

Note

Immunogenicity of a combined diphtheria–tetanus–acellular pertussis vaccine in adults

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Abstract

Two clinical studies were undertaken to evaluate the immunogenicity of an adult-type dTpa booster vaccine (BoostrixTM by Glaxo-SmithKline Biologicals). Blood samples taken prior to vaccination showed that 24.4 and 13.0% of subjects were seronegative for diphtheria and tetanus antibodies, respectively. Moreover, about one-third of the vaccinees had no detectable levels of antibodies to pertussis toxoid (PT) or pertactin (PRN). One month post-vaccination, more than 93% of all individuals, regardless of age or type of vaccine received, had seroprotective antibody levels for diphtheria and tetanus (≥ 0.1 IU/ml). In those individuals vaccinated with the adult-type dTpa vaccine (BoostrixTM), more than 98% were found to be seropositive for antibodies to all three pertussis antigens (PT, filamentous haemagglutinin (FHA), and PRN). These data suggest that immunity to diphtheria, tetanus and pertussis (DTP) in adults wanes and that booster vaccination with an adult-type combined dTpa vaccine would boost the serological response to diphtheria antitoxin, tetanus antitoxin and antibodies to *Bordetella pertussis* PT, FHA and PRN.

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1. Introduction

The incidence of infectious diseases such as diphtheria, tetanus and pertussis (DTP) has declined significantly over the years as a result of worldwide infant immunisation programmes. However, there is increasing evidence to suggest that a significant proportion of the population remains susceptible to infection. This was demonstrated by the recent diphtheria epidemic in the newly independent states of the former Soviet Union, which claimed over 4000 lives in the 1990s [1]. The re-emergence of epidemics such as this has led to the re-evaluation of disease control strategies, highlighting the importance of achieving and maintaining high vaccination coverage rates in children and closing the immunity gap in adults [2]. Sero-epidemiological studies have revealed that a significant proportion of the adult population in industrialised countries is unprotected from diphtheria (26–52%) and tetanus (19–51%) infection [3–8].

As a result of combined diphtheria, tetanus and pertussis vaccination campaigns, natural exposure to these diseases in childhood is now uncommon in many parts of the world and immunity at a young age is acquired almost exclusively through immunisation. It has been shown that immunity wanes over time—serological data suggest an age-related decrease in serum antibody concentrations to diphtheria and tetanus in the general population [3,9–12] and almost one in five people who were vaccinated against diphtheria as infants have antibody concentrations less than the pre-established limits of protection 25–30 years later [13]. This means that many adults have undetectable antibody levels for these vaccine-preventable toxin-mediated infections, suggesting they are unprotected or have never acquired immunity at all. A similar age-related decrease in antibody levels has also been observed for pertussis [14–16]. Although pertussis disease may not be serious in adulthood, infected adults may act as reservoirs of infection for non- or incompletely-immunised infants, in whom this disease is more severe and potentially life-threatening.

In light of these concerns, we present the combined results of two clinical vaccine studies performed in adult volunteers

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from Belgium and Australia [17] in order to investigate the serostatus of antibodies to diphtheria antitoxin, tetanus antitoxin and antibodies to *Bordetella pertussis* pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) in certain age groups of the general population. In addition, we assessed the immunogenicity of a booster vaccination, using either a dTpa vaccine or a licensed bivalent tetanus and diphtheria (Td) vaccine.

2. Methods

An assessment was made of the pre-vaccination serostatus of 824 adults enrolled in two clinical trials to evaluate the combined dTpa vaccine, Boostrix™ (GlaxoSmithKline Biologicals)—one trial was conducted in Belgium and the other in Australia. These clinical trials were randomised, controlled studies of healthy adults ≥ 18 years of age with (1) no history of diphtheria or tetanus vaccination, and (2) no previous exposure to disease, for at least 5 years. The mean age at the moment of vaccination for subjects enrolled in the Belgian trial was 39 years (S.D. = 11 years) with an age range of 19–70 years. In the Australian trial, the mean age of the individuals at the time of vaccination was 30 years (S.D. = 10.6) with an age range of 18–73 years. Subjects were randomised to receive either one dose of Boostrix™ or a licensed bivalent Td vaccine (ADT™, Commonwealth Serum Laboratories or Tedivax Adult™/Ditanrix™, GlaxoSmithKline Biologicals). Boostrix™ contains diphtheria and tetanus toxoids together with three purified pertussis antigens (PT, FHA and PRN). Blood samples were collected immediately before and 1 month after vaccination and antibody levels measured to assess immunogenicity.

