Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

Jenna Patterson [a,b,*], Benjamin M. Kagina [a,b], Michael Gold [c], Gregory D. Hussey [a,d], Rudzani Muloiwa [a,e]

[a] Vaccines for Africa Initiative, University of Cape Town, South Africa
[b] School of Public Health & Family Medicine, University of Cape Town, South Africa
[c] University of Adelaide, Discipline of Paediatrics, Women's and Children's Health Network, Adelaide, Australia
[d] Division of Medical Microbiology & Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa
[e] Department of Paediatrics & Child Health, Groote Schuur Hospital, University of Cape Town, South Africa

ARTICLE INFO

Article history:
Received 27 November 2017
Received in revised form 6 August 2018
Accepted 7 August 2018
Available online xxxx

Keywords:
Pertussis
Whole-cell pertussis
Acellular pertussis
Adverse event
Infectious diseases
Epidemiology

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

* Corresponding author. VACFA, Room N2.09A, Werner Beit North, Health Sciences Campus, Anzio Road, Observatory, 7925, South Africa.
E-mail addresses: PTTJEN005@myuct.ac.za (J. Patterson), benjamin.kagina@uct.ac.za (B.M. Kagina), michael.gold@adelaide.edu.au (M. Gold), gregory.hussey@uct.ac.za (G.D. Hussey), rudzani.muloiwa@uct.ac.za (R. Muloiwa).

https://doi.org/10.1016/j.vaccine.2018.08.022
0264-410X/

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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Table 2
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)

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

studies between the two authors were resolved through discussion and consensus with the assistance of the other authors.

2.4. Data extraction and management

Data was extracted from the included studies on a pre-designed data extraction form using TapForms software [14]. Data were then extracted and entered into STATA version 14 for analysis [15].

2.5. Risk of bias and quality assessment

Each article included was assessed for risk of bias and quality. Observational studies were assessed using the appropriate CASP

