

Pertussis Vaccines: Position Paper of Indian Academy of Pediatrics (IAP)

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Pertussis continues to be a major public health problem in both developing and developed countries. Data on exact burden and incidence of pertussis in the developing countries including India is sparse. However, the disease is widespread, even if not adequately measurable. Pertussis incidence has been increasing steadily in the last decade especially in industrialized countries. Outbreaks are reported from many developed countries in recent years despite widespread use of acellular pertussis vaccines with high coverage.

The current status of coverage with pertussis vaccines is still sub-optimal in many states of the country. There is scarcity of data on vaccine efficacies of both whole-cell and acellular pertussis vaccines from India and other developing countries. Most of the recommendations on pertussis vaccination are based on the experience gained from the use of them in industrialized countries. Taking in to the consideration the recent evidence of faster waning of acellular pertussis vaccines in

comparison to whole-cell vaccines and superior priming with whole-cell than acellular pertussis vaccines, Indian Academy of Pediatrics has now revised its recommendations pertaining to pertussis immunization in office practice. The Academy has now proposed whole-cell pertussis vaccines for the primary series of infant vaccination. Guidelines are also now issued on the preference of a particular acellular product. The Academy has also recommended use of Tdap during each pregnancy to provide protection to the very young infants. It urges the Government of India to initiate studies on the quality of available pertussis vaccines in India and to set indigenous national guidelines for the manufacturers to produce and market different pertussis vaccines in the country.

Keywords: *Pertussis, Whole cell pertussis vaccines, Acellular pertussis vaccines, Indian Academy of Pediatrics, Recommendations.*

The global incidence of pertussis declined to very low level with the advent of whole-cell pertussis (wP) vaccines by the 1970s. However, in the 1990s, safety concerns prompted a switch from wP to acellular-pertussis (aP) vaccines in most of the developed countries. Since 2009, large outbreaks of pertussis are regularly reported from many industrialized countries employing aP vaccines despite having very high vaccination coverage [1-10]. Outbreaks have also been reported from countries using wP vaccines like the one reported recently from Khairpur District of Sindh province of Pakistan [11]. However, another study from Pakistan conducted between 2005 and 2009 found that *B. parapertussis* was responsible for the pertussis outbreak against which the wP vaccines had shown little efficacy [12].

REASONS FOR RESURGENCE

There are multiple factors responsible for the recent resurgence of pertussis in industrialized countries. They include enhanced awareness, increased public health reporting, introduction of more sensitive tools like polymerase chain reaction (PCR) for diagnosing infection, suboptimal efficacy of aP vaccines, and the potential antigenic drift in circulating pertussis strains [8, 13-15]. But the major concern is the lower efficacy of

aP vaccines than wP vaccines [8,15]. Many reasons for apparent decreased efficacy of aP have been proposed, including observer bias in initial trials, reduced antigenic stimulation in aP, and mutation of *Bordetella pertussis* [15]. Antigenic shifts in circulating *Bordetella pertussis* strains [16] or the different immune responses from acellular and whole-cell priming [17] have also been proposed as probable reasons. Another hypothesis states that the lesser protection provided by aP may be due to linked epitope suppression when the initial exposure locks in the immune response to certain epitopes and inhibits response to other linked epitopes on subsequent exposures [18].

DURATION OF PROTECTION

Waning of protective immunity is noted with both wP and aP vaccines [19], and also after acquisition of immunity after natural infection. According to studies that provide the longest period of evaluation, the protection accorded by wP vaccines wanes by 50% over a period of 6-12 years [20-22]. Whereas little is known about the duration of protection following aP vaccination in developing countries, many studies in industrialized world documented faster waning with aP vaccines and showed that protection waned after 4-12 years [25-28]. A recent case-control study investigated

Kaiser Permanente Northern California outbreak in US and concluded that protection after aP (DTaP) vaccine waned substantially after administration of the 5th dose, and the odds of acquiring pertussis increased by an average of 42% per year after the fifth dose of DTaP [26]. The researchers found a lower incidence of PCR confirmed pertussis in children aged 12-15 years who had received wP vaccine as infant than in 8-11 years who had received all 5-doses of aP vaccine in their primary immunization series [26]. Similar conclusions were reached by another set of researches from North America [28]. They found vaccine effectiveness of aP vaccines as 41%, 24%, and 79% for children aged 2-7 years, 8-12 years, 13-18 years, respectively and concluded that the current schedule of aP vaccine was insufficient to prevent outbreaks of pertussis [28]. Misegades *et al.* studied the California outbreak in 15 counties and noticed progressive incremental decline in estimated vaccine effectiveness each year after the final dose of aP vaccine [29].

