

## REVIEW

# Decennial diphtheria-tetanus adult boosters: are they really necessary?

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## Key words

Diphtheria-tetanus • Vaccine • Booster

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## summary

Available epidemiological data shows that an average number of 59 cases of tetanus per year are still reported in Italy. Most of cases (80.2%) occur in subjects > 64 years-old. Furthermore, the proportion of females among subjects ≥ 65 years-old is significantly higher than males (87.7% vs. 64.4%,  $p < 0.0001$ ).

Seroprevalence data show that the percentage of subjects with protective tetanus antibody levels (> 0.1 IU/ml) decreases with increasing age. Most people aged ≥ 65 years are unprotected. The antibody levels are higher in males than females ( $p < 0.001$ ) in subjects > 25 years-old.

Conversely, extensive childhood immunization and adequate boosting vaccination of adults led to the near-elimination of diphtheria in Western countries.

The current Italian National Immunization Prevention Plan 2012-2014 recommends the administration of a primary vaccine course in the first year of life and booster at the preschool age, in ado-

lescents and in adults every 10 years. Nevertheless, the need for decennial booster doses is debated by some experts, who state that the best time to offer a single dose of vaccine against tetanus and diphtheria is the age of 50, since low levels of antibody titers are observed.

Considering the availability of combined vaccines against diphtheria, tetanus and pertussis (DTaP or dTaP), and the increasing incidence of pertussis in infants, who are at highest risk of serious complications, in adolescents and in adults, some countries have introduced decennial dTaP in the adults immunization schedule. It is desirable that this recommendation is also introduced in the future Italian Immunization Prevention Plan.

The present review overviews the epidemiological data and the immunization strategies against tetanus, diphtheria and pertussis in Italy, discussing the rationale not only of decennial dT booster but also of the dTaP booster.

## Introduction

Tetanus and diphtheria are two serious infectious diseases caused by powerful exotoxins produced by *Clostridium tetani* and *Corynebacterium diphtheriae* respectively, with often-fatal outcome.

*C. tetani* is an anaerobic gram-positive bacteria, that may develop a terminal spore. The spores are widely distributed in soil, in the inanimate environment and in animal intestinal tract and feces. Tetanus occurs by penetration of spores through contaminated wounds, lacerations and abrasions. Deep wounds, with lacerated and bruised margins, devitalized tissue, contaminated with soil, are at high risk of tetanus. Toxins disseminate via blood and lymphatics and interfere with release of neurotransmitters [1]. Tetanus is infectious, but not contagious and natural infection does not confer lifelong immunity. Unlike person-to-person transmissible diseases, high vaccination coverage (VC) in the pediatric age does not provide herd immunity. Furthermore, it is almost impossible to eliminate the disease because of the widespread presence of tetanus spores in the environment. Consequently, inadequately immunized subjects are potentially at risk [2].

Clinically, it is characterized by generalized rigidity and convulsive spasms of skeletal muscle and by autonomic nervous system dysfunctions, after an average incubation period of 7 days [3].

*C. diphtheriae* is a gram-positive, uncapsulated bacillus, most often transmitted via the aerosol route. Human asymptomatic carriers are a major source of infection. Whereas toxigenic strains of *C. diphtheriae* most frequently cause pharyngeal diphtheria, systemic toxicity, myocarditis and polyneuropathy, non-toxigenic strains usually cause cutaneous disease. The average incubation period of respiratory diphtheria is 2-5 days. Distinctive pathologic findings of severe respiratory diphtheria include mucosal ulcers with a pseudomembranous coating, which may extend from the pharynx into bronchial airways and may result in fatal airway obstruction. Cutaneous diphtheria is commonly a secondary infection that follows a primary skin lesion due to trauma, allergy or autoimmunity [4, 5].

The present review overviews the epidemiological data and the immunization strategies against tetanus, diphtheria and pertussis in Italy, discussing the rationale not only of decennial dT booster but also of the dTaP booster.

