

## Summary of WHO Position Paper on Diphtheria Vaccines, August 2017

This position paper, published in August 2017, replaces the corresponding WHO position paper on diphtheria vaccines published in the Weekly Epidemiological Record in 2006. In particular, it provides revised recommendations on the optimal number of doses and timing of diphtheria vaccination, as well as guidance on the alignment of vaccination schedules for different antigens included in routine childhood immunization programmes, considering the widespread use of combination vaccines.

### Background

Throughout history, diphtheria has been one of the most feared infectious diseases globally causing devastating epidemics with high case-fatality rates, mainly affecting children. Transmission of *C. diphtheriae* occurs from person to person through droplets and close physical contact. Infection can cause respiratory or cutaneous diphtheria. Morbidity and mortality are mediated by the diphtheria toxin. Respiratory diphtheria usually occurs after an incubation period of 2–5 days. The onset is usually relatively slow and characterized by mild fever and an exudative pharyngitis initially with progression of symptoms over 2 to 3 days. In classic cases, the exudate organizes into a pseudo-membrane that gradually forms in the nose, pharynx, tonsils, or larynx. The pseudo-membrane may extend into the nasal cavity and the larynx causing obstruction of the airways, which is a medical emergency that often requires tracheotomy. In rare cases, systemic diphtheria can occur damaging heart, kidneys and/or peripheral nerves. Diphtheria antitoxin (DAT), if administered in time, is highly effective and the gold standard for diphtheria treatment. However, global access to DAT is limited as most manufacturers have ceased production.

### Vaccines

In the 1940s, diphtheria toxoid, tetanus toxoid and pertussis antigens were combined in the diphtheria-tetanus-pertussis vaccine (DTP) used widely for childhood immunization throughout the world. DTP may also be combined with additional vaccine antigens, such as hepatitis B surface antigen (HBsAg) and *Haemophilus influenzae* type b (Hib) conjugates as pentavalent vaccines, and with inactivated polio vaccine (IPV) as hexavalent vaccines. Tetanus-diphtheria (Td, low-dose diphtheria toxoid) formulations and tetanus-diphtheria-acellular pertussis (Tdap) formulations are licensed for use from 5 years of age and 3 years of age, respectively. After the 3-dose primary series of DTP-containing vaccine, 94–100% of children have protective anti-diphtheria antibody levels >0.01 IU/mL, but booster doses are needed to ensure continuing protection. The effectiveness of the vaccine can be seen in outbreak settings: most recent data on vaccine effectiveness stem from the epidemic in the 1990s in countries of the former Soviet Union. Case-control studies showed that 3 or more doses of diphtheria toxoid induced 95.5% (95% CI: 92.1–97.4%) protective effectiveness among children aged <15 years. Protection increased to 98.4% (95% CI: 96.5–99.3%) after 5 or more doses of this vaccine. Diphtheria toxoid is one of the safest vaccines available.

## WHO Position

All children worldwide should be immunized against diphtheria. Every country should seek to achieve timely vaccination with a complete primary series plus booster doses. A primary series of 3 doses of diphtheria toxoid-containing vaccine is recommended, with the first dose administered as early as 6 weeks of age. Subsequent doses should be given with an interval of at least 4 weeks between doses. The third dose of the primary series should be completed by 6 months of age if possible. The diphtheria booster doses should be given in combination with tetanus toxoid using the same schedule, i.e. at 12–23 months of age, 4–7 years of age, and 9–15 years of age, using age-appropriate vaccine formulations.

Opportunities should be taken to provide or complete the 3-dose diphtheria toxoid-containing vaccine series for children aged  $\geq 1$  year, adolescents and adults who were not vaccinated, or incompletely vaccinated, during infancy. For previously unimmunized children aged 1–7 years, the recommended primary schedule is 3 doses with a minimum interval of 4 weeks between the first and the second dose, and an interval of at least 6 months between the second and third dose, using DTP-containing vaccine. Using Td or Tdap combination vaccine, the recommended schedule for primary immunization of older children ( $>7$  years), adolescents and adults is 3 doses with a minimum interval of 4 weeks between the first and the second dose, and an interval of at least 6 months between the second and a third dose. Two subsequent booster doses using Td or Tdap combination vaccines are needed with an interval of at least 1 year between doses. To further promote immunity against diphtheria, the use of Td rather than tetanus toxoid is recommended during pregnancy to protect against maternal and neonatal tetanus in the context of prenatal care, and when tetanus prophylaxis is needed following injuries.

As diphtheria toxoid is almost exclusively available in fixed combinations with other antigens, immunization programmes will need to harmonize immunization schedules between diphtheria, tetanus and pertussis. Diphtheria toxoid-containing vaccine can also be co-administered with other childhood and adolescence vaccines.

Vaccination during pregnancy is not necessary to protect neonatal infants against diphtheria, but diphtheria-containing vaccines combined with pertussis and tetanus can be used to protect young infants against tetanus and pertussis. Diphtheria toxoid-containing vaccines can be used in immunocompromised persons including HIV-infected individuals. All health-care workers should up to date with immunization as recommended in their national immunization schedules. Travellers are generally not at special risk of diphtheria, unless they travel to an endemic country or outbreak setting. They should be immunized as recommended in their national immunization schedules.

Efficient national surveillance and reporting systems, with district-level data analysis, are essential in all countries.

Further studies, including serosurveys, are required to generate information on the duration of protection and the possible need for booster doses in older age groups.