Public health control and management of diphtheria in England

2022 guidelines
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Executive summary

These guidelines were first developed in 1999 following the re-emergence of diphtheria in the former Soviet Union and Eastern Europe (1). A revision of the guidance published in 2015 was prompted by changes in local epidemiology, including an increasing number of toxigenic 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. This latest revision follows an audit of the clinical, laboratory and public health management of toxigenic C. diphtheriae, toxigenic C. ulcerans and NTTB infections in England between 2014 and 2017 following the introduction of the revised guidelines. In addition, the updated guidelines have been informed by the results from antimicrobial susceptibility testing of recent isolates and whole genome sequencing of NTTB strains to assess risk of reversion to toxigenic strains.

These guidelines present the rationale and recommendations for the control of diphtheria in England. On 1 October 2021 Public Health England (PHE) became part of the UK Health Security Agency (UKHSA) and these guidelines reflect the structures established in UKHSA. It is anticipated that these guidelines will complement the existing guidance from the World Health Organization (WHO) (1, 2).

The updated guidelines are intended for those involved in the public health control of diphtheria, including:

- Health Protection Teams in UKHSA
- National Health Service (NHS) staff at local and national levels in England

These guidelines are split into 2 sections:

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

Key changes to guidance 2015

These revised guidelines provide updated advice on the management of suspected cases including recommended antibiotic therapy, public health management of NTTB cases, as well as more detailed guidance on public health action for suspected zoonotic transmissions.

Key changes include:

- emphasis on prompt administration of diphtheria anti-toxin (DAT) for confirmed and probable cases if appropriate
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 (3, 4). Nasal diphtheria, usually mild and chronic, is marked by unilateral 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 (5). The classic description of diphtheritic lesions is that they are usually covered with an eschar, a hard bluish-grey membrane that is slightly raised. Individuals may have both respiratory and cutaneous symptoms.

Diphtheria is no longer easily diagnosed on clinical grounds as classic respiratory diphtheria is now rare in the UK due to the success of the routine immunisation programme. However, when healthcare systems are disrupted and vaccine coverage declines, diphtheria is one of the first of the vaccine preventable diseases to emerge as was the case in the former Soviet Union in the 1990s and, more recently, in camps of displaced Myanmar nationals in Bangladesh (6, 7).

Mild respiratory 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 2 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. Infections may still occur in fully vaccinated individuals as the diphtheria toxoid vaccine prevents the clinical manifestations of toxigenic strains but does not prevent acquisition of carriage (8). As the disease is increasingly rare, most clinicians will not have encountered a case before and therefore may miss the clinical diagnosis (3-5, 8, 9). 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 coincidental commensals. Not all laboratories routinely culture pharyngeal swabs for corynebacteria and wound swabs in particular may contain additional
potentially causative organisms, further increasing the potential for missed or delayed diagnosis (8, 10).

1.2 Microbiology

Respiratory or cutaneous diphtheria is caused by toxigenic strains (those expressing diphtheria toxin) 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 (11). *C. ulcerans* and *C. pseudotuberculosis* are zoonotic pathogens. There are many (>115) other species of corynebacteria including *C. pseudodiptheriticum* which are not able to carry the toxin gene and are thus unable to cause diphtheria. Four biovars of *C. diphtheriae* can be distinguished by colonial morphology and biochemical characteristics: gravis, intermedius, mitis, and belfanti (12). Recently, the biovar belfanti was reported to be clearly separated phylogenetically from *C. diphtheriae* biovar mitis and gravis and a new species, *Corynebacterium belfanti* sp. nov. has been proposed (13). The predominant toxigenic *C. diphtheriae* biovar in the UK has remained the same (77% of toxigenic strains are from cases with biovar mitis) followed by biovar gravis (23%) from 2015 to 2020 compared to 81% biovar mitis and 17% biovar gravis from 1986 to 2008 (14) (Fry and others, unpublished data). The clinical and public health management of patients and contacts is identical for all toxigenic strains; however, potentially zoonotic infections also require the involvement of colleagues in the Animal and Plant Agency (APHA). The microbiology of *C. ulcerans* is discussed in 1.5.

Toxigenic strains are lysogenic for a family of corynebacteriophages that carry the structural gene for diphtheria toxin, *tox*. The toxin is a 535 amino-acid 58 kDa exotoxin whose active form consists of 2 polypeptide chains linked by a disulphide bond (11, 15). Following infection, secretion of this exotoxin can cause local tissue necrosis and, when absorbed into the bloodstream, systemic manifestations including demyelinating peripheral neuritis and myocarditis can occur as late complications. Non-toxigenic strains of *C. diphtheriae* can cause severe infections, including myocarditis, endocarditis, bacteraemia, septic arthritis, osteomyelitis, neuritis and epiglottitis (15-26). Similarly, non-toxigenic strains of *C. ulcerans* have been isolated from ulcerative lesions. However, the mechanisms of the pathogenicity of non-toxigenic strains are not well understood. This is further discussed in section 1.6.

1.2.1 Laboratory confirmation

Laboratory confirmation is typically by a combination of culture, bacterial isolation and preliminary identification of *C. diphtheriae*, *C. ulcerans* or *C. pseudotuberculosis* in a clinical laboratory followed by confirmation and toxigenicity testing at a reference laboratory.

Dacron, Viscose or flocked applicator swabs should be used to collect samples from each suspected case and placed in a routine semi-solid transport medium, such as Amies, immediately after collection and sent to the local diagnostic laboratory for bacterial culture.
The swab containers should be labelled accordingly with unique identifiers, source of the specimen and collection date, clinical details should accompany the specimen.

The common isolation methods in use in most laboratories are microbiological culture on standard blood agar (or tellurite-containing media, such as Hoyle’s agar). These tellurite containing media are both partially selective and differential for the isolation of toxigenic corynebacteria. The potassium tellurite inhibits a variety of both Gram negative and Gram positive bacteria and allows for the detection of tellurite reduction, resulting in colonies with a grey/black appearance, which is typically, but not exclusively found in corynebacteria. Putative corynebacterial colonies which prove to be catalase positive, Gram-positive coryneform rods may be further identified by conventional biochemical testing using commercial systems, such as API Coryne (bioMérieux), VITEK microbial identification system (bioMerieux) or Matrix Assisted Laser Desorption/Ionization – Time of Flight Mass Spectrometry (MALDI-TOF MS) (for example, Bruker, BioMérieux, Shimazdu) (27).

Primary diagnostic laboratories should be able to putatively identify the potentially toxigenic corynebacteria C. diphtheriae and C. ulcerans to species level. If laboratories do not have access to MALDI-TOF or API Coryne, we recommend that in addition to Hoyle’s agar they also stock Tinsdale agar. This would assist in the identification of the potentially toxigenic corynebacteria species which are cystinase positive so would appear as grey-black colonies, surrounded by a brown/black halo on the agar whilst other corynebacterial species would not.

If primary diagnostic laboratories that do not have access to primary and selective agars such as Hoyle’s agar, then primary swabs may be sent to UKHSA Regional microbiology laboratories. Any isolate with an identification of C. ulcerans/ C. diphtheriae/ C. pseudotuberculosis should be sent promptly to the National Reference Laboratory.

All of the above methods can have good specificity but the confirmation of identification, and the determination of toxigenicity requires submission of the isolate to the Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU), UK Health Security Agency, London. Since 01 April 2014, the front-line test for confirmation of identification and the presence of the tox gene is qPCR. This assay uses DNA extracts from submitted isolates to identify C. diphtheriae, C. ulcerans / C. pseudotuberculosis targets, plus the presence of the tox gene (28). The assay targets the RNA polymerase β-subunit-encoding gene (rpoB) and the A-subunit of the diphtheria toxin gene (tox). When the tox gene is detected, the isolate undergoes an Elek immunoprecipitation test to confirm expression of the diphtheria toxin (28).

Sending of Isolate for toxigenicity testing

Please ensure the isolate and not the sample itself is sent for toxigenicity testing, as this would cause substantial delays. Submission of additional samples (such as membrane) should be discussed with the reference laboratory. Please notify the laboratory RVPBRU (telephone 0208 327 7887, Bacteriology triage or 0208 327 7331 Vaccine Preventable Bacteria Section) 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
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**Vaccine Preventable Bacteria Section request form R3** and ensure full contact telephone numbers are provided on the form to allow timely reporting of results.

Send isolates to:
UK Health Security Agency – Colindale
Vaccine Preventable Bacteria Section
Bacteriology Reference Department
Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU)
61 Colindale Avenue
London NW9 5HT

Isolates may also be sent by Hays DX, in which case the following address should be used:
Vaccine Preventable Bacteria Section
UKHSA Colindale
Bacteriology
DX 6530002
Colindale NW

1.2.2 Laboratory safety

Although rare, laboratory-acquired infections have been reported (29, 30). In the UK toxigenic *C. diphtheriae*, *C. ulcerans* and *C. pseudotuberculosis* are classified by the UK Advisory Committee on Dangerous Pathogens (ACDP) as Hazard Group 2. Laboratories should have their own local safety and risk assessment documentation and staff be made aware of the risks involved in working with toxigenic corynebacteria prior to work. Staff must comply with personal protective equipment regulations for that laboratory, wear suitable protective clothing when handling these organisms and must be deemed competent to perform the relevant Standard Operating Procedures. Wherever practical and for all procedures which may potentially generate an aerosol, a microbiological safety cabinet (MSC) should be used. The use of sterile disposable loops is recommended for the spreading of sample material onto culture media.

All staff that routinely handle cultures of potentially toxigenic corynebacteria should be fully vaccinated (including booster vaccinations).
1.2.3 Immunisation of laboratory staff

Recommendations for immunisation to protect against diphtheria are as per Green Book Chapter 12: Immunisation of healthcare and laboratory staff.

Recommended diphtheria antitoxin antibody levels are:

- 0.01 IU /mL for those in routine diagnostic laboratories
- 0.1 IU/mL for those handling or regularly exposed to toxigenic strains

Note: these antibody levels and interpretive criteria are based on those described by the World Health Organization’s recommendations using a functional (toxin neutralisation) assay (27).

The Vaccine Preventable Bacteria Section also offers testing for the determination of diphtheria antibody levels using a toxin neutralisation assay. All requests should be submitted using the R3: vaccine preventable bacteria section request form.

1.3 Transmission and carriage of diphtheria-causing organisms

The incubation period for diphtheria is usually 2 to 5 days (31), but may be longer, with duration of up to 10 days reported (25, 32). The common mode of transmission of C. diphtheriae is via droplet spread from a person with respiratory diphtheria. Alternative modes of transmission are direct contact with cutaneous diphtheria lesions, infected secretions or via contact with infected animals (C. ulcerans), or consumption of unpasteurised dairy products (C. ulcerans).

