6 and 13 who did not receive booster doses.

## Conclusion

Whole-cell and acellular pertussis vaccines currently on market are effective against severe pertussis morbidity. However, effectiveness wanes steadily after the administration of the final dose for acellular vaccines in particular, requiring the thoughtful implementation of vaccination schedules and programs that yield sustained protection in low-income countries.

# INTRODUCTION

## Description of the condition

Pertussis, or whooping cough, is a vaccine-preventable disease responsible for widespread childhood morbidity and mortality, caused principally by the gram-negative *Bordetella pertussis* (*B. pertussis*) coccobacillus. (1)

Pertussis can occur at any age; however, severe illness and death due to pertussis occurs most often in infants. Patients present with paroxysmal coughing followed by an audible inspiratory whoop and occasional posttussive vomiting. Although considered a typically relatively benign respiratory illness, pertussis can result in serious consequences, such as pneumonia, seizures, encephalopathy and death, especially among infants. Of note, immunized children, adolescents, and adults contracting pertussis may be asymptomatic or present with atypical manifestation of disease, such as a cough lasting several weeks. (1)

Recent estimates indicate that there are approximately 16 million pertussis cases annually worldwide among children, teenagers, and adults, 95% of which are in low-income countries. About 195,000 of those infected die of the disease annually. (2)

Prior to introduction of the pertussis vaccine in the 1940s, there were approximately 200,000 cases reported annually in the United States. Immunizations reduced disease rates, and in 1976 pertussis incidence reached 1,010 reported cases. (1)

Recent trends indicate a change in the epidemiology of pertussis in the older age group in countries that have achieved good control of pertussis. A marked increase in the number of cases reported has occurred in children and adolescents aged 6 to 10 years, following

completion of the vaccination series. In the US, 25,827 cases were reported in 2004, concurrent with a 19-fold increase of pertussis cases among adolescents. (3)

Waning vaccine-induced immunity is cited among several possible causes for the increasing incidence of pertussis disease. (4-9) Evidence of nasopharyngeal carriage of *B. pertussis* among nonhuman primates also has implications, as transmission to unvaccinated individuals remains a threat when in proximity to carriers. (10) Affected adolescents and adults act as reservoirs of the disease to the vulnerable population of infants, for whom the disease can be life-threatening. (11)

**Description of the intervention**

The global burden of pertussis is addressed principally through immunization-based intervention. (1) Whole-cell pertussis vaccine (typically prepared via heat and formalin inactivation) was introduced in the 1940s following reports of protection against disease in individuals receiving a vaccine composed of bacilli suspended in saline. The formulation and preparation of whole cell vaccines varies widely, with vaccine produced by several manufacturers worldwide; significant differences in immunogenicity and efficacy have been noted among these vaccines. (1)

Following concerns regarding high reactogenicity of wP vaccine, including potential association with neurological disorders, acellular pertussis (aP) vaccines underwent development and licensure in the 1970s and 80s. Acellular vaccines are comprised of purified antigenic components, namely pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin, and fimbriae type 2 and 3 (FIM 2 and 3). Various combinations and concentrations of these antigens are employed in aP vaccines currently on the market, and

post-licensure surveillance together with epidemiological studies have confirmed the real-world effectiveness of these vaccines. (1)

The mechanism of action of vaccine-induced immunity against *B. pertussis* remains poorly understood. Induction of antibodies to the components of *B. pertussis* may be associated with vaccine protection; it is thought that anti-*B. pertussis* IgG antibodies may also play a key role in preventing bacterial adherence. (12, 13) To date, no consensus has been reached regarding the exact role of the various aP antigens in conferring immunity.

Vaccine efficacy varies with dosage (typically administered as a three-dose primary series with up to two pediatric boosters, depending on region), type of vaccine in use (whole-cell versus acellular), formulation/preparation, and the combination of other vaccines with pertussis vaccine (e.g., DTaP in the US versus DTwP/Hep/Hib in Mexico). (1)Extensive research has been conducted on the efficacy and safety of various pertussis vaccines, with much data on acellular vaccine efficacy in particular sourced from nine large trials conducted between 1985 and 1993. (1, 14) The type of vaccine used today varies by country.

The real-world effectiveness of whole-cell and acellular pertussis vaccines is documented via disease surveillance and observational study. A marked increase in incidence of pertussis was found following the temporary suspension in the 1970s of whole-cell pertussis immunization programs in Japan due to safety concerns. (15) High acellular vaccine effectiveness has been demonstrated in Germany, where a nationwide, hospital-based surveillance system showed an age-adjusted effectiveness of 99.8 percent for

prevention of hospitalization due to pertussis among children who have completed the primary series. (16)

## Importance of this review

### *Other reviews*

Three systematic reviews have been conducted exploring the efficacy of pertussis vaccines. A Cochrane review, initially published in 1999 and most recently updated in 2012, reviewed acellular pertussis vaccine efficacy and safety trials in children under six. (14) The review indicated an efficacy of 84-85 percent of multi-component (combination of 3 or more antigens) acellular pertussis vaccines in preventing "typical" whooping cough. The Cochrane review found a meta-analysis of efficacy data inappropriate given multiple factors, including significant variability in dose schedule, case definitions, follow-up periods, and background pertussis rates. A response to the review supported the decision not to conduct a meta-analysis, while indicating concerns regarding the reviewers' conclusion of superiority of multi-component aP to one- or two-component aP vaccines. (14)

A systematic review of pertussis vaccine studies was conducted in 2003 by Jefferson et al, including a meta-analysis evaluating the absolute and relative efficacy of several wP and aP vaccines. (17) The review indicated comparable efficacy between three- and five-component vaccines and wP comparators against the WHO definition of pertussis, though significant heterogeneity was noted in the results. This review was subsequently critiqued for conducting the meta-analysis in light of the heterogeneity of the pooled studies'

characteristics. (18) However, together with the Cochrane review, the 2003 paper remains one of the most comprehensive reviews of pertussis efficacy studies to date.

A third review conducted in 2005 by Casey et al reported the outcomes of eight efficacy trials, but did not perform a meta-analysis of the selected studies. (19)

*Rationale*

Efficacy studies assess the protective effect of vaccines in idealized conditions, with coverage rates likely higher within the study population than would be found in real-world settings. (20) As discussed above, real-world pertussis vaccine effectiveness has been confirmed by continued surveillance and other means. However, both immunization coverage and vaccine effectiveness vary by region, requiring continued assessment of both wP and aP vaccine effectiveness as new formulations are brought to market and others withdrawn. Low-income countries are increasingly adopting aP vaccine in their immunization programs, though whole-cell vaccines remain widely used due to wide availability, low cost, and comparable efficacy to aP vaccines. (21) Within high-income countries including the US that utilize aP vaccine, coverage remains relatively high in areas that have recently experienced pertussis outbreaks (22) —suggesting that in these cases, the protective effect of the vaccine may play a significant role.

The reviews conducted to date include assessments of vaccines that are no longer licensed or used, warranting an updated review of wP and aP vaccines currently on market. Further, expert consensus on pertussis vaccine effectiveness does not reflect the effect of waning long-term protection, particularly with the newer acellular vaccines; the impact of this phenomenon has only recently been studied in depth. New data suggests that protection

conferred by aP vaccine may significantly decline in the five years following the fifth and final dose administered at age seven per the US schedule. (7, 9, 23) This phenomenon may be more pronounced in countries using similar vaccines but following a shorter or booster-free immunization schedule.

*Impact*

Reliable quantification of the impact of evidence-based interventions upon neonatal and child mortality is a critical concern for policymakers, particularly those developing cost-effective intervention packages for implementation in low-income countries. Recently, resources such as the Lives Saved Tool (LiST) have been developed to allow countries to model the effectiveness of maternal, neonatal and child health interventions prior to implementation. (24) Such tools attempt to provide a practical and evidence-based characterization of the effect of each intervention upon childhood morbidity and mortality.

Given that most, if not all, pertussis vaccine studies use incidence of typical pertussis or hospitalization due to pertussis as a primary outcome, the studies and reviews conducted to date may not paint a complete picture of the impact of pertussis vaccination on severe child morbidity. The Child Health Epidemiology Reference Group (CHERG) has developed standards that allow for the systematic classification of evidence indicating the effectiveness of various interventions against child morbidity and mortality. (25) This review will apply these standards, with findings made available for use in the evaluation of maternal, neonatal and child health interventions against cause-specific morbidity and mortality, particularly as modeled by the Lives Saved Tool.

## Objectives

This review aimed to assess the effectiveness and long-term protective effect of pertussis vaccines currently on market. The following questions were answered:

1. What is the overall effect of acellular and whole-cell pertussis vaccine with respect to child morbidity?

2. What is the impact, if any, of waning long-term protection on the effectiveness of pertussis vaccine?

# METHODS

## Criteria for considering studies for this review

*Types of studies*

Types of studies included randomized controlled trials and observational designs, including case-control, cohort, household contact, and screening studies, producing either

1) a pertussis vaccine efficacy or effectiveness estimate against a relevant outcome (all-cause mortality, pertussis-specific mortality, pertussis-specific hospitalization, or incidence or risk of typical or severe pertussis disease); or

2) an estimate of risk or odds of acquisition of pertussis with respect to time since completion of vaccination series.

We required some form of laboratory confirmation or epidemiological linkage of suspect cases to be performed within each study to ensure sufficient case definition specificity.

There was no restriction on date of publication.

*Types of participants*

Participants for studies assessing overall vaccine effect: Children under six years of age.

Participants for studies assessing long-term protective effect: Children under 13 years of age.

*Types of interventions*

Acellular or whole-cell pertussis vaccine, given generally as DTwP or DTaP in dose regimens of up to five doses (typically three primary series doses plus up to two DTwP/aP boosters), constitute the interventions under investigation.

Studies evaluating the absolute efficacy/effectiveness, protection against severe pertussis, or long-term protection of both aP and wP vaccines were included. Only aP or wP formulations currently on the market are of interest; studies exploring the effect of multiple aP or wP formulations were included if at least one on-market formulation was investigated.

