Public Health England

Protecting and improving the nation's health

Public health control and management of diphtheria (in England and Wales)

2015 Guidelines

Diphtheria Guidelines Working Group

About Public Health England

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Executive summary

Current guidelines for the management of diphtheria in Europe were prepared by the World Health Organization (WHO) European Region in response to the re-emergence of diphtheria in the former Soviet Union and Eastern Europe (1). The England and Wales guidelines were first developed in 1999. This revision of the England and Wales guidance was prompted by developments in local epidemiology, including the increasing number of *Corynebacterium ulcerans* cases, the introduction of routine real-time PCR (qPCR) testing of potentially toxigenic corynebacteria isolates by the national reference laboratory in April 2014 and the identification of circulating non-toxigenic toxin gene bearing (NTTB) *C. diphtheriae* strains in England.

These guidelines present the rationale and recommendations for control of diphtheria in England and Wales. They also take into account the new Public Health England (PHE) structures established in April 2013. It is anticipated that these guidelines will complement the existing guidance from the WHO (1). The updated guidelines are intended for those involved in the public health control of diphtheria, including:

- Health Protection Teams in PHE Centres (PHECs) and Public Health Wales (PHW)
- National Health Service (NHS) staff at local and national levels in England and Wales.

These guidelines are split into two sections:

Part One Background and rationale
Part Two Investigation and management of cases and close contacts

Part One – background and rationale

1.1 Clinical features of diphtheria

Classical respiratory diphtheria is characterised by the insidious onset of membranous pharyngitis with fever, enlarged anterior cervical lymph nodes, and oedema of the surrounding soft tissue, giving rise to the ‘bull neck’ appearance. Although not always present, the membrane is typically grey, thick, fibrinous, and firmly adherent. Laryngeal diphtheria is characterised by gradually increasing hoarseness and stridor and most commonly occurs as an extension of pharyngeal involvement in children (2, 3). Nasal diphtheria, usually mild and chronic, is marked by uni- or bilateral nasal discharge, which is initially clear and later becomes bloody. Cutaneous diphtheria usually appears on exposed limbs, particularly the legs. The lesions start as vesicles and quickly form small, clearly demarcated and sometimes multiple, ulcers that may be difficult to distinguish from impetigo (4). The classic description of diphtheritic lesions is that they are usually covered with an eschar, a hard bluish-grey membrane that is slightly raised.

Diphtheria is no longer easily diagnosed on clinical grounds as classic respiratory diphtheria is now rare in England and Wales. Mild cases of the disease resemble streptococcal pharyngitis and the classical pseudomembrane of the pharynx may not develop, particularly in people who have been vaccinated. With vaccine coverage for the routine childhood vaccination programme having been maintained at around 95% for the last two decades, the majority of cases within the UK now are mild infections in partially immunised individuals, or in adults that have been fully immunised but have waning immunity. As the disease is increasingly rare, most clinicians will not have encountered a case before and therefore may miss the clinical diagnosis (2-5). For example, potentially toxigenic corynebacteria infections are rarely included in the differential diagnosis of pharyngitis. Care should be taken when interpreting the presence of diphtheroids as representing coincident commensals, as established by a recent cutaneous case (6). Not all laboratories routinely culture pharyngeal swabs for corynebacteria, further increasing the potential for missed or delayed diagnosis (7).

1.2 Microbiology

Respiratory or cutaneous diphtheria is caused by toxigenic strains of *C. diphtheriae* and *C. ulcerans*, and, very rarely, *C. pseudotuberculosis*. *C. diphtheriae* is a non-sporing, non-encapsulated, and non-motile Gram positive bacillus (8). Four biovars of *C. diphtheriae* can be distinguished biochemically: gravis, intermedius, mitis, and belfanti (9). In the United Kingdom (UK), most infections in recent years have been caused by biovar mitis (around 80%) followed by biovar gravis (7). The clinical and public health management is identical for all toxigenic strains. The microbiology of *C. ulcerans* is discussed in 1.5.

Both *C. diphtheriae* and *C. ulcerans* can produce an exotoxin that causes local tissue necrosis and, when absorbed into the bloodstream, causes systemic complications including demyelinating peripheral neuritis myocarditis. The structural gene of the diphtheria toxin, *tox*, is carried by a family of corynebacteriophages. The toxin is a 535 amino-acid 58 kDa exotoxin whose active form consists of two polypeptide chains linked by a disulphide bond (10). The clinical and epidemiological significance of non-toxigenic *C. diphtheriae and C. ulcerans* is unclear. This is further discussed in section 1.6.

Laboratory diagnosis is by culture of an isolate of *C. diphtheriae, C. ulcerans or C. pseudotuberculosis* in a clinical laboratory. The common detection methods in use in most laboratories are microbiological culture on standard agar (or selective tellurite-containing media). Colonies which prove to be catalase positive, Gram-positive coryneform rods may be further identified by conventional biochemical testing or Matrix Assisted Laser Desorption/Ionization – Time of Flight (MALDI-TOF). These methods can have good specificity but the confirmation of identification, and the determination of toxigenicity requires submission of the isolate to the national reference laboratory, PHE Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU). Identification and the presence of the *tox* gene are tested for by qPCR. This assay identifies *C. diphtheriae*, *C. ulcerans* / *C. pseudotuberculosis,* plus the presence of the *tox* gene in DNA extracts from submitted isolates (11). The assay targets the *rpoB* gene and the A-subunit of the toxin gene (*tox*). If the *tox* gene is detected, the isolate goes on to have an Elek test to detect expression of toxin (11).

1.3 Transmission and carriage of diphtheria-causing organisms

The incubation period for diphtheria is usually two to five days (12), but occasionally is longer, with duration of up to 10 days reported (13). The common mode of transmission of *C. diphtheriae* is droplet spread from a person with respiratory diphtheria. Alternative modes of transmission are direct contact with cutaneous diphtheria lesions, infected secretions or infected animals (*C. ulcerans*), or consumption of unpasteurised dairy products (*C. ulcerans*).

Closeness and duration of contact are important in determining the spread of the disease, and prolonged close contact is usually required for spread, as reported in a study showing greater risk in children sharing a dormitory (14). In the absence of clear evidence on transmission of diphtheria, principles used in the public health management of meningococcal disease can be applied. Contacts considered at risk are those who have had prolonged close contact with a case or known carrier in a household-type setting, or those who have had transient close contact if they have been directly exposed to large particle droplets or secretions. Cutaneous diphtheria may be spread by direct contact with cutaneous lesions. Contact with articles soiled with the discharge of infected people or animals may play a role in transmission (12, 15).

Asymptomatic carriage of toxigenic corynebacteria may occur during the incubation period of diphtheria, during convalescence, or for an unknown duration in healthy people. Patients convalescing from diphtheria may harbour corynebacteria in the pharynx or nose for many weeks (10). Carriage can be eradicated by antibiotic treatment: erythromycin, clarithromycin, azithromycin, and penicillin are all likely to be effective but antimicrobial susceptibility testing may be required (see section 2.6.4).

In Western Europe, carriage and disease have become very uncommon since the introduction of routine immunisation, and isolation of the organism from healthy individuals is extremely rare. A carriage study conducted during a seven-month period in 2007-2008 in ten European countries identified only six toxigenic strains of *C. diphtheriae*: two were from symptomatic patients in Latvia (the country with the highest reported incidence of diphtheria in the European Union) and four (two cases, two carriers) were from Lithuania where the last reported case was in 2002 (16).

There is some evidence that cutaneous diphtheria may be more transmissible than respiratory diphtheria (17). In tropical countries, cutaneous diphtheria lesions may act as reservoirs of infection. Both cases and contacts of cutaneous diphtheria may develop respiratory diphtheria. (8, 17). In the UK and Europe, most cutaneous cases are caused by imported toxigenic *C. diphtheriae* infections (7, 18-22), although some cutaneous *C. ulcerans* infections have been reported (7, 23, 24). In the UK, a cutaneous *C. ulcerans* infection in 2011 was suspected to have been acquired from domestic companion animals (6) and in 2014 a case was reported that had had direct contact with a dog infected with a *C. ulcerans* strain (personal communication). Occasionally patients have developed respiratory diphtheria following cutaneous infection (25). More detailed information on transmission of *C. ulcerans* is in section 1.5.

