

Whole-Cell and Acellular Pertussis Vaccine: Reflections on Efficacy

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Highlights of the Study

- Pertussis vaccines had a pivotal role in changing disease epidemiology and related mortality.
- Both the whole-cell and acellular vaccines are effective in reducing symptomatic disease.
- Acellular pertussis vaccine is generally better tolerated with lower reactogenicity.
- Waning immunity is a growing issue leading to resurgence of pertussis among adolescents and adults.

Keywords

Whole-cell · Acellular pertussis · Pertussis · Vaccine · Efficacy

Abstract

Pertussis is a common respiratory infection caused by the bacterium *Bordetella pertussis*. Although most cases occur in developing countries, it is considered endemic globally. The World Health Organization estimates there are 20–40 million cases of pertussis annually. Pertussis vaccines played a pivotal role in reducing the burden of pertussis disease as well as infant morbidity and mortality. Although the two forms of pertussis vaccine are effective, each has its advantages and drawbacks. This review aims to review the current knowledge on pertussis vaccines, emphasizing vaccine effectiveness in different populations within a community. Clinical trials have shown favorable vaccine efficacy with acellular pertussis (aP)vaccine. However, observational and population-level studies showed that introducing at least a single

dose of whole-cell pertussis (wP) vaccine within the routine immunization schedule is associated with better disease protection and a longer duration of immunity. On the other hand, wP vaccine is more reactogenic and associated with higher adverse events. Therefore, the selection of vaccine should be weighed against the effectiveness, reactogenicity, and cost-effectiveness. Due to its safety profile, aP vaccine can be offered to wider population groups. Booster adolescent and pregnant immunization programs have been implemented globally to control outbreaks and protect vulnerable infants. Due to the variable effectiveness performance of both vaccines, different countries adopted distinctive immunization programs. Determining the right vaccination approach depends on financial consideration, immunization program infrastructure, adverse event monitoring, and pertussis surveillance in the community.

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Introduction

Pertussis was a common pediatric infection until the whole-cell pertussis (wP) vaccine was introduced in the 1940s. The wP vaccines played a pivotal role in changing the global epidemiology of pertussis. In the United States (USA), for example, annual pertussis cases dropped from more than 200,000 cases and 4,000 pertussis-related deaths in the early 1930s to 1,010 cases in 1976 [1]. By the 1980s, the acellular vaccine (aP) was developed and was first introduced in Japan in 1981 [2].

The World Health Organization estimates that there are 20–40 million cases of pertussis around the world annually, of which 90% occur in developing countries [3]. Nevertheless, pertussis remains endemic in most countries, with epidemics occurring every 2–5 years [4, 5]. Of developed countries, only Japan has reached the WHO pertussis control target with a disease incidence of less than 1 per 100,000 population, while Australia and Switzerland have the highest disease prevalence [6]. There is a growing recognition of pertussis being a significant cause of respiratory illness and chronic cough in adolescents and adults. Data from the Center for Disease Control and Prevention showed that the incidence in this age group increased by almost 100% during the period 1996–2000 [6]. In a study conducted in Canada among adults and adolescents who presented to emergency care with chronic cough (≥ 7 days), 1 of 5 (20%) had laboratory evidence of pertussis [7].

The wP vaccine contains various amounts of whole nonviable bacterial cells that include all major pertussis antigens such as pertussis toxin (PT), adenylate cyclase toxin, lipooligosaccharide, filamentous hemagglutinin, and agglutinogens. The vaccine is prepared by growing *Bordetella pertussis* bacteria in a liquid medium, and a specific cellular concentration is aliquoted after bacterial inactivation. Despite the simplicity of the procedure, the antigen content and, hence, vaccine immunogenicity of the wP vaccine varies between different manufacturers [8, 9]. Vaccine efficacy has been reported to range between 36 and 98%. Similarly, real-world data confirmed low vaccine effectiveness in preventing microbiologically confirmed pertussis [10, 11]. The aP vaccine, on the other hand, contains purified pertussis-related antigen. Most licensed aP vaccines contain between one and five separately purified antigens [12]. The amount and final concentration of each antigen vary between manufacturers and, similar to wP, may affect vaccine immunogenicity [13]. Also, the type of antigen present in the vaccine may affect the vaccine efficacy [13, 14].