*Types of outcome measures*

Primary outcomes

The primary efficacy/effectiveness outcome measures of interest included pertussis incidence, odds or risk of pertussis infection, and vaccine efficacy and effectiveness estimates.

Trials comparing aP/wP vaccines with a randomized placebo or DT-only group allowed for the determination of absolute vaccine efficacy, calculated as (1-RR) x 100%, where risk ratio equals the risk of disease in the vaccine group divided by the risk of disease in the placebo/DT group.

Together with controlled trials and conventional observational studies, an alternative means of calculating vaccine effectiveness is the screening method. (20) Rather than choosing one or more individual controls per case as in a typical case-control study, the entire population at risk (or a representative sample) is used as a reference group. To calculate vaccine effectiveness using this method, only three data points are needed from a given population:

1) the number of pertussis cases, typically available from surveillance,

2) the number of cases vaccinated, typically available from surveillance, and

3) the percent of the population vaccinated, often calculated from vaccine coverage surveys.

Population-based denominator data are not necessary. The screening method leverages data that may be collected for other analyses, and is consequently less resource-intensive than prospectively enrolled case-control studies and RCTs while providing a potentially useful estimate of real-world vaccine effectiveness in contexts where more rigorous designs are infeasible. (20)

Screening studies were included if a vaccine effectiveness estimate was provided, calculated as $(I_{unv}-I_{vac})/I_{unv}$ x 100%, or the difference in cumulative incidence (attack rate) of pertussis among unvaccinated and vaccinated populations (based on surveillance data or surveys of an appropriate sample of the general population) divided by the incidence in unvaccinated populations times 100 percent. (20)

Studies that did not evaluate absolute efficacy due to practical or ethical considerations (such as the lack of an unvaccinated comparison population) were included if the findings contributed information to the protective effect of wP/aP vaccine against severe pertussis or hospitalizations due to pertussis. All non-randomized controlled trial studies were categorized as effectiveness studies for the purposes of this review irrespective of the efficacy/effectiveness characterization made by the study authors. Assessments of comparative efficacy between wP and aP vaccine were not considered.

Pertussis vaccine efficacy/effectiveness estimates vary depending on case definition, with many studies reporting results against multiple case definitions. We included studies evaluating efficacy/effectiveness against the current WHO definition of “typical” pertussis (14 or more days of cough with at least one of paroxysmal cough, inspiratory whoop, or posttussive vomiting, plus laboratory confirmation or epidemiological linkage with a

household member who had culture-confirmed pertussis) or against a case definition closely corresponding to this definition. (26) This is the case definition currently recommended by WHO for pertussis surveillance.

As this study aimed to characterize the global effect of pertussis vaccine against severe child morbidity and mortality (of which few studies addressing the latter were expected to exist), and as clinical trials often evaluate outcomes against a more specific case definition than that used for disease surveillance, we also included studies evaluating effect against the WHO definition of "severe" pertussis (21 or more consecutive days of paroxysmal cough with confirmation of *B. pertussis* cases by culture, appropriate serology, or epidemiological linkage) or a similar definition. This was the recommended WHO case definition for pertussis vaccine clinical trials at the time the RCTs included in this review were conducted. (27)

Efficacy endpoints were reviewed for the population who received all scheduled doses of the randomized vaccine. Studies conducting an intent-to-treat (ITT) analysis were included in our review where data against a relevant outcome was available and only if at least one dose of pertussis vaccine was administered. Studies conducting ITT analyses were subjected to additional examination to ensure consistency of assumptions and strength of evidence.

Secondary outcomes

The long-term protection outcome measures included:

- Age-adjusted risk of pertussis infection with respect to time since completion of vaccination series (i.e., comparing incidence of pertussis within a fully-vaccinated population shortly after the final dose and at specific time intervals, with at least two years of post-vaccination follow-up);

- Age-adjusted odds of pertussis infection with respect to time since completion of vaccination series (i.e., comparing the characteristics of vaccination status of confirmed cases to a control group shortly after the final dose and at specific time intervals, with at least two years of post-vaccination follow-up); or

- Age-adjusted estimates of vaccine efficacy/effectiveness among fully vaccinated children calculated at least two years after the final dose.

Data on children who were confirmed or likely to have received a booster dose were excluded from consideration.

Given that older children and adolescents infected with *B. pertussis* may present with atypical symptoms, the secondary outcome case definition was broadened to enhance sensitivity, requiring a minimum of seven days unexplained cough illness. (28) Specificity was maintained by requiring laboratory or epidemiological confirmation as per the WHO case definition.

## Search methodology

### *Electronic searches*

Searches of multiple major publication databases were conducted, including PubMed, the Cochrane Library, Web of Science, EMBASE, and the WHO Regional Databases. Search terms included all terms potentially related to pertussis vaccine effect against relevant outcomes, including but not limited to “pertussis”, “whooping cough”, “vaccine”, “efficacy”, “effectiveness”, “DTaP”, “DTwP”, “outbreak”, “treatment outcome”, “morbidity”, “mortality”, and “hospitalization.”

Sample search string (PubMed):

“((((pertussis[Title] OR pertussis[MeSH Terms]) OR (DTP[Title] OR DTwP [Title] OR DTaP[Title])) AND vaccine[Title] AND efficacy[All Fields])
OR (("whooping cough"[Title] OR "whooping cough"[MeSH Terms])
AND vaccine [Title] AND efficacy[All Fields]))
AND (mortality[All Fields] OR morbidity[All Fields])”

### *Searching other resources*

References of selected papers, the Cochrane acellular efficacy review, and the Jefferson 2003 systematic review were manually searched for related studies or relevant correspondence. No systematic attempt was made to obtain unpublished articles. Searches were not limited to English language reports, given evidence that such limitation may constitute a source of bias.

## Data collection and analysis

### *Study selection*

Search results were imported into Endnote X7 and de-duplicated. One reviewer (TRF) screened all titles and abstracts in order to assess for eligibility for inclusion. Titles and abstracts clearly bearing no relevance to the study were discarded. Full texts of potentially eligible studies were obtained when required to assist screening for final inclusion. Uncertainty during the screening process with regard to the inclusion/exclusion of studies was resolved by discussion between the reviewer and principal investigator. Rationale for study exclusion was recorded as part of the screening process.

### *Data extraction and management*

All research studies meeting the inclusion criteria were abstracted into an Excel spreadsheet by one reviewer (TRF). Key variables were abstracted in order to grade each study according to the CHERG adaptation of the Grading of Recommendations Assessment, Development and Adaptation (GRADE) technique. (25) Following convention for CHERG intervention reviews, this spreadsheet is available as a Supplementary Table 1.

Data extracted included: study identifiers and context, including author, year of publication, outcome of interest, study timeframe, country, place within country, locality of study with urban/rural context, baseline mortality rate, and setting (e.g., hospital vs. community); study design and limitations information; and study intervention data, including target population, intervention definition (type of vaccine), concurrent

interventions, coverage of intervention, method of delivery of intervention, comparison group, outcome definition, what type of effect is measured (vaccine efficacy or effectiveness), intervention and control numerators and denominators, effect of intervention on outcome in terms of increase/decrease of risk/odds or effect on morbidity or mortality, and confidence intervals and p-values.

For studies publishing multiple measures against a range of outcomes (e.g., absolute aP efficacy versus aP efficacy relative to wP, or VE for multiple vaccine formulations or age groups), only values related to the outcomes of interest as described above were abstracted.

*Assessment of risk of bias in included studies*

CHERG has adapted the GRADE process to reflect the particular needs of its intervention reviews. This review employed the adapted process, which ranks quality of study evidence by four criteria: (i) study design; (ii) study quality; (iii) relevance to the objectives of the review; and (iv) consistency across studies. (25)

Randomized controlled trials were assigned a high initial score, followed by observational studies (case-control and cohort studies), vaccine screening studies (considered less robust and more prone to bias), and lastly evidence generated by other designs, which receive the lowest initial score. Scores are then modified based on a thorough assessment of study methods, sample size, potential for reporting bias, study execution, confounding and extent of control for potential confounders, and any inconsistencies with other data sources that bring validity of results into question. (25)

Studies producing an effect that varied widely from other studies of acceptable quality were examined to identify the source of the inconsistency.

*Measures of treatment effect*

Effect measures from both efficacy and effectiveness trials meeting selection criteria were abstracted, with VE calculated as 1-OR or 1-RR following the methodology used by the respective study. Risk ratio estimates were used over OR in efficacy trials providing both values.

*Missing data*

Following abstraction of data from selected studies, additional data required to fully characterize studies in an equitable fashion was imputed where acceptable. Specifically, risk/odds ratios were back-calculated from vaccine efficacy/effectiveness estimates for clinical trials, case-control studies, and cohort studies that only provided VE but remained otherwise robust.

Studies that did not meet an established minimum threshold of patient follow-up (one year after the final dose administered for the primary outcome) were excluded from the meta-analysis.

*Assessment of heterogeneity*

Among pertussis vaccine studies of sufficient consistency to warrant meta-analysis, heterogeneity of effect sizes was formally assessed using the Q and $I^2$ statistics:

Cochran's Q: A statistical test for heterogeneity distributed as a chi-square ($\chi^2$) statistic. This tests the null hypothesis that all studies have the same underlying magnitude of effect. A low p-value (P<0.1) therefore indicates significant heterogeneity. The $\chi^2$ statistic has low power to detect heterogeneity when there are few studies; when the number of studies is large, Q may detect heterogeneity of minimal biological or clinical importance.

$I^2$: An index that is not dependent on the number of studies, used to quantify the impact of heterogeneity.

$$I^2 = \frac{Q - df}{Q} * 100\%$$

$I^2$ represents the percentage of the total variation across studies due to heterogeneity rather than sampling error or chance, with values ranging from 0% (no observed heterogeneity) to 100%.

*Assessment of reporting biases*

The potential impact of selective reporting of outcomes on the findings of this review are addressed in the Discussion section.

