



Diphtheria

Introduction

Diphtheria is a vaccine-preventable bacterial disease caused by *Corynebacterium diphtheriae*, an aerobic, gram-positive, pleomorphic bacillus. The disease occurs worldwide but is especially prevalent in resource-poor countries where there is low vaccine coverage. *C. diphtheriae* can be infected by a bacteriophage carrying genes for diphtheria exotoxin; this toxin is responsible for the disease manifestations. The toxin inhibits cellular protein synthesis causing local tissue destruction and when it is systemically absorbed can lead to myocarditis and neuritis [1].

The major clinical manifestations are laryngeal/pharyngeal diphtheria (with the name diphtheria deriving from the characteristic 'leathery' membrane that is seen in the pharynx of persons with diphtheria), cutaneous ulceration, and systemic toxicity. Humans are the only natural hosts of diphtheria [2, 3].

Toxigenic *C. ulcerans* is also a documented cause of diphtheria which, although rare, can be fatal. Its natural host is cattle.

Epidemiology

Global Epidemiology

Before the implementation of routine immunisation against diphtheria in the 1940s and 1950s, diphtheria occurred throughout the world in large cyclical epidemics. In countries where vaccine coverage rates were high, diphtheria was largely controlled and by the 1980s, the global incidence of diphtheria had declined to low levels [4]. During the 1990s however, the incidence rose in the newly independent states of the former Soviet Union. The outbreak in these countries mainly affected adolescents and adults and was due in part to a failure of diphtheria control following the break up of the Soviet Union [5]. In resource-rich countries, diphtheria incidence tends to be low with most cases imported from endemic countries.

In resource-poor countries, however, where routine immunisation may not achieve high coverage, diphtheria remains a problem and can represent a risk to the unvaccinated traveller. Diphtheria is reported in high numbers from south Asia (in particular India, Nepal, and Bangladesh), South East Asia, the western Pacific (Indonesia, Philippines, Viet Nam, Laos, and Papua New Guinea), sub-Saharan Africa (Nigeria), South America (Brazil), and the middle east (Iraq and Afghanistan). In eastern Europe (Russian Federation, Ukraine, and other countries of the former Soviet Union) the number of cases has declined since the outbreak in the 1990s [6]. Reported data on diphtheria must be interpreted with caution due to variations in case definitions and reliability of surveillance systems. In 2002, the WHO estimated that about 5,000 deaths occur annually worldwide, 4,000 of them in children under five years of age [6]. In 2005 8,229 cases were reported to the WHO [7].

An outbreak of diphtheria occurred in Afghanistan in the summer of 2003, when 50 cases and three deaths were reported in a resettlement camp for internally displaced persons in Kandahar [8]. Outbreaks may quickly spread in situations of overcrowding and poverty.

Diphtheria in travellers from England and Wales¹

Toxigenic diphtheria is rarely reported in England and Wales but sporadic cases occur, usually associated with foreign travel or contact with a case that has travelled.

Between 1986 and 2006, there were 59 isolates of toxigenic *Corynebacterium diphtheriae*. The majority of cases were imported: 25 from the Indian sub-continent (ISC), ten from South East Asia, six from Africa, and one each from the Middle East, Russia, and western Europe. Seven isolates were presumed to have been acquired in the UK of which one, in 2003, was acquired in a laboratory, and nine did not have a country of infection stated. Nineteen cases were of cutaneous diphtheria [9,10], all of which were imported from Africa and south and South East Asia; the two most recent cases (in 2003) were imported from Bangladesh and Cambodia. The imported cases represent patterns of travel to areas where diphtheria is still endemic i.e. the ISC, and therefore highlights the importance of vaccination of travellers to those areas. Between 2001 and 2004, there were ten isolates of toxigenic *C. ulcerans* reported in England and Wales but all of them were thought to have been acquired in the UK [10].

Risks for Travellers

A widespread and effective vaccination programme has resulted in diphtheria being rare in resource-rich countries of the western hemisphere. Cases of diphtheria occasionally occur in unvaccinated travellers to endemic regions (see Epidemiology sections above), with those spending prolonged periods with the local population at particular risk. The normal reservoir of *C. ulcerans* is cattle, and human cases have been associated with the consumption of raw dairy products. Travel, and close contact with cattle or other farm animals, are potential risk factors for infection [11].

