Diphtheria is rare in Aotearoa New Zealand, largely due to successful vaccination (three primary series doses and two booster doses in the childhood immunisation schedule, and two adult booster doses). There have been international outbreaks, particularly in regions without effective vaccination programmes. The highest number of cases worldwide is in the World Health Organization South-East Asia region (data from 2000 to 2017).

Diphtheria is a bacterial infection caused by toxigenic strains of Corynebacterium diphtheriae, C. ulcerans and C. pseudotuberculosis, with the first being the most common human pathogen. Toxigenic C. diphtheriae can cause respiratory diphtheria with nasal, pharyngeal or laryngeal involvement and formation of the pathognomonic grey pseudomembrane, or non-respiratory diphtheria e.g., cutaneous diphtheria (non-healing ulcers). Distant complications of toxigenic C. diphtheriae include myocarditis, neuropathy and renal impairment. Non-toxigenic strains generally cause less severe disease, although bacteraemia and endocarditis have been reported.

Diphtheria is a notifiable disease. Isolates from around the country are sent to the national reference laboratory (Institute of Environmental Science and Research [ESR]) for polymerase chain reaction (PCR) testing for the tox gene. If positive, the isolate is reported as toxigenic.

Recent reports from Australia suggest an increasing number of cases of diphtheria notified to public health, particularly since 2011. Most cases were cutaneous. Within a clonal outbreak of 29 cases of toxigenic C. diphtheriae in Queensland, Australia, there were eight respiratory cases. In the Northern Territories, Australia, all 148 C. diphtheriae isolates in 2022 were from polymicrobial cutaneous samples. Of 41 isolates tested, none were toxigenic. Overall there is variation in the reports across Australia.

We sought to obtain an overview of the situation in Aotearoa New Zealand to determine the likely source of C. diphtheriae isolates, and the proportion that are toxigenic.

From 2012 to June 2023, a total of 550 isolates were referred to ESR. C. diphtheriae accounted for 538 (98%) of them. Auckland contributed 324 (59%), and Canterbury contributed 107 (19%) isolates. One fifth (117) of the isolates were referred in 2023 (up to June 2023). Of the 550 isolates, 16 (3%) were toxigenic, all C. diphtheriae. The trend over time in toxigenic isolates does not clearly show a rise above previous years (Figure 1). Of note, there was a decline in the number of isolates referred in 2020–2021 during the time of restricted international travel.

We sought to characterise the antimicrobial susceptibility pattern of all C. diphtheriae isolates from a tertiary hospital in Auckland. From 2012 to June 2023, LabPLUS Auckland City Hospital had 43 unique C. diphtheriae isolates. Antimicrobial susceptibility testing was performed according to the Clinical & Laboratory Standards Institute (CLSI) method until 2015, after which the European Committee on Antimicrobial Susceptibility Testing (EUCAST) method was followed. EUCAST provided interpretive criteria for Corynebacterium species until 2023, when species-specific interpretive criteria were provided for C. diphtheriae. Since there are now interpretive criteria for C. diphtheriae specifically, the historic susceptibility data were re-interpreted using the new criteria (Table 1). The EUCAST method did not change over this time. Testing was performed either by disk diffusion resulting in a zone diameter, or broth microdilution resulting in a minimum inhibitory concentration (MIC) of antibiotic.

Of the 43 unique C. diphtheriae isolates, 37 had penicillin susceptibility testing performed; all but one were categorised as “susceptible increased exposure” (I). All isolates were not tested using the same method; 19 isolates underwent MIC testing, and 26 isolates underwent disk diffusion testing. Eight isolates were tested via both methods. The minimum inhibitory concentration of penicillin...
at which 50% (MIC\textsubscript{50}) and 90% (MIC\textsubscript{90}) of isolates were inhibited were both 0.5mg/L.

Of the 43 isolates, four were toxigenic. These isolates had penicillin MICs in the range 0.25mg/L to 0.5mg/L. These penicillin MIC data observed are consistent with international reports.\textsuperscript{9,10}

The management of diphtheria includes antibiotics, antitoxin for toxigenic strains, public health notification and infection prevention and control measures (droplet precautions for respiratory diphtheria and contact precautions for cutaneous diphtheria). Close contacts may be offered prophylaxis with penicillin or a macrolide.\textsuperscript{11}

Our data show that almost all isolates were “susceptible increased exposure” to penicillin, so we expect penicillin treatment to be effective, although the specific regimen would depend on each individual case. Our macrolide susceptibility testing data were limited; it was not possible to draw conclusions on macrolide susceptibility.

Limitations of this analysis include that antimicrobial susceptibility data were available from one Auckland hospital laboratory only. However, we expect the results to be generalisable across the country, as most isolates in the national dataset are from Auckland. Laboratories performing in-house \textit{tox} gene PCR may only refer PCR positive isolates, so the total number of isolates referred

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**Figure 1:** The number of isolates referred to ESR per year by the type of sample. "Other" includes blood culture isolates and unknown sample type. The dark green line shows the number of toxigenic isolates per year.

**Table 1:** Penicillin susceptibility test results for all LabPLUS \textit{C. diphtheriae} isolates from 2012 to June 2023.

<table>
<thead>
<tr>
<th>Penicillin susceptibility test result</th>
<th>MIC (mg/L)</th>
<th>Zone diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=19</td>
<td>n=26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.12</td>
<td>&lt;12</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>12–50</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>≥50</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Eight isolates had both MIC and zone diameter results. For all these eight isolates the MIC and zone diameter resulted in the same categorical interpretation. Isolates with MIC >1.0mg/L or zone diameter <12mm to penicillin are categorised “resistant”. Isolates with MIC <0.001mg/L or zone diameter ≥50mm are categorised “susceptible”. Isolates with MIC or zone diameter results within these ranges are categorised “susceptible increased exposure”. The interpretation column provides the overall interpretation of the penicillin susceptibility based on MIC and zone diameter results for all 37 isolates. S is susceptible, I is susceptible increased exposure and R is resistant.
to ESR may not represent the true total number of isolates nationwide. Growth of *C. diphtheriae* in polymicrobial cultures may be missed without appropriate clinical details to guide laboratory scientists, contributing to under-reporting. It is unclear to what extent this may impact the data, although the impact should be consistent over time, so the trends observed would remain unchanged.

In conclusion, toxigenic *C. diphtheriae* isolates remain uncommon in Aotearoa New Zealand; we have not seen an increase in the number of toxigenic isolates over the past 11.5 years. We report a recent increase in non-toxigenic cutaneous cases. These are likely to be travel-related, particularly to tropical Australia and Pacific Island Countries and Territories.\(^7,8,12,13\) Clinicians should have a high index of suspicion in patients returning from tropical regions with chronic skin lesions and provide a documented travel history to inform laboratory scientists of the potential for uncommon pathogens such as *C. diphtheriae*.

With international travel we are likely to see non-immune travellers with respiratory or cutaneous presentations from countries that do not have effective vaccination programmes. This reinforces the importance of maintaining good vaccine coverage across our population. The public health and treatment implications of toxigenic strains necessitates careful risk assessment of cases while awaiting a *tox* gene PCR result, including risk assessment for respiratory symptoms, likely country of acquisition of infection and the patient's vaccination history.\(^11\)
COMPETING INTERESTS
Nil.

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