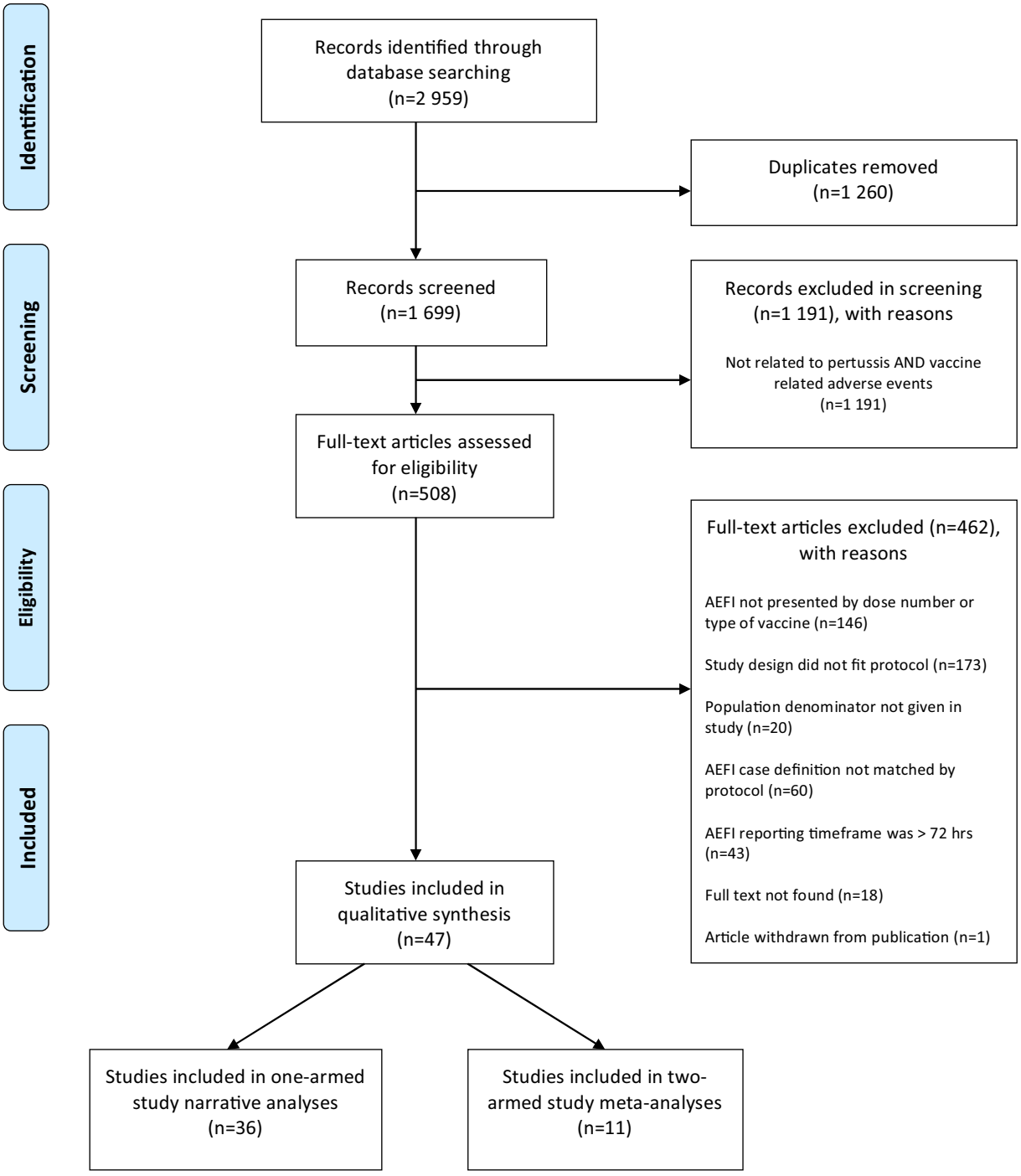

Fig. 1. Flow diagram for selection of studies.

checklists, while RCTs were assessed using RevMan5 criteria [16,17]. All risk of bias judgements were made by the first author and checked by BK.

2.6. Data synthesis and analyses

The Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) checklist was used in reporting the findings of this review [18]. As the data were collected from a series of independently performed studies which inherently included subjects from different populations, a random effects model was fitted to the data. The prevalence of AEFI were compared by vaccine type (wP and aP) in the data analysis. Where heterogeneity was found to be low in *meta*-analyses ($I^2 < 50$), pooled prevalence estimates were reported with 95% confidence intervals for each respective outcome. Where heterogeneity was found to be high in meta-analyses ($I^2 > 50$), narrative reporting was used to describe the mean and ranges of prevalence for each respective outcome. Due to insufficient data, none of the subgroup analyses outlined in the study's protocol were able to be carried out.

3. Results

In total 1 699 records were retrieved from the electronic database searches, of which 508 were selected for full-text review. A further 462 records were excluded, leaving 47 studies that met the final inclusion criteria (Fig. 1). The included studies were further split into one-armed studies that reported AEFI associated with either wP or aP vaccines (36 studies) or two-armed studies that compared the occurrence of AEFI associated with wP and aP vaccines in the same population (11 studies). The included studies were published between 1981 and 2014 in low-middle (2 studies), upper-middle (8 studies) and high (37 studies) income countries. The included literature was made up of 2 post-marketing surveillance studies, 10 cohort studies and 35 randomised controlled trials (RCTs). The studies included a total of 450 757 individuals. The characteristics of included studies are summarised in Table 3. Of

Table 3
Characteristics of studies included in the review.

