Cases of cutaneous diphtheria in New Zealand: implications for surveillance and management

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Abstract

Aim Diphtheria is an acute bacterial illness caused by toxigenic strains of Corynebacterium diphtheriae (C. diphtheriae). We describe two epidemiologically-linked cases of skin infections from which toxigenic C. diphtheriae was isolated, and discuss implications for diphtheria surveillance and management in New Zealand.

Method A public health investigation was undertaken to identify and manage close contacts of the index case. National and international guidelines on the surveillance and management of cutaneous diphtheria were reviewed, and data on toxigenic C. diphtheriae isolates identified in New Zealand from 1987–2009 were examined.

Results The index case was an adult male who developed a cutaneous infection after being tattooed in Samoa. A wound swab taken from the infected tattoo grew a toxigenic strain of C. diphtheriae (var gravis). A secondary case of toxigenic cutaneous diphtheria was identified in a household contact. Instances of respiratory diphtheria associated with toxigenic cutaneous lesions have been reported in the literature. The review of surveillance data revealed inconsistencies in the notification of toxigenic strains of C. diphtheriae isolated from cutaneous sites.

Conclusion These cases are an important reminder that diphtheria remains a threat in New Zealand. All cases with toxigenic C. diphtheriae isolated from a clinical specimen, regardless of the site of infection, should be notified to a Medical Officer of Health.

Diphtheria is an acute bacterial illness caused by infection with exotoxin-producing (toxigenic) strains of C. diphtheriae bacteria. The most common sites of infection are the respiratory tract and the skin.

Respiratory diphtheria is characterised by the development of a thick adherent greyish membrane on the pharynx. Symptoms can include sore throat, enlarged cervical lymph nodes, severe neck swelling (‘bull-neck’), dyspnoea, and progressive respiratory obstruction. The case-fatality proportion from respiratory diphtheria is reported as being between 5 and 10% in developed countries. Systemic toxic effects can occur due to the production of exotoxin. These effects include myocarditis and peripheral polynueropathy. Toxic effects can be reduced through prompt administration of diphtheria antitoxin.

Diphtheria vaccination has been widely available since the 1940s. The subsequent decades saw a marked decline in respiratory diphtheria incidence in New Zealand and other developed countries. However, the 1990s saw a re-emergence of respiratory diphtheria in the former Soviet Union, where more than 115,000 cases and 3,000 deaths occurred from 1990 to 1997.
The last case of respiratory diphtheria notified in New Zealand occurred in 1998 in an unimmunised 32-month-old European male, and was the first case of respiratory diphtheria notified in New Zealand in over 19 years. Notably, it was suggested that this case could have arisen through exposure to a family member’s infected abrasion, which had been acquired during a trip to Indonesia.

Skin infections caused by toxigenic *C. diphtheriae* have been implicated as a reservoir for the spread and transmission of respiratory diphtheria. As well as being a reservoir for respiratory diphtheria, prolonged outbreaks of cutaneous diphtheria requiring public health intervention have been reported. Transmission is thought to occur mainly via direct contact with exudate from skin infections or, more rarely, via items contaminated with discharges from an infected person.

Toxigenic cutaneous diphtheria typically occurs in tropical areas where *C. diphtheriae* is endemic. Classical features include punched out, well-circumscribed, non-healing ulcers with a grey membrane. In developed countries cutaneous diphtheria more frequently presents as an infection of an existing skin condition or traumatic skin lesion, so-called secondary toxigenic cutaneous diphtheria.

In these instances, the lesions are often indistinguishable from skin infections caused by other pathogens. In contrast to respiratory diphtheria, toxic sequelae rarely occur with cutaneous diphtheria, possibly due to a slower release of toxin across the skin barrier resulting in a more vigorous antitoxin immune response.

We report a case of toxigenic cutaneous diphtheria notified in New Zealand and the subsequent public health response that was undertaken. We review the implications of this event for the response to toxigenic cutaneous diphtheria and for the notification of extra-respiratory toxigenic strains of *C. diphtheriae* in New Zealand.

**Method**

Following a report of a case of toxigenic cutaneous diphtheria to a Medical Officer of Health, a public health investigation was undertaken to identify close contacts with the aim of preventing spread of the toxigenic *C. diphtheriae* strain.