Transmission

Diphtheria is spread between humans via respiratory droplets and occasionally through contaminated fomites or from exudates from infected skin lesions during close physical contact. Conditions of crowding and poor hygiene increase the risk of transmission. Chronic carriage and asymptomatic infections are common [3].

Signs and symptoms [1-3]

The incubation period is between two and seven days. The symptoms may be classified as local or systemic, depending upon whether or not the exotoxin has spread.

Respiratory tract diphtheria

There are several, often overlapping, syndromes associated with respiratory tract diphtheria. The most common is pharyngeal diphtheria affecting the soft palate, tonsils, and pharyngeal area. A tough, 'leathery' grey/yellow membrane is formed and is firmly attached to the underlying tissue. The lymph glands become swollen, prominent, and tender producing a 'bull neck'.

Infection may spread to the larynx leading to laryngeal diphtheria. As a result there will be a husky voice, a brassy cough and if there is airway obstruction, dyspnoea and cyanosis.

¹ Data on imported diphtheria was obtained from the Respiratory and Systemic Infections Laboratory and the Immunisation Department at the HPA Centre for Infections.

Nasal diphtheria is a localised infection of the anterior nares usually with a low grade fever, a nasal discharge, and crusting and erosion on the external nares.

Systemic spread of the exotoxin can lead to toxic effects primarily on the cardiac and neurologic systems. Cardiac toxicity occurs in 10% to 25% of persons with respiratory diphtheria, usually manifesting after one to two weeks of disease. The myocarditis is associated with electrocardiographic changes, dyspnea, weakness, congestive heart failure, and circulatory collapse.

Neurological complications can present as palatal and pharyngeal wall paralysis early in the course of the disease, or after several weeks, as cranial nerve palsies, paraesthesias, polyneuropathy and rarely encephalitis. Approximately 5% - 10% of respiratory cases are fatal.

Cutaneous diphtheria

Cutaneous diphtheria presents as a chronic non-healing ulcer and is usually co-infected with staphylococci and streptococci. It has typically been seen in the tropics, although cases have been described in western settings among homeless populations and in returning travellers [1]. Clinical findings can either be that of a punched out ulcer with non-distinct margins, covered with a grey/white to brown membrane, or a chronic non-specific rash. Systemic complications and fatalities are rare with the cutaneous form of infection. Most of the recent cases of diphtheria in travellers who have returned to the UK, have been cutaneous infections [9].

Treatment [1,3]

Treatment of diphtheria requires both anti-toxin to neutralise the diphtheria exotoxin, and antibiotics to eradicate and prevent carriage of the bacteria.

Antitoxin should be administered early in the course of infection to prevent disease progression. As the antitoxin is an equine product, anaphylaxis and serum sickness can occur, and patients should be skin-tested before administration.

Antibiotic treatment is usually with penicillins or macrolides. Intensive care is required in serious cases.

Prevention

The most important method for prevention of diphtheria is vaccination (See the section on Vaccination Information below). Maintaining high vaccination levels in a population will lead to herd immunity and decreased circulation of the bacteria and risk of disease. Improved sanitation and personal hygiene, as well as decreased population crowding will also lessen conditions leading to transmission of the bacteria. Travellers should be advised to avoid close contact with cattle/other farm animals and the consumption of raw dairy products in order to minimise their risk of *C. ulcerans*.

It is important to maintain lifelong immunity. In the UK, school leavers receive a diphtheria/tetanus/polio booster in order to maintain high levels of immunity [12].

Contacts of cases should be traced, screened for infection by throat culture, and treated as necessary. They should also receive a booster dose of diphtheria toxoid.

Diphtheria Vaccination information

The Summary of Product Characteristics (SmPC) for each vaccine product should be consulted for specific information [13-16].

Diphtheria toxoid vaccine is now only available as a combined vaccine. Separate diphtheria vaccine for use in adults and adolescents was discontinued in the UK in 2003.

Indications for use of vaccine [12]

Diphtheria vaccination is recommended for:

- All infants from two months of age (routine immunisation programme)
- Travellers to countries or areas where diphtheria is epidemic or endemic
- Individuals at risk for exposure to diphtheria through their work; e.g. health care workers and microbiology laboratory technicians.
- Individuals not previously immunised.