1.4 History and current control of diphtheria in England and Wales

Diphtheria is a notifiable disease under the Infectious Disease (Notification) Act of 1889 and the updated 2010 regulations. Doctors in England and Wales have a statutory duty to notify a 'proper officer', usually through the Health Protection Team (HPT) , of all forms of diphtheria diagnosed clinically, including cutaneous (26).

Also under these regulations, laboratories have a duty to notify isolates of *C. diphtheriae* and *C. ulcerans*. PHE also requests notification of isolates of *C. pseudotuberculosis* (27). Laboratories should notify the HPT in PHE Centres (PHEC) and Public Health Wales (PHW), and all such isolates should be referred to the national reference laboratory for toxigenicity testing (see section 2.3.2).

In 1914 there were 59,324 cases and 5,863 deaths due to diphtheria in England and Wales (28). Mass immunisation was introduced in 1942 and by 1957 there were only 37 cases and four deaths. There has been a significant change in diphtheria epidemiology over the past fifty years within England and Wales.

Diphtheria was initially monitored through notifications of clinical disease. In a review covering the period 1970 to 1987, 92 cases of diphtheria were notified, 21 of which were acquired overseas or through contact with a case who had acquired the infection overseas (29). Routine laboratory surveillance began in England and Wales in 1986, and allows monitoring of non-

toxigenic *C. diphtheriae* in addition to diphtheria cases. Data from 1986 onwards are available on the PHE website (19). These surveillance data show that between 1986 and 2013, 2662 *C. diphtheriae* isolates were received, of which 68 (2.6%) were toxigenic. An increase in laboratory reports of non-toxigenic *C. diphtheriae* was observed from 58 in 1992, peaking to 294 in 2000 before falling to 39 in 2009 and remaining around 30-60 isolates per year since then. This increase in reports may be attributed to increased case ascertainment as public health laboratories were encouraged at this time to routinely screen pharyngeal swabs for corynebacteria following the resurgence of diphtheria in the former Soviet Union (30).

Both *C. diphtheriae* and *C. ulcerans* are causes of diphtheria in the UK. Until the early 1990s, toxigenic infections were more commonly caused by *C. diphtheriae* than *C. ulcerans*, whereas since the 1990s, *C. ulcerans* has been the predominant cause of UK toxigenic infection (see section 1.5 for more details on *C. ulcerans*). The species cannot be linked to the clinical presentation. Since the start of laboratory surveillance in 1986, the clinical presentation in over 85% of toxigenic infections has been non classical respiratory diphtheria for both *C. diphtheriae* (59 of 68 isolates; 86.8%) and *C. ulcerans* (59 of 66 isolates; 89.4%) (see section 2.2 for case definitions). However, both *C. ulcerans* and *C. diphtheriae* have resulted in severe or fatal disease with six deaths between 1986 and 2013, four of which were caused by *C. ulcerans* (19).

Risk factors for acquisition of the two species do partially differ. Assessment of risk factors is based on standardised risk factor information collected since 1995; companion animal information was added in 2003 following recognition of risk (31). The main risk factor for all diphtheria is being unvaccinated; additionally *C. diphtheriae* is associated with travel to an endemic country. *C. ulcerans* was previously associated with consumption of raw dairy products, but has become more recently associated with contact with companion animals. In a review of 62 cases of *C. ulcerans* between 1986 and 2008, seven of 59 (12%) *C. ulcerans* cases were recorded as having consumed raw milk or dairy products, one of these had also had contact with cattle. However, all 19 cases reported between 2003 and 2008 had had contact with domestic pets (cats and dogs) (7). Since 2008, all seven *C. ulcerans* cases reported contact with domestic animals; contact with non-domesticated animals was also noted for three cases. The evidence on companion animal transmission to humans is limited because of the small number of cases, high exposure prevalence to companion animals in the general

population, and lack of swabbing of animal contacts (19). However, evidence is slowly accumulating. In the UK, a cutaneous *C. ulcerans* infection in 2011 was suspected to have been acquired from domestic companion animals (6) and in 2014 a case was reported that had had direct contact with a dog infected with toxigenic *C. ulcerans* (personal communication).

1.5 *Corynebacterium ulcerans*

C. ulcerans was first described in 1926 when the organism was isolated from human pharyngeal lesions and is known to produce diphtheria toxin (32). It has been associated with classical diphtheria (23, 33-36) as well as with milder symptoms (37-41). Several deaths in the UK have been attributed to this infection (7, 42).

C. ulcerans may infect the bovine udder and in the past an association between human *C. ulcerans* infection and drinking raw milk and unpasteurised milk products has been observed (37, 38). The organism appears to have a wide host range and has been isolated from many domestic and wild animals; more recently toxigenic *C. ulcerans* infections have been associated with contact with domestic and companion animals (18, 43). Person-to-person spread has never been documented, and most swabs from close contacts have been negative (35, 37, 40, 44), though in two incidents in 1996 and 1998 toxigenic *C. ulcerans* was found in asymptomatic contacts of cases, raising the possibility of person-to-person transmission (7).

In 1997, following two reports of cases of membranous pharyngitis caused by toxigenic *C. ulcerans*, the US Centers for Disease Control and Prevention recommended that people exposed to the index case should be treated along similar lines to cases exposed to toxigenic *C. diphtheriae*. This was later revised in 2011 to advise vaccination of unimmunised contacts rather than provision of prophylactic antibiotics. This advice was given because there is inadequate information about human-to-human transmission of this organism (45, 46). In the UK, because possible person-to-person transmission of toxigenic *C. ulcerans* has been observed (7), chemoprophylaxis of contacts of a toxigenic strain is recommended.

1.6 Non-toxigenic *C. diphtheriae* and *C. ulcerans*

Although non-toxigenic corynebacteria are more frequently identified than toxigenic strains, their clinical and epidemiological significance remains unclear. Most micro-organisms that

colonise the body, including those thought not to be pathogenic, can cause disease under predisposing circumstances (47). It is well established that the ability to produce toxin is mediated by infection of the bacterium by a bacteriophage and is unrelated to the biotype (48); however the mechanism of pathogenicity of non-toxigenic strains of *C. diphtheriae* is poorly understood (49).

Examples illustrating the diverse clinical presentations of non-toxigenic corynebacteria include two historical cases who accidentally ingested non-toxigenic *C. diphtheriae* biovar mitis in a laboratory, developing clinical diphtheria with a sore throat and tonsillar membrane (50). In Australia, seven aggressive cases of endocarditis due to non-toxigenic *C. diphtheriae* biovar gravis were reported in a single year in 1993, including four major vascular complications and one death (51). Other cases of endocarditis caused by non-toxigenic strains have been reported in India (52), the United States (53), Poland (54), New Zealand (55), and England (56). Non-toxigenic strains have also been associated with disease in immunocompromised individuals (57), and with recurrent pharyngitis in young adults (30). For example, cutaneous lesions have been reported in a Canadian homeless population (58), and there has been a recent increase in identification of disease-causing non-toxigenic strains of *C. diphtheriae* in Scotland, all presenting with persistent sore throat (59).

The number of isolates of non-toxigenic *C. diphtheriae* from pharyngeal swabs of children and young adults with sore throats in England and Wales (confirmed by the Public Health Laboratory Service Streptococcus and Diphtheria Reference Unit) rose from 17 in 1990 to a peak of 294 in 2000. Some of this rise in numbers again may be attributed to greater ascertainment through routinely screened pharyngeal swabs (30). Biotyping revealed that the increase was mainly non-toxigenic *C. diphtheriae* biovar gravis. Isolates of non-toxigenic *C. diphtheriae* from pharyngeal swabs declined to 68 in 2006, and further to 26 by 2013, reflecting the reversion of many laboratories to only screening clinically indicated pharyngeal swabs for *C. diphtheriae* (60) as the European epidemic subsided. Between 2003 and 2013, 14 non-toxigenic *C. ulcerans* isolates have been identified, 12 of which were from pharyngeal swabs.

