Children aged ten years or over, and adults

The primary course of diphtheria vaccination consists of three doses of a d-containing product with an interval of one month between each dose. Td/IPV is recommended for all individuals aged ten years or over. If the primary course is interrupted it should be resumed but not repeated, allowing an interval of one month between the remaining doses.

Reinforcing immunisation

Children under ten years should receive the first diphtheria booster combined with tetanus, pertussis and polio vaccines. The first booster of a diphtheria-containing vaccine should ideally be given three years after completion of the primary course, normally when the child is between three-and-a-half and five years of age. When primary vaccination has been delayed, this first booster dose may be given at the scheduled visit – provided it is one year since the third primary dose. This will re-establish the child on the routine schedule. DTaP/IPV or dTaP/IPV should be used in this age group. Td/IPV should not be used routinely for this purpose in this age group because it does not contain pertussis and has not been shown to give an equivalent diphtheria antitoxin response compared with other recommended preparations.

Individuals aged ten years or over who have only had three doses of a diphtheria-containing vaccine should receive the first diphtheria booster combined with tetanus and polio vaccines (Td/IPV).

The second booster dose of Td/IPV should ideally be given to all individuals ten years after the first booster dose. Where the previous doses have been delayed, the second booster should be given at the school session or scheduled appointment – provided a minimum of five years have elapsed between the first and second boosters. This will be the last scheduled opportunity to ensure long-term protection.

If a person attends for a routine booster dose and has a history of receiving a vaccine following a tetanus-prone wound, attempts should be made to identify which vaccine was given. If the vaccine given at the time of the injury was the same as that due at the current visit and given after an appropriate interval, then the routine booster dose is not required. Otherwise, the dose given at the time of injury should be discounted as it may not provide long-term protection against all antigens, and the scheduled immunisation should be given. Such additional doses are unlikely to produce an unacceptable rate of reactions (Ramsay *et al.*, 1997).

Vaccination of children with unknown or incomplete immunisation status

Where a child born in the UK presents with an inadequate immunisation history, every effort should be made to clarify what immunisations they may have had (see Chapter 11). A child who has not completed the primary course should have the outstanding doses at monthly intervals. Children may receive the first booster dose as early as one year after the third primary dose to re-establish them on the routine schedule. The second booster should be given at the time of school leaving to ensure long-term protection at this time. Wherever possible, a minimum of five years should be left between the first and second boosters.

Children coming to the UK who have a history of completing immunisation in their country of origin may not have been offered protection against all the antigens currently used in the UK. They will probably have received diphtheria-containing vaccines in their country of origin. For country-specific information, please refer to www.who.int/immunization_monitoring/en/globalsummary/countryprofileselect.cfm.

Children coming from developing countries, from areas of conflict, or from hard-to-reach population groups may not have been fully immunised. Where there is no reliable history of previous immunisation, it should be assumed that they are unimmunised and the full UK recommendations should be followed (see Chapter 11 on vaccine schedules).

Children coming to the UK may have had a fourth dose of a diphtheria-containing vaccine that is given at around 18 months in some countries. This dose should be discounted as it may not provide satisfactory protection until the time of the teenage booster. The routine pre-school and subsequent boosters should be given according to the UK schedule.

Travellers and those going to live abroad

All travellers to epidemic or endemic areas should ensure that they are fully immunised according to the UK schedule. Additional doses of vaccines may be required according to the destination and the nature of travel intended, for example for those who are going to live or work with local people in epidemic or endemic areas (Department of Health, 2001). Where tetanus, diphtheria or polio protection is required and the final dose of the relevant antigen was received more than ten years ago, Td/IPV should be given.

Diphtheria vaccination in laboratory and healthcare workers

Individuals who may be exposed to diphtheria in the course of their work, in microbiology laboratories and clinical infectious disease units, are at risk and must be protected (see Chapter 12).

Contraindications

There are very few individuals who cannot receive diphtheria-containing vaccines. When there is doubt, appropriate advice should be sought from a consultant paediatrician, immunisation co-ordinator or consultant in communicable disease control, rather than withholding the vaccine.

The vaccine should not be given to those who have had:

- a confirmed anaphylactic reaction to a previous dose of a diphtheria-containing vaccine, or
- a confirmed anaphylactic reaction to any of the components of the vaccine.

