Control of diphtheria: guidance for consultants in communicable disease control

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Summary: These guidelines for the control and management of diphtheria are intended for consultants in communicable disease control and regional epidemiologists in England and Wales. They are intended to complement existing guidance from the World Health Organization. The guidelines cover the immediate steps to be taken following identification of a case, what is required to confirm the diagnosis, steps to be taken to minimise the likelihood of further linked cases, and what should be done to disseminate information after a case.

Background

Microbiology and clinical aspects of diphtheria

Pharyngeal or cutaneous diphtheria is caused by toxigenic strains of Corynebacterium diphtheriae and occasionally by C. ulcerans. C. diphtheriae is a nonsporulating, unencapsulated, non motile Gram positive bacillus. Both C. diphtheriae and C. ulcerans can produce an exotoxin that causes local tissue necrosis and, when absorbed into the bloodstream, causes toxaemia and systemic complications including paralysis due to demyelinating peripheral neuritis and cardiac failure due to myocarditis. The structural gene of the diphtheria toxin, tox, is carried by a family of corynebacteriophages. It is a 535 residue, 58 kDa exotoxin whose active form consists of two polypeptide chains linked by a disulphide bond. Four biotypes of C. diphtheriae can be distinguished on biochemical testing: gravis, intermedius, mitis, and belfanti. Most infections in recent years have been caused by gravis or mitis biotypes, but the clinical and public health management is identical for all toxigenic strains.

Diphtheria is no longer easily diagnosed on clinical grounds. Mild cases of the disease resemble streptococcal pharyngitis and the classical pseudomembrane of the pharynx may not develop, particularly in people who have been vaccinated. As the disease is rare, many clinicians may never encounter a case and therefore miss the clinical diagnosis. Not all laboratories routinely culture throat swabs for C. diphtheriae, further increasing the potential for missed or delayed diagnosis.

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, which gives rise to a ‘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\(^1\). Nasal diphtheria, usually mild and chronic, is marked by uni- or bilateral nasal discharge, which is initially clear and later becomes bloody\(^1\). Cutaneous diphtheria usually appears on exposed parts, especially the legs. The lesions start as vesicles and quickly form small, clearly demarcated, and sometimes multiple ulcers\(^3\).

**Transmission and carriage of diphtheria**

The incubation period for diphtheria is usually two to five days, but may be longer\(^9\). The commonest mode of transmission is by infected droplet spread through contact with an infected person. Sources of infection include discharges from the nose, throat, or eye, or skin in the case of cutaneous diphtheria.

Asymptomatic carriage of *C. diphtheriae* may occur during the incubation period of diphtheria, during convalescence, or in healthy people. Patients convalescing from diphtheria may harbour *C. diphtheriae* in the throat or nose for many weeks\(^4\). Carriage can be eradicated by antibiotic treatment: erythromycin, clarithromycin, azithromycin, and penicillin are all effective (see section on antibiotic treatment, below).

In countries where diphtheria is endemic, between 3% and 5% of healthy individuals may harbour the organism in their throats\(^31\). In the West, where the disease has become very uncommon, isolation of the organism from healthy individuals has become extremely rare.

Cutaneous diphtheria is problematic in tropical countries and the lesions may act as reservoirs for transmission and spread of pharyngeal diphtheria\(^8\). Two cases of cutaneous diphtheria were reported in Bristol within seven weeks in 1992; both cases had recently returned from abroad\(^13\).

Closeness and duration of contact are important in determining the spread of the disease. Prolonged close contact is normally required for transmission. In a classic study of diphtheria, children sleeping in the same school dormitory were at greater risk than those in casual contact during working hours\(^13\). Infection may be spread to close contacts by droplets from an obvious clinical case, from a patient in the earliest stage of the disease or with a mild unrecognised attack, or from throat or nasal carriers. More rarely, contact with articles soiled with discharges from lesions of infected people may play a role in transmission\(^19\).

