



# Tetanus–diphtheria–acellular pertussis vaccination for adults: an update

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Although tetanus and diphtheria have become rare in developed countries, pertussis is still endemic in some developed countries. These are vaccine-preventable diseases and vaccination for adults is important to prevent the outbreak of disease. Strategies for tetanus, diphtheria, and pertussis vaccines vary from country to country. Each country needs to monitor consistently epidemiology of the diseases and changes vaccination policies accordingly. Recent studies showed that tetanus–diphtheria–acellular pertussis vaccine for adults is effective and safe to prevent pertussis disease in infants. However, vaccine coverage still remains low than expected and seroprevalence of protective antibodies levels for tetanus, diphtheria, and pertussis decline with aging. The importance of tetanus–diphtheria–acellular pertussis vaccine administration should be emphasized for the protection of young adult and elderly people also, not limited to children.

**Keywords:** Whooping cough, Diphtheria, Tetanus, Diphtheria-tetanus-acellular pertussis vaccines, Adult

## Introduction

Vaccines have been proven to have a positive effect on public infectious diseases, however, the importance of vaccination for the adult is often ignored [1]. Many of vaccines under development have targeted the childhood immunizations [2]. Globally, the elderly population has been increasing thanks to improved hygiene and healthcare system. Considering gradual decline of the immune response to vaccination with aging, it is important to emphasize adult vaccination and to develop worldwide strategies of vaccination [2].

Tetanus, diphtheria, and pertussis vaccination for adults is recommended in many countries. Tetanus has become a rare disease in developed countries with effective vaccination programs but still occurs in the elderly and insufficiently vaccinated population. *Clostridium tetani* which is an anaerobic gram-positive bacteria lives in the environment and the tetanus is caused by a neurotoxin from *C. tetani* infected in contaminated wounds [3]. The typical clinical symptoms of tetanus are the muscle spasm and contraction. The autonomic nervous system also may be influenced and seizure may occur [4]. Suspected tetanus wound needs surgical source control, tetanus immunoglobulin, and tetanus vaccination according to patient's vaccination history [3].

Diphtheria is known as an acute bacterial disease caused by *Corynebacterium diph-*

*theria*, a gram-positive unencapsulated bacillus. Diphtheria is usually transmitted by human's respiratory droplets. Toxigenic strains of *C. diphtheria* cause most of the pharyngeal infection, myocarditis, polyneuropathy, and systemic toxicity. However, non-toxigenic strains cause most of the cutaneous infection [5]. The pathologic findings of pharyngeal diphtheria include pseudomembrane-coated mucosal ulcers and respiratory diphtheria may result in airway obstruction. Diphtheria is a rare disease in most countries, however, still remains in some developing countries. Diphtheria can cause endemic disease in susceptible population as large part of the population has not received booster vaccination [6].

Pertussis is also known as a whooping cough, which is an acute bacterial disease caused by the gram-negative bacilli, *Bordetella pertussis* [7]. It is a highly contagious disease transmitted by respiratory droplets and a major cause of infant morbidity [8]. In adult cases, the symptoms may vary from asymptomatic disease to a severe coughing disease along with weight loss, subconjunctival hemorrhages, and syncope [9]. Despite children's vaccination program, pertussis is still endemic in many countries [9,10].

This review summarizes updated data of vaccination for tetanus, diphtheria, and pertussis, especially in the adult population.

### Several Tetanus-Diphtheria-Pertussis Vaccines

Vaccines against tetanus were first introduced in 1924 in the form of tetanus toxoid and were widely used during World War II [4]. Diphtheria toxoid was developed in 1921, and incorporated with tetanus toxoid and extensively used in the 1940s [4]. Tetanus toxoid is administered with diphtheria toxoid because pediatric population needs both antigens [4]. Single antigen diphtheria toxoid is not available [4]. Tetanus and diphtheria toxoids are derived from the strains of *C. diph-*