*Data synthesis*

Fixed effects and random effects meta-analyses were performed for studies yielding sufficient quality of evidence and sharing characteristics with other studies sufficient to warrant pooled analysis. The meta-analysis included only studies reporting estimates calculated between one and three years after the final dose administered. Estimates based

on effect among children who receive less than the recommended vaccine dose were excluded.

Per CHERG standards for candidate analyses for inclusion in LiST, fixed effects meta-analysis results are reported if there is not strong evidence of heterogeneity across pertussis vaccine studies, generating a point estimate and 95% confidence interval for the fixed effect. (25) Causes of significant heterogeneity were explored; if unexplained heterogeneity remained, but the direction of the effect remains consistent across studies, the results of the random effects meta-analysis are reported, indicating the average effect across studies.

As data on the efficacy/effectiveness of pertussis vaccine against death due to pertussis was expected to be sparse, the meta-analysis included studies examining morbidity outcomes. We then applied the CHERG rules for generating estimated intervention effects for use in LiST as appropriate.

Meta-analyses were stratified on type of vaccine (aP or wP) and type of study (efficacy or effectiveness), with pooled random effects estimates reported for studies demonstrating low heterogeneity ($I^2 < 50\%$). Per-protocol and intent-to-treat data were pooled within these strata. We did not perform comparative analyses of efficacy or effectiveness among aP vaccines on market.

Meta-analysis of the waning protection studies was not indicated due to significant heterogeneity in study characteristics, particularly in effect measures and methodology. Only the individual study estimates were reported. Average year-over-year change in

risk/odds/incidence of pertussis or protective effect of pertussis vaccine were calculated by the reviewer where feasible and reported in Table 2.

Meta-analyses were performed, and forest plots generated, using Microsoft Excel 2013 and Review Manager 5.2.

*Subgroup analysis and investigation of heterogeneity*

Meta-analyses were stratified both on efficacy/effectiveness and on type of vaccine studied (wP versus aP). Per-protocol and intent-to-treat data were pooled within these strata. Potential sources of heterogeneity in the meta-analyses are explored in the Discussion section.

*Sensitivity analysis*

We planned three sensitivity analyses, and conducted two.

The first analysis ranked studies providing intent-to-treat data usable in the meta-analyses using the GRADE standard (factoring in losses to follow-up, type of study, and other factors), then removing the least reliable study from the meta-analysis and assessing changes in effect size and significance. One aP efficacy study (Gustafsson 1996) provided ITT analysis; removing this study produced no significant change in effect size. No aP or wP effectiveness studies provided ITT data against a relevant outcome.

The second analysis removed any study contributing over 50 percent of the total weight to determine impact on pooled effect size. One wP effectiveness study (Simondon 1997)

contributed 73.5% of the total weight to the wP effectiveness meta-analysis; however, removing this study produced no significant change in effect size.

A trim-and-fill statistical test for asymmetry would have been performed if the number of included studies exceeded the recommended threshold of ten, in order to test for robustness against publication bias.

This review was not required to be submitted for IRB approval.

## RESULTS

### Description of studies

*Results of the search*

The initial literature search yielded 3,985 titles; of these, 175 abstracts were reviewed for eligibility. The majority of rejected abstracts were studies of vaccine immunogenicity or safety. Following abstract review, 28 full articles were assessed for eligibility. A final 18 articles were selected for this review, with ten articles considered ineligible for various reasons, principally due to vaccines under study no longer being on market (Figure 1).

*Studies included in the efficacy/effectiveness review*

We included two eligible randomized controlled trials (both conducted in Europe) of acellular and whole-cell vaccine efficacy in the review. A third RCT conducted in Senegal utilized a nested case-contact study to assess absolute vaccine effect, and was therefore categorized as an effectiveness study. (29-31) Other studies examining pertussis vaccine

effectiveness included two prospective cohort studies, three matched case-control studies, and four screening studies, conducted in Africa, the US, and Europe. (16, 32-39)

The efficacy and effectiveness studies each investigated acellular or whole-cell vaccines currently on market. (A study evaluating Tripedia®, a Sanofi Pasteur aP formulation discontinued in 2011, was included as the vaccine will remain available until stocks are depleted.) (33) Table 1 presents the summary characteristics and effect sizes of each outcome in a standardized CHERG format.

*Studies included in the waning protection review*

For the assessment of long-term protective effect of pertussis vaccine, we included nine effectiveness studies. (7, 9, 23, 34, 38-42) The studies included one prospective cohort study (a follow-up of the Greco 1996 efficacy trial conducted in Italy), two retrospective cohort designs, three case-control studies (one being a long-term follow-up study of the Gustafsson 1996 Sweden RCT), and three screening studies. Studies were conducted in the US, Sweden, Poland, and Australia.

The efficacy and effectiveness studies each investigated acellular or whole-cell vaccines currently on market. Summary characteristics of included studies are provided in Table 2.

*Excluded studies*

Of the final 28 candidate papers, ten were excluded for the following reasons:

- Eight studies examined the efficacy or effectiveness of vaccines no longer on the market;

- One study concurrently published with the Preziosi 2003 paper evaluated the same data against pertussis infectiousness instead of severity, with the severity VE assessment deemed to be of greater utility; (43)

- One study assessed long-term protective effect within a demographic outside of the scope of this review (high-school-age children). (44)

Of note, many of the eight studies of off-market vaccines excluded in our review were included in the Jefferson 2003, Casey 2005, and Cochrane pertussis vaccine reviews. (14, 17, 19)

**Effects of interventions**

*Acellular vaccine efficacy/effectiveness*

Seven of ten acellular vaccine efficacy/effectiveness studies provided a calculation of absolute effect against pertussis disease (using the WHO case definitions as described above for "typical" or "severe" pertussis or similar), with a further two providing VE estimates utilizing the screening method.

Two randomized controlled trials (Gustafsson 1996, Greco 1996) compared aP vaccine efficacy using both diphtheria-tetanus (DT) and placebo control arms; efficacy estimates were 84% (95% CI: 76-89%) and 85% (81-89%) respectively. The Gustafsson estimate was calculated via intent-to-treat analysis; all other studies in this review only conducted per-protocol analyses. Both of these studies were included in the Jefferson 2003 pertussis vaccine efficacy systematic review and meta-analysis.

A third RCT (Simondon 1997) conducted in Senegal was designed to compare aP efficacy directly to a wP control. Relative efficacy was not of interest for this review; however, the study also implemented a nested case-contact study using unvaccinated controls to determine absolute vaccine effect, giving an aP effectiveness estimate of 74% (51-86%).

Three matched case-control studies conducted in the US (Bisgard 2005, Misegades 2012) and Europe (Liese 1997) provided aP vaccine effectiveness estimates of 97% (91-99%), 89% (79-94%), and 93% (63-99%), respectively. The US study estimates are summary VE estimates for all aP vaccines administered to the study population; VE of individual formulations could not be provided.

Two nationwide screening studies conducted in Germany and Austria (Juretzko 2002, Rendi-Wagner 2006) provided acellular VE estimates of 100% (99-100%) and 92% (no CI given), respectively, against hospitalization due to pertussis. These are summary VE estimates for all aP vaccines administered to the study population.

One study, Preziosi 2003, provided an estimate of vaccine effectiveness against clinical severity based on a numerical scale. The study was a long-term follow-up of the Senegal trial, and reported a VE of 48% (39-55%) in reducing clinical severity of pertussis infection. This is a summary estimate of all vaccines administered to the study population (a prospective cohort comprised of RCT enrollees), including wP and aP recipients with wP administered to the majority (67%) of children in the study.

Applying the CHERG adapted GRADE procedure to each study and averaging the adjusted scores over each outcome resulted in the assignment of an overall outcome-specific quality

of evidence grade of “high” to acellular efficacy trials, and “moderate-low” to acellular effectiveness trials (Table 1).

In order to produce an overall effect size for LiST, fixed and random effects meta-analyses were performed that pooled estimates stratified on efficacy versus effectiveness (Figures 2-3). Screening studies were excluded due to low quality of evidence.

The efficacy meta-analysis generated a random effects pooled effect size of 84% (81-87%), with the test for overall effect indicating strong evidence of association ($p < 0.00001$). Heterogeneity was not significant at $I^2 = 0\%$. Though this level of heterogeneity suggests that fixed effects estimates are acceptable, we report the random effects results here out of caution.

The effectiveness meta-analysis generated significant heterogeneity; as a result, a pooled estimate is not reported here. Potential sources of this heterogeneity are explored in the Discussion section. The estimates of vaccine effectiveness reported in the studies ranged from 74% (51-86%) to 97% (91-99%).

On the strength of evidence of effect of acellular pertussis vaccine on severe morbidity due to pertussis, we applied Rule 5 of the CHERG rule set for generating estimated intervention effects for use in LiST to the estimate provided by the aP efficacy meta-analysis. (25) The estimated effect of acellular pertussis vaccine on severe pertussis morbidity in children aged <5 years recommended for LiST use was thus 84% (81-87%) (Table 3).

*Whole-cell vaccine effectiveness*

No studies were found that evaluated the efficacy of on-market wP vaccines (the Connaught wP formulation evaluated in the Greco 1996 and Gustafsson 1996 studies is no longer on market).

Three of seven whole-cell vaccine effectiveness studies provided a calculation of absolute VE against pertussis disease (using the WHO case definitions as described above for "typical" or "severe" pertussis or similar), with a further three providing VE estimates utilizing the screening method. Bisgard et al evaluated wP vaccines that are no longer on market, and so their study was excluded from the wP review.

One RCT (Simondon 1997) conducted in Senegal was designed to compare aP efficacy directly to a wP control. Relative efficacy was not of interest for this review; however, the study also implemented a nested case-contact study using unvaccinated controls to determine absolute vaccine effect, giving a wP effectiveness estimate of 92% (81-97%).

Three nationwide screening studies conducted in Australia (Torvaldsen 2003), Poland (Zielinski 2004), and Austria (Rendi-Wagner 2006) provided wP VE estimates of 97% (83-90%), 74% (52-85%) and 74% (no CI given), respectively, against either typical pertussis or hospitalization due to pertussis. These are summary VE estimates for all wP vaccine formulations administered to the study population.

