

BMJ Open Adverse events following primary and secondary immunisation with whole-cell pertussis: a systematic review protocol

Jenna Patterson,^{1,2} Benjamin M Kagina,^{1,2} Michael Gold,³ Gregory D Hussey,^{1,2} Rudzani Muloiwa⁴

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For numbered affiliations see end of article.

Correspondence to

Jenna Patterson;
PTTJEN005@myuct.ac.za

ABSTRACT

Introduction: Pertussis is a contagious respiratory illness caused by the bacterium *Bordetella pertussis*. Two types of vaccines are currently available against the disease: whole-cell pertussis (wP) and acellular pertussis (aP). With the shift of high-income countries from wP to aP as a result of adverse events following immunisation (AEFI), an upsurge in reported cases of pertussis has been noticed. Owing to this, it is proposed to use wP as a prime and aP for boost vaccination strategy. However, a comparison of the AEFI with the first doses of wP and aP are not clearly documented.

Methods and analysis: The primary outcomes of interest are AEFI with dose 1 of wP, subsequent doses of wP and dose 1 of aP. As a secondary outcome frequency of AEFI with wP will be compared with the AEFI of doses 2 and 3 of wP and dose 1 of aP. Electronic databases will be searched and two authors will screen the titles and abstracts of the output. Full texts will then be independently reviewed by the first author and two other authors. Qualifying studies will then be formally assessed for quality and risk of bias using a scoring tool. Following standardised data extraction, statistical analysis will be carried out using STATA. Where data are available, subgroup analyses will be performed. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines will be followed in reporting the findings of the systematic review and meta-analysis.

Ethics and dissemination: No ethics approval is required as the systematic review will use only published data already in the public domain. Findings will be disseminated through publication in a peer-reviewed journal.

Trial registration number: This protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42016035809.

INTRODUCTION

Background

Pertussis, or ‘whooping cough’, is a highly contagious respiratory illness. It is caused

Strengths and limitations of this study

- comprehensive and exhaustive search for relevant studies from several databases;
- lack of standardised criteria in reporting adverse events following immunisation (AEFI) across studies;
- routine combination of the whole-cell pertussis (wP) vaccine with other vaccines, which leaves it impossible to decipher AEFI specifically associated with wP from other vaccines.

mainly by the gram-negative bacterium *Bordetella pertussis*, a highly communicable, exclusively human pathogen.¹ *B pertussis* binds to the cilia in the respiratory tract and produces a number of toxins including, most importantly, the pertussis toxin (PTx).² This leads to the development of a characteristic severe spasmodic cough associated with a high-pitched inspiratory ‘whoop’.³ Most pertussis-related deaths are associated with bacterial pneumonia as a secondary complication.³

There are two types of pertussis vaccines currently licensed for use: whole-cell pertussis (wP) and acellular pertussis (aP). The wP vaccine was the first to be developed and is composed of a suspension of formalin-inactivated *B pertussis* cells in combination with diphtheria and tetanus toxoid, commonly called DTP.⁴ In the mid-1970s reports were published about safety concerns that shed doubts on the value of wP vaccines. These vaccines were associated with side effects at the injection site and with serious systemic reactions, including whole-limb swelling, febrile seizures and persistent crying.^{5 6} For example, in 1974 Kulenkampff *et al* presented evidence of neurological complications associated with pertussis immunisation among 36 children in a retrospective study.⁶

Their report, along with popular media, including the television documentary DTP: Vaccine Roulette, sparked public interest in the risks associated with whole-cell DTP vaccinations.⁷ These adverse events contributed to a reduction of pertussis vaccine acceptance in different countries. The widespread apprehension surrounding wP prompted the development of acellular vaccines that contain purified proteic antigenic components of *B pertussis*.

The aP vaccine is a subunit vaccine, which contains purified, inactivated components of *B pertussis* cells.^{4 7} In the mid-1990s, many high-income countries began to use aP exclusively, as reports of wP adverse events following immunisation (AEFI) fuelled safety concerns.⁷⁻⁹ Following the switch from the use of wP to aP vaccines, a change in pertussis epidemiology has occurred.¹⁰ The WHO reported almost 140 000 cases and 89 000 pertussis-related deaths in 2014, despite an estimated 86% worldwide coverage of pertussis vaccines.¹¹ Factors that may have played a role in the observed resurgence include the overlapping effects of improved diagnosis of the disease, decreases in the rates of vaccine administration, loss of vaccine efficacy due to genetic changes of *B pertussis* strains and, most notably, the switch from the use of wP to aP vaccines.¹⁰

