

# Diphtheria and diphtheria vaccination

This disease is notifiable in the UK – see **NOIDs** article for more detail.

## What is diphtheria?<sup>[1]</sup>

Diphtheria is a toxin-mediated bacterial acute upper respiratory tract infection, but sometimes it infects the skin. Hippocrates first described the disease in the 4th century BC and major epidemics swept through Europe in the 17th century. It was known as 'the strangling angel of children'.

## Pathogenesis<sup>[2]</sup>

The organism is pathogenic only in humans.

- *Corynebacterium diphtheriae* is a Gram-positive, aerobic, non-motile, rod-shaped bacterium.
- The bacterium is classified as *gravis*, *mitis*, *intermedius*, or *belfanti*.
- Pharyngeal or cutaneous diphtheria is caused by toxigenic strains of *C. diphtheriae* and occasionally by *Corynebacterium ulcerans*. The latter is usually an infection of cattle.
- Toxin production occurs only when the bacillus is infected by viruses (corynebacteriophages) containing the *tox* gene.
- Diphtheria toxin inhibits cellular protein synthesis. Toxin production leads to local tissue destruction and the formation of the classical fibrinous pseudomembrane, usually on the respiratory mucosa.
- Diphtheria toxin can also be absorbed into the bloodstream, causing distant organ dysfunction, including polyneuropathy, nephritis, and myocarditis.

## How common is diphtheria? (Epidemiology) <sup>[3]</sup>

- Diphtheria mainly occurs in epidemics.
- A vaccine was introduced to the UK in 1941. This was highly effective. The number of cases fell from over 61,000 (3,283 deaths) in 1940, to 38 cases (six deaths) in 1957.
- Diphtheria is rare in the UK. In 2021, there were 10 cases of diphtheria in the UK, 3 of which were toxigenic *Corynebacterium diphtheriae*. <sup>[4]</sup>
- However, an outbreak occurred in 2022; from January to November 2022, toxigenic *C. diphtheriae* was isolated from 50 asylum seekers recently arrived in England, with one probable fatality. It was felt that infection was most likely have been acquired in the country of origin, or during the extended journey to the UK through Europe. <sup>[4]</sup>
- Diphtheria cases are mainly from Southeast Asia, South America, Africa and India. Many UK citizens travel to and from these regions, and imported cases have occurred in returning travellers. <sup>[3]</sup>
- Maintaining high vaccination coverage is essential to prevent indigenous *C. ulcerans* and re-emergence of *C. diphtheriae*. <sup>[5]</sup>
- More recently, *C. ulcerans* has been increasingly isolated as an emerging zoonotic agent of diphtheria from pets such as cats or dogs. <sup>[1]</sup>

### Risk factors

- In countries where hygiene is poor, cutaneous diphtheria is the predominant clinical manifestation and source of infection.
- Poor living conditions and lack of immunisation, especially where there is not an immunisation programme, increase risk.
- Spread is via respiratory droplets or contact with exudate from skin lesions.
- Adults are at risk as they lose protection from childhood vaccines unless they have boosters.

## Symptoms of diphtheria (presentation) <sup>[2]</sup> <sup>[3]</sup>

- Non-toxinogenic *C. diphtheriae* causes a mild pharyngitis.

- Toxinogenic *C. diphtheriae* also commonly affects the pharynx and tonsils. The onset of pharyngitis is gradual and symptoms may be similar to more common upper respiratory tract infections initially.
- Often diphtheria presents with a nasal discharge that is initially watery and becomes purulent and blood-stained. The nostril can be sore or crusted with the pseudomembrane sometimes visible within the nostril.
- Incubation period is usually 2–5 days, but may be up to 10 days.
- In diphtheria of the upper respiratory tract, there is a membranous pharyngitis (often referred to as a pseudomembrane) with fever, enlarged anterior cervical lymph nodes and oedema of soft tissues giving a 'bull neck' appearance.
- The pseudomembrane may cause respiratory obstruction.
- Swallowing may be made difficult by unilateral or bilateral paralysis of the muscles of the palate.
- The exotoxin also affects other parts of the body, including the heart and nervous systems. It may cause paralysis and cardiac failure.
- Milder infections resemble streptococcal pharyngitis and the pseudomembrane may not develop, particularly where there has been previous vaccination.
- Carriers do not usually have any symptoms.