Enhanced surveillance conducted during the mid-1990s showed that no other pathogen was isolated in 66% of cases but that viral cultures were rarely attempted (30). As most cases of acute pharyngitis are caused by viral infections this may suggest that the acute illness was not

due to the *C. diphtheriae* isolated (61). Even if obtained and processed in ideal circumstances, pharyngeal culture cannot reliably differentiate acute infection from chronic carriage (62). Studies have looked at the occurrence of non-toxigenic *C. diphtheriae* in pharyngeal swabs (30, 63-66). However, it has not been possible to determine if non-toxigenic *C. diphtheriae* was the cause of pharyngitis, or whether it was merely a coloniser, especially in the absence of a control group.

A recent multi-centre European carriage study identified that carriage rates of non-toxigenic corynebacteria ranged from zero (Bulgaria, Finland, Greece, Ireland, Italy) to 4.0 per 1000 (95% CI 2.0–7.1) in Turkey, though the zero estimates may have been due to small sample sizes (16).

Clinical management of non-toxigenic corynebacteria depends on case presentation and site of disease: detailed instructions for treatment are outside the scope of these guidelines. Although, there is no public health action required for most individuals with a non-toxigenic strain, further investigation and management should be considered for individuals with non-toxigenic toxin gene bearing (NTTB) *C. diphtheriae* (see section 1.6.1).

1.6.1 Non-toxigenic toxin gene bearing *C. diphtheriae* and *C. ulcerans* (NTTB)

Non-toxigenic *C. diphtheriae* usually lack the entire *tox* gene. Exceptionally some non-toxigenic strains can also carry variants of the *tox* gene that cannot be expressed phenotypically. These strains are designated NTTB. The PCR employed by RVPBRU is able to detect some of these non functional *tox* gene versions, so an NTTB will usually appear PCR *tox* positive, Elek-negative. These strains were originally described during the diphtheria epidemics in countries of the former Soviet Union within the WHO European region in the 1990s (67). In a study of 828 *C. diphtheriae* non-toxigenic strains isolated in different regions of Russia between 1994 and 2002, approximately 14% were found to be NTTB and differed from the epidemic toxin producing strains in both biotype and ribotype.

Four NTTB strains of *C. diphtheriae* were isolated from humans in the UK between March 2011 and June 2012, and one isolate from a cat (68). From August to October 2014, five NTTB *C. diphtheriae* strains were isolated in the UK; three were epidemiologically linked and two were linked geographically (De Zoysa *et al* unpublished data). Retrospective analyses of culture

collections have revealed NTTB *C. diphtheriae* in Canada (from 1999-2003) (69) and Romania (from 1963 to 2007) (70). Similar NTTB strains of *C. ulcerans* have also been isolated from game animals in Germany indicating potential reservoirs for human infection (71, 72).
As described earlier, discovery of these NTTB strains has been largely due to the use of PCR assays (both standard and real-time) targeting the *tox* gene together with use of the Elek test. (section 1.2).

A number of mechanisms have been postulated which could allow NTTB corynebacteria to become toxigenic. Depending on the version of the *tox* gene present, a genetic event may allow it to revert to a functional state. The probability of this depends on the type of genetic event and is difficult to quantify. In addition, like any non-toxigenic Corynebacterium of the potentially toxigenic species, the organism can undergo lysogenisation by phage which provides a new copy of a functional *tox* gene. Within the UK, the risk of bacteria becoming toxigenc by phage lysogenisation is low.

NTTB corynebacteria are not known to cause diphtheria and so patients are not treated with antitoxin unless they exhibit signs of systemic disease. However, due to their higher (albeit unquantifiable) risk of becoming toxigenic, it is recommended that they are eliminated using antibiotics in the same way as fully toxigenic (ie Elek-positive, toxin-expressing) strains. This includes both patients and asymptomatic carriers. It is also advisable to initiate contact tracing amongst close contacts of the ‘case’ (see section 2.9.2).

1.7 Rationale for the guidelines

Incidents of confirmed diphtheria are rare and it would be unusual for a local health protection lead to have personal experience of managing a case. The increased identification of non-toxigenic strains following the recommendation to routinely screen pharyngeal swabs for *C. diphtheriae* led to increased expectations of local health protection leads to provide advice on the basis of preliminary microbiological findings (60), prompting development of the original 1999 guidelines (73). Delay in starting treatment could prove fatal for the case and wider spread of the agent could occur in the community if control measures are not promptly initiated. Conversely, there is a risk of inappropriate use of antibiotics and antitoxins.

These guidelines therefore aim to:

1) maintain awareness amongst clinicians and prompt consideration of diphtheria as a part of the differential diagnoses; and
2) assist health protection leads in undertaking the risk assessment; and
3) provide clarity as to the clinical and public health actions that should be taken on the basis of the risk assessment for the different potentially toxigenic corynebacteria.

Part Two – management and investigation of cases and close contacts

2.1 Risk assessment of cases

The management of suspected diphtheria involves a risk assessment to determine whether public health actions should be commenced prior to laboratory confirmation of a toxigenic strain. The local HPT should undertake the risk assessment ideally in discussion with the Immunisation, Hepatitis, and Blood Safety Department (IHBSD) PHE Colindale team or duty doctor. Information that should be collected on each case to inform the risk assessment includes:

Demographics

- Name, date of birth, gender, ethnicity, birthplace, NHS number
- Address including postcode, phone number
- GP name and contact details (address and phone number).

Clinical details

- Symptoms and signs – onset and severity of symptoms*; presence of classic respiratory symptoms [presence of sore throat, fever, adherent greyish membrane (bleeds when manipulated or dislodged) of the tonsils pharynx or nose], other presentations (eg otic, genital, laryngeal), skin lesions
- Results of laboratory investigations (local and/or reference laboratory) – anatomical site of samples, toxigenicity results if available or when these can be expected, and any other organisms detected
- Differential diagnoses considered, eg Lancefield Group A haemolytic *Streptococcus*, *Staphylococcus aureus*, oral *Candida albicans, Arcanobacter haemolyticum, Borelia vincenti* (Vincent's angina), adenovirus, Epstein-Barr virus, *Herpes simplex*, *Haemophilus influenzae*
- Drugs – some drugs may rarely cause a membrane eg methotrexate.

* Note that a previously immunised/partially immunised case may only have a sore throat even when infected with a toxin-producing strain

Epidemiological details

- Immunisation history (primary course and boosters, including dates)
- Occupation eg work in a clinical microbiology laboratory, or similar occupation, where potentially toxigenic *Corynebacterium* spp. may be handled.

- Within the last 10 days has the patient:
  - Had contact with a confirmed case?
  - Travelled abroad to a high-risk area (particularly Indian subcontinent, South East Asia, Africa, South America, former Soviet States and Eastern Europe)?
  - Had contact with someone who has been to a high-risk area?
  - Had contact with any animals (including household pets, visiting a farm or petting zoo)?
  - Recent consumption of any type of unpasteurised milk or dairy products

2.2 Case definitions

Cases should be classified according to clinical and laboratory criteria (see below). These are adapted from previous surveillance reporting definitions (4, 62).

Confirmed case of toxigenic infection

- Classic respiratory diphtheria[1] *AND*
- EITHER Laboratory confirmation of a toxigenic strain[2] *OR*
- Epidemiological link to a laboratory-confirmed case with a toxigenic strain

OR

- Laboratory confirmation of a toxigenic strain[2] with other presentations of diphtheria[3].

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[1] **Classic respiratory diphtheria:** a patient with an upper respiratory tract illness characterised by sore throat, low grade fever, and an adherent membrane of the tonsils, pharynx or nose.