A significant difference in the immune responses generated by wP and aP vaccines has been found to exist, as a lower incidence of pertussis has been observed in children primed with wP compared with those primed with aP.¹² *B pertussis*-naïve infants and children who are primed with aP (receive aP as the first dose in primary vaccination schedule) have been found to experience higher rates of pertussis compared with those who are primed using wP (receive wP as the first dose in the primary vaccination schedule).^{12 13} In a 2001 Italian randomised controlled trial, the comparison of incidence of pertussis in children vaccinated with aP versus wP yielded a statistically significant incidence rate ratio of 1.76.¹⁴ In a recent immunologic study, priming with wP was shown to offer superior protective benefits following challenge with *B pertussis* in naïve primates compared with that with aP.¹⁵ Another study observed that aP reduces the severity of pertussis but does not protect against *B pertussis* colonisation and secondary transmission.¹⁶ Owing to these immunologic findings along with cost-effectiveness, WHO has issued a no-switch policy to countries currently exclusively using the wP vaccine.¹⁷

Recent immunological evidence show that aP protects against pertussis disease but not against *B pertussis* colonisation and secondary transmission in naïve primates challenged with *B pertussis*.¹⁵ A modelling study by DeAnglelis *et al*¹⁶ suggests that priming with wP was more effective in reducing the incidence of pertussis than using aP. Based on this, many healthcare settings are currently considering if future pertussis control methods should involve a combination vaccine approach. This combination vaccine approach is set to include priming *B pertussis*-naïve infants and children

using wP and boosting with aP.¹⁶ The combination approach is hypothesised to induce immunity more effectively compared with current exclusive aP approaches and to result in fewer AEFI than current exclusive wP approaches.¹⁶

Rationale

Though a combination vaccine approach is being considered for future pertussis control, a knowledge gap of the AEFI profile associated with wP still exists. It is necessary to conduct this review in order to systematically describe the AEFI of wP and to compare the AEFI associated with the first doses of wP and aP vaccines. If priming *B pertussis*-naïve infants and children with a single dose of wP is to be suggested as a preferred pertussis vaccination strategy, evidence that AEFI associated with the first dose of wP are less or comparatively similar in frequency and severity to the first dose of aP must be established.

A systematic review will be best used to meet the study outcomes as it will allow for efficient integration of existing AEFI information across healthcare settings. The systematic review design will also allow for the consistency of data on AEFI associated with pertussis vaccines to be assessed and will provide findings that can rationally support future pertussis control decision-making.

In summary, our study proposes to review qualifying literature of studies involving children 6 years and younger who received a dose of pertussis vaccine primary schedule. We will compare the frequency of AEFI associated with the first dose of wP and subsequent doses of wP as well as review the frequency of AEFI with first dose wP compared with those experienced with first dose aP.

METHODS

Objective

To describe the profile of AEFI associated with wP and to determine if AEFI associated with the first dose of wP are less or comparatively similar in frequency and severity to the first dose of aP in a primary vaccination schedule.

Primary objective

- ▶ to describe the profile of AEFI associated with wP in a systematised way.

Secondary objectives

- ▶ to assess if the severity and frequency of AEFI associated with wP is associated with the number of doses received;
- ▶ to assess if the profile of AEFI differs according to the brand of vaccine administered (wP and aP);
- ▶ to assess if the profile of AEFI differs according to the vaccination schedule (wP and aP);
- ▶ to determine the severity and frequency of AEFI associated with the first dose of aP;
- ▶ to compare the AEFI associated with first dose of wP versus the AEFI associated with the first dose of aP.

Eligibility criteria

Types of participants

The review will include studies that meet the inclusion criteria involving infants and children 6 years or younger vaccinated against pertussis worldwide in a primary vaccination schedule.

Case definition

Included studies must have clearly stated case definitions of an adverse event following immunisation. The broad case definition for AEFI defined by the WHO causality assessment of AEFI include:^{18 19}

- ▶ Reactions associated with the route and/or site of administration of the vaccine product or vaccine-specific characteristics;
 - pain at the time of injection and associated physiological responses.
- ▶ Immune-mediated vaccine reaction;
 - local reactions, with involvement of the injection site, due to one or more vaccine components;
 - multisystem (generalised) reactions due to one or more vaccine components;
 - organ-specific reactions due to one or more vaccine components.
- ▶ Reactions as a consequence of replication of vaccine-associated microbial agent(s) in the vaccine or in a close contact of the vaccine;
 - the microbial agent(s) could be:
 - an attenuated vaccine agent;
 - a wild-type vaccine agent due to insufficient inactivation during the manufacturing process;
 - a contaminant introduced into vaccine during the manufacturing process.
- ▶ Direct toxic effect of a vaccine component or contaminant.