*theria* and *C. tetani* in the form of cell-free purified toxin. Formaldehyde causes conversion of the toxin to toxoid and aluminum salt is added for immunogenicity. Pediatric diphtheria-tetanus toxoid (DT) contains 3-4 times as much diphtheria toxoid as the adult formulation of tetanus-diphtheria toxoid (Td) and has a similar volume of tetanus toxoid [4]. Whole cell pertussis vaccine was first approved in the United States in 1914 and composed of a formaldehyde-treated *B. pertussis* cells. In 1948, whole-cell pertussis vaccine combined with diphtheria and tetanus toxoid (DTP) was developed, however, adverse events were common; local and systemic reactions reduced the rate of vaccination [4]. Consequently, whole-cell pertussis vaccines were replaced with acellular pertussis (aP) vaccines in the 1990s, which are subunit vaccines containing inactivated components of *B. pertussis* cells. Several aP vaccines have been developed for different age groups. Pediatric formulation (diphtheria-tetanus-acellular pertussis [DTaP]) of vaccines are currently available for use in the United States under the brand names as Infanrix (GlaxoSmithKline) and Daptacel (Sanofi Pasteur). Adolescent and adult formulation (tetanus-diphtheria-acellular pertussis [Tdap]) of vaccines which were licensed for adolescents in 2005 are in use under the brand names as Boostrix (GlaxoSmithKline) and Adacel (Sanofi Pasteur) in the United States. Tdap vaccination was recommended for adults younger than 65 years in 2006. These adult form of vaccines have a similar amount of tetanus and diphtheria toxoid compared to the adult form of Td vaccines. Boostrix is licensed for persons 10 years of age and older and has a reduced quantity of pertussis antigens compared with the Infanrix. Adacel is licensed for persons 10 through 64 years of age and has a reduced quantity of pertussis toxin compared with Daptacel [4]. Table 1 shows the composition of various tetanus, diphtheria, pertussis vaccines [11-14]. Combined vaccines are also available as diphtheria/tetanus/acellular pertussis/inactivated polio vaccine (DTaP-IPV), diphtheria/tetanus/acellular pertussis/inactivated polio vaccine/*Hae-*

**Table 1.** Approved tetanus-diphtheria-acellular pertussis vaccines, by FDA

Trade name	Manufacturer	FDA-approved age for use	Pertussis antigens (µg)				Diphtheria toxoid (Lf)	Tetanus toxoid (Lf)
			Pertussis toxin (µg)	Filamentous hemagglutinin (µg)	Pertactin (µg)	Fimbriae (µg)		
Infanrix	GlaxoSmithKline Biologicals	6 wk through 6 yr	25	25	8	-	25	10
Daptacel	Sanofi Pasteur	6 wk through 6 yr	10	5	3	5	15	5
Boostrix	GlaxoSmithKline Biologicals	10 yr and older	8	8	2.5	-	2.5	5
Adacel	Sanofi Pasteur	11 through 64 yr	2.5	5	3	5	2	5

FDA, Food and Drug Administration.