The estimated efficacy and effectiveness of wP and aP vaccines ranged between 70 and 90% depending on pertussis case definition, targeted population, and study design [15–17]. Despite a relatively high efficacy and vaccination uptake, there has been a resurgence of pertussis over the last 30 years [15, 17]. Multiple factors could have played a role in the recent rise in pertussis, including waning immunity related to vaccination, increased physician awareness, improved diagnostics, and the use of molecular testing [18]. For these reasons, the immunization of adolescents and adults with the aP vaccine has become an essential public health intervention in limiting pertussis transmission.

Due to differences in vaccine performance, reactogenicity, and financial considerations, several approaches have been adopted by different immunization programs globally. Here, we review current knowledge on pertussis vaccine, emphasizing vaccine effectiveness in different populations in a community.

Search Strategy

References for this review were identified through searches of PubMed for articles published until June 2021, by use of the terms “pertussis,” “vaccine,” “efficacy,” “effectiveness,” “adverse events,” “reactogenicity,” and “cost-effectiveness.” Further relevant articles were identified through searches in the authors’ personal files and in Google Scholar. Articles resulting from these searches and relevant references cited in those articles were reviewed. Only articles published in English were included.

Efficacy and Effectiveness

The acellular pertussis vaccine is immunogenic and is effective in preventing pertussis but less reactogenic than the wP vaccine [19]. However, compared with the best wP vaccines, aP vaccines are not as effective in mass immunization programs [5, 20]. Vaccine efficacy varied between studies due to variation in vaccine components and concentration of aP, the content of wP protective units, and case definitions (Table 1). Both vaccines demonstrated higher vaccine efficacy when the stricter case definition (≥ 21 days of symptoms) was used. Efficacy of the aP is lower when a shorter duration of cough is used for case definition [21, 22]. A meta-analysis of available RCTs comparing aP vaccine (3- and 5-component formula-

Table 1. Summary of main controlled trials and observational studies comparing Ap to Wp

A Randomized control trials evaluating vaccine efficacy of both aP and wP vaccines

Study	DTaP vaccine	aP composition			wP composition	Case definition	Vaccine efficacy % (95% CI)		Notes
		PT	FHA	Pn			Fim	DTaP	
Gustafsson et al. [71], 1996	CLL-4F2	+	+	+	+	≥21 days of cough + one of: culture, serology, PCR, close contact of a confirmed case	85 (81–89)	48 (37–58)	The whole-cell vaccine was associated with significantly higher rates of protracted crying, cyanosis, fever, and local reactions than the other vaccines
Greco et al. [72], 1996	SKB-2	+	+	+	+	5.7 protective units	59 (51–66)	48 (37–58)	
Trollfors et al. [80], 1995	B5c-3P	+	+	+	+	5.7 protective units	84 (76–90)	36 (14–52)	Local and systemic adverse events were significantly more frequent after the administration of the whole-cell vaccine
Stehr et al. [73], 1998	SKB-3P (Infanrix)	+	+	+	+	5.7 protective units	84 (76–89)	36 (14–52)	
Simondon et al. [22], 1997	NAV-1	+	+	+	+	NA	71 (63–78)	NA	DTaP versus DT
Olin et al. [74], 1997	LPT-4F	+	+	+	+	≥4 protective units	72 (62–79)	83 (76–88)	Side reactions were significantly less after DTaP compared with DTP Efficacy against <i>B. parapertussis</i> : ~31%
						≥21 days of cough	83 (76–88)	93 (89–96)	
						≥21 days of cough + one of: culture, serology, PCR or epi link	53 (23–71)	74 (55–85)	320 cases among 13,476 study population
						≥21 days of paroxysmal cough + one of: culture, serology, PCR or epi link	85 (66–93)	96 (86–99)	

B Randomized trial in which wP was the control									
Study	Vaccine	PT	FHA	Pn	Fim	Case definition	RR compared to wP	Attack rate (per 1,000 at risk)	
Olin et al. [74], 1997	SKB-2	+	+	+	+	Culture-proven pertussis with or without cough	Not assessed	6.7	Low-moderate baseline risk of pertussis
	CV-3	+	+	+	+		2.55 (1.5–4.33)	3.5	
	PMC-5	+	+	+	+		1.4 (0.78–2.52)	1.5	
	wP						1.00	1.8	

Table 1 (continued)

C Observational studies

Study	DTaP vaccine	aP composition			wP composition	Case definition	Vaccine efficacy % (95% CI)		Notes	
		PT	FHA	Pn			Fim	aP		wP
Heininger et al. [75], 1998	LPT-4F	+	+	+	+	≥7 days of cough caused by <i>B. pertussis</i>	≥4 protective units	58 (30–75)	84 (65–93)	The study evaluated vaccine efficacy in preventing secondary infection from household contacts. The population were subjects enrolled in RCT
						≥21 days of typical cough		86 (62–95)	94 (77–99)	
						Any cough (without pertussis confirmation)		38 (13–56)	54 (32–69)	

FHA, formalin-treated hemagglutinin; Fim, fimbriae; Pn, pertactin; PT, pertussis toxin.

tions) and wP vaccine from 3 different manufacturers yielded overall vaccine effectiveness of 84% (95% CI: 81–87%) and 94% (95% CI: 88–97%), respectively [23].

