

WHO Position Paper on Diphtheria vaccine

Selected references

The disease

Kadirova R, Kartoglu HU, Strebel PM. Clinical characteristics and management of 676 hospitalized diphtheria cases, Kyrgyz Republic, 1995. *J Infect Dis.* 2000 Feb;181 Suppl 1:S110-5

The Kyrgyz Republic experienced a widespread resurgence of diphtheria during 1994-1998. To describe the clinical characteristics and management of diphtheria patients hospitalized in 1995, a retrospective chart review was conducted. Physician-diagnosed cases of diphtheria were classified according to the system recommended by the World Health Organization and UNICEF. Among 676 patients hospitalized with respiratory diphtheria, 163 (24%) were carriers, 186 (28%) had tonsillar forms, 78 (12%) had combined types or delayed diagnosis, and 201 (30%) had severe forms of diphtheria. The highest age-specific incidence rates occurred among persons 15-34 years old, and 70% of cases were among those ≥ 15 years of age. Myocarditis occurred among 151 patients (22%), and 19 patients died (case fatality ratio: 3%). Diphtheria antitoxin was administered to 507 patients (75%), and all patients received antibiotics (penicillin or erythromycin). Respiratory diphtheria remains a potentially fatal disease, commonly presenting with a typical membranous pharyngitis. Early diagnosis and treatment of cases with diphtheria antitoxin and antibiotics are the cornerstones of effective treatment.

Nandi R, De M, Browning S, Purkayastha P, Bhattacharjee AK. Diphtheria: the patch remains. *J Laryngol Otol.* 2003 Oct;117(10):807-10.

This study analysed the number of patients admitted with diphtheria to a teaching hospital in the state of Assam in India over a period of five years and compared the disease characteristics and management with outcomes and incidences of diphtheria reported in the literature. It was a retrospective analysis of data elicited from clinical records of patients admitted to hospital. A total of 101 admissions were recorded during a five-year period between March 1997 to March 2002, mostly with pharyngeal diphtheria (90 per cent). The majority of patients had no history of immunization (70 per cent). Significant presenting features were a tonsillar patch, sore throat, respiratory distress and fever. All patients were treated with anti-diphtheritic serum and intravenous antibiotics. Steroids were given to 81 per cent of patients and tracheostomy was carried out in 10 per cent of cases. The mortality was 16 per cent. Diphtheria of the respiratory tract remains a potentially fatal disease commonly presenting with membranous pharyngitis. Early diagnosis and treatment with anti-diphtheritic serum and antibiotics remain the cornerstone of treatment. Inadequate immunization cover is deemed responsible for the continued menace of diphtheria.

The vaccine – diphtheria toxoid

Kjeldsen K, Simonsen O, Heron I. Immunity against diphtheria 25-30 years after primary vaccination in childhood. *Lancet.* 1985 Apr 20;1(8434):900-2.

In Denmark primary vaccination against diphtheria is offered in the 5th, 6th, and 15th month of life with doses of 50 Lf. Only those doing military service are routinely revaccinated (with 12 1/2 Lf, given once). 403 persons offered primary vaccination 25-30 years ago were screened for diphtheria antitoxin titres by the use of neutralisation and haemagglutination tests. 19% of these (10% of the males and 26% of the females) were unprotected (less than 0.01 IU/ml). Among those not revaccinated 22% had antitoxin titres below protective level. This accords with the continuing decline of diphtheria antitoxin titre after vaccination. Among those revaccinated against diphtheria in adolescence 5% became unprotected. Thus, persons who were offered

primary vaccination against diphtheria 25-30 years ago may be susceptible to diphtheria and its toxic complications. So may those revaccinated more than 10 years ago. Should diphtheria emerge in a community those who received their primary vaccination more than 2 years ago or revaccination more than 10 years ago ought to be revaccinated. Revaccination is also advisable for those travelling to countries with endemic diphtheria. Moreover, since 10% of the present population were unprotected against tetanus it seems advisable to increase the immunity against diphtheria and tetanus by routine revaccination with a combined diphtheria-tetanus vaccine. Only a documented history of vaccinations should be relied on when a decision is being made as to whether to carry out primary vaccination or revaccination.

Myers MG, Beckman CW, Vosdingh RA, Hankins WA. Primary immunization with tetanus and diphtheria toxoids. Reaction rates and immunogenicity in older children and adults. JAMA. 1982 Nov 19;248(19):2478-80.

The reaction rates and immunogenicity of primary immunization with tetanus (5 flocculation [Lf] units) and diphtheria (1.5 Lf units) toxoids were evaluated in older children and adults. Eight of 42 subjects had local reactions to one or more doses of vaccine. All subjects had protective titers to tetanus and 94% to diphtheria after two injections. Titers of antitoxins were greater in younger patients; in those younger than 19 years, they were inversely related to age.

Simonsen O, Klaerke M, Klaerke A, Bloch AV, Hansen BR, Hald N, Hau C, Heron I. Revaccination of adults against diphtheria. II: Combined diphtheria and tetanus revaccination with different doses of diphtheria toxoid 20 years after primary vaccination. Acta Pathol Microbiol Immunol Scand [C]. 1986 Oct;94(5):219-25.

