Australian Centre for Disease Control

Summary of evidence and rationale – Diphtheria

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Introduction

This summary of evidence and rationale refers to the evidence review and recommendation process undertaken during the development to Version 1 of the Diphtheria Communicable Diseases Network Australia (CDNA) National Guidelines for Public Health Units.

Revision history

Version	Publication date	Revised by	Comments
1	21 August 2026	N/A	Developed by Australian CDC

Contributors

This review of evidence was undertaken by the Public Health Advisory Section of the Preparedness Branch of the Australian Centre for Disease Control.

Evidence review and recommendations process

A semi-systematic review of the available evidence was undertaken to develop the Diphtheria CDNA National Guidelines for Public Health Units.

The evidence base underpinning Version 1 of the guidance was reviewed across all sections. This included review of national and international guidelines, technical handbooks and manuals. Targeted literature reviews were also performed to identify new evidence.

This evidence review was conducted by a single staff member in the Australian CDC; searches and screening were not repeated by a second person. The evidence summary was presented to the CDNA Diphtheria Series of National guidance (SoNG) working group, which had the opportunity to provide additional information, feedback on the interpretation of the evidence, and rationale for recommendations.

The findings of these reviews are summarised below by topic.

Public health approach

Public health importance

Evidence review

The evidence for the public health importance of diphtheria was reviewed. National and international guidelines, technical handbook and manual searches were conducted.

Database searches were conducted on the 25 March 2026, using the search terms in the table below.

Table 1. Database search terms

Databases	Search terms
Pubmed, Ovid Embase, Cochrane library	Population – human, people, population, community Exposure – diphtheria, Corynebacterium diphtheriae, C. diphtheriae, Corynebacterium ulcerans, C. ulcerans Comparator – no comparator terms used Outcome – epidemiology, surveillance, incidence, prevalence, case fatality Context – worldwide or Australia

Screening of identified studies was conducted using the following inclusion and exclusion criteria:

Inclusion criteria	• Publications about toxigenic diphtheria
Exclusion criteria	• Publication types out of scope (opinion piece, editorial, commentary, conference abstracts) • Publication not in English • Withdrawn or superseded studies • Incomplete data (ongoing study, no outcomes of interest)

Evidence summary

Respiratory diphtheria is a disease of colder months in temperate zones. In the tropics, seasonal trends are less distinct; inapparent cutaneous and wound diphtheria are much more common. Diphtheria epidemics can occur in susceptible populations (1).

Notifications of *Corynebacterium diphtheriae* have significantly reduced since the early twentieth century, largely due to vaccination (introduced in 1932) (2). In 2021, the global age-standardised incidence rate (ASIR) (0.19 per 100,000 population, 95% UI: 0.13, 0.27 per 100,000 population) and age-standardised mortality rate (ASMR) (0.06 per 100,000

population, 95% UI: 0.04, 0.08 per 100,000 population) for diphtheria were both very low (3).

Reported case fatality ratios vary across settings, ranging from 29% (4), to as high as 50% in resource-limited settings (5, 6).

In 2021, Across all Global Burden of Disease region, gender, and socio-demographic index categories, they were below 1.20 per 100,000 population (ASIR) and 0.40 per 100,000 population (ASMR). The global age-standardised disability-adjusted life years (DALY) rate was estimated at 4.75 per 100,000 population (95% UI: 3.19–6.82 per 100,000 population). Compared to 1990, diphtheria ASIR, age standardised DALY rate, and ASMR all decreased by at least 85.00% (3).

There was no significant difference between sexes in reported incidence rates. In 2021, global diphtheritic ASIR in males (0.19 per 100,000 population, 95% UI: 0.13, 0.28 per 100,000 population) and females (0.20 per 100,000 population, 95% UI: 0.12, 0.29 per 100,000 population) were very close. Similarly, the age standardised DALY rates in males (4.99 per 100,000 population, 95% UI: 3.27, 7.45 per 100,000 population) and females (4.50 per 100,000 population, 95% UI: 2.87, 6.59 per 100,000 population) were also close (3).

Diphtheria is now more commonly seen in adults than in children in industrialised countries for several reasons (7). Firstly, improved living conditions impacted on the incidence of childhood diphtheria even before vaccines became available. Smaller families and less overcrowding meant that preschool children were not exposed to the same intensity of infection as previous. As a result, many reached adulthood without having been exposed to diphtheria and therefore lacking natural immunity (7). Secondly, the implementation of mass childhood vaccination programs further reduced both the incidence of diphtheria and the circulation of toxigenic *C. diphtheriae*, so there were fewer opportunities to acquire natural immunity or to boost waning vaccine-induced immunity (7, 8).

Diphtheria remains a disease of significant global public health importance, with large outbreaks occurring where population immunity declines (1), and potential for resurgence through international travel and gaps in vaccination coverage (2, 7, 9).

At the height of the 1921 epidemic, in Australia, there were 23,199 notifications (annual notification rate 426 per 100,000 population). In the decade between 1926 and 1935, there were 4,043 deaths from diphtheria (7). Between 1991 and 1998, 23 cases were notified in Australia, including one fatality. Most (64%) of these cases were aged at least 15 years (range 1-78 years), in contrast to the pre-vaccine era when less than 30% of cases were aged 15 years and older (7). Outbreaks in Australia during the 1990's were concentrated in under-vaccinated groups with greater disadvantage living in crowded conditions. Higher

notification rates were seen amongst Indigenous peoples, with a higher proportion of adult cases (7). A review from 2022 highlighted that 98% of diphtheria notifications in Australia between 1999 and 2019 occurred after 2011 (2).

In 2022, the numbers of notifications of locally acquired diphtheria cases had increased in Queensland, with 4 (0.1 per 100,000 population) respiratory cases and 20 (0.4 per 100,000 population) cutaneous cases. Cases were predominantly reported in North Queensland Indigenous communities with genomic clustering demonstrated (10). In 2022, a study in the Northern Territory showed that of the 41 *C. diphtheriae* cutaneous isolates tested, none were found to be toxin positive on in-house PCR (2). This study also showed the frequency of *C. diphtheriae* in wound culture in a tropical setting but rarity in throat carriage (2).

Through 2025 and 2026, locally acquired cases of cutaneous and respiratory diphtheria were detected in Aboriginal and Torres Strait Islander communities across Western Australia (11) and the Northern Territory (12).

