Australian vaccine preventable disease epidemiological review series: diphtheria 1999–2019

Noni E Winkler, Aditi Dey, Helen E Quinn, Davoud Pourmarzi, Stephen Lambert, Peter McIntyre, Frank Beard
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Original Article

Australian vaccine preventable disease epidemiological review series: diphtheria 1999–2019

Noni E Winkler, Aditi Dey, Helen E Quinn, Davoud Pourmarzi, Stephen Lambert, Peter McIntyre, Frank Beard

Abstract

Background

Diphtheria is rare in Australia, but an increasing number of cases have been notified in recent years. Alongside notifications from 1999 to 2019, we analysed other relevant national data sources to evaluate trends over the past two decades.

Methods

Diphtheria notifications (National Notifiable Diseases Surveillance System [NNDSS]), hospitalisations (National Hospital Morbidity Database [NHMD]) and deaths (Australian Bureau of Statistics and the Australian Coordinating Registry) were separately analysed by site of infection, age group, sex, state/territory, Aboriginal and Torres Strait Islander status, and vaccination status.

Results

During the study period, eight (0.002 per 100,000 population per year) cases of respiratory diphtheria and 38 (0.008 per 100,000 population per year) cases of cutaneous diphtheria were recorded in the NNDSS, with 45/46 reported in the nine years since 2011. Corynebacterium diphtheriae accounted for 87% of notified cases, who had a median age of 31.5 years (respiratory diphtheria) and 52.5 years (cutaneous diphtheria); no respiratory diphtheria was notified in those under 15 years of age. A majority of the cutaneous diphtheria cases (27/38; 71%) were acquired overseas, as were 3/8 (38%) of the respiratory diphtheria cases. Rates of both presentation types were higher in Aboriginal and Torres Strait Islander people (respiratory: 0.007 per 100,000 population per year; cutaneous: 0.021 per 100,000 population per year) than were rates in the overall population. Queensland had the highest rate of notified respiratory cases (0.007 per 100,000 population per year), and the Northern Territory the highest rate of cutaneous notifications (0.043 per 100,000 population per year). There were 29 hospitalisations with a principal-diagnosis diphtheria code in the NHMD between 2002 and 2018, of which eight were designated as respiratory (0.002 per 100,000 population per year), eight as cutaneous (0.002 per 100,000 population per year), and 13 with an unknown site of infection. Among notified cases, two deaths were reported in unvaccinated people in Queensland.

Conclusions

Although diphtheria remains rare in Australia, 45 cases were notified in the years 2011–2019, compared with one case between 1999 and 2010. Robust surveillance remains important to detect all cases. High immunity will need to be maintained across all age groups to prevent outbreaks, and travel and adult booster doses should be encouraged.

Keywords: Diphtheria; disease surveillance; immunisation; epidemiology; vaccine preventable disease
Introduction

Globally, diphtheria incidence declined dramatically following the implementation of vaccination programs in the 1940s, with many industrialised countries having largely eliminated the disease by the 1980s. However, subsequent outbreaks have occurred, the largest in the Newly Independent States of the former Soviet Union in the 1990s, and in Yemen and Bangladesh from 2017. Resurgence of diphtheria has been driven by health system disruption and by declines in childhood vaccination coverage, often associated with civil unrest and population movement.

Diphtheria is caused by toxigenic strains of *Corynebacterium diphtheriae*, *C. ulcerans*, and, very rarely, *C. pseudotuberculosis*. The most common clinical presentations are respiratory and cutaneous infection, with subsequent clinical manifestations caused by diphtheria toxin produced by the bacilli. Classic respiratory diphtheria is characterised by a sore throat, fever, swelling of the neck, and a membrane that forms over the back of the throat causing difficulty swallowing and breathing. The toxin can also cause later cardiac and neurological complications. Case fatality rates range from 5% to higher than 20% depending on vaccination status and availability of treatment. Cutaneous diphtheria typically presents as a non-healing ulcerative lesion. Toxin-related complications can occur in cutaneous diphtheria, but are rare due to slow absorption of the toxin from skin lesions.