Cutaneous infection is usually mild, but chronic:

- Typical findings are vesicles or pustules that quickly rupture to form a 'punched-out' ulcer up to several centimetres in diameter.
- It often appears on the lower legs, feet and hands.
- It may be painful in the first week or two and covered with a dark pseudomembrane which separates to show a haemorrhagic base which may have exudate.
- The surrounding tissue is pink or purple and oedematous.
- It usually heals in 2–3 months to leave a depressed scar.

- Infections at other mucocutaneous sites include [otitis media](#), [conjunctivitis](#) and vulvovaginitis.

## Effects of toxin

- Cardiomyopathy and myocarditis are usually evident by the 10th to 14th day. There may be arrhythmias early or late in the illness. Myocardial involvement accounts for around half of all deaths.
- Neuritis affects motor nerves, firstly with paralysis of the soft palate, causing dysphagia and nasal regurgitation, then ocular nerves, peripheral nerves and diaphragm with resulting infection and respiratory failure.
- Nephritis and proteinuria may occur.
- Thrombocytopenia may be present.

## Differential diagnosis

- Infection with *C. ulcerans* also causes membranous tonsillitis, but is rarely toxic.
- *C. pseudodiphtheriticum* does not produce a toxin, but can cause exudative pharyngitis with a pseudomembrane.
- The disease may also resemble [infectious mononucleosis](#), streptococcal or viral [tonsillitis](#), [peritonsillar abscess](#), [oral thrush](#), [epiglottitis](#), [herpes simplex](#) and [impetigo](#).
- If there are neurological symptoms and a lumbar puncture is performed, elevated protein in the cerebrospinal fluid may lead to a false diagnosis of [Guillain-Barré syndrome](#).

## Investigations

- Definitive diagnosis of diphtheria requires a positive culture from respiratory tract secretions or cutaneous lesions, and a positive toxin assay.
- Routine laboratory results are usually nonspecific and may include a moderately elevated white blood cell count and proteinuria.
- Toxigenicity tests are usually undertaken by specialist laboratories.

# Management of diphtheria<sup>[3]</sup>

## Pharmacological

- Diphtheria anti-toxin (produced from horse serum) should be considered urgently for probable and confirmed cases of toxinogenic diphtheria.<sup>[6]</sup>
  - Diphtheria antitoxin significantly reduces morbidity and mortality from diphtheria.
  - It is much more effective if given early, before diphtheria toxin has bound to tissues.
  - In the UK, diphtheria antitoxin is issued by the UK Health Security Agency at Colindale.
- Antibiotics are given to eliminate the organism and prevent spread. The antibiotics of choice are usually erythromycin, azithromycin, clarithromycin or penicillin.
- Patients should be immunised in the convalescent stage because clinical infection does not always induce adequate levels of antitoxin. They should receive a complete course or a reinforcing dose according to their age and immunisation history.
- Completely immunised individuals should receive a single reinforcing dose of a diphtheria-containing vaccine according to their age.

## Management of contacts<sup>[3]</sup>

- All contacts of either a person with diphtheria or a carrier should be given antibiotic prophylaxis. This is usually with erythromycin or penicillin.
- Contacts of cases with *C. ulcerans* also need to be given antibiotic prophylaxis.
- Contacts need treatment to eliminate both incubating disease and to prevent carriage to others.
- Partially immunised or unimmunised individuals should complete immunisation according to the UK schedule. Completely immunised individuals should receive a single reinforcing dose of a diphtheria-containing vaccine according to their age.

