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Diphtheria in England: 2016

- Diphtheria is a life-threatening, but vaccine-preventable infection;
- From January to December 2016 six toxigenic strains of corynebacteria were reported in England; four *Corynebacterium diphtheriae* and two *C. ulcerans*;
- Since April 2014, a real-time PCR service has been available at the national reference laboratory at PHE which confirms the identity of referred isolates of *C. diphtheriae*, *C. ulcerans* or *C. pseudotuberculosis* and determines whether the gene for the diphtheria toxin (*tox*) is present. Confirmation of toxin expression is determined using the Elek test for all isolates in which the toxin gene is detected.

This 2016 review updates a previous annual review of diphtheria cases in England for 2015 [1]. Reports of diphtheria are based on the date of onset. 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 2016, toxigenic strains of corynebacteria were identified from six persons by the Public Heath England (PHE) Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU), which is the National Reference Laboratory (NRL) for diphtheria, compared to six toxigenic strains in 2015. No non-toxigenic *tox* gene bearing (NTTB) *C. diphtheriae* or *C. ulcerans* strains were identified during this period.

Diphtheria is a notifiable disease in accordance with the amended Public Health (Control of Disease) Act 1984 and accompanying regulations [2]. Nine diphtheria notifications were received from NOIDs during this period; laboratory investigation identified one toxigenic *C. ulcerans* infection, seven non-toxigenic *C. diphtheriae* infections, and one which was not a *Corynebacterium* spp.

In the same period, NRL received a total of 67 isolates for toxigenicity testing and confirmed a further three toxigenic *C. diphtheriae* strains and two toxigenic *C. ulcerans* strain (both from the same patient) from samples referred from patients who were not formally notified as having suspected diphtheria (table 1). An additional toxigenic *C. ulcerans* strain was confirmed from a companion animal epidemiologically linked to a case. Of the remaining strains 53 were non-toxigenic *C. diphtheria* one was non-toxigenic *C. ulcerans,* five were not *C. diphtheria, C. ulcerans, or C. pseudotuberclerosis* and one duplicate isolate was not tested.

Table 1. Diphtheria notifications and total isolates of toxigenic corynebacteria by strain, England: 2016

Total diphtheria notifications	**9***
Number due to toxigenic *C. diphtheriae*	0
Number due to toxigenic *C. ulcerans*	1
Number due to non-toxigenic *C. diphtheriae*	6
All toxigenic *corynebacteria isolates*	**5**
Toxigenic *C. diphtheriae*	4
Toxigenic *C. ulcerans*	2
All isolates referred to NRL for toxigenicity testing	67
Toxigenic *C. diphtheriae*	3†
Non-toxigenic *C. diphtheriae*	53
Toxigenic *C. ulcerans*	4
Non-toxigenic *C. ulcerans*	1
Other – not *C. diphtheria, C. ulcerans, or C. pseudotuberclerosis*	5
Not tested (duplicate isolate received)	1

* *Corynebacterium* spp. not isolated from one samples

† One additional case acquired a toxigenic *C. diphtheriae* strain in 2016, however, the isolate was received in 2017.

C. diphtheriae

Four toxigenic *C. diphtheriae* var mitis strains were identified in 2016; all were isolated from wound swabs (cutaneous diphtheria) from patients who had recently travelled to a country which was endemic for *C. diphtheriae* (Somalia (2), Sri Lanka and Philippines). Three were children (5-6 years) of which only one was age-appropriately vaccinated. The other was a young adult whose vaccination status is not known. All were treated with antibiotics and vaccinated when recovered; none received diphtheria anti-toxin nor experienced systemic complications and all recovered from their infection. Contact tracing identified over 20 asymptomatic close contacts including household contacts (11), relatives (6), and health care workers (13). All were offered chemoprophylaxis, vaccination as appropriate, and had throat swabs taken which were all negative for corynebacteria.

C. ulcerans

Two toxigenic *C. ulcerans* strains were isolated in 2016 from adult females (55+ years); one from a wound swab (cutaneous diphtheria) and from one a throat swab (severe respiratory diphtheria). Both patients were treated with antibiotics and were vaccinated when recovered. The patient with (severe respiratory diphtheria was unvaccinated and also received diphtheria anti-toxin. The patient with cutaneous diphtheria had a history of primary immunisations but had underlying conditions which increased their susceptibility to bacterial infections. Neither case experienced systemic complications and both recovered from their infection.

Contact tracing identified 20 close contacts including household contacts (4), relatives (8), and health care workers (5). All of the close contacts were asymptomatic, offered chemoprophylaxis, vaccination as appropriate, and had throat swabs taken which were negative for *C. ulcerans*.

Risk factors for *C. ulcerans* include consumption of raw milk products and contact with companion animals (2-4) and both patients reported contact with dogs and one contact with cats (no raw milk products). Pharyngeal swabs were taken from two dogs and one cat. The dog which had contact with the respiratory case tested positive for toxigenic *C. ulcerans* and was successfully treated with appropriate chemoprophylaxis.

Table 2: Clinical presentation of diphtheria cases and causative organism, England 2016

	Causative organism			
Clinical presentation of cases	Toxigenic *C. diphtheriae*	Toxigenic *C. ulcerans*	NTTB *C. diphtheriae*	**Total**
Severe respiratory diphtheria (sore throat with exudate)	–	1	–	1
Mild respiratory diphtheria (sore throat/pharyngitis)	–	–	–	0
Cutaneous diphtheria	4	1	–	5

Microbiological laboratories are encouraged to submit all suspect isolates of *C. diphtheriae* and other potentially toxigenic corynebacteria to PHE RVPBRU using the laboratory request form R3 [3]. From 1 April 2014, the test result which helps inform public health action is a real-time PCR result 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 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 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%, the World Health Organisation (WHO) target [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 real-time PCR. If the tox gene is detected, the isolate is tested for expression of diphtheria toxin using the Elek test [7]. Non-toxigenic *C. diphtheriae* and *C. ulcerans* 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. diphtheriae* [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]. 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.

References/notes

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