Author, Year [citation]	Study Design	Country	Income Level	Vaccine (s)	Sample size	Reporting Method	Time
Anderson, 1988 [19]	RCT	USA	High	wP and aP	39	Doctor/Nurse Consult	72
Auerbach, 1992 [20]	RCT	USA	High	aP	160	Doctor/Nurse Consult	24
Barkin, 1984 [21]	RCT	USA	High	wP	54	Doctor/Nurse Consult	72
Bell, 1999 [22]	RCT	UK	High	aP	251	Parental reporting card	72
Bernstein, 2011 [23]	RCT	USA	High	aP	568	Parental interview	72
Beyazova, 2013 [24]	RCT	Turkey	Upper-middle	wP and aP	778	Parental reporting card	72
Black, 1993 [25]	RCT	USA	High	wP	946	Parental interview	72
Carlsson, 1998 [26]	RCT	Sweden	High	aP	235	Parental reporting card	72
Cody, 1981 [27]	RCT	USA	High	wP	4964	Parental questionnaire	72
Dagan, 1994 [28]	RCT	Israel	High	wP	73	Parental reporting card	72
Decker, 1995 [29]	RCT	USA	High	wP and aP	2184	Parental reporting card	72
Deloria, 1995 [30]#	RCT	USA	High	wP and aP	2127	Parental interview	48
Ducusin, 2000 [31]	Post-marketing surveillance	Philippines	Low-middle	wP	1036	Parental questionnaire	72
Fateh, 2014 [32]	RCT	Iran	Upper-middle	wP	235	Doctor/Nurse Consult	48
Feery, 1982 [33]	Cohort	Australia	High	wP	3565	Parental interview	72
Greenberg, 2000 [34]	RCT	USA	High	aP	405	Parental reporting card	72
Halperin, 1996 [35]	RCT	Canada	High	wP and aP	208	Parental interview	48
Hoppenbrouwers, 1999 [36]	RCT	Turkey	Upper-middle	aP	258	Parental reporting card	72
Huang, 2010 [37]	Cohort	USA	High	aP	388,335	Surveillance system	72
Hussey, 2002 [38]	Cohort	South Africa	Upper-middle	wP	129	Parental reporting card	72
Kallings, 1988 [39]	RCT	Sweden	High	aP	2847	Parental reporting card	24
Kayhty, 2005 [40]	Cohort	Sweden	High	aP	101	Parental reporting card	72
Korkmaz, 2014 [41]	Cohort	Turkey	Upper-middle	wP and aP	1324	Parental reporting card	72
Langue, 1999 [42]	RCT	France	High	wP	213	Parental reporting card	72
Lee, 1999 [43]	RCT	China	Upper-middle	aP	67	Parental reporting card	48
Liese, 2001 [44]	Cohort	Germany	High	aP	1779	Parental reporting card	72
Long, 1990 [45]	RCT	USA	High	wP	536	Parental reporting card	48
Mallet, 2000 [46]	RCT	France	High	aP	848	Parental reporting card	72
Martins, 2007 [47]	Cohort	Brazil	Upper-middle	wP	9259	Parental interview	48
Miller, 1991 [48]	RCT	UK	High	wP and aP	176	Doctor/Nurse Consult	24
Miller, 1995 [49]	RCT	UK	High	wP and aP	177	Doctor/Nurse Consult	24
Monteiro, 2010 [50]	Post-marketing surveillance	Brazil	Upper-middle	wP	3178	Surveillance system	12
Murphy, 1983 [51]	RCT	USA	High	wP	206	Parental reporting card	24
Nolan, 1997 [52]	RCT	Australia	High	wP	812	Parental reporting card	12
Paradiso, 1993 [53]	RCT	USA	High	wP	188	Parental reporting card	72
Pichichero, 1992 [54]	RCT	USA	High	wP and aP	290	Parental interview	48
Pichichero, 1994 [55]	RCT	USA	High	wP and aP	80	Parental reporting card	72
Pichichero, 2002 [56]	Cohort	Sweden	High	wP and aP	110	Parental reporting card	48
Pollock, 1984 [57]	RCT	UK	High	wP	5408	Parental interview	12
Prymula, 2008 [58]	Cohort	Czech Republic	High	aP	2479	Parental reporting card	72
Schmitt, 1996 [59]	RCT	Germany	High	aP	2455	Parental reporting card	24
Simondon, 1996 [60]	RCT	Senegal	Low-middle	wP and aP	241	Doctor/Nurse Consult	72
Trollfors, 1995 [61]	RCT	Sweden	High	wP	1724	Parental reporting card	48
Usonis, 1996 [62]	RCT	Lithuania	High	wP	119	Parental interview	72
Vadheim, 1993 [63]	RCT	USA	High	wP	1834	Parental reporting card	72
Waight, 1983 [64]	Cohort	UK	High	wP	144	Doctor/Nurse Consult	24
Watemberg, 1991 [65]	RCT	Israel	High	wP	56	Parental reporting card	72

Abbreviations: wP = whole-cell pertussis, aP = acellular pertussis, RCT = randomized control trial, time = maximum adverse event reporting time, # insufficient data for inclusion in comparative *meta*-analysis of two-armed studies.

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the selected studies, although 12 investigated both wP and aP interventions, one did not have sufficient data for inclusion in the comparative meta-analysis.

3.1. Methodological quality

Bias assessment of included observational studies was categorised by a score of low, moderate or high derived from CASP checklists (Table 4). Risk of bias assessments of included randomised control trials is displayed in Fig. 2.

3.1.1. Single-Armed studies

As heterogeneity was found to be high between all single-armed studies assessing the prevalence of AEFI with both wP and aP vaccines, prevalence estimates for these studies were not pooled. Due to a wide range of wP and aP vaccine brands utilized in the included studies, prevalence of AEFI according to vaccine brand could not be assessed.

3.1.1.1. Adverse events associated with first dose of whole-cell and acellular pertussis. Fever over 38 °C was the most commonly surveyed AEFI following first dose of wP (18 studies), while hypotonic- hyporesponsive episode (HHE) was the least commonly surveyed (3 studies). The prevalence of any AEFI with first dose of wP ranged from 0 to 75%, with irritability reported as most prevalent.

Fever over 38 °C was the most commonly surveyed AEFI following first dose of aP (14 studies). None of the studies using aP reported on seizure or HHE occurrence. The prevalence of AEFI with first dose of aP ranged from 0 to 39%, with irritability as most prevalent. Fig. 3A represents a narrative forest plot comparison of mean prevalence with ranges for AEFI at first dose of wP and aP vaccines. Adverse events (except persistent crying) were more prevalent following first dose of wP as compared to first dose of aP. The mean prevalence of persistent crying, however, was 11% for wP as compared to 23% for first dose of aP. The frequency of AEFI showed noticeably higher variability for wP estimates as compared to aP estimates.