CHOICE OF VACCINES: WHOLE CELL VERSUS ACELLULAR PERTUSSIS VACCINES

Several randomized trials (*Web Table 1*) conducted in the 1990s compared the efficacy of aP vaccines with wP vaccines. At least five trials found that wP vaccines had greater efficacy than aP vaccines [7]. Many later trials have also hinted that the efficacy of the aP vaccine may not be as robust as reported in the initial studies [30-32]. Studies after the recent outbreaks in US, UK and Australia have now concluded that the change from wP to aP vaccines contributed to the increase in pertussis cases [33-35]. Recent data from US and Australia have suggested reduced durability of vaccine-induced immunity after the aP vaccination in comparison to wP vaccines [28, 29]. World over, the experts now believe that aP vaccines may be less effective than previously believed when contrasted with wP vaccines [30, 33, 34].

Witt *et al.* [33] studied 263, 496 persons in age group of 8-20 years in US province of Kaiser Permanente (KP) and concluded that a vaccination schedule that contained all aP vaccine series was significantly less effective and durable than one that contained the traditional wP vaccine. There was a markedly increased risk of disease with the use of former. Addition of a 6th dose of pertussis vaccine (Tdap) though mitigated, but not completely eliminated this risk. They found receipt of 1 or more wP doses markedly augmented the durability of immunity from subsequent aP doses [33]. The superior priming with wP vaccines in comparison to aP vaccine was also confirmed by two different studies from Australia [34] and US [35]. Sheridan and

colleagues in Australia have found a 3-fold higher rate of pertussis in the aP recipients 10 years after primary vaccination during both pre-epidemic and outbreak periods [34]. Another study conducted by Liko *et al.* [35] among children born during the 1997-1999 transition periods (from wP to aP) in Oregon state of US documented significantly higher rates of the disease in those who underwent priming with aP rather than wP vaccine. These findings suggest that priming with wP is more effective at sustained prevention of pertussis disease than aP vaccines.

Hence, the current evidence is tilted heavily in favor of wP vaccines as far as effectiveness of the pertussis vaccines is concerned. However, the industrialized world would not take the risk of reverting to wP vaccines considering the low acceptance of these vaccines by the public in the past. Few middle income group countries sitting on the fence and on the verge of shifting to acellular products would like to wait further till a better alternative is available.

PREFERENCE OF A PARTICULAR ACELLULAR VACCINE PRODUCT

There is no consensus so far on the antigenic composition of an ideal aP vaccine [36-38]. Currently available aP vaccines in India include 5-component vaccines, 3-component vaccines, and a 2-component combination vaccine [37] (*Table 1*). The exact contribution of the different aP antigens in according protection is not clear. The currently available aP vaccines should be regarded as different and unique products because of the presence of different components in different concentrations, and with different degree of adsorption to different adjuvants, individual antigens derived from different strains of *B. pertussis*, and purified by different methods [39]. This heterogeneity in production of different aP vaccines explains why direct comparison of protective efficacy of different aP vaccines in human is not possible.

Nevertheless, different researches have studied the impact of number of components in an aP vaccine on relative protective efficacy of different aP products. In a recent retrospective study in US following a huge outbreak of pertussis in California [29], the researchers found that 5-component aP vaccine had an estimated efficacy of 88.7% (95% CI, 79.4%-93.8%) [29]. According to a systematic review involving 49 RCTs [40], aP vaccines containing 3 or more components had much higher absolute efficacy (80-84%) than those containing only 1 and 2 components (67-70%). A Cochrane review by Zhang *et al.* [41] of 6 aP vaccine efficacy trials and 52 safety trials concluded that the