As reported in the acellular results, one study, Preziosi 2003, provided an estimate of VE against clinical severity based on a numerical scale. The study was a long-term follow-up of the Senegal trial, and reported vaccine effectiveness of 48% (39-55%) in reducing

clinical severity of pertussis infection. This is a summary estimate of all vaccines administered to the study population (a prospective cohort comprised of RCT enrollees), including wP and aP recipients with wP administered to the majority (67%) of children in the study.

Applying the CHERG adapted GRADE procedure to each study and averaging the adjusted scores over each outcome resulted in the assignment of an overall outcome-specific quality of "moderate-low" to wP effectiveness trials (Table 1).

In order to produce an overall effect size for LiST, fixed and random effects meta-analyses were performed that pooled estimates stratified on efficacy versus effectiveness (Figure 4). As no wP efficacy studies were included, only effectiveness studies reporting an absolute wP effectiveness estimate were pooled. Screening studies were excluded due to low quality of evidence.

The effectiveness meta-analysis generated a random effects pooled effect size of 94% (88-97%), with the test for overall effect indicating strong evidence of association ($p < 0.00001$). Heterogeneity was not significant at $I^2 = 0\%$. Though this level of heterogeneity suggests that fixed effects estimates are acceptable, we report the random effects results here out of caution.

On the strength of evidence of effect of whole-cell pertussis vaccine on severe morbidity due to pertussis, we applied Rule 5 of the CHERG rule set for generating estimated intervention effects for use in LiST to the estimate provided by the wP effectiveness meta-analysis. (25) The estimated effect of whole-cell pertussis vaccine on severe pertussis

morbidity in children aged <5 years recommended for LiST use was thus 94% (88-97%) (Table 3).

*Long-term protective effect of acellular and whole-cell vaccine*

Recent outbreaks have prompted in-depth examination of the long-term protective effect of acellular vaccine. One screening study included in this review (Witt 2012) was conducted in the midst of a 2010 pertussis outbreak in California, and reported aP vaccine effectiveness of 24% (0-40%) among children ages 8-12 years. (23) VE for children ages 13-18 was 79% (no CI), reflecting increased protection following the recommended aP booster dose.

Table 2 summarizes relevant characteristics of selected studies assessing the long-term protective effect of pertussis vaccine. These studies reported their findings using a variety of outcome measures. Given the heterogeneity of outcome measures, a meta-analysis was not indicated, and so the individual study estimates are detailed here.

All included aP studies evaluated long-term vaccine effectiveness. One study (Salmaso 2001) revisited the Greco 1996 Italy aP trial, which produced effectiveness estimates following a three-dose series of Infanrix® or Acelluvax® completed by age 6 months. Salmaso et al established a prospective cohort comprised of trial enrollees plus newly-enrolled non-trial controls. The authors reported a VE of 86% (79-91%) against the WHO definition of pertussis, and concluded that protection conferred by the aP vaccine under study did not wane during the follow-up period. However, this study only followed children until age 6; later evidence of waning effect was found primarily among children ages 7 and older. (7, 42)

Gustafsson et al revisited their 1996 Sweden trial in a 2006 study, tracking long-term effectiveness of vaccination among children ages 3-11 receiving a variety of aP vaccines at 3, 5, and 12 months of age in the initial study. Age-specific incidence of pertussis remained low for about five years following the final dose (supporting findings of sustained protection by Salmaso et al, which followed a similar dose regimen). However, pertussis incidence increased significantly in children aged 6 to 8 years from 32 (24-40) to 48 (34-61) per 100,000 person-years. Summarizing the waning protection of aP over the study period, the authors reported an overall risk of pertussis infection of 1.75 (0.93-3.28) for children receiving 3 doses of Pentavac® 2-component aP vaccine compared to those receiving an Evans wP formulation.

Two recent retrospective cohort studies conducted in the US (Tartof 2013, Witt 2013) evaluated the risk of pertussis several years after administration of the fifth and final dose. Tartof et al reported summary relative risks of pertussis of 8.9 (6.0-13.0) and 4.0 (1.9-8.4) among Minnesota and Oregon children respectively (indicating relative risk of pertussis among children 2-6 years after their final dose versus 1 year after the last dose). Witt et al indicated a risk of pertussis of 5.74 (no CI given) among individuals receiving all-aP vaccine doses versus individuals receiving at least one wP dose in the 5-dose series.

Two recent matched case-control studies (Misegades 2012, Klein 2012) were included. Misegades et al stratified VE estimates by time since fifth dose, reporting an estimated VE of 71% (46-85%) among individuals 60 months or more since their fifth dose, a decrease of 27% from the 98% (96-99%) VE reported for children under one year since the fifth dose. (The reviewer calculated an average year-over-year decrease in VE of -6.1% between one and five years post-fifth dose.) Klein et al performed a well-controlled study comparing

PCR-positive children against PCR-negative controls. Authors reported an odds ratio for pertussis of 1.42 per year (1.21-1.66), indicating a 42% year-over-year increase in odds of contracting pertussis.

Data on long-term protective effect of whole-cell vaccine was included for comparison to aP estimates. No efficacy trials were found that assessed the long-term protective effect of whole-cell vaccine. However, two screening studies (Torvaldsen 2003, Zielinski 2004) examined cases in fully-immunized children up to age 13, reporting VE by age group. Torvaldsen et al reported a whole-cell VE of 78% (72-82%) among children in New South Wales, Australia ages 9-13, a decrease in VE of 10 percent from the next youngest (5-8 year) age bracket. Similarly, Zielinski et al reported a wP VE of 69% (55-79%) among children in Poland ages 6-9 in the last year of the study, a decrease in VE of 6% from the next youngest (2-5 year) age bracket.

For the long-term protective effect outcome, applying the CHERG adapted GRADE procedure to each study and averaging the adjusted scores over each outcome resulted in the assignment of an overall outcome-specific quality of evidence grade of “moderate” to acellular effectiveness trials and “low” to wP effectiveness trials (Table 2). Assessed individually, the Klein et al study received the highest quality of evidence score, due to a robust design utilizing two sets of controls, extensive demographic data, and precise data on vaccination status and timing of dosage.

The implications of waning long-term protection, and the utility of this review of long-term protective effect in informing immunization programs in various contexts, are explored in the Discussion section.

# DISCUSSION

## Summary of main results

### *Vaccine efficacy/effectiveness*

Taken together, the efficacy and effectiveness data for acellular and whole-cell pertussis vaccines allow us to conclude that both vaccines are highly effective in preventing typical pertussis infection, as well as deaths due to pertussis.

Our pooled analyses of acellular vaccine were stratified by efficacy and effectiveness data. We recognize the differing opinions on the matter of applicability of meta-analysis with respect to pertussis vaccines, given the evident heterogeneity in study characteristics and vaccines used. (18) However, no single efficacy or effectiveness study in our review possesses sufficient generalizability of intervention (due to only one or two on-market vaccine formulations evaluated per study). Arguments in favor of meta-analysis of effectiveness data in particular cite the increasing importance of evaluating these data in contexts where ethical considerations limit the ability to conduct controlled trials with a placebo group. (45)

As our aP effectiveness meta-analysis demonstrated significant heterogeneity, we took the pooled effect size from our aP efficacy meta-analysis as our estimate recommended for decision-making models such as LiST. (The meta-analysis of aP efficacy conducted in the Jefferson 2003 review included the two studies pooled here, though studies evaluating off-market formulations were also included in that analysis.) (17) Coupled with the range of VE estimates reported in the included aP effectiveness studies, the generation of a single

efficacy-based estimate of effect will be of significant utility in modeling the impact of increased pertussis vaccine coverage in low-income countries.

Though we made no direct comparisons between aP and wP effectiveness, the results of our pooled analyses do suggest that acellular vaccines currently on the market may be of comparable or slightly inferior effectiveness than that of certain whole-cell vaccines. However, several issues complicate the direct comparison of effectiveness of aP and wP vaccines. Most obvious is the lack of consistent comparisons among studies between specific formulations of aP and wP vaccine, as well as the sheer diversity of whole-cell variants in use and the associated wide range of efficacy and effectiveness estimates. (1)

While our review included studies independently evaluating the effect of wP vaccine in various contexts, our meta-analysis of wP effect was limited to studies evaluating wP vaccines concurrently with aP vaccines on the market, with the aim of ensuring the real-world relevance of the pooled analysis. However, as we cannot assure the generalizability of the wP effect to countries utilizing any of a wide range of available wP vaccines, the wP effect should be interpreted with caution.

*Waning protection*

Our findings strongly suggest that the protective effect of acellular vaccines on the market, and to a lesser extent certain whole-cell vaccines, diminishes significantly in the years following the final dose administered. Protection is maintained at high levels for one or two years following the final dose, with progressive reductions in protection over subsequent years as demonstrated by increased incidence of pertussis in older children who have not received a booster dose. Results also indicate that the long-term risk of pertussis

is also higher among those receiving aP-only vaccine compared to individuals who received at least one dose of wP vaccine in childhood. The finding of waning long-term protection is uniformly reported across our selected effectiveness studies conducted in the US, Europe, and Australia, though with different magnitude of effect.

It is important to note that improved case detection and diagnostic capacity may contribute to increased reporting of pertussis cases in high-income countries with high acellular vaccine coverage. (14) This would have the effect of reducing the calculated effectiveness of vaccine compared to eras when detection methods were not as robust.

**Overall completeness and applicability of evidence**

The CHERG Rules for Evidence Review protocol allowed for the rigorous and systematic evaluation of the strength of evidence presented by each included study against outcomes of interest. All available studies exploring the protective effect of on-market acellular pertussis vaccine against child morbidity and mortality were included in this evaluation. Likewise, several whole-cell formulations currently in use were included in the assessment (using only studies concurrently evaluating aP and wP vaccines).

Regional variation in pertussis vaccine effectiveness may exist as a result of a variety of factors, including type of vaccine used, dosage schedule, background incidence of pertussis, and quality of vaccine. (1) For example, the Senegal case-contact study may indicate evidence of reduced vaccine effectiveness in low-resource settings, which are otherwise poorly represented in this review.