**Diphtheria in England and Wales**

Diphtheria was made a notifiable disease under the *Infectious Disease (Notification) Act 1889*. All forms of diphtheria, including cutaneous diphtheria, are notifiable. Doctors in England and Wales have a statutory duty to notify a ‘proper officer’ of the local authority (usually the consultant in communicable disease control (CCDC)) of all cases. It is equally important to de-notify a case that is later found to have been incorrectly identified. In 1914 there were 59324 cases and 5863 deaths due to diphtheria in England and Wales\(^14\). Mass immunisation was introduced in 1942 and by 1957 there were only 37 cases and four deaths.

In a review of diphtheria in England and Wales, covering the period 1970 to 1987, 92 cases were notified, 21 of which were acquired overseas or through contact with a case who had acquired infection overseas\(^15\). A microbiological review identified 19 reports of toxigenic *C. diphtheriae* from 1990 to 1996. Twelve reports were of people who had acquired infection abroad; five had had contact with people who had recently returned from countries where *C. diphtheriae* is prevalent; the other two isolates were from separate incidents in which no likely source of infection was identified\(^16,17\).

Seventy-six per cent (164) of the 215 confirmed isolates of corynebacteria received by the PHLS Streptococcus and Diphtheria Reference Unit (SDRU) between 1986 and 1993 were non-toxigenic *C. diphtheriae*, 15% (33) were toxigenic *C. diphtheriae*, 6% (13) were toxigenic *C. ulcerans*, and 2% (5) were non-toxigenic *C. ulcerans*. The numbers of isolates of *C. diphtheriae* and *C. ulcerans* confirmed each year were similar until 1990 when the numbers of non-toxigenic *C. diphtheriae* isolates started to increase. Biotyping revealed that the increase was mainly among non-toxigenic *C. diphtheriae var gravis*\(^18\).

**Non-toxigenic *C. diphtheriae***

The clinical and epidemiological significance of non-toxigenic *C. diphtheriae* is unclear. Most microorganisms that colonise the body, including those thought not to be pathogenic, can cause disease under predisposing circumstances\(^39\). It is known that the ability to produce toxin is mediated by infection of the bacterium by a bacteriophage and is unrelated to the biotype\(^20\), but the mechanism of pathogenicity of non-toxigenic strains of *C. diphtheriae* is not known. Two cases who accidentally ingested non-toxigenic *C. diphtheriae var mitis* in a laboratory developed sore throat with tonsillar membrane\(^21\). In Australia, seven cases of endocarditis due to non-toxigenic *C. diphtheriae var gravis* have been reported\(^22\). The infection was aggressive: four patients suffered major vascular complications, and one died\(^22\).

The number of isolates of non-toxigenic *C. diphtheriae* from throat swabs of children and young adults with sore throats in England and Wales (confirmed by SDRU) rose from 17 in 1990 to 135 in 1995. These numbers underestimate the incidence because not all laboratories screen throat swabs for *C. diphtheriae*\(^22\); some of the rise observed since 1990 may be due to greater laboratory ascertainment. Enhanced surveillance has shown that no other pathogen was isolated in 66% of cases and that viral cultures were rarely attempted\(^23\). This may be important as most cases of acute pharyngitis are caused by viral infections\(^24,25\). Even if obtained and
processed in ideal circumstances, throat culture cannot reliably differentiate acute infection from chronic carriage34.

Four reports26-29 have looked at the occurrence of non-toxigenic C. diphtheriae in throat swabs. From these studies it was not possible to state if non-toxigenic C. diphtheriae was the cause of pharyngitis, or whether it was a mere coloniser, especially in the absence of a control group.

Corynebacterium ulcerans
C. ulcerans was first described in 1926, when the organism was isolated from human throat lesions30. C. ulcerans is known to be able to produce diphtheria toxin. It has been associated with classical diphtheria31,32 as well as with milder symptoms33-37. At least one death has been attributed to such infection38.

