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Use of Tetanus-diphtheria (Td) vaccine in Children 4–7 years of Age: World Health Organization Consultation of Experts

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Abstract

For lifetime protection against diphtheria and tetanus, the World Health Organization (WHO) recommends six doses of diphtheria and tetanus containing vaccines. Td (reduced diphtheria toxoid, ≥2–5 IU) vaccines are currently licensed for ages 7 years and older, but use of Td vaccine for ages 4 years and older would have advantages for immunization programs in many low- and middle-income countries. For this reason, WHO convened an expert consultation to review the currently available evidence for the use of Td vaccine from 4–7 years of age which concluded: (1) no relevant biological difference in immune response in the relevant age group compared with children over 7 years of age; (2) adequate seroprotection in several studies with Td vaccine in the 4–7 age group and many studies using combination vaccines; (3) durable and protective response of at least 9–11 years duration in several longitudinal and modelling studies, (4) less reactogenicity compared with use of full-dose diphtheria vaccine, potentially improving the vaccination experience; and (5) adequate control of diphtheria in several countries using Td-containing combination vaccines in 4–7 year old children. On this basis, the experts concluded that from a

[1]Some higher income countries use a spaced '2+1' DTCV immunization schedule with the first two doses separated by 2 months and the third booster dose provided around the first birthday. A '3+1' schedule is more common and includes delivery of three doses, usually separated by 4 weeks and completed within the first 6 months of life, and a booster dose in the second year of life. Both schedules provide robust immunity, although the latter is optimal for the epidemiological and programmatic context of low and middle-income countries [14, 15].

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programmatic perspective, Td vaccine given in ages 4–7 years, as a second booster dose in a six-dose series, would provide adequate protection against diphtheria and tetanus and recommended steps to include this age extension in the package insert.

Keywords

Diphtheria; Tetanus; vaccine; boosters; childhood; life-course

1. Background

In its most recent position papers on Diphtheria Vaccine (2017) and Tetanus Vaccine (2017), the World Health Organization (WHO) recommends six doses of diphtheria and tetanus containing vaccines (DTCV) for optimal lifetime protection against diphtheria and tetanus, including a primary series of three doses to be completed by 6 months of age and three booster doses given at: 12–23 months of age; 4–7 years of age; and 9–15 years of age. Ideally, an interval of at least 4 years between booster doses should be maintained [1, 2]. WHO recommended that as the second booster dose after the primary series, tetanus-diphtheria (Td) vaccine with reduced diphtheria toxoid (≥2–5 IU) may be used and is preferred for children aged 4 years and older because it has programmatic advantages such as simplified health worker training, allowing for fewer products in the cold chain and lower vaccine wastage [1, 3].

Worldwide, only 136 (70%) of 194 countries provide one or more DTCV booster doses during childhood [4]. As member states move towards achieving and sustaining Maternal and Neonatal Tetanus Elimination, issues around the need for booster doses and broader tetanus and diphtheria control have been raised [1, 2, 5]. Recent clusters of tetanus cases associated with the voluntary medical male circumcision program in Africa and diphtheria outbreaks occurring worldwide have highlighted the necessity to switch from tetanus toxoid (TT) to DTCVs and to protect all persons across the life course through provision of booster doses [1, 2, 5, 6]. Thus, Gavi the Vaccine Alliance will be supporting introduction of tetanus-diphtheria-pertussis containing vaccine (DTPCV) booster doses in low-income countries starting in 2021 [7].

Most Td combination vaccines, e.g., with acellular pertussis (aP) and/or inactivated poliovirus vaccine (IPV), have been licensed for ages ≥3, ≥4, or ≥5 years. However, currently available Td vaccines (e.g. products not in combination with other antigens) are only licensed for use in individuals over 7 years of age. Thus, the current WHO programmatic advice to use Td vaccine in ages ≥4 years is, in effect, an off-label recommendation [8]. To support this recommendation and with the aim of exploring what would be necessary to have this younger age group indication included in the summary of product characteristics and the package insert, WHO convened a consultation to review the available evidence on immunogenicity and safety of Td vaccine use in 4–7 year old children.

2. WHO Consultation of Experts

A Consultation of Experts on the "Use of Td vaccine in Children 4–7 years of Age" was convened in Menthon St. Bernard, France from 6–7 May 2019. Participants included subject matter experts in diphtheria, immunology, tetanus, vaccine regulation, and representatives of public health agencies (see list of participants at the end of the article). All manufacturers of WHO-prequalified Td vaccine products for children (5 manufacturers) were invited to participate, and representatives from three vaccine manufacturers participated in the first day of the two-day consultation.

