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Diphtheria in England and Wales: 2014

Diphtheria is a life-threatening but preventable infection. From January to December 2014 only one toxigenic strain of Corynebacterium ulcerans *was reported in England. (Five non-toxigenic tox gene bearing* C. diphtheriae *strains were reported during the period.) This report updates the previous three-year review of diphtheria cases in England and Wales for 2011-13 [1] and highlights newly published recommendations for public health control and management of of the infection [2]. Data sources for the enhanced surveillance of diphtheria include notifications, reference and NHS laboratory reports, death registrations, and individual case details such as vaccination history, source of infection, and severity of disease obtained from hospital records and general practitioners.*

This 2014 review updates a previous three-year review of diphtheria cases in England and Wales for 2011-2013 [1] and highlights the newly published recommendations for the public health control and management of diphtheria [2]. Data sources for the enhanced surveillance of diphtheria include notifications, reference and NHS laboratory reports, death registrations, and individual case details such as vaccination history, source of infection, and severity of disease obtained from hospital records and general practitioners.

During 2014, one toxigenic strain of corynebacteria, from a cutaneous case of *C. ulcerans*, was identified by the Public Heath England (PHE) Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU), which is the National Reference Laboratory for diphtheria. No toxigenic isolates were identified from Wales.

Fourteen case notifications were received during this period; three were non-toxigenic *tox* gene bearing (NTTB) *C. diphtheriae,* 10 were non-toxigenic *C. diphtheriae* infections, and one was a non-toxigenic *Corynebacterium* spp. infection. In the same period, RVPBRU identified one toxigenic *C. ulcerans* strain and two additional NTTB *C. diphtheriae* strains from samples referred from patients who were not formally notified as suspected diphtheria (table 1).

Table 1. Diphtheria notifications and isolates of toxigenic corynebacteria, England: 2014

Total notifications	**14***
Number due to non-toxigenic *C. diphtheriae*	10
Number due to toxigenic *C. diphtheriae*	0
NTTB *C. diphtheriae*	3
Number due to toxigenic *C. ulcerans*	0
All toxigenic *corynebacteria isolates*	**1**
Toxigenic *C. diphtheriae*	0
NTTB *C. diphtheriae*	5
Toxigenic *C. ulcerans*	1

* *Corynebacterium* spp. isolated from a one sample

C. diphtheriae

No toxigenic *C. diphtheriae* strains were isolated in 2014.

There were five NTTB *C. diphtheriae* var. mitis strains isolated, three were isolated from tissue samples from patients with skin lesions and two were isolated from nasopharyngeal samples from patients with sore throats (table 2). The patients were aged 24 to 41 years, three were female and two were male. Two patients were reported as have complete primary immunisations; one was reported as immunised but a full vaccination history was not available; one was unimmunised; the immunisation history of the fifth was unknown.

None of the patients reported contact with anyone who had symptoms suggestive of respiratory or cutaneous diphtheria or travel to an endemic country. The three patients with skin lesions all had a similar underlying medical condition which increased their susceptibility to bacterial infections. Neither of the patients with mild respiratory symptoms; had any identifiable risk factors.

In total, 34 close contacts of the patients were identified, including household contacts, social contacts, and healthcare workers. Where possible the contacts were offered chemoprophylaxis, vaccination as appropriate, and swabbed. One contact exhibited symptoms consistent with a mild respiratory infection; however, swabs taken from this contact did not yield *C. diphtheriae*. None of the remaining 33 close contacts exhibited cutaneous or respiratory symptoms and no swabs yielded *C. diphtheriae*.

All five patients were treated with antibiotics and offered vaccination as appropriate, none experienced systemic complications, and all recovered from their infection with a corynebacterium strain.

C. ulcerans

One toxigenic *C. ulcerans* strain was isolated from a wound swab (cutaneous diphtheria) in 2014. The patient was an adult male who had an unknown immunisation history who presented with a post-surgical wound which had become infected; earlier samples taken from the wound did not yield *C. ulcerans*. The patient was treated with antibiotics and received a dose of diphtheria containing vaccine; there were no systemic complications and he recovered from his illness.

Risk factors for *C. ulcerans* include contact with companion animals [2-4] and the patient reported contact with a dog but no other risk factors were identified. Pharyngeal swabs taken from the dog tested positive for toxigenic *C. ulcerans*. The animal was treated with antibiotics under veterinary guidance and clearance swabs taken once treatment was complete did not yield *C. ulcerans.* Throat swabs from four close contacts of the patient were all negative for corynebacteria.

Table 2: Clinical presentation of diphtheria cases and causative organism, England 2014

	Causative organism			
Clinical presentation of cases	Toxigenic *C. diphtheriae*	NTTB *C. diphtheriae*	Toxigenic *C. ulcerans*	**Total**
Classic respiratory diphtheria (with pseudomembrane)	0	0	0	**0**
Mild respiratory diphtheria (sore throat/pharyngitis)	0	2	0	**2**
Cutaneous diphtheria	0	3	1	**4**

Since April 2014, a new PCR service has been available at the national reference laboratory at PHE which confirms the identity of *Corynebacterium diphtheriae*, *C. ulcerans* or *C. pseudotuberculosis* and determines whether the gene for the diphtheria toxin (tox) is present. A subsequent Elek test is used to confirm the expression of diphtheria toxin.

