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## Diphtheria in England and Wales: 2015

*Diphtheria is a life-threatening but preventable infection. From January to December 2015 six toxigenic strains of corynebacteria were reported in England: three* Corynebacterium diphtheriae *and three* C. ulcerans*. Since April 2014, a PCR service has been available at the national reference laboratory at PHE which confirms the identity of* C. 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. One additional non-toxigenic tox gene bearing the* C. diphtheriae *strain was reported during this period*.

This 2015 review updates a previous annual review of diphtheria cases in England and Wales for 2014 [1]. 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 2015, six toxigenic strains of corynebacteria were 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. Diphtheria is a notifiable disease under the Public Health (Control of Disease) Act 1984 (as amended) and accompanying regulations [2]. Nine official case notifications were received from NOIDS during this period; laboratory investigation identified four as non-toxigenic *C. diphtheriae* infections, one was a toxigenic *C. diphtheriae* infection, two were toxigenic *C. ulcerans* infections, and two were not *Corynebacterium* spp. In the same period, RVPBRU identified a further two toxigenic *C. diphtheriae* strains, one toxigenic *C. ulcerans* strain and one additional non-toxigenic *tox* gene bearing (NTTB) *C. diphtheriae* strain 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: 2015**

| **Total notifications** | **9*** |
|---|---|
| Number due to non-toxigenic *C. diphtheriae* | 4 |
| Number due to toxigenic *C. diphtheriae* | 1 |
| NTTB *C. diphtheriae* | 0 |
| Number due to toxigenic *C. ulcerans* | 2 |
| | |
| **All toxigenic *corynebacteria isolates*** | **7** |
| Toxigenic *C. diphtheriae* | 3 |
| NTTB *C. diphtheriae* | 1 |
| Toxigenic *C. ulcerans* | 3 |

* *Corynebacterium* spp. isolated from two samples

### *C. diphtheriae*

Three toxigenic *C. diphtheriae* var. mitis strains were identified in 2015; all were isolated from wound swabs (cutaneous diphtheria). All three patients had recently travelled to a country which was endemic for *C. diphtheriae,* were treated with antibiotics and offered vaccination as appropriate; one also received diphtheria anti-toxiin. None of the patient's experienced systemic complications and all recovered from their infection. Contact tracing identified over 80 close contacts including household contacts, relatives, and health care workers. All were offered chemoprophylaxis and vaccination as appropriate. Throat swabs taken from the close contacts of the patients were all negative for corynebacteria.

An additional NTTB *C. diphtheriae* var. mitis strain was isolated from a tissue sample (cutaneous diphtheria) from a patient with skin lesions due to an underlying medical condition which increased susceptibility to bacterial infections (table 2). The patient was treated with antibiotics and offered vaccination, and recovered without experiencing systemic complications. In total, four close contacts of this patient, including household contacts and healthcare workers, were identified. All were offered chemoprophylaxis, vaccination as appropriate, and were swabbed. None of the close contacts exhibited cutaneous or respiratory symptoms and no swabs yielded *C. diphtheriae*.

### *C. ulcerans*

Three toxigenic *C. ulcerans* strains were isolated in 2015; one from a wound swab (cutaneous diphtheria), swab (cutaneous diphtheria), one a throat swab (mild respiratory diphtheria), and one from pus drained from a lymph node (other presentation). The patients were treated with antibiotics and offered vaccination as appropriate; none experienced systemic complications, and all recovered from their infection.

Contact tracing identified 13 close contacts of the three patients. All of the close contacts were offered chemoprophylaxis, vaccination as appropriate, and were swabbed. None of the close contacts exhibited cutaneous or respiratory symptoms and no swabs yielded *C. ulcerans*.

Risk factors for *C. ulcerans* include contact with companion animals (2-4) and all of the patients reported contact with dogs. Pharyngeal swabs were taken from six dogs belonging to two of the patients; none tested positive for toxigenic *C. ulcerans*. Two of the patients also had underlying conditions which increased their susceptibility to bacterial infections.

**Table 2: Clinical presentation of diphtheria cases and causative organism, England 2015**

| | **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 | 0 | 1 | **1** |
| Cutaneous diphtheria | 3 | 1 | 1 | **5** |
| Other | 0 | 0 | 1 | **1** |

Microbiological laboratories are encouraged to submit all suspect isolates of *C. diphtheriae* and other potentially toxigenic corynebacteria to PHE RVPBRU using the form R3 [3]. From 1 April 2014, the test result which helps inform public health action is a PCR which confirms the identity *of C. 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 [3]. 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 [3].

## 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% [4]. 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) [5,6].

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 [7]. 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 [6]. 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* [6].

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 [8,9]. 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 health protection  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 [10]. These guidelines were updated in 2015; 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 suspected 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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