The purpose of the consultation was to review the currently available evidence on the use of Td vaccine in children aged 4–7 years and to determine what additional data could be generated to support a change to the indication for the market authorization. WHO conducted a literature search and compiled relevant evidence in advance of the consultation for the experts to review. Notably, reviews of published and unpublished evidence on the use of Td containing vaccines for booster doses in preschool age conducted by public health agencies of several countries were considered [9–11]. This report provides a summary overview of the currently available evidence and the experts' assessment of the data.

3. No relevant changes in maturity of the immune system between 4 and 7 years of age

Major changes and maturation of the immune system are known to occur rapidly in the first year of life. Through exposure to multiple antigens through early childhood, a specific antibody repertoire is generated and immunological memory is established. Between the ages of 4 and 7 years, the number and function of immune cells appear to be similar, with only minor differences in quantity and intrinsic function such as the response to polysaccharide antigens, but not protein antigens like diphtheria and tetanus toxoids [12, 13]. For toxin-mediated diseases such as diphtheria and tetanus, protective levels of toxin-neutralizing antibodies must be present at, or shortly after, exposure to prevent clinical disease, sequalae, and death (Box 1) [14, 15]. Available vaccine studies, across multiple antigens, suggest only minor differences in antibody response and persistence among vaccine recipients between 4 and 7 years of age compared with those older than 7 years [16, 17]. This trend is observed with combination vaccines that include tetanus and low dose diphtheria antigens as well as other combination vaccines.

Use of Td vaccines containing low dose diphtheria toxoid (≥2–5 IU) are often preferred to full dose (≥30 IU) DT containing vaccines in children aged ≥7 years, adolescents, and adults, in order to reduce the high rates of local and systemic adverse effects related to diphtheria booster vaccination in these age groups [14, 15]. Many studies have shown appropriate immune responses with the use of low dose diphtheria vaccine in these populations [14, 15]. Since immunological maturity and response to vaccines are similar in children 4–7 years compared to children over 7 years of age, the use of Td vaccine, from an immunological perspective can be supported in children 4–7 years of age.

4. Evidence base for immunogenicity of Td vaccines among children aged 4–7 years is limited, but supportive

For children aged 4–7 years who have received a three-dose DTCV primary series and a booster dose in the second year of life, there is one randomized controlled trial which assessed the immunogenicity of Td versus DT [18]. This study included children 6 years of age and showed similar seroprotection rates when Td was compared directly to DT as a booster dose. Two other studies demonstrated that Td vaccine provided a sufficient boost to diphtheria immunity in children aged 4–6 years and 6–9 years, respectively, but did not do a head-to-head comparison with DT [19, 20].

Data from 14 studies of combination vaccines using low-dose diphtheria antigen in combination with inactivated poliovirus (IPV) or combinations of acellular (aP) or whole-cell pertussis (wP) antigen were also reviewed. Since wP vaccine has been shown in some instances to elicit a greater immune response than aP vaccine [21, 22], studies of Td-containing vaccines among children 4–7 years were reviewed separately based on the type of pertussis containing vaccine (aP or wP) used for the primary series (Table 1). Despite differences in the study design and laboratory methods used, all of the studies reviewed showed sufficient seroprotection following a second booster dose (fifth dose) with a low dose diphtheria containing vaccine in children aged 4 to 7 years, irrespective of which pertussis vaccine was used in the primary series (Table 1 and Box 1). Interestingly, some studies even showed similar seroprotection rates when low-dose diphtheria antigen was given as the fourth dose (i.e., after a 2+1 primary schedule) of diphtheria containing vaccine, rather than the fifth dose (i.e., after a 3+1 primary schedule) as recommended by WHO (Table 1).[1]

Up to a 2-fold higher geometric mean antibody titre was observed one month after vaccination between those who received full-dose versus low-dose diphtheria vaccine (Table 1). Since higher anti-diphtheria antibody titres above a threshold value of 0.1 IU/ml correlate with a more robust and durable protection against disease (Box 1), it was important to consider what impact, if any, this higher titre would have on the duration of immunity from vaccination with low-dose versus full-dose diphtheria vaccine.

