CURRENT TOPIC

Diphtheria: are we ready for it?

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Pharyngeal or cutaneous diphtheria is caused by toxigenic strains of *Corynebacterium diphtheriae* and occasionally by *Corynebacterium ulcerans*. Both organisms are capable of producing an exotoxin that causes local tissue necrosis, and when absorbed into the bloodstream causes toxæmia and systemic complications that include demyelinating peripheral neuritis with associated paralysis and myocarditis with cardiac failure.¹ Non-toxigenic strains cause a mild disease that resembles localised disease caused by toxigenic strains.

Before the introduction of mass immunisation programmes in the 1940s and 50s, the infection was endemic in most countries, with a seasonal increase in the colder months in temperate regions and periodic epidemics. The highest incidence of diphtheria was in preschool children, although the disease was uncommon in the first year of life.

Diphtheria still remains endemic in many developing countries. Case fatality rates have remained between 5 and 10% in most countries despite reductions in disease incidence and availability of antitoxin treatment.² In the former Soviet Union, diphtheria has re-emerged in recent years and has now reached epidemic proportions; 15 211 cases were reported in 1993 (fig 1).³ The outbreak in the former USSR has spread to visitors from neighbouring countries and from western Europe, including Bulgaria, Poland, Finland, Norway, Estonia, Latvia, Lithuania, and Germany.⁴ There appear to be three main factors contributing to the epidemic: inadequate vaccine coverage in young children, waning vaccine induced immunity in adults, and mass population movements.

Transmission

Man is the only reservoir of infection. The commonest mode of transmission is through infected droplets or contact with an infected person. Diphtheria bacilli have also been isolated from the floor dust in hospital wards and articles of clothing have been shown to play a part in its transmission.⁵ Raw milk and milk products have also served as a vehicle, especially for infections caused by *C. ulcerans*.⁶

The importance of closeness and duration of contact in determining the spread of the disease was first described by Dudley in 1923. Children sleeping in the same school dormitory were at greater risk than those in casual contact during working hours.⁷

In tropical countries, the principal source of infection is from cutaneous diphtheria lesions. Cutaneous diphtheria often causes no toxicity but produces natural immunity.⁸ In a study from India, 15% of 1100 skin lesions swabbed were positive for *C. diphtheriae*.⁹ It has also been suggested that cutaneous diphtheria may be an important reservoir of infection in epidemics of faucial diphtheria among non-immune populations.¹ In one outbreak, cases of cutaneous diphtheria were shown to be more infective and responsible for more environmental spread than pharyngeal cases.¹⁰ There is also evidence that toxigenic *C. diphtheriae* can be recovered from skin lesions for up to three years, despite repeated antibiotic treatment.¹

Communicability normally lasts for two weeks in the absence of antibiotics, but may last for as long as four weeks. Antibiotic treatment

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Figure 1 Reported cases of diphtheria in the WHO European Region, Russia, and the Ukraine 1980-93.

Figure 2 Diphtheria notifications and deaths in England and Wales 1914-93 (source: Office of Population Censuses and Surveys); *provisional.

usually stops bacterial shedding within 48 hours.

Diphtheria in England and Wales

Diphtheria was made a notifiable disease in 1889. Notifications since 1914 are shown in fig 2. In that year, there were 59 324 cases and 5863 deaths due to diphtheria in England and Wales.¹¹ Diphtheria was then a leading cause of death among children in the 4 to 10 year age group. Mass immunisation was introduced in 1942, and by 1957 there were only 37 cases and four deaths. Between 1970 and 1987, 92 cases were notified, of which 21 (23%) were acquired overseas or from contact with a case who had acquired the infection overseas. During the same period 247 isolates of toxigenic *C diphtheriae* were reported, of which 50 (20%) were associated with overseas travel. Most of the importations were from the Indian subcontinent particularly from Bangladesh, but importations were reported from Africa, South East Asia, the Caribbean, Europe, and Australia.¹²

In a review of 215 confirmed corynebacterium isolates received by the Diphtheria Reference Unit at the Central Public Health Laboratory, Colindale between 1986 and 1993, 164 (76%) were non-toxigenic *C diphtheriae*, 33 (15%) were toxigenic *C diphtheriae*, 13 (6%) were toxigenic *C ulcerans*, and five (2%) were non-toxigenic *C ulcerans*. One hundred and seventy nine isolates (83%) were from clinical cases, 23 (11%) from contacts of cases and 13 (6%) were asymptomatic carriers (table 1). Since 1990, the proportion of non-toxigenic *C diphtheriae* isolates has increased, due primarily to an increase in the biotype *C diphtheriae var gravis* which causes a less severe form of the disease. Between 1990 and 1993 approximately 65% of all isolates were this biotype compared with the 20% in the previous four years. The toxigenic *C diphtheriae* strains were predominantly of the biotype *var mitis*.¹³