# Complications of diphtheria<sup>[2]</sup>

- • • **Paralysis.** This often involves the muscles of the palate and the hypopharynx is seen in 10-20% of patients, beginning as early as the first 10 days of illness.
- **Difficulty swallowing and nasal speech.** These are often the first signs of neurological involvement.
- **Involvement of other cranial nerves.** This may be delayed until as late as seven weeks after infection and produce oculomotor paralysis and blurred vision. Diffuse, usually bilateral, motor function deficits resulting from involvement of the anterior horn cells of the spinal cord may be seen as late as three months after initial disease, with progression of weakness either from proximal-to-distal regions or, more commonly, from distal-to-proximal regions.
- **Diaphragmatic paralysis.** This will result if the phrenic nerve is involved. This may occur at any time between the 1st and 7th weeks of illness.
- **Cardiac complications.** These may arise during the first 10 days of the illness or they may be delayed for 2-3 weeks by which time pharyngeal disease is subsiding:
  - The first sign of cardiac involvement is tachycardia disproportionate to the degree of fever. Fever is rarely above 39°C.
  - Heart block of first, second or third degree may be seen.
  - Atrioventricular dissociation and ventricular tachycardia can develop and congestive heart failure may result.
  - Echocardiogram may demonstrate dilated or hypertrophic cardiomyopathy.
  - In patients who survive, cardiac muscle regeneration and interstitial fibrosis lead to recovery of normal cardiac function, unless toxic damage has led to a permanent arrhythmia.

- **Airway obstruction.** This is caused by the diphtheritic membrane and peripharyngeal oedema causing the 'strangling', and emergency tracheostomy may be required.

## Prognosis

- Overall, there is a 5-10% mortality rate, but it is up to 20% in those younger than 5 years and older than 40 years.<sup>[7]</sup>
- Recovery is slow and particular caution should be advised after myocarditis.
- Complete recovery from neurological damage is usual in those who survive.

## Prevention of diphtheria

Vaccination confers protection against disease by production of antibodies to the diphtheria toxin. When treated with formaldehyde and heat, diphtheria toxin loses its ability to bind to cells and its enzymatic activity, but retains its immunogenicity. This treatment converts diphtheria toxin to a toxoid. The vaccine is produced from purified inactivated toxin from a strain of *C. diphtheriae*.

### Diphtheria vaccines<sup>[3]</sup>

Diphtheria vaccines are available in two strengths according to dose of toxoid:

- High-dose - vaccines contain  $\geq 30$  IU of diphtheria toxoid and are used to achieve satisfactory primary immunisation of children - as in diphtheria/tetanus/acellular pertussis (DTaP) vaccine (capital D = high-dose).
- Low-dose - vaccines contain approximately 2 IU of toxoid and are used for primary immunisation of those aged over 10 years and for subsequent boosters (lower case d signifies low-dose as in dTaP).

Monovalent diphtheria vaccine is not available. Vaccination can only be given as a component of the following combination products:



- • • Diphtheria/tetanus/acellular pertussis/inactivated polio/*Haemophilus influenzae* type b vaccines (DTaP/IPV/Hib).
- Diphtheria/tetanus/acellular pertussis/inactivated polio vaccines (DTaP/IPV or dTaP/IPV).
- Tetanus/diphtheria/inactivated polio (Td/IPV).

## Administration

- • • Five doses of a diphtheria-containing vaccine are given intramuscularly.
- Upper arm or anterolateral thigh sites are recommended to minimise risks of local reactions.
- Other vaccinations such as measles, mumps and rubella (MMR), meningitis C or hepatitis B can be given at the same time but should be injected at an alternative site and preferably in a different limb.