TABLE I COMPOSITION OF AVAILABLE ACELLULAR PERTUSSIS VACCINES (IN COMBINATION) BRANDS IN INDIA

<i>Product</i>	<i>Infanrix</i>	<i>Tripacel</i>	<i>Pentaxim*</i>	<i>Adacel**</i>	<i>Boostrix**</i>
Tetanus Toxoid	5 Lf	5 Lf	5 Lf	5 Lf	5 Lf
Diphtheria Toxoid	15 Lf	15 Lf	15 Lf	2 Lf	2.5 Lf
<i>Acellular Pertussis:</i>					
Pertussis Toxoid (PT)	25 µg	10 µg	25 µg	2.5 µg	8 µg
Filamentous Haemagglutinin (FHA)	25 µg	5 µg	25 µg	5 µg	8 µg
Pertactin (PRN)	8 µg	3 µg	---	3 µg	2.5 µg
Fimbriae Types 2 and 3 (FIM)	---	5 µg	---	5 µg	---

*A combination of acellular pertussis, IPV and Hib vaccines; **Tdap vaccines.

efficacy of multi-component (≥ 3) aP vaccines varied from 84% to 85% in preventing ‘typical whooping cough’ and from 71% to 78% in preventing mild disease. In contrast, the efficacy of one- and two-component vaccines varied from 59% to 75% against ‘typical whooping cough’ and from 13% to 54% against mild disease [41].

Though few countries have demonstrated high levels of effectiveness of mono- and bi-component aP products in preventing pertussis by employing them in their immunization programs [36], the available evidence favors multi-component (≥ 3) aP vaccines over mono- or bi-component aP vaccines.

VACCINATION OF ADOLESCENTS AND ADULTS

Pertussis in adolescents and adults is responsible for considerable morbidity in these age groups and also serves as a reservoir for disease transmission to unvaccinated/partially vaccinated young infants [37]. Several developed countries have instituted routine booster immunization of adolescents and adults with standard quantity tetanus toxoid and reduced quantity diphtheria and aP vaccine (Tdap) instead of Td in their national immunization programs [36]. The IAP has also recommended only a single one-time dose of Tdap to adolescents aged 10-12 years of age [37]. The US Advisory Committee on Immunization Practices (ACIP) recommended routine administration of Tdap booster for adolescents in 2005, the vaccine coverage still remains low, with only 56% of adolescents and 8.2% of adults vaccinated in 2012 [42]. There is no data on the coverage of Tdap in adolescents and adults in India since it is being used exclusively in private health sector.

Objectives and rationale of adolescents and adult pertussis vaccination: There are two main objectives—first, to protect vaccinated persons against pertussis, and second, to reduce the reservoir of pertussis in the population at large and thereby potentially decrease

exposure of persons at increased risk for complicated infection (e.g., infants). However, adequate evidence is lacking to support the recommendation of adding booster doses in these age groups in order to achieve the primary goal of reducing severe pertussis in infants [36]. Repeat doses of Tdap at 5 or 10 years interval in adolescents and adults have also failed to confer lifelong protection.

Efficacy and effectiveness of Tdap: Wei, *et al.* [32] evaluated effectiveness of Tdap booster among adolescents in the Virgin Islands in 2007, and found effectiveness of 61.3% (95% CI: 52.5–90.2) and 68.3% (95% CI: -126.4–95.6) against probable and laboratory-confirmed pertussis, respectively [32]. However, a recently conducted unpublished trial reported that Tdap was modestly effective [vaccine effectiveness: 55.2% (95% CI 44.1-64.1%)] at preventing PCR-confirmed pertussis among Kaiser Permanente Northern California (KPNC) adolescents and adults. According to a summary presented at ACIP February 2013 meeting, the Tdap effectiveness was noticed ranging from 66 % to 78% in field observational studies. The preliminary data suggest effectiveness wanes within 3-4 years among aP vaccine recipients and there was no evidence of herd immunity.

MATERNAL IMMUNIZATION-A PROMISING STRATEGY TO PREVENT INFANT PERTUSSIS

In 2006, the ACIP recommended a dose of Tdap to pregnant women immediately postpartum and all other close contacts of infants aged <12 months to reduce the risk for transmission of pertussis to infants [43]. However, immunization of adolescents and adults, and postpartum administration of Tdap failed to have appreciable impact on laboratory-confirmed pertussis in very young infants [36,44]. Several strategies like maternal immunization including pregnant women, cocooning, neonatal immunization, have been proposed

to reduce the burden of pertussis in those infants too young to have been immunized. Amongst all these strategies, immunization during pregnancy appears to be most effective strategy to have the most impact on infantile pertussis, especially during the first few weeks after birth [45]. The effective transplacental transmission of maternal pertussis antibodies would protect the infant against pertussis during the first months of life. Though the transplacentally acquired antibodies may be detectable at least up to first few weeks of life (at 6–8 weeks), the age at which the first pertussis-containing vaccine is due, the concentration of antibodies required for protection against pertussis in newborns is not known [46]. In 2011, the ACIP recommended a dose of Tdap to all pregnant women after 20 weeks gestation to provide protection for both the mother and her newborn during the infant's earliest weeks of life [47].