5. Duration of protection declines over time but seroprotection is maintained until the next booster dose

Antibody titres following diphtheria booster vaccination sharply decline during the subsequent year, followed by a more gradual linear decline of the titres over time [14, 15]. As a result, 5 years after the booster dose, several longitudinal studies have demonstrated no significant difference in antibody titres between low (Td) and full dose (DT) diphtheria vaccine recipients [23–25]. Furthermore, mathematical modeling studies using these results

[1]Some higher income countries use a spaced ‘2+1’ DTCV immunization schedule with the first two doses separated by 2 months and the third booster dose provided around the first birthday. A ‘3+1’ schedule is more common and includes delivery of three doses, usually separated by 4 weeks and completed within the first 6 months of life, and a booster dose in the second year of life. Both schedules provide robust immunity, although the latter is optimal for the epidemiological and programmatic context of low and middle-income countries [14, 15].

have estimated very little decline in antibodies between 5 and 10 years post-vaccination, regardless of booster dose formulation [26, 27]. The majority of recipients (as per modelled estimates) had seroprotective levels of antibody 9 and 10 years after the booster dose, with no major differences observed between vaccine groups [26, 27]. The model estimates for one study were extended to 11 years (i.e., one additional year, to simulate the case of a child receiving low dose diphtheria containing vaccine at 4 years of age, followed by a booster dose at 15 years of age) and similar results were observed (M. Voysey, personal communication) [27]. Therefore, evidence from longitudinal studies as well as modeled estimates suggest a durable response even when low-dose diphtheria vaccine is used as a second booster dose of diphtheria vaccine in children 4 to 7 years, similar to immunological studies in adolescents and adults that have demonstrated adequate seroprotection 10 years after Tdap booster vaccination [28, 29].

6. Low-dose diphtheria containing vaccines are less reactogenic

The original recommendation to use low-dose diphtheria antigen preferentially in children over 7 years was based upon a more favorable reactogenicity profile of this vaccine [14, 15]. Among the studies that compared reactogenicity between a low-dose and a full-dose diphtheria containing vaccine given as a booster dose in children ages 4–7 years, most demonstrated fewer injection site reactions in the low-dose diphtheria group (Table 1, see table footnote 3). Fewer injection site reactions improves the overall experience of immunization and enhances trust in vaccines. A few observational studies have noted decreased numbers and rates of spontaneously reported adverse events following immunization (AEFI) after a change to low dose diphtheria containing products [30, 31].

7. Experience in several countries indicates adequate population immunity and control of diphtheria when using Td vaccines as a booster in children 4–7 years of age

Many countries already provide Td-containing combination vaccines to children aged 4–7 years as part of their national immunization schedules, including Canada [32], Chile [33], Denmark [34],[2] Iceland [35], Ireland [36], Israel [37], Germany [38], Luxembourg [39], Netherlands [40], and South Africa [41]. In the U.K., both TdaP-IPV and DTaP-IPV have been deemed suitable for the preschool booster vaccination starting from 3 years and 4 months of age, regardless of the vaccine used for primary vaccination [42]. In Italy, a low-dose diphtheria booster vaccine (Tdap) is included for children aged 5–6 years in several regions, with a note in the national schedule recommending high vaccination coverage for the adolescent dose [10, 43].

Given that multiple national immunization programmes provide Td-containing combination vaccines to children aged 4–7 years and have been successful in controlling diphtheria, there is some empirical data to suggest that a low-dose vaccine would provide adequate protection

[2]Denmark has announced plans to change from low-dose diphtheria (DiTeKiPol-booster produced locally) to a full-dose booster (Tetravac) at age 5 years in 2019 under a new vaccine tender agreement with Sanofi Pasteur: https://en.ssi.dk/news/news/2019/new-vaccine-formulation-in-the-childhood-vaccination-programme.

as a second booster dose. Serosurveys available from several countries providing Td-containing vaccines at preschool/school entry, including Israel, Netherlands, and other in countries in Western Europe, have shown adequate population immunity and the effect of an immunity boost in this age group [44–46]. No substantial differences were noted in comparisons with countries providing a full-dose diphtheria booster dose at school entry, and all countries have had dramatic reductions in their reported number of diphtheria cases as a result of their immunization programmes [44].