Transmission of *C. diphtheriae* is predominantly from human to human by respiratory droplets or by direct contact with infected lesions. Secondary respiratory cases and outbreaks can arise due to transmission from both respiratory and cutaneous cases. Widespread immunisation is the principal means of prevention, but control measures, including isolation of cases, contact tracing, and antibiotic chemoprophylaxis of both cases and contacts, are also required. *C. ulcerans* and *C. pseudotuberculosis* are linked to transmission from animals.

*D. ulcerans* transmission occurs through contact with respiratory droplets from colonised companion animals, or through direct contact with, or consumption of, unpasteurised milk from colonised livestock. *C. pseudotuberculosis* transmission pathways are less well documented.

Diphtheria vaccines contain diphtheria toxoid (a chemically inactivated form of the toxin), and are highly effective at preventing symptomatic disease. While vaccination does not prevent colonisation or asymptomatic infection, asymptomatic individuals transmit infection at a reduced rate. Diphtheria vaccines are funded under the Australian National Immunisation Program (NIP) as a three-dose primary course at 2, 4, and 6 months of age, with booster doses at 18 months, 4 years, and 11–13 years of age, the latter introduced in 2004. The 18-month combination diphtheria-tetanus-pertussis (acellular) (DTPa) booster was removed from the NIP in 2003 and reintroduced in 2016 as part of efforts to improve pertussis control. Doses of adult diphtheria-tetanus-pertussis (acellular) (dTpa) vaccine for parents and carers of newborn babies, to protect them from pertussis (cocoon strategy), were funded by jurisdictions at varying times between 2008 and 2013, replaced by dTpa vaccination for pregnant women, initially funded by jurisdictions from 2014 and then NIP-funded from 2018.

The last detailed review of diphtheria, covering the period from 1991 to 1998, identified 23 notifications for diphtheria in 1991 and 1992 but none between 1993 and 1998. In the most recent decade there have been several changes to the national diphtheria case definition, an increase in the number of notified cases, and the first deaths from diphtheria since 1992. In this epidemiological review we analyse administrative data on diphtheria in Australia from 1999 to 2019.
Methods

Data sources

Notifications

The Australian National Notifiable Diseases Surveillance System (NNDSS) was established in 1990 and contains data on more than 50 notifiable diseases. Notifications are made to each state or territory health department, and electronic, de-identified notification data are supplied to the Australian Government Department of Health and Aged Care on a daily basis. For this analysis, included data were NNDSS notifications for confirmed or probable diphtheria, as per the case definition in place at the time (Appendix A, Table A.1), with an onset date between 1 January 1999 and 31 December 2019. Where the onset date was not available, the earliest of the specimen date, notification date, or notification received date was used. Where site of infection (respiratory or cutaneous) was recorded as ‘unknown’ in the initial dataset, this was obtained through direct communication with the relevant jurisdiction.

Hospitalisations

Hospitalisation data were obtained from the Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity Database (NHMD), which contains line-listed, episode-level records for all hospital admissions in Australian public and private hospitals. Included were any hospitalisations with an admission date between 1 January 2002 and 31 December 2018 (earliest and latest full calendar year of hospitalisation data available) with an International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modifications (ICD-10-AM) principal or additional diagnosis code for diphtheria (A36.0 [pharyngeal diphtheria]; A36.1 [nasopharyngeal diphtheria]; A36.2 [laryngeal diphtheria]; A36.3 [cutaneous diphtheria]; A36.8 [other diphtheria]; or 36.9 [diphtheria, unspecified]). Length of stay was capped at 30 days in the dataset provided by AIHW, so hospitalisations reported with a 30-day length of stay may represent longer hospitalisations. Admission year was not supplied by AIHW where length of stay was greater than 30 days. Where admission year was not available, separation year was used. Counts less than 5 are expressed as a range (1–4) to comply with the data release condition that small counts be suppressed in published reports.