IMMUNIZATION OF PREGNANT WOMEN

There are few concerns that need to be addressed before this practice becomes universal.

Titers and duration of the maternal antibodies: According to CDC, 80–100% of women immunized with wP vaccine during pregnancy had considerable increases in agglutinin antibodies [46]. Limited data suggest that aP vaccine given to pregnant women will result in significantly increased antibody concentrations in newborns, but the duration of the maternal antibodies and the potential requirement for booster doses with subsequent pregnancies has not been sufficiently explored [36]. However, according to a recent report [48] the newborns born to mothers who received Tdap during pregnancy had significantly higher antibody titers to diphtheria toxin ($P < 0.001$), tetanus toxin ($P = 0.004$), PT ($P < 0.001$), FHA ($P = .0002$), PRN ($P < 0.0001$) and fimbriae type 2/3 ($P < 0.001$) when compared with newborns born to unimmunized mothers [48]. ACIP has now recommended Tdap vaccination in every pregnancy [47].

Decreased immune response of primary series of pertussis vaccines: There is a concern that high concentrations of maternal antibodies may interfere with proper take of pertussis vaccines during primary immunization [36]. Earlier studies have demonstrated that infant immune responses to aP vaccines were not affected by preexisting antibodies against PT, but interference was seen with the wP vaccine [49,50]. A recent study by Hardy-Fairbanks *et al.* [51] demonstrated that infants whose mothers had received Tdap vaccine during pregnancy had higher pertussis antibody concentrations between birth and the first vaccine dose

than the cohort whose mothers did not receive the vaccine. After primary series of aP vaccines, the antibody concentrations to pertussis antigens were lower in the Tdap group (0.7- to 0.8-fold lower), except for fimbriae types 2 and 3 (1.5-fold greater). However, the antibody concentrations to pertussis antigens before and after booster dose were comparable. The researchers concluded that though after the primary pertussis vaccine series, there was some blunting of the response to the infant series, children did develop adequate antibodies by the end of the series [51]. The results of this study is quite reassuring and adds evidence to support the practice of vaccinating pregnant mothers to protect their children against pertussis, however, more studies with larger sample size are needed. Nevertheless, vaccination of pregnant women has a good likelihood of preventing pertussis in very young infants, without the risk of just increasing it at a later age. So, the strategy of vaccinating pregnant women may be effective.

Safety of Tdap during pregnancy: Although there are limited safety data on Tdap administration in pregnant women, the existing Tdap safety data from the CDC, US FDA and the pharmaceutical pregnancy registries do not indicate any adverse safety effect [48]. In the past, even 3-6 doses of wP vaccines were administered during single pregnancy in 5 different clinical trials conducted in US and no serious untoward local or systemic reactions were noted. There was no adverse pregnancy outcome [46].

OTHER STRATEGIES TO PREVENT INFANT PERTUSSIS

'Cocooning': 'Cocooning' and neonatal immunization are the two other notable strategies to prevent pertussis in very young infants. Though there is no conclusive evidence in favor of cocooning strategy, the available data indicate that a decreased risk of infection in newborns can be achieved with the immunization of all family members who could have a strict contact with a newborn. Cost and logistical barriers to widespread implementation of this strategy appear to be major limitations [52].

Neonatal immunization: Neonatal vaccination seems to be an attractive strategy for protecting neonates and young infants, but the vaccine administered at birth would need to be only acellular vaccine and not the combination DTaP. There is concern that administration of aP vaccine at birth could lead to the generation of an excessive Th2 immune response with a decreased Th1 response [53]. Further, it was observed that, the newborn dose of aP (as DTaP) had suppressing effect on the immune responses to subsequent doses of DTaP and other co-administered vaccines [54, 55].

