

# Diphtheria vaccine

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

April 2017

### Background

#### Disease

Diphtheria is a disease caused by exotoxin-producing *Corynebacterium diphtheria* or –less frequently– *C. ulcerans*. There are 4 biotypes of *C. diphtheria* (gravis, mitis, belfanti and intermedius). The most common manifestation is respiratory diphtheria, which usually affects the pharynx and tonsils, though larynx or nasal tissues may be involved as well. In severe cases, obstructive pseudo-membranes in the upper respiratory tract (croup) can develop; other complications are myocarditis or polyneuritis. The overall case-fatality for diphtheria is 5–10%. Cutaneous manifestation of diphtheria can occur, resulting in indolent skin infection.

#### Passive and active immunization

Passive immunization via diphtheria antitoxin (DAT) of equine origin is highly efficacious in treating diphtheria though it is not a replacement for active immunization using diphtheria toxoid. Nevertheless, antitoxin is an important treatment of diphtheria and can reduce both morbidity and mortality. DAT should be administered as soon as possible after disease onset, once the toxin has entered the host cells it is unaffected by the antitoxin. The entire therapeutic dose should be administered at one time. The amount of antitoxin recommended varies between 20.000 and 120.000 units with larger amounts recommended for persons with extensive local lesions and with longer interval since onset. Global production and supply for equine antitoxin have been challenging as almost all traditional manufacturers have ceased their production. Novel approaches include the development of monoclonal antibodies to diphtheria toxin or development of recombinant modified diphtheria toxin receptor molecules to bind diphtheria toxin.<sup>1</sup> However, to date, no monoclonal antibody to diphtheria toxin is authorised for clinical use, therefore treatment still is dependent upon DAT.

Diphtheria toxoid is used for active immunization. Diphtheria vaccines are based on diphtheria toxoid, a modified bacterial toxin that induces protective antitoxin. Diphtheria toxoid is available in combination with tetanus toxoid (T) as DT (for use <7 years of age) or Td (for use  $\geq 7$  years of age), or with tetanus and pertussis vaccine (acellular=a, wholecell=w) as DT(a)(w)P or TdaP. Diphtheria toxoid may also be combined with additional vaccine antigens, such as polio (IPV), hepatitis B and *Haemophilus influenzae* type b.

In regard to the population level, it is believed that vaccine coverage of 80%–85% must be maintained in order to induce herd immunity/community immunity and reduce the threat of an outbreak.<sup>1</sup>

### Vaccine efficacy and effectiveness

No controlled clinical trial of the efficacy of the toxoid in preventing diphtheria has ever been conducted. There is, however, strong evidence from observational studies to support the effectiveness of vaccination, although effectiveness of diphtheria toxoid does not reach 100%:

- Halifax epidemic 1940-1941<sup>2</sup>: Among those immunized (most individuals had received 3 primary doses), the monthly incidence of diphtheria fell to 24.5 per 100,000 population, about one seventh of the rate in the unimmunized children during that same period (168.9 per 100,000).
- Britain 1943<sup>3</sup>: the rate of clinical diphtheria among the unimmunized was 3.5 times that among the immunized, and mortality was 25-fold greater.
- Eglin, Texas 1970<sup>4</sup>: In an outbreak only two of 205 fully immunized, exposed elementary schoolchildren acquired the disease.
- San Antonio, Texas 1970<sup>5</sup>: Vaccine efficacy was estimated at only 54%, though data were difficult to interpret.
- Yemen<sup>6</sup>: the protective efficacy of diphtheria toxoid was determined to be 87% among those who had received 3 or more doses by the case-control method.

The largest outbreak of the recent past was reported from the Russian Federation in the 1990. More than 115,000 cases and 3000 deaths were reported from 1990 to 1997.<sup>7</sup> Most of the cases and deaths occurred among adults. Markina et al suggest that contributing factors included the accumulation of susceptible individuals among both adults and children, the probable introduction of a new biotype of *C. diphtheria* and social factors such as migrating populations. Vaccine quality, vaccine supply, or access to vaccine providers was assessed to not have significantly contributed to the epidemic.

- Ukraine 1992<sup>8</sup>: The effectiveness of three or more doses was 98.2% (95% confidence interval [CI], 90.3%-99.9%).
- Russia 1993<sup>9</sup>: The effectiveness of three or more doses was 96.9% (95% CI, 94.3%-98.4%), increasing to 99.0% for five or more doses (95% CI, 97.7%-99.6%).

### Effect of vaccination on diphtheria carriage

Miller et al. 1970<sup>4</sup> suggests that diphtheria vaccination prevents symptomatic infections, though it does not prevent carriage or spread of diphtheria. This hypothesis is based on throat swabs of 306 school children and staff during an outbreak investigation in Eglin Texas. *C. diphtheria* was isolated from 104 (34%) individuals of which 15 (14%) were cases and 89 (86%) were carriers. Of the 104 positive, 73 were fully, 28 inadequately and 3 not immunized. The presence of the phage (referring to the phage that induces toxin production in the bacterium) is thought to confer survival advantage to the bacterium by increasing the probability of transmission; transmission may be facilitated by local tissue damage resulting from the toxin.<sup>1,10,11</sup> The United States Immunization Practices Advisory

Committee (ACIP) states, that immunization does not eliminate carriage of *C. diphtheriae* in the pharynx, nose or on the skin.<sup>12</sup>

### WHO position paper on Diphtheria vaccine<sup>13</sup> - Information on and recommended schedule

The current WHO recommendation which dates back from 2006 states that a primary series of DTwP- or DTaP-containing vaccines should be administered in 3 doses, starting as early as 6 weeks of age, and given with a minimum interval of 4 weeks. To compensate for the loss of natural boosting, industrialized countries should add childhood boosters of diphtheria toxoid to the primary immunization series of infancy. Booster doses should be given after the completion of the primary series. Boosting at the age of 12 months, at school entry and just before leaving school are all possible options, based on the local epidemiology. In addition to childhood (and adolescent) immunizations, 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.