These issues demand careful consideration of the generalizability of any estimated effect to other contexts. Our original intent was to provide regional estimates of effect of wP and aP vaccine; however, the vast majority of qualifying studies took place in the US and Europe, and so an analysis of vaccine effect stratified by region was infeasible. We therefore calculated a single global VE estimate for each vaccine type, relying on the overall strength of evidence provided by these studies of the effect of these vaccines on typical pertussis per the WHO definition.

With the aforementioned limitations in mind, and given the base of evidence available, the analyses conducted in this review indicate strong applicability of evidence of vaccine effectiveness against pertussis disease to the principal outcome of interest (global effect of pertussis vaccine against severe pertussis morbidity) (Table 3).

We made no attempt to evaluate the relative efficacy of the various acellular vaccines on the market given the heterogeneity among comparison groups, dosage, and vaccine formulation, and given ongoing debate regarding the validity of earlier attempts to characterize relative efficacy. (14)

**Quality of evidence**

The quality of each study was assessed as detailed in the Methods section, with summary measures of outcome-specific quality reported in Tables 1 and 2.

Significant heterogeneity ($I^2$ = 74%) was evident following our meta-analysis of acellular effectiveness studies. As we pooled studies of multiple formulations of aP vaccine, heterogeneity was expected, and did not invalidate our findings of vaccine effect as all

studies indicated a significant protective effect for acellular vaccine. However, other causes of the heterogeneity warrant further consideration.

The Greco 1996 and Gustafsson 1996 acellular trials were rigorously designed and served as benchmarks against which later studies were compared. (1) Both studies shared closely coordinated protocols, dose schedules, case definitions and laboratory assays. As a result, there is little evidence of significant between-study heterogeneity in their aP results (the off-market wP vaccine evaluated by both studies is not discussed here).

Causes of heterogeneity within other studies included in the review may be found in the usage of case definitions of varying sensitivity and specificity (as in our inclusion of studies evaluating effect against "typical" or "severe" pertussis), reporting sources/methods (clinic/hospital versus community-based, self-reporting versus field surveys, etc.), immunization schedules, study populations, and periods of follow-up.

WHO case definitions were used extensively in our review as the majority of included studies adhered to these definitions. The Global Pertussis Initiative has recently published recommended pertussis case definitions taking into account the differential presentation of pertussis in infants versus older children. Future studies would benefit from standardization on these definitions in order to mitigate a major source of heterogeneity while increasing case definition specificity and sensitivity. (46)

Study setting may have played a significant role in the Simondon 1997 trial in rural Senegal, where a low aP VE of 74% (51-86%) was reported against a high background of infectious disease and child mortality, as well as nutritional status and household size. Transportation and storage become concerns in low-resource environments, with poor

practices adversely affecting vaccine integrity. Though the Senegal study was included in our analysis due to its utility in assessing real-world effectiveness in low-resource settings, it was a major contributor to statistical heterogeneity in the aP analysis.

Lastly, heterogeneity may also be introduced by the synergistic action of indirect vaccination effects in community-based observational studies, with herd immunity effects increasing the perceived effectiveness of the vaccine in study populations with high coverage.

**Risk of bias in included studies/in the review process**

The potential for bias, particularly in included observational studies, must not be overlooked. A major limitation of our review is the inability to correct for potential bias within studies during meta-analysis; we may only include or exclude studies on the basis of strength of evidence (which takes potential bias into account, per CHERG/GRADE standards). Supplemental Table 1 briefly lists concerns regarding bias for each study.

Among all studies, misclassification/case ascertainment bias may differentially affect reporting of cases between vaccinated and unvaccinated/control groups. This bears consideration particularly in studies reporting a low number of cases within either comparison group. Vaccinated individuals and older children infected with pertussis may present with less severe symptoms than unvaccinated individuals and younger children (28); the differences between studies in clinical case definition sensitivity (in terms of duration of cough and associated paroxysmal cough, whoop, or posttussive vomiting) suggests that each study was at differing risk of differential misclassification. The impact of diagnostic diligence on this bias was further explored in a follow-up to a study by Stehr

et al of an off-market aP formulation, where local physicians serving as study investigators were stratified into three groups based on the proportion of their patients who underwent investigation for pertussis. (47) Reported efficacies were significantly different between these groups, reflecting the importance of consistency in diagnosis.

Vaccine efficacy and effectiveness estimates may also be subject to variation on the basis of case definition specificity. Stricter case definitions tend to reduce the number of confirmed cases, rendering comparisons across studies difficult. (14) Many included studies reported outcomes against a spectrum of case definitions; we chose to the WHO definition of typical pertussis as our outcome as it struck a balance between uniformity among studies and representativeness of serious morbidity due to pertussis.

The Senegal study by Simondon et al considers certain sources of potential bias that have implications for future studies in low-resource settings. Case classification conducted to estimate absolute effectiveness relied in part on parent knowledge of immunization status, which may have increased case detection among unvaccinated children. (1) Also, though deaths due to pertussis were not recorded, the high background infant mortality rate may complicate efforts to attribute deaths to a specific cause.

The use of erythromycin as post-exposure prophylaxis constitutes one potential source of confounding that is poorly documented among studies. Gustafsson et al assumed that use of erythromycin occurred in accordance with national recommendations, but did not document usage. Schmitt et al controlled for erythromycin usage, which was prevalent and differential at 51.8% of index cases with contacts vaccinated with DTaP versus 72.0% of index cases with contacts vaccinated with DTwP. Treatment reduced the attack rate of

typical pertussis in the unvaccinated subjects from 64.1% to 50.5%, though the difference was not significant. (37) No other studies documented erythromycin usage within the study population. The Cochrane review suggests that erythromycin prophylaxis is unlikely to have significantly affected reported efficacy; however, documentation of usage in future studies should be considered a prudent precaution against confounding. (14)

Though valuable as an inexpensive means of assessing vaccine effectiveness, vaccine screening studies are subject to unique biases. Screening studies rely on estimates of the proportion of individuals vaccinated and unvaccinated in a population, calculating VE based on the attack rate among both groups. These studies typically use surveillance and immunization registry data to obtain the estimates needed for these calculations; however, as reporting protocols are generally not coordinated in advance of the screening study, differences in case ascertainment and reporting across the study population lead to decreased confidence in estimates. (48) More importantly, the process of generalizing the screening estimate to the overall population precludes the adjustment of confounding beyond basic demographic data such as age and gender. The relative lack of strength of evidence of these studies was accounted for in our scoring process, and screening studies were not included in our meta-analyses as a result. (48)

The potential for publication bias toward published data exists within this review as with all systematic reviews. However, given the consistent evidence of strong protective effect of pertussis vaccine among all aP and wP studies, both for on- and off-market formulations, the existence of an unpublished trial or trials of sufficient strength of evidence to materially affect our findings is unlikely. (Greco and Gustafsson reported unexpectedly low efficacy estimates for an off-market wP vaccine; however, both estimates still indicated statistically

significant protective effect. (30, 31)) Pre-planned selection criteria and sensitivity analyses mitigated the risk of bias in the methods of the review.

The authors of this review were not blinded to study authorship or journal of publication, allowing for potential bias during study selection and data extraction.

## Conclusions and future directions

### *Implications for research*

Many gaps remain in our knowledge of whole-cell and acellular pertussis vaccine. We restricted our review to evaluation of the effect of pertussis vaccine on severe child morbidity rather than mortality, due to the lack of pertussis studies reporting child mortality outcomes. Though ascertainment of the direct impact these vaccines have upon pertussis-specific child mortality is significantly more difficult than evaluating effect against pertussis disease, retrospective observational studies in settings maintaining detailed child mortality records would go far in fully characterizing this effect.

More generally, the need is evident for additional effectiveness studies in low-income countries. As ethical barriers to use of a placebo group significantly limit the prospects for additional efficacy studies, and since such studies may not adequately reflect real-world effect, effectiveness studies become increasingly important in the characterization of vaccine protection. (45) Though the acellular vaccine effectiveness outcomes in this review were considered sufficiently generalizable to other settings, particularly in countries adopting aP vaccine, the continued extensive use of wP vaccine (and the lack of adequate

data on both efficacy and effectiveness of the wide variety of wP vaccines in use) demonstrate that more must be known about the real-world experience with pertussis vaccine in resource-poor settings. Simondon et al note that though the diminished level of protection offered by a three-dose-only series can be countered with booster doses in early childhood, children in low-income settings may be deprived of vaccination after the first year of age, indicating the need to further examine effectiveness in the rural/low-resource context.

In view of the consistency of evidence of diminishing protective effect of acellular pertussis vaccine, additional research characterizing this trend in multiple contexts, particularly in low-income countries, are warranted. No long-term protection studies included in this review were conducted in low-resource settings, where regional characteristics, differing vaccine schedules, and variations in vaccine quality may result in altered long-term effectiveness profiles. Additionally, studies examining the impact of implementing a booster dose at 7-9 years on morbidity and mortality outcomes would help inform cost-effectiveness assessments of vaccination programs in countries considering a revised schedule.

Lastly, continued investigation of pertussis vaccine effectiveness in outbreak settings will shed additional light on the ability of current vaccines to mitigate the odds of future outbreaks.

*Implications for practice*

Together with the findings of this review, the studies detailed above will be of use to policymakers attempting to justify investment in increased vaccine program coverage. In

the future, refined intervention models taking into account the changing protective effect of pertussis vaccination over time may be beneficial in predicting long-term morbidity outcomes.

In terms of effectiveness against severe morbidity in children under 5, the suggestion of equivalence of protective effect of aP vaccines on the market compared to wP vaccines in this review, together with extensive data supporting the lower reactogenic profile of aP vaccines, should help assure policymakers of the utility of aP vaccines in practice.

## SUPPLEMENTARY DATA

The data abstraction table for this review is provided as Supplemental Table 1.

## FUNDING

This study was supported by funding from the US Fund for UNICEF from the Bill and Melinda Gates Foundation (grant 43386 to 'Promote evidence-based decision making in designing maternal, neonatal and child health interventions in low- and middle-income countries').