Closeness and duration of contact are important in determining the likelihood of 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 (33). In the absence of clear evidence on transmission of diphtheria, principles used in the public health management of meningococcal disease can be applied (34). 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 (24, 28, 31, 35).

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 (15). Carriage can be eradicated by antibiotic treatment: macrolides (erythromycin, clarithromycin and azithromycin) and penicillin are all likely to be effective but antimicrobial susceptibility testing is required (see section 2.6.4).
In Western Europe, carriage and disease has become very uncommon since the introduction of routine immunisation and isolation of the organism from healthy individuals is extremely rare. Although vaccination does not eliminate carriage it reduces transmission by up to 60% in an outbreak setting (36). A carriage study conducted during a 7 month period in 2007 to 2008 in 10 European countries identified only 6 toxigenic strains of *C. diphtheriae*: 2 were from symptomatic patients in Latvia (the country with the highest reported incidence of diphtheria in the European Union) and 4 (2 cases, 2 carriers) were from Lithuania where the last reported case was in 2002 (10).

There is some evidence that cutaneous diphtheria may be more transmissible than respiratory diphtheria (37). In tropical countries, cutaneous diphtheria lesions may act as reservoirs of infection. Both cases and contacts of cutaneous diphtheria may develop respiratory diphtheria (11, 37). In the UK and Europe, most cutaneous cases are caused by imported toxigenic *C. diphtheriae* infections (14, 38-42), although some cutaneous *C. ulcerans* infections have been reported (8, 14, 43, 44). Occasionally patients have developed respiratory diphtheria following cutaneous infection (45). More detailed information on transmission of *C. ulcerans* is in section 1.5.

### 1.4 Epidemiology and control of diphtheria in England

Diphtheria is a notifiable disease under the Infectious Disease (Notification) Act of 1889 and the updated 2010 regulations. Doctors in England 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 (10).

Also under these regulations, laboratories have a duty to notify human isolates of *C. diphtheriae* and *C. ulcerans* (46). The UKHSA also requests notification of human isolates of *C. pseudotuberculosis* (47). Laboratories should notify the HPT in UKHSA, and all potentially toxigenic isolates from these 3 species should be referred promptly to the National Reference Laboratory for toxigenicity testing (see section 2.3.2).

Diphtheria was once one of the most feared childhood diseases in the UK, with more than 61,000 cases and 3,283 deaths in 1940 (48), this has dramatically reduced following introduction of mass immunisation in 1942 and by 1957 there were only 38 cases and 6 deaths (48, 49).
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Diphtheria cases* and deaths, England and Wales†, 1914 to 2021

![Graph showing diphtheria cases and deaths from 1914 to 2021 with routine vaccination mark]

Diphtheria cases* and deaths, England and Wales†, 1914 to 2021

![Graph showing diphtheria cases and deaths from 1914 to 2021]

* notifications up to 1985, laboratory confirmed cases 1986 to 2021  
† from 2016, data from England only
Diphtheria vaccine is made from inactivated diphtheria toxin (toxoid) and protects individuals from the effects of toxin-producing corynebacteria. In the UK, diphtheria toxoid is included in the immunisation schedule at 8, 12 and 16 weeks of age followed by 2 boosters (at approximately 3 and 14 years of age), with further boosters recommended for travel and as part of the maternal pertussis immunisation programme due to inclusion in the pertussis booster vaccine (48, 50). In addition, CRM197 containing vaccines (a non-toxigenic mutant of diphtheria toxin used as a carrier protein), such as pneumococcal conjugate vaccine provide additional boosting (51).

Data on the duration of the protective effectiveness conferred by a complete diphtheria vaccine course are limited (52), however, serological studies have demonstrated that vaccine-derived immunity wanes over time for both fully immunised and partially immunised individuals. The proportion of individuals with fully-protective antibody levels declines by approximately 0.6% per year since vaccination (36). Full vaccination with 3 or more doses has been shown to be 87% effective against symptomatic disease (up to 99% with 5 doses) and 81% effective in preventing severe disease. Diphtheria toxoid vaccines do not prevent colonisation (estimated 17% effective) but 3 doses have been estimated to reduce transmission by 60% (36).

Diphtheria vaccine coverage in the UK remains high; coverage of the primary course evaluated at one and 2 years of age has been between 91% and 95% since the early 1990s. Assessment of preschool booster coverage started in 1999 to 2000; coverage remained between 78% and 82% during the following decade, before increasing to 86% in 2009 to 2010 and remaining between 86% and 89% since.

Coverage assessment of the tetanus, diphtheria and polio adolescent booster began in 2016, and is approximately 85% in children aged 14 to 15 years old in the UK (53). However, the coronavirus (COVID-19) pandemic has had an impact on vaccination coverage. Coverage for the completed 3 dose course of DTaP/IPV/Hib/HepB for children aged 12 months old during quarter one of 2021 to 2022 was 1.3 percentage points lower than for children aged 12 months old during quarter one in 2020 to 2021 (54). The closure of educational settings due to the COVID-19 pandemic impacted the delivery of school immunisation programmes and coverage of Td/IPV adolescent booster in 13 to 14 year olds dropped to 57.6% compared to 87.6% in the previous year’s cohort (53).

There have been significant changes in diphtheria epidemiology over time in the UK, including the identification of the zoonotic risk of C. ulcerans (see section 1.5) and changes in disease presentation, such as the increase of mild respiratory disease in partially vaccinated individuals and a relative increase in the reports of cutaneous cases (8, 14). From the start of laboratory surveillance in 1986 until the end of 2021, there have been 119 toxigenic cases of diphtheria in England and Wales with the number of cases per year varying from one to 11.

Until the early 1990s, toxigenic infections were more commonly caused by C. diphtheriae than C. ulcerans, whereas between the 1990s and 2008, C. ulcerans was the predominant cause of UK toxigenic infection, responsible for more than two-thirds of cases. Epidemiological data for the period 2009 to 2017 has shown a relative increase in C. diphtheriae cases, particularly of a cutaneous presentation (8). From 2018 onwards, the majority of cases (21 of 32) have been C. ulcerans. Both species may be isolated from both respiratory and cutaneous presentations.
From the start of laboratory surveillance in 1986 until 2013, the clinical presentation in over 85% of toxigenic infections was non-classical respiratory diphtheria for both *C. diphtheriae* (59 of 68 isolates; 87%) and *C. ulcerans* (59 of 66 isolates; 89%) (see section 2.2 for case definitions). However, both *C. ulcerans* and *C. diphtheriae* resulted in severe or fatal disease with 6 deaths between 1986 and 2013, 4 of which were caused by *C. ulcerans* (39).

Since 2014, 52% of toxigenic diphtheria infections have been cutaneous. Cases with toxigenic *C. diphtheriae* have been more likely to be cutaneous in presentation, (14 of 22 isolates, 64%), with 2 cases with mild respiratory presentation, 4 asymptomatic cases, one case with other presentation and one case with classical respiratory diphtheria. There was a further clinical case of classical respiratory diphtheria in 2018; no diphtheria organism was isolated; however, the case responded well to treatment with diphtheria anti-toxin (DAT). Cases with toxigenic *C. ulcerans* have similarly been more likely to be cutaneous in presentation (12 of 28 isolates, 43%), with 8 cases being of mild respiratory presentation, 3 cases with classical respiratory diphtheria, 2 asymptomatic cases and 3 cases with other presentation. Three cases died during this period, all with *C. ulcerans* infection and all of whom were inadequately immunised.

Eighteen NTTB *C. diphtheriae* (see section 1.6.1) have also been detected since the introduction of PCR testing until the end of 2021. An increase in the detection of cutaneous cases has coincided with an increase in the submission for testing of isolates from wound swabs (see section 1.7), suggesting changes in testing and identification methods at frontline laboratories such as the use of MALDI-TOF MS may be at least partially responsible.

Risk factors for acquisition of the 2 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 (55). The main risk factor for all diphtheria cases is being unvaccinated; between 2009 and 2017, 67% of cases were inadequately vaccinated (8); and 69% from 2018 onwards. However, 43% of cases during this time period were fully vaccinated, mostly younger individuals presenting with mild cutaneous or mild respiratory forms of both *C. diphtheriae* and *C. ulcerans*. *C. ulcerans* was more commonly seen in older individuals with unknown or partial vaccination history. Suboptimal diphtheria vaccination status for both toxigenic *C. diphtheriae* and *C. ulcerans* infections was strongly associated with the risk of hospitalisation and death.

Toxigenic *C. diphtheriae* infections in England were also associated with travel to an endemic country including Asia, Africa, Oceania and South America, and for cases between 2009 and 2017, 78% of cases were characterised as imported (8); since 2018, this has decreased to 18% but this is likely due to a decrease in international travel due to the COVID-19 pandemic. Toxigenic *C. ulcerans* infections were previously associated with consumption of raw dairy products, but have become more recently associated with contact with companion animals. In a review of 62 cases of *C. ulcerans* between 1986 and 2008, 7 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) (14).
Since 2009, all 34 *C. ulcerans* cases reported contact with domestic animals; contact with non-domesticated animals was also noted for 7 cases and 4 reported a history of consuming unpasteurised dairy products. The evidence on companion animal transmission to humans is limited because of the relatively small number of cases, high exposure prevalence to companion animals in the general population, and lack of (or timing of) swabbing of animal contacts (39). However, evidence is slowly accumulating. In England, since 2009, swabs were taken from 42 companion animals in 23 cases, most commonly from dogs and cats; in 7 cases, at least one companion animal screened positive for toxigenic *C. ulcerans* (4 dogs and one cat; 3 cases had contact with the same positive dog). *Corynebacterium ulcerans* was not detected in any of the other companion animals that underwent swabbing although a zoonotic source of infection was considered most likely in these incidents.

The first documented transmission of toxigenic *C. diphtheriae* in the UK for over 30 years occurred in the East of England in 2017, when a contact of a case with cutaneous *C. diphtheriae* infection who had recently returned from Africa, but had not herself travelled, developed a mild respiratory diphtheria infection (56). There was also a cluster of cases in South Yorkshire in 2017 and 2018 which belonged to the same Sequence Type by multi-locus sequence typing (MLST) with further cases confirmed from late 2021 in the same geographical region. As no direct epidemiological link between the early cases was identified despite extensive investigation, screening of close and subsequently wider contacts was undertaken which identified further asymptomatic carriers. Further cases of identical biovar and MLST were identified in late 2021 and investigations on a potential epidemiological link are still ongoing. None of the cases involved in this cluster had a history of travel. This incident represents the largest cluster of toxigenic diphtheria in the UK in recent years, and only the second suspected event of onward transmission in 3 decades. Other positive contacts have been identified for cases of *C. diphtheriae* with a shared history of travel and for household contacts of *C. ulcerans* with a shared infected domestic animal, but it is not possible to state in these cases whether human-human transmission had occurred.