In light of WHO's Optimizing Immunization Schedules project, the comparative efficacy or effectiveness of different immunization schedules during the first 5 years of life against diphtheria were assessed.<sup>14</sup> The review yielded, among other, the following results: For both diphtheria and tetanus, 2 primary doses resulted in substantially lower antitoxin mean titres than 3 primary doses. A birth dose prior to a 2,4,6-month primary schedule did not provide higher antitoxin geometrical mean concentrations (GMC) against diphtheria or tetanus between age 6 through 9 months or after a booster in the second year of life. The data suggest substantial increase in diphtheria and tetanus antibody due to booster vaccination at 18 months, following an initial 3,4,5-month primary schedule. The quality of the retrieved evidence varies.

The recently published WHO tetanus vaccine position paper<sup>15</sup> recommends 6 doses (3 primary plus 3 booster doses prior to adolescence). As tetanus and diphtheria vaccines are frequently administered together, it would be programmatically advantageous to harmonize the schedules, granted that 6 doses of diphtheria vaccine prior to adolescence confer adequate levels of protection throughout adulthood.

### Correlate of protection

On the basis of studies of diphtheria antitoxin levels early in the course of disease, persons with diphtheria antitoxin levels of less than 0.01 International Units (IU)/mL appear to be highly susceptible to disease, and higher levels are generally associated with progressively less severe symptoms.<sup>1,16,17,18,19</sup>

Probably no level of circulating antitoxin confers absolute protection; Ipsen reported two cases of fatal diphtheria in patients with antitoxin levels above 30 IU/mL the day after onset of symptoms.<sup>16</sup>

Overall, the data allow some general conclusions regarding protective levels in most circumstances. An antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection, and 0.1 IU/mL is considered a protective level of circulating antitoxin. Levels of 1.0 IU/mL and greater are associated with long-term protection.<sup>20</sup>

The WHO Immunological Basis Series for Diphtheria Immunization<sup>21</sup> confirm that there is no sharply defined level of antitoxin that gives complete protection from diphtheria. A certain range of

variation must be accepted and the same concentration of antitoxin may give unequal protection in different persons. Other factors may influence vulnerability to diphtheria including the infecting dose and virulence of the diphtheria bacilli, and the general immune status of the person infected. Thus, an antibody concentration between 0.01 and 0.09 IU/mL may be regarded as giving basic immunity, whereas a higher titre may be needed for full protection.

The tissue culture neutralization assay is regarded as the most accurate *in vitro* procedure for measuring diphtheria antitoxin, whereas the ELISA and passive haemagglutination methods are known to be inaccurate in the low antitoxin range.<sup>22</sup>

### Duration of vaccine-induced protection

Both the diphtheria toxoid formulation and the schedule of administration affect the level of diphtheria antitoxin achieved and the duration of protection. After three doses of primary diphtheria toxoid immunization, most children achieve antitoxin titers greater than the minimally protective level.<sup>23</sup> However, in the absence of ongoing exposure, immunity wanes over time, requiring booster doses of diphtheria toxoid to maintain protective antitoxin levels. In the absence of a booster dose at 4 to 6 years, protection may not be maintained throughout the school-age years.

In countries with long-standing childhood immunization programs, adults who have neither been exposed to diphtheria nor received booster doses of diphtheria toxoid may become susceptible to diphtheria as a result of waning immunity.<sup>23</sup> During the outbreak in the former Soviet Union, waning of immunity was thought to contribute to the high incidence rate observed among adults. A large proportion of the population of adults, although seronegative, were previously primed by prior immunization or infection with toxigenic *C. diphtheriae*, as evidenced by development of protective titers after a single booster dose of toxoid.<sup>24,25,26,27</sup>

### Seroepidemiological data<sup>1</sup>

The seroepidemiology of diphtheria in Czech Republic, Hungary, Ireland, Latvia, Luxembourg, Slovakia and Israel showed that increasing age is related to a gradual increase in seronegative subjects (< 0.01 IU/ml of diphtheria antitoxin antibodies). This may reflect waning immunity following childhood vaccination without repeated booster vaccinations in adults. Differences in seronegativity were also found according to gender. In subjects aged 1–19 years, geometric mean titres of antitoxin are clearly related to the different vaccination schedules used in the participating countries but most individuals between 1 and 19 years of age were seropositive (>0.01 IU/ml).<sup>28</sup>

In Luxembourg, approximately 2.5% of individuals under the age of 20 were seronegative while 42% of individuals over the age of 40 years were seronegative. This finding supports the presumption that seronegativity tends to increase with age. A sex difference was found between males and females over the age of 50 years in Luxembourg but this difference was attributed to vaccinations given during military service which was made compulsory for males from 1944 to 1967.<sup>29</sup>

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<sup>1</sup> Presented here, a non-systematically retrieved, limited selection of seroepidemiological studies.

