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Diphtheria in England: 2018

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Key points

- diphtheria is a life-threatening, but vaccine-preventable infection
- from January to December 2018 11 toxigenic strains of corynebacteria were reported in England; eight *Corynebacterium diphtheriae* and three *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.

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 [1].

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 and more recently with companion animals) [2]. 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 [3].

There are differing clinical presentations of diphtheria. 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 [2]. Cutaneous presentations, characterised by ‘rolled edge’ ulcers, are also common, particularly in tropical regions [3]. Treatment involves diphtheria anti-toxin (DAT) for severe cases and clearance with antibiotics. Public health management of clinical cases of diphtheria in the UK is provided by health protection teams, including identification, assessment and prophylaxis of close contacts [3].

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 in England requires submission of the isolate to Public Heath England (PHE) Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU), which is the National Reference Laboratory (NRL) for diphtheria. 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 [4].

Cases of diphtheria in England in 2018

This 2018 review updates a previous annual review of diphtheria cases in England for 2017 [5]. 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 2018, toxigenic strains of corynebacteria were identified from eleven persons by the RVPBRU. This compares with five toxigenic strains in 2017 and six toxigenic strains in 2016. Two non-toxigenic *tox* gene bearing (NTTB) *C. diphtheriae* strains, were also identified during this period. A further person was diagnosed with and treated for respiratory diphtheria on clinical suspicion, but no causative organisms were isolated.

Diphtheria is a notifiable disease in accordance with the amended Public Health (Control of Disease) Act 1984 and accompanying regulations [6]. Twenty-one diphtheria notifications were received from NOIDs in 2018 for England**;** laboratory investigation identified two as toxigenic *C. diphtheriae* infections, one as a NTTB infection and the remaining 18 as non-toxigenic *C. diphtheriae* infections. Eight of the toxigenic cases were not formally notified. During 2018, the National Reference Laboratory received a total of 123 isolates for confirmation and toxigenicity testing from 110 individuals (108 human and 2 companion animals) from England in comparison to 105 isolates from 92 individuals in 2017. Isolates from eight individuals were identified as toxigenic *C. diphtheriae* strains and from three individuals as toxigenic *C. ulcerans*, only two of which were formally notified as having suspected diphtheria (Table 1). One non-toxigenic *tox* gene bearing (NTTB) *C. diphtheriae* was also notified. Two further toxigenic *C. ulcerans* strains were confirmed from companion animals which were not epidemiologically linked to a human case. Of the remaining isolates, 85 were non-toxigenic *C. diphtheriae,* two

were non-toxigenic *C. ulcerans* and 12 were not *C. diphtheriae, C. ulcerans, or C. pseudotuberculosis.*

Table 1: Summary of (a) Diphtheria notifications (NOIDs) (b) toxigenic corynebacteria by strain and (c) NRL toxigenicity testing, England: 2018

(a) Total diphtheria notifications in 2018	
Number due to toxigenic *C. diphtheriae*	2
Number due to toxigenic *C. ulcerans*	0
Number due to non-toxigenic toxin gene bearing (NTTB) *C. diphtheriae*	1
Number due to non-toxigenic *C. diphtheriae*	18
(b) All toxigenic *corynebacteria isolates from human cases in 2018*	
Toxigenic *C. diphtheriae*	8
Toxigenic *C. ulcerans*	3
NTTB *C. diphtheriae*	2
(c) All isolates referred to NRL for toxigenicity testing in 2018 (duplicates from same person excluded)	
Toxigenic *C. diphtheriae*	8
Non-toxigenic non-tox gene bearing (NTTB) *C. diphtheriae*	2
Non-toxigenic *C. diphtheriae*	85
Toxigenic *C. ulcerans**	5
Non-toxigenic *C. ulcerans*	1
Other – not *C. diphtheriae, C. ulcerans, or C. pseudotuberclerosis*	12

*includes two isolates from companion animals not epidemiologically linked a case