## Epidemiology of tetanus and diphtheria in Italy

### TETANUS

From the second half of 1950s to the mid of 1960s 722 cases of tetanus (1.4 cases per 100,000 population) were notified yearly in Italy. Up to the half of 1970s the number of cases considerably decreased, as a consequence of the introduction of universal childhood immunization during 1960s. Subsequently, the decrease of the cases occurred more slowly, reaching the all-time low of 65 cases in 1991. From 1992 to 2000 the number of cases remained stable, with a mean of 102 cases per year (0.2 cases per 100,000 population). The last case of neonatal tetanus dates back to 1982. The reduction in the incidence observed between the 1970s and 1990s was evident in all age groups. During the considered period, the highest incidence rate was observed in subjects  $\geq 65$  years-old. The greatest reduction (20-fold) in incidence occurred in the 15-24 years age group. Conversely, the incidence in the elderly decreased only by a half. Furthermore, the percentage of cases  $\geq 65$  years of age increased from 40% in the 1970s to 70% in the 1990s. These observations have been confirmed by the analysis of the median age of cases, which increased from 58 years in the 1970s to 63 years in the 1980s and 71 years in the 1990s. Analyzing epidemiological data by gender, in the 1990s, rates were higher in woman than in male among subjects  $\geq 65$  years. This is probably due to the fact that in this age group male counterparts were vaccinated as military recruits or because of job-related risks. As incidence rate, the case-fatality also decreased from 64% in the 1970s to 40% in the 1990s [2].

Available data about the decade 2001-2010 shows that an average number of 59 cases (range: 46-71) per year (1 per 1,000,000 population) are still reported in Italy. Despite high VC were achieved, Italy accounts for most cases reported in the European Union (EU) [6] and tetanus incidence in Italy is about 10 times higher than the average incidence reported in the USA and Australia [7, 8]. As observed in previous years and in other developed countries [9], most of cases (80.2%) occur in subjects  $> 64$  years-old, with an incidence rate equal to 4.1 per 1,000,000 population. The estimated incidence in Italy in the decade 2001-2010 in female is 5.2 per 1,000,000 population (68% of cases), that is over three-fold higher than in male (1.4 per 1,000,000 population). The estimated incidence in Italy in the decade 2001-2010 in female is 5.2 per 1,000,000 population (68% of cases), that is over three-fold higher than in male (1.4 per 1,000,000 population). Furthermore, the proportion of female among subjects  $\geq 65$  years-old was significantly higher than males (87.7% vs. 64.4%,  $p < 0.0001$ ). The average annual hospitalization rate of 1.6 per 1,000,000 population, with a median length of stay of 25 days. 79.8% of patients was  $> 64$  years-old and 69% involved female. The estimated case fatality ratio was 16.5%. National mortality data were available for the years 2001-2003 and 2006-2010. 169 deaths were reported, with a mean annual number of 21 (range: 17-

27). Seroprevalence data about the same period are also available and show that the percentage of subjects with protective tetanus antibody levels ( $> 0.1$  IU/ml) decreases with increasing age from 87% (95% CI: 84.1-89.5) in the age group 15-24 years to 43.4% (95% CI: 38.6-48.3), 26.6% (95% CI: 21.4-32.2), 27.9% (95% CI: 22.3-33.9) and 17.1% (95% CI: 6.6-33.6) in the age groups 45-64, 65-74, 75-84 and  $\geq 85$  years, respectively. Therefore, most people aged  $\geq 65$  years are unprotected and this is probably due to inadequate VC. Furthermore, most elderly people probably never received a primary vaccination course. Low antibody levels observed in young adults suggest poor compliance with booster recommendations. The observed antibody levels were higher in males than females ( $p < 0.001$ ) from age 25 years. This is probably due to the fact that males had more opportunities for being vaccinated compared to female, such as compulsory military service or work. Then, despite the availability of safe and effective vaccines, too many cases and deaths still occur, especially among older adults [10].

### DIPHTHERIA

Before the introduction of universal vaccination with aluminum-containing toxoids in 1939 in Italy, the disease was a widespread disease and major cause of death, especially in children. The number of reported cases per year and deaths until 1940 were 20-30,000 and 1,500, respectively. In the 1950s and 1960s, the number of reported cases reached several thousands per year. Then, between 1973 and 1982 the number of cases fell to a few per year. Since then the disease has become exceptional: only 5 cases of diphtheria were registered between 1990 and 1998, one of which was imported. From 1999 to 2006 no case has been reported. Extensive childhood immunization and adequate boosting vaccination of adults led to the near-elimination of diphtheria in Western countries [11, 12]. Data obtained from a seroprevalence study conducted in eight Italian cities from June 1993 to June 1995, demonstrated the progressive reduction in antibody titers as age increases. The percentage of subjects with unprotective antitoxin concentrations progressively increased from 7.2% in the 1-10 years age group to 33.4% in subjects aged  $> 60$  years. This is related to the fact that, at that time, no further booster was recommended after the childhood immunization course and it suggests that the immunological memory declines with age [13].