During a period of limited global vaccine supply in 2015–2016 [47], the German regulatory authority conducted a review of published and unpublished data that supported the revision of the age indication for specific Tdap-IPV products to permit their use starting from 3 years of age [11]. In Germany, Tdap vaccines are used for booster vaccination (at ages 5–6 and 9–14 years and in adults) following a 3+1 primary immunization series. In Sweden and Norway, the public health agencies jointly conducted a rapid review to examine whether Tdap-IPV vaccines might replace the full-dose DTaP-IPV booster in children aged 4–8 years. Their national immunization schedules consist of 2+1 primary series, followed by a booster dose at 4–8 years of age (fourth dose). In the context of a 2+1 primary immunization series, these Nordic countries concluded that while there was some evidence to support the use of some of the Tdap-IPV products in ages 4–7 years, it was not considered sufficient to shift to programmatic use of the vaccine type as a fourth dose of diphtheria antigen [9]. This is in contrast to the WHO-recommended schedule for diphtheria containing vaccine, which consists of three-dose primary series followed by a booster dose in the second year of life (3+1) and another booster dose at ages 4–7 years (fifth dose) of diphtheria containing vaccine, for which the low-dose antigen is proposed. [1]

In the 1990s, a diphtheria epidemic emerged in the Russian Federation and spread to all of the former states of the U.S.S.R. By 1994, due to susceptibility in older ages and vaccine hesitancy issues that resulted in low coverage of infants with diphtheria containing vaccines (60%–80%, or even lower in some areas) [48, 49]. In addition, several alternative immunization schedules were implemented using Td for the primary infant series, as well as at school entry; the age for this dose was also temporarily shifted from 6 to 9 years [48, 50]. A case-control study conducted at the end of the outbreak among school children aged 6–8 years demonstrated the effectiveness of a Td booster dose provided at school entry to protect against diphtheria [50].

8. A possible pathway for extending the age indication of Td vaccines

Vaccines, like medicines, must be licensed through the appropriate regulatory body at a country level. Regulatory approval for use of vaccines is product specific and based on the data submitted by the manufacturer requesting the market authorization. As a part of the regulatory review, the indications for use depend on the clinical evidence submitted and need to be provided in the summary of product characteristics (smPC) and package insert. Vaccine indications include age, immunization schedule, method of administration, and special considerations, along with other parameters. A WHO recommendation is considered “off-label” if the recommended use is not included in the indications within the smPC and package insert [8].

Manufacturers of Td vaccines (non-combination products) have not submitted safety and impact (efficacy and/or immunogenicity) data for use of their products in children 4–7 years of age, and, hence, do not have regulatory authorization for use of their products in this age group. Noting that Td containing vaccines have an established and longstanding history of immunogenicity and safety (Table 1) [14, 15], it was the consensus of the consultation that product specific immunogenicity and safety studies in the relevant age group would be sufficient for a public health programmatic recommendation to extend the use of Td vaccines to children from 4 years of age (see Conclusions section). Additional available data from Td combination vaccines provides supportive evidence for immunogenicity and safety.

To support product label extension, an immunogenicity study could possibly be sufficient, using a single arm design with Td vaccination of children aged 4–7 years who have received a documented 3+1 primary immunization series (doses at 6, 10, 14 weeks and 12–23 months), preferably with vaccine containing whole cell pertussis in countries that do not provide childhood booster doses. Analysis of immunogenicity and safety data collected before and one month after Td booster vaccination to demonstrate a boosting of antibody levels. A more robust randomized control trial comparing DT and Td vaccine in children aged 4–7 years with similar parameters to those above and a longer follow-up (e.g., 1, 3.5 and 5 years) would be helpful in terms of providing further generalizable evidence, but might not be essential for regulatory approval of each product.[3] Careful attention should be paid to the study design and laboratory testing (validation of serology with international standards) to ensure interpretability of results (Box 1) [14, 15]. Additionally, publishing observational or post-marketing studies (i.e., epidemiological data) from countries introducing the preschool/school entry Td booster dose would be useful additional data for a change to the indication in the package insert. Finally, further strengthening of surveillance for diphtheria disease and AEFIs should be promoted to monitor the use of Td vaccination as the second booster dose in a six-dose series.