C. ulcerans may infect the bovine udder and an association between human C. ulcerans infection and drinking raw milk has been observed33,34. The organism has been also been report to cause illness in wild squirrels in the United States (US)39. Person to person spread has never been documented32, and swabs from close contacts have been negative32,33,35, but the US Centers for Disease Control and Prevention – in a recent report of a case of membranous pharyngitis caused by toxigenic C. ulcerans – has recommended that people exposed to the index case should be treated along similar lines to cases exposed to C. diphtheriae. This advice was given because it was considered that there was inadequate information about human to human transmission40.

Although there is no direct evidence, it does seem possible that person to person spread may occur. Only two out of 12 cases with isolates of C. ulcerans referred to the SDRU between 1995 and June 1997 had drunk raw milk. For six cases there was no apparent source of infection and two of these isolates were from siblings, raising the possibility of person to person spread (M Ramsay, personal communication). Many cases may be unrecognised, as potentially toxigenic corynebacteria infections are rarely included in the differential diagnosis of pharyngitis. It may be inappropriate to interpret the presence of diphtheroids as representing coincident commensals37.

Immediate action required after a case or suspected case of diphtheria is identified

**Rationale**

Incidents of diphtheria are rare and it would be unusual for a CCDC to have personal experience of managing a case. The identification of non-toxigenic strains has increased since PHLS Standard Operating Procedures (SOPs), which recommend routine screening of C. diphtheriae in laboratories, were implemented. This has increased expectations of CCDCs to provide advice on the basis of preliminary microbiological findings41. Delay in starting treatment could prove fatal for the case; wider spread of the agent could occur in the community if control measures are not promptly initiated.

**Recommendations: immediate action required**

All cases, whether suspected or confirmed, should be notified immediately to the local CCDC. CCDCs must ensure that general practitioners and hospital doctors are aware of the need to notify. Good communication between the microbiology team and the CCDC is vital. Microbiological advice should be sought from SDRU (0208 200 4400 ext 4289) early, and the public health management of the case should be discussed with the Immunisation Division at PHLS Communicable Disease Surveillance Centre (CDSC) (0208 200 6868).

CCDCs should ask the advice of a consultant in infectious disease if the diagnosis of a suspected case is in doubt. The decision whether to implement control measures before the results of toxigenicity testing are available should be based on the likelihood that the patient is infected with a toxigenic strain12. (See recommendations concerning confirming the diagnosis below). No special precautions are necessary during transfer to hospital.

Control measures include:

- Isolation and treatment of the index case
- Tracing and taking nose and throat swabs from close contacts
- Providing prophylactic antibiotics and booster vaccination for close contacts

If a case of diphtheria is confirmed an incident control team should be convened and the Department of Health should be informed. Membership of the team will vary depending on local circumstances, but would typically include:

- CCDC
- consultant microbiologist
- regional epidemiologist
- infection control nurse
- press officer

**Confirming the diagnosis**

**Rationale**

The management of cases and contacts depends on confirmation of the identity of the causative organism. The diagnosis may be delayed, especially in a mild case, in whom the diagnosis is considered unlikely. The hint of the diagnosis may come from the microbiology laboratory, reporting the presence of the organism in a throat swab.

**Recommendations: confirming the diagnosis**

Details of the microbiological identification of C. diphtheriae and C. ulcerans are described elsewhere in this journal12. All laboratory isolates should be submitted for toxigenicity testing and strain confirmation to SDRU at the PHLS Central Public Health Laboratory (tel 0208 200 4400 ext 4289). The service is available 24 hours a day, seven days a week. Cultures should be submitted to the laboratory by courier, after contacting the laboratory to inform staff that a culture is on the way43.
TABLE Dosage of antitoxin recommended for various types of diphtheria