Since June 2022, there has been an increase in cases of diphtheria caused by toxigenic *C. diphtheriae* reported among asylum seekers arriving in England and mirroring a wider situation across a number of European countries (57, 58). Supplementary guidance on the management of these cases is available on the UKHSA website.

The most effective treatment of severe cases of diphtheria involves the prompt administration of diphtheria anti-toxin (DAT) which binds to and neutralises circulating toxin which has not yet bound to the tissue (47). Clearance of the organism is also achieved with appropriate antibiotics (see section 2.6.3). DAT was first produced in the late 19th century and is still produced using serum from horses hyperimmunized with diphtheria toxoid. Currently there is one equine DAT product available in the UK for treatment of probable or confirmed diphtheria cases (59).

Public health management of clinical cases of diphtheria in the UK is provided by Health Protection Teams, including identification, assessment and prophylaxis of close contacts (see section 2). Guidance on the use of DAT can be found on the UKHSA website.
1.5 Corynebacterium ulcerans

The first report of the isolation of *Corynebacterium ulcerans* was in January 1920 when the organism was cultured from a patient who had clinically recovered from diphtheria previously that year (60). It has been associated with a range of clinical symptoms including, relatively mild respiratory (for example, sore throat) and/or cutaneous to classical respiratory diphtheria with pseudomembrane (43, 61-69). Several deaths in the UK have been attributed to this infection (8, 14).

*Corynebacterium ulcerans* may infect the bovine udder and previously an association between human *C. ulcerans* infection and drinking raw milk and unpasteurised milk products was observed (65, 66). The organism has a wide host range and has been isolated from domestic, wild and captive animals (70). More recently an increase in toxigenic *C. ulcerans* infections associated with close contact to domestic (71) and companion animals has been reported (8, 38, 72-76). To date, person-to-person spread has not been definitively documented and the majority of swabs taken from close contacts have been culture-negative for *C. ulcerans* (62, 65, 68, 77). However, a number of incidents have raised this as a possibility. In 1996 and 1998 toxigenic *C. ulcerans* was isolated from asymptomatic contacts of cases (14). In more recent cases in Germany and Belgium, in 2014 and 2016 respectively, asymptomatic contacts also tested positive for toxigenic *C. ulcerans* which belonged to the same DNA sequence type (by MLST) as the index cases (78, 79). In Germany, the contact was a grandmother living on the same farm as the symptomatic index case, who had limited contact with the animals on the farm, including the suspected animal source. The contact of the Belgian case was a nurse caring for the patient, suggesting that a shared animal source was unlikely, further supporting the possibility of person-to-person transmission of *C. ulcerans*.

In 1997, following 2 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 was inadequate information about human-to-human transmission of this organism (80, 81). In the UK, because possible person-to-person transmission of toxigenic *C. ulcerans* has been observed (14), chemoprophylaxis of contacts of a case, from whom isolation of a toxigenic strain has been confirmed, is recommended.

1.6 Non-toxigenic C. diphtheriae and C. ulcerans

There are more than 115 species of Corynebacterium described to date, isolated from a wide range of human, veterinary and environmental sources (82). Approximately 50% have been isolated from human clinical specimens, many of which are considered part of the normal flora, but may also opportunistically cause disease (83). It is well established that the ability of *C. diphtheriae*, *C. ulcerans* and *C. pseudotuberculosis* to produce diphtheria toxin is mediated by
infection of these species by bacteriophages carrying the tox gene. However, the mechanism of pathogenicity of non-toxigenic strains of C. diphtheriae and C. ulcerans in humans is not well understood although a number of additional (potential) virulence factors have been described, including pili in both species and phospholipase D in C. ulcerans (64, 84, 85).

Examples illustrating the diverse clinical presentations of non-toxigenic corynebacteria include 2 historical cases who accidentally ingested non-toxigenic C. diphtheriae biovar mitis in a laboratory, developing clinical diphtheria with a sore throat and tonsillar membrane (80). In Australia, 7 aggressive cases of endocarditis due to non-toxigenic C. diphtheriae biovar gravis were reported in a single year in 1993, including 4 major vascular complications and one death (23). Other cases of endocarditis caused by non-toxigenic strains have been reported in India (16), the United States (17), Poland (26), Germany (25), New Zealand (18) and England (19). Non-toxigenic strains have also been associated with disease in immunocompromised individuals (20), and with recurrent pharyngitis in young adults (21). For example, cutaneous lesions have been reported in a Canadian homeless population (22), 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 (86).

A 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 to 7.1) in Turkey, though the zero estimates may have been due to small sample sizes (10).

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. There is no public health action required for individuals either with a non-toxigenic strain or NTTB C. diphtheriae or C. ulcerans (see section 1.6.1).

Routine laboratory surveillance began in England and Wales in 1986 and allows monitoring of non-toxigenic C. diphtheriae and C. ulcerans in addition to diphtheria cases. Data from 1986 onwards is available on the UKHSA website (39). These surveillance data show that between 1986 and 2013, 2,662 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 to 60 isolates per year. 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 (21). Between 2014 and 2021, 448 human C. diphtheriae isolates have been received, of which 22 (4.9%) were toxigenic. Between 2014 and 2021, 48 human C. ulcerans isolates have been received, of which 31 (64.6%) were toxigenic. Most isolates are from throat swabs, but an increasing proportion of isolates from wound swabs have been received in the last few years.

Analysis of the total index case isolates submitted for species identification and toxigenicity since 2009 highlighted a significant difference in toxigenicity rates between C. diphtheriae and C. ulcerans, with approximately 5% of samples being toxin-producing for C. diphtheriae and 50% to 60% toxin-producing for C. ulcerans. Since submissions to the RVPBRU are based on
isolates from symptomatic cases, they are not useful for estimation of overall non-toxigenic corynebacteria carriage rate in the UK, but a minimum incidence rate of carriage in symptomatic cases of 0.73 cases per 100,000 population per year was estimated, which is in line with estimates from other European countries (10).

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

Non-toxigenic strains C. diphtheriae, C. ulcerans (and C. pseudotuberculosis) usually lack the entire tox gene. Exceptionally some non-toxigenic strains can also carry variants of the tox operon such that the diphtheria toxin cannot be expressed phenotypically. These strains are designated non-toxigenic toxin gene-bearing (NTTB) and to date NTTB clinical isolates of both C. diphtheriae and more rarely in C. ulcerans have been reported. The qPCR employed by the RVPBRU is able to detect some of these non-functional tox gene variants, so an NTTB will usually appear qPCR tox positive, Elek-negative. These NTTB strains were originally described during the diphtheria epidemics in countries of the former Soviet Union within the WHO European region in the 1990s (83). 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 biovar and ribotype.

Four NTTB strains of C. diphtheriae were isolated from humans in the UK between March 2011 and June 2012. From August 2014 to March 2021, 7 NTTB C. diphtheriae strains were isolated from 5 epidemiologically linked cases in the UK (Fry and others, unpublished data). Since 2014, 5 other NTTB C. diphtheriae strains were isolated in the UK with geographical, but no known epidemiological links. The World Health Organization Collaborating Centre for Diphtheria and Streptococcal Infections, Colindale, London has also confirmed 2 non-UK NTTB isolates: a C. diphtheriae from a cat from Belgium in 2021 (55), and a C. ulcerans from a human case from Sweden in 2015.

Retrospective analyses of culture collections have revealed NTTB C. diphtheriae in Canada (from 1999 to 2003) (87) and Romania (from 1963 to 2007) (88). Similar NTTB strains of C. ulcerans have also been isolated from game animals in Germany indicating potential reservoirs for human infection (89, 90). 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, and also retrospective testing. (section 1.2).

In an investigation of a cluster and subsequent transmission of NTTB (with a deletion in tox) over a 7 year period, no evidence of reversion to diphtheria toxin expression or isolation of toxigenic strain was observed. The likelihood of NTTB gaining the ability to become toxigenic is considered highly unlikely and therefore updated advice included in these guidelines is to manage such cases as non-toxigenic.
1.7 History of guidelines

These guidelines were first developed in 1999 following the re-emergence of diphtheria in the former Soviet Union and Eastern Europe (91). A revision of the guidance, published in 2015, was prompted by changes in disease epidemiology, including the increasing number of C. ulcerans cases, the introduction of routine qPCR testing of potentially toxigenic corynebacteria isolates by the national reference laboratory in April 2014, and the identification of circulating NTTB C. diphtheriae strains in England.

The 2015 guidelines were assessed during an audit of the clinical, laboratory and public health management of qPCR diphtheria toxin gene positive C. diphtheriae and C ulcerans cases and NTTB C. diphtheriae infection in England between 2014 and 2017 (92). The audit concluded that there was good recording of clinical presentation and case definitions, and in most cases, appropriate public health actions were initiated according to the case definition. Travel, animal contact and immunisation history risk factors were well-documented, but other factors such as occupation, contact with other travellers less so. There was limited documentation of clearance swabs having been taken or clinical details, such as whether patients had been hospitalised, type of antibiotic received and whether they had been assessed for anti-toxin, although this may reflect record keeping rather than an absence of this having taken place. Only one third of cases were formally notified via the Notifications of infectious diseases (NOIDs) system. All Health Protection Teams (HPTs) collected information on close contacts, but healthcare workers (HCWs) were not always included at early stages. It was concluded that timeframes for public health actions should be more clearly specified in the UKHSA guidance, including a need for Incident Management Teams (IMTs) to be convened, preferably within 24 hours. There should be improved efforts to consider and identify HCW contacts (both at primary and secondary care) and improved documentation of infection control and emphasis on the importance and role of anti-toxin and antimicrobial therapy.

1.8 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. 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 very limited supplies of antitoxins.

These guidelines therefore aim to:

- maintain awareness amongst clinicians and prompt consideration of diphtheria as a part of the differential diagnoses
- assist health protection leads in undertaking the risk assessment
- 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

The NHS clinician will notify UKHSA of a suspected case. This notification may come to the local HPT or the national centre at Colindale. The UKHSA duty doctor at Colindale will provide Public Health management support to the NHS and local HPT and coordinate the issuing of DAT, if required. For advice regarding clinical management or other queries relating to the treatment (including antibiotics) of suspected cases during office hours, please contact the on call duty Consultant Microbiologist, UKHSA Colindale on 0208 327 7887. Out of hours please contact the UKHSA duty doctor on call on 0208 200 4400 for all queries and advice.