**Table 2.** Vaccination guidelines against tetanus, diphtheria, and pertussis

Country	Adults (18-65 yr)	Elderly (>65 yr)	No. of cases of tetanus in 2015	No. of cases of diphtheria in 2015	No. of cases of pertussis in 2015	Total population in 2015 (in thousands)
USA [13,16]	Every 10 yr <sup>a</sup> Tdap for each pregnant women	Every 10 yr <sup>a</sup>	25 (in 2014 the latest available year)	0	18,166	321,774
Canada [16,17]	Every 10 yr <sup>a</sup>	Every 10 yr <sup>a</sup>	4	3	3,510	35,940
Austria [16,18]	Every 10 yr <sup>b</sup>	Every 5 yr <sup>c</sup>	0 (in 2012 the latest available year)	0	579	8,545
Belgium [16,18]	Every 10 yr <sup>a</sup>	Every 10 yr <sup>a</sup>	0 (in 2012 the latest available year)	2	1,203	11,299
Bulgaria [16,18]	Every 10 yr <sup>d</sup>	Every 10 yr <sup>d</sup>	0	0	35	7,150
Croatia [16,18]	Td at age 60 yr		3	0	57	4,240
Cyprus [16,18]	Every 10 yr <sup>d</sup>	Every 10 yr <sup>d</sup>	0	0	2	1,165
Czech Republic [16,18]	Every 10-15 yr <sup>e</sup>	Every 10-15 yr <sup>e</sup>	1	0	585	10,543
Denmark [16,18]	-	-	1 (in 2013 the latest available year)	1	962	5,669
Estonia [16,18]	Every 10 yr <sup>d</sup>	Every 10 yr <sup>d</sup>	0	0	77	1,313
Finland [16,18]	Every 10 yr <sup>d</sup>	Every 10 yr <sup>d</sup>	NA	0 (in 2013 the latest available year)	192 (in 2013 the latest available year)	5,503
France [16,18]	Td-IPV at age 25 and 45 yr <sup>f</sup>	Every 10 yr <sup>d</sup>	10 (in 2013 the latest available year)	14	36	64,395
Germany [16,18]	Every 10 yr <sup>a</sup>	Every 10 yr <sup>a</sup>	NA	14	9,000	80,689
Greece [16,18]	Every 10 yr <sup>h</sup>	Every 10 yr <sup>h</sup>	2 (in 2014 the latest available year)	0 (in 2014 the latest available year)	16 (in 2014 the latest available year)	10,955
Hungary [16,18]	-	-	2	0	6	9,855
Iceland [16,18]	-	-	0	0	4	329
Ireland [16,18]	Tdap for each pregnant women	-	1	1	118	4,688
Italy [16,18]	Every 10 yr <sup>i</sup>	Every 10 yr <sup>d</sup>	47	1	225 (in 2012 the latest available year)	59,798
Latvia [16,18]	Every 10 yr <sup>d</sup>	Every 10 yr <sup>d</sup>	0	10	210	1,971
Liechtenstein [16,18]	Booster at age 25-29, 45, and 65 yr <sup>j</sup>	Every 10 yr <sup>d</sup>	NA	NA	NA	NA
Lithuania [16,18]	Every 5-10 yr	Every 5-10 yr	2	0	60	2,878
Luxembourg [16,18]	Every 10 yr <sup>k</sup>	Every 10 yr <sup>k</sup>	0	0	0	567
Netherlands [16,18]	-	-	0 (in 2014 the latest available year)	0 (in 2014 the latest available year)	8,960	16,925
Norway [16,18]	-	-	2	2	1,902	5,211
Poland [16,18]	Td at age 19 yr	-	14 (in 2013 the latest available year)	0 (in 2013 the latest available year)	2,183	38,612
Portugal [16,18]	Every 10 yr <sup>d</sup>	Every 10 yr <sup>d</sup>	2 (in 2014 the latest available year)	0 (in 2014 the latest available year)	73 (in 2014 the latest available year)	10,350
Romania [16,18]	Every 10 yr <sup>d</sup>	Every 10 yr <sup>d</sup>	7	0	93	19,511
Slovakia [16,18]	Every 15 yr	Every 15 yr	0	0	334	5,426
Slovenia [16,18]	Every 10 yr <sup>d</sup>	Every 10 yr <sup>d</sup>	3	0	68	2,068
Spain [16,18]	Td at age around 65 yr		3	1	2,342 (in 2013 the latest available year)	46,122
Sweden [16,18]	Every 20 yr	Every 20 yr	0	1	603	9,779
United Kingdom [16,18]	Tdap for each pregnant women	-	6	1	5,207	64,716
Australia [16,19]	Every 10 yr from age ≥50 yr <sup>a</sup> Tdap for each pregnant women	Every 10 yr <sup>a</sup>	3	2	22,508	23,969

(continued to the next page)

Table 2. Continued

Country	Adults (18-65 yr)	Elderly (>65 yr)	No. of cases of tetanus in 2015	No. of cases of diphtheria in 2015	No. of cases of pertussis in 2015	Total population in 2015 (in thousands)
India [16,20]	Every 10 yr <sup>a)</sup>	Every 10 yr <sup>a)</sup>	2,268	2,365	25,206	1,311,051
Japan [16,21-23]	-	-	120	0	2,675	126,573
China [16,24]	-	-	426 (in 2014 the latest available year)	0	6,658	1,376,049
South Korea [16,25]	Every 10 yr <sup>a)</sup> Tdap for pregnant women without previous Tdap vaccination before pregnancy or right after delivery	Every 10 yr <sup>a)</sup>	22	0	205	50,293

Tdap, tetanus–diphtheria–acellular pertussis vaccine; Td, tetanus-diphtheria vaccine; NA, not available; Td-IPV, tetanus-diphtheria-acellular pertussis-inactivated poliomyelitis vaccine.