[2] **Laboratory identification and confirmation of diphtheria**: Isolation of diphtheria toxin-producing corynebacteria (indicated by PCR and/or confirmed by Elek test) from a clinical specimen by a reference laboratory. For the purposes of public health action, a strain with *tox* gene detected by PCR is considered to be laboratory confirmed.

[3] **Other presentations of diphtheria:** a patient with mild respiratory symptoms but no membrane or a patient with a skin lesion in whom a laboratory report of an isolate of *C. diphtheriae* or *C. ulcerans* from a pharyngeal swab or skin lesion swab has been obtained. Very rarely, endocardial, laryngeal, conjunctival, otic and genital involvement may be seen.

Probable case of toxigenic infection

- Classic respiratory diphtheria[1] *AND*
- No laboratory confirmation (*C. diphtheriae*, *C. ulcerans* or *C. pseudotuberculosis* has not yet been isolated from a relevant swab, or where a strain has been isolated **BUT** toxigenicity status has not yet been confirmed) *AND*
- No epidemiological link to a laboratory-confirmed case with a toxigenic strain

OR

- A severely unwell patient with *C. diphtheriae*, *C. ulcerans* or *C. pseudotuberculosis* isolated from a relevant swab, **BUT** toxigenicity status has not yet been confirmed (eg laryngeal disease).

OR

- Other presentations of diphtheria[3] with a confirmed epidemiological link to a laboratory confirmed case[2].

Possible case of toxigenic infection

- Other presentations of diphtheria[3] (see 2.1.2) *AND*
- Isolation of *C. diphtheriae, C. ulcerans* or *C. pseudotuberculosis* in a pharyngeal, skin, or other appropriate swab, **BUT** toxigenicity status has not yet been confirmed.

Asymptomatic carrier of toxigenic strain

- No symptoms *AND*
- Laboratory confirmation of toxigenic strain[2] from any anatomical site.

Case of non-toxigenic toxin gene bearing (NTTB) Corynebacteria infection

- Other presentations of diphtheria[3] (see 2.1.2) *AND*
- Isolation of non toxigenic-toxin gene bearing (NTTB) corynebacteria (PCR toxin gene positive, Elek negative) in a pharyngeal, skin, or other appropriate swab,

Asymptomatic carrier of NTTB strain

- No symptoms *AND*
- Laboratory confirmation of NTTB corynebacteria (PCR toxin gene positive, Elek negative) strain from any anatomical site.

Discarded

- If other compatible organisms are isolated, or if corynebacteria are isolated but are confirmed to be a non-toxigenic strain, they would no longer fit the case definition of a probable or possible case.

2.3 Laboratory confirmation and timing of public health actions (see Appendix 1)

Following isolation of corynebacteria at the local microbiology laboratory, confirmation will be based on further testing by PHE RVPBRU. It is sometimes appropriate to initiate public health actions before the confirmatory toxigencity result is available from RVPBRU. The decision should be made, ideally in consultation with PHE IHBSD Colindale team or out of hours duty doctor, and on the basis of the risk assessment as follows:

For a **confirmed** or **probable** diphtheria case or asymptomatic carrier of toxigenic *C. diphtheriae, C*. *ulcerans* or *C. pseudotuberculosis*, initiate full public health actions immediately without waiting for toxigenicity results.

For a **possible case** of diphtheria, public health actions can usually be delayed until toxigenicity results are available, at which point the case will either be reclassified as confirmed toxigenic infection or NTTB corynebacteria, or will be discarded.

In certain situations some public health actions, such as initiating swabbing and chemoprophylaxis, and exclusion of close contacts in high risk occupations, should be considered for a **possible case** of diphtheria before toxigenicity results are available, such as:

- If there are epidemiological factors that increase likelihood of toxigenicity (see 2.1) *OR*
- If there is a high public health risk but inconsistent or absent clinical or epidemiological information, eg suspected case in a healthcare worker with undetermined immunisation status and travel to an endemic region *AND*
- Toxigenicity results are unlikely to be available within 24 hours.

Following toxigenicity results:

- For a case which is confirmed as a toxigenic strain, complete management of close contacts.
- For a case with NTTB corynebacteria (PCR *tox* positive, Elek negative), management of close contacts should be considered (discuss with IHBSD).
- For a case which is discarded, stop public health actions. Discontinue investigation and management of contacts. In the rare event that a contact has been swabbed and grown *C. diphtheriae*, *C. ulcerans* or *C. pseudotuberculosis*, toxigenicity testing should be performed and a risk assessment undertaken.

2.3.1 Culture

Swabs (nasopharyngeal, throat, wound or skin lesions) should be obtained for culture before starting treatment. Where a pseudomembrane or membrane is present, if possible, swabs should be taken from underneath the pseudomembrane or a piece of the membrane should be removed.

If antibiotics have already been commenced, specimens for culture should still be taken.

Clinicians should alert the local laboratory that diphtheria is suspected.

2.3.2 Toxigenicity testing

All isolates of potentially toxigenic corynebacteria (*C. diphtheriae, C. ulcerans* or *C. pseudotuberculosis*) should be submitted to PHE RVPBRU for confirmation of identification and toxigenicity testing (74).

Identification/confirmation and toxigenicity testing is performed initially by realtime PCR (qPCR) on a DNA extract of the submitted isolate. Isolates which are qPCR positive for the *tox* gene will also be tested by the Elek test for toxin expression.

Although *C. diphtheriae, C. ulcerans*, and *C. pseudotuberculosis* toxin gene PCR positive results will be confirmed by the Elek test, **a toxin gene PCR positive result should be acted upon without waiting for the Elek result.**

As already described, rare isolates of *C. diphtheriae* are *tox* gene positive by PCR but do not express toxin, ie negative on Elek test (NTTB, see section 1.6.1). These are very rare in the UK (68). They will not cause diphtheria and so patients are not treated with antitoxin. If detected in symptomatic patients or asymptomatic carriers, they should, however, be eliminated using antibiotics in the same way as fully toxigenic strains (see section 2.9).

Sending an isolate for toxigenicity testing

Notify RVPBRU (telephone 0208 327 7887) before sending potentially toxigenic isolates for toxigenicity testing within working hours on a weekday. Outside these hours, please notify the Colindale duty doctor on 0208 200 4400. Always use the RVPBRU Request Form (R3)[4] and ensure full contact telephone numbers are provided on the form. Send isolates to:

Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU),
Bacteriology Reference Department,
Public Health England – Colindale,
61 Colindale Avenue,
London NW9 5HT

To ensure timely processing of samples we recommend that isolates are sent via courier rather than Hays DX.

Service

As of publication, isolates received by 12 noon Monday to Friday (in normal working week) will be processed that day with the result available by the end of the working day. Isolates received after 12 noon Monday to Thursday will be reported on the following day (or earlier depending on time of arrival). Isolates received between Friday 12 noon and Saturday 12 noon will be processed and reported on Saturday afternoon (or earlier). Isolates received after 12 noon on

[4] RVPBRU Request Form (R3) available at:
https://www.gov.uk/government/publications/vaccine-preventable-bacteria-section-request-form

Saturday will usually be processed on Monday. An on call service equivalent to a Saturday service will be available for Bank Holiday Mondays. It is essential that you telephone before sending isolates for Saturday or Bank Holiday testing as otherwise they will not be processed. If you require any further details out of hours, please contact the Colindale duty doctor (0208 200 4400). Test results will be reported by phone to the telephone number provided on the Request Form (R3)[4]. Ensure that full contact details to assist reporting are provided (including out-of-hours numbers if required).