2.1 Risk assessment of cases

The public health 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 UKHSA Immunisation and Vaccine Preventable Diseases Colindale team or duty doctor out of hours. Information that should be collected on each case to inform the risk assessment includes the following.

Demographics:

- name, date of birth, sex, ethnicity, birthplace, NHS number
- current address including postcode, phone number
- GP name and contact details (address and phone number)

Clinical details:

- symptoms and signs – date of 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 (such as otic, genital, laryngeal), skin lesions
- results of laboratory investigations (local and/or reference laboratory) – anatomical site of samples, antimicrobial sensitivity results, toxigenicity results if available or when these can be expected and any other organisms detected
- differential diagnoses considered
  - the most common respiratory presentation for non-toxigenic C. diphtheriae is presentation of a patient with sore throat to a GP with the presence of another
causative pathogen: for example, Lancefield Group A Streptococcus (or other Lancefield type C, G and so on)

- common cutaneous presentations are wounds/ ulcers/ abscesses / infected insect/animal bites from which toxigenic or non-toxigenic C. diphtheriae or C. ulcerans may be isolated. Other causative pathogens may also be present: for example, Staphylococcus spp., Streptococcus spp.
- drugs – some drugs may rarely cause a membrane (for example, 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, for example work in a clinical microbiology laboratory, or similar occupation, where potentially toxigenic Corynebacterium spp. may be handled
- membership of community with sub-optimal immunisation coverage and/or frequent travel links to high-risk areas
- within the 10 days prior to onset of symptoms 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/or Eastern Europe)?
  - had contact with someone who has been to a high-risk area?
  - had contact with any animals (including household pets or visiting a farm or petting zoo)?
  - recently consumed 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 (5,86).

Confirmed case of toxigenic infection:

- classic respiratory diphtheria¹ AND
- either laboratory confirmation of a toxigenic strain² OR
- epidemiological link to a laboratory-confirmed case with a toxigenic strain²
  OR
- laboratory confirmation of a toxigenic strain² with other presentations of diphtheria including mild respiratory or cutaneous³
Probable case of toxigenic infection:

- classic respiratory diphtheria¹ 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 (for example laryngeal disease)  
  OR
- other presentations of diphtheria³ with a confirmed epidemiological link to a laboratory confirmed case²

Possible case of toxigenic infection:

- other presentations of diphtheria³ (see 2.1) 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 strain² from any anatomical site

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

- other presentations of diphtheria³ (see 2.1) AND
- isolation of 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
Public health control and management of diphtheria in England

Not confirmed or non-toxigenic case (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

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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 toxin gene PCR detection and 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 nose or throat swab or skin lesion swab has been obtained. Very rarely, endocardial, laryngeal, conjunctival, otic and genital involvement may be seen.
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 UKHSA RVPBRU. It is sometimes appropriate to initiate public health actions before the confirmatory toxigenicity result is available from RVPBRU. The decision should be made in consultation with UKHSA Immunisation and Vaccine Preventable Diseases 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, for example 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 is not necessary and public health actions can be stopped
- 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 (nose, 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. Nose and throat swabs should also be taken in cases of cutaneous diphtheria to exclude respiratory carriage of toxigenic strains. Dacron, Viscose or flocked applicator swabs should be used to collect samples from each suspected case and placed in a routine semi-solid transport medium, such as Amies, immediately after collection and sent to the hospital microbiology laboratory for culture.

The swab containers should be labelled accordingly with unique identifiers, source of the specimen and collection date.

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 promptly to the Vaccine Preventable Bacteria Section (VPBS), UK Health Security Agency (UKHSA), Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU) for confirmation of identification and toxigenicity testing using the R3 laboratory request form.

Identification/confirmation and toxigenicity testing is performed initially by real-time PCR (qPCR) on a DNA extract of the submitted isolate. This qPCR assay targets the RNA polymerase β-subunit-encoding gene (rpoB) and the A subunit of the diphtheria toxin gene (tox) to detect and identify Corynebacterium diphtheriae and Corynebacterium ulcerans / Corynebacterium pseudotuberculosis and detection of the diphtheria toxin gene. All isolates which are qPCR positive for the tox gene will also be tested by the Elek immunoprecipitation test for toxin expression.

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

As already described, some isolates of C. diphtheriae are tox gene positive by PCR but do not express toxin and so they are negative on the Elek test (NTTB, see section 1.6.1). These are rare in the UK and to date no UK NTTB C. ulcerans have been reported (unpublished data) (47). Strains of NTTB do not cause diphtheria and so patients are not treated with antitoxin. If NTTB are 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

Please ensure the isolate and not the sample itself is sent for toxigenicity testing, as this would cause substantial delays. Submission of additional samples (for example, membrane) should be discussed with the reference laboratory. Please notify the laboratory RVPBRU (telephone 0208 327 7887, via the Bacteriology Reference Department triage or 0208 327 7331 Vaccine Preventable Bacteria Section) 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 Vaccine Preventable Bacteria Section request form (R3) and ensure full contact telephone numbers are provided on the form to allow timely reporting of results.

Send isolates to:
Vaccine Preventable Bacteria Section
Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU)
Bacteriology Reference Department
UK Health Security Agency – Colindale
61 Colindale Avenue
London, NW9 5HT

Isolates may be sent by Hays DX in which case the following address should be used:
Vaccine Preventable Bacteria Section
UKHSA Colindale
Bacteriology
DX 6530002
Colindale NW

However, depending on the urgency a same-day courier may be required.

Service:
Monday to Friday (in the normal working week): isolates received before midday are processed same day with the qPCR result available by the end of the working day.
Monday to Friday (in the normal working week): isolates received after midday this is contingent on time of arrival in the laboratory and if possible will be processed same day with
the qPCR result available by the end of the working day. If late arrival precludes this, then the results will be reported on the following day.

Out-of-hours: Saturday / Bank Holiday* This may also be used to test/complete an isolate arriving late on a Friday. If sending an urgent isolate on Saturday for the Saturday service or on a Bank Holiday please ensure it arrives by midday to allow processing/reporting time.

*this is usually a Monday but may on occasion be a Tuesday or Friday

Out-of-hours: Sunday The Colindale site is manned 24/7 so isolates may be sent to Colindale on Sunday to be tested first thing Monday morning. The packages will be placed in the out of hours fridge by our Security team.

For the out-of-hours service it is essential that you telephone prior to 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). Please 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.

HPTs should ensure the case is formally notified in the case management system to ensure they are counted by the NOIDs system. In addition to mandatory notifications, there should be good communication between the HPT, microbiology team, infectious disease physicians, other hospital doctors, general practitioners and the relevant team at UKHSA Colindale (Immunisation and Vaccine Preventable Diseases Division and/or Emerging Infections and Zoonoses Team, and RVPBRU). The local HPT should discuss out-of-hours cases with the duty doctor at UKHSA Colindale (0208 200 4400).

Enhanced surveillance of diphtheria for England is also carried out by the Immunisations and Vaccine Preventable Diseases Division, UKHSA. HPTs are requested to complete the national surveillance form available at [https://www.gov.uk/government/publications/diphtheria-surveillance-form-for-follow-up](https://www.gov.uk/government/publications/diphtheria-surveillance-form-for-follow-up) and to send this to the National Team (email: diphtheria_tetanus@ukhsa.gov.uk or phe.diphtheria.tetanus@nhs.net). HPTs may need to consult NHS clinical colleagues to complete the form.

Figure 1 details the various interactions of the local laboratory, local health protection service, the reference laboratory and Immunisation and Vaccine Preventable Diseases Division at UKHSA Colindale.
The attending clinician should send samples to the local laboratory and await the result from the laboratory. They should also notify their local HPT.

The local laboratory will receive the sample from the attending clinician and will share the results with them. The local laboratory should notify the local HPT via a laboratory notification and they will send the isolate to the UKHSA Colindale RVPBRU for confirmation toxigenicity testing.

The local HPT will receive a clinical notification from the attending clinician and/or receive a laboratory notification from the local laboratory. They will liaise with the UKHSA Colindale Immunisation and Vaccine Preventable Diseases division (in hours) and the duty doctor (out-of-hours). In addition, the local HPT will conduct enhanced surveillance in conjunction with the UKHSA Colindale team and the attending clinician.

The UKHSA Colindale RVPBRU will receive the isolate for toxigenicity testing from the local laboratory and will share the result from toxigenicity testing with the local laboratory. They will also liaise with the UKHSA Colindale Immunisation and Vaccine Preventable Diseases division (in hours) and the duty doctor (out-of-hours).

The UKHSA Immunisation and Vaccine Preventable Diseases Division will liaise with the patient’s GP and attending clinician (if DAT was administered) to complete the remaining enhanced surveillance forms for follow up of confirmed cases.
2.5 Incident Management Team

For most cases of confirmed or probable diphtheria, an Incident Management Team (IMT) / Outbreak Control Team (OCT) should be convened WITHIN 24 hours of the PCR toxigenicity result; however, an IMT may be convened earlier if it is deemed necessary, particularly where epidemiological or clinical suspicion is high. Membership of the team will vary depending on local circumstances, but would typically include:

- consultant in communicable disease control / consultant in health protection
- local consultant microbiologist (NHS)
- regional microbiologist/consultant in public health infection (UKHSA)
- local authority public health team
- consultant physician responsible for care of the patient
- consultant in infectious disease
- infection control nurse
- representation from UKHSA Colindale
- communications team
- APHA as appropriate (see section on zoonotic source investigations)

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

The UKHSA duty doctor is requested to discuss all suspected cases with the on-call Consultant Microbiologist if calls are received during working hours. For advice regarding clinical management of cases or other queries relating to suspected cases during offices hours, please contact the on call duty Consultant Microbiologist, UKHSA Colindale on 020 8327 7887. Out of hours please contact the UKHSA duty doctor on call 0208 200 4400 for all queries and advice.

2.6.1 Isolation

For those confirmed or probable cases admitted to 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 (93). Continue isolation until 2 cultures from the nose 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 (12).

If the case is well and not hospitalised, advise to restrict contact with others for the first 6 days of an appropriate course of antibiotics. During this time the case should not attend GP practice for further tests. Clearance swabs should be obtained 24- and 48-hours after completion of
antibiotics to ensure elimination of carriage. In the rare event that the case remains positive following completion of the recommended antibiotic course, further advice on additional treatment should be sought from the national team.

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

2.6.2 Referral

All probable or confirmed cases must be referred to the local specialist infectious disease (ID) unit/consultant for a face to face clinical review and assessment of whether anti-toxin treatment is required. The responsibility of the HPT is to check that this clinical review has taken place.