Corynebacterium diphtheriae

Toxigenic *C diphtheriae* strains from eight patients were identified in 2018; three cases were female, and the age range was four to 49 years. One mild respiratory case was identified in a child who was fully vaccinated for age and had no history of travel. The case was geographically close to and of identical biotype (var gravis), antibiotic sensitivity and MLST type to a case of severe respiratory diphtheria in 2017. However no direct epidemiological links between the cases were identified despite extensive investigation. In the absence of a source for this case based on screening of close contacts, and the similarity to the previous case, screening was undertaken in the year group at the case's school and a further two asymptomatic carriers were identified in children who were fully vaccinated for age, which were indistinguishable from both case 1 and case 2 based on MLST typing. Neither of these asymptomatic carriers had a history of travel, and thus it is thought that the infections were indigenously acquired and transmitted within the school community. A further suspected clinical case of classical respiratory diphtheria was identified in an unrelated unvaccinated individual within the same geographical area although with no clear epidemiological links to previous confirmed cases. This case was admitted with swollen neck and grey membrane over the tonsils, fever, tachycardia and hypertension and responded rapidly to treatment with diphtheria anti-toxin but had no microbiological evidence to support the diagnosis. This incident represents the largest cluster of toxigenic diphtheria in the UK in recent years, and only the second suspected event of onward transmission in three decades [7].

In addition to the cluster, there were two strains (var mitis) identified from wound swabs (cutaneous presentation) after travel to a country which was endemic for *C. diphtheriae* (Cambodia or Senegal), both in individuals with uncertain vaccination history (one adult and one non-UK born child). A further strain (var mitis) was identified from a wound swab in an individual who had not recently travelled herself, but had been in contact with a family member who had recently returned from Senegal, and had previously reported cutaneous lesions. The contact was not symptomatic at the time of confirmation, and had not been when the lesions were present. The remaining two cases were a family group. The index case was a child who was fully vaccinated for age. He had an ear infection and toxigenic *C. diphtheriae* (var mitis) was isolated from an infected discharge. A positive throat swab was identified in the mother during contact tracing. Her vaccination status was not known. Neither case reported a recent history of personal travel, although the child had reported intermittent ear symptoms since a

visit to Sri Lanka several months previously. These cases further highlight the risk of onward transmission from diphtheria cases and the importance of their public health management.

Two NTTB (non-toxigenic toxin-bearing) strains *(*var mitis*)* were identified in 2018 from individuals with mild respiratory symptoms. Both cases had received at least four doses of diphtheria-containing vaccine and neither had a history of travel to endemic areas. The cases were not epidemiologically linked.

All cases of toxigenic *C. diphtheriae or* NTTB were treated with antibiotics and were advised to have a booster dose of vaccine following their illness. No confirmed cases received anti-toxin or experienced systemic complications. Contact tracing was carried out in total for 419 contacts, including 328 children and teachers as part of the school screening exercise. The remaining 91 identified close contacts included household contacts (45), non-household contacts (19), and healthcare workers (27). All were offered chemoprophylaxis, vaccination as appropriate, and had throat swabs taken, of which all but the three asymptomatic contacts already discussed were negative for corynebacteria.

Corynebacterium ulcerans

Three toxigenic *C. ulcerans* cases were identified in 2018, of which two had a cutaneous presentation and one had a mild respiratory infection. All three were in women over the age of 65 and none had a history of receiving any diphtheria-containing vaccines. One case was hospitalised, and all three were treated with antibiotics and responded to treatment. Risk factors for *C. ulcerans* include consumption of raw milk products and contact with farm and companion animals [3] and all three patients reported contact with companion animals only. One case reported contact with dogs and the other two with cats. Swabs were taken from two dogs and three cats but none were positive for corynebacteria.

Contact tracing identified thirteen close contacts including two household contacts, one non-household contacts and 10 healthcare workers. 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 2018

	Causative organism				
Clinical presentation of cases	Toxigenic *C. diphtheriae*	Toxigenic *C. ulcerans*	NTTB C. diphtheriae	None detected	**Total**
Severe respiratory diphtheria (sore throat with exudate or membrane)	0	0	0	1	1
Mild respiratory diphtheria (sore throat/pharyngitis)	1	1	2	0	4
Cutaneous diphtheria	3	2	0	0	5
Asymptomatic	3*	0	0	0	3
Other (ear infection)	1	0	0	0	1

*All contacts of symptomatic cases

Further information

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 [8]. 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 confirm expression of toxin [4]. 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].

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 strains of *C. diphtheriae,* and therefore interpretation of notification data should be undertaken with caution.

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About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. We do this through world-class science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health and Social Care and are a distinct delivery organisation with operational autonomy to advise and support government, local authorities and the NHS in a professionally independent manner.

About Health Protection Report

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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