<sup>a)</sup>One of the booster doses should contain the pertussis antigen (Tdap) for those who have not previously received a single dose of Tdap.

<sup>b)</sup>Diphtheria, tetanus, acellular pertussis (DTaP) and inactivated poliomyelitis vaccine (DTaP-IPV) should be given every 10 years between 18 and 60 years of age.

<sup>c)</sup>DTaP-IPV should be given every 5 years from 65 years of age.

<sup>d)</sup>Td every 10 years for adults after receiving the childhood immunization schedule.

<sup>e)</sup>Subsequent booster dose of tetanus every 10-15 years. One of the booster doses should contain the pertussis antigen (Tdap). A single dose of Tdap is recommended to be given in pregnancy, ideally in the third trimester, between pregnancy weeks 28 and 36.

<sup>f)</sup>For those who did not receive a dose of pertussis-containing vaccine during the past 5 years, a booster with a quadrivalent vaccine (DTaP-IPV) is recommended when Td-IPV booster is administered at age 25.

<sup>g)</sup>Td-IPV every 10 years should be given from 65 years of age.

<sup>h)</sup>Td booster should be given every 10 years. One of the booster doses should be administered with Tdap or Tdap-IPV.

<sup>i)</sup>Tdap booster given 10 years after completing primary vaccination with DTaP-containing vaccines

<sup>j)</sup>First booster preferably administered before having a first child, in order to protect the newborn against pertussis.

<sup>k)</sup>Subsequent Tdap-IPV booster should be given every 10 years.

*mophilus influenza* type b (DTaP-IPV-Hib), and diphtheria/tetanus/acellular pertussis/hepatitis B/inactivated polio vaccine (DTaP-HebB-IPV).

### Vaccination Guidelines and Epidemiology

Incidence and policies of tetanus, diphtheria, and pertussis in North America, Europe, Australia, and some Asia countries are explained in Table 2 [13-25]. Almost all developed countries show a tendency of a low incidence of tetanus and diphtheria, and yet the vaccination is still important as elderly population is at risk for getting diseases [1,26-29]. The incidence of tetanus in Italy decreased greatly in population 15-24 years of age, and yet the incidence of elderly age group reduced only by a half. As a result, ≥65 years of age group accounted for 70% of all tetanus cases in the 1990s from 40% in the 1970s [5]. Tetanus is a disease with high case-fatality, preventable by vaccine [26,27]. In developing countries, tetanus is still endemic and the number of travelers going to those countries is on the rise [30-32]. Tetanus is not contagious and the immunity does not offer lifelong protection after natural infection. As *C. tetani* is found in soil, tetanus vaccines do not provide

herd immunity [5].

Diphtheria spread through human’s droplets may cause an outbreak among unvaccinated population [33,34]. Before the vaccination was available, diphtheria was a major cause of death in children. Until 1940, the number of reported death per year was 1,500 in Italy. After diphtheria vaccines were widely used, diphtheria is nearly eliminated in developed Western countries [5]. However, up to 80% cases of the epidemic diphtheria still occurs in adults and one of the reasons for the outbreak in adults is thought to be a lack of immunization [4]. Asymptomatic carriers particularly are the main source of an outbreak [5]. The World Health Organization recommends regular tetanus-diphtheria booster immunization throughout lifetime after completion of vaccination series against tetanus-diphtheria during childhood [1,35].