2.6.3 Antitoxin treatment

Diphtheria antitoxin should only be used in a hospital setting for CONFIRMED or PROBABLE cases of diphtheria. Diphtheria antitoxin should be given to classic respiratory cases without waiting for laboratory confirmation. Early treatment with DAT is critical to neutralise free-circulating toxin before it can irreversibly bind to tissues causing organ damage. The effectiveness therefore declines with time since onset of symptoms.

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 (for example more than 2cm²) and especially if it were membranous, then antitoxin would be justified (48).

Diphtheria antitoxin is based on horse serum and therefore severe, immediate anaphylaxis occurs more commonly than with human immunoglobulin products. However, from our experience in England of treating patients with DAT, anaphylaxis is very rare. 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 UKHSA Colindale duty doctor in and 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 and will issue DAT as indicated. Further details are provided in Guidance of the Use of Diphtheria Antitoxin available on the UKHSA website.

2.6.4 Antibiotic treatment

Antibiotic treatment to eliminate the organism and prevent spread is not a substitute for antitoxin treatment if indicated. All specimens should be collected BEFORE antibiotic treatment is started if possible. If antibiotics have already been started then samples should still be taken.

Guidance for antibiotic administration is shown in Table 1. For mild disease, such as small cutaneous lesions with no evidence of systemic toxicity, the preferred empirical antibiotic is a macrolide (either clarithromycin, azithromycin or erythromycin).
For severe disease, intravenous benzylpenicillin at the maximum appropriate dose should be combined with a macrolide. In patients who are extremely systemically unwell, consider a third agent such as vancomycin until local susceptibility results are available.

Table 1: Guidance for the administration of antibiotics for confirmed cases and close contacts (adults and children age 12 years and above)\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>Duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild disease/community treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500mg bd</td>
<td>14</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>500mg qds</td>
<td>14</td>
</tr>
<tr>
<td>Second Line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1g first day, then 500mg od</td>
<td>7-10</td>
</tr>
<tr>
<td>If unable to take macrolide, discuss with UKHSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Severe disease/hospital treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV Benzylpenicillin + macrolide as above</td>
<td>As per BNF</td>
<td>14</td>
</tr>
<tr>
<td>Add Vancomycin if extremely systemically unwell</td>
<td>As per BNF</td>
<td></td>
</tr>
<tr>
<td>Second Line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discuss with UKHSA</td>
<td></td>
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</tr>
<tr>
<td>For close contacts of confirmed / probable cases / asymptomatic carriers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500mg bd</td>
<td>10</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1g first day, then 500mg od</td>
<td>5</td>
</tr>
</tbody>
</table>

Distribution of MICs for antimicrobial susceptibility testing (AST) performed between 2017 and 2022 are shown in Table 2.

\textsuperscript{1} Consult BNF for paediatric dosing

\textsuperscript{2} Dosages refer to the management for individual cases and their close contacts. Recommended dosage may vary during outbreak management.
AST was performed on toxigenic isolates of *C. diphtheriae* and *C. ulcerans* using gradient strip testing and MICs were interpreted using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints when available.

Reduced susceptibility to penicillin has been observed in toxigenic *Corynebacterium diphtheriae* in the UK although the clinical significance is unclear, however in at least one case a penicillin-based regimen was not successful.

There are no clinical breakpoints for macrolides therefore formal categorisation of the MIC is not possible. The macrolides MICs determined between 2017 and 2022 mostly ranged from ≤0.016 mg/L to 0.5 mg/L suggesting that macrolides remained active.
Table 2: Penicillin and macrolides MICs distributions for toxigenic *Corynebacterium diphtheriae* and *Corynebacterium ulcerans* received between 2017 and 2022

<table>
<thead>
<tr>
<th></th>
<th>Number of isolates with indicated MIC (mg/L)</th>
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<tbody>
<tr>
<td></td>
<td>≤0.016</td>
</tr>
<tr>
<td>Toxigenic <em>Corynebacterium diphtheriae</em> (n = 15)</td>
<td></td>
</tr>
<tr>
<td>penicillin* (S ≤0.125 mg/L; S &gt;0.125 mg/L)</td>
<td></td>
</tr>
<tr>
<td>clarithromycin</td>
<td>6</td>
</tr>
<tr>
<td>erythromycin</td>
<td>9</td>
</tr>
<tr>
<td>azithromycin</td>
<td>1</td>
</tr>
<tr>
<td>Toxigenic <em>Corynebacterium ulcerans</em> (n = 29)</td>
<td></td>
</tr>
<tr>
<td>penicillin (S ≤0.125 mg/L; S &gt;0.125 mg/L)</td>
<td>2</td>
</tr>
<tr>
<td>clarithromycin</td>
<td>8</td>
</tr>
<tr>
<td>erythromycin</td>
<td>4</td>
</tr>
<tr>
<td>azithromycin</td>
<td>3</td>
</tr>
</tbody>
</table>

*As stated by EUCAST, the current breakpoint for benzylpenicillin (S ≤0.125 mg/L; R >0.125 mg/L is not useful for *C. diphtheriae*)
Public health control and management of diphtheria in England

The local clinical microbiology laboratory should undertake susceptibility testing according to their local method. Antimicrobial susceptibility testing can also be confirmed by UKHSA Colindale, with a published turnaround time of 15 days (Bacteriology reference department user manual).

Antibiotic treatment should continue for 14 days based on local antimicrobial susceptibility testing. For azithromycin, given the long half-life, a reduced course of 7 to 10 days can be given. Elimination of the organism should be confirmed after antibiotic treatment has been completed by obtaining nose and throat swabs for culture, or in cases of cutaneous diphtheria by obtaining nose, throat 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 (see below). For adults with a complete immunisation history (5 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 UKHSA’s Green Book: Immunisation against Infectious Disease. For further advice on travel vaccination, please refer to the National Travel Health Network and Centre website.

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 (1) to:

- immunised children up to 10 years of age – one injection of adsorbed diphtheria-containing vaccine (either 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 (for example, Td/IPV)
- unimmunised children under 10 years of age – 3 injections of adsorbed full dose diphtheria-containing vaccine (for example DTaP/IPV/Hib/HepB) at monthly intervals
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- Unimmunised children aged 10 years and over, and adults – 3 injections of adsorbed low-dose diphtheria-containing vaccine (for example, Td/IPV) at monthly intervals
- A person with immunisation status unknown – where there is no reliable history of previous immunisation, it should be assumed that they are unimmunised and follow as above

Laboratory and pathology staff: recommendations for immunisation to protect against diphtheria are as per Green Book Chapter 12 Immunisation of healthcare and laboratory staff.

2.6.6 Fomites

There is little evidence of transmission of diphtheria through fomites and it can be assumed to be very rare. Depending on circumstances, an individual risk assessment should be undertaken based on vulnerability of contacts and level of potential risk (for example, extensive skin shedding). It is recommended that bedding or toys in close contact with infected person or animals, in particular ulcerative wounds, should be hot (>60°C) washed.

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:

1. 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 UKHSA RVPBRU for toxigenicity testing (see 2.3.2). Liaise with the relevant microbiologists (local and reference laboratories).

2. 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). This should be confirmed by HPT and documented on the case management system.

3. Treatment: Treatment of the case is undertaken on clinical grounds only. Antibiotic therapy should include a macrolide (clarithromycin, azithromycin or erythromycin) or appropriate penicillin (see 2.6.4).

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 and dosage as cases. Nose and throat swabs (as well as skin swabs, if appropriate) should be taken 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 managed as non-toxigenic strains with antibiotic therapy only if clinically indicated. In the event of the report of a suspected cluster of NTTBs, please discuss with UKHSA Immunisation and Vaccine Preventable Diseases Division.

2.10 Management of close contacts of diphtheria cases, asymptomatic carriers (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 in the following circumstances: 1) if the contact is with a case or known carrier in a household type setting; 2) those who have had transient close contact particularly if they have been directly exposed to large particle droplets or secretions (following the same principles of meningococcal disease); or, 3) if they have been exposed to an undressed wound of a cutaneous case.

Examples of contacts who should be considered for prophylaxis are:

- 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
- a childminder or carer having regular close contact with the case for 6 or more hours
Examples of healthcare workers (HCW) who should be considered for prophylaxis:

- this will depend on the presentation of diphtheria in the index case, which body sites were positive on swabbing, and what personal protective equipment (PPE) the HCW wore while attending the case – as a minimum, HCW attending to a case (possible, probable or confirmed) of diphtheria should wear a fluid-repellent surgical face mask and, depending on the situation, disposable gloves and aprons for wound care plus eye protection for any aerosol, respiratory secretion generating procedures
- for respiratory cases, HCW who have given mouth to mouth resuscitation to or intubated the index case (without appropriate PPE) would normally be considered as close contacts
- for HCW where eye protection has not been worn and droplet exposure has occurred (for example, a patient has coughed during the collection of a throat swab)

Types of contact who are unlikely to require prophylaxis:

- friends, relations, and caregivers who have visited the home during the infectious period
- school classroom contacts
- those who share the same room at work
- health care staff that have had contact with the index case without exposure to droplet or open wound
- laboratory workers if they are following their best practice for handling and culturing respiratory pathogens

The risk of transmission in other types of settings should be assessed on a case by case basis by the IMT chair or Consultant in Health Protection.

Experience of other droplet-spread infectious diseases suggests that the risk of transmission of disease on an aircraft is low, and contact tracing is not recommended (94). 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 (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, skin lesions) and advise them to seek urgent medical attention if they become unwell. Travel history should be obtained 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. After 10 days, the HPT should check that the contact has remained well and this information should be documented on the case management system. For those unable to self-monitor the health protection staff should follow up daily with the contact or their carer.

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 nose and throat swab and swabs of any skin lesions, taken before chemoprophylaxis. This will identify any asymptomatic carriers. For more details of types of swabs, where to send them and methods of identification please see section 1.2.

ii) Chemoprophylaxis of close contacts

After nose 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

The recommended agents for chemoprophylaxis are a 5-day course of azithromycin or 10-day course of clarithromycin. Most of the trial experience comes from erythromycin but UKHSA/PHE have had no reported treatment failures with contacts that have received azithromycin or clarithromycin.

As an alternative, in certain circumstances when more easily administered, a single intramuscular (IM) dose of benzylpenicillin can be given with dosing according to the British National Formulary.

If initial swabs for contacts are culture positive for Corynebacterium diphtheriae, C. ulcerans or C. pseudotuberculosis they should be managed as per appendix 1 and
samples should be submitted to RVPBRU for confirmation and toxigenicity testing (section 2.3.2).

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:

- health and social care workers
- those who work with unimmunised children
- those involved in milk production (for *C. ulcerans*)

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 IMT based on an individual risk assessment.