A literature review on the management of cutaneous diphtheria was undertaken, and national and international guidelines on the notification and management of diphtheria were reviewed. National surveillance data were obtained from the Institute of Environmental Science and Research Limited (ESR) on toxigenic *C. diphtheriae* isolates identified in New Zealand from 1987–2009. National surveillance reports and notification data were also reviewed to identify any reported cases of infection arising from toxigenic *C. diphtheriae*.

**Results**

**Index case**—The index case was an adult male who had recently travelled to Samoa. The case had been tattooed on his lower leg while in Samoa. There was uncertainty about whether traditional or machine-based tattooing methods were used.

On arrival back in New Zealand, the case presented to his Medical Centre complaining of swelling and pain in the lower leg associated with the tattoo. A course of oral flucloxacillin was prescribed, although it later became apparent that this prescription had not been dispensed. The case re-presented to the Medical Centre with worsening pain, ulceration and redness around the tattoo site.
A wound swab was taken from the ulcerated tattoo and clinical details, including the history of a tattoo acquired in Samoa were noted on the laboratory request form. A seven-day course of erythromycin was prescribed to cover the possibility of methicillin-resistant Staphylococcus aureus (MRSA). It was uncertain whether the case had ever received a primary diphtheria immunisation course, but he had received a tetanus-diphtheria (Td) booster six years previously.

Laboratory staff noted the clinical history and added testing for C. diphtheriae. C. diphtheriae (var gravis) and S. aureus were isolated from the wound swab. The C. diphtheriae isolate was sent to ESR for urgent diphtheria toxin gene testing by polymerase chain reaction (PCR), and was confirmed to be a toxigenic strain.

Following the result of the wound swab, the case was reviewed again in primary care. Only six doses of the erythromycin course had been taken. The case was hospitalised with fever and worsening lower leg cellulitis, and was successfully treated with intravenous flucloxacillin and erythromycin. Nose and throat swabs were taken to test for nasopharyngeal C. diphtheriae carriage and were negative. Cardio-respiratory monitoring was undertaken during admission as a precaution but there were no signs of toxin-related effects or respiratory diphtheria.

To confirm bacteriological clearance, two sets of swabs (nose, throat and wound) were taken 24 hours after completion of antibiotic treatment, and more than 24 hours apart. Both sets of swabs were negative for toxigenic C. diphtheriae. Booster immunisation (Td) was given.

Contact tracing and management of contacts—All close contacts were screened for diphtheria symptoms (including cutaneous lesions) and were swabbed to test for nasopharyngeal C. diphtheriae carriage. Close contacts were also offered antimicrobial prophylaxis with either 10 days of oral erythromycin or a single dose of intramuscular (IM) benzathine penicillin. The diphtheria immunisation status of each contact was determined, and Td booster vaccination was offered if not received in the past five years (diphtheria-tetanus-pertussis (dTap) boosters were used in younger contacts). A total of 19 household and close family contacts were identified, as well as four health care workers who had examined the wound.

Verbal and written advice was given to all contacts outlining the symptoms of respiratory diphtheria, with instructions to seek urgent medical attention if any symptoms occurred. Due to the potential for environmental contamination arising from cutaneous lesions, the family was advised to clean all bedding, clothes and soft furnishings.

A secondary case of toxigenic cutaneous diphtheria was subsequently identified in a fully immunised 11-year-old household contact. The child had an existing traumatic laceration on the arm, and a wound swab grew toxigenic C. diphtheriae (var gravis) and S. aureus. This child had not travelled to Samoa. Nasopharyngeal screening swabs were negative, and the child was restricted from school and successfully treated with a 10-day course of oral erythromycin and flucloxacillin. Bacteriological clearance was confirmed with two sets of swabs (nose, throat and skin) taken more than 24 hours after the completion of antibiotics. There were no signs of respiratory disease or toxin-related symptoms.
School contacts of this case were provided with information on the signs and symptoms of diphtheria. Children from the same class had recently received their 11-year-old scheduled dTap boosters, and swabbing and antibiotic prophylaxis was deemed unnecessary due to minimal contact with the case (the wound had been well-covered). Staff members who had dressed the child’s wound were offered Td boosters (as needed), swabbed for carriage and offered antibiotic prophylaxis.