<table>
<thead>
<tr>
<th>Type of diphtheria</th>
<th>Dosage (units)</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal</td>
<td>10000 - 20000</td>
<td>Intramuscular (IM)</td>
</tr>
<tr>
<td></td>
<td>15000 - 25000</td>
<td>IM or intravenous (IV)</td>
</tr>
<tr>
<td></td>
<td>20000 - 40000</td>
<td>IM/IV</td>
</tr>
<tr>
<td>Pharyngeal or laryngeal</td>
<td>40000 - 60000</td>
<td>IV</td>
</tr>
<tr>
<td>Combined types or delayed diagnosis</td>
<td>40000 - 100000</td>
<td>IV or part IV and part IM</td>
</tr>
</tbody>
</table>

Antibiotic treatment
Antibiotic treatment is needed to eliminate the organism and prevent spread; it is not a substitute for antitoxin treatment. The antibiotics of choice are erythromycin, azithromycin, clarithromycin, or penicillin, all of which are active in vitro against C. diphtheriae. Compliance with erythromycin may be poor because of gastrointestinal side effects. All specimens should be collected before antibiotic treatment is started. The recommended dose regimens for erythromycin and benzylpenicillin are as follows:

Parenteral erythromycin
40-50mg/kg/day (maximum 2g/day) until the patient can swallow comfortably, when erythromycin in four divided doses (or alternative macrolide) or oral penicillin (125mg-250mg four times daily) may be substituted

Benzylpenicillin
Children IM 25000-50000 units/kg/day in two divided doses
Adults IM 1.2 million units/day in two divided doses

Antibiotic treatment should be continued for 14 days. Elimination of the organism should be confirmed after antibiotic treatment has been completed, by obtaining nasopharyngeal swabs for culture. An additional 10 day course of antibiotics should be prescribed if cultures are positive.

Immunisation
Patients should be immunised in the convalescent stage of their disease because clinical infection does not always induce adequate levels of antitoxin. Individuals should be given a complete course or a reinforcing dose according to their age and immunisation history as follows. (NB A booster is not required if the last dose was given less than 12 months earlier):

Immunised children up to 10 years of age
one injection of adsorbed diphtheria vaccine (D)

Immunised children aged 10 years and over, and adults
one injection of adsorbed low dose diphtheria vaccine for adults (d) or adsorbed tetanus/low dose diphtheria vaccine for adults (Td)

Unimmunised children under 10 years of age
three injections of D (or adsorbed diphtheria/tetanus/pertussis (DTP) and polio vaccines if appropriate) at monthly intervals

Unimmunised children aged 10 years and over, and adults
three injections of d or Td at monthly intervals

Immunisation status unknown
Obtain a blood specimen for diphtheria antitoxin testing then give one injection of adsorbed vaccine (D or d, depending on age). Complete the course of three injections if antitoxin is not detected in the prevaccination specimen. SDRU undertake testing for diphtheria antitoxin.
Reducing the risk of linked cases

**Rationale**

Diphtheria contacts are given prophylaxis for two reasons: firstly, to treat incubating disease in recently exposed contacts and, secondly, to eliminate carriage and thereby reduce the risk of exposure to other susceptible contacts.

Anyone who has been in close contact with a case of diphtheria caused by toxigenic *C. diphtheriae* or *C. ulcerans* (whatever the clinical presentation) in the previous seven days should be considered as potentially at risk. Contacts of cases due to non-toxigenic *C. diphtheriae* or *C. ulcerans* are not at risk. The risk of infection is directly related to the closeness and duration of contact. It is important to identify any asymptomatic carriers as they may transmit the organism. The search for infected carriers should be limited to circumstances in which intimate respiratory or physical contact may have occurred. Ask contacts about recent travel, as the contact may be the source of the patient’s infection.

Contact with a case on public transport is likely to carry a low risk. Experience of other droplet spread infectious diseases suggests that the risk of transmission of disease on an aircraft is low, especially if contact with the affected person is for less than eight hours. Close proximity may be defined as being seated or working in the same cabin section as the infected passenger, depending on the aircraft design.

Those at greatest risk will be:

- those sleeping in the same household as the index case
- kissing/sexual contacts of the index case
- health care workers who have given mouth to mouth resuscitation to the index case or have dressed the wounds of a cutaneous case

Students in a hall of residence in the same corridor and/or sharing kitchen facilities or a childminder looking after one or more children for many hours daily should be regarded as household contacts.