All should have a nose 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 for *C. ulcerans*, *C. diphtheriae*, or *C. pseudotuberculosis* they must remain excluded from work until the toxigenicity result is known and the second nose and throat swab taken 24 hours after the completion of the course is negative. They can return to work after a negative culture has been obtained.

iv) Immunisation of close contacts

Vaccination status of close contacts should be assessed. For those who are appropriately immunised for age, 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 (1). Please refer to schedule outlined in section 2.6.5. For those who are not appropriately immunised, a diphtheria-containing dose should be given immediately, and the schedule completed according to the guidelines available on vaccination of individuals with uncertain or incomplete immunisation status.
2.11 Management of close contacts of asymptomatic and symptomatic non-toxigenic toxin gene-bearing (NTTB) corynebacteria cases (see section 2.9)

No public health follow up of contacts is required. In cases where public health actions have commenced in response to a positive PCR toxigenicity case, these can be stood down when a negative Elek test result is received.

2.12 Investigation into zoonotic sources of infection for confirmed human toxigenic C.ulcerans cases

Where a case of toxigenic *C. ulcerans* is identified, investigations should aim to identify any history of exposure to animals or unpasteurised dairy products. Consideration should be given to domestic settings, where companion animals may be present, as well as farms, where there is potential for contact with multiple animals or species. Where contact with animals is identified, the species of animal(s), nature of the contact, and presence of symptoms in the animal(s) should be noted, for example wound infections or nasal discharge. If a zoonotic source of infection is suspected for a confirmed toxigenic *C. diphtheriae* or *C. pseudotuberculosis* case, the same process should be followed.

APHA should be invited to attend the IMT meetings where a zoonotic source of infection may exist. The IMT will risk assess settings where animals are present and agree on appropriate actions to manage potential animal source(s) of infection. It may be necessary to determine carriage in potential animal sources by taking samples from animals; this includes animals in close contact with the case or unpasteurised milk or dairy products.

*C. ulcerans* is not a notifiable disease in animals and investigation and treatment is unlikely to be covered by pet insurance policies if the animal is otherwise healthy. Therefore prior to testing animal contacts, it is important to discuss who will cover the costs of swabbing by the private veterinary surgeon (PVS) and the implications of a positive test with the owner, this 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 the owners or PVS.

The natural history of *C. ulcerans* in animals is not fully understood and animals may pass on the infection to humans without exhibiting signs of illness themselves. As it
Public health control and management of diphtheria in England can be difficult to obtain good quality swabs from some animals and they may no longer be carrying the infection when swabbed, it may not always be possible confirm the presence of toxigenic *C. ulcerans* infection in an animal(s) that appears to be the likely source of a human infection.

### 2.12.1 Sample collection and testing

APHA, with UKHSA, will advise on collection and analysis of animal samples. Sample collection usually involves taking throat swabs from companion animals within the case’s household or animals with which the case has regular close contact. Any skin lesions present should also be swabbed. Charcoal swabs should be used for bacterial culture. The swabbing is carried out through the animal’s PVS, but swabs are then sent to the APHA Regional Laboratory in Starcross, Devon where cultures to identify the presence of *C. ulcerans* are undertaken. If *C. ulcerans* is confirmed the positive isolates should be sent to UKHSA RVPBRU for toxigenicity testing. Testing of potentially toxigenic isolates from animal samples at RVPBRU will generally only be carried out during routine working hours.

### 2.12.2 Antibiotic treatment

APHA will advise on appropriate antibiotic treatment of animals found to be positive for *C. ulcerans*. Antimicrobial sensitivity results will guide appropriate antibiotic choices. In 2 cases where an indistinguishable strain was identified from a dog and human, a 10 day course of a combination of spiramycin and metronidazole was found to successfully clear the organism from the dog (89). Where daily administration of tablets is not possible, a long-acting antibiotic injection may be advised. To confirm clearance of toxigenic *C. ulcerans*, repeat swabs should generally be taken 5 to 7 days following completion of the antibiotic course.

Where there is more than one companion animal present in a defined setting but only one tests positive for toxigenic *C. ulcerans*, APHA may recommend treatment of all animals due to the risk of transmission of infection through close contact or sharing of food or water bowls.

### 2.12.2 Cost of animal investigations

While APHA will cover the costs of culturing the swabs taken from animals, there are other costs associated with investigating animals as a zoonotic source of toxigenic *C. ulcerans* and these will usually need to be covered by the owner. The initial costs will include PVS consultation with swab collection, but consideration should be given to how antibiotics will be paid for if the animal tests positive for *C. ulcerans* on swabbing and the likely costs of subsequent clearance swabs.

Unfortunately, it is not possible to give an accurate estimate for these costs, as they will vary depending on the size and number of animals involved, the number of appointments needed, type and amount of antibiotic required, and the PVS involved.
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The IMT should discuss alternative funding options in the event that the owner is unable to cover the costs.

For the public health management of suspected and confirmed toxigenic *C. ulcerans* cases in animals where there are no associated human infections, please see separate guidance document.

### 3.0 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 (see Appendix 4). Key messages could include:

- a case has occurred
- the chance of another case is very small as most people are protected by immunisation
- advice for close contacts of cases including the importance of having swabs taken and completing the appropriate antibiotic course
- 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.

If a case has recently travelled to another country or a contact has left the UK, it may be necessary to share information with that country to enable them to take appropriate public health actions. International information sharing for public health purposes is communicated securely through the UK International Health Regulations national focal point (IHRNFP) to the equivalent IHRNFP in the other country. Contact the UK IHRNFP ([IHRNFP@phe.gov.uk](mailto:IHRNFP@phe.gov.uk)) with details of the country involved, details of the individual who has travelled, dates of travel and relevant contact details.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>APHA</td>
<td>Animal and Plant Health Agency</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>DAT</td>
<td>Diphtheria Anti-Toxin</td>
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<tr>
<td>Defra</td>
<td>Department for the Environment, Food and Rural Affairs</td>
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<tr>
<td>DTaP/IPV</td>
<td>Diphtheria/tetanus/acellular pertussis/inactivated polio vaccine</td>
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<tr>
<td>GP</td>
<td>General Practitioner</td>
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<td>HPA</td>
<td>Health Protection Agency</td>
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<td>Health Protection Team</td>
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<td>IHBSD</td>
<td>Immunisation, Hepatitis, and Blood Safety Department</td>
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<td>I&amp;VPDD</td>
<td>Immunisation and Vaccine Preventable Diseases Division</td>
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<td>IHRNFP</td>
<td>International Health Regulations national focal point</td>
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<td>IM</td>
<td>Intramuscular</td>
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<td>IMT</td>
<td>Incident Management Team</td>
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<tr>
<td>IU</td>
<td>International Units</td>
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<td>International Units per millilitre</td>
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<td>M unit</td>
<td>Mega unit</td>
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<tr>
<td>kDa</td>
<td>Kilodaltons</td>
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<tr>
<td>NHS</td>
<td>National Health Service</td>
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<td>NTTB</td>
<td>Non-toxigenic toxin gene-bearing</td>
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<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<td>Public Health England</td>
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<td>RVPBRU</td>
<td>Respiratory and Vaccine Preventable Vaccine Bacteria Reference Unit</td>
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<td>Td/IPV</td>
<td>Tetanus/low dose diphtheria/inactivated polio vaccine</td>
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<td>WHO</td>
<td>World Health Organization</td>
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References

1 Begg N and others. ‘Manual for the management and control of diphtheria in the European Region’. Copenhagen, WHO Regional Office for Europe, 1994

2 WHO. ‘Operational protocol for clinical management of Diphtheria Bangladesh, Cox’s Bazar’ World Health Organization, 2017

3 Ganeshalingham A and others. ‘Fatal laryngeal diphtheria in a UK child’ Archives of Disease in Childhood 2012: volume 97 number 8

4 Farizo K and others. ‘Fatal Respiratory Disease Due to Corynebacterium Diphtheriae: Case Report and Review of Guidelines for Management, Investigation, and Control’ Clinical Infectious Diseases 1993: volume 16 number 1


6 Finger F and others. ‘Real-time analysis of the diphtheria outbreak in forcibly displaced Myanmar nationals in Bangladesh’ BioMed Central Medicine 2019: volume 17 number 1

7 Polonsky JA and others. ‘Epidemiological, clinical, and public health response characteristics of a large outbreak of diphtheria among the Rohingya population in Cox's Bazar, Bangladesh, 2017 to 2019: A retrospective study’ Public Library of Science Medicine 2021: volume 18 number 4

8 Gower CM and others. ‘The changing epidemiology of diphtheria in the United Kingdom, 2009 to 2017’ Eurosurveillance 2020: volume 25 number 11

9 Bowler ICJ and others. ‘Diphtheria – The continuing hazard’ Archives of Disease in Childhood 1988: volume 63 number 2

10 Wagner KS and others. ‘Screening for Corynebacterium diphtheriae and Corynebacterium ulcerans in patients with upper respiratory tract infections 2007–2008: a multicentre European study’ Clinical Microbiology and Infection 2011: volume 17 number 4


12 Efstratiou A and others. ‘Microbiology and Epidemiology of Diphtheria’ Reviews and Research in Medical Microbiology 1996: volume 7 number 1

Public health control and management of diphtheria in England

14 Wagner KS and others. ‘Diphtheria in the United Kingdom, 1986 to 2008: The increasing role of Corynebacterium ulcerans’ Epidemiology and Infection 2010: volume 138 number 11


16 Menon T and others. ‘Native valve endocarditis caused by a non-toxigenic strain of Corynebacterium diphtheriae’ Indian Journal of Pathology and Microbiology 2010: volume 53 number 4

17 Belko J and others. ‘Endocarditis caused by Corynebacterium diphtheriae: Case report and review of the literature’ Pediatric Infectious Disease Journal 2000: volume 19 number 2


19 Booth LV and others. ‘An atypical case of case of corynebacterium diphtheriae endocarditis and subsequent outbreak control measures’ Journal of Infection 1995: volume 31 number 1

20 Wojewoda CM and others. ‘Bloodstream infection caused by nontoxigenic Corynebacterium diphtheriae in an immunocompromised host in the United States’ Journal of Clinical Microbiology 2012: volume 50 number 6

21 Reacher M and others. ‘Nontoxigenic Corynebacterium diphtheriae: An emerging pathogen in England and Wales?’ Emerging Infectious Diseases 2000: volume 6 number 6

22 Lowe CF and others. ‘Cutaneous diphtheria in the urban poor population of Vancouver, British Columbia, Canada: A 10-year review’ Journal of Clinical Microbiology 2011: volume 49 number 7

23 Tiley S and others. ‘Infective Endocarditis Due to Nontoxigenic Corynebacterium Diphtheriae: Report of Seven Cases and Review’ Clinical Infectious Diseases 1993: volume 16 number 2