Confirmed anaphylaxis occurs extremely rarely. Data from the UK, Canada and the US point to rates of 0.65 to 3 anaphylaxis events per million doses of vaccine given (Bohlke *et al.*, 2003; Canadian Medical Association, 2002). Other allergic conditions may occur more commonly and are not contraindications to further immunisation. A careful history of the event will often distinguish between anaphylaxis and other events that are either not due to the vaccine or are not life-threatening. In the latter circumstance, it may be possible to continue the immunisation course. Specialist advice must be sought on the vaccines and circumstances in which they could be given. The risk to the individual of not being immunised must be taken into account.

Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation may be postponed until they have fully recovered. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any signs or symptoms to the adverse effects of the vaccine.

Systemic and local reactions following a previous immunisation

This section gives advice on the immunisation of children with a history of a severe or mild systemic or local reaction within 72 hours of a preceding

vaccine. Immunisation with diphtheria-containing vaccine **should** continue following a history of:

- fever, irrespective of its severity
- hypotonic-hyporesponsive episodes (HHEs)
- persistent crying or screaming for more than three hours
- severe local reaction, irrespective of extent.

Children who have had severe reactions as above have continued and completed immunisation with diphtheria-containing vaccines without recurrence (Vermeer-de Bondt *et al.*, 1998; Gold *et al.*, 2000).

In Canada, a severe general or local reaction to DTaP/IPV/Hib is not a contraindication to further doses of the vaccine (Canadian Medical Association, 1998). Adverse events after childhood immunisation are carefully monitored in Canada (Le Saux *et al.*, 2003), and experience there suggests that further doses were not associated with recurrence or worsening of the preceding events (S Halperin and R Pless, pers. comm., 2003).

Pregnancy and breast-feeding

Diphtheria-containing vaccines may be given to pregnant women when the need for protection is required without delay. There is no evidence of risk from vaccinating pregnant women or those who are breast-feeding with inactivated viral or bacterial vaccines or toxoids (Plotkin and Orenstein, 2004).

Premature infants

It is important that premature infants have their immunisations at the appropriate chronological age, according to the schedule. The occurrence of apnoea following vaccination is especially increased in infants who were born very prematurely.

Very premature infants (born ≤ 28 weeks of gestation) who are in hospital should have respiratory monitoring for 48-72 hrs when given their first immunisation, particularly those with a previous history of respiratory immaturity. If the child has apnoea, bradycardia or desaturations after the first immunisation, the second immunisation should also be given in hospital, with respiratory monitoring for 48-72 hrs (Pfister *et al.*, 2004; Ohlsson *et al.*, 2004; Schulzke *et al.*, 2005; Pourcyrous *et al.*, 2007; Klein *et al.*, 2008).

As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Immunosuppression and HIV infection

Individuals with immunosuppression or with HIV infection (regardless of CD4 counts) should be considered for diphtheria-containing vaccines in accordance with the recommendations above. However, these individuals may not develop a full antibody response if they are immunosuppressed, and vaccine protective efficacy has not been studied. Re-immunisation should be considered after treatment is finished and recovery has occurred. Specialist advice may be required.

Further guidance is provided by the Royal College of Paediatrics and Child Health (www.rcpch.ac.uk), the British HIV Association (BHIVA) *Immunisation guidelines for HIV-infected adults* (BHIVA, 2006) and the Children's HIV Association of UK and Ireland (CHIVA) immunisation guidelines (www.bhiva.org/chiva).

Neurological conditions

Pre-existing neurological conditions

The presence of a neurological condition is not a contraindication to immunisation. Where there is evidence of a neurological condition in a child, the advice given in the flow chart in Figure 15.2 should be followed.

If a child has a stable pre-existing neurological abnormality such as spina bifida, congenital abnormality of the brain or perinatal hypoxic-ischaemic encephalopathy, they should be immunised according to the recommended schedule. When there has been a documented history of cerebral damage in the neonatal period, immunisation should be carried out unless there is evidence of an evolving neurological abnormality.