The risk of disease in other types of contacts will depend on the duration of contact and immunisation status of the person in contact with the index case. Examples of these types of contact would include:

- friends, relations, and caretakers who regularly visit the home
- school classroom contacts
- those who share the same room at work
- other health care staff who have had contact with the index case

The occurrence of a single case provides an opportunity to check the vaccination status of contacts as defined above. If it is suspected or shown that a group is not fully immunised against diphtheria, it may be necessary to treat that group as a close contact group. Advice may be sought from the Immunisation Division at CDSC (tel 0208 200 6868) in such cases.

**Recommendations: reducing the risk of linked cases**

**Clinical surveillance**

Current guidelines suggest that close contacts should be assessed and monitored for signs/symptoms of diphtheria for at least seven days. An alternative recommended approach (self-surveillance) is to explain the symptoms of diphtheria, asking close contacts to seek urgent medical attention if necessary. If this approach is adopted the contacts’ general practitioners should also be informed, using – perhaps – a letter based on the one shown in the appendix. Assess the ability of the contact to understand the implications of self-surveillance and the likelihood of compliance. For those for whom self-surveillance is not suitable, daily active follow up (either by telephone or visit) is required. Those whose occupations involve handling food, especially milk, or close association with unimmunised children, should be excluded from that work until bacteriological examination confirms that they are not carriers.

**Laboratory investigations**

Nasal and pharyngeal swabs should be obtained for culture and swabs should taken from any wounds or skin lesions before starting chemoprophylaxis. Close contacts who are found to be carriers of a toxigenic strain will need to be isolated and treated, taking control measures as described for a case. The contact should be barrier nursed until two cultures from both nose and throat (and skin lesions in cutaneous diphtheria) taken over 24 hours after stopping antimicrobial chemotherapy, and at least 24 hours apart, fail to show diphtheria bacilli.

**Antibiotics**

The recommended regimen for use in close contacts is either

- a single dose of IM benzylpenicillin
  - 600000 units for children <6 years of age
  - 1.2M units for anyone ≥6 years of age

or

- a seven day course of erythromycin
  - 125mg every 6 hours for children under 2 years of age
  - 250mg every 6 hours for children aged 2 to 8 years
  - 250-500mg every 6 hours for anyone over 8 years of age

Erythromycin eradicates *C. diphtheriae* from the nose and throat of carriers in an average of three days. Other macrolide antibiotics such as azithromycin or clarithromycin may also be used.

Elimination of the organism should be confirmed after antibiotic treatment has been completed, by obtaining nasopharyngeal swabs for culture. A further 10 day course of antibiotics should be prescribed if cultures are positive.
Immunisation
Close contacts should be offered immunisation according to the schedule outlined above. Immunisation is not required if the most recent dose was given less than 12 months earlier.

Management of toxigenic C. ulcerans infections
Rationale
Sporadic cases of diphtheria caused by toxigenic C. ulcerans have been reported in humans. Human to human transmission has not been reported, but this is an area in which there is limited information.

Recommendation: management of toxigenic C. ulcerans infections
Ask about consumption of raw milk. If it seems that a case may be connected with an animal source seek advice from the senior veterinary investigation officer at the local Veterinary Investigation Centre (P Gayford, personal communication).

It is prudent to advise the same management for close contacts of toxigenic C. ulcerans as recommended for people exposed to cases of diphtheria caused by C. diphtheriae. The additional public health impact of such measures is likely to be minimal.

Management of non-toxigenic C. diphtheriae
Rationale
Non-toxigenic C. diphtheriae has been associated with invasive disease, but it is often impossible to know if it causes illness in cases of pharyngitis or whether it is a mere coloniser. Non-toxigenic C. diphtheriae was identified in swabs from the nasopharynx and from skin lesions in outbreaks among alcoholics in Seattle. The analysis of a carrier survey conducted after a 10 week old child developed membranous tonsillitis in 1977 showed that non-toxigenic C. diphtheriae had converted to a toxigenic strain through lysogenic conversion by corynephage brought into the area by a healthy carrier.