## CONFLICTS OF INTEREST

None reported.

## REFERENCES


1. Plotkin SA, Orenstein WA, Offit PA. *Vaccines*. 6th edition / ed.:448-492.
2. Black RE, Cousens S, Johnson HL, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet* 2010;375(9730):1969-87.
3. Jajosky RA, Hall PA, Adams DA, et al. Summary of notifiable diseases--United States, 2004. *MMWR Morb Mortal Wkly Rep* 2006;53(53):1-79.
4. van Boven M, de Melker HE, Schellekens JF, et al. Waning immunity and sub-clinical infection in an epidemic model: implications for pertussis in The Netherlands. *Mathematical biosciences* 2000;164(2):161-82.
5. Sin MA, Zenke R, Ronckendorf R, et al. Pertussis outbreak in primary and secondary schools in Ludwigslust, Germany demonstrating the role of waning immunity. *Pediatr Infect Dis J* 2009;28(3):242-4.
6. Mooi FR, NA VDM, De Melker HE. Pertussis resurgence: waning immunity and pathogen adaptation - two sides of the same coin. *Epidemiol Infect* 2013:1-10.
7. Tartof SY, Lewis M, Kenyon C, et al. Waning immunity to pertussis following 5 doses of DTaP. *Pediatrics* 2013;131(4):e1047-e52.
8. Lai FY, Thoon KC, Ang LW, et al. Comparative seroepidemiology of pertussis, diphtheria and poliovirus antibodies in Singapore: Waning pertussis immunity in a highly immunized population and the need for adolescent booster doses. *Vaccine* 2012;30(24):3566-71.
9. Klein NP, Bartlett J, Rowhani-Rahbar A, et al. Waning protection after fifth dose of acellular pertussis vaccine in children. *New England Journal of Medicine* 2012;367(11):1012-9.
10. Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. *Proceedings of the National Academy of Sciences of the United States of America* 2014;111(2):787-92.
11. Brooks DA, Clover R. Pertussis infection in the United States: role for vaccination of adolescents and adults. *Journal of the American Board of Family Medicine : JABFM* 2006;19(6):603-11.
12. van den Berg BM, Beekhuizen H, Mooi FR, et al. Role of antibodies against Bordetella pertussis virulence factors in adherence of Bordetella pertussis and Bordetella parapertussis to human bronchial epithelial cells. *Infect Immun* 1999;67(3):1050-5.

13. Hijnen M, Mooi FR, van Gageldonk PG, et al. Epitope structure of the Bordetella pertussis protein P.69 pertactin, a major vaccine component and protective antigen. *Infect Immun* 2004;72(7):3716-23.
14. Zhang L, Prietsch SO, Axelsson I, et al. Acellular vaccines for preventing whooping cough in children. *The Cochrane database of systematic reviews* 2012;3:CD001478.
15. Kimura M, Kuno-Sakai H. Current epidemiology of pertussis in Japan. *Pediatr Infect Dis J* 1990;9(10):705-9.
16. Juretzko P, Von Kries R, Hermann M, et al. Effectiveness of acellular pertussis vaccine assessed by hospital-based active surveillance in Germany. *Clinical Infectious Diseases* 2002;35(2):162-7.
17. Jefferson T, Rudin M, DiPietrantonj C. Systematic review of the effects of pertussis vaccines in children. *Vaccine* 2003;21(17-18):2003-14.
18. Desauziers E, Hessel L, Decker MD, et al. Systematic review of the effects of pertussis vaccines in children. *Vaccine* 2004;22(21-22):2681-4; author reply 5.
19. Casey JR, Pichichero ME. Acellular pertussis vaccine safety and efficacy in children, adolescents and adults. *Drugs* 2005;65(10):1367-89.
20. Weinberg GA, Szilagyi PG. Vaccine epidemiology: efficacy, effectiveness, and the translational research roadmap. *J Infect Dis* 2010;201(11):1607-10.
21. Omer SB, Salmon DA, Orenstein WA, et al. Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases. *N Engl J Med* 2009;360(19):1981-8.
22. Centers for Disease C, Prevention. Pertussis epidemic--Washington, 2012. *MMWR Morb Mortal Wkly Rep* 2012;61(28):517-22.
23. Witt MA, Katz PH, Witt DJ. Unexpectedly limited durability of immunity following acellular pertussis vaccination in preadolescents in a north American outbreak. *Clinical Infectious Diseases* 2012;54(12):1730-5.
24. Boschi-Pinto C, Young M, Black RE. The Child Health Epidemiology Reference Group reviews of the effectiveness of interventions to reduce maternal, neonatal and child mortality. *Int J Epidemiol* 2010;39 Suppl 1:i3-6.
25. Walker N, Fischer-Walker C, Bryce J, et al. Standards for CHERG reviews of intervention effects on child survival. *Int J Epidemiol* 2010;39 Suppl 1:i21-31.
26. Ghanaie RM, Karimi A, Sadeghi H, et al. Sensitivity and specificity of the World Health Organization pertussis clinical case definition. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2010;14(12):e1072-5.

27. World Health Organization. Division of Communicable Diseases. *WHO meeting on case definition of pertussis, Geneva, 10-11 January 1991*. Geneva: World Health Organization; 1991.
28. Singh M, Lingappan K. Whooping cough: the current scene. *Chest* 2006;130(5):1547-53.
29. Simondon F, Preziosi MP, Yam A, et al. A randomized double-blind trial comparing a two-component acellular to a whole-cell pertussis vaccine in Senegal. *Vaccine* 1997;15(15):1606-12.
30. Gustafsson L, Hallander HO, Olin P, et al. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. *New England Journal of Medicine* 1996;334(6):349-55.
31. Greco D, Salmaso S, Mastrantonio P, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. Progetto Pertosse Working Group [electronic article]. *The New England journal of medicine*. (DOI:10.1056/NEJM199602083340601).
32. Bisgard KM, Rhodes P, Connelly BL, et al. Pertussis vaccine effectiveness among children 6 to 59 months of age in the United States, 1998-2001. *Pediatrics* 2005;116(2):e285-e94.
33. Liese JG, Meschievitz CK, Harzer E, et al. Efficacy of a two-component acellular pertussis vaccine in infants. *Pediatric Infectious Disease Journal* 1997;16(11):1038-44.
34. Misegades LK, Winter K, Harriman K, et al. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. *JAMA - Journal of the American Medical Association* 2012;308(20):2126-32.
35. Preziosi MP, Halloran ME. Effects of pertussis vaccination on disease: Vaccine efficacy in reducing clinical severity. *Clinical Infectious Diseases* 2003;37(6):772-9.
36. Rendi-Wagner P, Kundi M, Mikolasek A, et al. Hospital-based active surveillance of childhood pertussis in Austria from 1996 to 2003: Estimates of incidence and vaccine effectiveness of whole-cell and acellular vaccine. *Vaccine* 2006;24(33-34):5960-5.
37. Schmitt HJ, von Konig CH, Neiss A, et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. *Jama* 1996;275(1):37-41.
38. Torvaldsen S, Simpson JM, McIntyre PB. Effectiveness of pertussis vaccination in New South Wales, Australia, 1996-1998. *European journal of epidemiology* 2003;18(1):63-9.
39. Zielinski A, Rosinska M, Czarkowski M, et al. The effectiveness of vaccination with whole-cell pertussis vaccine by age group in Poland 1996-2001. *Scandinavian Journal of Infectious Diseases* 2004;36(2):114-8.

40. Witt MA, Arias L, Katz PH, et al. Reduced risk of pertussis among persons ever vaccinated with whole cell pertussis vaccine compared to recipients of acellular pertussis vaccines in a large US cohort. *Clinical Infectious Diseases* 2013;56(9):1248-54.
41. Salmaso S, Mastrantonio P, Tozzi AE, et al. Sustained efficacy during the first 6 years of life of 3-component acellular pertussis vaccines administered in infancy: the Italian experience. *Pediatrics* 2001;108(5):E81.
42. Gustafsson L, Hessel L, Storsaeter J, et al. Long-term follow-up of Swedish children vaccinated with acellular pertussis vaccines at 3, 5, and 12 months of age indicates the need for a booster dose at 5 to 7 years of age. *Pediatrics* 2006;118(3):978-84.
43. Preziosi MP, Halloran ME. Effects of pertussis vaccination on transmission: Vaccine efficacy for infectiousness. *Vaccine* 2003;21(17-18):1853-61.
44. Berger F, Njamkepo E, Minaberry S, et al. Investigation on a pertussis outbreak in a military school: Risk factors and approach to vaccine efficacy. *Vaccine* 2010;28(32):5147-52.
45. Shrier I, Boivin JF, Steele RJ, et al. Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. *American journal of epidemiology* 2007;166(10):1203-9.
46. Cherry JD, Tan T, Wirsing von Konig CH, et al. Clinical definitions of pertussis: Summary of a Global Pertussis Initiative roundtable meeting, February 2011. *Clin Infect Dis* 2012;54(12):1756-64.
47. Cherry JD, Heininger U, Stehr K, et al. The effect of investigator compliance (observer bias) on calculated efficacy in a pertussis vaccine trial. *Pediatrics* 1998;102(4 I):909-12.
48. Cohen AL, Taylor T, Jr., Farley MM, et al. An assessment of the screening method to evaluate vaccine effectiveness: the case of 7-valent pneumococcal conjugate vaccine in the United States. *PLoS One* 2012;7(8):e41785.