## Schedule

### Primary immunisation

- • • All infants should receive the primary immunisation course involving three doses of diphtheria-containing vaccine.
- It is recommended that DTaP/IPV/Hib be given at 2, 3 and 4 months of age as levels of passively acquired maternal antitoxin decline.
- However, if necessary, the same dosing schedule can be used in children up to 10 years of age.
- Older individuals (aged >10 years) should receive three doses of a d-containing preparation (usually Td/IPV) at monthly intervals.

### Boosters

- • • The first booster dose is given to children between the ages of 3½ and 5 years.
- Either DTaP/IPV or dTaP/IPV will elicit an adequate immune response.
- If primary immunisation has been delayed, the first booster dose must be given at least one year after completion of the initial course.
- All individuals aged over 10 years who require a first booster should be given a dose of Td/IPV.

The second booster dose is offered to those aged 13-18 by the school health service:

- • • The Td/IPV preparation should always be used.
- If previous doses have been delayed, the second booster should be given at least five years after the first booster.
- Note that patients may have inadvertently already received a diphtheria booster associated with tetanus toxoid.

## **Other recipients**

### **Immigrants**

Children from developing countries may not be fully immunised against diseases such as diphtheria. If the history is unclear, children are considered unimmunised and should complete the full UK schedule.

### **Travellers**

Travellers to endemic areas should be fully immunised according to the UK schedule before travel. Travellers to developing countries for over one month's duration, who had their last diphtheria booster dose more than 10 years previously, should be offered a further booster of Td/IPV.

### **Laboratory and healthcare workers**

Individuals who may be exposed to diphtheria at work must be fully immunised and should be offered a booster dose. Further boosters should be given every 10 years if risks persist. Workers who are unimmunised should undergo the complete vaccination schedule with subsequent antibody testing as proof of immunity.

## Contra-indications<sup>[3]</sup>

There are very few individuals who are unable to receive diphtheria-containing vaccines. The diphtheria vaccination should not be administered to patients with:

- • • Confirmed anaphylactic reaction to diphtheria toxoid-containing vaccine.
- Confirmed anaphylactic reaction to any of the components of the vaccine.

Confirmed anaphylaxis is extremely rare.

The following situations do **not** prohibit diphtheria vaccination:

- • • History of a stable neurological condition, seizures or febrile convulsions (without neurological deterioration).
- If there is evidence of current neurological deterioration, including poorly controlled epilepsy, immunisation should be deferred and the child should be referred to a child specialist for investigation to see if an underlying cause can be identified. If a cause is not identified, immunisation should be deferred until the condition has stabilised. If a cause is identified, immunisation should proceed as normal.
- Fever, persistent screaming or crying (even for more than three hours), severe local reactions or hypotonic-hyporesponsive episodes following previous diphtheria vaccinations.
- A history of severe local reaction to the vaccine.
- Immunosuppression including HIV infection (but individuals may not achieve an adequate immunological response).

This vaccine can be given to women who are pregnant or who are breast-feeding.

# Adverse reactions

- Pain, swelling, redness or a transient nodule at the injection site may occur.
- Fever, convulsions, screaming, pallor, cyanosis and hypotonic-hyporesponsive episodes.
- Allergic reactions and (very rarely) anaphylactic episodes.

**Disclaimer:** This article is for information only and should not be used for the diagnosis or treatment of medical conditions. Egton Medical Information Systems Limited has used all reasonable care in compiling the information but makes no warranty as to its accuracy. Consult a doctor or other healthcare professional for diagnosis and treatment of medical conditions. For details see our [conditions](#).

Authored by:	Peer Reviewed by: Dr Colin Tidy, MRCP	
Originally Published: 20/11/2023	Next review date: 23/05/2023	Document ID: doc_2064

View this article online at: [patient.info/doctor/diphtheria-and-diphtheria-vaccination](http://patient.info/doctor/diphtheria-and-diphtheria-vaccination)

Discuss Diphtheria and diphtheria vaccination and find more trusted resources at [Patient](#).



To find out more visit [www.patientaccess.com](http://www.patientaccess.com)  
or download the app



Follow us