The public health management of these infections can be complex, including managing the emergence of antibiotic resistance. The emergence of antimicrobial resistance in *C. diphtheriae* strains globally is described in the literature (13).

Priority populations

Evidence review

The evidence for the priority populations of diphtheria was reviewed. National and international guidelines, technical handbook and manual searches were conducted and stakeholder submissions reviewed.

Database searches were conducted on the 16 March 2026, using the search terms in the table below.

Table 2. Database search terms

Databases	Search terms
Pubmed, Ovid Embase, Cochrane library	Population – priority population, high risk groups, high risk, vulnerable population, vulnerable, at risk population, at risk Exposure – diphtheria, Corynebacterium diphtheriae, C. diphtheriae, Corynebacterium ulcerans, C. ulcerans Comparator – no comparator terms used Outcome – risk, risk assessment, mortality, case fatality infection risk, fatality risk Context – worldwide

Screening of identified studies was conducted using the following inclusion and exclusion criteria:

Inclusion criteria	• Publications about toxigenic diphtheria
Exclusion criteria	• Publication types out of scope (opinion piece, editorial, commentary, conference abstracts) • Publication not in English • Withdrawn or superseded studies • Incomplete data (ongoing study, no outcomes of interest)

Evidence summary

Persons of any age who are unvaccinated or under-vaccinated are at highest risk of respiratory disease (9, 14), particularly if it is more than 10 years since the last dose (9).

A United Kingdom (UK) study demonstrated that the main risk factor for diphtheria cases was being unvaccinated (15), with surveillance in the UK between 2009 and 2017 showing that 67% of cases were inadequately vaccinated (15). Suboptimal diphtheria vaccination status for both toxigenic *C. diphtheriae* and *C. ulcerans* infections was also strongly associated with the risk of hospitalisation and death (15). Truelove et al's systematic review found the case fatality ratio in unvaccinated individuals infected with toxin-producing strains was 29% (4).

While fully vaccinated individuals can still have diphtheria, the cases are usually less severe as seen in the UK surveillance data between 2009 and 2017, where 43% of cases were mostly younger fully vaccinated individuals who presented with mild respiratory or mild cutaneous forms of *C. diphtheriae* and *C. ulcerans* (15).

During this period in the UK, *C. ulcerans* was more commonly seen in older individuals with unknown or partial vaccination history (15). Increased risk of infection from *C. ulcerans* is more frequently seen in those who have contact with animals, including companion animals (16).

Surveillance in Indonesia in the period from 2010 to 2017 showed the highest number of cases occurred in the 5-9 years age group, followed by 1-4 years, which accounted for 32.5% and 19.1% of overall diphtheria cases in 2017, respectively. The report concluded that this demonstrated routine immunisation coverage had not reached target levels and equal distribution across the regions had not been obtained. The case distribution was also reported among the adults aged 19-40 years, accounting for 19% of overall cases. The authors considered the utility of routine additional doses of diphtheria-containing vaccine in adults (14).

A study examining paediatric infections during wartime identified two distinct groupings of countries based on trends in incidence of diphtheria. The first included those with high incidence of diphtheria, where the majority of cases occurred in unimmunised individuals who were mostly aged under 15 years. The second group included countries with only sporadic diphtheria and usually had better immunisation rates. Cases in this group occurred more often in individuals with partial immunisation, who were often over the age of 15. This study highlights the impact which population-level immunisation status has on the affected population, and that that waning immunity is a risk factor for adults in countries with higher levels of immunisation (17).

Outside of natural exposure, immunity is known to wane over time (1, 18). Seroepidemiological surveys of non-endemic countries have demonstrated seropositivity well below that required for immunity in older age groups (1, 18). A study in Germany showed inadequate immunity to diphtheria in more than 90% of the 400 individuals tested, including 4% who completely lacked immunity (titre < 0.01 IU/ml), a further 20% with minimal protection (titre 0.01-0.1 IU/ml) and the majority (69%) who showed relative protection for less than one year (titre 0.1-1.0 IU/ml). Only 7% exhibited lasting protection for more than five years (titre > 1.1). Newborns and persons over 50 years of age constituted the least protected groups, with significantly lower median antitoxoid titres than the other age groups ($p < 0.001$). The absence of protective immunity in 7 of the 50 newborns examined (14%) reflects the inadequate protection of women of reproductive age. Children aged 1 to 10 years were the best immunised and protected group. The results suggest that routine booster immunisations of the majority of the adult population would be advisable in view of the ongoing migration from and the visits to high-risk areas (19).

One case series report noted that partial immunity was a possible explanation for the relatively mild presenting symptoms in the index patient (18). Incomplete immunisation was a critical factor identified in another case study, with serious disease and death reported in a child who has not completed the full diphtheria vaccination series. Although vaccines are highly effective at preventing clinical disease, they do not always prevent colonisation. Unvaccinated or partially vaccinated children are at much higher risk of developing severe toxin-mediated illness (20).

When healthcare systems are disrupted and vaccine coverage declines, diphtheria may re-emerge. This has been observed in places like the former Soviet Union in the 1990s, in camps of displaced Myanmar nationals in Bangladesh (5, 21), Yemen, which has been engaged in a civil war since 2014, and Venezuela, whose health system has been in a state of collapse for nearly a decade (17). In East Africa, recurrent outbreaks and sporadic cases have been reported, particularly in settings affected by displacement, malnutrition, and gaps in routine childhood vaccination programs (20). A study from a refugee settlement in

Brazil identified other factors such as comorbidity, family history, type of shelter, and unhygienic practices; participants who visited traditional healers and history of surgical operation were significantly associated with having an infectious disease, including diphtheria (22). Refugees are a heterogeneous group with varied medical needs based on the country of origin and country of transit, the length of time as a refugee, and quality of healthcare prior to arrival. All displaced people are at increased risk of vaccine preventable disease (VPD) due to poor vaccine availability and failing public health systems in their country of origin (23).

There is a particular risk for persons travelling to regions with vaccine program disruptions and where diphtheria remains more common (9). To reduce the risk of imported cases of diphtheria in Australia, travellers need to be up-to-date with their vaccinations (7).