Mortality

Mortality data were obtained from the Australian Coordinating Registry (ACR) for deaths from 2006 onwards, and from the Australian Bureau of Statistics (ABS) for deaths prior to 2006. Data included were deaths with diphtheria recorded as an underlying or associated cause (only underlying cause available for ABS data), defined using the ICD-10-AM code A36, from 1 January 2003 (earliest full calendar year of data available) to 31 December 2019. Counts less than 6 are expressed as a range (1–5) to comply with the data release condition that small counts be suppressed in published reports. Deaths were also identified from the ‘separation mode’ field within the NHMD hospitalisation dataset, and from the ‘died’ field in the NNDSS.

Population estimates

Mid-year Australian resident population estimates by age and jurisdiction were obtained from the ABS. Aboriginal and Torres Strait Islander population estimates for 2001 to 2019 were taken from the back-cast and projected estimates as provided by the ABS based on the 2016 census. Aboriginal and Torres Strait Islander population estimates for 1999 and 2000 were derived by calculating the average age-specific annual increase in population for the years 2001 to 2006 and deducting this from the 2001 estimated population to provide a 2000 estimate, and then from the 2000 estimate to provide a 1999 estimate.
Data analyses

Data were analysed descriptively, including proportions and rates. Variables analysed from the NNDSS dataset included: confirmation status (confirmed/probable); age at onset; sex; Aboriginal and Torres Strait Islander status; year of diagnosis; whether died of the disease; vaccination status; state/territory; and place of acquisition. All variables were assessed for data completeness. The following derived variables were created: age group from onset age; and overseas/local acquisition from place of acquisition.

Variables analysed from the AIHW hospitalisation dataset included: age; sex; Aboriginal and Torres Strait Islander status; state of residence; admission year; length of stay; separation mode; and principal and additional diagnosis fields. ICD-10-AM codes A36.0, A36.1, and A36.2 were combined for analysis as respiratory diphtheria, and A36.8 and A36.9 were combined as unknown diphtheria (unspecified site).

Rates were calculated using mid-year ABS population data, or jurisdiction or age-specific ABS population estimates, or Aboriginal and Torres Strait Islander population projections as appropriate, and presented per 100,000 population per year. Summary statistics, including median and interquartile range (IQR), were calculated for age and length of stay.

Analysis was performed using Microsoft Excel 2010 and Stata 14.2 (Statacorp LLC, College Station, TX, USA).

Ethics

This epidemiological review was approved by the Australian Capital Territory (ACT) Human Research Ethics Committee (HREC) (2019/ETH12123) and the Australian National University HREC (2020/162).

Results

Notifications

Secular trends

A total of 46 notifications for diphtheria were recorded between 1999 and 2019. Of these, 38 (83%) were cutaneous diphtheria and eight (17%) were respiratory diphtheria. Forty-five of the cases (98%) were reported from 2011 onwards, with only one notification of cutaneous diphtheria (2001) between 1999 and 2010 (Figure 1). The average annual notification rate was 0.008 per 100,000 population per year for cutaneous diphtheria and 0.002 per 100,000 population per year for respiratory diphtheria. The rate was higher in the second half of the study period (2010 to 2019): 0.016 per 100,000 population per year for cutaneous diphtheria, and 0.003 per 100,000 population per year for respiratory diphtheria.

Age and sex

The median age among the eight notified cases of respiratory diphtheria was 31.5 years (range: 21–85 years; IQR: 22.75–50.25); for the 38 cases of cutaneous diphtheria, the median age was 52.5 years (range: 6–83 years; IQR: 25.25–60.0). The highest rate of notifications for respiratory diphtheria was in the 15–24 year age group, and the highest rate for cutaneous diphtheria was in the ≥65 age group, followed by the 50–64 year and 15–24 year age groups (Figure 2). Females were over-represented among notified cases of respiratory diphtheria (n = 6; 75%) and males among notified cutaneous diphtheria (n = 27; 71%).