In the included studies, wP was administered as a dose of standalone DTwP or commonly as DTwP in a combination formulation with polio, hepatitis B, and haemophilus influenzae type B. Fig. 3B represents a narrative forest plot of the mean prevalence with ranges for AEFI at first dose of wP administered as a standalone dose of DTwP or in DTwP combination formulation. Standalone and combined formulations showed an overlap in the frequency of AEFI with the exception of drowsiness and vomiting. Only three studies, however, were available in each arm to assesses drowsiness, while two and three were available in each are to

Table 4
Risk of bias assessment for observation studies.

Author, Year	Risk of Bias	CASP Score Description
Auerbach, 1992	Low	
Barkin, 1984	Low	
Bell, 1999	Moderate	(a) study was not blinded, (b) aside from the intervention, groups were not treated equally, (c) could not tell if all patients at the beginning of trial were accounted for at conclusion
Bernstein, 2011	Low	
Black, 1993	Low	
Carlsson, 1998	Low	
Cody, 1981	Moderate	(a) could not tell if groups were similar at start of trial
Dagan, 1994	Low	
Deloria, 1995	Moderate	(a) could not tell if study was blinded, (b) could not tell if groups were similar at start of trial
Ducusin, 2000	Moderate	(a) could not tell if confounding variables were taken into account in analysis
Fateh, 2014	Low	
Feery, 1982	Low	
Greenberg, 2000	Low	
Gustafsson, 1996	Moderate	(a) could not tell if groups were similar at start of trial, (b) could not tell if all clinically important outcomes were considered
Hoppenbrouwers, 1999	Moderate	(a) could not tell if study was blinded
Huang, 2010	Moderate	(a) could not tell if confounding variables were taken into account in analysis
Hussey, 2002	Low	
Kallings, 1988	Moderate	(a) could not tell if all clinically important outcomes were considered
Kayhty, 2005	Low	
Langue, 1999	Low	
Lee, 1999	Low	
Liese, 2001	Low	
Long, 1990	Low	(a) could not tell if groups were similar at start of trial
Mallet, 2000	Low	
Martins, 2007	Moderate	(a) could not tell if confounding variables were taken into account in analysis
Monteiro, 2010	Moderate	(a) could not tell if confounding variables were taken into account in analysis
Murphy, 1983	Low	
Nolan, 1997	Low	
Paradiso, 1993	Low	
Pollock, 1984	High	(a) could not tell study was randomised, (b) could not tell if study was blinded, (c) could not tell if all patients at beginning of trial were accounted for at conclusion
Prymula, 2008	Low	
Schmitt, 1996	Moderate	(a) could not tell if study was blinded, b) could not tell if groups were treated equally apart from intervention
Trollfors, 1995	Low	
Usonis, 1996	Moderate	(a) could not tell if groups were similar at start of trial
Vadheim, 1993	Low	
Vanura, 1994	Moderate	(a) could not tell if groups were similar at start of trial
Waight, 1983	Low	
Watember, 1991	Low	

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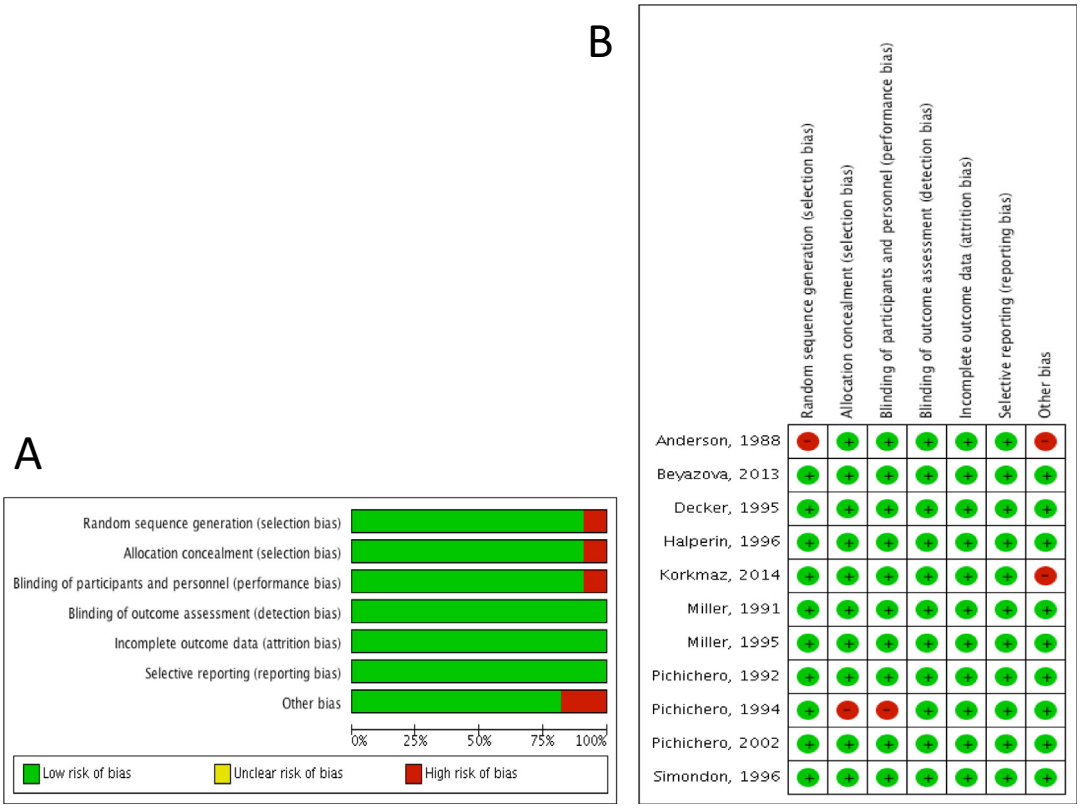