Healthcare system disruptions seen during the COVID-19 pandemic have resulted in declines in childhood immunisation coverage which have not yet recovered, leaving many countries susceptible to higher VPD incidences (24). During 2010 to 2019, global coverage with Diphtheria/Pertussis/Tetanus (DTP) combined vaccines remained relatively unchanged: first dose DTP coverage was 89% in 2010 and 90% in 2019. However, the number of zero-dose children decreased by 19%, from 15.8 million children in 2010 to 12.8 million children in 2019 (24). From 2019 to 2023, DTP coverage decreased in countries in every World Bank economic classification. The decline was most notable in low-income countries, where third dose DTP decreased by 7 percentage points (75% in 2019 to 68% in 2023); countries in all other income groups returned to within 1 percentage point of 2019 coverage levels. In 2023, the number of zero-dose children rose again, with 14.5 million children globally who had not received a first dose of DTP (24).

Aboriginal and Torres Strait Islander Peoples and Communities – Culturally appropriate and safe responses to infectious diseases and outbreaks

Evidence review

The evidence for culturally appropriate and safe responses to infectious diseases and outbreaks in Aboriginal and Torres Strait Islander communities were reviewed. National guidelines searches were conducted and stakeholder submissions reviewed.

Database searches were conducted on 23 April 2026, using the search terms in the table below.

Table 3. Database search terms

Databases	Search terms
Pubmed, Ovid Embase, Cochrane library	Population – Aboriginal and Torres Strait Islander Exposure – disease, infection, outbreak Comparator – no comparator terms used Outcome – culturally appropriate, culturally safe, disease response, outbreak response

Screening of identified studies was conducted using the following inclusion and exclusion criteria:

Inclusion criteria	• Publications about response to infectious diseases • Publications related to Australia
Exclusion criteria	• Publication types out of scope (opinion piece, editorial, commentary, conference abstracts) • Publication not in English • Withdrawn or superseded studies • Incomplete data (ongoing study, no outcomes of interest)

Evidence summary

New South Wales Health and Queensland Health Diphtheria control guidelines both highlight that early consultation and partnership with community leaders and representatives is important when managing diphtheria cases and contacts in Aboriginal and Torres Strait Islander communities. They note that if an outbreak control team is convened, it is recommended to include appropriate Aboriginal and Torres Strait Islander stakeholders (25, 26).

The Aboriginal Health Council of Western Australia in their COVID-19 Response Review note that governments must ensure that authentic partnerships with Aboriginal people and organisations are established both prior to and during health emergencies. Partnerships are necessary at all levels of government (Commonwealth, state and local) and across all stages of emergency management (prevention, preparedness, response and recovery). Partnerships must respect Aboriginal leadership and expertise, and decision-making must be genuinely shared. Decentralised planning and locally-led solutions must be supported (27). Research by Massey et al highlights that communities placed a high value on partnerships and collaborations. The message to government was that through "Collaboration. . . people [are] more likely to take notice" (28).

An evaluation of the Aboriginal Community Controlled Health sector's COVID-19 initiatives noted that enablers of significant achievements during the pandemic included strong leadership from Aboriginal and Torres Strait Islander people, including Elders, dedication from Aboriginal Community Controlled Health Organisations (ACCHO) staff, strong communication methods that enhanced social capital, and effective collaboration between National Aboriginal Community Controlled Health Organisation (NACCHO), Affiliates, ACCHOs, non-government and government organisations (29). The evaluation highlighted that Aboriginal Community Controlled Health (ACCH) sector demonstrated sovereign governance in pandemic response – mobilising collective knowledge, kinship networks, and cultural leadership to safeguard communities in ways mainstream systems could not. Concluding that participation and engagement with the ACCH sector were crucial to successful, culturally safe responses across Australian communities (29).

Research by Graham et al emphasises that leadership and Eldership need to come from community and findings highlighted the importance of engaging Elders and acknowledging their cultural knowledge and life experience (30). Community-led involvement at all stages of prevention, preparedness, response and recovery activities are key to self-determination. Engaging community panels and embedding Aboriginal and Torres Strait Islander cultural governance structures prior to a response will support self-determination during a response (31). Engaging Community Panels for community-led planning is an evidence-based approach that provides a deeper understanding of how to design and implement response strategies (32, 33).

Embedding Aboriginal and Torres Strait Islander cultural governance in a public health emergency management system will prioritise genuine Aboriginal and Torres Strait Islander engagement in planning, response and recovery (34). Cultural safety also requires health care providers and institutions to recognise their own culture and ameliorate approaches which diminish, demean or disempower the cultural identities and wellbeing of patients (35).

Family, housing and mobility patterns must be considered during preparedness planning and response with Aboriginal and Torres Strait Islander communities. Family is central to all aspects of health in Aboriginal and Torres Strait Islander communities, so family centred approaches to prevention, preparedness, response and recovery are most effective (28, 31).

Governments must ensure that the needs of Aboriginal and Torres Strait Islander people, families and communities (urban, regional and remote) are properly considered and addressed at all stages of health emergency management. Mainstream services during health emergencies must be culturally safe, accessible and prioritised according to need. Pandemic planning must address the social determinants of health—particularly housing (27).

Research also highlights a need for government and organisations to enter into a dialogue with Aboriginal and Torres Strait Islander communities, to discover what communities wanted to know before telling them. Respondents in a study by Massey reported that it was important that authorities listened to what was really meant, and then shared the information needed. One of the local Aboriginal health professionals interviewed described this process as "We don't educate – we share" (28). Culturally safe information provided to Aboriginal and Torres Strait Islander communities must be informed by Aboriginal and Torres Strait Islander people at state and local levels. This information must consider social determinants and Aboriginal and Torres Strait Islander ways of living, including multi-generational living arrangements and accessibility of health services (31). In another example, Aboriginal participants in a study on HTLV-1 management consistently articulated that they and their communities should be informed of, and can hold, knowledges pertaining to the disease (36).

Participants in a study on COVID-19 commented that equipping First Nations peoples with reliable, timely and accurate information is the most important and achievable action to reduce the spread of infectious diseases among First Nations communities. It is also imperative that First Nations peoples are well-informed about the reasons behind public health actions and directives, which can help facilitate trust with government and health authorities (33). Participants emphasised that information must be communicated in a way that is meaningful, accessible, easy-to-understand, and considers the diversity of First Nations peoples and culture. Participants identified that local networks and trusted community leaders are critical in ensuring the dissemination of health messages (33).