CURRENT STATUS OF PERTUSSIS VACCINATION AND DISEASE EPIDEMIOLOGY IN INDIA

Pertussis continues to be a serious public health problem in India. There is passive reporting of whooping cough cases from the public sector, the data is maintained by the Government of India and also shared with WHO. In India, the incidence of pertussis declined sharply after launch of Universal of Immunization Program (UIP). Prior to UIP, India reported 200,932 cases and 106 deaths in the year 1970 with a mortality rate of <0.001%. During the year 1987, the reported incidence was about 163,000 cases which came down to 40, 508 in 2010 and 39, 091 in 2011 reflecting a decline of about 75% [56]. Andhra Pradesh, Madhya Pradesh, Jharkhand, West Bengal, and Bihar reported the maximum cases in 2010. In 2010 only 6 and in 2011 a total of 11 deaths were reported [56]. However, the reliability and quality of the data is questionable. A large number of cases go unreported, and many non-pertussis cases are reported and clubbed under the head of 'whooping cough' cases. Hence, the available figures lack specificity. The actual number may be high considering that the coverage with three doses of DTP vaccine in infancy was 71.5% and only 41.4% children in the age group of 18-23 months had received first DTP booster [57]. The data on pertussis disease and infection in adolescents and adults is sorely lacking. Further, there is no data on *Bordetella pertussis* infection rates in the community.

India is employing only wP vaccines in their national immunization program since the adoption of Expanded Program of Immunization (EPI) in 1978. Though aP vaccines are also licensed and available, they are mainly prescribed by the private sector and coverage is still miniscule. Private health sector is responsible for offering vaccination to only 9% of the population in India (57). According to most recent estimates, the national coverage of 3 doses of DPT is 71.3% amongst children aged 12-23 months whereas first booster immunization of DTP is only 41.4 % amongst 18-23 months old children [57]. Surprisingly, despite low coverage figures, there is poor documentation of large scale outbreaks of pertussis in the country unlike the recent large scale outbreaks reported in many developed countries [1-7]. Either many large scale outbreaks are totally ignored and go unreported or wP vaccines are providing adequate protection. There are two scenarios of pertussis epidemiology in a given population based on coverage of pertussis vaccine. Since the overall coverage is not very high, pertussis in major parts of the country continues mainly to be a problem of young children. However, many states having very good immunization rates behave like developed countries

with high coverage in pediatric age group with resultant more frequent disease in adolescents and adults.

Regarding the safety of wP vaccines, there is still no report of higher rates of serious adverse effects of following immunization (AEFIs), and public acceptance of the vaccine is still not a serious concern. The resistance amongst the community and adverse publicity of the wP vaccines, were the main reasons why developed countries discontinued vaccination with wP vaccines and switched to more safer aP vaccines. These are the reasons why they will not be reverting to older product in future also despite the reports of poor performance of aP vaccines.

IAP POSITION ON PERTUSSIS VACCINATION

Recommendations for public health: IAP believes that pertussis is a highly prevalent pediatric illness having significant morbidity and mortality in the country. Though reliable data on exact burden and incidence of pertussis in the country are scarce, and laboratory confirmation is not readily available, pertussis is widespread. Immune protection, both natural and vaccine-induced, is not long lasting. All the available figures are based on rough estimates of pertussis-like illnesses. There is an urgent need of an effective surveillance to evaluate both the burden of infection and the impact of immunization. The Academy unambiguously supports the current immunization policy of employing only wP vaccines (in form of DTwP) in UIP because of its proven efficacy, safety, adequate public acceptance, and absence of documentation of significant waning.

Recommendations for individual use: Since there is scarcity of data on vaccine efficacies of both wP and aP vaccines in India and other developing countries, most of the recommendations of the academy in regard to pertussis vaccination are based on the experience gained and data obtained from the use of these vaccines in industrialized countries. However, the continuous decline in reported pertussis cases in last few decades has demonstrated good effectiveness of wP vaccine (of whatever quality) in India. There is no data on the effectiveness of aP vaccines in India.

Primary immunization: The primary infant series should ideally be completed with 3 doses of wP vaccines. Vaccination must start at 6 weeks. Acellular pertussis (aP) vaccines should be avoided for the primary series of infant vaccination. The aP vaccine combinations should also be avoided for the primary series. However, the aP vaccines may be preferred to wP vaccines in children with history of severe adverse effects after previous

dose/s of wP vaccines or children with neurologic disorders, if resources permit. The parents should be counseled about the probable efficacy related disadvantages of using aP vaccines for the primary series. The schedule is same as with wP (DTwP) vaccines. Like DTwP vaccines, DTaP vaccines must not be used in children 7 years or older because of increased reactogenicity. The contraindications are the same for both the vaccines.