## Prevention of tetanus and diphtheria

### A) THE AVAILABLE VACCINES

In the 1920s, Ramon at the Institut Pasteur developed a method for inactivating tetanus and diphtheria toxins, which led to the development of tetanus and diphtheria toxoids, which were nontoxic but highly immunogenic [1, 5]. Tetanus and diphtheria toxoids are produced from the cell-free purified toxins extracted from the strain of *C. diphtheriae* and from *C. tetani*. They are treated with

formaldehyde to convert toxin into toxoid and it is then adsorbed onto an aluminum salt to improve its immunogenicity [1, 5, 14].

Tetanus toxoid is available as a single-antigen preparation, combined with diphtheria toxoid as pediatric diphtheria-tetanus toxoid (DT) or reduced tetanus-diphtheria (Td) formulated for adolescents and adults, and with both diphtheria toxoid and acellular pertussis vaccine as DTaP or Tdap. DTaP replaced DTP (diphtheria and tetanus toxoids and whole-cell pertussis vaccine) in 1997 [3]. Tetanus toxoid is also available as combined products diphtheria/tetanus/acellular pertussis/inactivated polio vaccine (DTaP-IPV), diphtheria/tetanus/acellular pertussis/hepatitis B/inactivated polio vaccine (DTaP-HepB-IPV) and diphtheria/tetanus/acellular pertussis/inactivated polio vaccine/*Haemophilus influenzae* type b (DTaP-IPV-Hib) [1, 5, 14].

Seroprotection rate evaluated up to 10 years after booster vaccination of children at pre-school age demonstrated that almost all subjects achieve antitoxin levels against both diphtheria and tetanus considerably greater than the protective level of 0.1 IU/ml. Nevertheless, antitoxin levels decrease with time in adulthood [15].

#### B) STRATEGIES FOR PREVENTING DIPHTHERIA, TETANUS (AND WHOOPING COUGH) IN ITALY

Tetanus toxoid vaccine was introduced in 1938 as compulsory vaccine only for military personnel. In 1963 it became compulsory also for children two-year-old and for specific work categories and in 1968 the vaccine is administered during the first year of life [10].

Immunization with diphtheria toxoid is available from 1929 and it has been compulsory for all newborns since 1939. Since 1969, diphtheria vaccine is administered combined with tetanus toxoid. Furthermore all newborn receive a primary course that includes three doses since 1981 [13].

The current Italian National Immunization Prevention Plan 2012-2014 recommends the administration of the vaccine against tetanus and diphtheria (in association with the vaccine against polio, whooping cough, hepatitis B and *Haemophilus influenzae* type b) in the first year of life (3 doses) [16]. In the preschool age a booster of diphtheria, tetanus, pertussis and polio (DTP-IPV) is recommended and a second booster with the adult formulation (dTpa) is timetabled in adolescent age (11-18 years). In adults dT booster doses are recommended every 10 years, even if it is recommended that if the adult has never been vaccinated for DT one of three doses of vaccine should

also contain antigens for pertussis. It is recommended that adults with unknown dT immunization history begin or complete the primary course. The adult primary course included two doses of dT and a third dose with dTap vaccine. The following booster should be administered every 10 years after the primary course and at least one of the booster doses should be replaced by a dTap dose.

Booster recommendations vary among countries, taking into account the seroepidemiological data of tetanus and diphtheria and the incidence in different age groups [9, 17-20]. Nevertheless, the need for decennial booster doses is debated by some experts [21-25]. Some authors stated that the interval between adult boosters could be wider, maybe of 20 years [25]. Furthermore, according to some experts, the best time to verify tetanus immunization status and to offer a single Td dose is the age of 50 [26]. This strategy could be appropriate even in Italy, considering that the lowest level of antibody titers was found in adults  $\geq 45$  years of age [10]. Surely, strategies to improve vaccine uptake in this age group should be implemented.

#### Post-exposure prophylaxis for tetanus

Appropriate wound management in the Emergency Departments is also essential for preventing tetanus [27]. Wound management requires the consideration of the need for (i) passive immunization with tetanus immune globulins (TIG); and (ii) active immunization with vaccine (Tdap or Td). The TIG affords temporary immunity by directly providing antitoxin. This ensures the achievement of protective levels of antitoxin even if an immune response has not yet occurred [1]. The type of treatment depends on the tetanus risk assessment of wounds and the patient's immunization history (Tab. I).