The narrow case definition for adverse events following pertussis immunisation is defined by the WHO Global Vaccine Safety observed rates of vaccine reactions:¹⁸

- ▶ Mild AEFI
 - Local reactions including:
 - injection site swelling
 - injection site tenderness
 - decreased arm movement where injection took place.
 - Systemic reactions including:
 - fever over 38°C and irritability
 - drowsiness
 - loss of appetite
 - vomiting
 - persistent crying.
- ▶ Severe AEFI
 - Local reactions including:
 - injection site swelling
 - injection site tenderness
 - decreased arm movement where injection took place.
 - Systemic reactions including:
 - fever over 38°C and irritability
 - drowsiness

- loss of appetite
- vomiting
- persistent crying
- seizure
- hypotonic–hyporesponsive episodes.

Broad and narrow case definitions will be used for outcome estimation.

Exclusion criteria

Review articles, position papers and/or studies conducted with participants older than 6 years will be excluded.

Outcomes

Primary outcomes

- ▶ incidence or prevalence of AEFI associated with first dose of wP;
- ▶ incidence or prevalence of AEFI with subsequent doses of wP;
- ▶ incidence or prevalence of AEFI associated with the first dose of aP.

Secondary outcomes

- ▶ comparison of incidence or prevalence of AEFI associated with first dose of wP with incidence or prevalence of AEFI with subsequent doses of wP;
- ▶ comparison of incidence or prevalence of AEFI associated with first dose of wP with incidence or prevalence of AEFI associated with the first dose of aP.

Types of studies

The review will include cohort studies, case–control studies, cross-sectional studies, postmarketing vaccine surveillance studies and randomised controlled trial studies published in peer-reviewed journals, without language or time restrictions. Google translator software will first be used to enable preliminary screening of non-English records by titles or abstracts that appear likely to be included. If the article still appears likely for inclusion, translation support will then be sought out.

Search strategy

The literature search strategy will use text words and medical subject heading (MeSh) terms. It will include the following terms: adverse event, pertussis vaccine, whole cell pertussis vaccine and acellular pertussis vaccine. These terms will be adapted for use in each database and then will be combined with a relevant filter to select studies including human participants 6 years or younger. An example of the PubMed search strategy is shown in [table 1](#).

Electronic databases

The following electronic databases will be searched for relevant literature: Africa-Wide, CINAHL, ClinicalKey, CENTRAL, MEDLINE via PubMed, PDQ Evidence, Scopus, Web of Science Biological Abstracts, Web of Science Core Collection and WHOLIS.

Table 1 Search strategy for PubMed

Query	Search term
#1	adverse event OR adverse effect OR adverse events following immunisation OR AEFI
#2	"Pertussis Vaccine" (MeSH) OR pertussis vaccine OR whooping cough vaccine
#3	whole cell OR wP OR DTP OR DwPT
#4	"Vaccines, Acellular/adverse effects" (MeSH) OR acellular OR aP OR DaPT
#5	#1 AND #2 AND (#3 OR #4)

Human participants and age of participants are included in search filter.

Selection of eligible studies

The first author and one other author (RM) will screen the search outputs using titles and abstracts. Two authors will then independently go through the full text of all potentially eligible studies in the database to assess whether they meet the inclusion criteria as defined by the protocol. Discrepancies in the list of eligible studies between the two authors will be resolved through discussion and consensus with the assistance of the other authors, including the senior author.

Data collection process

Data will be independently extracted from the included studies by the first author and recorded on a pre-designed extraction form. If units of analysis do not match or missing data are found, corresponding authors for the included studies will be contacted where the data are unclear. Among other elements, the following data will be captured from studies to be included in the review:

- ▶ study characteristics: period, design, objectives and inclusion criteria;
- ▶ study population: country, setting, type of facility and prevalence of pertussis in the population;
- ▶ participant characteristics: age and sex;
- ▶ vaccine characteristics: type and dose of vaccine administered and age of vaccine in primary vaccination schedule;
- ▶ diagnostic methods: clinical definitions of AEFI;
- ▶ type and frequency of AEFI.

Risk of bias in individual studies

Critical Appraisal Skills Programme (CASP) checklists will be used to assess the risk of bias in individual studies selected for inclusion in the review.

In order to assess the risk of reporting bias in individual studies, protocols will be assessed, when available, to compare the outcomes in the protocol and published reports. If the study protocols are not available, then the outcomes listed in the methods section will be compared with the reported outcomes.