Availability of vaccine

There are four combined vaccines containing diphtheria toxoid that are licensed for use in the UK. Only one of these vaccines, Revaxis™ (dT/IPV), is licensed for use in adults. Diftavax™ is no longer being supplied and has been replaced by Revaxis™. See the table below for details.

Further information on the UK childhood vaccine program can be found on the [Department of Health website](#) [12].

Vaccine Schedules

Vaccine	Manufacturer/distributor	Schedule	Length of protection	Age range
Pediacel™ [13] (diphtheria, tetanus, 5 component acellular pertussis, inactivated polio vaccine and <i>Haemophilus influenzae</i> type b vaccine – DTaP/IPV/Hib)	Sanofi Pasteur MSD	Primary immunisation at 2, 3 and 4 months	Three years, DTaP/IPV, single lifetime dose for Hib	2 months to 10 years
Repevax™ [14] (low dose diphtheria, tetanus, 5 component acellular pertussis and inactivated polio vaccine – dTaP/IPV)	Sanofi Pasteur MSD	Pre-school booster; single dose	Seven years for the dT/IPV. No data on aP.	3 years to 5 years
Infanrix IPV™ [15] (diphtheria/tetanus/3-component acellular pertussis/inactivated polio vaccine (DTaP/IPV))	GlaxoSmithKline	Pre-school booster; single dose	Boosted in adolescence and adulthood. No data on aP	Booster from 16 months to 13 years of age
Revaxis™ [16] (low dose diphtheria, tetanus and inactivated polio vaccine Td/IPV)	Sanofi Pasteur MSD	Single dose booster.	10 years	10 years and older

Interrupted courses

It is unnecessary to restart an interrupted series of a vaccine or toxoid or to add extra doses, because the immune system has been primed [5]. Longer than recommended intervals between doses do not reduce antibody concentrations upon completion of the series,



although protection may not be attained until the recommended number of doses has been administered [17].

Contraindications to Pediacel™ [13] Repevax™ [14] Infanrix IPV™ [15] & Revaxis™ [16]

Hypersensitivity reaction after previous administration of diphtheria, tetanus, pertussis or polio vaccines.

Known hypersensitivity to any component of the vaccine or to neomycin, polymyxin B or formaldehyde (which may be present in the vaccine as trace residues of manufacture).

Neurological complications of unknown origin within 7 days of previous vaccination.

Infanrix-IPV should not be administered to subjects who experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with a pertussis containing vaccine.

Adverse Events [reviewed in 12]

Pain, swelling or redness at the injection site are common and may occur more frequently following subsequent doses. A small, painless nodule may form at the injection site that usually resolves spontaneously. The incidence of local reactions is lower with diphtheria vaccines combined with acellular pertussis vaccines, than the reactions following vaccines combined with whole-cell pertussis, and are similar to reactions after DT vaccine.

Fever convulsions high pitched screaming and episodes of pallor, cyanosis and limpness occur rarely but with equal frequency after both DTaP and DT vaccines.

Confirmed anaphylaxis occurs extremely rarely. Data from the UK, Canada and the US point to rates of 0.65 to three anaphylaxis events per million doses. Other allergic conditions may occur more commonly and are not contraindications to further immunisation.

All suspected adverse reactions to vaccines occurring in children, or in individuals of any age after vaccines labelled with a black triangle (▼), should be reported to the Medicines and Healthcare Products Regulatory Agency using the [Yellow Card Scheme](#). Serious suspected adverse reactions to vaccines in adults should also be reported through the Yellow Card Scheme.

References

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Reading List

- Cook G, Zumla A, ed. Manson's Tropical Diseases. 21st ed. London: WB Saunders Co Ltd; 2003
- Plotkin S, Orenstein W, editors. Vaccines 4th Edition. Philadelphia: WB Saunders Co Ltd; 2004

Links

- Committee to Advise on Tropical Medicine and Travel (CATMAT)
http://www.phac-aspc.gc.ca/im/vpd-mev/diphtheria_e.html
- Department of Health. Joint Committee of Vaccination and Immunisation (JCVI).
<http://www.advisorybodies.doh.gov.uk/jcvi>
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