A study from Singapore<sup>30</sup> assessed that overall, 92.0% (95% CI: 91.1–92.9%) of 3293 adults aged 18–79 years had at least basic protection against diphtheria (antibody levels 0.01 IU/ml). Lowest seroprevalence was reported in those aged 50–59 (85.5%). Seroprevalence ranged from 87.7 to 92.7% among the elderly aged 60–79.

Age stratified data from China showed that the highest positivity rate of 97.63% was observed in children aged 1–4 years. The rates further decreased to 83.80% at 10–14 years and 73.64% at 15–19 years of age, despite a diphtheria booster dose at 15 years. The positivity rates were around 52% in those aged 25–29 years. The lowest level of 34.11% was observed in subjects older than 40 years.<sup>31</sup>

## Objective

In view of the recent diphtheria outbreaks in South-East Asia such as in Lao People's Democratic Republic from 2012–2013<sup>32</sup>, in India<sup>33</sup> 2015 and 2016, Myanmar 2016, Philippines 2016 and Malaysia 2016 as well as a recent shortages of diphtheria antitoxin and cases<sup>34</sup> reported from the WHO European Region, the Strategic Advisory Group of Experts (SAGE) on Immunisation requested to review the available data and assess the need to revisit the current recommendation.

Objective of this literature review was to assess long-term diphtheria vaccine effectiveness (VE) or level of immunogenicity conveyed by doses beyond the three-dose primary immunization and a 3 dose childhood/adolescent booster dose schedule in order to inform on the afforded duration of vaccine-induced protection and to allow for the assessment of the need for diphtheria (decennial) booster doses. This review will inform the deliberations of SAGE at the April 2017 meeting and facilitate the formulation of related recommendations on the use of the vaccine. These recommendations will be reflected in an update of the current 2006 diphtheria vaccine WHO position paper.<sup>13</sup> Based on the results, it is aimed to harmonize recommendations on the vaccination schedule across the WHO diphtheria vaccine, pertussis vaccine and tetanus vaccine position paper.

## Methods

To identify relevant literature, the following search strategy to answer the specific Population (P), Intervention (I), Comparison (C), Outcome (O)- question guided the review.

- **Population:** Immunocompetent children and adults.
- **Intervention:** Vaccination with diphtheria toxoid (-containing) vaccination
- **Comparison:** No vaccination
- **Outcomes:** Cases of respiratory diphtheria

**PICO Question:** What is the duration of continued protection (effectiveness) of diphtheria vaccination beyond the primary immunization schedule ( $\geq 3$  doses) against cases of respiratory diphtheria conveyed by a specific schedule of diphtheria toxoid (-containing) vaccination and 3 booster doses until adulthood.

A systematic search was conducted using the National Library of Medicine's online search utility PubMed. The search terms can be found in Annex 1. No restrictions were made to range of years, thus the start date was from the beginning of the candidate database to January 2017. No language restrictions were made. In addition, references of eligible reviews were screened to identify further

publications. The literature review considered published, peer-reviewed literature as the primary source of data. All study designs that allowed the assessment of vaccine effectiveness were included (RCTs, case control studies, cohort studies, case-cohort studies). Studies were included when they reported VE by time (or time-interval) since vaccination being 10 years or more among individuals who received at least the primary series (i.e. 3 vaccine doses) plus 3 booster doses during childhood and/or adolescence.

Due to insufficient data being retrieved from the initial search focusing on diphtheria-related clinical endpoints to guide SAGE's decision-making process, the search was expanded to include serological endpoints. Studies were included if they provided any estimate of vaccine-induced serum antibodies levels provided by primary immunization (i.e. 3 vaccine doses) plus 3 booster doses during childhood and/or adolescence and the interval to the receipt of at least primary immunization of diphtheria containing vaccine was  $\geq 10$  years. The search terms can be found in Annex 1.

- **Population:** Immunocompetent children and adults.
- **Intervention:** Vaccination with diphtheria toxoid (-containing) vaccination
- **Comparison:** No vaccination, or different duration between vaccination and serological testing
- **Outcomes:** Diphtheria serum antibody levels/ seroprevalence

**PICO Question:** What is the duration of continued seroprotection of diphtheria vaccination ( $\geq 10$  years) conveyed by a specific schedule of diphtheria toxoid (-containing) vaccination which is comprised of at least 3 vaccine doses (primary series) and 3 booster doses until adulthood.

For both searches, article titles and abstracts were manually examined by two reviewers (OW and MM) and appropriate articles were selected for further review.

Extracted variables included: place, year, number of subjects included in study, any available measure of age, number of diphtheria vaccine doses and time since immunization in the affected individuals, vaccine used and calculated VE (See Annex 2). For the review on seroprotection information on the diagnostic test, the cut-off level as well as antibody levels or proportion of study population being seroprotected were abstracted. The results of this review are provided to SAGE ahead of the April 2017 meeting.