Data synthesis

Proportions as percentages will be used to represent measures of occurrence and association prioritised by the primary and secondary outcomes of the study. These measures include prevalence and incidence. If sufficient data are available, the secondary outcomes will be quantified using ORs. If sufficient data does not exist, the secondary outcomes will be assessed using qualitative methods.

Studies included in the review will be assessed for heterogeneity using the I^2 statistic. Where sufficient homogeneity exists ($I^2 < 50$) between studies, data will be pooled in a meta-analysis using Mantel-Haenszel random effects model and an inverse-variance model.

STATA software V.12 (STATA Corporation, College Stations, Texas, USA) will be used to compute all statistical analyses.

Subgroup analysis

If sufficient data exist, subgroup analyses will be conducted according to study period and income level of the country in which the study took place as defined by the World Bank. Other variables that will be considered for subgroup analysis include maternal socioeconomic status and participants' maternal pertussis vaccination status at birth. Should a sufficient number of two-armed studies comparing wP and aP be included in the review, a subgroup analysis will be conducted to assess the study outcomes solely in these comparative studies.

Sensitivity analysis

For the meta-analysed data, a sensitivity analysis will be performed to determine if the exclusion of highly biased studies (as determined using CASP checklists) will change the findings of the meta-analysis.

Data management

Data management will be the responsibility of the first author in consultation with the last author (RM). An electronic parent folder with the name of this study will be created. Subsequently, subfolders will be created that contain details of different tasks completed such as all records retrieved, records included and excluded, risk of bias assessment results, analyses and full systematic review manuscript drafts. Two backups of the parent folder will be created and stored on a memory stick and a hard drive.

Reporting of the review

The study will be presented according to the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews and meta-analyses. The study selection process will be summarised using flow diagrams. Tables will be used to summarise quantitative data from individual studies as well as the systematic review. Qualitative data such as assessment of risk of bias and strength of evidence will be described in text.

DISCUSSION

To the best of our knowledge, this will be the first comprehensive and systematised description of AEFI associated with wP. Many countries exclusively use aP as they have long since concluded that wP is unsafe for use due to an observed high incidence of AEFI associated with its administration.⁷ It is imperative to create a more in-depth understanding of AEFI associated with wP if the combination pertussis vaccine approach is going to be considered for adoption in countries where the burden of pertussis remains high.

It is clear that new and effective pertussis control strategies are required as the incidence of pertussis continues to rise even in the face of high vaccination rates.¹⁰ The combination vaccine strategy currently under consideration poses great promise in reducing the incidence of the disease; however, safety concerns are the key limitation to this strategy. It is critical, therefore, that a detailed description of the AEFI associated with wP be carried out. This systematic review study will provide the necessary description of AEFI associated with wP and may be used as guidance for vaccination policymakers who may consider adopting the prime-boost combination vaccine strategy in order to gain better control of pertussis.

Our study results will be reported according to PRISMA guidelines. As described in the methods section, our search for relevant studies from several databases will be comprehensive and exhaustive. Lack of standardised criteria in reporting AEFI across studies as well as routine combination of the wP vaccine with other vaccines, which leaves it impossible to decipher AEFI specifically associated with wP from other vaccines are the study limitations. To mitigate these limitations, we will only include studies that have defined AEFI as stated in our study methods. Since AEFI for other vaccines combined with pertussis vaccines are well documented, we will consider AEFI beyond the documented AEFI to be associated with the pertussis vaccines in this review. These limitations will be addressed in the discussion section of the review and will be taken into consideration when recommending the weighting of the study's results in the decision-making of vaccination policymakers.

Author affiliations

¹Vaccines for Africa Initiative, Division of Medical Microbiology, University of Cape Town, Observatory, South Africa

²Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Observatory, South Africa

³Discipline of Paediatrics, Women's and Children's Health Network, University of Adelaide, Adelaide, South Australia, Australia

⁴Department of Paediatrics and Child Health, Groote Schuur Hospital, University of Cape Town, Observatory, South Africa

Contributors RM, BMK and GDH conceived this study. JP developed the study protocol and will implement the systematic review under the supervision of RM and BMK. JP will provide the statistical analysis plan of the study and will conduct the data analysis. JP and RM will perform the study search, screening and extraction of data while BMK, MG and GDH will review

the work. JP wrote the first manuscript draft and all authors gave input to the final draft of the protocol.

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Competing interests None declared.

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Data sharing statement All unpublished data will be made available at request. The first author, JP, should be contacted for unpublished data requests.

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