Organism

C. diphtheriae accounted for most notifications (40 cases; 87%). The first C. ulcerans case was notified in 2013, with three of the six total C. ulcerans notifications in 2018. Of the 40 C. diphtheriae notifications, six (15%) were respiratory
and 34 (85%) were cutaneous infections, and of the six \textit{C. ulcerans} cases, two (33%) were respiratory and four (67%) were cutaneous.

Place of acquisition

The Northern Territory had the highest rate of cutaneous notifications (n = 2; 0.043 per 100,000 population per year), followed by Queensland (n = 26; 0.029 per 100,000 population per year) (Table 1). Queensland accounted for 6/8 (75%) respiratory notifications (0.007 per 100,000 population per year), with one in each of New South Wales and Victoria; 3/8 (38%) were acquired overseas and four of the five locally-acquired cases (80%) occurred in Queensland. The average annual rate for Queensland and the Northern Territory combined was approximately ten times higher than the rate for the other jurisdictions combined, in both the full study period (1999–2019; 0.03 per 100,000 population per year compared to 0.003 per 100,000 population per year) and the second half (2010–2019; 0.054 per 100,000 population per year compared to 0.005 per 100,000 population per year). Of 38 cutaneous diphtheria notifications, infection was acquired overseas in 27 (71%); locally in seven (18%); and unknown in four (11%). All seven local acquisitions and 18/27 (67%) overseas acquisitions were from Queensland, with 12 notified between 2013 and 2016. Of cases acquired in Australia, we were unable to identify which may have been import-linked. Of the 30 notifications where infection was acquired overseas, 21 (70%) were acquired in the Western Pacific Region and nine (30%) in the South East Asia Region. Of the 18 overseas-acquired cutaneous cases in Queensland, countries of acquisition comprised Papua New Guinea (n = 4); Solomon Islands (n = 6); Cambodia (n = 1); Philippines (n = 2); Sri Lanka (n = 1); New Zealand (n = 1); and Vanuatu (n = 3).
Table 1: Number and rate per 100,000 population per year of notified diphtheria cases by site of infection, place of acquisition, and reporting jurisdiction, Australia, 1999–2019

<table>
<thead>
<tr>
<th>Notifying jurisdiction</th>
<th>Respiratory diphtheria</th>
<th>Cutaneous diphtheria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Place of acquisition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overseas</td>
<td>Local</td>
</tr>
<tr>
<td></td>
<td>WPR&lt;sup&gt;c&lt;/sup&gt;</td>
<td>SEAR&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>New South Wales</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Northern Territory</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Queensland</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>South Australia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Victoria</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Western Australia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data source: National Notifiable Diseases Surveillance System.

<sup>b</sup> No cases were reported in the Australian Capital Territory or Tasmania.

<sup>c</sup> WPR: Western Pacific Region; SEAR: South East Asia Region.
Aboriginal and Torres Strait Islander status

Of the eight respiratory diphtheria notifications, one (13%) was reported to be in an Aboriginal and Torres Strait Islander person (in Queensland); six (75%) were reported in non-Indigenous people; with one (13%) for which Indigenous status was not recorded. Of 38 cutaneous diphtheria notifications, three (8%) were reported to be in Aboriginal and Torres Strait Islander people (two in Queensland and one in Victoria); 32 (84%) in non-Indigenous people; and three (8%) for which Indigenous status was not recorded. The rate of respiratory and cutaneous notifications in Aboriginal and Torres Strait Islander people was 0.007 (3.9 times higher than the overall population rate) and 0.021 per 100,000 population per year (2.5 times higher than the overall population rate), respectively.

Vaccination status

Among the 4/8 respiratory notifications with a recorded vaccination history, one had four doses recorded, one had one dose recorded, and two were unvaccinated, both of whom died of the disease. Among 25 cutaneous notifications with a known vaccination history, five (20%) were unvaccinated and 20 had recorded doses (five with 4–5 doses, 15 with 1–2 doses). All six cases (any site of infection) reported as having 4–5 previous doses of diphtheria-containing vaccine were younger than 25 years of age.