2.4 Notification of cases

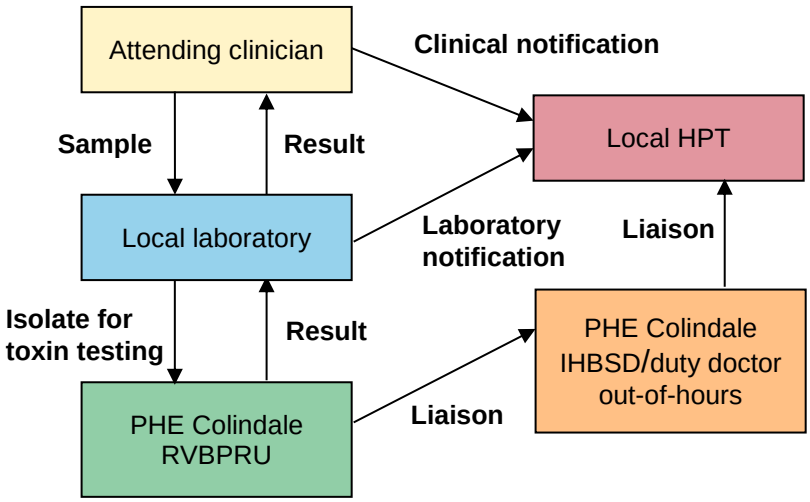
Notification must be undertaken as per the statutory duties outlined in section 1.4. Clinicians should notify all cases, whether confirmed, probable or possible, or asymptomatic carriers, by phone on the same day to the local HPT.

Microbiology departments should notify **all** *C. diphtheriae*, *C. ulcerans*, and ideally *C. pseudotuberculosis* isolates by phone to the local HPT.

In addition to mandatory notifications, there should be good communication between the microbiology team, infectious disease physicians, other hospital doctors, general practitioners, the local health protection lead, and PHE Colindale IHBSD, and RVPBRU. The local HPT should discuss out-of-hours cases with the duty doctor at PHE Colindale (0208 200 4400).

Figure 1 details the various interactions of the local laboratory, local health protection service, the reference laboratory and the IHBSD at PHE Colindale.

Figure 1: Case notification flowchart and interaction between departments



2.5 Incident Control Team

For most cases of confirmed or probable diphtheria, an Incident Control Team (ICT) (Outbreak Control Team (OCT) in Wales) should be convened. Membership of the team will vary depending on local circumstances, but would typically include:

- Deputy director for health protection
- Consultant in Communicable Disease Control / Consultant in Health Protection
- Local consultant microbiologist
- Consultant physician responsible for care of the patient
- Consultant in infectious disease
- Infection control nurse
- Representation from PHE Colindale (IHBSD and RVPBRU)
- Communications team

In addition, the PHE Centre Director, Director of Public Health in the Local Authority (England only), and Consultant Epidemiologist from the Field Epidemiology Service

should be alerted, and may be included in the ICT[5,6]. Confirmed cases should be reported by the national centre to the relevant section of the Department of Health.

In cases of toxigenic *C. ulcerans* infection, include a local representative of the Animal and Plant Health Agency (APHA) in the ICT/OCT if the source is suspected to be an indigenous animal and/or unpasteurised milk product from a UK farm, or thought to be from imported milk products. The APHA representative will ensure that the Department for Environment, Food and Rural Affairs (DEFRA) are kept informed of the case details and will liase with the local veternary colleagues as appropriate.

2.6 Management of cases of confirmed or probable diphtheria due to *C. diphtheriae*, *C. ulcerans*, or *C. pseudotuberculosis* (see Appendix 2)

2.6.1 Isolation

Isolate confirmed or probable cases in hospital. Institute precautions appropriate for droplet borne infection and/or direct contact measures, for example side room with use of gloves, apron and surgical mask (75). Continue isolation until two cultures from the nasopharyngeal and throat (or skin lesions if cutaneous diphtheria) taken at least 24 hours apart and more than 24 hours after completing antibiotics are negative for toxigenic *C. diphtheriae, C. ulcerans* or *C. pseudotuberculosis* (9).

If the case is well and not hospitalised, advise to restrict contact with others until completion of an appropriate course of antibiotics eg case should not attend GP practice for further tests.

It is also advisable to take nasopharyngeal and throat swabs from close contacts of the index case (see section 2.9).

[5] The PHE ”Communicable disease outbreak management: operational guidance” document details further information forming an incident team, available at https://www.gov.uk/government/publications/communicable-disease-outbreak-management-operational-guidance

[6] The Welsh Government "Communicable disease outbreak plan for Wales” available at http://wales.gov.uk/topics/health/protection/communicabledisease/publications/outbreakplan/?lang=en

2.6.2 Referral

Refer probable or confirmed cases to a specialist infectious disease (ID) unit / consultant.

2.6.3 Antitoxin treatment

Diphtheria antitoxin should only be used for confirmed or probable cases of diphtheria in a hospital setting. Diphtheria antitoxin should be given to classic respiratory cases without waiting for laboratory confirmation. In most cutaneous infections, large-scale toxin absorption is unlikely and therefore the risk of giving antitoxin is usually considered to be substantially greater than any benefit. Nevertheless, if the ulcer in cutaneous diphtheria infection were sufficiently large (ie more than $2cm^2$) and especially if it were membranous, then antitoxin would be justified (76).

Diphtheria antitoxin is based on horse serum and therefore severe, immediate anaphylaxis occurs more commonly than with human immunoglobulin products. Tests to exclude hypersensitivity to horse serum should be carried out as described in the Summary of Product Characteristics (SPC). Local policies for the management of anaphylaxis should be followed.

Contact the PHE Colindale IHBSD or duty doctor out-of-hours if considering the use of antitoxin (0208 200 4400). They will advise on details of current stock and dosing as suppliers change and dosing is product-specific (details in immunoglobulin handbook https://www.gov.uk/government/publications/immunoglobulin-when-to-use), and provide details of contact in one of the five English issuing centres or the public health organisation in the devolved organisations.

2.6.4 Antibiotic treatment

Treat confirmed or probable cases to eliminate the organism and prevent spread. This is not a substitute for antitoxin treatment.
All specimens should be collected **before** antibiotic treatment is started. If antibiotics have already been started then samples should still be taken.

The empirical choice of antibiotics are macrolides (erythromycin, azithromycin, or clarithromycin), or benzylpenicillin, all of which are active in vitro against *C. diphtheriae* and *C. ulcerans* (77). If erythromycin cannot be tolerated (because of gastrointestinal side effects) an alternative macrolide such as azithromycin or clarithromycin should be given (1). Parenteral benzylpenicillin or erythromycin should be used until the patient can swallow comfortably, when erythromycin or penicillin V should be continued, using doses as per the British National Formulary. In severe disease it may be prudent to give both benzylpenicillin and erythromycin parenterally until local susceptability results are availible. In the UK, there is little information available regarding the antibiotic susceptibility of circulating *C. diphtheriae* and *C. ulcerans* strains.

Antibiotic treatment should continue for 14 days based on local antimicrobial susceptibility testing. Elimination of the organism should be confirmed after antibiotic treatment has been completed by obtaining nasopharyngeal and throat swabs for culture, or in cases of cutaneous diphtheria by obtaining nasopharyngeal and skin swabs for culture. If microbiological clearance is not achieved an additional 10 day course of antibiotics should be prescribed following discussion with local microbiologists.

Treatment of confirmed or probable cases of cutaneous diphtheria also includes thorough cleaning of the lesion.

2.6.5 Immunisation

Infection does not always induce adequate levels of anti-toxin so confirmed or probable cases should receive a booster dose of a diphtheria-toxoid containing vaccine or immunisation appropriate to age and immunisation history (Figure 2). For adults with a complete immunisation history (five doses of diphtheria-containing vaccine) this is likely to be tetanus/low dose diphtheria/inactivated polio vaccine (Td/IPV). No booster dose is required if the last dose was given within the last 12 months.

Cases should be immunised once they are clinically stable.

For further details on diphtheria immunisation, see Chapter 15 in PHE's Green Book: Immunisation against Infectious Disease available at https://www.gov.uk/government/publications/diphtheria-the-green-book-chapter-15.