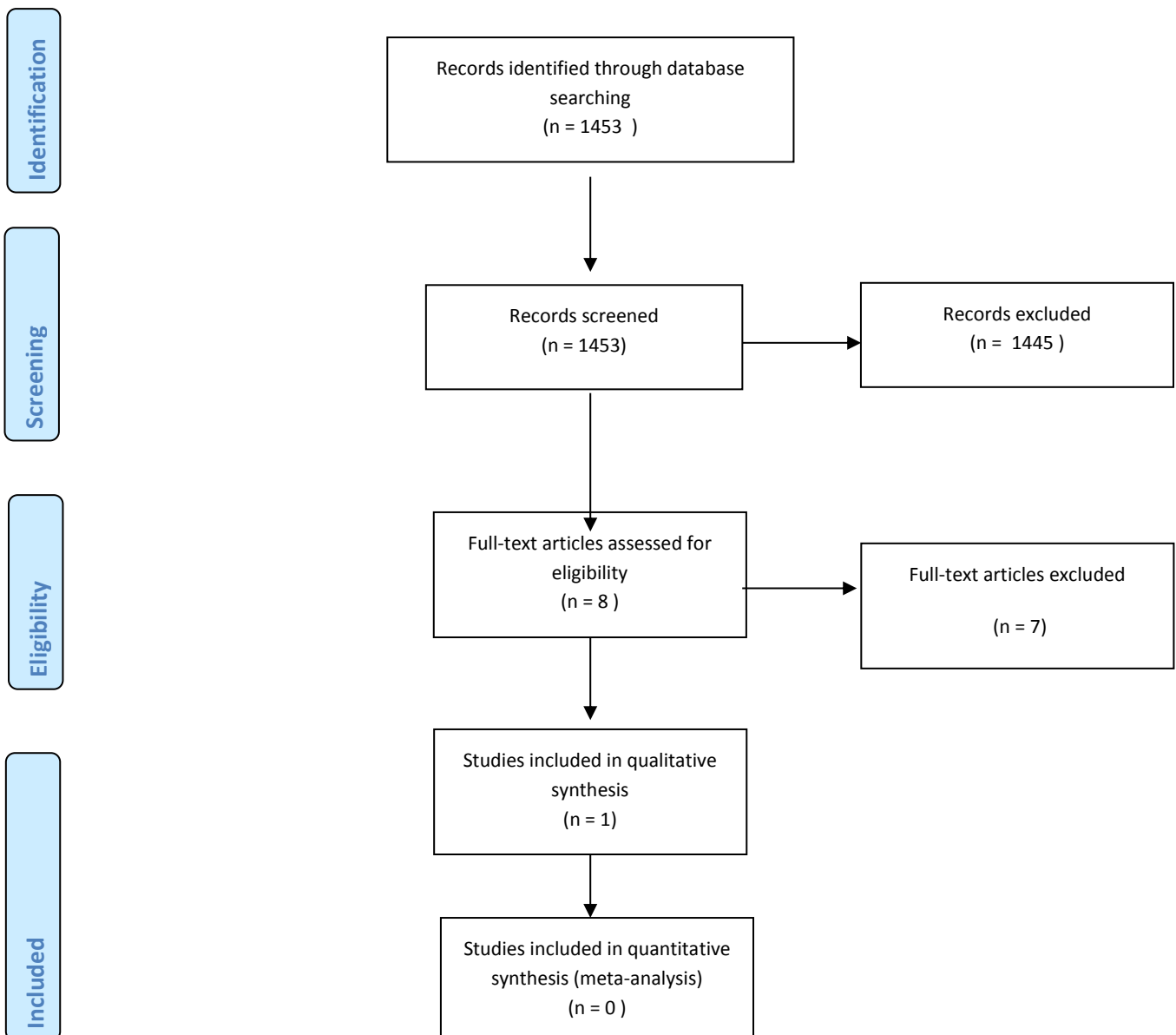
## Results

### Effectiveness data

The search on the effectiveness and duration of protection yielded a total of 1453 reviews. After screening of titles and abstracts, 8 full-text articles<sup>35,36,37,38,39,40,41,42</sup> were assessed for eligibility of which 1<sup>36</sup> was included in the qualitative synthesis. 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, though the results of 1 study was included for descriptive analysis (see Figure 1).

Brennan et al. 2000<sup>36</sup> 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. This age-group in 1995 were born during 1946–1955 and grew up during a period in the Russian Federation when routine childhood immunization had begun but coverage was not complete and circulation of *C. diphtheria* was diminishing, hence were the least likely of any age group to be immunologically protected by either natural infection or vaccination. Cases who had not received any dose in the previous 10 years were excluded. 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) when comparing to cases who received their last dose 0-4 years ago. However, it was unknown if the cases had received during their childhood a complete primary series of three vaccine doses and potentially also booster doses, or if they were completely naïve. Therefore, this study does not provide any evidence in respect to the duration of protection following 6 doses of diphtheria toxoid (-containing) vaccines.