(A) Review authors' judgments about each risk of bias item presented as percentages across all included studies
(B) Review authors' judgements about each risk of bias item for each included study

Fig. 2. Risk of bias graphs for randomized control studies.

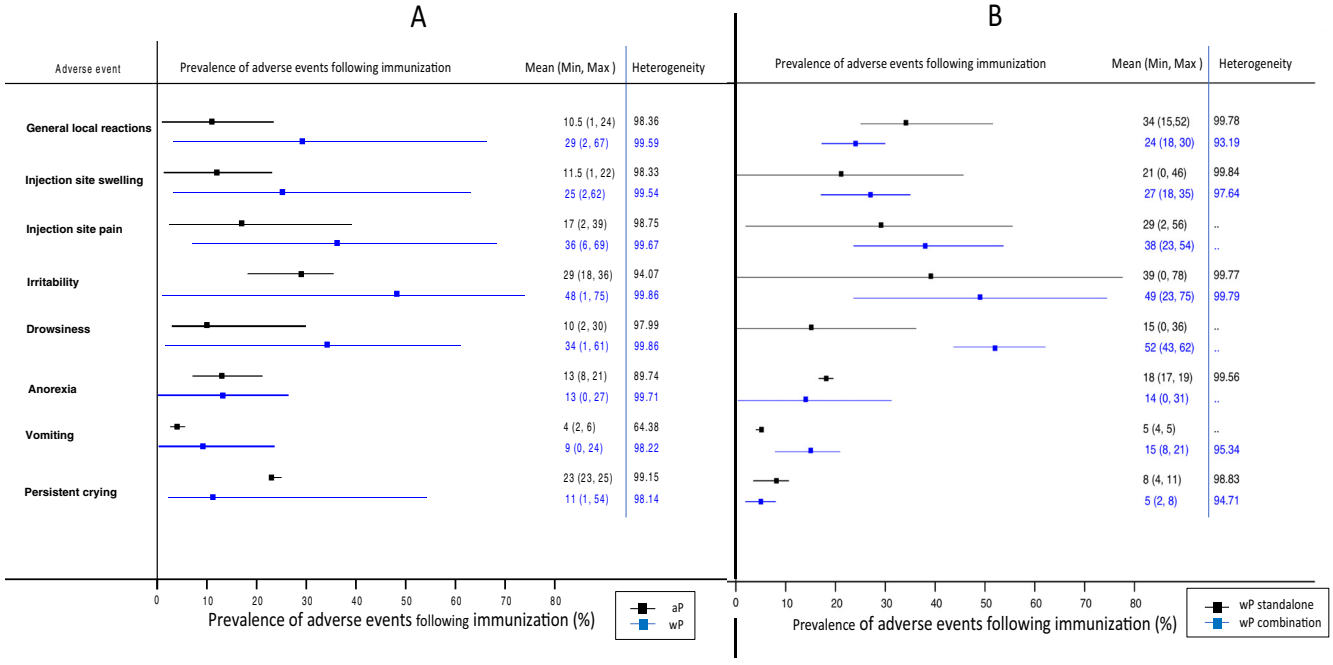


Fig. 3. Mean prevalence and range of adverse events following first dose of whole cell and acellular vaccine (A) and following standalone DTwP and combination vaccines (B).

assess vomiting. Analysis of aP AEFI by vaccine combination was not possible due to insufficient data.

3.1.1.2. Adverse events associated with subsequent doses of whole-cell pertussis. The first dose of wP vaccines was compared with second and third doses of wP to assess whether the noted higher frequency of AEFI with first wP dose changed with subsequent doses. High heterogeneity did not allow for pooled AEFI prevalence estimates to be reported at second or third dose of wP. Insufficient data did not allow for a meta-analyses of injection site tenderness and HHE following second dose of wP. An effect estimate was not reported for seizure following second dose of wP as only one study reported this AEFI (Monteiro, 2010). The prevalence of AEFI with second dose of wP ranged from 0 to 71%, with irritability being the most prevalent. The prevalence ranges for third dose of wP spanned from 0 to 61%, with local reactions occurring most frequently.