Five non-toxigenic tox gene bearing *Corynebacterium diphtheriae* strains were reported during this period.

Microbiological laboratories are encouraged to submit all suspect isolates of *C. diphtheriae* and other potentially toxigenic corynebacteria to PHE RVPBRU using the form R3 [2]. From 1 April 2014, the test result which helps inform public health action is a PCR which confirms the identity *of Corynebacterium diphtheriae*, *C. ulcerans* or *C. pseudotuberculosis* and determines whether the gene for the diphtheria toxin (tox) is present. If the tox gene is detected, the isolate goes on to have an Elek test to detect expression of toxin [2]. RVPBRU also provides advice on all aspects of laboratory diagnostics and testing for diphtheria and related infections. Advice on immunisation against diphtheria, provision of vaccine and provision of diphtheria antitoxin for

therapeutic use is available from the PHE Colindale Immunisation Department and in the recently published revised guidance for public health control and management of diphtheria [2].

Background

Diphtheria became rare in England following the introduction of mass immunisation in 1942, when the average annual number of cases was about 60,000 with 4,000 deaths. Primary vaccine coverage (three doses) in the United Kingdom (UK) for children aged two has been at least 94% since 2001 and is currently 96%, above the World Health Organisation (WHO) target of 95% [3]. Diphtheria vaccine is made from inactivated diphtheria toxin and protects individuals from the effects of toxin-producing corynebacteria. Three *Corynebacterium* spp. can potentially produce toxin; *C. diphtheriae* (associated with epidemic person-to-person spread via respiratory droplets and close contact), *C. ulcerans* and *C. pseudotuberculosis* (both less common globally and traditionally associated with farm animal contact and dairy products) [4,5].

Laboratory confirmation of diphtheria can be made by isolation of *C. diphtheriae, C. ulcerans or C. pseudotuberculosis*or detection of its DNA by, eg, PCR. The determination of toxigenicity requires submission of the isolate to the national reference laboratory, PHE RVPBRU. Identification and the presence of the *tox* gene are tested for by qPCR. If the *tox* gene is detected, the isolate is tested for expression of diphtheria toxin using the Elek test [6]. Non-toxigenic *C. diphtheriae* usually lack the entire *tox* operon, however, a small proportion of non-toxigenic strains carry incomplete *tox* variants,but do not express the diphtheria toxin protein. These strains are designated non-toxigenic toxin gene bearing (NTTB).

Classic respiratory diphtheria is characterised by a swollen ‘bull neck’ and strongly adherent pseudomembrane which obstructs the airways; a milder respiratory form of the disease where patients present with sore throat or pharyngitis is reported in immunised or partially immunised individuals [5]. Cutaneous presentations, characterised by ‘rolled edge’ ulcers, are usually associated with travel to tropical areas of the world. A recent review of diphtheria in the UK between 1986 and 2008 emphasises the changing epidemiology of the disease with the majority of toxigenic isolates in recent years associated more often with *C. ulcerans* than *C. diphtheria* [5].

The normal reservoir of *C. ulcerans* is cattle and human cases traditionally have been associated with the consumption of raw dairy products, however, recent studies have suggested that cats and dogs could also be potential reservoirs for this organism [7,8]. Travel and close contact with cattle, other farm animals and horses are other potential risk factors for infection. Although there is no direct evidence of person-to-person transmission of *C. ulcerans* infection there have been incidents that suggest this mode of transmission is possible. The guidelines for

consultants in communicable disease control (CCDCs) on the control of diphtheria recommend that anyone who has been in close contact in the previous seven days with a case of infection caused by toxigenic *C. diphtheriae* or *C. ulcerans* should be considered at risk [9]. These guidelines have recently been updated; however, the above recommendation remains largely unchanged. Additionally, although NTTB corynebacteria are not known to cause diphtheria it is recommended that they are eliminated using antibiotics in the same way as fully toxigenic (ie Elek-positive, toxin-expressing) strains.

As a disease becomes rare, the completeness and accuracy of surveillance information become more important and each clinical diagnosis (ie notification) needs to be confirmed by laboratory diagnosis. In addition to notifications, enhanced surveillance for diphtheria incorporates data from reference and NHS laboratories, death registration, and individual case details such as vaccination history, source of infection and severity of disease obtained from hospital records, general practitioners and local incident team reports. Linkage of notified cases of diphtheria and confirmatory laboratory data shows that most notifications are cases of pharyngitis associated with isolation of non-toxigenic or non-toxigenic tox gene bearing strains of *C. diphtheriae,* and therefore interpretation of notification data should be undertaken with caution.

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