The importance of having local people who are well informed and can advise on what to do in the event of an infectious disease incident is highlighted in Massey et al's study on pandemic influenza. It was noted that having a local person meant that people in the community would have someone they could trust and could access easily. Study participants commented that they were much less likely to contact someone from another

community or area with whom they were not familiar. A local person would need training and support from the health service to meet this need. When asked about who these local contacts should be, most study participants identified Aboriginal health workers and ACCHS staff as the best 'go to' people (37). These people are important for "delivering the health message and they do not frighten the community by keeping the message culturally appropriate by being there to translate immediately any misinterpretation" (28).

A need for clear communication with each community was also described in the literature. Information was required in a clear and simple format, while demonstrating respect for the local culture. Specifically, people wanted to know what symptoms of illness they should be alert to and what they should do in the event of these symptoms appearing. Aboriginal and Torres Strait Islander radio programs and newsletters from Aboriginal and Torres Strait Islander organisations with locally made announcements were considered necessary if the messages were to be successful. Written information, such as posters and pamphlets with key messages, was considered helpful but needed to be supported by local people with photos or quotes to illustrate that these messages were supported by local, trusted people (37). To connect effectively, participants advised that the communication needed to be "localised, personalised and humourised", using established local community networks and local languages. The importance of ensuring that information related to community members using identifying colours, people and logos, was reported. As described by study participants "The more you can localise something the better it is received. Use of local people promotes ownership" and "If you see an ad with Aboriginal person, you can't wait to see it again" (28).

Participants in Graham et al's COVID-19 study expressed that positive health messaging (i.e., focusing on what people are able to do, rather than focusing on restrictions) can enhance community self-determinism, growth and empowerment. Emergency responses that strengthen and empower communities can aid recovery from the pandemic. Participants reported that transparent communication between government agencies and communities is essential. They also spoke about the need for holistic support for communities (30).

A paper reviewing the response to HIV notes that successful management of disease is the result of multiple factors. These include early recognition by Indigenous peoples of the potential effect that HIV could have on their communities; the supply of health hardware; the development and implementation of culturally appropriate health promotion messages; the inclusion of dedicated Aboriginal and Torres Strait Islander Sexual Health Workers in communities; and an inclusive policy and partnership approach. Furthermore, the efforts of peak Aboriginal health organizations and their member services, have all contributed to prevention success (38).

The evaluation of the ACCH sector's COVID-19 initiatives reported that sustainable transformation requires binding, structural inclusion of Aboriginal and Torres Strait Islander co-governance for health responses, rather than being reliant on individual relationships. All levels of government need to contribute towards Priority Reform 1 of Closing the Gap and incorporate structures that automatically involve the ACCH sector in the decision-making, cultural authority and resource control for their respective communities (29). The evaluation affirms the need to centre Aboriginal and Torres Strait Islander sovereignty, self-determination, governance, and knowledges in the health system. The pandemic response demonstrated that when Aboriginal and Torres Strait Islander communities lead responses, resourcing is better targeted, trust is higher, and outcomes improved. Future emergency preparedness must not only include Aboriginal and Torres Strait Islander leadership, but be built upon it (29).

Disease summary

Transmission

Evidence review

The evidence for the transmission of diphtheria was reviewed. National and international guidelines, technical handbook and manual searches were conducted and stakeholder submissions reviewed.

Database searches were conducted on the 14 April 2026 using the search terms in the table below.

Table 4. Database search terms

Databases	Search terms
Pubmed, Ovid Embase, Cochrane library	Population – human Exposure – diphtheria, respiratory diphtheria, cutaneous diphtheria Comparator – no comparator terms used Outcome – transmission, person-to-person, contact, exposure Include – case reports, case series, public health investigation, contact investigation Exclude – review, guideline, editorial, comment, vaccine, post-exposure prophylaxis, PEP, prevalence, incidence, epidemiology

Screening of identified studies was conducted using the following inclusion and exclusion criteria:

Inclusion criteria	• Publications about toxigenic diphtheria
Exclusion criteria	• Publication types out of scope (opinion piece, editorial, commentary, conference abstracts) • Publication not in English • Withdrawn or superseded studies • Incomplete data (ongoing study, no outcomes of interest)

Evidence summary

Corynebacterium diphtheriae

Respiratory diphtheria

C. diphtheriae transmission occurs person-to-person via respiratory droplets or direct contact with respiratory secretions (4, 8, 39-41).

Both symptomatic and asymptomatic individuals can transmit diphtheria, although it is estimated that asymptomatic carriers cause 76% (95% CrI, 59%–87%) fewer infections than symptomatic cases over the course of carriage (4).

Cutaneous diphtheria

Due to prolonged bacterial shedding, cutaneous diphtheria plays a role in transmission to susceptible persons, via contact with the wound exudate or contaminated fomites (4, 8, 42).

As humans are assumed to be the sole reservoir of *C. diphtheriae*, cutaneous diphtheria likely plays an important role in transmission during interepidemic periods (4). In tropical countries, cutaneous diphtheria lesions may act as reservoirs of infection (43).

Cutaneous transmission has been reported in an adult male in New Zealand who developed a cutaneous infection after being tattooed in Samoa and an 11-year-old household contact with no travel history, who also developed cutaneous diphtheria caused by *C. diphtheriae* (44).

Transmission from cutaneous lesions can cause respiratory disease in cases and contacts (42, 43, 45). The first documented transmission of toxigenic *C. diphtheriae* in the UK for over 30 years occurred in the East of England in 2017, when a contact of a case with cutaneous *C. diphtheriae* infection who had recently returned from Africa, but had not herself travelled, developed a mild respiratory diphtheria infection (46).

Corynebacterium ulcerans

Toxigenic *C. ulcerans* infections were previously associated with consumption of raw dairy products but have become more recently associated with contact with companion animals, including cats and dogs (47-53). In a review of 62 cases of *C. ulcerans* in the UK between 1986 and 2008, 7 of 59 (12%) *C. ulcerans* cases were recorded as having consumed raw milk or dairy products, with one of these also having had contact with cattle (47). Infection with *C. ulcerans* after contact with sheep (54) and pigs (55) has also been reported. Additionally, cases of possible human-to-human transmission of *C. ulcerans* have been reported in Germany and the UK (47, 49).

Infectious agent and clinical condition

Evidence review

The evidence for the infectious agent and clinical condition of diphtheria was reviewed. National and international guidelines, technical handbook and manual searches were conducted and stakeholder submissions reviewed.