Anti-diphtheria antibody concentrations were measured by enzyme-linked immunosorbent assay (ELISA) and, for those subjects seronegative by ELISA, by an in vitro VERO cell neutralisation assay and expressed as IU/ml by calibration with a reference standard. Anti-tetanus antibody concentrations were measured by ELISA alone. Antibody concentrations against pertussis toxoid, filamentous haemagglutinin and pertactin were measured by ELISA and expressed as EL.U/ml by calibration with a reference standard (all tests were performed in the same validated laboratory—GlaxoSmithKline Biologicals, Rixensart, Belgium).

Seroprotection was defined as: anti-diphtheria antibody concentrations ≥ 0.1 IU/ml (ELISA) or ≥ 0.016 IU/ml (VERO assay); anti-tetanus antibody concentrations ≥ 0.1 IU/ml (ELISA) [18,19]. The cut-off for pertussis was 5 EL.U/ml (5 EL.U/ml is higher than the limit of quantitation and much higher than the limit of detection of the assay, ensuring the laboratory to measure the antibody levels below cut-off of 5 EL.U/ml).

The imprecision, expressed as percentage coefficient of variation, is $<20\%$ for the five assays.

Table 1

Percentage of subjects seronegative for antibodies against diphtheria, tetanus and pertussis prior to vaccination with either the combined dTpa vaccine Boostrix™ or a licensed Td vaccine

Group	<i>n</i>	Seronegative (%)	95% CI	
Diphtheria ^a				
All	824	24.4	21.5	27.5
<40 years	505	21.4	17.9	25.2
>40 years	319	29.2	24.2	34.5
Tetanus ^b				
All	824	13.0	10.8	15.5
<40 years	523	5.7	3.9	8.1
>40 years	323	24.8	20.2	29.9
Pertussis anti-PT ^c				
All	836	31.5	28.3	34.7
<40 years	519	31.2	27.3	35.4
>40 years	317	31.9	26.8	37.3
Pertussis anti-PRN ^c				
All	846	28.7	28.3	34.7
<40 years	522	28.0	24.2	32.0
>40 years	324	29.9	25.0	35.3
Pertussis anti-FHA ^c				
All	831	2.1	1.2	3.3
<40 years	512	2.5	1.4	4.3
>40 years	319	1.3	0.3	3.2

^a Seronegative defined as antibody titre <0.1 IU/ml by ELISA or ≤ 0.016 IU/ml by VERO assay.

^b Seronegative defined as antibody titre <0.1 IU/ml by ELISA.

^c Seronegative defined as antibody titre <5 EL.U/ml by ELISA.

3. Results

3.1. Seronegativity status

A significant proportion of the 824 adults tested were found to be seronegative for antibodies against diphtheria and tetanus (Table 1). Almost one-quarter of adults (24.4%; 95% CI: 21.5–27.5%) had anti-diphtheria antibody and 13% (95% CI: 10.8–15.5%) anti-tetanus antibody concentrations below 0.1 IU/ml, respectively. The proportion of seronegative adults (for tetanus and diphtheria) was highest in older individuals.

About 30% of individuals had no detectable levels of antibodies to the PT or PRN pertussis antigens.

There were no marked differences in pre-vaccination serostatus between the two study groups, except for tetanus antibody levels, where 6.4% (95% CI: 3.9–9.8%) of adults in the Belgian study were seronegative compared to 16.6% (95% CI: 13.6–20.0%) in the Australian study.

3.2. Serological profile 1 month post-vaccination

Almost all individuals, regardless of their age or the type of vaccine used, demonstrated a serological response for both diphtheria and tetanus with antibody levels ≥ 0.1 IU/ml following booster vaccination. In individuals vaccinated with the dTpa vaccine, Boostrix™, 93.0 and 99.8%

Table 2

Percentage of subjects with seroprotective antibody concentrations 1 month after vaccination with either the combined dTpa vaccine BoostrixTM or a licensed Td vaccine

Vaccine	Group	<i>n</i>	Seroprotected (%)	95% CI	
Diphtheria ^a					
Boostrix™ (dTpa)	All	513	93.0	90.4	95.0
	<40 years	282	95.0	91.8	97.3
	>40 years	231	90.5	85.9	93.9
Td	All	205	93.2	88.8	96.2
	<40 years	139	97.1	92.8	99.2
	>40 years	66	84.9	73.9	92.5
Tetanus ^b					
Boostrix™ (dTpa)	All	532	99.8	99.0	100.0
	<40 years	297	100.0	98.8	100.0
	>40 years	235	99.6	97.7	100.0
Td	All	209	99.5	97.4	100.0
	<40 years	143	100.0	97.5	100.0
	>40 years	66	98.5	91.8	100.0
Pertussis anti-PT ^c					
Boostrix™ (dTpa)	All	525	98.7	97.3	99.5
	<40 years	293	99.0	97.0	98.8
	>40 years	232	98.3	95.6	99.5
Pertussis anti-PRN ^c					
Boostrix™ (dTpa)	All	531	99.4	98.4	99.9
	<40 years	295	99.7	98.1	100.0
	>40 years	236	99.2	97.0	99.9
Pertussis anti-FHA ^c					
Boostrix™ (dTpa)	All	517	100.0	99.3	100.0
	<40 years	289	100.0	98.7	100.0
	>40 years	228	100.0	98.4	100.0

^a Seroprotection defined as antibody titre ≥ 0.1 IU/ml by ELISA or ≥ 0.016 IU/ml by VERO assay.