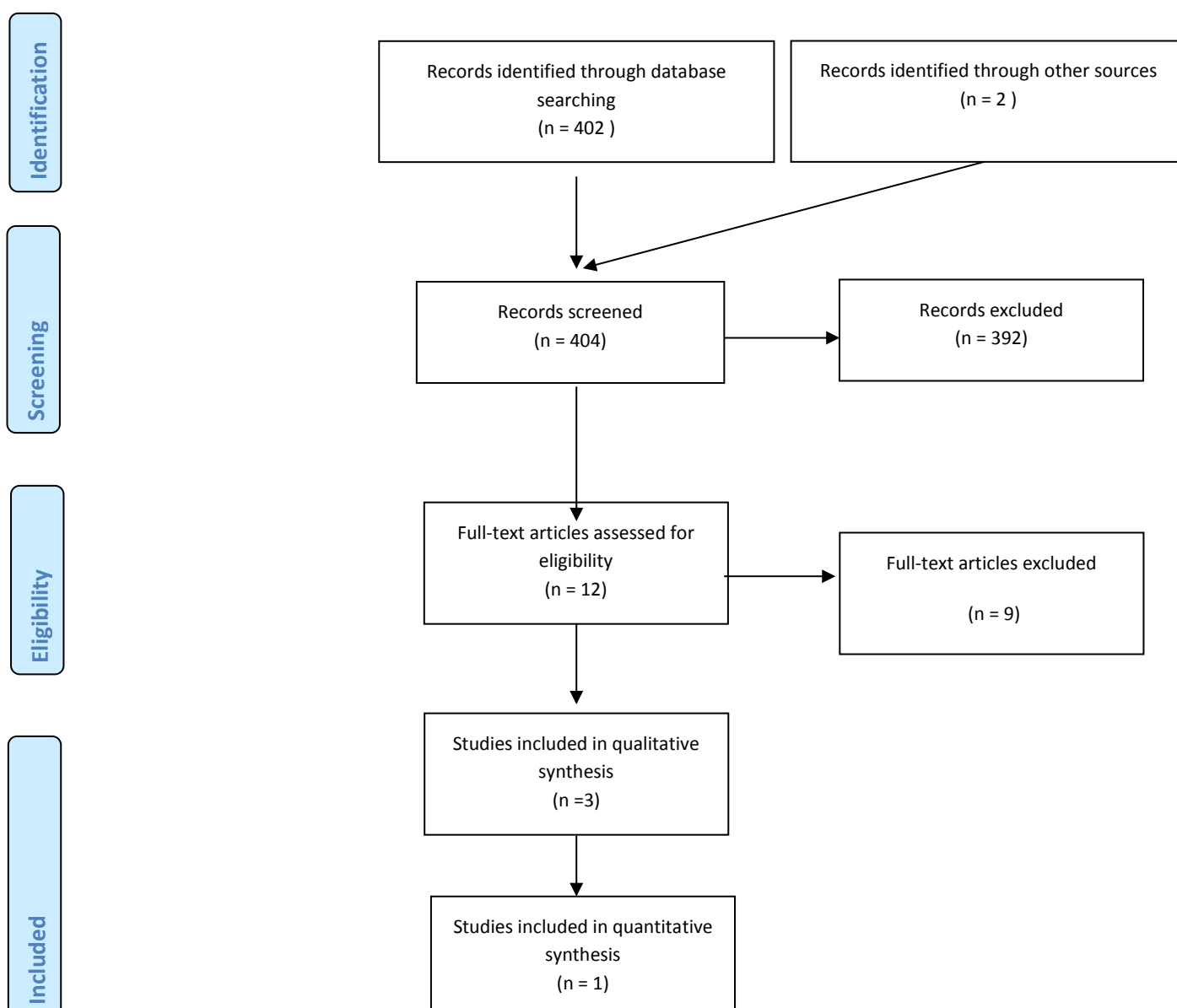
Figure 1: PRISMA Flow Diagram



## Immunogenicity data

The systematic review of literature on the immunogenicity conferred by diphtheria-containing vaccine yielded a total of 402 publications of which 10 were included for full text review<sup>43,44,45,46,22,47,48,49,50,51</sup>. The search was complemented by screening of references as well as a systematic review of literature conducted by the United States Center for Disease Control and Prevention (US CDC), identifying diphtheria serosurvey studies which yielded two additional studies<sup>52,53</sup> for full text consideration. Of these 12 publications, only one publication<sup>48</sup> 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 (see Figure 2). Two additional studies<sup>22,44</sup> provided some information on level of protection, though no direct evidence on the number of vaccine doses in relation to the time since last vaccination was provided. One study<sup>52</sup> was identified as supportive evidence and is described below.

Figure 2: PRISMA Flow Diagram



Swart et al 2016<sup>48</sup> present the results of two population-based cross-sectional representative seroepidemiological studies performed in the Netherlands in 1995/1996 and in 2006/2007. Antibody levels below 0.01 international units per ml (IU/ml) were considered as non-protective, levels of 0.01 IU/ml–0.1 IU/ml were considered to provide basic protection and levels above 0.1 IU/ml were considered to provide full protection against diphtheria. Data were provided on the persistence of diphtheria IgG antibody in 10 to 34 and 10 to 39 year old individuals, in the national sample of the 1995/1996 serosurvey (n = 961) and 2006/2007 serosurvey (n = 971), who were completely immunized against diphtheria according to the national immunization programme (NIP) (3 infant doses followed by booster doses at 11 months, 4 years and 9 years of age), without evidence of re-vaccination. Overall, 0.8% (95%CI: 0.3-1.4) within the 1995/1996 serosurvey and 3.5% (95%CI: 2.3–4.7) within the 2006/2007 serosurvey were not protected (seroprevalence <0.01 IU/ml). The highest percentages, 5.8% (95%CI: 0.0–12.1) and 8.3% (95%CI: 1.9–14.7), of individuals below the protective threshold (<0.01 IU/ml) were seen in the age group from 30-34 years within the 1995/1996 serosurvey and 2006/2007 serosurvey, respectively.

When combining the data from both serosurveys, within the age group of 30-34 years of age, 7.3% (95%CI: 0.0-13.7) remain below the protective threshold (Table 1).

**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)

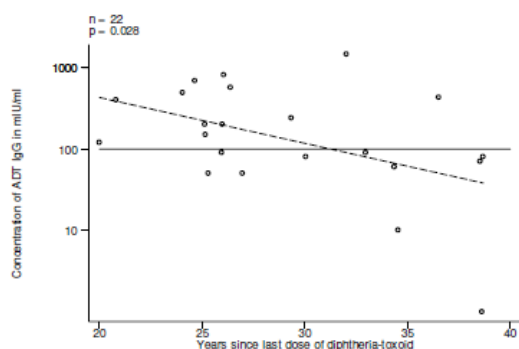
\*Data from 2006/2007 serosurvey only.