Conclusions

Based on the available evidence reviewed, the experts participating in the consultation concluded that from a public health perspective, the use of Td vaccine in 4–7 year old children as a second booster dose is fully supported on the following basis:

- Biologically, there is no relevant difference or developmental change in the immune systems of children aged 4–7 years versus children over 7 years of age;
- Adequate seroprotection using low-dose diphtheria as a booster dose in 4–7 year old children has been demonstrated in several studies with Td vaccine and many studies using Td in combination with other antigens;
- Longitudinal studies as well as modelling, suggest a durable and protective response of at least 9–11 years when low dose diphtheria antigen is given as booster dose in 4–7 year old children;

[3]Design of study should be discussed and agreed upon with the NRA of licensure.

- Low-dose diphtheria containing vaccines are generally less reactogenic in 4–7 year old children than full dose diphtheria containing vaccines, hence potentially improving the vaccination experience; and
- Experience from several countries indicates adequate control of diphtheria when using Td-containing combination vaccines as a second booster dose (fifth dose overall) in 4–7 year old children.

The experts emphasized the importance of providing an additional booster dose of Td vaccine between 9–15 years of age for lifetime protection in accordance with the WHO recommendations [1, 2].

To facilitate regulatory authorization for the use of low dose diphtheria containing vaccines in children 4–7 years, manufacturers are encouraged to discuss the submission of supportive data to their relevant regulatory authority. This data could be generated using a study design with immunogenicity and safety end points. The evidence summarized in this report also provides supporting evidence that can be used in regulatory applications. WHO committed to follow-up with the three major producers of Td vaccine and their respective National Regulatory Agencies to discuss implementing further studies for each product that would allow for an indication change in the package insert.

As an interim measure, WHO has distributed the report of the Consultation to all manufacturers of WHO pre-qualified Td vaccine products and inquired if they would add mention of the WHO recommendation for the use of Td as a second booster dose for 4–7 year old children to the product package inserts and vaccine labels [51].[4]

The Experts who participated in the consultation agreed that the ability to use Td vaccine in the 4–7 year age group as a second booster dose would potentially confer programmatic benefits and give countries greater flexibility for ensuring adequate immunity against diphtheria and tetanus as a part of a life course approach to immunization [5].

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Appendix

The Expert Group on the Use of Td vaccine in Childhood:

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[4]For precedence, please see Green Cross Corporation, Trivalent Seasonal Influenza vaccine (GC FLU inj) product insert where the following statement was added:
6. Administration for pregnant or lactating woman …..WHO recommends “For countries considering the initiation or expansion of programmes for seasonal influenza vaccination, pregnant women should have the highest priority. Pregnant women should be vaccinated with TIV at any stage of pregnancy. This recommendation is based on evidence of a substantial risk of severe disease in this group and evidence that seasonal influenza vaccine is safe throughout pregnancy and effective in preventing influenza in the women as well as in their young infants, in whom the disease burden is also high [52, 53].

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†Provided additional analysis of data from a published study[27] and did not participate in formulation of recommendations.

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Highlights

- Low-dose tetanus-diphtheria (Td) vaccine is currently not licensed for children age 4–7 years
- Evidence suggests using Td as a second booster in ages 4–7 years yields durable immunity
- Evidence supports the recommendation to use Td booster dose in ages 4–7 years

Box. 1 Correlates of Diphtheria Protection and Considerations for Laboratory and Clinical Trials

Diphtheria antitoxin levels

- Measured in International Units per millilitre (IU/ml) by correlation to the WHO International Standard reference sera (10/262) through available laboratory methods [14, 15].
- A concentration of 0.01 IU/mL is considered the minimum level required for some degree of protection, generally correlating with protection against death [14, 15].
- Levels of ≥0.1 IU/mL are considered protective against disease, with higher levels generally correlating with less severe symptoms [14, 15].
- Levels of ≥1.0 IU/mL are associated with long-term protection [14, 15].

Diphtheria Laboratory Assays

- The Vero cell neutralization test (NT) is a functional *in vitro* assay for diphtheria antibodies that correlates highly with *in vivo* neutralization tests, and hence, is considered the reference assay [14, 15].
- Standard enzyme-linked immunosorbent assays (ELISA) are available, but only correlate well with NT results above 0.1 IU/ml, necessitating use of ≥0.1 IU/ml as a cutoff [14, 15].
- Other laboratory methods such as the double antigen ELISA (DAE), dissociation-enhanced lanthanide fluorescent immunoassay (DELFIA), toxin binding inhibition (ToBI) assay, and newer bead-based multiplex immunoassays (MIA) are more accurate than standard ELISAs and can be used for accurately measuring lower seroprotective levels (0.01–0.1 IU/ml) [14, 15].
- Although all anti-diphtheria IgG results are given in IU/ml, care must be taken when comparing results from different laboratories, as has been demonstrated in a recent External Quality Assessment (EQA) for diphtheria serology within the European Diphtheria Surveillance Network [66].