If there is evidence of current neurological deterioration, including poorly controlled epilepsy, immunisation should be deferred and the child should be referred to a child specialist for investigation to see if an underlying cause can be identified. If a cause is not identified, immunisation should be deferred until the condition has stabilised. If a cause is identified, immunisation should proceed as normal.

A family history of seizures is not a contraindication to immunisation. When there is a personal or family history of febrile seizures, there is an increased risk of these occurring after any fever, including that caused by immunisation. Seizures associated with fever are rare in the first six months of life, and most common in the second year of life. After this age the frequency falls, and they are rare after five years of age.

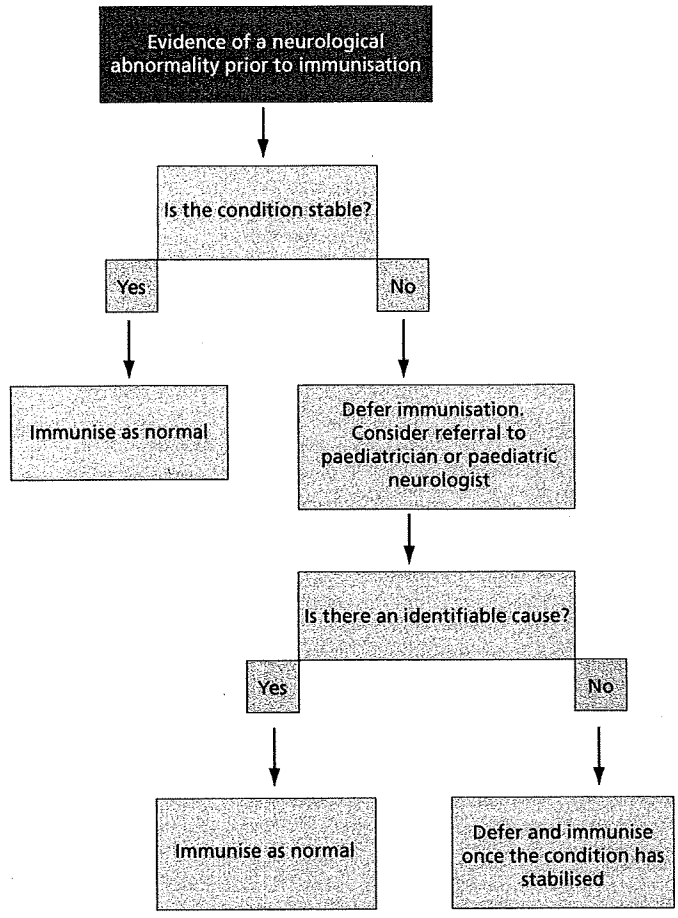

Figure 15.2 Flow chart for immunisation procedure if there is evidence of a neurological condition before immunisation

When a child has had a seizure associated with fever in the past, with no evidence of neurological deterioration, immunisation should proceed as recommended. Advice on the prevention and management of fever should be given before immunisation.

When a child has had a seizure that is not associated with fever, and there is no evidence of neurological deterioration, immunisation should proceed as recommended. When immunised with DTP vaccine, children with a family or personal history of seizures had no significant adverse events and their developmental progress was normal (Ramsay *et al.*, 1994).