In total, 27 close contacts of both cases were identified, including household contacts, close family members (who had slept in the same house as the index case), health care workers, and school contacts. All 27 contacts had nasal and throat swabs taken for *C. diphtheriae*, with no nasopharyngeal carriage detected, and were offered booster immunisation if not received in the past five years. Antibiotic prophylaxis was also offered.

During the course of the investigation, it was discovered that family members living in Samoa had been tattooed by the same tattooist. Attempts were made to identify the tattooist involved; however difficulties were encountered obtaining this information. The Ministry of Health liaised with Samoan health authorities to follow-up the tattooist and other family members who may have been tattooed in Samoa.

*C. diphtheriae* isolates in New Zealand—The review of toxigenic *C. diphtheriae* isolates from 1987 to 2009 revealed that, in addition to the two cases described here (notified in 2009), there were five other toxigenic isolates detected by ESR (Table 1).

A review of surveillance and other reports was undertaken to determine whether these five cases had been notified. This revealed that two of these cases were notified: a respiratory case in 1998, and a case in a four-year old with septic arthritis of the hip in 2002. A cutaneous infection in a traveller in 1987 was also investigated. However, for two of the toxigenic cutaneous isolates (one in 2008 and one in 2009), there was no evidence that they had been notified to a Medical Officer of Health.

<table>
<thead>
<tr>
<th>Year*</th>
<th>Number of Isolates</th>
<th>Source and biovar (type)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Respiratory</td>
<td>Cutaneous and other extra-respiratory</td>
</tr>
<tr>
<td>1987</td>
<td>1</td>
<td>mitis</td>
</tr>
<tr>
<td>1998</td>
<td>1</td>
<td>intermedius</td>
</tr>
<tr>
<td>2002</td>
<td>1</td>
<td>gravis (hip aspirate)</td>
</tr>
<tr>
<td>2008</td>
<td>1</td>
<td>gravis</td>
</tr>
<tr>
<td>2009</td>
<td>3</td>
<td>gravis</td>
</tr>
</tbody>
</table>

* No toxigenic isolates were identified in the intervening years.
Discussion

This report describes the first cases of toxigenic cutaneous diphtheria reported in New Zealand since 1987, and the first notifications of toxigenic *C. diphtheriae* isolates in New Zealand since 2002.

These two cases were diagnosed based on the isolation of toxigenic *C. diphtheriae* from infected skin lesions. The clinical features in both cases were consistent with cases of secondary toxigenic cutaneous diphtheria reported in the literature. As occurred in this outbreak, secondary toxigenic cutaneous diphtheria is difficult to distinguish from skin infections caused by other pathogens. Both cases were found to be co-infected with *S. aureus*, which has been frequently reported in cases of toxigenic cutaneous diphtheria in both developing and developed countries. The isolation of *S. aureus* also raises the possibility that this bacterium may have been the primary pathogen for skin infection in these cases.

As illustrated by this event, most cases of toxigenic cutaneous diphtheria in developed countries occur in individuals returning or arriving from tropical areas where toxigenic *C. diphtheriae* remains endemic. As such, toxigenic cutaneous diphtheria should be considered in any person with chronically or acutely infected skin lesions returning from disease-endemic regions, including the Pacific Islands.

In this outbreak, one of the cases had been tattooed in Samoa. In New Zealand, traditional tattooing has been recognised as a risk factor for serious skin infections, and the Ministry of Health has published guidelines around traditional tattooing. While it was unclear in this case whether traditional or machine-based tattooing methods were used, the tattoo is likely to have been a risk factor for infection, and the possibility remains that contaminated tattooing tools may have been the mode of transmission in the index case.

Toxigenic cutaneous diphtheria infections have been implicated in cases of respiratory diphtheria, including in New Zealand, the United Kingdom (UK), Europe and North America. Prolonged outbreaks of cutaneous diphtheria requiring public health intervention have also been reported, particularly within socioeconomically deprived communities. Therefore, cases of toxigenic cutaneous diphtheria require public health action to help prevent the spread of both cutaneous and respiratory disease.