Evidence summary

Pathogen

Diphtheria is a disease caused primarily by toxigenic *Corynebacterium diphtheriae* bacteria, a non-sporing, non-encapsulated, and non-motile gram-positive bacillus. Toxigenicity occurs when the bacillus becomes infected with a specific virus (corynebacteriophage) which carries the gene for the toxin (tox gene). The potent exotoxin is the major virulence mechanism leading to human disease (1, 4, 8, 9, 43, 47).

Four biovars of *C. diphtheriae* can be distinguished by colonial morphology and biochemical characteristics: gravis, intermedius, mitis, and belfanti (1, 56, 57).

Corynebacterium ulcerans and, rarely, *Corynebacterium pseudotuberculosis* bacteria can also carry the phage and cause toxigenic diphtheria. They are predominantly animal pathogens but cause human disease as zoonotic infections (8, 9, 43, 56). There are many (at least 115) other species of corynebacteria including *C. pseudodiptheriticum,* which are not able to carry the toxin gene and are thus unable to cause diphtheria (56). Nontoxigenic strains occasionally cause disease of varying severity, particularly in vulnerable populations. These do not meet the definition of diphtheria (1, 8).

Reservoir

Humans are assumed to be the main reservoir of *C. diphtheriae* (1, 4, 42) carrying diphtheria in the pharynx or nose (58). Horses, cattle and domestic cats are thought to be possible, less common, reservoirs (42).

C. ulcerans has a wide host range and has been isolated from domestic, wild and captive animals (47, 59).

Incubation period

The incubation period for respiratory diphtheria is usually 2 to 5 days (1) but may be longer, with duration of up to 10 days reported (60).

Other estimates from a systematic review by Truelove et al suggest that the median time from infection to prodromal symptom onset for respiratory disease is 1.4 days (95% credible interval [CrI],1.0–1.9) (4).

Infectious period

Asymptomatic carriage of toxigenic corynebacteria may occur during the incubation period of diphtheria, during convalescence, or for an unknown duration in healthy people. Patients convalescing from diphtheria may harbour corynebacteria in the pharynx or nose for many weeks (58). A systematic review found that untreated individuals remain colonised for an average of 18.5 days (95% CrI, 17.7–19.4 days), with 5% remaining

colonised longer than 48 days (95% CrI, 46–51 days) (4). There was no statistical evidence for different colonisation times between symptomatic and asymptomatic infections, absent treatment (difference in Watanabe-Akaike information criterion, −3.4 [95% confidence interval [CI], −10.0 to 3.3]) (4).

Asymptomatic cases cause 76% fewer cases than symptomatic cases and appropriate vaccination with diphtheria toxoid vaccine reduces transmission by 60% (4).

Patients receiving antibiotic treatment were found to clear C. diphtheriae respiratory colonisation within 5.2 days (95% CrI, 4.4–6.1 days) of initiating treatment on average, reducing the average duration of infectiousness by as much as 2 weeks (4).

Clinical features

Clinical features are due to a toxin-mediated illness where the toxin causes local tissue necrosis. The disease presents as two main forms—respiratory and cutaneous diphtheria (9).

Respiratory diphtheria

Cases of asymptomatic or mild respiratory infection (without a pseudomembrane) are more common in vaccinated persons as the vaccine is protective against the effects of the toxin (9). Many colonised individuals never develop symptoms with 31% (95% CrI, 18%–55%) of infections in unvaccinated individuals being asymptomatic (4).

Nasal diphtheria, usually mild and chronic, is marked by unilateral or bilateral nasal discharge, which is initially clear and later becomes bloody (1).

Onset is often gradual, with symptoms of low-grade fever, sore throat and malaise (8, 42).

Primary respiratory diphtheria most commonly affects the tonsils and pharynx (4, 42), where toxin-mediated local tissue necrosis leads to the development of isolated white or grey spots appear which extend and coalesce to form a confluent, sharply demarcated pseudomembrane (9, 42). This thickens, darkens, may extend into the lower airway (8), and can cause airway obstruction and severe systemic disease (1).

An estimated 80% of untreated symptomatic cases progress to membranous diphtheria 2–3 days after symptom onset (4).

In moderate to severe cases of respiratory diphtheria, the throat may be moderately to severely sore with enlarged and tender cervical lymph nodes and together with marked swelling of the neck, can give rise to a characteristic "bull neck" appearance (1, 61, 62).

Cutaneous diphtheria

The lesions of cutaneous diphtheria are variable, usually appear on limbs, particularly legs and are typically chronic (63). They often starting as vesicles and quickly form small, clearly demarcated and sometimes multiple, ulcers that may be difficult to distinguish from impetigo (1, 9, 64). The ulcers can be covered with a grey-white necrotic slough or membrane (9).

Cutaneous diphtheria lesions are often associated with infected insect bites (63), and are frequently coinfected with pathogens such as *S. aureus* and *S. pyogenes* (44, 63, 65-67).

Complications and outcomes

Respiratory diphtheria

Dislodging the pseudomembrane, mechanically or as the disease progresses, may cause profuse bleeding, asphyxiation and death. Progression to death from asphyxia due to airway obstruction within 1–2 weeks after symptom onset is responsible for 60%–65% of deaths and is associated with laryngeal infection (4).

Toxic cardiomyopathy may occur 7–14 days after the onset of respiratory symptoms (1, 4) in up to 10%–25% of patients and is responsible for 20%–25% of deaths (4).

Neurological disorders, such as hypoesthesia, polyneuropathy (that can mimic Guillain-Barre syndrome) (1), and cranial neuropathies, develop weeks to months later and occur in 20%–25% of untreated cases and are responsible for up to 15% of deaths (4).

The case fatality rate of respiratory diphtheria is estimate to be 5–10%, even with appropriate treatment (1, 9). A systematic review by Truelove et al estimated the case fatality ratio for untreated, never-vaccinated cases is 29.0% (95% credible interval [CrI], 28.8%–29.2%). Vaccination and treatment substantially reduce the case fatality ratio (4).

Other studies found that the case fatality ratios in resource-limited settings are highly variable but, in some outbreaks, can be as high as 50% (5, 6).