# TABLES

**Table 1** Quality assessment of studies exploring pertussis vaccine efficacy

| Study author and year | Quality Assessment | | | Directness | | Summary of Findings: No of events | | Summary of Findings: Effect | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | Design | Limitations[1] | Consistency | Generalizability to Population of Interest | Generalizability to Intervention of Interest | Intervention | Control | VE (95% CI) | |
| **Outcome: Acellular vaccine efficacy/effectiveness among children <6 years** | | | | | | | | | |
| **Efficacy against typical pertussis (Outcome-specific quality: high)** | | | | | | | | | |
| Greco 1996 (31) | RCT | None | No concerns | Multi-site trial conducted in Europe (Italy) | Vaccines administered are on market and follow typical dose schedule | 37 | 74 | 84% (76-89%) | |
| Gustafsson 1996 (30) | RCT | None | No concerns | Multi-site trial conducted in Europe (Sweden) | Vaccines administered are on market and follow typical dose schedule | 59 | 371 | 85% (81-89%) | |
| **Effectiveness against typical pertussis (Outcome-specific quality: moderate-low)** | | | | | | | | | |
| Simondon 1997 (29) | Case-contact nested in RCT | Low number of cases and controls | Borderline heterogeneity from meta-analysis (P=0.11) | Rural, conducted in Senegal; applicability to developing contexts | Vaccine administered is on market and follows typical dose schedule | 24 | 8 | 74% (51-86%) | |
| Preziosi 2003 (35) | Prospective cohort | Combined wP and aP VE estimate | Not included in meta-analysis | Rural, conducted in Senegal; applicability to developing contexts | Vaccine administered is on market and follows typical dose schedule | 190 | 149 | 48% (39-55%) | Follow-up study from Senegal RCT; evaluates effect of aP in reducing clinical severity |
| Schmitt 1996 (37) | Prospective cohort | Low number of cases and controls | No concerns | Multi-site conducted in Germany | Vaccine administered is on market and follows typical dose schedule | 7 | 96 | 89% (77-95%) | |
| Liese 1997 (33) | Matched case-control | Low number of cases and controls | No concerns | Multi-site conducted in Germany | Vaccine administered is on market and follows typical dose schedule | 4 | 81 | 93% (63-99%) | |
| Bisgard 2005 (32) | Matched case-control | VE of multiple aP vaccines combined | No concerns | Multi-site conducted in multiple states in US | Vaccines administered are on market and follow typical dose schedule | 20 | 48 | 97% (91-99%) | |
| Misegades 2012 (34) | Matched case-control | VE of multiple aP vaccines combined | No concerns | Multi-site conducted in US (California) | Vaccines administered are on market and follow typical dose schedule | 629 | 53 | 89% (79-94%) | |

**Table 1** Continued

| Study author and year | Quality Assessment | | | | | Summary of Findings | | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Directness | | No of events | | Effect | |
| | Design | Limitations[1] | Consistency | Generalizability to Population of Interest | Generalizability to Intervention of Interest | Intervention | Control | VE (95% CI) | |
| Juretzko 2002 (16) | Screening study | Hospital cases only; VE of multiple aP vaccines combined | Not included in meta-analysis | Nationwide screening conducted in Germany | Vaccines administered are on market and follow typical dose schedule | 1 | --[2] | 100% (99-100%) | |
| Rendi-Wagner 2006 (36) | Screening study | Hospital cases only; VE of multiple aP vaccines combined | Not included in meta-analysis | Nationwide screening conducted in Austria | Vaccines administered are on market and follow typical dose schedule | 65 | --[2] | 92% (no CI given) | |
| **Outcome: Whole-cell vaccine efficacy/effectiveness among children <6 years** | | | | | | | | | |
| **Effectiveness against typical pertussis (Outcome-specific quality: moderate-low)** | | | | | | | | | |
| Simondon 1997 (29) | Case-contact nested in RCT | Low number of cases and controls | No concerns | Rural, conducted in Senegal; applicability to developing contexts | Vaccine administered follows typical dose schedule | 7 | 8 | 92% (81-97%) | |
| Preziosi 2003 (35) | Prospective cohort | Combined wP and aP VE estimate | Not included in meta-analysis | Rural, conducted in Senegal; applicability to developing contexts | Vaccine administered follows typical dose schedule | 190 | 149 | 48% (39-55%) | Follow-up study from Senegal RCT; evaluates effect of aP in reducing clinical severity |
| Schmitt 1996 (37) | Prospective cohort | Low number of cases and controls | No concerns | Multi-site conducted in Germany | Vaccine administered follows typical dose schedule | 1 | 75 | 98% (83-100%) | |
| Liese 1997 (33) | Matched case-control | Low number of cases and controls | No concerns | Multi-site conducted in Germany | Vaccine administered follows typical dose schedule | 1 | 81 | 97% (79-100%) | |
| Torvaldsen 2003 (38) | Screening study | None | Not included in meta-analysis | Multi-site screening conducted in New South Wales, Australia | Confounding due to patients receiving 4 doses instead of intended 3 | 223 | 198 | 87% (83-90%) | |
| Zielinski 2004 (39) | Screening study | None | Not included in meta-analysis | Nationwide screening conducted in Poland | Formulation and dosage intervals not given | 157 | 12 | 74% (52-85%) | |

**Table 1** Continued

| Study author and year | Quality Assessment | | | | | Summary of Findings | | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Directness | | No of events | | Effect | |
| | Design | Limitations[1] | Consistency | Generalizability to Population of Interest | Generalizability to Intervention of Interest | Intervention | Control | VE (95% CI) | |
| Rendi-Wagner 2006 (36) | Screening study | Hospital cases only; VE of multiple aP vaccines combined | Not included in meta-analysis | Nationwide screening conducted in Austria | Vaccine follows typical dose schedule | 11 | --[2] | 79% (no CI given) | |

[1]Limitations listed are in addition to those inherent in study design.

[2]Data not available; VE methodology uses estimate of attack rate in unvaccinated population in place of control group.

**Table 2** Quality assessment of studies exploring waning protection

| Study author and year | Quality Assessment | | | Directness | | Summary of Findings | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | No of events | | Effect | | |
| | Design | Limitations[1] | Consistency[2] | Generalizability to Population of Interest | Generalizability to Intervention of Interest | Intervention | Control | Measure of effect (95% CI)[3] | Average annual change in effect (type of measure)[4] | |
| **Outcome: Acellular vaccine long-term protection among children <13 years** | | | | | | | | | | |
| **Effectiveness against typical pertussis (Outcome-specific quality: moderate)** | | | | | | | | | | |
| Salmaso 2001 (41) | Prospective cohort | Does not follow children beyond 6 years of age | NA | Study conducted in Europe (Italy) | Vaccines administered are on market and follow typical dose schedule | 33 | 54 | VE: 86% (79-91%) | | Follow-up of Greco 1996 study; VE reported for Infanrix versus DT control |
| Tartof 2013 (7) | Retrospective cohort | Unable to calculate absolute VE | NA | Study conducted in USA (Minnesota, Oregon) | Vaccine administered follows typical dose schedule | 547 | N/A[5] | RR: 8.9 (6.0-13.0) Minnesota; 4.0 (1.9-8.4) Oregon | +49% Minnesota; +34% Oregon (risk) | RR reported for risk of pertussis 2-6 years after final dose versus 1 year after final dose |
| Witt 2013 (40) | Retrospective cohort | Unable to calculate absolute VE | NA | Study conducted in USA | Vaccines administered are on market and follow typical dose schedule | 383 | 27 | RR: 5.74 (no CI given) | N/A | RR reported for risk of pertussis between pts receiving 5 doses aP and pts receiving at least one of five doses wP |
| Gustafsson 2006 (42) | Matched case-control | Unable to calculate absolute VE | NA | Study conducted in Europe (Sweden) | Vaccines administered are on market and follow typical dose schedule | 47 | 27 | RR: 1.75 (1.06-2.74) | +39% (incidence/PY) | Follow-up of Gustafsson 1996 study; RR reported for risk of pertussis for Pentavac aP versus wP |
| Klein 2012 (9) | Matched case-control | Unable to calculate absolute VE | NA | Study conducted in USA (California) | Vaccines administered are on market and follow typical dose schedule | 277 | 9681 | OR: 1.42 (1.21-1.66) | +42% (odds) | OR reported for PCR-positive cases versus negative controls |
| Misegades 2012 (34) | Matched case-control | None | NA | Study conducted in USA (California) | Vaccines administered are on market and follow typical dose schedule | 231 | 53 | VE: 71% (46-85%) | -6.1% (VE) | VE reported for >=60 months after final dose |
| Witt 2012 (23) | Screening study | None | NA | Study conducted in USA (California) | Vaccines administered are on market and follow typical dose schedule | 88 | 15 | VE: 24% (0-40%) | N/A | VE reported for 8-12 year age bracket (decrease in VE of 42% from 2-7 year age bracket) |

**Table 2** Continued

| Study author and year | Quality Assessment | | | Directness | | Summary of Findings | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | No of events | | Effect | | |
| | Design | Limitations[1] | Consistency[2] | Generalizability to Population of Interest | Generalizability to Intervention of Interest | Intervention | Control | Measure of effect (95% CI)[3] | Average annual change in effect (type of measure)[4] | |
| **Outcome: Whole-cell vaccine long-term protection among children <13 years** | | | | | | | | | | |
| **Effectiveness against typical pertussis (Outcome-specific quality: low)** | | | | | | | | | | |
| Torvaldsen 2003 (38) | Screening study | Potential overestimation of effectiveness (variance in number of doses received) | NA | Study conducted in Australia (New South Wales) | Vaccine administered follows typical dose schedule | 394 | 183 | VE: 78% (72-82%) | N/A | VE reported for 9-13 year age bracket (decrease in VE of 10% from 5-8 year age bracket) |
| Zielinski 2004 (39) | Screening study | No information on vaccine formulation or administration schedule | NA | Study conducted in Europe (Poland) | Vaccine series completed by age 2; variance in dosage (3 or 4 doses); no schedule or formulation given | 325 | 30 | VE: 69% (55-79%) | N/A | VE reported for 6-9 year age bracket, 2001 data (decrease in VE of 6% from 2-5 year age bracket) |

[1]Limitations listed are in addition to those inherent in study design.

[2]No meta-analyses performed due to variation in effect measures.

[3]Value reported is for measure most indicative of long-term vaccine efficacy, pertussis incidence, or risk/odds.

[4]Change in effect calculated by reviewer for all studies where annualized data was available (except for Klein 2012)

[5]Compared to baseline; no control group.