Endpoints for Clinical Trials

- The primary endpoint measurement for vaccine clinical trials is usually immunogenicity, which in this case is diphtheria seroprotection assessed at a defined threshold, which can vary depending on the trial (0.01 IU/ml, 0.1 IU/ml, or 1.0 IU/ml).
- Antibody levels, usually expressed as geometric mean concentration (GMC), and reactogenicity, or the percentage of vaccinees reporting specific side effects, are usually reported as secondary endpoints.

Table 1.

Immunogenicity results from studies of low-dose diphtheria vaccine in children aged 4–7 years

Country, year, and reference	Age group	Time point	Low-dose diphtheria vaccine			Full-dose diphtheria vaccine		
			Vaccine	% seroprotection [95% CI][1]	GMC in IU/ml [95% CI]	Vaccine	% sero-protection [95% CI][1]	GMC in IU/ml [95% CI]
Primary series containing whole cell pertussis (wP)[2]								
Israel, 1999 [54][3]	4–7y	Pre	tdap	58	--	DTaP	46	--
		1m		100	7.6 [5.8–9.9]		100	13.3 [10.3–17.1]
Italy, 2001 [18][2,3,4]	**6y**	**Pre**	**Td**	**51**	**0.10 [0.07–0.14]**	**DT**	**49**	**0.09 [0.07–0.12]**
		1m		**99**	**7.7 [5.6–10.5]**		**100**	**14.1 [11.8–16.9]**
Thailand, 2003 [55][3]	4–6y	Pre	Tdap	71	0.27	DTwP	85	0.40
		1m		99	3.12		99	4.98
England, 2004 [56],[3]	3.5–	Pre	TdaP−IPV	67 [57–76]	0.44 [0.28–0.67]	DTaP −IPV	78 [68–86]	0.50 [0.32–0.78]
2015 [24],	5y	1m		100 [96–100]	11 [8–16]		100 [96–100]	23 [16–34]
2016 [27][1]		1y		89 [75–96]	0.99 [0.62–1.58]		97 [85–99]	1.42 [0.88–2.23]
		3y		72 [56–84	0.22 [0.14–0.35]		69 [51–83]	0.29 [0.17–0.50]
		5y		75 [61–85]	0.23 [0.15–0.35]		79 [64–90]	0.34 [0.22–0.52]
		Pre	TdaP + OPV	63 [53–72]	0.41 [0.25–0.68]			
		1m		99 [95–100]	17 [12–24]			
		1y		96 [86–99]	1.10 [0.76–1.60]			
		3y		75 [61–85]	0.28 [0.19–0.40]			
		5y		67 [53–78]	0.23 [0.16–0.33]			
Taiwan, 2005 [57]	6–8 y	Pre	Tdap	--	--	--	--	--
		1m		100 [94–100]	4.7 [3.6–6.2]			
Taiwan, 2008 [58]	6–8 y	Pre	Tdap-IPV	79 [68–87]	0.22 [0.18–0.28]	--	--	--
		1m		100 [96–100]	4.39 [3.53–5.47]			
China, 2010 [59][3]	6–8y	Pre	Tdap	68 [60–75]	0.11 [0.10–0.12]	DT	72 [65–79]	0.12 [0.11–0.13]
		1m		100 [98–100]	1.06 [0.99–1.14]		99 [97–100]	1.04 [0.97–1.12]
Primary series containing acellular pertussis (aP)[2]								