24 Lake JA and others. ‘A case of necrotizing epiglottitis due to nontoxigenic corynebacterium diphtheriae’ Pediatrics 2015: volume 136 number 1

25 Dangel A and others. ‘Geographically diverse clusters of nontoxigenic corynebacterium diphtheriae infection, Germany, 2016–2017’ Emerging Infectious Diseases 2018: volume 24 number 7

26 Zasada AA and others. ‘The first case of septicemia due to nontoxigenic Corynebacterium diphtheriae in Poland: case report’ Annals of Clinical Microbiology and Antimicrobials 2005: volume 4

27 WHO. ‘WHO laboratory manual for the diagnosis of diphtheria and other related infections’ World Health Organization 2021
Public health control and management of diphtheria in England

De Zoysa A and others. ‘Detection of diphtheria toxin gene-bearing and non-toxin gene-bearing Corynebacterium diphtheriae and Corynebacterium ulcerans/ Corynebacterium pseudotuberculosis using a quadruplex Rotor-Gene Q PCR assay’ European Scientific Conference on Applied Infectious Diseases Epidemiology (ESCAIDE) 5 to 7 November 2014, Stockholm, Sweden


Thilo W and others. ‘A case report of laboratory-acquired diphtheria’ Eurosurveillance 1997: volume 2 number 8


McGouran DCR and others. ‘A Case of Cutaneous Diphtheria in New Zealand’ New Zealand Medical Journal 2012: volume 125 number 1350

Truelove SA and others. ‘Clinical and Epidemiological Aspects of Diphtheria: A Systematic Review and Pooled Analysis’ Clinical Infectious Diseases 2020: volume 71 number 1

Koopman JS and others. ‘Role of Cutaneous Diphtheria Infections in a Diphtheria Epidemic’ The Journal of Infectious Diseases 1975: volume 131 number 3

Wagner KS and others. ‘Diphtheria in the postepidemic period, Europe, 2000 to 2009’ Emerging Infectious Diseases 2012: volume 18 number 2

PHE. ‘Diphtheria: guidance, data and analysis’ PHE 2018

Lindhusen-Lindhé E and others. ‘Imported laryngeal and Cutaneous diphtheria in tourists returning from western Africa to Sweden, March 2012’ Eurosurveillance 2012: volume 17 number 23

Orouji A and others. ‘Cutaneous diphtheria in a German man with travel history’ Acta Dermato-venereologica 2012: volume 92 number 2

Wren MWD and others. ‘Infections with Corynebacterium diphtheriae: Six years’ experience at an inner London teaching hospital’ British Journal of Biomedical Science 2005: volume 62 number 1

Wagner J and others. ‘Infection of the Skin Caused by Corynebacterium ulcerans and Mimicking Classical Cutaneous Diphtheria’ Clinical Infectious Diseases 2001: volume 33 number 9
Public health control and management of diphtheria in England

44 Corti MAM and others. ‘Rare human skin infection with Corynebacterium ulcerans: Transmission by a domestic cat’ Infection 2012: volume 40 number 5

45 De Benoist AC and others. ‘Imported Cutaneous Diphtheria, United Kingdom’ Emerging Infectious Diseases 2004: volume 10 number 3

46 UK Health Security Agency (UKHSA). ‘Notifications of infectious diseases (NOIDs)’ UKHSA 2022

47 Zakikhany K and others. ‘Emergence and molecular characterisation of non-toxigenic tox gene-bearing corynebacterium diphtheriae biovar mitis in the United Kingdom, 2003 to 2012’ Eurosurveillance 2014: volume 19 number 22


49 Begg N and others. ‘Diphtheria: are we ready for it?’ Archives of Disease in Childhood 1995: volume 73 number 6

50 UKHSA. ‘Complete routine immunisation schedule’ UKHSA 2022

51 Wagner KS and others. ‘Immunity to tetanus and diphtheria in the UK in 2009’ Vaccine 2012: volume 30 number 49

52 WHO. ‘Diphtheria vaccines: WHO position paper – August 2017’ WHO 2017

53 UKHSA. ‘School leaver booster (Td/IPV): vaccine coverage estimates’ UKHSA 2022

54 UKHSA. Impact of COVID-19 on routine childhood vaccinations: early vaccine coverage data to August 2021 in England 2021’ UKHSA 2021

55 De Zoysa A and others. ‘Characterization of toxigenic Corynebacterium ulcerans strains isolated from humans and domestic cats in the United Kingdom’ Journal of Clinical Microbiology 2005: volume 43 number 9

56 Edwards D and others. ‘Transmission of toxigenic Corynebacterium diphtheriae by a fully immunised resident returning from a visit to West Africa, United Kingdom, 2017’ Eurosurveillance 2018: volume 23 number 39

57 ECDC. ‘Risk Assessment: Increase of reported diphtheria cases among migrants in Europe due to Corynebacterium diphtheriae, 2022’ ECDC 2022

58 ECDC. ‘Communicable Disease Threats Report, 23-29 October 2022, week 43’ ECDC 2022

59 Amirthalingam G and others. ‘Guidance on the use of Diphtheria Anti-toxin (DAT)’ PHE 2021

60 Gilbert R and others. ‘Corynebacterium ulcerans: a pathogenic microorganism resembling C. diphtheriae’ Journal Laboratory and Clinical Medicine 1926: volume 12

61 Fakes RW and others. ‘Toxic reaction to Corynebacterium ulcerans’ Lancet 1970: volume 1 number 7641

62 Meers PD and others. ‘A case of classical diphtheria, and other infections due to Corynebacterium ulcerans’ Journal of Infection 1979: volume 1
Public health control and management of diphtheria in England

63 Sing A and others. ‘Classical Diphtheria Caused by Corynebacterium ulcerans in Germany: Amino Acid Sequence Differences between Diphtheria Toxins from Corynebacterium diphtheriae and C. ulcerans’ Clinical Infectious Diseases 2005: volume 40 number 2

64 Hacker E and others. ‘Corynebacterium ulcerans, an emerging human pathogen’ Future Microbiology 2016: volume 11

65 Hart RJC. ‘Corynebacterium ulcerans in humans and cattle in North Devon’ Journal of Hygiene 1984: volume 92 number 2

66 Bostock AD and others. ‘Corynebacterium ulcerans infection associated with untreated milk’ Journal of Infection 1984: volume 9 number 3

67 Mattos-Guaraldi AL and others. ‘First detection of Corynebacterium ulcerans producing a diphtheria-like toxin in a case of human with pulmonary infection in the Rio de Janeiro metropolitan area, Brazil’ Memorias do Instituto Oswaldo Cruz 2008: volume 103 number 4


70 Tiwari TSP and others. ‘Investigations of 2 cases of diphtheria-like illness due to toxigenic Corynebacterium ulcerans’ Clinical Infectious Diseases 2008: volume 46 number 3

71 Gubler J and others. ‘Classical Pseudomembranous Diphtheria Caused by Corynebacterium Ulcerans’ Schweizerische Medizinische Wochenschrift 1990: volume 120 number 48

72 Meinel DM and others. ‘Zoonotic transmission of toxigenic Corynebacterium Ulcerans strain, Germany, 2012’ Emerging Infectious Diseases 2015: volume 21 number 2

73 Berger A and others. ‘Toxigenic Corynebacterium ulcerans in woman and cat’ Emerging Infectious Diseases 2011: volume 17 number 9

74 Vandentorren S and others. ‘Toxigenic Corynebacterium ulcerans in a fatal human case and her feline contacts, France, March 2014’ Eurosurveillance 2014: volume 19 number 38


76 Monaco M and others. ‘Respiratory diphtheria due to Corynebacterium ulcerans transmitted by a companion dog, Italy 2014’ Infection 2017: volume 45 number 6
Public health control and management of diphtheria in England

77 Olson ME and others. ‘Gangrenous dermatitis caused by Corynebacterium ulcerans in Richardson ground squirrels’ Journal of the American Veterinary Medical Association 1988: volume 193 number 3

78 Konrad R and others. ‘Possible human-to-human transmission of toxigenic Corynebacterium ulcerans’ Clinical Microbiology and Infection 2015: volume 21 number 8

79 Martini H and others. ‘Diphtheria in Belgium: 2010 to 2017’ Journal of Medical Microbiology 2019: volume 68 number 10

80 CDC. ‘Notes From the Field: Respiratory Diphtheria-Like Illness Caused by Toxigenic Corynebacterium Ulcerans – Idaho, 2010’ Morbidity and Mortality Weekly Report 2011: volume 60 number 3


82 Parte AC and others. ‘Genus: Corynebacterium in List of Prokaryotic names with Standing in Nomenclature (LPSN) moves to the DSMZ’ International Journal of Systematic and Evolutionary Microbiology 2020: volume 70


84 Ott L and others. ‘Corynebacterium diphtheriae invasion-associated protein (DIP1281) is involved in cell surface organization, adhesion and internalization in epithelial cells’ BioMed Central Microbiology 2010: volume 10 number 2

85 Oliveira A and others. ‘Insight of genus Corynebacterium: Ascertaining the role of pathogenic and non-pathogenic species’ Frontiers in Microbiology 2017: volume 8

86 Edwards B and others. ‘Recent cases of non-toxigenic Corynebacterium diphtheriae in Scotland: Justification for continued surveillance’ Journal of Medical Microbiology 2011: volume 60 number 4

87 DeWinter LM and others. ‘Human clinical isolates of Corynebacterium diphtheriae and Corynebacterium ulcerans collected in Canada from 1999 to 2003 but not fitting reporting criteria for cases of diphtheria’ Journal of Clinical Microbiology 2005: volume 43 number 7

88 Dinu S and others. ‘New diphtheria toxin repressor types depicted in a Romanian collection of Corynebacterium diphtheriae isolates’ Journal of Basic Microbiology 2014: volume 54 number 10

89 Contzen M and others. ‘Corynebacterium ulcerans from Diseased Wild Boars’ Zoonoses and Public Health 2011: volume 58 number 7

90 Rau J and others. ‘Corynebacterium ulcerans infection in roe deer (Capreolus capreolus)’ (in German) Berliner Munchener Tierarztliche Wochenschrift 2012: volume 125 number 3 to 4
Public health control and management of diphtheria in England


92 Scobie A and others. ‘Audit of the English public health and laboratory diphtheria service’ (internal PHE) 2018

93 Coia JE and others. ‘Guidance on the use of respiratory and facial protection equipment’ Journal of Hospital Infection 2013: volume 85 number 3

94 Kotila SM and others. ‘Systematic review on tuberculosis transmission on aircraft and update of the European centre for disease prevention and control risk assessment guidelines for tuberculosis transmitted on aircraft (RAGIDA-TB)’ Eurosurveillance 2016: volume 21 number 4
Appendix 1. Algorithm for management of a suspected diphtheria case