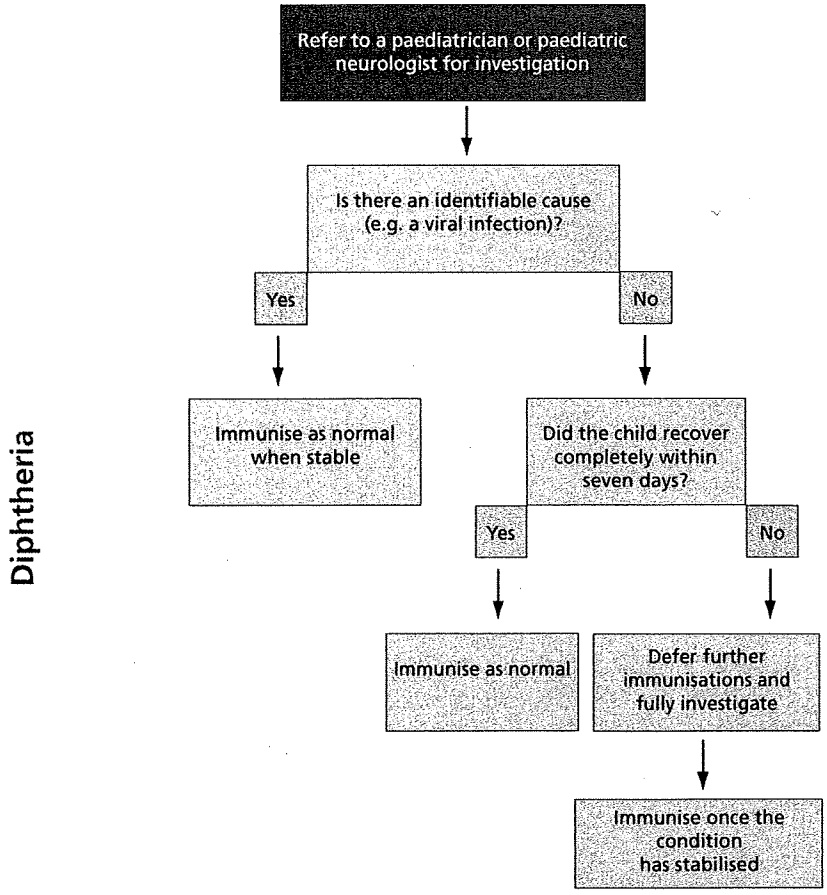

Figure 15.3 Flow chart for encephalitis or encephalopathy occurring within seven days of immunisation

Neurological abnormalities following immunisation

If a child experiences encephalopathy or encephalitis within seven days of immunisation, the advice in the flow chart in Figure 15.3 should be followed. It is unlikely that these conditions will have been caused by the vaccine, and they should be investigated by a specialist. Immunisation should be deferred until the condition has stabilised in children where no underlying cause was found, **and** the child did not recover completely within seven days. If a cause is identified or the child recovers within seven days, immunisation should proceed as recommended.

If a seizure associated with a fever occurs within 72 hours of an immunisation, further immunisation should be deferred if no underlying cause has been found **and** the child did not recover completely within 24 hours, until the condition is stable. If a cause is identified or the child recovers within 24 hours, immunisation should continue as recommended.

Deferral of immunisation

There will be very few occasions when deferral of immunisation is required (see above). Deferral leaves the child unprotected; the period of deferral should be minimised so that immunisation can commence as soon as possible. If a specialist recommends deferral, this should be clearly communicated to the general practitioner and he or she must be informed as soon as the child is fit for immunisation.

Adverse reactions

Pain, swelling or redness at the injection site are common and may occur more frequently following subsequent doses. A small, painless nodule may form at the injection site; this usually disappears and is of no consequence. The incidence of local reactions is lower with diphtheria vaccines combined with acellular pertussis vaccines than with whole-cell pertussis vaccines, and similar to that after DT vaccine (Miller, 1999; Tozzi and Olin, 1997).

Fever, convulsions, high-pitched screaming, and episodes of pallor, cyanosis and limpness (HHE) occur rarely but with equal frequency after both DTaP and DT vaccines (Tozzi and Olin, 1997).

Confirmed anaphylaxis occurs extremely rarely. Data from the UK, Canada and the US point to rates of 0.65 to 3 anaphylaxis events per million doses of vaccine given (Bohlke *et al.*, 2003; Canadian Medical Association, 2002). Other allergic conditions may occur more commonly and are not contraindications to further immunisation.

All suspected adverse reactions to vaccines occurring in children, or in individuals of any age after vaccines labelled with a black triangle (▼), should be reported to the Commission on Human Medicines using the Yellow Card scheme. Serious suspected adverse reactions to vaccines in adults should also be reported through the Yellow Card scheme.

Management of cases, contacts, carriers and outbreaks

As diphtheria is a notifiable disease in the UK, for public health management of cases, contacts and outbreaks, all suspected cases should be notified to the local health protection unit immediately.

Management of cases

Diphtheria antitoxin is only used in suspected cases of diphtheria in a hospital setting. Tests to exclude hypersensitivity to horse serum should be carried out. Diphtheria antitoxin should be given without waiting for bacteriological confirmation. It should be given according to the manufacturer's instructions, the dosage depending on the clinical condition of the patient.