The quality of the retrieved evidence was assessed using the GRADE approach (see Annex 2).

Goncalves et al 2007<sup>44</sup> assessed the levels of diphtheria and tetanus specific IgG of Portuguese adult women, before and after vaccination with adult type Td and the duration of immunity following vaccination. Twenty-two women had begun their vaccination in childhood with DTP before the age of 7 (n=20) or with DT between 7-9 years (n=2). These women were born between 1956 and 1973 and - at time of study recruitment- less than 50 years of age. All women had completed their primary immunization (National schedule in Portugal since 1966: 3 primary doses, and booster doses at 18-24 months and 5-6 years. Since 2001: Td is recommended for decennial booster doses). In these 22 women, the last dose of diphtheria toxoid was received 20-39 years ago. On univariate analysis, anti-diphtheria toxin (ADT) IgG levels increased with the number of doses of diphtheria toxoid received (p = 0.013). The laboratory analysis were performed using a commercial enzyme immunoassay. ADT IgG levels ≥100 mIU/ml were considered protective, as recommended in the WHO Immunological

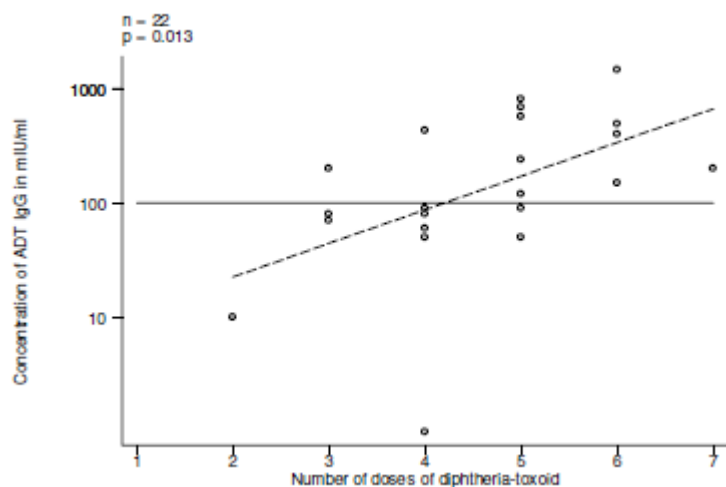
Basis Series for Diphtheria Immunization<sup>21</sup> when EIA technique is performed; according to that threshold, women were classified as "immune" or "susceptible" to diphtheria. Additionally, we considered those with levels  $\geq 1000$  mIU/ml as having "long-term protection". All women who had received 6+ were immune (threshold level of 100 mIU/ml). On univariate analysis ADT IgG levels were also associated with time since last dose ( $p = 0.028$ ), all susceptible women had received diphtheria toxoid more than 25 years before. For those who began vaccination in childhood with DPT/DT, the total number of doses and time since last vaccination were determinant factors; 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. (Figure 3)

**Figure 3: ADT IgG levels, by time since last dose of diphtheria-toxoid, in pre-vaccination sera of women who had been vaccinated with diphtheria-toxoid. Regression line (stippled) and threshold level of 100 mIU/ml (from Goncalves 2007 et al).**



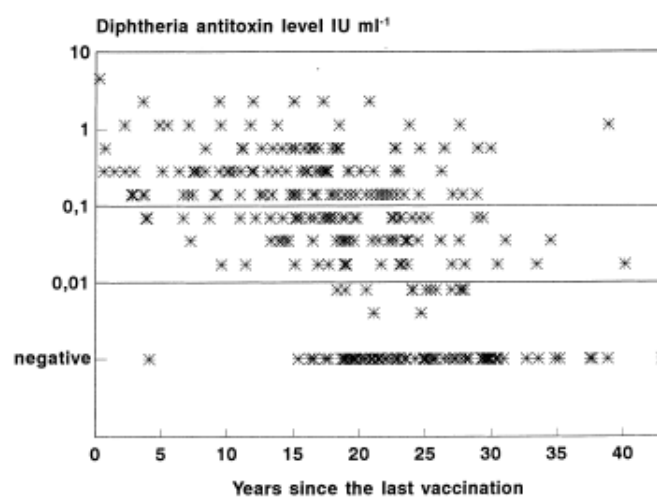
Of those women, having received 6 or more doses, all had ADT IgG levels above the protective threshold. (Figure 4)

**Figure 4: ADT IgG levels, by number of doses of diphtheria-toxoid administered, in pre-vaccination sera of women who had been vaccinated with diphtheria toxoid. Regression line (stippled) and threshold level of 100 mIU/ml (from Goncalves 2007 et al).**