Hospitalisations

From 2002–2018, there were 327 hospitalisations with diphtheria listed as a diagnosis but only 29 (9%; 0.008 per 100,000 per year) with diphtheria recorded as the principal diagnosis. Of these 29, eight (28%; 0.002 per 100,000 population per year) were respiratory; eight (28%; 0.002 per 100,000 population per year) were
cutaneous; and 13 (45%; 0.003 per 100,000 population per year) were unknown. The median length of stay for diphtheria (principal diagnosis) was 3 days (IQR: 1–6; respiratory 2 days [IQR: 1.8–4], cutaneous 4 days [IQR: 2.5–5.25]). Of the 29 principal-diagnosis hospitalisations, 13 (45%) occurred in years with no notifications, including all three hospitalisations from the Northern Territory.

Of the 298 hospitalisations with diphtheria as an additional diagnosis, 133 (45%) were in the Northern Territory, and 198 (66%) were cutaneous. Common principal diagnoses among these 298 hospitalisations included endocarditis (n = 25) and skin infection-related codes, such as cellulitis, ulcers, and wound infections (n = 50).

Deaths

There were 1–5 deaths recorded in the ACR causes of death data with diphtheria as the underlying or an associated cause of death between 2006 and 2019, and no related deaths recorded in the ABS data between 2003 and 2005. There were five deaths recorded in hospitalisations coded as due to diphtheria (one principal and four additional diagnosis) in the AIHW data, and two deaths recorded in notified cases in the NNDSS. These individuals may overlap across datasets.

The two deaths reported in the NNDSS both occurred in Queensland and were acquired in Australia; both were in the 20–29 years age group and were unvaccinated.

Discussion

Both respiratory and cutaneous diphtheria remain rare in Australia, with an average annual incidence of notified cases of 0.002 per 100,000 population per year for respiratory diphtheria and 0.008 per 100,000 population per year for cutaneous diphtheria from 1999 to 2019. In the last detailed review of diphtheria, there were no cases reported between 1993 and 1998. In this review, there was one case reported in the NNDSS between 1999 and 2010, with 37 cutaneous cases and eight respiratory cases occurring since 2011, and two deaths. Both deaths reported in the NNDSS were in unvaccinated young adults in Queensland who acquired infection locally, with the 2011 death occurring in a close contact of a partially-vaccinated case who acquired infection in Papua New Guinea, while the source of infection for the 2018 death has not been documented. Notification rates in Aboriginal and Torres Strait Islander peoples, although 2–4 times higher than the overall population, were low.

Both cutaneous and respiratory diphtheria occurred mostly among adults in Australia, with no cases of respiratory diphtheria reported in children aged < 15 years between 1999 and 2019. This absence of respiratory cases in children reflects the high coverage achieved by the childhood immunisation program in Australia. This is particularly evident over the last two decades, with coverage (4 doses of DTPa at 24 months of age) above 90% since 2000. This shift in respiratory diphtheria epidemiology away from childhood was already present in the previous review period (1991–1998) and is consistent with findings in other high-coverage countries. Both the 1997–1998 and 2007 Australian national serosurveys found high immunity in children, decreasing to approximately 60% in adults aged 50 years or older, suggesting that almost half of older adults may be susceptible to diphtheria. The occurrence of respiratory diphtheria predominantly in adults over our study period is likely due to a combination of waning post-vaccination immunity in adulthood and lower historical childhood immunisation coverage, which was estimated at 59–75% in the 1970s and 1980s. A single booster dose of diphtheria-containing vaccine is recommended for adults at 50 years of age (introduced in 2000, replacing previous recommendation for a booster dose every 10 years) and again at 65 years of age. If travelling overseas, a booster is recommended if more than 10 years has passed since the most recent dose (or five years for high-risk travel), introduced in 2013 to address concerns about waning immunity. Ascertaining diphtheria immunisation status
pre-travel remains important, with the majority of cutaneous cases and a third of respiratory cases acquired overseas.