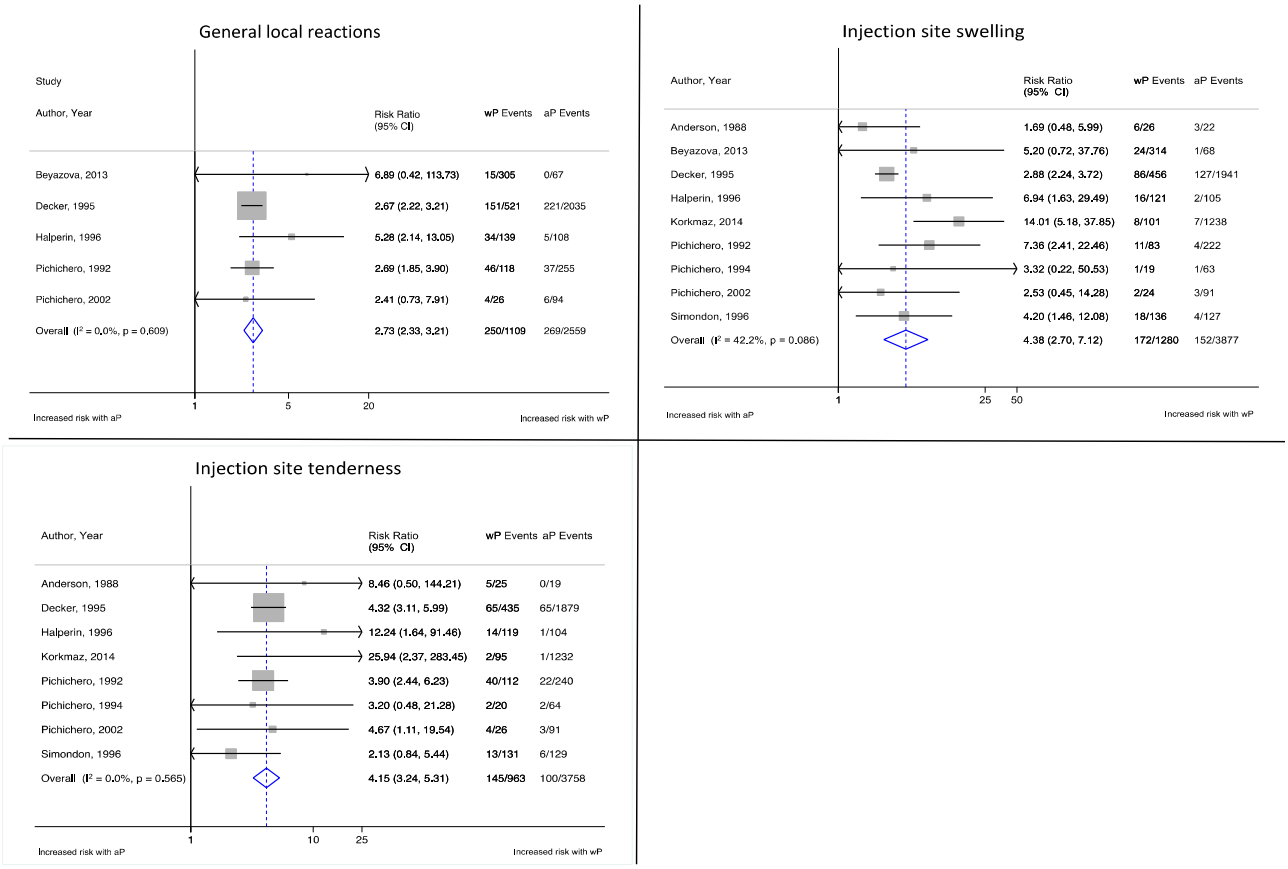
3.1.2. Meta-analyses comparing adverse events associated with first doses of wP and aP

Although twelve of the included studies were two-armed studies that assessed AEFI by vaccine type, only eleven of the two-armed studies were included in the meta-analyses as one (Deloria, 1995) did not contain data on AEFI at first dose of either vaccine type. 14 864 participants were included in meta-analyses to calculate risk ratios for AEFI at first dose of wP as compared to first dose of aP.

Local reaction risk ratios (general local reactions, injection site swelling and injection site tenderness) are displayed in Fig. 4, while systemic reaction risk ratios (fever over 38 °C, drowsiness, vomiting and anorexia) are displayed in Fig. 5. The pooled risk ratio for irritability could not be reported due to high heterogeneity (I^2 = 84.4%). Although heterogeneity for anorexia (I^2 = 54.7%) was slightly above the threshold, the risk ratio was retained as a forest plot as it showed the pooled summary consistently with the visual distribution of the data from individual studies. All calculated risk ratios were >1 which showed an increased risk following first dose of wP compared to first dose of aP [generalised local reactions RR 2.73 (2.33, 3.21), injection site tenderness 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)]. Seizures were reported by three wP studies with frequencies of 0.0004%, 0.03% and 11.3%, while HHE were reported by three wP studies with frequencies of 0.0005%, 0.0006%, and 32.3%. Meta-analyses could not be performed for persistent crying, seizure or HHE as no included studies reported on these AEFI at first dose of aP.