Figure 2: Recommended immunisations according to age and status for cases of confirmed or probable diphtheria

If a dose of diphtheria-containing vaccine has not been given in the last 12 months:

Immunised children up to 10 years of age: one injection of adsorbed diphtheria-containing vaccine (eg Td/IPV, dTaP/IPV or DTaP/IPV)

Immunised children aged 10 years and over, and adults: one injection of adsorbed low dose diphtheria-containing vaccine for adults (eg Td/IPV)

Unimmunised children under 10 years of age: three injections of adsorbed full dose diphtheria-containing vaccine (eg DTaP/IPV/Hib) at monthly intervals

Unimmunised children aged 10 years and over, and adults: three injections of adsorbed low-dose diphtheria-containing vaccine (eg Td/IPV) at monthly intervals

Immunisation status unknown: Where there is no reliable history of previous immunisation, it should be assumed that they are unimmunised and follow as above.

2.7 Management of cases of possible diphtheria due to *C. diphtheriae*, *C. ulcerans* or *C. pseudotuberculosis* (see Appendix 2)

The following actions should be taken:

- **Isolation**: Isolate possible cases who are in hospital as per section 2.6.1, and dress cutaneous lesions. Possible cases who are well at home should be advised to restrict

contact with those outside the immediate household until further microbiological results are obtained. Ensure isolates are sent to the PHE RVPBRU for toxigenicity testing (see 2.3.2). Liaise with the relevant microbiologists (local and reference laboratories).

- **Referral**: Possible cases should be assessed by a local clinician to ensure that they do not have clinical symptoms compatible with classic diphtheria (and should therefore be reclassified as a probable case).
- **Treatment**: Treatment of the case is undertaken on clinical grounds only. Antibiotic therapy should include a macrolide (erythromycin/clarithromycin) or appropriate penicillin (see 3.3.4).
- **Immunisation**: Most possible cases will be reclassified following toxigenicity results and immunisation can be decided accordingly. If not possible to reclassify, ensure individuals are up to date with immunisation with diphtheria-toxoid containing vaccine (Figure 2).

2.8 Management of asymptomatic carriers

Asymptomatic carriers of toxigenic strains should be treated with the same antibiotic regime as contacts, with nasopharyngeal and either throat or skin swabs taken as appropriate on completion of therapy to ensure eradication.

2.9 Management of cases of non-toxigenic toxin gene bearing (NTTB) corynebacteria

Individuals identified with a NTTB strain should be treated with antibiotics (see section 1.6.1) and should be offered immunisation according to Figure 2, as a precautionary measure.To ensure eradication, nasopharyngeal and throat swabs, or in cases of cutaneous diphtheria nasopharyngeal and skin swabs, should be taken on completion of antibiotic therapy.

2.10 Management of close contacts of diphtheria cases, asymptomatic carriers and NTTB corynebacteria cases (see Appendix 3)

2.10.1 Definition of close contacts

As the risk of infection is directly related to the closeness and duration of contact, prophylaxis is required if the contact is with a case or known carrier in a household type setting, or those who have had transient close contact if they have been directly exposed to large particle droplets or secretions (following the same principles of meningococcal disease) or if they have been exposed to an undressed wound of a cutaneous case.

Examples of contacts who should be considered for prophylaxis are listed in Figure 3.

Figure 3: Examples of contacts who should be considered for prophylaxis

- Those sleeping in the same household as the index case
- Students in a hall of residence in the same corridor/flat/shared kitchen facilities with the index case – adapt to local situation (needs to mimic household contact)
- Kissing/sexual contacts of the index case
- Health care workers who have given mouth-to-mouth resuscitation to or intubated the index case or have dressed the wound(s) of a single cutaneous case (not required if full infection control procedures in place for wound dressing and safe disposal of all clinical waste). See section 2.12 for management of a cluster.

The risk of transmission in other types of settings should be assessed on a case by case basis by the local health protection lead. Types of contact who are **unlikely** to require prophylaxis:

- Friends, relations, and caregivers who regularly visit the home;
- School classroom contacts;
- Those who share the same room at work;
- Health care staff that have had contact with the index case without droplet or wound exposure.

Experience of other droplet-spread infectious diseases suggests that the risk of transmission of disease on an aircraft is low, especially if contact with the affected person is for less than eight hours (76). Contact with a case on public transport is also likely to carry a low risk.
The maximum incubation period for diphtheria is 10 days; however, there may be longer duration of carriage in asymptomatic carriers but there is little evidence. Therefore close contacts should be identified from 10 days before onset of diphtheria symptoms in a case. For asymptomatic carriers, identify current close contacts; if there was a suspected time of acquisition, identify close contacts since that time and any recent vulnerable contacts.

2.10.2 Management of close contacts of confirmed and probable diphtheria cases, NTTB corynebacteria cases or asymptomatic carriers (see Appendix 2)

This will be led by the local HPT.

i) Investigation and monitoring of close contacts

Inform and self-monitor: Health protection staff should inform the close contacts that they may have been exposed to diphtheria, and should explain the symptoms (fever, sore throat, swollen neck glands, development of a membrane) and advise them to seek urgent medical attention if they become unwell. Travel history should be requested as the close contact may be the source of the case's infection. Close contacts should be advised to self-monitor for 10 days from the date of the last contact with the case. For those unable to self-monitor (eg children), the health protection staff should liaise with individuals responsible for the care of that person (eg GP, care home staff, family).

Swabbing: Health protection staff should inform the GP of the situation, and provide the fact sheet on diphtheria (Appendix 3). They should then arrange for swabbing of the close contact. This should include a nasopharyngeal and throat swab and swabs of any skin lesions, taken before chemoprophylaxis. This will identify any asymptomatic carriers.

ii) Chemoprophylaxis of close contacts

After nasopharyngeal and throat swabs have been taken, close contacts of confirmed or probable diphtheria cases and asymptomatic carriers should be given prophylactic antibiotics, regardless of culture result, to:

- treat incubating disease in recently exposed contacts AND
- eliminate carriage and thereby reduce the risk of exposure to other susceptible contacts.

Recommended agents for chemoprophylaxis are either erythromycin (7 days) or, if more easily administered, a single intramuscular (IM) dose of benzylpenicillin, with dosing as in the British National Formulary.

If erythromycin cannot be tolerated an alternative macrolide such as azithromycin or clarithromycin should be given.

If initial swabs are positive for corynebacterium they should be managed as per section 2.10.

Note: Diphtheria antitoxin is no longer used in the UK for diphtheria prophylaxis because of the risk of hypersensitivity.

iii) Exclusion of close contacts in high-risk occupations

Close contacts of confirmed or probable cases of diphtheria and asymptomatic carriers who work in the following high-risk occupations should be excluded from work and started on chemoprophylaxis.

- Food handlers (especially those involved in milk production for *C. ulcerans*)
- Health and social care workers
- Those who work with unimmunised children

This list is not exhaustive and there may be other instances where exclusion would be appropriate. The decision to exclude close contacts should be made by the local health protection lead based on an individual risk assessment.

All should have a nasopharyngeal and throat swab taken prior to the start of antibiotics. If the initial culture is negative they can go back to work while completing the course. In cases where the initial culture is positive they must remain excluded from work and have a second

nasopharyngeal and throat swab taken 24 hours after the completion of the course. They can return to work after a negative culture has been obtained.

iv) Immunisation of close contacts

Close contacts of confirmed or probable diphtheria cases and asymptomatic carriers should be immunised with a diphtheria-toxoid containing vaccine, unless a diphtheria-toxoid containing vaccine has been given within the previous 12 months. Please refer to schedule outlined in Figure 2.

2.11 Management of close contacts with *C. diphtheriae, C. ulcerans* or *C. pseudotuberculosis* isolated from throat or nasopharynx

Relevant isolates from contacts should be sent for toxigenicity testing immediately.
If the contact is symptomatic, commence antibiotic treatment as clinically appropriate. If the contact is asymptomatic, wait for the toxigenicity result.