Children aged <5 years are more likely to die from symptomatic infection than adults >20 years of age (relative risk [RR], 1.5 [95% CrI,1.4–1.6]), whereas children 5–19 years of age are less likely to die from infection than adults aged >20 years (RR, 0.8 [95% CrI, 0.8–0.9]) (4)

Cutaneous diphtheria

Systemic toxic manifestations are uncommon among immunised persons. Skin lesions absorb toxin slowly and can induce high levels of antibodies that produce natural immunisation (9, 63).

Recommendation rationale

Infectious period

Importance of outcome

There is importance in defining the infectious period, as it directly informs contact tracing timeframes and public health management decisions. However, the available evidence base is limited, and the distinction between a 7-day and 10-day infectious period is not well supported by data.

Resource use

A consistent 7-day approach, including for cases with unclear onset such as long-standing wounds (using 7-days prior to swab), was considered to reduce complexity and workload for cases and public health units.

Acceptability

High acceptability of the 7-day approach was reported. This timeframe was indicated to already be in use in practice and considered to be reasonable and familiar.

Feasibility

A 7-day infectious period was considered to be highly feasible in practice. Shorter, clearly defined timeframes support more reliable case recall and more manageable contact tracing processes.

It was recognised that the chosen approach is primarily pragmatic rather than evidence-driven, balancing epidemiological considerations with operational needs.

Case classification and management

Case management

Evidence review

The evidence for case management of diphtheria was reviewed. National and international guidelines, technical handbook and manual searches were conducted.

Evidence summary

Treatment

Antibiotics

Antibiotic treatment is not a substitute for antitoxin treatment if indicated (68), but it will work to eliminate *C. diphtheriae*, halt toxin production, and reduce communicability (1). A systematic review by Truelove et al found that patients receiving antibiotic treatment cleared *C. diphtheriae* respiratory colonisation within 5.2 days (95% CrI, 4.4–6.1 days) of initiating treatment on average, reducing the average duration of infectiousness by as much as 2 weeks (4).

In patients with suspected or confirmed diphtheria, the World Health Organization (WHO) recommends using macrolide antibiotics (azithromycin, erythromycin) in preference to penicillin antibiotics (69). Recent evidence suggests that there is increasing resistance to penicillins and less resistance to macrolide antibiotics. This evidence is largely informed by one randomised clinical trial (n=86) which compared penicillin (benzylpenicillin followed by penicillin V) with erythromycin for the treatment of diphtheria (69).

Macrolide antibiotics include azithromycin and erythromycin. Parenteral administration of macrolide antibiotics is possible. However, it is typically indicated where oral administration is not possible, such as when patient is unable to swallow oral medications. The choice of macrolide will be based on availability and feasibility (69).

In scenarios where macrolide antibiotics are not available and susceptibility testing demonstrates sensitivity to penicillin. Penicillin can be given orally or parentally (intravenous or intramuscular). Parenteral administration is used primarily to achieve adequate tissue concentrations, especially in patients with severe disease (69).

UK guidance recommends that for severe disease, intravenous benzylpenicillin sodium at the maximum appropriate dose should be combined with a macrolide. In patients who are

extremely systemically unwell, consider a third agent such as IV vancomycin or linezolid until susceptibility results are available (68).

WHO guidance notes that the use of macrolides, compared with penicillins, probably does not affect mortality or rate of serious side-effects, but that erythromycin may increase the rate of gastrointestinal side-effects. The treatment effect of macrolide antibiotics, compared with penicillin antibiotics, is very uncertain for the outcomes of rate of myocarditis, hospitalisation, need for airway intervention, new cases of diphtheria, or treatment failure. However, the point estimate of treatment failure favours macrolides over penicillins (69). Antimicrobial susceptibility testing is vital to ensure the ongoing appropriate use of antibiotics (69).

Diphtheria antitoxin (DAT)

The most effective treatment of severe cases of diphtheria involves the prompt administration of diphtheria antitoxin (DAT), which binds to and neutralises circulating toxin which has not yet bound to tissue (70). Clearance of the organism should also be achieved with appropriate antibiotics.

A systematic review by Truelove et al found that in cases of respiratory diphtheria, postinfection administration of DAT reduced mortality by 76% (RR, 0.24 [95% CrI, 0.22–0.28]). However, because antitoxin only neutralises circulating toxin, not intracellular toxin, its effectiveness depends on prompt administration relative to symptom onset. It was estimated that the probability of mortality increases daily, from 4.2% (95% CrI, 2.5%–7.1%) if administered within 24-48 hours, to 24% if administered on day 5 or later, approximately doubling with each day of delay. It was not clear at what point the delay negated any benefit (4).

In most cutaneous infections, large-scale toxin absorption is unlikely and therefore the risk of giving DAT is usually considered to be substantially greater than any benefit. Nevertheless, if the ulcer in cutaneous diphtheria infection were sufficiently large (e.g., more than 2cm^2) and especially if it were membranous, then DAT would be justified (71).

DAT was first produced in the late 19th century and is still produced using serum from horses hyperimmunised with diphtheria toxoid (69, 72). Due to the potential for immediate allergic reactions to infusions of DAT, some manufacturers have recommended sensitivity testing, an incremental exposure of the patient to small doses of DAT during a period of observation. If no adverse events are noted, the full dose is given. If there is evidence of a reaction to DAT, desensitisation using progressive administration of escalating doses can be performed in an effort to enable allergic patients to receive treatment (69). In patients with suspected or confirmed diphtheria, WHO recommends not performing routine sensitivity testing prior to administration of DAT (69). The evidence on routine sensitivity

testing before DAT is from single-arm interventions reporting rates of adverse events related to antitoxin use. In a systematic review conducted by WHO, the decision analysis undertaken by the methods incorporated evidence from 14 single-arm studies, and provided moderate certainty evidence that routine sensitivity testing increases mortality (69).

Mortality was modelled at 12.5% without DAT, and 3% with DAT, by applying the relative risk ratio of 0.24 (69). Key assumptions were that: 1) incomplete administration of DAT had no clinical benefit; 2) complete administration of DAT is attained in 95% of cases where given with concurrent antihistamine and corticosteroid administration; 3) Serious adverse events (SAE) associated with DAT occur at 3% (anaphylaxis); 4) Serious adverse events associated with DAT administration have trivial (zero) mortality (73).

Early treatment may reduce overall DAT usage by avoiding the higher doses required once disease has progressed (69).

