

Diphtheria vaccine

Review of evidence on vaccine effectiveness and immunogenicity to assess the duration of protection ≥ 10 years after the last booster dose.

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Outline of presentation

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Background

WHO position on the use of diphtheria vaccine

- WHO position paper on diphtheria vaccine dates back to 2006.
- Primary series of DTwP- or DTaP-containing vaccines should be administered in 3 doses.
- To compensate for the loss of natural boosting, industrialized countries should add childhood boosters of diphtheria toxoid to the primary immunization series of infancy.
- Boosting at the age of 12 months, at school entry and just before leaving school are all possible options, based on the local epidemiology.
- WHO currently recommends that people living in low-endemic or non-endemic areas may require booster injections of diphtheria toxoid at about 10-year intervals to maintain life-long protection.

Objective

- Assess long-term diphtheria vaccine effectiveness (VE) or level of immunogenicity conveyed by a three-dose primary immunization and a 3 dose childhood/adolescent booster dose schedule.
- Assess the need for (decennial) booster doses.
- Assess the potential to harmonize schedules with the excising position paper on tetanus vaccine.

Methods

PICO Questions

- PICO Question 1: What is the duration of continued protection (**effectiveness**) of diphtheria vaccination (≥ 10 years) against cases of respiratory diphtheria conveyed by 3 primary and 3 booster doses until adulthood.
- PICO Question 2 : What is the duration of continued **seroprotection** of diphtheria vaccination (≥ 10 years) against cases of respiratory diphtheria conveyed by 3 primary and 3 booster doses until adulthood.

Inclusion criteria

- Studies were included if they:
 - reported VE/ levels of serum antibodies by time (or time-interval) since last vaccination, minimum time-interval 10 years.
 - Receipt of 3 primary doses and 3 booster doses during childhood and/or adolescence.

Results

Effectiveness

- The search on VE and duration of protection yielded a total of 1453 articles.
- 8 full-text articles were assessed for eligibility of which 1 was included in the qualitative synthesis only.
- None of the studies fulfilled the inclusion criteria and provided an effect estimate on the outcome of continued (≥ 10 years) duration of protection conveyed by a specific schedule of diphtheria-containing vaccines
- Brennan et al. 2000 calculated the matched odds ratio (OR) for time since last dose being 0-4 years (reference) or ≥ 5 years in adults 40–49 years of age during the Russian diphtheria epidemic of the 1990s.
 - The OR for cases having received the last dose of vaccine ≥ 5 years in the past was 12.7 (95%CI: 1.5–106.6)
 - Unknown if the cases had received during their childhood a complete primary series of three vaccine doses and potentially also booster doses.

Results

Immunogenicity

- The systematic review of literature on immunogenicity conferred by diphtheria-containing vaccine yielded a total of 402 publications of which 10 were included for full text review.
- One publication was considered to meet the inclusion criteria, by providing information on immunogenicity levels in relation to time since the receipt of a 3 primary and 3 booster schedule until adolescence.
- 3 studies included in qualitative synthesis.

Results

Immunogenicity

- Swart et al 2016 present the results of two population-based cross-sectional representative seroepidemiological studies performed in the Netherlands in 1995/1996 and in 2006/2007.
- Data were provided on the persistence of diphtheria Immunoglobulin G (IgG) antibody in 1932 individuals 10 to 34 and 10 to 39 years of age.
- Data from individuals who were completely immunized against diphtheria according to the national immunization programme:
 - 3 infant doses followed by booster doses at 11 months, 4 years and 9 years of age.
 - No evidence of re-vaccination.

Results

Immunogenicity

Table 1: Age seroprevalences (%) of diphtheria antibody in 10 to 39 year old individuals, combining the national samples of the 1995/1996 serosurvey (n = 961) and 2006/2007 serosurvey (n = 971), who were completely immunized against diphtheria according to the NIP, without evidence of revaccination.

Age (years)	N	<0.01 IU/ml (%)	(95% CI)	>=0.01 IU/ml (%)	(95% CI)
<u>1995/1996 and 2006/2007 serosurvey</u>					
Overall	1932	2.2	(1.5-2.5)	97.8	(97.5-98.5)
10–14	738	0.5	(0.0-1.0)	99.5	(98.9-100)
15–19	499	1.2	(0.3-2.2)	98.8	(97.8-99.8)
20–24	335	3.9	(1.8-6.0)	96.1	(94.1-98.2)
25–29	199	4.0	(1.3-6.8)	96.0	(93.3-98.7)
30–34	124	7.3	(2.7-11.8)	92.7	(88.2-97.3)
35–39*	37	5.4	(0.0-13.7)	94.6	(87.3-100)

*Data from 2006/2007 serosurvey only.

Diphtheria antitoxin levels:

Less than 0.01 International Units (IU)/mL susceptible,
between 0.1 IU/mL and 1.0 IU/mL protective,
1.0 IU/mL and greater long-term protection

Results

Immunogenicity- Supporting evidence

- Goncalves et al 2007 assessed the levels of diphtheria and tetanus specific IgG of Portuguese adult women, before and after vaccination with adult type tetanus diphtheria (Td) and the duration of immunity following vaccination.
- Twenty-two women had begun their vaccination in childhood with diphtheria-tetanus-pertussis (DTP) before the age of 7 (n=20) or with DT between 7-9 years (n=2).
- In the 20 women who had received a complete DTP primary series (3 doses) during childhood and at least one booster, no susceptibles were observed before 20 years had elapsed from the last dose.
- Of those women, having received 6 doses, all had IgG levels above the protective threshold.

Results

Immunogenicity- Supporting evidence

- Hasselhorn et al 1998 recruited a total of 287 healthy adults (154 women and 133 men: mean age 26.4 years; range 17–54, ± 6.1) in Germany for whom a complete record of diphtheria vaccination was available and who had received at least basic immunization (mean of 4.4 diphtheria vaccinations (range: 3–8, ± 1.1)).
- All individuals, with only one exception, had protective antibody levels in the 15 years after the last vaccine dose.

Results

Immunogenicity- Supporting evidence

- Hammarlund et al 2016 performed a cross-sectional analysis of serum antibody titers in 546 vaccinated adult subjects living in the United States with primary diphtheria immunization.
- Approximately 99% of subjects <60 years of age (and 97% of the overall population) showed diphtheria-specific antibodies that were above the protective level of 0.01 IU/mL.
- Based on analysis of antibody levels as a function of time after vaccination, diphtheria-specific immunity declined in the model with a 27-year half-life (95% CI: 18–51 years)

Limitations

- No data on vaccine effectiveness retrieved.
 - including no data on possible differences in the vaccine effectiveness or duration of protection related to *Corynebacterium* other than diphtheria.
- Limited data on levels of protective immunogenicity.
 - In most studies, the exact vaccination status of participants (number of doses received during childhood) was unknown or not reported.
- Data from Swart et al.:
 - Combination of two different cohorts, having received the same number of doses, though potentially different vaccine combinations.
 - Follow-up only to age 39 years.

Conclusions

- Data from studies with clinical endpoints are inconclusive in respect to the duration of diphtheria vaccine-induced protection.
- Data on the duration of seroprotection after a 6-dose schedule are available from a large representative population study from the Netherlands. It demonstrated a very high seroprevalence above the protective threshold (~94%) up to 39 years of age and potentially longer.
 - Studies from Germany, Portugal and the US support this finding
- The available data do not support the recommendation of decennial booster doses beyond the 6-dose schedule. However, it remains to be assessed whether booster dose(s) will be needed in older age-groups.

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