^b Seroprotection defined as antibody titre ≥ 0.1 IU/ml by ELISA.

^c Seropositivity defined as antibody titre ≥ 5 ELU/ml by ELISA.

sero-responded for diphtheria and tetanus, respectively (Table 2) compared to 93.2 and 99.5% in those vaccinated with a Td vaccine. In addition, almost all individuals vaccinated with BoostrixTM became seropositive for the pertussis antigens PT (98.7%), FHA (99.4%) and PRN (100.0%) (Fig. 1).

4. Discussion

A significant proportion of the adult population of Belgium and Australia is seronegative for antibodies against diphtheria antitoxin and tetanus antitoxin despite the implementation of childhood vaccination programmes in these countries since the 1950s. Although no serological correlate of protection exists for pertussis, it is important to note that almost one in three people had no detectable antibody levels for the PT or PRN pertussis antigens, regardless of age. It is still debatable whether this reflects immunity or lack of immunity but it is reasonable to assume that these individuals could be susceptible to disease and represent a source for further transmission of disease [20].

There were no differences in serostatus between the Belgian and Australian study samples, with the exception of tetanus where the level of seropositivity was higher in the Belgian study. However, the broad similarity in serostatus between the two countries suggests that these findings are likely to apply to other industrialised countries with similar adult vaccination coverage and may reflect a more global situation.

Vaccination against diphtheria and tetanus diseases is the most widely recommended combination vaccine when travelling. Moreover, a range of combination booster vaccines is available that enable subjects to be immunised against multiple infectious diseases (e.g. diphtheria, tetanus and

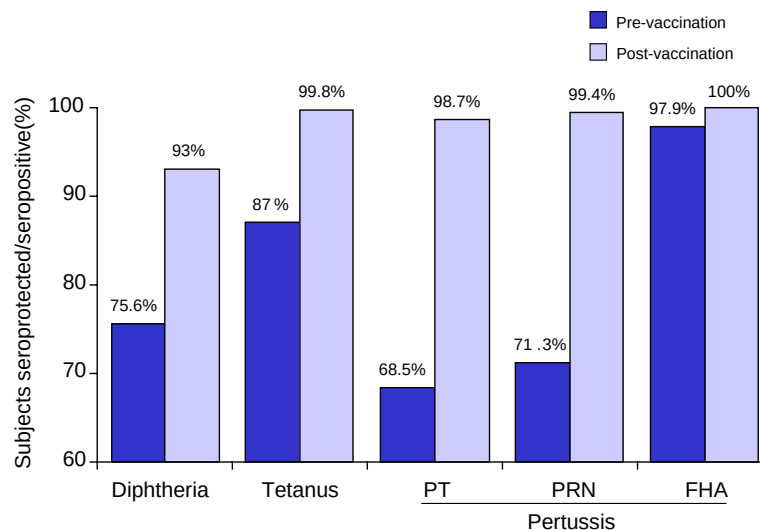


Fig. 1. Percentage of subjects with diphtheria and tetanus antibody concentrations ≥ 0.1 IU/ml and pertussis antibody levels above the 5 ELU/ml cut-off before and 1 month after vaccination with the combined dTpa vaccine, BoostrixTM.

pertussis) in a single visit to their practitioner. Such vaccines are not only economically attractive (by reducing the number of visits required to achieve immunity) and safe but may also increase compliance and extend vaccination coverage.

Despite the significant pre-vaccination seronegativity observed among participants in this study, booster immunisation with either a Td or dTpa vaccine was shown to make vulnerable individuals respond with antibodies against diphtheria antitoxin, tetanus antitoxin and antibodies to *B. pertussis* PT, FHA and PRN. At 1 month post-vaccination, almost all individuals of all ages had antibody concentrations above 0.1 IU/ml for diphtheria and tetanus. The dTpa vaccine, BoostrixTM, had the added value of inducing antibody response to *B. pertussis* PT, FHA and PRN, as well.

Therefore, based on the epidemiological data from the recent literature, as well as data from clinical trials with combined dTpa vaccines, a group of international experts has recommended diphtheria, tetanus and acellular pertussis booster vaccination for all adults, particularly those in contact with younger children and infants as well as those planning to travel [21,22].

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