Recent outbreaks in England and Wales

Only eight incidents where transmission has occurred in England and Wales have been documented since 1967. In 1967, pharyngeal diphtheria caused by a toxigenic strain occurred in Manchester in the father of a family from Pakistan. Three children in the family who had recently arrived from Pakistan also had the same strain in their throats and one child had an infected foot ulcer.¹⁴

In 1969, after the return of an adult member of a family from Sardinia with a sore throat,

pharyngeal diphtheria developed in three children in the family in Manchester. Nine other carriers were discovered among related families and school contacts.¹⁴

In 1971, an outbreak of diphtheria occurred in an adult and eight children in Manchester and has to be considered as indigenous as no overseas source of infection could be identified. Among 3000 contacts screened, 28 carriers with toxigenic strains and 19 with non-toxigenic strains were identified.¹⁴

In 1975, five children in a family in London developed pharyngeal diphtheria due to *C diphtheriae var gravis*. None of them had a definite history of immunisation against diphtheria. Two of their earlier neighbours who had arrived from Bangladesh in the previous six weeks were subsequently identified as pharyngeal carriers. The phage type of their isolates was indistinguishable from that of the five cases. The five cases in turn were suspected to have transmitted the infection to two other immunised children in a crowded hostel for the homeless.¹⁵

In 1982, an indirect link was postulated between an English girl in Winchester and a Bangladeshi girl in Westminster, both of whom had pharyngeal diphtheria, were unimmunised, and had an identical strain. Contacts and asymptomatic carriers were identified for both children, one of whom may have acquired the infection from an unidentified source, believed to have originated in the Indian subcontinent.¹⁶

In 1985, a 6 year old unimmunised boy with no history of overseas travel was diagnosed to have pharyngeal diphtheria in Manchester. After investigations, a 5 year old fully immunised classmate, who had returned from Bangladesh three weeks earlier, was identified with cutaneous diphtheria and swabbing identified a total of 16 pharyngeal carriers among school and home contacts. Some of these contacts were in other classes and schools. The failure of herd immunity to prevent transmission of the infection among the unimmunised in this community was demonstrated.¹⁷

Four clinical cases and one carrier were identified in St Albans in 1986, in an unimmunised family of eight members, two weeks after they arrived from Bangladesh. Among 245 primary contacts of the index case swabbed, only four siblings of the index case were positive (Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre, unpublished data).

In 1993, two fully immunised white teenagers with no history of overseas travel were reported in London. Both had toxigenic strains of *C diphtheriae*, one was *var gravis* and the other *var mitis*.¹⁸

In summary, imported cases have resulted in limited secondary spread of the infection. The presence of asymptomatic carriers of both toxigenic and non-toxigenic strains among immunised and unimmunised contacts of the cases, however, demonstrates the potential for wider spread of the infection.

Table 1 Isolates of Corynebacterium sp, England and Wales, 1986–93; figures are number (%)

Classification	C diphtheriae		C ulcerans		Total
	Toxigenic	Non-toxigenic	Toxigenic	Non-toxigenic	
Clinical case	14 (42.4)	147 (89.6)	13 (100)	5 (100)	179 (83.3)
Contact of case	11 (33.3)	12 (7.3)	0	0	23 (10.7)
Carriers	8 (24.2)	5 (3.0)	0	0	13 (6.0)
Total	33 (100)	164 (100)	13 (100)	5 (100)	215 (100)

Table 2 Susceptibility to diphtheria in the UK population

Reference	Population studied	Location and year	No tested	Type of test	Age group (years)	% Susceptible
Working Group ²⁰	Children and adults*	London, Reading, Oxford mid-1970s	771	Schick test or antitoxin assay	>34 <35	44 26
Masterson <i>et al</i> ²¹	RAF recruits†	UK 1983	775	Indirect haemagglutination	16–20	63
Miller and Rush ¹⁹	Diagnostic sample residues‡	UK 1991	2862	ELISA	15–34 35–54 >54	26 32 43
Maple <i>et al</i> ²²	Blood donors	London 1993	267	Toxin neutralisation on vero cells	20–59	42

*Groups tested included staff from two hospitals, school children, police, and factory workers.

