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Comparison of adverse events following immunisation with acellular and whole-cell pertussis vaccines: A systematic review

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ABSTRACT

Introduction: Two types of vaccines are currently licensed for use against pertussis: whole-cell (wP) and acellular pertussis (aP). There is evidence that wP confers more durable immunity than aP, however wP has been more frequently associated with adverse events following immunisation (AEFI). A comparison of the frequency of AEFI with the first doses of wP and aP has not yet been clearly documented. This must be done in light of recent considerations to move towards a wP prime-aP boost vaccination strategy in low and middle-income countries.

Objectives: To compare the frequency of AEFI associated with the first dose of the wP and aP vaccines. We also compared the frequency of AEFI associated with subsequent doses of wP.

Methods: This systematic review was carried out in strict accordance with the published protocol.

Results: High heterogeneity amongst included one-armed studies did not allow for pooling of prevalence estimates. The prevalence estimates of AEFI at first vaccine dose of wP ranged from 0 to 75%, while the prevalence estimates of AEFI at first vaccine dose of aP ranges from 0 to 39%. The prevalence estimates of adverse events following second and third vaccine dose of wP ranged from 0 to 71% and 0 to 61%, respectively.

Risk ratios among two-armed studies showed an increased risk of adverse events with first dose of wP compared to aP [local reaction RR 2.73 (2.33, 3.21), injection site pain RR 4.15 (3.24, 5.31), injection site swelling RR 4.38 (2.70, 7.12), fever over 38 °C RR 9.21 (5.39, 15.76), drowsiness RR 1.34 (1.18, 1.52) and vomiting RR 1.28 (0.91, 1.79)].

Conclusion: Our results confirm that, when comparing the first dose, wP is more reacotgenic than aP. The proposed wP prime followed by aP boost pertussis vaccine strategy should be approached with caution.

1. Introduction

Pertussis, or "whooping cough", is a highly contagious respiratory illness. It is caused by the gram-negative bacterium *Bordetella pertussis (B. pertussis),* an exclusively human pathogen [1]. *Bordetella pertussis* is spread from person to person through respiratory droplets dispersed by coughing and sneezing [2]. Currently, there are two types of pertussis vaccines licensed for use: whole cell pertussis (wP) and acellular pertussis (aP). Unlike aP, wP vaccines have been frequently associated with adverse events following immunisation (AEFI) [3]. Public concerns due to reports of AEFI associated with wP vaccines led to many middle and high-income countries to use of aP vaccines beginning in the 1980s [4].

Immunisation with either wP or aP vaccines as well as natural infection do not confer lifelong immunity against *B. pertussis*. Consequently, cyclical peaks in the incidence of the disease have historically occurred every 3 to 5 years [5,6]. In recent years, the peaks have begun to occur more frequently, indicating a possible rise in pertussis incidence [6]. In spite of estimated global pertussis vaccination coverage being as high as 82% for 3 doses, the disease continues to occur worldwide [4,7]. Interestingly, a number of countries (e.g. Australia, Portugal, the UK and the USA) that have switched from the using wP to aP have reported pertussis resurgence several years following the switch [4]. Although there are

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conflicting reports regarding which of the two pertussis vaccines has better efficacy, aP vaccines are reported to confer shorter duration of protection in comparison to wP vaccines [8].

The World Health Organization's (WHO) 2015 pertussis position paper recommends that countries currently using wP for primary schedules (doses 1–3) should continue to do so [4]. The WHO suggests that switching from use of wP to aP should only be considered if additional boosters and/or maternal immunisation can be sustained at a national level, which could impose financial implications on countries [4]. A combination vaccination strategy has been suggested, which would include "priming" infants and children using wP at first dose and thereafter completing the primary schedule with aP [9–11]. Immunological and modelling evidence suggests that, if implemented, this combined approach could induce better protective immunity than the current exclusive aP approaches. Additionally, it is hoped that the combined vaccination strategy would result in fewer AEFI than currently experienced with the exclusive use of wP [12].

An important factor in considering this combined vaccination strategy is the safety of wP vaccines at first dose. It is, therefore, necessary to estimate the prevalence of AEFI associated with the first dose of wP and to assess how these estimates compare in frequency and severity to those associated with the first dose of aP vaccines. To the best of our knowledge, there is currently no published and systematised comparison of AEFI at first dose of pertussis vaccines.

1.1. Objectives of review

This systematic review identified all qualifying literature that involved children six years and younger who received a vaccine dose against pertussis in a primary vaccination schedule (doses 1–3) (See Methods).

Primary objectives:

- To describe the frequencies of AEFI associated with first dose of wP vaccines
- To describe the frequencies of AEFI associated with second and third dose of wP vaccines
- To describe the frequencies of AEFI associated with first dose of aP vaccines

Secondary objectives:

- To compare the frequencies of AEFI associated with first dose of wP and aP vaccines
- To compare the frequencies of AEFI associated with first and second/third dose of wP vaccines

2. Methods

Systematic review methods used in conducting this study have been published elsewhere and the study protocol registered on PROSPERO (registration number CRD42016035809) [13].

2.1. Eligibility criteria

Literature inclusion was restricted to published studies that evaluated pertussis vaccine-related AEFI in participants 6 years old or younger within 72-hours of vaccine administration. Criteria for including studies are outlined in Table 1.

2.2. Search strategy

The following databases were searched for the 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. A combination of the following search terms (including the use of MeSH) was used: adverse event, pertussis vaccine, whole cell pertussis vaccine, and acellular pertussis vaccine. The search strategy, as applied to PubMed, is outlined in Table 2. The initial search was run in May 2016 and updated in September 2017. The updated search did not yield any new literature to add to the review.

2.3. Screening and study selection

Two authors (JP and RM) screened the search outputs using titles and abstracts first. Thereafter, the two authors independently went through the full text of all potentially eligible studies to assess if they met the inclusion criteria. Discrepancies in the list of eligible

Table 1
Criteria for study inclusion.

Characteristic	Inclusion criteria
Type of study	Cohort studies, case-control studies, cross-sectional studies, post-marketing vaccine surveillance studies, or randomised controlled trials published in a peer reviewed journal
Participants	Including infants and children 6 years or younger vaccinated against pertussis in a primary vaccination schedule
Case definition	Pertussis vaccine-related adverse events occurring within 72 h of vaccination, which include: • Generalised local reactions (ex. Injection site redness) • Injection site swelling • Injection site tenderness • Decreased injected limb movement • Fever over 38 °C • Irritability • Drowsiness • Anorexia • Vomiting • Persistent crying • Seizure • Hypotonic-hyporesponsive episode
Outcome measures	Primary outcomes: • Prevalence of adverse events following immunisation associated with first vaccine dose of wP • Prevalence of adverse events following immunisation associated with first vaccine dose of aPSecondary outcomes: • Prevalence of adverse events following immunisation with second and third vaccine doses of wP

Abbreviations: wP = whole-cell pertussis, aP = acellular pertussis.

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