**Table 3** Application of standardized rules for choice of final outcome to estimate the effect of pertussis vaccine on pertussis-specific morbidity

| Acellular pertussis outcome measure | Studies | Effect size | Application of standard rules |
|---|---|---|---|
| All-cause mortality | 0 | N/A | Rule 1: Do not apply |
| Cause-specific mortality | 0 | N/A | Rules 1,2,3,4: Do not apply |
| Incidence of severe pertussis (>=21d paroxysmal cough) | 2 | 84% (81-87%) | Rule 5: Apply[1] |

Strong evidence of serious morbidity reduction with acellular vaccine: **Highly plausible**

| Whole-cell pertussis outcome measure | Studies | Effect size | Application of standard rules |
|---|---|---|---|
| All-cause mortality | 0 | N/A | Rule 1: Do not apply |
| Cause-specific mortality | 0 | N/A | Rules 1,2,3,4: Do not apply |
| Incidence of severe pertussis (>=21d paroxysmal cough) | 4 | 94% (88-97%) | Rule 5: Apply |

Strong evidence of serious morbidity reduction with whole-cell vaccine: **Highly plausible**

[1]Pooled aP efficacy estimate used (high heterogeneity in pooled aP effectiveness estimate).

**Supplemental Table 1, "Pertussis study data abstraction table,"**

**is submitted as an addendum to this document.**

# FIGURES & FIGURE LEGENDS

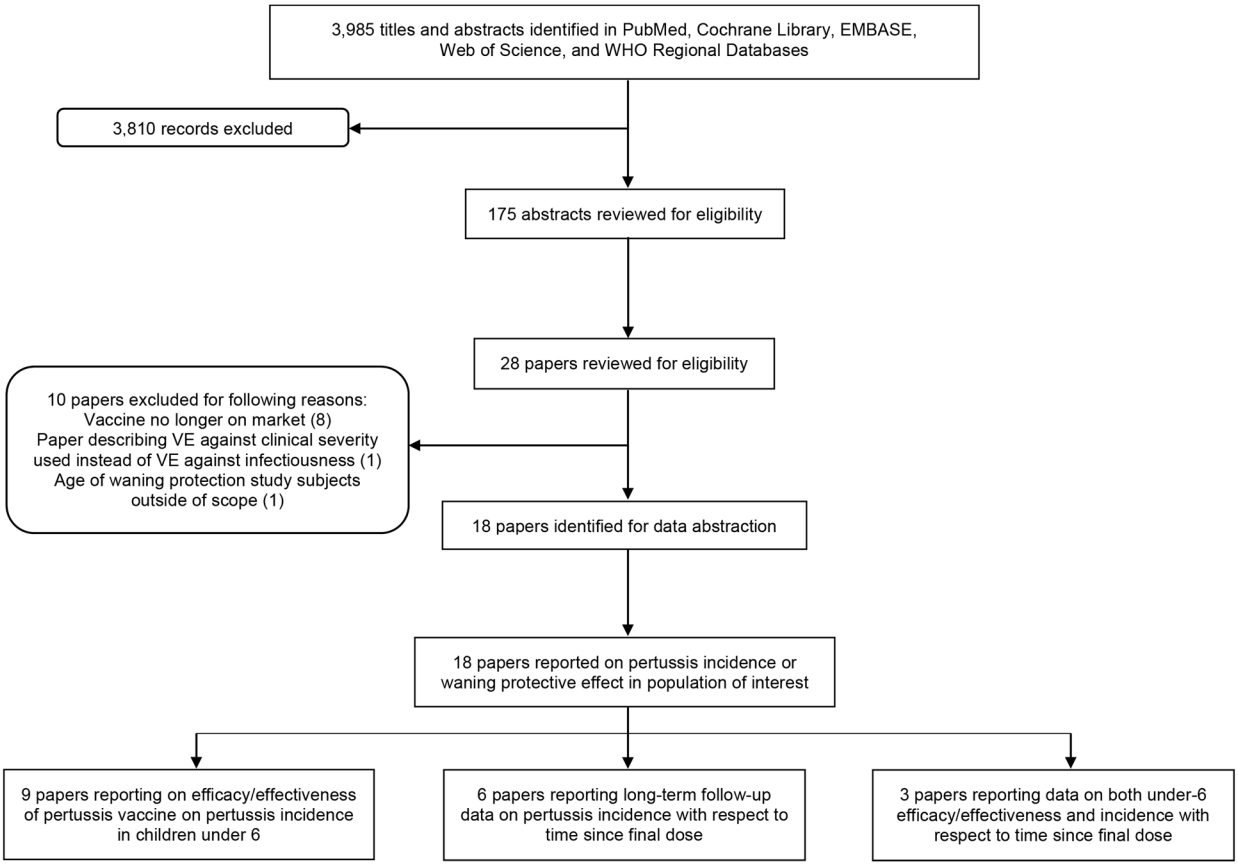


**Figure 1** Pertussis study selection flowchart

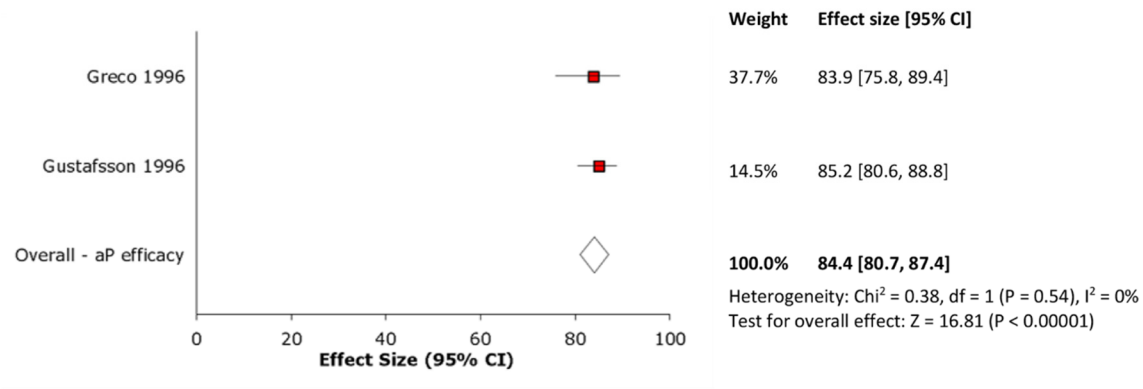


**Figure 2** Forest plot of acellular pertussis vaccine efficacy studies

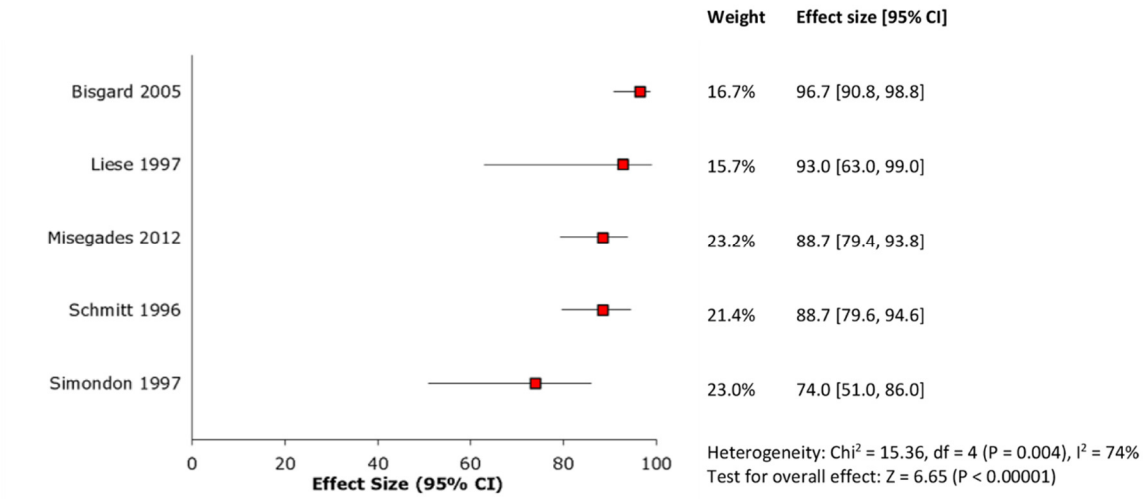


**Figure 3** Forest plot of acellular pertussis vaccine effectiveness studies

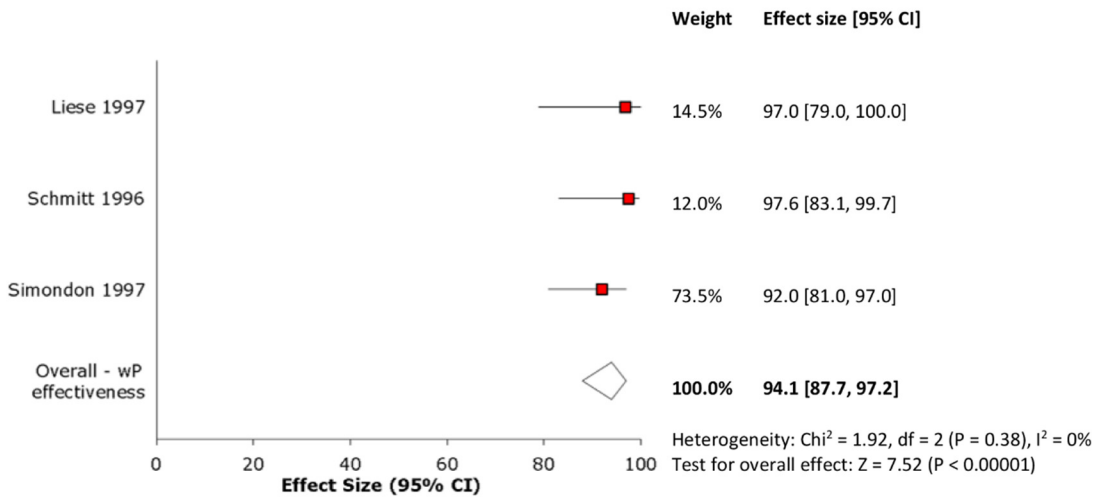


**Figure 4** Forest plot of whole-cell pertussis vaccine effectiveness studies