Before there was a vaccine, pertussis was a common disease in children and incidence of pertussis was about 150 cases per 100,000 population in the 1940s in the United States [4]. However, following an introduction of whole-cell pertussis vaccine, pertussis incidence gradually declined, reaching approximately 8 per 100,000 population in the 1960s [4]. Based on World Health Organization report, pertussis in the United

States occurred 1,730 cases in 1980 and the number of reported cases gradually increased from 4,570 cases in 1990 to 7,867 cases in 2000, and 48,277 cases in 2012. Children under 6 months of age accounted for 24% of reported pertussis cases in 2002, however, in 2004 and 2005 about 60% of cases were among persons of 11 years and older. The increased incidence of pertussis may be due to acellular pertussis vaccinations in the 1990s [4]. To reduce the incidence of pertussis, Advisory Committee on Immunization Practices (ACIP) in the United States recommends a single dose of Tdap to replace a single booster dose of Td for adults 19 years of age and older who have previously not received Tdap [4]. Tdap can be given regardless of interval from the last time Td vaccines. In 2012, ACIP recommends Tdap for all the third trimester of pregnant women during each pregnancy, regardless of past Tdap immunization history [36]. This strategy is designed for preventing pertussis in infants using maternal antibody [37]. As for the non-pregnant person, antipertussis antibodies show a peak during the first month after Tdap administration and gradually decline after 1 year [38,39]. The highest concentration of maternal antibodies is transferred closer to delivery [40]. Active transport of maternal immunoglobulin G occurs after 30 weeks of gestation [41]. After Tdap is administered, the antibody response approaches peak levels by day 14, and breast milk levels of antibody against pertussis are first detected on day 7 [42]. Optimal timing for Tdap administration is between 27 and 36 weeks' gestation, which is 85% more effective than postpartum immunization against pertussis in infants under 8 weeks of age [43]. Tdap vaccination during early pregnancy or vaccination before pregnancy was not sufficient to prevent pertussis among infants at ages 2 months [40]. Tdap vaccines for postpartum women did not reduce pertussis in infants under 6 months of age according to a cross-sectional study [44]. Australia, Ireland, and the United Kingdom recommend Tdap vaccines for every pregnant woman (Table 2). ACIP also advises that adults who have close contact with an infant younger than 1 year of age have to receive Tdap vaccine (the cocooning strategy) if they have no history of past Tdap. Ideally, these population should receive Tdap at least 2 weeks before beginning close contact with the infant [4]. From 2005, ACIP has recommended booster Tdap in people between the ages of 11-64 years, and then adults older than 65 years having contact with infants younger than 12 months in 2010. However, since 2012, ACIP recommended Tdap for all persons aged 65 years and older regardless of infant contact, for preventing pertussis illness [45,46].

## Vaccine Coverage and Seroprevalence

In the United States, Td and Tdap vaccine coverage in the adult population ( $\geq 18$  years) were 57.5% and 28.9%, and the coverage in pregnant women was 41.7% in 2013 [10,47]. According to the Vaccine European New Integrated Collaboration Effort consortium, adult vaccination coverage for tetanus and diphtheria was 61%-74% in 2010/2011 [48]. In Korea, the seroprevalence of pertussis was 41.4% (male 44.7% and female 38.2%) in the 2012. The seroprevalence was 38.9% in 11-20 years age group, 36.0% in 21-30 years, 41.8% in 31-40 years, 39.9% in 41-50 years, 45.0% in 51-60 years, and 48.1% in  $\geq 61$  years age group. The anti-pertussis toxin immunoglobulin G titers were not statistically different with aging [49]. In Thailand following of whole-cell pertussis vaccination, seroprevalence of pertussis antibodies were 12.8% in 0-10 years age group, 5.22% in 11-20 years, 4.53% in 21-30 years, 3.76% in 31-40 years, 6.04% in 41-50 years, and 5.57% in  $>50$  years age group in 2014, respectively [50]. A study on China reported that adult population was generally unprotected against diphtheria and pertussis [24]. In a nationwide seroepidemiological study in the Netherlands, the national sample in the 2006/2007 showed that 91% of the population had diphtheria antitoxin immunoglobulin G levels above 0.01 IU/mL (partial protection level) compared to 88% in the 1995/1996 serosurvey ( $p < 0.05$ ) [51]. In 1993-1995 seroprevalence study on Italy showed that low titer of diphtheria antibody was observed; 7.2% in the 1-10 years age population, and 33.4% in  $>60$  years [5]. Seroprevalence data in Italy also showed that protective tetanus antibody levels ( $>0.1$  IU/mL) are 87% in the 15-24 years age group, 43.4% in 45-64 years, 26.6% in 65-74 years, 27.9% in 75-84 years, and 17.1% in  $\geq 85$  years, respectively. In Korea, the seroprevalence of tetanus was 56.4% (male 61.0% and female 51.8%) in the 2012. The seroprevalence was 92.0% in 11-20 years age group, 95.7% in 21-30 years, 72.3% in 31-40 years, 33.3% in 41-50 years, 17.3% in 51-60 years, and 19.3% in  $\geq 61$  years age group. The anti-tetanus immunoglobulin G titers decreased with aging ( $p < 0.001$ ) [52]. Several studies reported that protective tetanus and diphtheria antibody levels declined with aging since the last vaccination, and antibodies had on estimated the half-life of 11 years [1,53]. These data explain why most elderly age group lacks protective antibody. The antibody levels were significantly higher in males from  $\geq 25$  years age, due to military service and work related pressure [5].