Queensland reported the highest rate of respiratory notifications and the second-highest rate of cutaneous notifications. As cutaneous diphtheria occurs mostly in the tropics, the Queensland climate may contribute, with all seven local acquisitions of cutaneous diphtheria over the study period occurring in Queensland. Other reasons for higher case numbers in Queensland may include travel patterns, better ascertainment of cases through clinical diagnosis, and more complete notification. Due to changes to the national surveillance case definition, cutaneous diphtheria cases were not required to be notified to NNDSS from 2013 to 2016. However, Queensland did not incorporate these changes in its local case definition, notifying 12 cutaneous cases over this period. Although the Northern Territory reported the highest rate of cutaneous notifications, this corresponds to only two cases. The Northern Territory also recorded the highest rate of hospitalisations during the study period. As the diphtheria ICD-10-AM codes do not distinguish between toxigenic and non-toxigenic disease, this is likely a reflection of the burden of non-toxigenic diphtheria, which remains endemic in Central Australia. Non-toxigenic diphtheria, while not notifiable in Australia, is emerging as a cause of substantial infections internationally, including persistent sore throats, endocarditis, septic arthritis, and cutaneous infections. Non-toxigenic strains can acquire the toxin gene if lysogenised by a bacteriophage.

Vaccination status was unknown for half of the respiratory notifications; two cases, representing half of those with a known status, were unvaccinated and died of the disease. Of the two-thirds of cutaneous cases with known vaccination status, the proportion that had received at least four doses and the proportion unvaccinated were the same (one-fifth), reflecting the limited effectiveness of vaccination in preventing wound colonisation. Wounds are also often co-infected with other pathogens, such as *Staphylococcus aureus*, so it may be unclear whether *Corynebacterium* detected is the causative organism or only commensal. Nevertheless, as in respiratory cases, appropriate prophylactic antibiotics remain important for contacts of cutaneous cases, along with catch-up vaccination if required, to prevent transmission.

Similarly to Australia, increases in diphtheria cases have been documented in Belgium since 2010, and in the UK since 2015. Internationally, *C. ulcerans* is playing an increasing role in the burden of diphtheria in highly vaccinated populations becoming the dominant organism in the UK since the 1990s due to locally-acquired *C. ulcerans* cases associated with exposure to domestic animals. In Australia, *C. diphtheriae* still accounted for 85% of notified cases from 1999 to 2019. *C. ulcerans* was added to Australia’s case definition in 2004, but no cases were notified until 2013. Vaccination appears to be effective against *C. ulcerans* toxin; however, concerns have been raised that the greater diversification of the toxin gene in *C. ulcerans*, compared to *C. diphtheriae*, could lead to decreased effectiveness of the vaccine over time. *C. pseudotuberculosis* has been made notifiable in some European countries to better characterise disease caused by this organism.

While there have been several changes to the Australian surveillance case definition between 1999 and 2019, there were few cases during the period with the broadest case definition (2004 to 2012). During this time, two out of the three notified respiratory cases were asymptomatic carriers, with the national case definition changed in 2013 to require the presence of clinical symptoms. This suggests that the minor re-emergence of respiratory notifications in the years following was unlikely to be due to case definition changes. The increased number of notified cases seen since 2011 largely comprised cutaneous cases. Although cutaneous diphtheria was notifiable from 2004 to 2012, it is unclear to what extent cases were routinely notified. The case definition was changed in
2017 to specifically include cutaneous presentations, which may have encouraged notification and may account for some of the increase in cutaneous cases since 2011.

Ascertaining diphtheria immunisation status pre-travel remains important, particularly if travelling to a high-risk area, with the majority of cutaneous cases and a third of respiratory cases in our study acquired overseas. Since 2000, the South East Asia region has reported the highest number of diphtheria cases each year out of all World Health Organization regions, with India, Nepal, and Indonesia collectively reporting 96–99% of South East Asia cases. Only 30% of cases in our study acquired infection in South East Asia, with the remaining 70% acquired in the Western Pacific region where diphtheria also remains endemic in many countries; however, comparison and interpretation of distribution patterns is difficult due to the small number of cases involved.

