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Diphtheria in England: 2017

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- Diphtheria is a life-threatening, but vaccine-preventable infection.
- From January to December 2017 five toxigenic strains of corynebacteria were reported in England; four *Corynebacterium diphtheriae* and one *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.

Cases of diphtheria in England in 2017

This 2017 review updates a previous annual review of diphtheria cases in England for 2016 [1]. Reporting years of diphtheria cases are based on the date of onset rather than specimen date. 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 2017, toxigenic strains of corynebacteria were identified from five 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 2016. One non-toxigenic *tox* gene bearing (NTTB) *C. diphtheriae* strains, was also identified during this period. A further toxigenic isolate was identified in 2017 but the date of onset of disease was in 2016.

Diphtheria is a notifiable disease in accordance with the amended Public Health (Control of Disease) Act 1984 and accompanying regulations [2]. Thirteen diphtheria notifications were received from NOIDs during this period**;** laboratory investigation identified all as non-toxigenic *C. diphtheriae* infections. None of the toxigenic cases were formally notified. During 2017, the National Reference Laboratory received a total of 105 isolates for confirmation and toxigenicity testing from 92 individuals, from which five toxigenic *C. diphtheriae* strains, one of which had a date of onset in 2016, and one toxigenic *C. ulcerans* strain from samples referred from patients

in England, none of whom were not formally notified as having suspected diphtheria (Table 1). One non-toxigenic *tox* gene bearing (NTTB) *C. diphtheriae* was also identified. A further toxigenic *C. ulcerans* strain was confirmed from a companion animal epidemiologically linked to a case. Of the remaining isolates, 67 were non-toxigenic *C. diphtheriae,* four were non-toxigenic *C. ulcerans* and 12 were not *C. diphtheriae, C. ulcerans, or C. pseudotuberclerosis.*

Table 1: Summary of (a) Diphtheria notifications, (b) toxigenic corynebacteria by strain and (c) NRL toxigenicity testing, England: 2017

(a) Total diphtheria notifications in 2017	
Number due to toxigenic *C. diphtheriae*	0
Number due to toxigenic *C. ulcerans*	0
Number due to non-toxigenic *C. diphtheriae*	13
(b) All toxigenic *corynebacteria isolates from cases with onset date in 2017*	
Toxigenic *C. diphtheriae*	4
Toxigenic *C. ulcerans*	1
(c) All isolates referred to NRL for toxigenicity testing in 2017 (duplicates from same person excluded)	
Toxigenic *C. diphtheriae**	5
Non-toxigenic non-tox gene bearing (NTTB) *C. diphtheriae*	1
Non-toxigenic *C. diphtheriae*	67
Toxigenic *C. ulcerans***	2
Non-toxigenic *C. ulcerans*	4
Other – not *C. diphtheriae, C. ulcerans, or C. pseudotuberclerosis*	12

*Includes one isolated tested in 2017 from a patient whose date of onset was December 2016
**includes one isolate from a companion animal epidemiologically linked a case

C. diptheriae

Toxigenic *C diphtheriae* strains from four patients were identified in 2017; three cases were female, and the age range was four to 81 years. Two strains (one *var mitis* and one *var gravis*) were identified from wound swabs (cutaneous presentation) after travel to a country which was endemic for *C. diphtheriae* (in both cases to Ghana). Another *var mitis* strain was isolated from a throat swab of a family member of the index case, identified through contact

tracing, who had mild respiratory symptoms but had not travelled herself. This, therefore, represents the first documented case of onward transmission in the UK in three decades. A second *var gravis* strain was isolated from a pseudomembrane of a child with classical respiratory diphtheria. This child had no history of personal travel to an endemic area, or contact with a person known to have travelled, and thus their source of infection remains unknown. This child was incompletely immunised, having received only two vaccinations from their primary course and no boosters. The two cutaneous cases were both fully immunised for age and had received a booster within the last four years, while the elderly symptomatic contact had an unknown vaccination history. All were treated with antibiotics and vaccinated following their illness; the case with classical respiratory diphtheria received diphtheria anti-toxin but experienced severe systemic complications.

Contact tracing for the four cases identified over 86 close contacts including household contacts (13), non-household contacts (24), and health care workers (49). All were offered chemoprophylaxis, vaccination as appropriate, and had throat swabs taken, of which all but one (the documented transmission event) were negative for corynebacteria.

Non-toxigenic toxin gene (NTTB) bearing isolates were identified from skin swabs at different time points (several months apart) from the same patient, who had an underlying genetic condition which increased their susceptibility to skin infections. They had previously had a NTTB infection in 2015 and the case and contacts had received antibiotics and vaccination at that time. Further treatment of the case and contacts was not undertaken in 2017 as there was no evidence of disease, and it was not thought possible to eradicate carriage due to extensive skin damage in this patient.

C. ulcerans

Only one toxigenic *C. ulcerans* was identified in 2017, from a throat swab of a male child over 10 years old with a mild respiratory presentation. He was fully vaccinated for age and was treated with antibiotics and vaccinated when recovered. Risk factors for *C. ulcerans* include consumption of raw milk products and contact with companion animals [3-5] and the patient reported contact with dogs, cats, tortoises and chickens but no raw milk products. Pharyngeal

swabs were taken from four dogs the patient had contact with but none tested positive for toxigenic *C. ulcerans*.

Contact tracing identified four close contacts; three household contacts and healthcare worker. All close contacts were asymptomatic, offered chemoprophylaxis, vaccination as appropriate, and had throat swabs taken which were negative for *C. ulcerans*.

Table 2: Clinical presentation of diphtheria cases and causative organism, England 2017

	Causative organism		
Clinical presentation of cases	Toxigenic *C. diphtheriae*	Toxigenic *C. ulcerans*	**Total**
Severe respiratory diphtheria (sore throat with exudate)	1	0	**1**
Mild respiratory diphtheria (sore throat/pharyngitis)	1	1	**2**
Cutaneous diphtheria	2*	0	**2**

* both also had mild respiratory symptoms

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 [6]. 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 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 [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. diphtheriae* [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 [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 WHO 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 (i.e. Elek-positive, toxin-expressing) strains.

As a disease becomes rare, the completeness and accuracy of surveillance information become more important and each clinical diagnosis (i.e. 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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Health Protection Report is a national public health bulletin for England and Wales, published by Public Health England. It is PHE's principal channel for the dissemination of laboratory data relating to pathogens and infections/communicable diseases of public health significance and of reports on outbreaks, incidents and ongoing investigations.

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