Once toxigenicity results are available, manage as follows:
- Asymptomatic with non-toxigenic isolate detected: no further antibiotics
- Asymptomatic with toxigenic isolate detected: manage as asymptomatic carrier (section 2.8)
- Symptomatic with non-toxigenic isolate detected: manage as clinically appropriate
- Symptomatic with toxigenic isolate detected: manage as confirmed case (section 2.6)
- Asymptomatic and symptomatic with NTTB (PCR *tox* positive, Elek negative) isolate detected: manage as NTTB corynebacteria (section 2.9).

2.12 Management of animal contacts in confirmed toxigenic *C. ulcerans* cases only

Discuss with the incident / outbreak control team and the APHA to decide on appropriate actions to identify and manage potential animal source(s) and to risk assess animal settings such as farms, where there is potential for contact with multiple animals or species.

Occasionally it may be necessary to determine carriage in potential animal sources by taking samples eg where unpasteurised milk or dairy products, or an animal in close contact with the case is the suspected source. APHA with PHE RVPBRU will advise on collection and analysis of animal samples. *C. ulcerans* is not a notifiable disease in animals and it is unlikely to be

covered by pet insurance policies. Therefore prior to testing animal contacts, it is important to discuss implications of a positive test with the owner which many include: i) the cost of any private veterinary consultations, ii) the cost and potential outcome of antibiotic treatment, including possible side effects, iii) clearance swabs, and iv) potential for further treatment. It is appropriate for veterinary staff from APHA to discuss veterinary issues with owners. In the two cases where indistinguishable strain strain was identified from the dog and human a 10 day course of a combination of spiramycin and metronidazole was found to successfully clear the organism from the dog (78).

2.13 Management of clusters of NTTB corynebacteria

Although rare, with the advent of PCR testing, clusters of NTTB *C. diphtheriae*/*C. ulcerans* are more likely to be identitfied. The identification of a cluster of NTTBs should be followed by sequence typing at RVPBRU to confirm that the isolates are related. Management includes:

- Convening an ICT (see section 2.5)
- Management of the case (see section 2.6)
- Considering active management of close contacts of the cases; (this is usually appropriate). The ICT should decide whether the definition of close contacts is appropriate to the setting (see section 2.9) For example, in a healthcare setting, healthcare workers who have not worn appropriate personal protective equipment may be considered close contacts
- Discussing the case with PHE Colindale IHBSD.

2.14 Communications

Disseminate information promptly and appropriately to contacts to aid understanding, minimise anxiety and control rumours (a factsheet can be found in Appendix 3).

Consider informing institutions such as schools and nurseries, and in some situations, the wider community, as appropriate.

For confirmed cases, a reactive press statement should be prepared. Key messages could include:

- A case has occurred
- The chance of another case is very small as most people are protected by immunisation
- Close contacts of cases should have swabs taken and be given antibiotics as a precaution
- Immunisation status of close contacts will be checked and immunisation will be offered if necessary.

The local health protection lead should use this opportunity to emphasise the general importance of immunisation in the prevention of infectious diseases.

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Abbreviations

APHA	Animal and Plant Health Agency
CI	Confidence Interval
Defra	Department for the Environment, Food and Rural Affairs
DTaP/IPV	Diphtheria/tetanus/acellular pertussis/inactivated polio vaccine
GP	General Practitioner
HPA	Health Protection Agency
HPT	Health Protection Team
ICT	Incident Control Team
IHBSD	Immunisation, Hepatitis, and Blood Safety Department
IM	Intramuscular
IU	International Units
M unit	Mega unit
kDa	Kilodaltons
NHS	National Health Service
NTTB	Non-toxigenic toxin gene bearing
PCR	Polymerase Chain Reaction
PHE	Public Health England
PHW	Public Health Wales
RVPBRU	Respiratory and Vaccine Preventable Vaccine Bacteria Reference Unit
Td/IPV	Tetanus/low dose diphtheria/inactivated polio vaccine
UK	United Kingdom
US	United States
WHO	World Health Organization

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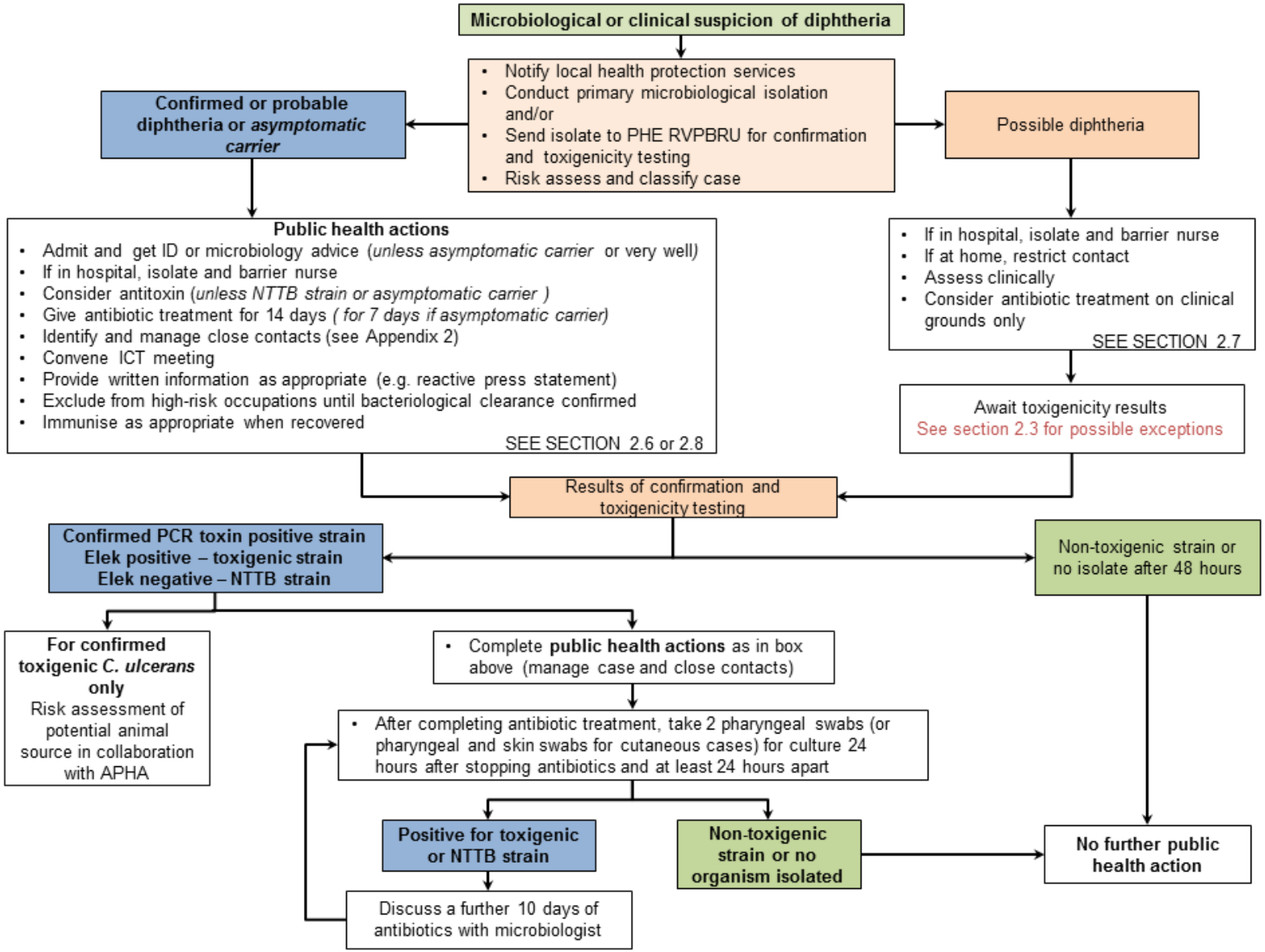
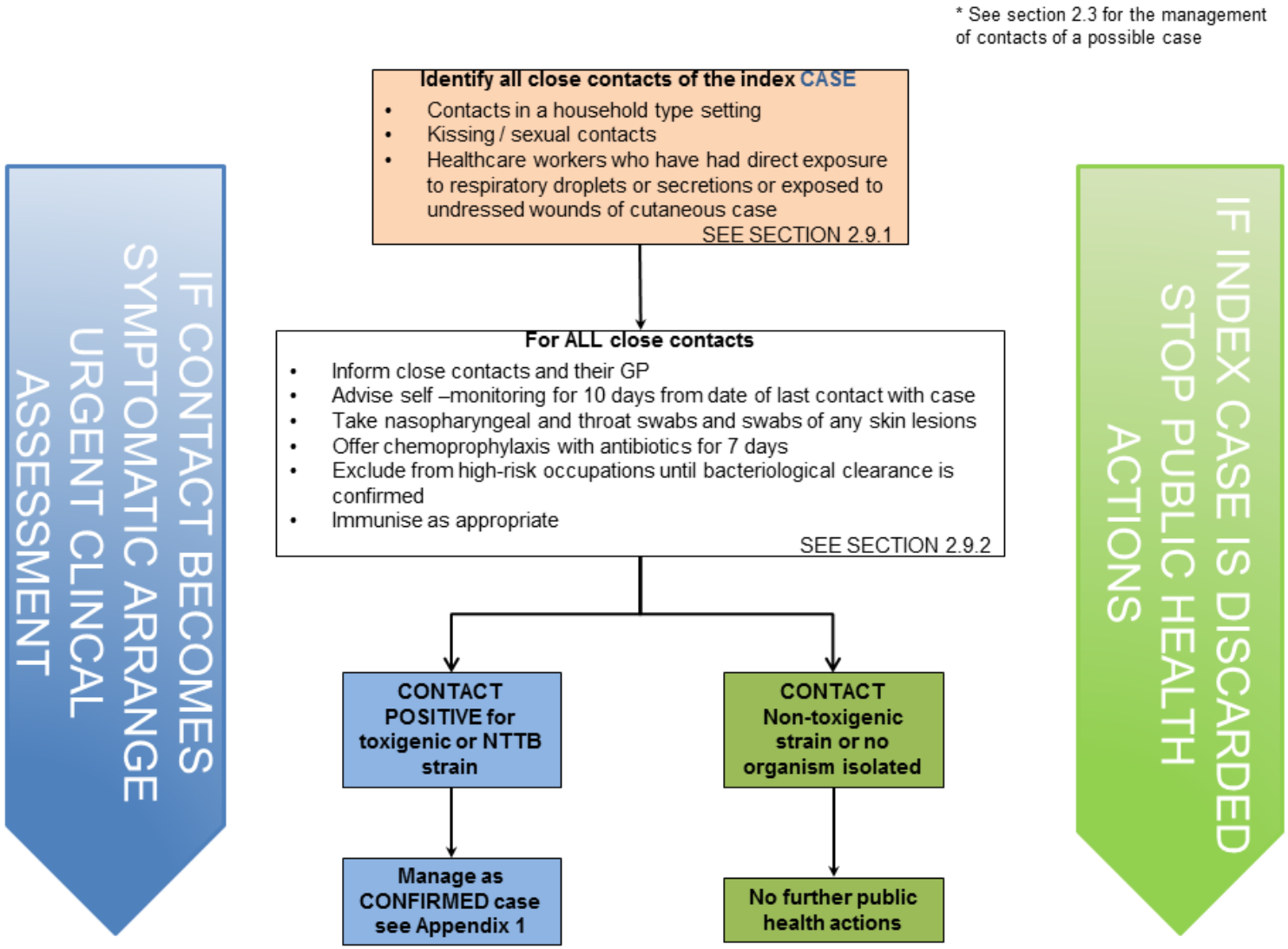
Appendix 1: Algorithm for management of a suspected diphtheria case