Recommendation: management of non-toxigenic C. diphtheriae
Non-toxigenic C. diphtheriae, whenever identified, should be regarded as a potential pathogen. If the patient has symptoms, start treatment with penicillin or erythromycin for seven days. Investigate for the presence of other pathogenic organisms. There is no need to carry out clearance swabs or to trace contacts of these individuals.

Disseminating information
Rationale
Disseminating information promptly will aid understanding and prevent the spread of anxiety and rumours in the affected community. The provision of information about the symptoms and signs of the disease safeguards contacts who are not among those being monitored closely.

Recommendation: disseminating information
Information about diphtheria should be widely and quickly distributed after a case has occurred. Written information (for example, see appendix 2) should be given to household or other contacts whether or not they are given prophylaxis.

If a case has been identified in a nursery, playgroup, or school the CCDC or other public health professional should liaise closely with the manager or headteacher to inform parents that:

- a case has occurred
- the chance of another case is very small
- close classroom contacts are to have nose and throat swabs taken and to be given antibiotics as a precaution
- the vaccination status of close classroom contacts will be checked and re-vaccination will be offered if necessary

The CCDC may use this opportunity to emphasise the general importance of immunisation in the prevention of disease. General practitioners of the case should be informed. Sometimes the press know of cases before the public health department; have a press statement ready.

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References
**Appendix 1**

Suggested model letter to be given to the general practitioner and contacts of the index case

**Date**

Dear doctor

Re: patient (name)

date of birth

address

This patient has been in close contact with a case or carrier of diphtheria. The last contact was on (date). If he/she becomes unwell during the seven days following this last contact please consider the diagnosis of diphtheria. Typical symptoms include sore throat, fever, swollen neck glands, and a grey membrane on the back of the throat (this may not be present).

If you suspect diphtheria, please do the following:

1. If possible, take a throat swab, informing the laboratory of the contact history.
2. Inform the local consultant in communicable disease control (telephone number)
3. Consider admission of the patient to the local infectious disease unit with a copy of this letter.

Yours sincerely

Dr (name of CCDC)
Consultant in Communicable Disease Control

Copy to patient

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**Appendix 2**

Information sheet for contacts of a case

**What is diphtheria?**

Diphtheria is an uncommon infection which is caused by a bacterium (germ) and may affect the throat or nose, and sometimes the eyes or skin. Some diphtheria germs are more dangerous than others and can cause serious illness.

**Who can get diphtheria?**

Anyone can get diphtheria, but it is less likely to cause a problem if you have been fully vaccinated. Diphtheria is more common in some countries, especially the former Soviet Union, so it is most important to make sure your vaccinations are up to date if you are travelling there.

**How is the germ spread?**

The germ is spread by being in very close contact over a period of time with someone who is known to have the illness or is a carrier of the germ. It is occasionally caused by drinking unpasteurised milk.

**What are the symptoms of diphtheria?**

This depends on where the infection is. The illness may start with a sore throat and fever. There may be a hoarse voice or cough. If the skin is affected there may be an ulcer that does not heal. The illness may be more serious in infants and young children. If you suspect you or a member of your family has diphtheria it is important to seek medical advice immediately.

**How long is a person infectious?**

A person is no longer infectious after they have received a full course of treatment, which is usually given in hospital.

**How long does it take for the illness to develop?**

The illness may develop up to seven days after contact with the germ.

**Should I receive preventive treatment?**

You should receive preventive treatment if you are a close contact of the person who has diphtheria. A close contact is typically someone who has slept in the same household or has had sexual contact with the affected person in the previous week. School classroom contacts and those who share the same the room at work are not normally considered to be close contacts. A doctor or nurse will take a swab test from your nose and throat and you will be given a prescription for a course of antibiotics. It is important to finish the whole course of treatment. You will also receive a booster vaccination if required.