Microbiological or clinical suspicion of diphtheria

- notify local health protection teams
- seek local ID or microbiology advice
- conduct primary microbiological isolation and
- send isolate to UKHSA RVPBRU for confirmation and toxigenicity testing
- risk assess and classify case

Possible diphtheria

- if in hospital, isolate and barrier nurse
- if at home, restrict contact
- assess clinically
- consider antibiotic treatment on clinical grounds only

See section 2.7

No further public health action

Non-toxigenic strain, no organism isolated or NTTB strain

Confirmed PCR toxin positive strain
Elek positive – toxigenic strain
Elek negative – NTTB strain

Confirmed or probable diphtheria or asymptomatic carrier

- admit and refer to ID specialist (unless asymptomatic carrier or very well)
- if in hospital, isolate and barrier nurse
- consider diphtheria antitoxin (unless NTTB strain or asymptomatic carrier)
- give antibiotic treatment for 14 days (for NTTB only if clinically indicated)
- identify and manage close contacts (see Appendix 2)
  - convene IMT meeting
  - provide written information as appropriate (such as a reactive press statement)
  - exclude case from high-risk occupations until bacteriological clearance confirmed
  - immunise as appropriate when recovered

See section 2.6 or 2.8

Public health actions

Results of confirmation and toxigenicity

Await toxigenicity results.
See section 2.3 for possible exceptions

Non-toxigenic strain or no isolate grown after 48 hours

For confirmed toxigenic C. ulcerans only
Risk assessment of potential animal source in collaboration with APHA

Complete public health actions as in box above (manage case and close contacts)

Positive for toxigenic

After completing antibiotic treatment, take 2 nose and throat swabs (or nose, throat and skin swabs for cutaneous cases) for culture 24 hours after stopping antibiotics and at least 24 hours apart.

Non-toxigenic strain, no organism isolated or NTTB strain

Discuss a further 10 days of antibiotics with microbiologist

Confirmed or probable diphtheria or asymptomatic carrier
Public health control and management of diphtheria in England

Accessible text version of the algorithm for management of a suspected diphtheria case

1. When there is a microbiological or clinical suspicion of diphtheria, the first actions are:
   - notify local health protection teams
   - conduct primary microbiological isolation and
   - send isolate to UKHSA RVPBRU for confirmation and toxigenicity testing
   - risk assess and classify case as either possible or probable or confirmed or asymptomatic carrier

2. If the case is possible, then please see section 2.7 and carry out the following actions while awaiting results of toxigenicity testing:
   - if in hospital, isolate and barrier nurse
   - if at home, restrict contact for the first 6 days of appropriate antibiotic course
   - assess clinically
   - consider antibiotic treatment on clinical grounds only
   - wait for toxigenicity results, please see section 2.3 for possible exceptions

3. If the case is confirmed or probable or an asymptomatic carrier, then carry out these public health actions (see section 2.6 or 2.8):
   - admit and get ID or microbiology advice (unless asymptomatic carrier or very well)
   - if in hospital, isolate and barrier nurse
   - consider antitoxin (unless NTTB strain or asymptomatic carrier)
   - give antibiotic treatment for 14 days (for NTTB only if clinically indicated)
   - identify and manage close contacts (see Appendix 2)
   - convene IMT meeting
   - provide written information as appropriate (such as a reactive press statement)
   - exclude case from high-risk occupations until bacteriological clearance confirmed
   - immunise as appropriate when recovered

4. Once there are PCR results and the possible case is confirmed as a PCR toxin gene positive then carry out public health actions in step 3.

5. If the results of the confirmation testing show the case is a non-toxigenic strain or there is no isolate grown after 48 hours then no further public health action is needed.

6. If the Elek test shows that the strain is NTTB, then stop public health actions.
7. For confirmed toxigenic *C. ulcerans* only, carry out a risk assessment of potential animal source in collaboration with APHA.

8. For all confirmed cases, after completing antibiotic treatment, take 2 nose and throat swabs (or nose, throat and skin swabs for cutaneous cases) for culture 24 hours after stopping antibiotics and at least 24 hours apart.

9. If the clearance swabs are non-toxigenic strain, no organism isolated or NTTB strain, then no further public health action.

10. If the clearance swabs are positive for a toxigenic strain, then discuss a further 10 days of antibiotics with microbiologist.
Appendix 2: Algorithm for the management of close contacts of confirmed and probable diphtheria cases*

1. Identify all close contacts of the index case of confirmed or probable diphtheria (see section 2.10.1), if the case is possible, please see section 2.3. Close contacts include:

- contacts in a household type setting
- kissing / sexual contacts
- healthcare workers who have had direct exposure to respiratory droplets or secretions or exposed to undressed wounds of cutaneous case

2. Carry out these actions for all close contacts (see section 2.10.2):

- inform close contacts and their GP
- advise self-monitoring for 10 days from date of last contact with case
- take nose and throat swabs and swabs of any skin lesions
- offer chemoprophylaxis with antibiotics for 5 days (if azithromycin) or 10 days (if clarithromycin)
- exclude from high-risk occupations until bacteriological clearance is confirmed
- immunise as appropriate
- if the contact becomes symptomatic then arrange urgent clinical assessment

3. If a contact is positive for a toxigenic strain, then manage them as a confirmed case (Appendix 1).

4. If a contact has a non-toxigenic strain, no organism isolated or NTTB strain, then stop public health actions.

5. If the index case is discarded, then stop public health actions.
Identify all close contacts of the index case of confirmed or probable diphtheria
- contacts in a household type setting
- kissing or sexual contacts
- healthcare workers who have had direct exposure to respiratory droplets or secretions or exposed to undressed wounds of cutaneous case

For all close contacts (see section 2.10.2)
- inform close contacts and their GP
- advise self-monitoring for 10 days from date of last contact with case
- take nose and throat swabs and swabs of any skin lesions
- offer chemoprophylaxis with antibiotics for 5 days (if azithromycin) or 10 days (if clarithromycin)
- exclude from high-risk occupations until bacteriological clearance is confirmed
- immunise as appropriate

Contact Positive for toxigenic strain
- Manage as confirmed case
  See Appendix 1

Contact Non-toxigenic strain, no organism isolated or NTTB strain
- No further public health actions

If contact becomes symptomatic
arrange urgent clinical assessment

If index case is discarded stop public health actions

* See section 2.3 for the management of contacts of a possible case
Appendix 3: Diphtheria fact sheet: for cases and close contacts

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. You are receiving this fact sheet because you or a close contact has been diagnosed with diphtheria.

Due to the success of a highly effective vaccination programme it is uncommon to see diphtheria in the UK. The majority of cases acquired within the UK are mild infections in people who have been incompletely immunised or in older adults that have been fully immunised but may have waning immunity.

Although diphtheria can be a serious illness, there are effective treatments available including antibiotics. There are also steps that you can take to prevent yourself from either spreading diphtheria to your friends and loved ones, and to prevent yourself from catching diphtheria if you are a close contact. These steps are included in this fact sheet.

What is diphtheria?

Diphtheria is a vaccine preventable, infectious and potentially life-threatening (if left untreated) infection, caused by a toxin (poison) made by bacteria. *Corynebacterium diphtheriae* and *Corynebacterium ulcerans* are the 2 most common bacteria that can cause diphtheria but it can also be caused by *Corynebacterium pseudotuberculosis*, although this is very rare.

Symptoms of diphtheria

Symptoms usually begin 2 to 5 days after being in contact with 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 to 3 days, a membrane may form 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 also cause small skin sores that form larger ulcers, usually appearing on exposed limbs, particularly the legs. This is known as cutaneous diphtheria.
Transmission of diphtheria

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. Prolonged close contact (such as living in the same household) is normally required for the infection to be transmitted to others.

*Corynebacterium ulcerans* infection has been associated with prolonged close contact with animals (for example pets in the home, through working on a farm, as a veterinarian) or consumption of unpasteurised milk and dairy products.

Diphtheria vaccination

Diphtheria vaccination protects against the disease and is very effective. It gives protection against disease by producing antibodies to the diphtheria toxin. The vaccine 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 childhood 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 8, 12 and 16 weeks 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.

Diagnosis

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.

Treatment of diphtheria for individuals and their close contacts

A doctor will prescribe antibiotics to treat diphtheria and particularly in cases of severe respiratory diphtheria they will also advise other medicines (such as anti-toxin) to stop the effects of toxins produced by the bacteria. Cases will be advised to isolate until their antibiotic treatment is completed and follow up swabs have shown clearance of the infection.

Close contacts, considered to be people who share a house or are in close contact with the infected person, will be offered a swab to screen for diphtheria infection. All close contacts will also be treated with antibiotics as a precautionary measure.

If you have not been fully vaccinated against diphtheria (received 5 doses of a diphtheria vaccine), you will be offered additional vaccines to complete the course by your GP. If you have been fully vaccinated previously but this was more than 12 months ago, you will be offered a
booster dose to boost your immunity against the infection. If you are unsure about your vaccine status, please check with your GP.

Sources of information

Additional information about diphtheria that you may find helpful can be found on the NHS website.
Appendix 4: Diphtheria reactive press statement

A UKHSA spokesperson said:

[Include 2 sentences here on what has happened, what public health measures are being put in place and what is the level of risk to the public.]

“The best way to protect against diphtheria is vaccination and those affected will be given a prescription for antibiotics to help prevent the development of diphtheria and offered an additional booster vaccination.

“We realise this kind of situation can be worrying and we want to reassure everyone that diphtheria is extremely rare in England due to the effective vaccination programme we have in place. The planned actions we are taking now will lower the risk to the public.”

Background

[Provide a few bullets here about the incident: who infected, when and where.]

Diphtheria is a bacterial infection that mainly affects the nose and throat and, sometimes, the skin.

It can cause symptoms including a sore throat, high temperature, a thick, grey-white coating at the back of the throat and, in severe cases, breathing difficulties.

Close and prolonged contact with someone who has diphtheria infection is needed for it to be passed on.

People could carry the bacteria that causes diphtheria in their nose or throat without having any symptoms of being ill.

Diphtheria can easily be treated with a course of antibiotics to prevent it from causing illness.

Anyone who has any concerns about symptoms they or someone they know may have should contact their GP or NHS 111 for further information and advice.
About the UK Health Security Agency

UKHSA is responsible for protecting every member of every community from the impact of infectious diseases, chemical, biological, radiological and nuclear incidents and other health threats. We provide intellectual, scientific and operational leadership at national and local level, as well as on the global stage, to make the nation health secure.

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For queries relating to this document, please contact: Immunisation.Lead@ukhsa.gov.uk

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