#### Rationale for DTaP booster

The immunological pressure exerted by high VC against pertussis achieved in the pediatric age and the relatively short duration of induced immunity against the disease, have allowed a reduction not only in the pertussis incidence in children, but also the chances of natural boosting and the subsequent increasing number of cases among adolescents or adults who have lost their immunological protection and in infants that have not yet begun or completed their primary immunization course [28-31]. For these reasons, most countries that have included vaccination against pertussis in their national immunization schedule, recommend a booster dose at preschool age and a second booster in adolescents, after the primary

Tab. I. Preventive strategies of postexposure tetanus.

Immunization history (number of doses) for tetanus	Tetanus risk assessment of wounds			
	Low-risk wounds		High-risk wound	
	dT-DTP-dTp <sup>1</sup>	TIG <sup>2</sup>	dT-DTP-dTp <sup>1</sup>	TIG <sup>2</sup>
Unknown or < 3 doses	Yes	No	Yes	Yes
$\geq 3$ doses	No <sup>3</sup>	No	No <sup>4</sup>	No

<sup>1</sup> Administration of combined vaccine against diphtheria and tetanus (dT) or against diphtheria, tetanus and pertussis (DTP or dTp); <sup>2</sup> administration of anti-tetanus immunoglobulin; <sup>3</sup> yes, if  $\geq 10$  years have elapsed since the last tetanus toxoid-containing vaccine dose; <sup>4</sup> yes, if  $\geq 5$  years have elapsed since the last tetanus toxoid-containing vaccine dose.

course of DTaP in the first year of life. Furthermore, in some countries a decennial booster in adults is recommended, in consideration of the relative limited duration of immunity induced both by natural infection and vaccination [32, 33].

In Italy in accordance to the “Lifetime Vaccination Calendar” proposed by a coalition of scientific societies and professional organizations, such as the Italian Society of Hygiene, Preventive Medicine and Public Health (SItI), the Italian Federation of Paediatricians (FIMP), the Italian Society of Pediatrics (SIP) and the Italian Society of General Practitioners (SIMMG), a decennial dTap booster is recommended in adults (e.g., childcare workers, healthcare workers, teachers, etc.) [34].

Furthermore, the current Italian National Immunization Prevention Plan 2012-2014 recommends that the adults who have never been vaccinated for DT receive one dose of dTap among the three doses of the primary course [16].

#### *Prevention of pertussis in infants (the “Cocoon” strategy)*

Available epidemiological data show that the burden of pertussis in terms of incidence mainly involves infants, adolescents and adults. Infants suffer from the most serious complications of the disease, including death. A decreased risk of infection in newborns can be achieved with the immunization of parents, family members and cohabitants who have a close contact with newborns, who are unvaccinated or incompletely immunized. The booster dose should be administered preferably in the months preceding the birth or immediately after the delivery. The vaccination of pregnant women during the third trimester or late second trimester is recommended also by the ACIP, in conjunction with the American College of Obstetrics and Gynecology and is included in the vaccination schedules of some Western countries, e.g. Netherlands and United Kingdom [32, 33, 35, 36].

This strategy might be combined with a booster targeting adults at high risk of transmitting *B. pertussis* infection to vulnerable infants (e.g., childcare workers, healthcare workers, teachers, etc.), as recommended in the current Italian National Immunization Prevention Plan 2012-2014 [16].

#### *Objectives of vaccine strategies against diphtheria-tetanus-pertussis implemented in Italy*

The implemented strategies should achieve the following objectives [16]:

- achievement and maintaining VC with three doses of DTaP administered at 24 months of age and with the booster dose at the pre-school age  $\geq 95\%$ ;
- achievement and maintaining of VC with the “booster” dose of DTaP administered in adolescents  $\geq 90\%$ .

## Conclusions

The question “are dT boosters really necessary every 10 years?” should be rephrased as follows: “are dTap boosters really necessary every 10 years?”

The answer is “yes, certainly”, especially taking into account the estimated duration of immunity against pertussis (no more than 10 years) and the need to maintain high protective vaccine-induced antibody titers. Furthermore, the decennial booster involves the advantage of maintaining high protection even against tetanus and diphtheria, thanks to the availability of safe and effective combined vaccines.

It is desirable that this recommendation will also introduced in the future National Immunization Prevention Plan.

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