3.1.3. Sensitivity analysis

Studies assessed as having high risk of bias were planned to be removed from meta-analyses in order to assess how bias may have affected the review findings. No studies, however, were deemed to have a high risk of bias, therefore, a sensitivity analysis was not carried out.



Abbreviations: wP=whole-cell pertussis containing vaccine, aP=acellular pertussis containing vaccine

Fig. 4. Local reaction risk ratios following first dose of pertussis vaccines.

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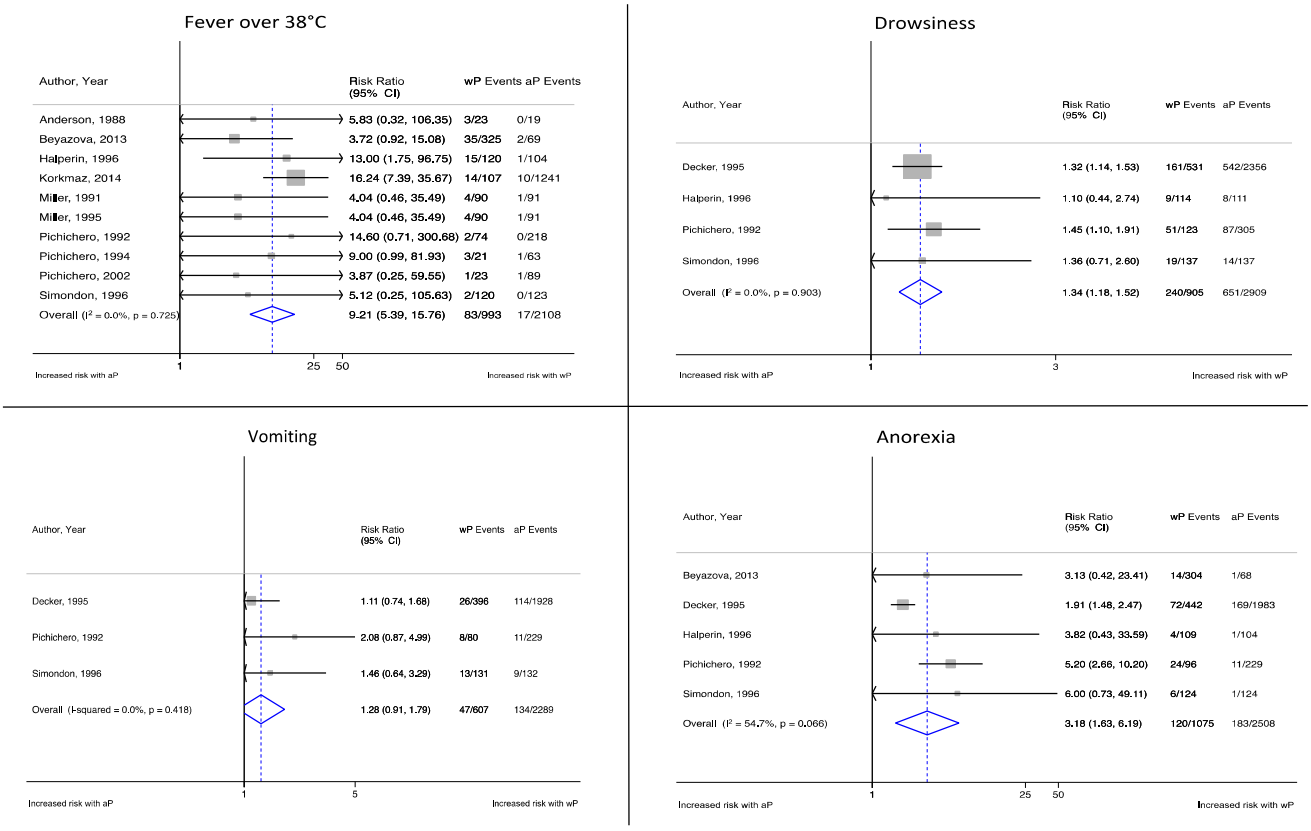

Abbreviations: wP=whole-cell pertussis containing vaccine, aP=acellular pertussis containing vaccine

Fig. 5. Systemic reaction risk ratios following first dose of pertussis vaccines.

