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Diphtheria in England 2020: main points

The main conclusions of this report are that:

- diphtheria is a life-threatening, but vaccine-preventable infection
- from January to December 2020 one toxigenic case of diphtheria caused by *C. ulcerans* and one non-toxigenic toxin gene-bearing (NTTB) case was reported in England
- the toxigenic case had both cutaneous and mild respiratory symptoms while the NTTB case had a mild respiratory infection
- the toxigenic *C. ulcerans* case was linked to a companion animal.

Background

Diphtheria has become increasingly rare in England due to 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 is a range of 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 England is provided by local 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, for example, PCR. The determination of toxigenicity in England requires submission of the isolate to Public Heath England’s (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]. The availability of both PCR and Elek testing has identified a number of *C. diphtheriae* isolates carrying the tox gene (PCR-positive) but not expressing the toxin (Elek-negative), termed non-toxigenic toxin gene-bearing strains (NTTB) [3]. The pathogenesis and clinical significance of isolation of this organism are not yet well understood; NTTB are not thought to cause diphtheria but owing to their potential but unknown risk of becoming toxigenic through a genetic event, it is currently recommended in the UK that they are managed in the same way as as fully toxigenic (that is, Elek-positive, toxin-expressing) diphtheria cases and eliminated using antibiotics from patients and contacts.

## Cases of diphtheria in England in 2020

This 2020 review updates a previous annual review of diphtheria cases in England for 2019 [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 2020, a toxigenic strain of *C. ulcerans* was identified from one person at the RVPBRU. This compares with 10 toxigenic strains in 2019, 11 toxigenic strains in 2018 and 5 toxigenic strains in 2017. One non-toxigenic tox gene bearing (NTTB) *C. diphtheriae* strain, was also identified during the 2020 period.

Diphtheria is a notifiable disease in accordance with the amended Public Health (Control of Disease) Act 1984 and accompanying regulations [6]. One diphtheria notification was received from NOIDs in 2020 for England; this case had an onset date in December 2019 and laboratory investigation identified this case as non-toxigenic *C. diphtheriae* infection. The toxigenic case from 2020 was not notified. During 2020, the National Reference Laboratory received a total of 34 isolates for confirmation and toxigenicity testing from 30 individuals (25 human and 5 companion animals) from England in comparison to 108 from 107 individuals in 2019. Isolates from one person were identified as toxigenic *C. ulcerans* (Table 1). Two further toxigenic *C. ulcerans* strains were confirmed from companion animals, both of which were not epidemiologically linked to a human case.

Of the remaining isolates, 22 were non-toxigenic *C. diphtheriae*, 1 was non-toxigenic *C. ulcerans* and 3 were not *C. diphtheriae*, *C. ulcerans*, or *C. pseudotuberculosis*. One non-toxigenic tox gene bearing (NTTB) *C. diphtheriae* was also isolated. There were no toxigenic *C. diphtheriae* isolates.
Table 1. Summary of (a) Diphtheria notifications (NOIDs) (b) toxigenic corynebacteria by strain and (c) NRL toxigenicity testing, England: 2020

(a) Total diphtheria notifications in 2020

<table>
<thead>
<tr>
<th>Strain Description</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number due to toxigenic <em>C. diphtheriae</em></td>
<td>0</td>
</tr>
<tr>
<td>Number due to toxigenic <em>C. ulcerans</em></td>
<td>0</td>
</tr>
<tr>
<td>Number due to non-toxigenic toxin gene bearing (NTTB) <em>C. diphtheriae</em></td>
<td>0</td>
</tr>
<tr>
<td>Number due to non-toxigenic <em>C. diphtheriae</em></td>
<td>1</td>
</tr>
</tbody>
</table>

(b) All toxigenic corynebacteria isolates from human cases in 2020

<table>
<thead>
<tr>
<th>Strain Description</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxigenic <em>C. diphtheriae</em></td>
<td>0</td>
</tr>
<tr>
<td>Toxigenic <em>C. ulcerans</em></td>
<td>1</td>
</tr>
<tr>
<td>NTTB <em>C. diphtheriae</em></td>
<td>1</td>
</tr>
</tbody>
</table>

(c) All isolates referred to NRL for toxigenicity testing in 2020 (duplicates from same person excluded)

<table>
<thead>
<tr>
<th>Strain Description</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxigenic <em>C. diphtheriae</em></td>
<td>0</td>
</tr>
<tr>
<td>Non-toxigenic non-tox gene bearing (NTTB) <em>C. diphtheriae</em></td>
<td>1</td>
</tr>
<tr>
<td>Non-toxigenic <em>C. diphtheriae</em></td>
<td>22</td>
</tr>
<tr>
<td>Toxigenic <em>C. ulcerans</em></td>
<td>3</td>
</tr>
<tr>
<td>Non-toxigenic <em>C. ulcerans</em></td>
<td>1</td>
</tr>
<tr>
<td>Other – not <em>C. diphtheriae, C. ulcerans, or C. pseudotuberculosis</em></td>
<td>3</td>
</tr>
</tbody>
</table>

* Includes 2 isolates from companion animals not epidemiologically linked to a case.

**Corynebacterium diphtheriae**

No toxigenic *C. diphtheriae* strains were identified in England in 2020. One NTTB (non-toxigenic toxin-bearing) strain was identified in 2020 in a partially immunised male aged 42. The case presented with mild respiratory symptoms. Contact tracing identified 14 close contacts including 7 household contacts, 3 visiting family members and 4 healthcare workers. All household contacts were asymptomatic, offered chemoprophylaxis, vaccination as appropriate, and had swabs taken. Correct use of personal protective equipment while in contact with the case was reported for the remaining 7 contacts requiring no further actions. No additional cases were identified.
Corynebacterium ulcerans

One toxigenic *C. ulcerans* case was identified in 2020 in a male aged 99. The case presented with both cutaneous and mild respiratory symptoms and was hospitalised. The case’s vaccination status was unknown with no boosters recorded since 2010 although he was unlikely to have had childhood vaccinations due to his age. The case was treated with antibiotics; treatment with diphtheria anti-toxin was not required.

Risk factors for *C. ulcerans* include consumption of raw milk products and contact with farm and companion animals [3]. The case did not report a history of eating raw milk products or contact with farm animals; however, the case lived with a dog. Swabs were taken from the dog and found to be negative for corynebacteria.

Contact tracing identified 10 close contacts including 5 household contacts and 5 healthcare workers as well as 6 contacts that were patients from the same bays at hospital. All close contacts were asymptomatic, offered chemoprophylaxis, vaccination as appropriate, and had throat swabs taken. Healthcare workers were excluded from work for duration of antibiotic treatment.

Table 2. Clinical presentation of diphtheria cases and causative organism, England 2020

<table>
<thead>
<tr>
<th>Clinical presentation of cases</th>
<th>Causative organism</th>
<th>Toxigenic <em>C. diphtheriae</em></th>
<th>Toxigenic <em>C. ulcerans</em></th>
<th>NTTB <em>C. diphtheriae</em></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe respiratory diphtheria (sore throat with exudate or membrane)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mild respiratory diphtheria (sore throat or pharyngitis)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cutaneous diphtheria</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mild respiratory and cutaneous</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
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 (that is, 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.
References

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