There are several limitations to this study. Notification data are generally not considered to be representative of all cases in the population, but the sensitivity of notification datasets may be better for rare and serious conditions such as respiratory diphtheria. Notification data were incomplete for a number of fields, including Aboriginal and Torres Strait Islander status and vaccination status, and recorded vaccinations in notified cases may not reflect complete vaccination history, particularly for vaccinations received prior to the introduction of the Australian Childhood Immunisation Register in 1996. Completeness of vaccination status should improve over time as vaccination data for more birth cohorts are captured in the Australian Immunisation Register. Public health unit staff following up diphtheria notifications should ensure other important fields such as Aboriginal and Torres Strait Islander status, site of infection, and death are completed, to optimise accuracy of data on this rare but important condition. The number of hospitalisations for diphtheria is disproportionately high compared to the number of notifications. This is likely due to a lack of specificity in diphtheria ICD-10-AM codes and may also be due, in part, to errors in coding, which are more common for rare diseases. Additionally, hospitalisation data are episode-level records and may include multiple records for individual cases transferred between hospitals or readmitted. This, in combination with a large proportion of hospitalisations with an unknown site of infection, limited our ability to describe severe disease due to toxigenic respiratory and cutaneous diphtheria. There were also discrepancies in the numbers and details of deaths across datasets.

In summary, despite an increase in cases over the past decade, diphtheria remains rare in Australia. It is, however, important to maintain high levels of vaccination coverage. In particular, pre-travel booster vaccination should continue to be encouraged, in line with recommendations in the Australian Immunisation Handbook.
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## Appendix A

### Table A.1: Changes to the diphtheria national surveillance case definition

<table>
<thead>
<tr>
<th>Year</th>
<th>Case definition</th>
<th>Main changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>Isolation of toxigenic <em>C. diphtheriae</em> and one of the following: pharyngitis and/or laryngitis (with or without membrane) or toxic (cardiac or neurological) symptoms</td>
<td>N/A</td>
</tr>
</tbody>
</table>
| 2004 | **Confirmed case** Isolation of toxigenic *C. diphtheriae* or toxigenic *C. ulcerans*.  
**Probable case** Isolation of *C. diphtheriae* or *C. ulcerans* (toxin production unknown) and one of the following presentations as clinical evidence: pharyngitis and/or laryngitis (with or without membrane) or toxic (cardiac or neurological) symptoms or Clinical evidence as above and an epidemiological link to a confirmed case | Inclusion of *C. ulcerans* in confirmed case definition. Does not require clinical evidence/symptoms to be a confirmed case. Inclusion of a probable case definition. Cutaneous diphtheria notifiable. |
| 2013 | **Confirmed case** Isolation of toxigenic *C. diphtheriae* or toxigenic *C. ulcerans* AND clinical evidence  
**Probable case** Isolation of *C. diphtheriae* or *C. ulcerans* (toxin production unknown) and clinical evidence or Clinical evidence and an epidemiological link to a confirmed case  
**Clinical evidence:** pharyngitis and/or laryngitis (with or without membrane) or toxic (cardiac or neurological) symptoms | Requires clinical evidence to be a confirmed case. Cutaneous diphtheria notifiable only with toxic symptoms. |
| 2017 | **Confirmed case** Isolation of toxigenic *C. diphtheriae* or toxigenic *C. ulcerans* from upper respiratory tract infection or skin lesion  
**Probable case** Isolation of *C. diphtheriae* or *C. ulcerans* from a respiratory tract specimen (toxin production unknown) AND Upper respiratory tract infection with an adherent membrane of the nose, pharynx, tonsils or larynx or Upper respiratory tract infection with an adherent membrane of the nose, pharynx, tonsils or larynx AND Epidemiological link to a confirmed case | Specific inclusion of skin lesion in confirmed case definition. Cutaneous diphtheria notifiable. |