The vaccine given in infants' primary series may influence the subsequent risk of pertussis in adulthood. One study demonstrated that teenagers who previously received the wP vaccines in the first 2 years of life appeared to have more protection against pertussis. The odds of developing pertussis were five times higher in teenagers who received four DTaP doses in their infancy than teenagers who received the same number of doses of DTwP. The protection developed after receiving the wP vaccine correlated to the number of vaccine doses received [24]. Furthermore, the odds were about four times higher in teenagers who received mixed vaccines (DTaP and DTwP) than those who received all DTaP vaccines [25]. Similarly, in a large cohort of 263,496 persons aged 8–20, around 900 cases of pertussis were identified. The risk of developing pertussis was significantly higher in those who received the aP vaccine alone compared to individuals who received at least one dose of wP vaccine as part of their immunization series [26].

The effectiveness of aP vaccines seems to drop with age. Recent studies on outbreaks in highly immunized populations demonstrated a decrease in immunity in older children and adolescents and a corresponding increase in cases in this age group [25, 27]. Other concerns that have been raised regarding the aP vaccine include decreased subsequent booster responsiveness, which may be dependent on the type of vaccine used in the primary series [28, 29]. Furthermore, the aP vaccine may have lower efficacy in eliminating pertussis in asymptomatic carriers. In animal models, unlike the wP vaccine, the aP vaccine failed to eradicate pertussis carriage despite adequate disease prevention [30]. This may partially contribute to the ongoing outbreaks and asymptomatic transmission in developed countries [31, 32]. Lastly, the emergence of *B. pertussis* with mutations in key aP vaccine antigens, specifically PT and pertactin, may escape protective immunity and contribute to the resurgence of pertussis [33, 34].

Waning Immunity

The wP vaccine simulates natural infection better than the aP vaccine. Unlike natural infection and wP vaccination, aP vaccines do little to induce cellular immunity and Th1 responses, which are essential for clearance of *Bordetella pertussis* and may be the key to sustained protection [18, 35]. Acellular pertussis vaccine is adjuvanted with aluminum, which preferentially stimulates Th2 respons-

es, leading to high antibody levels, which do not necessarily correlate well with protective immunity [36]. Also, despite an initially strong response, antibody levels fall several folds between aP doses [37].

Cell-mediated immunity, including memory T-cells, persists in recipients of aP, but more robust lymphocyte proliferation, specifically memory Th1 and Th17 cells, and cytokine responses are observed in those primed with wP compared to aP [29, 38]. Tissue-resident memory cells (T_{RM}) were found to play a fundamental role in the clearance of *B. pertussis* from respiratory mucosa. Also, the presence of T_{RM} cells in mucosal tissue may provide protection against reinfection [39]. In a murine model, mice vaccinated with wP, rather than aP, had a lower risk of pulmonary infection and nasal colonization. Moreover, the degree of protection was associated with increased IL-17-secreting T_{RM} cells [38–40]. Suboptimal stimulation of T_{RM} by aP vaccine may not only contribute to waning immunity but also in failure to eradicate nasal colonization and asymptomatic infection. This may contribute to the ongoing community outbreaks in developed countries where aP vaccine is the sole pertussis vaccine used.

A cohort study in Canada showed a significant waning of immunity in those who received aP vaccine with vaccine effectiveness of 41% (95% CI: 0–66%) after more than 8 years of the last vaccination dose. The decline in effectiveness was slower in those who received at least a single dose of the wP vaccine [41]. For the aforementioned reasons, and despite the fact that waning immunity to pertussis was observed in both types of vaccines, protection against pertussis seems to be better and longer lasting in people vaccinated with wP. Adolescent and older children who received wP in their primary vaccination series were better protected against pertussis than those who received aP only or mixed vaccination [5, 25].