Appendix 2: Algorithm for the management of close contacts of confirmed and probable diphtheria case*, NTTB case, or asymptomatic carriers



Appendix 3: Diphtheria fact sheet: for cases and close contacts

What is diphtheria?

Diphtheria is a contagious and potentially life-threatening infection caused by a toxin (poison) made by bacteria. *Corynebacterium diphtheriae* and *Corynebacterium ulcerans* are the two most common bacteria that can cause diphtheria but it can also be caused by *Corynebacterium pseudotuberculosis*, although this is very rare.

What are the symptoms?

Symptoms usually begin two to five days after exposure to the diphtheria bacteria. Symptoms will depend on the site of infection but the most severe form of diphtheria affects the throat and tonsils. This is known as **respiratory diphtheria**.

The first symptoms are usually a sore throat, loss of appetite and a mild fever. Within 2-3 days, a membrane forms over the throat and tonsils that can make it hard to swallow and breathe. The infection can also cause the lymph glands and tissues on both sides of the neck to swell (sometimes referred to as a "bull neck").

The bacteria responsible for diphtheria can cause small skin sores that form larger ulcers, usually appearing on exposed limbs, particularly the legs. This form of the disease is known as **cutaneous diphtheria**. The sores can be difficult to distinguish from impetigo.

Illness can also occur with non-toxin-producing strains of the diphtheria bacteria; in these cases the disease is generally milder though in some cases it may also be severe.

How is it spread?

Diphtheria bacteria can live in the mouth, nose, throat or skin of people with the infection. It is commonly spread when a person comes into contact with airborne droplets after an infected person has sneezed or coughed. Less frequently, the infection can be passed on through close contact with skin lesions in a person with the cutaneous form of the illness. Prolonged close contact is normally required for the infection to be transmitted to others.

Corynebacterium ulcerans infection has been associated with consumption of unpasteurised milk or through prolonged close contact with animals (eg through working on a farm or as a veterinarian).

How is it prevented?

Diphtheria vaccination protects against the disease and is very effective. It gives protection against disease by production of antibodies to the diphtheria toxin. The vaccine is produced from purified inactivated toxin from a strain of *C. diphtheriae* and prompts the body to produce antibodies against the diphtheria toxin so that if the person comes into contact with diphtheria later in life, the body's immune system will be able to protect itself.

Diphtheria vaccination is given as part of the UK's primary immunisation programme. All infants should receive the primary immunisation course of 3 doses of a diphtheria-containing vaccine in the first year, usually given at 2, 3 and 4 months of age. Children should receive a first booster dose between 3.5 and 5 years of age and a second booster between 13 and 18 years of age.

Because of this highly effective vaccination program it is uncommon to see diphtheria in the UK nowadays and the majority of cases acquired within the UK now are mild infections in partially immunised individuals or in adults that have been fully immunised but have low levels of immunity.

How is it diagnosed?

Diagnosis is made based on a clinical examination and the testing of swabs, usually taken from the throat but also sometimes from sores in the case of cutaneous diphtheria. Special laboratory tests are needed to detect the toxin and confirm the diagnosis.

What happens if I or a family member gets diphtheria?

A doctor will prescribe antibiotics to treat diphtheria and in some cases they will also administer anti-toxin.

Close contacts, considered to be people who share a house or are in close contact with the infected individual, will be offered screening for diphtheria infection. Close contacts will be

treated with antibiotics as well. A person is no longer infectious after they have received a full course of antibiotic treatment.

If you have diphtheria or come into close contact with someone with diphtheria and you have not been vaccinated against the disease, you will be offered a full course of the vaccination. If you have been vaccinated previously but this was more than 12 months ago, you will be offered a booster dose to boost your immunity against the infection.

Diphtheria is a notifiable disease in the UK, which means that when a doctor suspects that someone has diphtheria they must inform the public health authorities. If you or a close contact has been diagnosed with diphtheria, your local Public Health England Centre will contact you to give advice on actions to protect you and others around you.

Where can I get more information?

Online sources of information that you may find helpful:

https://www.gov.uk/government/collections/diphtheria-guidance-data-and-analysis
http://www.nhs.uk/conditions/Diphtheria/Pages/Introduction.aspx

If you are concerned that you or someone close to you has diphtheria, please seek urgent medical attention.