Steroids and antihistamines have been used in some outbreak settings, the largest of which reported very low rates of adverse events (3% with no deaths). However, indirect evidence from antitoxin administration in other diseases treated (snake bite), did not find significant difference in reduction of adverse events when antihistamines were given (74). Pre-medication should not delay administration of DAT, and where they are considered, standard doses for antihistamines can be used (69).

Due to the risk of allergic reaction, WHO recommend that DAT should be administered in a monitored setting. Clinical settings should have trained staff, emergency medicines, equipment and protocols available to manage anaphylaxis or other serious adverse events. This includes:

- monitoring equipment: pulse oximeter, blood pressure monitoring, thermometer
- emergency medicines: adrenaline (1:1000), salbutamol, intravenous antihistamine (e.g. chlorphenamine), corticosteroid (e.g. prednisolone, hydrocortisone), intravenous fluid (Ringer's lactate or 0.9% w/v saline), oxygen supply and delivery devices
- emergency equipment: age-appropriate equipment for airway management and suction, oxygenation (bag valve mask and oxygen), and cardiovascular support (intravenous cannulae and giving sets) (69).

Vaccination

Patients should be vaccinated (with the age-appropriate formulation) in the convalescent phase of their disease as clinical infection may not induce adequate immunity (9).

Exclusion and restrictions

UK guidelines recommend that if the case is well and not hospitalised, they should be advised to restrict contact with others for the first 6 days of an appropriate course of antibiotics. Clearance swabs should be obtained 24- and 48-hours after completion of antibiotics to ensure elimination of carriage. In the rare event that the case remains positive following completion of the recommended antibiotic course, further advice on additional treatment should be sought from an infectious diseases specialist (68).

Isolate possible cases who are in hospital (or other community healthcare settings) and dress cutaneous lesions. Possible cases who are well at home should be advised to restrict contact with those outside their immediate household until further microbiological results are obtained (68).

Infection prevention and control

All health and care workers' vaccines should be up to date with an age-appropriate diphtheria toxoid-containing vaccine, including booster doses (75).

Cases with respiratory infection should be managed with standard, contact and droplet precautions. Droplet and contact precautions should remain until two negative nasopharyngeal and throat cultures taken at least 24 hours apart and more than 24 hours after the cessation of appropriate antimicrobial therapy are obtained (56, 76, 77).

Cases with cutaneous diphtheria should be managed with standard and contact precautions. Precautions in place until all wounds are clinically improving and can be covered by an occlusive waterproof dressing or have healed, and 72 hours of appropriate antimicrobial therapy has been completed (76).

Recommendation rationale

Diphtheria antitoxin (DAT)

Importance of the outcome

The WHO guidelines, outline that there is very low certainty on the impact of different DAT dosing regimens on mortality. However, it was noted that the current standard of care using escalating dosing regimens is well established in clinical practice globally (69, 72, 78) and that clear guidance was needed to enable timely administration of DAT.

Resource use

DAT supply in Australia and worldwide is limited and dosing is partly constrained by availability. This supports optimised and careful use, including consideration of lower dosing in the context of constrained supply.

Acceptability

While dosing ranges provide flexibility, they may make clinical decision-making more difficult, particularly for clinicians with limited experience managing diphtheria. As a result, it was preferred to use the upper dosing limits to provide clarity, with the option to use lower doses in the context of limited supply.

Feasibility

Dosing ranges may be difficult to operationalise in practice, particularly where clinician experience with diphtheria is limited. Specifying upper dosing limits was considered more feasible to support clear and timely decision-making, while allowing flexibility to use lower doses where DAT availability is constrained and clinical circumstances permit.

Contact classification and management

Contact management

Evidence review

The evidence for contact management of diphtheria was reviewed. National and international guidelines, technical handbook and manual searches were conducted.

Evidence summary

Chemoprophylaxis

Antibiotics are also used to prevent the development of diphtheria in close contacts of infectious patients; WHO recommendations on this topic are under development (69).

The UK recommend that as the risk of infection is directly related to the closeness and duration of contact, prophylaxis is required if the contact:

- is with a case or known carrier in a household type setting
- has been directly exposed to large particle droplets or secretions (following the same principles of meningococcal disease)
- has been exposed to an undressed wound of a cutaneous case (68).

In addition to close contacts, risk assessment of healthcare workers (HCW) who should be considered for prophylaxis is recommended. The risk assessment will depend on the presentation of diphtheria in the index case, which body sites were positive on swabbing, and what personal protective equipment (PPE) the HCW wore while attending the case. As a minimum, HCW attending to a case (possible, probable or confirmed) of diphtheria should wear disposable gloves and aprons for wound care and depending on the situation either a fluid repellent surgical face mask or a FFP3 mask for any aerosol generating procedures (68). For respiratory cases, HCW who have given mouth to mouth resuscitation to or intubated the index case (without appropriate PPE) would normally be considered as close contacts (68).

Individual risk assessment can be performed if no gloves were worn during wound assessment but there was likely no splash or droplet contamination and prompt hand washing occurred, then prophylaxis may not be indicated (68).

Regarding the administration of chemoprophylaxis, Heymann recommends chemoprophylaxis for all close contacts, regardless of immunisation status. Contacts who

do not receive prophylaxis should be monitored for 7 days and treated as diphtheria if symptoms develop (1).

Choice of antibiotics and dosing regimen should take into account antibiotic sensitivities, clinical tolerance and nature of contact with the case (26). Check sensitivities of the isolate before recommending antibiotic prophylaxis and seek the advice of an infectious diseases physician if sensitivities are pending or conflict with recommended antibiotics. Alternative antibiotics may be recommended (25, 26). If the case's isolate is resistant to the antibiotics commenced by the contact, the contact will need to restart with a course of appropriate antibiotics (25).

In 1997, following 2 reports of cases of membranous pharyngitis caused by toxigenic *C. ulcerans*, the US Centers for Disease Control and Prevention recommended that people exposed to the index case should be treated along similar lines to cases exposed to toxigenic *C. diphtheriae*. This was later revised in 2011 to advise vaccination of unimmunised contacts rather than provision of prophylactic antibiotics. This advice was given because there was inadequate information about human-to-human transmission of this organism (79, 80).

In the UK, because possible person-to-person transmission of toxigenic *C. ulcerans* has been observed (47), chemoprophylaxis of contacts of a case, from whom isolation of a toxigenic strain has been confirmed, is recommended.