Adolescents

wP vaccines are licensed for children younger than 7 years of age. Due to their safety profile, aP vaccines have offered the possibility of vaccinating older children, adolescents, and adults. Reduced-dose aP vaccines were tested for efficacy in a trial among American adolescents and adults and were found to have a point estimate of the efficacy of 92% (95% CI: 32–99%) [42]. Another study found vaccine efficacy to be around 85% for laboratory-confirmed diseases when the vaccine was given to adolescents and adults [43]. Southern et al. [44] evaluated three formulations of Tdap vaccines and showed that all aP-containing vaccines were immunogenic and safe. The

rate of adverse events did not differ from that of the Td vaccine [44]. Booster aP vaccine to adolescents has become an intervention followed by many countries to combat pertussis outbreaks.

Mixed Vaccination and Interchangeability

Individuals primed with wP and boosted with aP in adolescence had a longer duration of protection than individuals primed and boosted with aP [25, 45, 46]. Trials on vaccine interchangeability during primary series between aP and wP are limited. However, population-level data have shown that individuals who receive mixed aP and wP series have more prolonged and higher vaccine effectiveness than those who received aP vaccine only [41]. According to the WHO, a single dose of wP vaccine is being used as part of aP-based primary series in several countries. For example, the routine immunization schedule in Jordan included wP vaccine at the age of 18 months old, Mexico at the age of 4 years old, at 6 months in Bahrain and the United Arab Emirates (UAE), and at 6 and 18 months in Oman [47]. Also, interchangeability between different vaccine brands, especially with aP, in which other antigens may exist, is unknown [48].

Neonatal Disease

Despite active placental transfer of pertussis-specific IgG (115% of maternal serum), neonatal pertussis-specific IgG was found to be negligible in mothers who do not receive booster vaccine during pregnancy [16]. In the UAE, the current pertussis vaccination program consists of a series of consecutive doses of acellular or wP (as part of a DT combination vaccine) at the age of 2, 4, 6, and 18 months, then, twice in school (first and the eleventh grades). No further doses are routinely given in adulthood. In the year 2018, pertussis-containing vaccine's coverage estimate for the UAE was 99%. Despite that, PT-IgG was undetectable in 75% of pregnant women attending antenatal clinic at the Oasis hospital, Al Ain, UAE. PT-IgG geometric mean did not differ among women of different age groups [49].

Antepartum vaccination aP was found to be safe and effective in preventing early infant morbidity and mortality related to pertussis [50] (Table 2). However, concerns of blunting in infant immunological response after completion of the primary series were raised [51]. However, a similar effect after the primary series with wP was not evaluated. In addition, whether this finding has any clinical impact or not is unknown. Maternal postpartum vaccination has shown to be ineffective in preventing neonatal pertussis (VE 24%, 95% CI: –28 to 55%) [24].

Table 2. Effectiveness of aP vaccination during pregnancy

Study	Vaccine administration	VE for infection, % (95% CI)	VE for hospitalization, % (95% CI)
<i>Case-control</i>			
Skoff et al. [76], 2017	Third trimester	77.7 (48.3–90.4)	90.5 (65.2–97.4)
Dabrera et al. [77], 2015	28–38 weeks of gestation	93 (81–97)	
<i>Retrospective cohort</i>			
Baxter et al. [24], 2017	≥8 days before birth	87.9 (41.4–97.5)	–
Winter et al. [78], 2017	16% first and second trimester 76% during third trimester	72 (49–85)	58 (15–80)
Winter et al. [78], 2017	27–36 weeks of gestation	85 (33–98)	–
Amirthalingam et al. [79], 2014	Third trimester	91 (84–95)	–

Reactogenicity

Compared to wP vaccines, aP vaccines are associated with a significantly reduced frequency of systematic reactions (fever, vomiting, fretfulness, anorexia) and local reactions (swelling, redness, warmth, tenderness). Most notably, the risk of persistent crying, convulsions, and hypotonic-hyporesponsive episodes was significantly lower in those who received aP vaccine [52]. The various efficacy trials in the 1990s and the subsequent postmarketing surveillance, as well as national surveillance systems, such as the Vaccine Adverse Event Reporting System in the USA, have produced a large amount of data confirming reduced reactogenicity of aP vaccines [52].

Despite reduced reactogenicity of aP vaccines, particular concern was raised regarding the observation of gross limb swelling after vaccination, which was not painful, and did not interfere with overall health but troubled parents. A systematic review showed that this type of side effect occurs in 2–6% of children receiving DTaP and resolves without sequelae. In addition, a similar reaction was observed with non-aP-containing vaccines, but at a smaller rate [53]. A recent study showed that only 20% of children who experienced this reaction had a recurrence of limb swelling after subsequent exposure to the aP vaccine [54].