Immunity following diphtheria vaccination in childhood is temporary, and recent outbreaks of diphtheria in adult populations evoked interest in the effect of and side-reactions to revaccination of adults. 237 military recruits were randomly allocated to revaccination with 6 Lf tetanus toxoid or 6 Lf tetanus toxoid combined with 2 Lf or 5 Lf diphtheria toxoid. Side-reactions were recorded one week later, and antitoxin response was assessed after 4 weeks. Protective serum diphtheria antitoxin levels were attained by all subjects receiving diphtheria toxoid containing vaccines. Antibody response was related to dose, indicating a safer long-term protection by revaccination with 5 Lf diphtheria toxoid. All vaccinees, except one without documentation for primary vaccination, attained high tetanus antitoxin levels. Interference phenomena between toxoids were insignificant. Mild local reactions were reported by 22% of the vaccinees. More pronounced local reactions were experienced by 5% and systemic reactions by 3%, independent of vaccine. No serious reactions were observed. Reactions were significantly related to tetanus antitoxin response only. It was concluded that combined revaccination of adults, primary vaccinated around 20 years previously, may be performed without immune assessments.

Trollfors B, Taranger J, Lagergard T, Sundh V. Reduced immunogenicity of diphtheria and tetanus toxoids when combined with pertussis toxoid. Pediatr Infect Dis J. 2005 Jan;24(1):85-6.

The effect of pertussis toxoid on the immunogenicity of diphtheria and tetanus toxoids (DT) was studied during a double blind efficacy trial of an acellular pertussis vaccine. Infants received DT with or without pertussis toxoid at 3, 5 and 12 months of age. Geometric mean concentrations were higher in the DT than in the DT-pertussis toxoid group 1 month (diphtheria toxoid 4.76 versus 3.58 IU/mL, $P = 0.009$; tetanus toxoid 4.42 versus 2.66 IU/mL, $P < 0.0001$) and 2 years after the third injection (diphtheria toxoid 0.15 versus 0.10 IU/mL, $P < 0.0001$; tetanus toxoid 0.38 versus 0.18 IU/mL, $P < 0.0001$). Pertussis toxoid causes a small but significant reduction of the immunogenicity of diphtheria toxoid and tetanus toxoid.

Epidemiology and control strategies

Hardy IR, Dittmann S, Sutter RW. Current situation and control strategies for resurgence of diphtheria in newly independent states of the former Soviet Union. *Lancet*. 1996 Jun 22;347(9017):1739-44.

Since 1990, an epidemic of diphtheria has spread throughout the newly independent states of the former Soviet Union, and by 1995 a total of 47 808 cases were reported. During the early stages of the epidemic, adequate control measures were not taken and vaccine was in short supply; possible contributing factors to the spread of the epidemic are the presence of highly susceptible child and adult populations, socioeconomic instability, population movement, and a deteriorating health infrastructure. Although WHO views the epidemic as an International public-health emergency and, together with UNICEF and the International Red Cross, has formulated a strategy to combat the epidemic, the necessary funds have not been made fully available. Current vaccination recommendations also need to be reviewed to ensure that population immunity will be adequate to prevent any resurgence of diphtheria in Europe and North America.

Galazka AM, Robertson SE. Diphtheria: changing patterns in the developing world and the industrialized world. *Eur J Epidemiol*. 1995 Feb;11(1):107-17.

*In the past, diphtheria was considered one of the most serious childhood diseases because it took a heavy toll in health and life among preschool-aged children. Prior to the widespread availability of diphtheria toxoid, nearly 70% of cases were in children younger than 15 years of age. In the industrialized countries, immunization against diphtheria became widespread in the 1940s and 1950s. This led to a marked decrease in the incidence of diphtheria. There was also a decrease in circulating toxigenic *Corynebacterium diphtheriae* organisms, resulting in less natural boosting of antibody levels. This had led to gaps in the immunity of the adult population. Since 1990, diphtheria has made a spectacular comeback in several European countries, with a high proportion of cases in adults. In developing countries, immunization of infants with diphtheria toxoid was introduced with the Expanded Programme on Immunization in the late 1970s. Coverage rose slowly to 46% in 1985 and 79% in 1992. Because the pool of immunized persons is not yet large, the process of maintaining immunity still operates through natural mechanisms, including frequent skin infections caused by *C. diphtheriae*. But recently, several developing countries where coverage has been high for 5-10 years have reported diphtheria outbreaks. These outbreaks have been characterized by high case fatality rates, a large proportion of patients with complications, and their occurrence in both young and older age groups. In all countries, priority should be given to efforts to reach at least 90% coverage with three doses of diphtheria toxoid in children below one year of age. In countries where diphtheria has been successfully controlled, immunity levels should be maintained by booster doses.*

WHO document: Core information for the development of immunization policy: 2000 update. WHO/V&B/02.28. (no summary).

Halperin SA. Pertussis--a disease and vaccine for all ages. *N Engl J Med*. 2005 Oct 13;353(15):1615-7. No abstract available.