As seen in this outbreak, treatment of individual cases of toxigenic cutaneous diphtheria involves isolation, disinfection of potentially contaminated environments, and treatment with appropriate antibiotics. While systemic toxic effects are less common than in respiratory diphtheria, antitoxin treatment should be considered, although lower doses may be recommended compared to those required for respiratory diphtheria.

Close contacts should be screened for *C. diphtheriae* carriage by having nasal and pharyngeal swabs obtained for culture, and swabs should also be taken from any wounds or other skin lesions. Close contacts should also be offered a 7-10-day course of oral erythromycin or a single dose of IM benzathine penicillin. Contacts at greatest risk include household contacts, and healthcare workers involved in dressing cutaneous infections. Booster diphtheria immunisation should also be
offered to cases and contacts who have had a primary immunisation course, if no booster has been given in the preceding five years. Unimmunised contacts should be offered a complete immunisation course. Unimmunised contacts and older immunised contacts (who may have waning immunity) are most at risk of developing infection.

As well as cutaneous diphtheria, other extra-respiratory presentations of toxigenic diphtheria have been described including septic arthritis, conjunctivitis, and genital and external auditory canal infections. Such cases have been described in New Zealand, with a four-year-old with toxigenic *C. diphtheriae* isolated from a hip aspirate notified in 2002. While there is minimal information on the infective potential of toxigenic *C. diphtheriae* isolated from these extra-respiratory sites, similar public health action to that required for respiratory and cutaneous infection may be appropriate. Notably, routine notification of extra-respiratory isolates of toxigenic *C. diphtheriae* (including cutaneous isolates) occurs in a number of countries, including the UK and the European Union (EU).

Our review of surveillance reports and guidelines revealed some inconsistencies in the current notification of toxigenic *C. diphtheriae* isolates to Medical Officers of Health (and subsequent public health action) in New Zealand. Diphtheria has been a notifiable disease in New Zealand since 1901, however, the current New Zealand case definition for diphtheria only refers to respiratory diphtheria and excludes cutaneous diphtheria from notification. In contrast, the New Zealand *Direct Laboratory Notification* guidelines require all toxigenic *C. diphtheriae* (and *C. ulcerans*) isolates to be reported to a Medical Officer of Health. Thus, cases of toxigenic cutaneous diphtheria are notifiable via this direct laboratory notification pathway.

Adopting a similar approach to the UK and the EU by including extra-respiratory presentations of toxigenic *C. diphtheriae* in the diphtheria case definition, would help ensure that consideration is given to the level of public health action required for such cases, and improve consistency.

As observed in this event, primary care practitioners have key roles to play in identifying atypical skin infections and initiating treatment of toxigenic cutaneous diphtheria. Having a lower threshold for wound swabbing in the presence of risk factors for atypical skin infections (e.g. recent overseas travel and tattooing) is likely to bolster the early identification and management of toxigenic cutaneous diphtheria in New Zealand.

Culture for *C. diphtheriae* is not necessarily routine and providing complete clinical information on the laboratory request form is essential for alerting laboratories to the possibility of atypical organisms, such as toxigenic *C. diphtheriae*. *Corynebacterium* species are common skin commensals so identification of toxigenic *C. diphtheriae* relies on additional testing, including referring specimens to ESR for urgent toxigenicity testing. In this case, if the specific diphtheria culture had not been performed, the diagnosis would have been delayed (or missed), risking further spread of this toxigenic strain.

Immunisation remains an important public health measure to prevent the development and spread of diphtheria. This outbreak is a timely reminder that toxigenic
C. diphtheriae strains continue to occur in New Zealand and that respiratory diphtheria remains a risk for susceptible individuals. Immunisation confers long but not lifelong immunity. National and international serological studies have highlighted waning immunity in adults.31,32 The current New Zealand immunisation schedule includes booster Td vaccine doses at age 45 and 65 years.10 However, more could be done to increase awareness of these booster vaccinations in adulthood.

These cases of toxigenic cutaneous diphtheria are an important reminder that diphtheria remains a threat in New Zealand, and that clinical suspicion for toxigenic C. diphtheriae infection is prudent medical practice, especially when a skin infection has been acquired in a disease-endemic area. Given ongoing transmission in Pacific countries, and the potential for missed diagnosis, there remains a small but real risk of an outbreak of diphtheria in New Zealand, particularly among groups with low immunisation coverage.

Competing interests: None declared.

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