†All RAF recruits joining new between September and November 1983.

‡From six public health laboratories.

Immunity to diphtheria in the UK

The potential for the spread of diphtheria is related to the proportion of the population that is susceptible. It is generally considered that if 70–75% of the population have protective antibody levels, herd immunity will prevent spread of the disease.¹⁹

Vaccination coverage in UK children is close to 95% and therefore not many susceptibles would be expected in the younger age groups. In the adult population, however, many may not have received primary immunisation and among those who did, immunity may have waned over the years.

Four studies published between the mid-1970s and early 1990s showed that susceptibility to diphtheria ranged from 26% to 63% (table 2).^{19–22} The age groups tested were mostly young adults and older persons and the test methodology varied. The largest group studied used 2862 blood diagnostic and screening sample residues in six public health laboratories and represented persons aged 15 years or more, resident in eight regions in the country. A third in age groups 15 years and more had antibody concentrations below 0.1 IU/ml, the level required for individual protection, and susceptibility increased with age (table 2).¹⁹

Are current control and containment measures adequate?

Routine immunisation with diphtheria toxoid was introduced in the UK in 1942. Five doses are currently recommended: a primary series of three doses at 2, 3, and 4 months of age, a booster dose at school entry or three years after primary immunisation, and since 1994 a booster dose at 15–19 years.²³ Coverage levels exceed 90% in all NHS regions; however, in some inner city districts coverage is 85% or less.

Diphtheria immunisation does not always prevent asymptomatic carriage of the organism. Among the 33 patients from whom toxigenic *C diphtheriae* was isolated in England and Wales between 1986 and 1993, 13 children had received full primary immunisation, of whom eight had also received a preschool booster. Of the 13 who had received full primary immunisation, eight were asymptomatic carriers or contacts of cases.¹³ Despite good vaccination coverage, up to a third of the adult population has been shown to be susceptible; and indigenous transmission

incidents, although rare, do occur from time to time.

Early detection and containment are needed to prevent the spread of infection from imported cases. Diphtheria is a notifiable disease. All suspected cases should be notified immediately to the local consultant in communicable disease control (CCDC). In England and Wales, the PHLS Communicable Disease Surveillance Centre and in Scotland, the Scottish Centre for Infection and Environmental Health provides advice to CCDCs on the management of incidents, and undertakes national surveillance of diphtheria. When a case of diphtheria is identified, it is the task of the CCDC to initiate control measures. These include isolation and treatment of the index case, tracing and swabbing close contacts, and providing prophylactic antibiotics and immunisation for those contacts judged to be at risk. All laboratory isolates should be submitted for toxigenicity testing and strain confirmation to the PHLS Diphtheria Reference Unit at the Central Public Health Laboratory in Colindale. Because diphtheria is now rare, the diagnosis is likely to be missed, particularly in vaccinated individuals among whom symptoms may be mild. In addition, many laboratories do not routinely culture throat swabs for *C diphtheriae*, thereby increasing the potential for missed or delayed diagnosis. Delay in starting treatment could prove fatal for the case, and for the community it may result in wider spread of the agent. The timeliness of response to a suspected case is hence of paramount importance.

The measures needed for management of cases and close contacts of diphtheria are summarised in fig 3.

Conclusions

Diphtheria is still a common illness in many parts of the world and is increasing in some areas, notably eastern Europe. Cases imported into Britain have largely been unimmunised children from the Indian subcontinent, particularly from Bangladesh, where the more infectious cutaneous forms of diphtheria may be more common. Imported cases have developed clinical illness and caused limited spread among close contacts within a few weeks after reaching Britain. As children coming to Britain from developing countries are often inadequately immunised, their immunisation status should be reviewed and

Figure 3
Recommendations for case management and investigation of close contacts in diphtheria (reproduced from Begg³).

completed by the family physician as soon as possible. Booster vaccination (or where relevant a full primary course) for travellers to countries where diphtheria is endemic would provide individual protection and reduce the risk of importation of cases into Britain. Currently, gaps in immunity exists especially among the older age groups, with a third or more of the population aged 35 or more years susceptible to the infection. In spite of this, imported cases have not been responsible for any major outbreaks. However, such a potential does exist, for which surveillance and control measures are in place through a

network of communicable diseases specialists and public health laboratories.

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