There is no data on either the efficacy/effectiveness of individual wP product or comparative evaluation of different available wP combinations in the Indian market. Few brands in India have achieved WHO prequalification, but not all the products have uniformly attained it. IAP urges the government of India to undertake studies on the quality of available wP and aP vaccines in Indian market. The national regulatory authority (NRA) must set indigenous national guidelines to manufacture and market different pertussis vaccines in the country.

The recommendation on the use of wP vaccine in primary immunization series is based on the experience with wP vaccines in India and on demonstration of faster waning with aP vaccines in comparison to wP vaccines and superior priming with wP vaccines than aP vaccines in studies conducted in the industrialized countries after recent resurgence of pertussis in many of these countries using aP vaccines.

Boosters: The 1st and 2nd booster doses of pertussis vaccines should also be of wP vaccine. However, considering a higher reactogenicity, aP vaccine/combination can be considered for the boosters, if resources permit.

Choice of aP vaccines: Considering the strong evidence in favor of superiority of multi-component (≥ 3) aP vaccines in comparison to one- and two-component aP vaccines from recent systematic reviews and meta-analysis, IAP now recommends that if any aP containing vaccine is used, it must at least have 3 or more components, the more the better.

Administration and schedule: The standard dose of pertussis vaccine is 0.5 mL; this is administered intramuscularly in the anterolateral thigh of children aged <12 months and in the deltoid muscle in older age groups. The standard primary vaccination schedule is three primary doses at 6, 10 and 14 weeks and two boosters at 15-18 months and 5 years. Early completion of primary immunization is desirable as there is no effective maternal antibody for protection against pertussis. The booster should be given ³6 months after

the last primary dose. The last dose of the recommended primary series should be completed by the age of ≥ 6 months. All infants, including those who are HIV-positive, should be immunized against pertussis.

Schedule for catch up vaccination: Three doses at 0, 1 and 6 months interval should be offered. The 2nd childhood booster is not required if the last dose has been given beyond the age of 4 years. It is essential to immunize even those recovering from pertussis as natural disease does not offer complete protection.

Recommendations for adolescents and adults: Immunity against pertussis following primary/ booster wP/aP vaccination wanes over the next 4-12 years. The Academy therefore recommends offering Tdap vaccine instead of Td/TT vaccine to all children/adolescents/adults who can afford to use the vaccine in the schedule discussed below:

- In those children who have received all three primary and the two booster doses of DTwP/DTaP, Tdap should be administered as a single dose at the age of 10-12 years.
- Catch up vaccination is recommended till the age of 18 years.
- Persons aged 7 through 10 years who are not fully immunized with the childhood DTwP/DTaP vaccine series, should receive Tdap vaccine as the first dose in the catch-up series; if additional doses are needed, Td vaccine should be used. For these children, an adolescent Tdap vaccine is not required.
- A single dose of Tdap may also be used as replacement for Td/TT booster in adults of any age if they have not received Tdap in the past.
- Tdap can now be given regardless of time elapsed since the last vaccine containing tetanus toxoid or diphtheria toxoid.
- There is no data at present to support repeat doses of Tdap.
- IAP recommends decennial Td booster for those who have received one dose of Tdap (5 years for wound management).

Only aP-containing vaccines should be used for vaccination in aged more than 7 years.

Tdap during pregnancy: Maternal immunization, particularly of pregnant women may be an effective approach to protect very young infants and neonates. IAP therefore now suggests immunization of pregnant women with a single dose of Tdap during the third

trimester (preferred during 27 through 36 weeks gestation) regardless of number of years from prior Td or Tdap vaccination. Tdap has to be repeated in every pregnancy irrespective of the status of previous immunization (with Tdap). Even if an adolescent girl who had received Tdap one year prior to becoming pregnant will have to take it since there is rapid waning of immunity following pertussis immunization.

Interchangeability of brands: In principle, the same type of wP-containing or aP-containing vaccines should be given throughout the primary course of vaccination. However, if the previous type of vaccine is unknown or unavailable, any wP vaccine or aP vaccine may be used for subsequent doses.

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