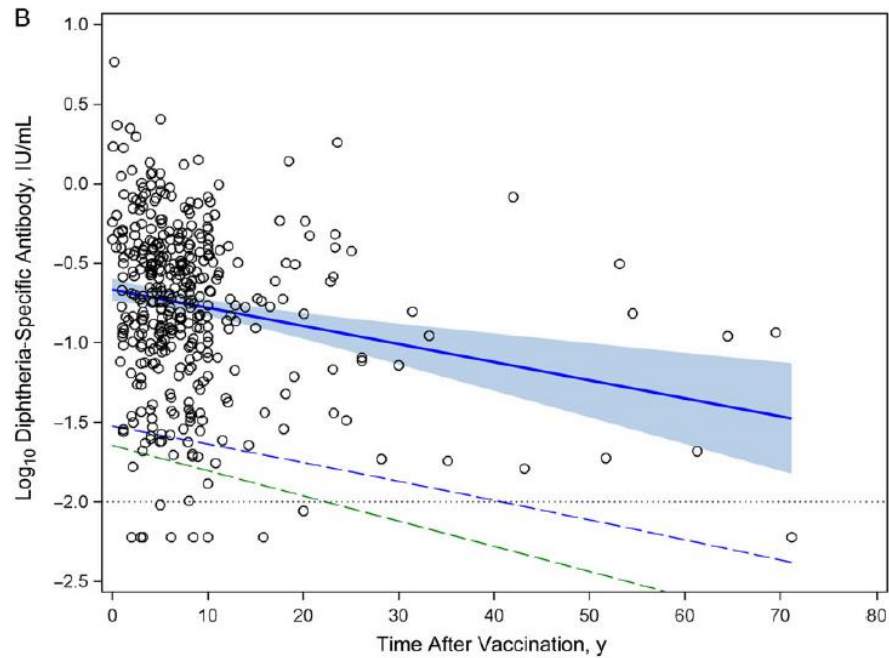
Hasselhorn et al 1998<sup>22</sup> recruited a total of 287 healthy adults (154 women and 133 men: mean age 26.4 years; range 17–54,  $\pm 6.1$ ) in Germany. Participation was limited to those for whom a complete record of diphtheria vaccination was available and who had received basic immunization. The participants had received a mean of 4.4 diphtheria vaccinations (range: 3–8,  $\pm 1.1$ ). The last vaccination being 19.2 years (mean) before (range: 3 months–43.0 years,  $\pm 7.8$  years). Ninety (31.4%) out of the 287 participants were ‘probably susceptible’ to diphtheria, 76 (26.5%) had ‘basic protection’ and 121 (42.2%) had ‘fully protective’ antitoxin levels. The results suggest that diphtheria antitoxin levels wane with the time elapsed since the last vaccination, but that –with only one exception- all individuals had protective antibody levels in the 15 years after the last vaccine dose (See Figure 5). However, the paper does not provide any information on the total number of vaccine doses among individuals who had no or non-protective antibodies levels >15 years after the doses.

**Figure 5: Diphtheria antitoxin levels by time interval since last vaccination. Stages:  $<0.01 \text{ IU ml}^{-1}$ =probably susceptible;  $0.01\text{--}0.1 \text{ IU ml}^{-1}$ =basic protection;  $\geq 0.1 \text{ IU ml}^{-1}$ =full protection. GMT=0.04  $\text{IU ml}^{-1}$ ; negative values treated as 0.001.  $n_{\text{total}}=287$  (from Hasselhorn 1998 et al.).**



One study was identified as supportive evidence in regard to the research question. Hammarlund et al 2016<sup>52</sup> performed a cross-sectional analysis of serum antibody titers in 546 adult subjects living in the United States. Approximately 99% of subjects <60 years of age (and 97% of the overall population) showed diphtheria-specific antibody responses that were above the protective level of 0.01  $\text{IU/mL}$ . 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) (see Figure 6). Also in this study the exact number of previous vaccine doses is unknown.

Figure 6: Humoral immunity to diphtheria as a function of age and time after vaccination. Diphtheria-specific serum antibody responses were measured in adult subjects and plotted versus age (A) or time after vaccination (B). Dotted line in each panel represents level of antibody required for protection, equivalent to 0.01 IU/mL. B, Solid blue line is the fitted regression line representing the antibody half-life decay rate, and the shaded blue region represents the upper and lower bound of 95% confidence interval (CI) for the antibody half-life estimation. Dashed blue line represents a 1-sided lower bound 95% CI based on a 27-year half-life and indicates when diphtheria-specific antibody titers would decline to 95% seroprotection by crossing the protective threshold of 0.01 IU/mL (ie,  $-2 \log_{10}$  IU/mL) at 42 years after vaccination. Dashed green line is based on an estimated 19-year half-life<sup>54</sup> and indicates that 95% of the population will remain protected against diphtheria for 30 years after vaccination (from Hammarlud et al 2016).



## Conclusions

No data in observational studies on long-term clinical effectiveness of diphtheria-containing vaccine could be retrieved, though limited evidence suggests that the risk of disease increased with time since last vaccination but clearly also depends on the total number of received vaccine doses.<sup>36</sup>

Only one study retrieved assessed the duration of protection from diphtheria vaccination within the outbreak setting of the Russian Federation diphtheria epidemic of the 1990s.<sup>36</sup> Adults having received the last dose  $\geq 5$  years in the past was associated with a higher OR for being a case (12.7 (95%CI: 1.5–106.6)). Certain limitations apply, that the duration of protection was assessed for having received the last dose of diphtheria vaccine only  $\geq 5$  years vs  $\geq 10$  years in the past and no information was provided on the total number of doses received as outlined in the inclusion criteria. Further, the small sample size did not allow distinguishing between time since last dose and number of doses because both variables were highly correlated.

Given the limited evidence in respect to the effectiveness of the vaccine in conferring long-term protection, the systematic review assessed the levels of protective immunogenicity conferred by diphtheria vaccination.