4. Discussion

In this review, we have systematically compared and quantified the prevalence of AEFI at first doses of wP and aP vaccines. The main findings of this review include: 1) primary vaccination with either wP or aP vaccines was associated with a number of adverse events at varying frequencies; 2) the first dose of wP was associated with higher frequencies of AEFI than the first dose of aP; 3) the diversity and range of AEFI with second and third doses of wP did not differ to that of first dose of wP; 4) most of the published information on AEFI with wP and aP vaccines is from high income countries. Taken together, our review results corroborate the existing notion that primary doses [1–3] of wP vaccines are more reactogenic than primary doses of aP vaccines. Based upon the WHO's AEFI causality assessment, we presume the AEFI reported in this review to be resultant of the vaccine products [66]. Although interesting, these results are not surprising as the formulation of wP vaccines is crude and complex while purified components of pertussis bacteria are contained in aP vaccines.

There is no known medical intervention that is considered to be 100% safe. Optimal safety (absence of serious adverse reactions), however, is a universal prerequisite to any vaccine being used [67]. Our results show first dose vaccination with both wP and aP causes local and systemic adverse events. The most common local reactions induced by both vaccine types was swelling at the injection site. This type of local reaction, which is due to tissue inflammation, is expected and common to adjuvanted vaccines [68]. Local reactions are generally considered minor in clinical trials [66]. Both local and systemic reactions were more commonly reported following first dose of wP as compared to first dose of aP. Persistent crying, however, was found to be more frequent following first dose of aP and these results may be due to lack of standardized AEFI case definitions. The frequencies of local and systemic AEFI were not found to differ by the number of wP doses administered. Two AEFI (drowsiness and vomiting) seemed to occur more frequently when DTwP was given in combination formulation with other antigens as compared to a standalone dose, however there was insufficient data to make any conclusions regarding this finding. The other vaccines included with DTwP in the same formulation are generally considered to have good safety profiles when used on their own, thus the apparent association between formulation and some AEFI warrants further investigation. Except for vomiting, the most severe AEFI such as seizure and HHE were reported with wP but not with aP. Even though the occurrence of these severe AEFI following wP administration were rare, such reactions are of concern to parents and may contribute to vaccine hesitancy and loss of public confidence in vaccines [69]. For example, Japan temporarily suspended vaccination against *B. pertussis* after two infants died within 24 h of receiving the wP vaccine in 1974 [70]. Sporadic reports of rare and severe AEFI with wP were enough to warrant the switch to aP in many high-income countries.

The switch from wP to aP has not yet taken place in many low and middle-income countries (LMICs) [4]. Therefore, the pertussis vaccine safety profiles collated in this review contain data predominantly from high income countries in regard to aP. Due to suboptimal surveillance systems in LMICs, it may be possible that AEFI are being under-reported in these settings [71]. There is,

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however, effort to improve pharmacovigilance in LMICs as optimal AEFI surveillance systems are crucial for strengthening immunisation programs [67].

The number and type of antigens contained in aP vaccines may be a factor in AEFI, however due to insufficient data, this could not be explored. Other limitations of this study include the lack of standardised criteria to assess and define AEFI across all studies, which limited the quality of the data in this review. Thirdly, some AEFI reports such as reports of extensive limb swelling associated with aP may have been excluded due to the strict 72-hour observation time limit applied in the inclusion criteria of review. The WHO and Brighton Collaboration are dedicating recourses to standardising AEFI criteria for future studies. Our review, however, utilised a strict AEFI definition and assessment criteria to mitigate this limitation. Lastly, many studies were excluded from inclusion in this review because adverse events were not reported by dose number, a point we urge future studies to consider. Despite the exclusion of many studies, the sample size of this review remained large.

5. Conclusion

Our results confirm that the first dose of wP is more reactogenic compared to aP and as such the proposed wP prime followed by aP boost pertussis vaccination strategy should be approached with caution. The WHO recommends a switch from wP to aP only where countries are able to afford adding periodic booster doses and maternal immunisation to the vaccination schedule. Our results suggest that in addition to cost and efficacy, the safety profile of wP vaccines could be a large factor limiting the continuation of wP use in LMICs. Irrespective of reports suggesting greater efficacy of wP compared to aP, the association of severe AEFI with wP may compromise vaccine uptake in the long run. Vaccines with low reactogenicity are crucial to ensuring high coverage in national immunisation programmes.

Executive license statement

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Author’s contributions

RM, BMK and GDH conceived this study. JP developed the study protocol and implemented the systematic review under the supervision of RM and BMK. JP provided the statistical analysis plan of the study and conducted the data analysis. JP performed the study search, screening, and extraction of data under the guidance of BMK, MG, GDH and RM. JP wrote the first manuscript draft and all authors gave input to the final draft.

Funding statement

The Vaccines for Africa Initiative (VACFA) received an unconditional grant from Sanofi Pasteur for capacity development. The funding covered costs for the research and dissemination of the results, including publications. Sanofi Pasteur did not have any input on the design and/or conduct of this study nor the intepretation of the results.

Competing interests

All authors have no competing interests.

Ethics approval

No ethics approval was required for this study as it is a systematic review using pre-existing, publicly published data.

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