## Vaccine Impact against Pertussis

There were a few studies of the efficacy of tetanus, diphtheria, and pertussis vaccines. A study of Tdap vaccine effectiveness between aged 11-19 years showed that overall vaccine effectiveness was 68.5% (95% confidence interval, 37.7 to 86.2) during a pertussis outbreak [54]. However, another study of Tdap vaccine effectiveness against pertussis showed that Tdap was moderately effective during the first year after vaccination, and then effectiveness wanes to less than the 9% after 4 years among teenagers who have only received acellular pertussis vaccines [55]. The strategy of protecting newborns from pertussis with adult immunization has been proven to be effective. Vaccination during gestation and an immunized father decreased the risk of pertussis in children aged 4 months and younger by 51% [56]. In Brazil, a study of maternal Tdap vaccination showed a cost-effective practice for preventing pertussis [7]. However, low vaccine coverage among those having close contacts of infants probably makes it difficult to implement the cocooning strategy [57]. A recent study in Netherlands reported that vaccine coverage is associated with mortality of vaccine-preventable diseases. Before there was a vaccine, the mortality burden of diphtheria, tetanus, and pertussis were 1.4%, 0.1%, and 3.8%, respectively. After the vaccine was available, the burden decreased to near zero [58].

## Adverse Events after Vaccination

Guillain-Barré syndrome and peripheral neuropathy are well known of adverse events following tetanus vaccine administration [4]. Reported adverse events associated with Tdap vaccines include generalized urticaria, anaphylaxis, or local reactions [4]. Recently, a study reported that there was a potential risk of acute disseminated encephalomyelitis following Tdap vaccination [59]. Several studies have reported that tetanus-containing vaccines with intervals less than 5 years may increase local reactions and systemic reactions like fever, even though increased risk of severe dermal inflammation, vascular necrosis and endothelial damage (Arthus reactions) have not been reported [60-62]. A retrospective study in 29,155 pregnant women receiving Tdap vaccines shows no significant differences in adverse events rates or adverse birth outcomes related to timing since prior tetanus-containing vaccination less than 2 years before or 2-5 years before or more than 5 years before [63]. A prospective study for evaluation of the infants safety of Tdap vaccination during pregnancy reported no sig-

nificant differences compared with baseline infants population data [64]. In the Vaccine Adverse Event Reporting System during 2011-2015, there was no unexpected adverse event among routine maternal Tdap vaccination population, however, chorioamnionitis after Tdap vaccination was found in 5 cases [65,66]. According to Centers for Disease Control and Prevention reports, data from the various monitoring programs supports the fact that of maternal Tdap vaccination is safe [67].

## Conclusion

In this review, we have summarized the epidemiology, vaccine coverage, seroprevalence, and recommendations of vaccination policies against tetanus, diphtheria, and pertussis, including recently updated vaccine impacts and adverse events reports. Strategies for the vaccines vary from country to country. Each country needs to monitor consistently the diseases and to adapt the policies of vaccination. Unfortunately, adult vaccination tends to be neglected. The importance of Tdap vaccine administration should be emphasized for the protection of young adult and elderly people also, not limited to children.

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