Data on the duration of seroprotection from a large representative population study from the Netherlands, using a complete 3-dose primary series plus 3-dose booster series prior to adolescence<sup>48</sup> indicate that this schedule confers a very high seroprevalence above the protective threshold ( $\geq 0.01$  IU/ml) up to 39 years of age and potentially longer. A seroprevalence of 94.6% (95%CI: 87.3–100) was observed even in this oldest age group (up to age 39). When combining the two serosurvey studies from 1995/1996 and 2006/2007, a high level of protection with narrow confidence intervals could be observed. Nevertheless, certain caveats remain in regard to combining both two cohorts. The schedule with six diphtheria vaccinations has been in use for both cohorts, however, the combination vaccines used in the NIP in the Netherlands have changed several times in composition and of manufacturer.<sup>55</sup> In 2003 Haemophilus influenza (Hib) vaccine was added to the DTWP-IPV vaccine for infants (DTWP-IPV/Hib) and in 2005 the infant whole-cell pertussis vaccine was replaced by an acellular pertussis vaccine (DTaP-IPV/Hib).<sup>56</sup> In 2006 a seven-valent pneumococcal vaccine conjugated to a non-toxic, fully immunogenic mutant of diphtheria toxin (CRM197) was added to the NIP at two, three, four, and 11 months of age for all children born in or after April 2006. In addition, in July/August 2006, acellular pertussis vaccine was added to the booster combination vaccine for 4-year-olds (DTaP-IPV).

Given the likely low number of reported cases of diphtheria in the Netherlands in the past years,<sup>34</sup> one can assume limited circulation of the disease and hence the limited chance of exposure conveying natural boosting. Therefore, the observed high levels of protective immunity are most likely to be attributable to the 6 dose immunization schedule used in the country.

These data suggest, that the immediate administration of decennial booster doses following a 3 dose primary and 3 dose booster schedule may not be needed however this needs to be monitored long-term with increasing life expectancy in large parts of the world. No data could be retrieved on the duration of protection conferred by this schedule beyond 39 years of age. This evidence is supported by a seroprevalence study from the United States, which modelled a half-life for diphtheria-specific immunity of 27-year (95% CI: 18–51 years); however in this study it cannot be

excluded that some individuals had received some or all decennial booster doses according to the United States recommendations.

Based on supportive evidence<sup>52</sup> and on selected seroepidemiological studies<sup>28,29,30,31</sup>, in some settings, immunity gaps may exist in older age groups, either due to waning immunity or due to no or incomplete vaccination. It remains to be demonstrated whether the 6-dose schedule provides live-long protection to the vast majority of vaccinated individuals or if revaccination of older age groups may be needed.

## Recommendations

To harmonize the vaccination schedules across the diphtheria, tetanus and pertussis vaccine position papers, SAGE should consider the following draft recommendations:

1. A primary series of 3 doses of diphtheria-containing vaccine (completed by 6 months of age if possible) should be administered;
2. Three booster doses of diphtheria-containing vaccine should be administered in childhood and completed by adolescence.
3. The booster doses of diphtheria-containing vaccine should be given at: 12–23 months of age; 4–7 years of age; and 9–15 years of age.
4. Immunity gaps may exist in the older populations due to waning immunity or non-vaccination. Further research is required to fully assess the duration of protection against diphtheria in the older populations.

## **Annex 1**

### *Search Strategy 1:*

(Vaccin\* OR immunisation OR immunization)

AND (Diphtheria)

AND (efficacy) OR (effectiv\*)

### *Search Strategy 2:*

((Vaccin\* OR immunisation OR immunization)

AND (Diphtheria))

AND ((antibod\*) OR (seroprotecti\*) OR (serology) OR (immunogenicity) OR (immunity)

AND (waning OR duration of protection OR durability OR decay OR long-term OR continued OR lasting OR decline))

## Annex 2

### GRADE Table : Duration of continued seroprotection

**Population:** Immunocompetent children and adults.

**Intervention:** Vaccination with diphtheria toxoid (-containing) vaccination

**Comparison:** No vaccination, or different duration between vaccination and serological testing

**Outcomes:** Serum antibody levels/ seroprevalence

<b>PICO Question:</b> What is the duration of continued seroprotection of diphtheria vaccination (≥10 years) conveyed by a specific schedule of diphtheria toxoid (-containing) vaccination which is comprised of at least 3 vaccine doses (primary series) and 3 booster doses until adulthood.				
			Rating	Adjustment to rating
<b>Quality Assessment</b>	No of studies/starting rating		1 observational <sup>2</sup>	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	<b>Final numerical rating of quality of evidence</b>			<b>2</b>
<b>Summary of Findings</b>	<b>Statement on quality of evidence</b>		Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.	
	<b>Conclusion</b>		6 doses of diphtheria-containing vaccine in childhood and adolescence, without administration of booster doses confer high levels of seroprotection up until 39 years of age and potentially longer.	

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Swart et al. Long-Term Protection against Diphtheria in the Netherlands after 50 Years of Vaccination: Results from a Seroepidemiological Study. PLoS ONE 11(2): e0148605

<sup>2</sup> Swart et al. suggests that 6 doses of diphtheria-containing vaccine, administered in infancy and childhood, induce seroprevalence levels above the protective threshold (≥0.01 IU/ml) in 92.7% (95%CI: 88.2%-97.3%) for both national serosurveys combined (1995/1996 and 2006/2007) in persons aged 30-34 years and 94.6% (95%CI: 87.3%-100%) for persons aged 35-39 years (2006/2007 serosurvey only).

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