Cost Consideration

Cost-effectiveness and reduction will depend on disease incidence and degree of *Bordetella pertussis* circulation in the community. Comparative analysis and modeling between aP and wP showed that wP is more cost-effective when considering disease prevention alone.

However, aP becomes more cost-effective when vaccine-related healthcare visits are accounted for [55]. Using the Vaccine Utilization Surveillance in Ontario and analyzing data on more than 560,000 children, Hawken et al. [56] estimated that approximately 90 emergency room visits and nine admissions could be avoided per month after switching to aP vaccine [56].

Universal Adolescent and/or Adult Vaccination Strategy

A model simulation performed using USA data showed that at a disease incidence of 360 per 100,000, a one-time adult vaccination strategy would prevent 2.8 million cases with a cost of USD 2.1 billion. This translates to <USD 50,000 per quality-adjusted life-year saved when the disease incidence >120 cases per 100,000 population [57]. In a Canadian simulation model, the use of the aP vaccine in adolescents would prevent 4,400 cases of pertussis and avert 50 hospital admission in the province of Ontario. This was associated with cost-saving of CAD 858,106 over a 10-year period [58]. In another USA modeling study, the use of the aP vaccine was most cost-effective in all adolescents 10–19 years of age, followed by adults with chronic obstructive pulmonary disease and adults ≥50 years of age (this study did not include pregnant women as vaccine group) [59].

Pregnant Women Vaccination Programs

Almost 90–100% of pertussis-related mortality occurs in infants less than 3 months. Antepartum vaccination of pregnant women reduces pertussis-related mortality. This approach was found to be cost-effective based on modeling data from the USA that showed that antepartum maternal vaccination incurred a cost of USD 114,000 per quality-adjusted life-year. However, paternal vaccination, in the same model, was not cost-effective [60].

Future Directions

To improve vaccine efficacy, alternative administration practices and vaccine platform is being evaluated. Simulating natural infection by presenting the vaccine in the intranasal or parental route is one of these approaches. Two studies that evaluated intranasal administration of the wP vaccine in adult volunteers showed high secretory antibody responses [40, 61, 62]. Similarly, oral administration of the wP vaccine to newborn infants was shown to be effective and comparable to vaccination through the intramuscular route [63]. Also, a novel live-attenuated pertussis vaccine, BPZE1, showed in phase 2 trials to be highly immunogenic in adults [64].

Other approaches to improve vaccine effectiveness include the use of outer membrane vesicle vaccine and integration of novel adjuvants for the aP vaccine. Zurita et al. [65, 66] have demonstrated that an outer membrane vesicle-based vaccine was able to induce long-term T_{RM} memory cells as well as protect mice against pertactin-deficient *B. pertussis* isolates. Replacing aluminum adjuvant in aP vaccine may enhance vaccine response and prolong protective immunity [67]. This includes the use of toll-like receptor (TLR) agonist (2, 4, 7, 9) and stimulator of interferon genes (STING) [68]. The use of TLR7 agonist adjuvants in aP vaccine induced similar immune response to wP vaccine in animal models [69]. Similarly, results on the use of novel TLR7/8 agonist (CRX-727; UM-3003) showed enhanced aP vaccine immunogenicity in a mouse model [70].

Conclusion

Pertussis vaccines have changed the epidemiology and global landscape of pertussis-related morbidity and mortality. Both vaccines, wP and aP, are immunogenic and effective in preventing pertussis. However, each of the available vaccines has its advantages and drawbacks. The whole-pertussis vaccine provides longer lasting immunity against pertussis, but it is more reactogenic. The increased risk for adverse events limits its utility in outbreak management and use among adolescents and adults. On the other hand, the adverse event profile of the aP vaccine is favorable, and it is safe to be given to all age groups. However, it is more expensive, and waning immunity has been a concern for ongoing pertussis outbreaks among adolescents and adults. Globally, there is not a single approach used to control pertussis. However, different countries adopted various pertussis immunization practices, including aP vaccine in primary infant series and subsequent boosters in at-risk popu-

lation, or mixed vaccination approach where wP is used for all doses or part of the primary series and aP is used for booster doses. Determining the right vaccination approach will depend on financial consideration, immunization program infrastructure, adverse event monitoring, and pertussis surveillance in the community.

Statement of Ethics

Ethics approval was not required for this review.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Mohammad Alghounaim: conceptualization, literature search, writing original draft, and supervision. Zainab Alsaif: literature search and writing original draft. Abdulla Alfraj, Saadoun Bin-Hasan, and Entesar Hussain: conceptualization, writing, review, and editing. All authors critically reviewed the manuscript.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article.

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