Diphtheria antitoxin is based on horse serum and therefore severe, immediate anaphylaxis occurs more commonly than with human immunoglobulin products. If anaphylaxis occurs, adrenaline (0.5ml or 1ml aliquots) should be administered immediately by either intramuscular (0.5ml of 1:1000 solution) or intravenous (1ml of 1:10,000 solution) injection. This advice differs from that for treatment of anaphylaxis after immunisation because the antitoxin is being administered in the hospital setting.

In most cutaneous infections, large-scale toxin absorption is unlikely and therefore the risk of giving antitoxin is usually considered substantially greater than any benefit. Nevertheless, if the ulcer in cutaneous diphtheria infection were sufficiently large (i.e. more than $2cm^2$) and especially if it were membranous, then larger doses of antitoxin would be justified.

Antibiotic treatment is needed to eliminate the organism and to prevent spread. The antibiotics of choice are erythromycin, azithromycin, clarithromycin or penicillin (Bonnet and Begg, 1999).

The immunisation history of cases of toxigenic diphtheria should be established. Partially or unimmunised individuals should complete immunisation according to the UK schedule. Completely immunised individuals should receive a single reinforcing dose of a diphtheria-containing vaccine according to their age.

Management of contacts

Contacts of a case or carrier of toxigenic diphtheria should be promptly investigated, kept under surveillance and given antibiotic prophylaxis and vaccine. The immunisation history of all individuals exposed to toxigenic diphtheria should be established. Partially immunised or unimmunised individuals should complete immunisation according to the UK schedule (see above). Completely immunised individuals should receive a single reinforcing dose of a diphtheria-containing vaccine according to their age.

Contacts of a case or carrier of toxigenic diphtheria should be given a prophylactic course of erythromycin or penicillin. Contacts of cases of toxigenic *C. ulcerans* do require prophylaxis as, although it is rare, person-to-person transmission cannot be ruled out (Bonnet and Begg, 1999).

Supplies

Vaccines

- Pediacel (diphtheria/tetanus/5-component acellular pertussis/inactivated polio vaccine/*Haemophilus influenzae* type b (DTaP/IPV/Hib) – manufactured by Sanofi Pasteur MSD.
- Repevax (diphtheria/tetanus/5-component acellular pertussis/inactivated polio vaccine (dTaP/IPV)) – manufactured by Sanofi Pasteur MSD.
- Infanrix IPV (diphtheria/tetanus/3-component acellular pertussis/ inactivated polio vaccine (DTaP/IPV)) – manufactured by GlaxoSmithKline.
- Revaxis (tetanus/diphtheria/inactivated polio vaccine (Td/IPV)) – manufactured by Sanofi Pasteur MSD.

These vaccines are supplied by Healthcare Logistics (Tel: 0870 871 1890) as part of the national childhood immunisation programme.

In Scotland, supplies should be obtained from local childhood vaccine holding centres. Details of these are available from Scottish Healthcare Supplies (Tel: 0141 282 2240).

Diphtheria antitoxin is supplied by the Butantan Institute, in 10ml vials containing 10,000IU. It is distributed in the UK by the Health Protection Agency, Centre for Infections, Immunisation Department (Tel: 020 8200 6868).

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Control of diphtheria: guidance for consultants in communicable disease control

JM Bonnet, NT Begg

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.*

Key words:
communicable disease control
diphtheria
guidelines

Commun Dis Public Health 1999; 2: 242-9.

Introduction

Current guidelines for the management of diphtheria in Europe were prepared by the World Health Organization (WHO) European Region in response to the re-emergence of diphtheria in the former Soviet Union[1]. A recent incident in London, in which a laboratory diagnosed a case of diphtheria in error and caused a false alarm[2], led us to review the guidelines and revise them to apply more specifically to circumstances in England and Wales.

The aim of these guidelines is to present the rationale and recommendations for control of diphtheria in England and Wales. They cover four main topics:

- What immediate steps should be taken following identification of a case
- What is required to confirm the diagnosis
- What steps should be taken to minimise the likelihood of further linked cases
- What should be done to disseminate information after a case is identified

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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[3]. 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[4]. Four biotypes of *C. diphtheriae* can be distinguished on biochemical testing: *gravis, intermedius, mitis,* and *belfanti*[5]. 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[6]. Not all laboratories routinely culture throat swabs for *C. diphtheriae*, further increasing the potential for missed or delayed diagnosis[7].