Country, year, and reference	Age group	Time point	Low-dose diphtheria vaccine			Full-dose diphtheria vaccine		
			Vaccine	% seroprotection [95% CI][1]	GMC in IU/ml [95% CI]	Vaccine	% seroprotection [95% CI][1]	GMC in IU/ml [95% CI]
Germany, 2000 [20][4]	**6–9y**	**Pre**	**Td**	**52**	**0.10 [0.08–0.12]**	--	--	--
		1m		**100**	**5.64 [4.79–6.65]**			
		Pre	Td−IPV	59	0.11 [0.09–0.13]			
		1m		100	4.38 [3.81–5.02]			
Sweden, 2001 [60][2]	5.5y	Pre	TdaP−IPV	14 [9–19]	0.01 [0.01–0.01]	DT + IPV	16 [11–22]	0.01 [0.01–0.02]
		1m		97 [94–99]	2.47 [2.00–3.06]		99 [96–100]	5.73 [4.71–6.96]
		Pre	TdaP + IPV	15 [11–21]	0.01 [0.01–0.02]			
		1m		99 [97–100]	3.68 [3.03–4.47]			
Canada, 2005 [61][3]	4–6y	Pre	Tdap	79	0.16 [0.13–0.21]	DTaP −IPV	57	0.13 [0.11–0.17]
		1m		100	3.8 [3.2–4.4]		100	6.4 [5.3–7.7]
Canada, 2007 [62][3]	4–7y	Pre	Tdap + IPV	--	--	DTaP −IPV	--	--
		1m		90 [86–93]	6.10 [5.42–6.86]		94 [90–96]	13.6 [11.5–16.0]
Italy, 2012 [63][2,3]	5–6y	Pre	Tdap−IPV	--	--	DTaP −IPV	--	--
		1m		100	9.2 [8.1–10.5]		100	21.3 [19.2–23.4]
Germany, 2007 [64][3], 2010 [25]	4–8y	Pre	Tdap−IPV	67 [64–71]	0.19 [0.18, 0.21]	--	--	--
		1m		100 [99–100]	4.46 [4.16, 4.79]			
		1y		100 [99–100]	1.28 [1.16, 1.43]			
		5y		98[5]	--			
		Pre	Tdap + IPV	64 [55–73]	0.18 [0.15, 0.23]			
		1m		100 [97–100]	4.10 [3.43, 4.9]			
		1y		100 [94–100]	1.19 [0.91, 1.56]			
		5y		95[5]	--			
Germany, 2008 [19][3], **2004** [26][1,4]	**4–6y**	Pre	Tdap	85 [79–90]	0.30 [0.24–0.37]	DTaP	85 [76–92]	0.33 [0.25–0.44]

Country, year, and reference	Age group	Time point	Low-dose diphtheria vaccine			Full-dose diphtheria vaccine		
			Vaccine	% seroprotection [95% CI][1]	GMC in IU/ml [95% CI]	Vaccine	% seroprotection [95% CI][1]	GMC in IU/ml [95% CI]
		1m		100 [98–100]	11.1 [9.7–12.8]		100 [96–100]	24.4 [20.2–29.5]
		3.5y		100 [97–100]	0.66 [0.57–0.77]		100 [95–100]	1.01 [0.80–1.26]
		Pre	**Td**	**86 [78–93]**	**0.43 [0.31–0.60]**			
		1m		**100 [96–100]**	**10.1 [8.1–12.5]**			
		3.5y		**100 [92–100]**	**0.84 [0.66–1.1]**			
France, 2001 [65], 2015 [23][2]	6y	Pre	Td−IPV	--	--	DT−IPV	--	--
		1m		99 [96–100]	3.7 [3.1– 4.4]		99 [98–100]	23.3 [19.5–27.9]
		5y		63 [54–72]	0.24 [0.18–0.33]		86 [79–91]	0.62 [0.48–0.81]

Abbreviations: aP or Pa=acellular pertussis; CI=confidence interval; d=low-dose diphtheria toxoid; D=full-dose diphtheria toxoid; GMC=geometric mean concentration; IPV=inactivated poliovirus vaccine; IU/ml=international units per milliliter; m=month (post-vaccination); Pre=pre-vaccination; T=tetanus toxoid; y=year (post-vaccination); wP=whole cell pertussis

[1]For better comparison across studies, seroprotection at the 0.1 IU/ml cutoff is reported in cases where a variety of cutoffs were included.

[2]The primary immunization series for studies conducted in Italy and Sweden was 2+1 doses; the rest of the studies were 3+1 doses (See footnote 1 in text). The Gajdos studies pre-dated France's change from 3+1 to 2+1 doses in 2013.

[3]Each of these studies demonstrated fewer injection site reactions in the low-dose diphtheria group compared with full-dose diphtheria vaccine.

[4]This Italian study is the only clinical trial with a direct comparison of Td and DT vaccine in the relevant age group; two German studies assessed immunogenicity of Td vaccine compared to combination vaccines.

[5]These results are from the Vero cell neutralization test. Results from ELISA were 89% seroprotection (≥0.1 IU/ml) for Tdap-IPV and 86% for Tdap + IPV.