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[8]. 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[9].

Transmission and carriage of diphtheria

The incubation period for diphtheria is usually two to five days, but may be longer[10]. 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[11]. 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[5]. Two cases of cutaneous diphtheria were reported in Bristol within seven weeks in 1992; both cases had recently returned from abroad[12].

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[10].

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[19]. 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*[23]; 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 carriage[24].

Four reports[26-29] 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 lesions[30]. *C. ulcerans* is known to be able to produce diphtheria toxin. It has been associated with classical diphtheria[31,32] as well as with milder symptoms[33-37]. At least one death has been attributed to such infection[38].

C. ulcerans may infect the bovine udder and an association between human *C. ulcerans* infection and drinking raw milk has been observed[33,34]. 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 documented[32], and swabs from close contacts have been negative[32,33,35], 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 transmission[40].

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 commensals[37].

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 findings[41]. 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 strain[12]. (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 journal[42]. 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 way[43].

TABLE Dosage of antitoxin recommended for various types of diphtheria[44]

Type of diphtheria	Dosage (units)	Route
Nasal	10 000 - 20 000	Intramuscular (IM)
Tonsillar	15 000 - 25 000	IM or intravenous (IV)
Pharyngeal or laryngeal	20 000 - 40 000	IM/IV
Combined types or delayed diagnosis	40 000 - 60 000	IV
Severe diphtheria – for example, with extensive membrane and/or severe oedema (bull-neck diphtheria)	40 000 - 100 000	IV or part IV and part IM

Rapid methods such as polymerase chain reaction (PCR) have improved the identification of diphtheria toxin[42]. In the absence of typical symptoms or history of exposure to a case (for example, travel to an endemic region or a laboratory worker exposed to the organism) it is appropriate to withhold control measures while toxigenicity testing is undertaken[15].

Management of the index case

The patient 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, have failed to show diphtheria bacilli[10]. Treatment of cutaneous diphtheria includes thorough cleansing of the lesion with soap and water. Follow up cultures should be taken at least two weeks after completion of treatment[20].

Specific treatment will normally be provided under the direction of a consultant in infectious disease. Depending on the clinical condition of the patient, diphtheria antitoxin may be given intramuscularly or intravenously without waiting for bacteriological confirmation. Take a serum specimen for antitoxin testing before giving antitoxin. The dose of antitoxin depends on the site, the degree of toxicity, and the duration of the illness (table 1). Antitoxin is derived from horse serum, therefore tests with a trial dose to exclude hypersensitivity should precede its use. Patients must be asked about known allergy first and tested with a drop of 1: 10 dilution of diphtheria antitoxin instilled onto the conjunctiva or 0.02mL of 1:10 - 1: 100 dilution injected intradermally (enough to raise a small intradermal wheal), with adrenaline available for immediate administration[3]. Antitoxin is probably of no value for cutaneous disease, although some authorities advise giving 20000 to 40000 units because toxic sequelae have been reported[20]. If acute anaphylaxis develops, give adrenaline quickly.

Diphtheria antitoxin is supplied in vials containing 1000 IU per mL. Manufactured by Pasteur Merieux MSD Ltd and distributed in the United Kingdom by CDSC (tel 0208 200 6868). In Northern Ireland the source of diphtheria antitoxin is the Public Health Laboratory, Belfast City Hospital, Lisburn Road, Belfast (tel 01232 329241).

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*[45]. 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[1]:

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[44]. (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[46] 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[1,8]. An alternative recommended approach (self-surveillance)[15] 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[10].

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[10].

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[47]. 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[38].

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*[38]. 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[48]. 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[49].

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.

Acknowledgements

We thank the following for their helpful comments: Androulla Efstratiou, Robert George, Mary Ramsay, the Public Health Medicine Environmental Group, the PHLS Standing Scientific Committee on Vaccination and Immunisation, PHLS Standing Scientific Committee on Systemic Infections, and regional epidemiologists.

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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

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.