Vaccination

Diphtheria vaccination records of all contacts of each case should be reviewed. Unvaccinated contacts should receive a full course of diphtheria toxoid-containing vaccine and under-vaccinated contacts should receive the doses needed to complete their vaccination series (81).

Heymann recommends that previously immunised contacts should receive an additional dose of diphtheria toxoid if more than 5 years have elapsed since their last dose, and in non-immunised contacts, a primary series should be initiated (1).

UK guidelines recommend that for those who are not appropriately immunised, a diphtheria-containing dose should be given immediately, and the schedule completed according to the guidelines available on vaccination of individuals with uncertain or incomplete immunisation status (68). Additionally for those who are appropriately immunised for age, close contacts of confirmed or probable diphtheria cases and asymptomatic carriers should be immunised with a diphtheria-toxoid containing vaccine, unless a diphtheria-toxoid containing vaccine has been given within the previous 12 months (82).

Exclusions and restrictions

International guidance recommends that close contacts of confirmed or probable cases of diphtheria and close contacts of asymptomatic carriers who work in the following high-risk occupations should be excluded from work and started on chemoprophylaxis:

- health and care workers (68)
- those who work with unimmunised children (1, 68)
- those involved in milk production (for *C. ulcerans*) (1, 68).

All contacts should have a nose and a throat swab taken prior to the start of antibiotics. If the initial culture is negative, they can go back to work (1, 26) while completing the course (68). In cases where the initial culture is positive for *C. ulcerans*, *C. diphtheriae*, or *C. pseudotuberculosis* they must remain excluded from work until the toxigenicity result is known (68).

Nationally, Queensland Health and New South Wales Health guidelines recommend that high-risk contacts of *C. diphtheriae* should minimise interaction with the following people vulnerable to diphtheria and start on chemoprophylaxis:

- infants aged 6 months and under (25, 26)
- care of the sick, elderly, and those requiring dependent care (25, 26)
- immunosuppressed individuals (25, 26).

In the household this requires avoidance and in work situations this requires exclusion from the workplace (26).

These restrictions apply until 72 hours of an appropriate course of antibiotics have been completed OR until cultures from the nose, throat and wounds are proved to be negative for toxigenic diphtheria bacilli, whichever is shorter (25, 26).

Healthcare workers who have cared for a case of either respiratory or cutaneous diphtheria without appropriate precautions should be excluded from patient care or work until negative nasopharyngeal and throat swabs are returned (25, 26). If the healthcare worker is unable to remain excluded from the workplace, additional precautions may be needed according to local infection control policies (such as wearing a surgical mask) (25).

The Northern Territory recommends that high-risk community and health worker contacts of respiratory diphtheria are to be excluded from school, work and community until ≥3 days of appropriate antibiotics are completed, or clearance swabs are negative and contact remains asymptomatic (83). High-risk community and health worker contacts of cutaneous diphtheria are to avoid contact with the following at-risk populations:

- infants aged 6 months and under
- care of the sick, elderly, and those requiring dependent care

- immunosuppressed individuals

These restrictions apply until ≥3 days of appropriate antibiotics are completed, or clearance swabs are negative and contact remains asymptomatic (84).

There are no exclusion requirements for medium risk contacts unless any high-risk features present (83, 84).

Exclusion of asymptomatic contacts of *C. ulcerans* is generally not required (26).

Recommendation rationale

Contact definitions

Importance of the outcome

Those with direct close contact (e.g., household-like contacts) are considered to be at highest risk of developing diphtheria and priority is placed on being able to identify and manage those at highest risk of developing disease.

Resource use

The follow-up of contacts at moderate risk was considered and with little evidence that they are at increased risk compared to low-risk groups, the decision was made to focus resources on high-risk contacts. Contact tracing and interventions in broadly exposed groups (e.g., shared spaces without direct contact) may generate substantial workload with limited yield. Swabbing of asymptomatic contacts, particularly in low-risk groups, may place strain on laboratory capacity and is questioned in terms of cost-benefit. Resource allocation should prioritise high risk contacts and symptomatic individuals, especially during outbreaks.

Acceptability

A two-tiered approach (high vs low risk) is deemed more acceptable to public health practitioners, as complex multi category systems are difficult to apply consistently. Reducing unnecessary follow up of low yield groups helps avoid operational burden and stakeholder confusion. Flexibility to adapt to local context (e.g. via expert advisory input) was considered important and acceptable.

Feasibility

The feasibility of distinguishing multiple risk categories (high, medium, low) was considered and was determined to be operationally challenging and difficult to justify in practice. Some areas reported difficulty consistently applying even high-risk interventions (e.g. swabbing), particularly in large or resource constrained settings. A binary high-low framework was determined to be more feasible, with clear definitions based on close, household like exposure.

Population level prevention

Preventative measures

Evidence review

The evidence for the role of vaccination for diphtheria was reviewed. National and international guidelines, technical handbook and manual searches were conducted and stakeholder submissions reviewed.

Evidence summary

The effective control for diphtheria is widespread active immunisation with diphtheria toxoid (1), to reduce the risk of toxigenic carriage translating into severe disease (2). Immunisation should be initiated in infancy with a formulation containing diphtheria toxoid, tetanus toxoid and either diphtheria/tetanus and acellular pertussis vaccine (DTaP) or diphtheria/tetanus and whole-cell pertussis vaccine (DTwP) (1).

Diphtheria toxoid vaccine protects against symptomatic disease by stimulating production of antitoxin antibodies. One meta-analysis by Truelove et al, found that full vaccination (≥3 doses) with DTP vaccine is 87% (95% CrI, 68%–97%) effective against symptomatic respiratory disease, whereas incomplete vaccination (1–2 doses) is 71% (95% CrI,17%−92%) effective (4). The authors noted that previous studies have found that vaccine effectiveness increases by dose, reaching 99% with 5 doses (4). Truelove et al found that among those who developed symptomatic respiratory disease, prior history of diphtheria toxoid vaccine reduced the risk of severe disease and death. Vaccination with ≥3 doses was 81% (95% CrI, 74%–86%) effective in preventing severe disease and 93% (95% CrI, 90%–96%) effective in preventing death. Incomplete vaccination was 47% (95% CrI, 23%–63%) effective against severe disease and 68% (95% CrI, 56%–77%) effective in preventing death (4).

Diphtheria toxoid vaccine does not prevent colonisation with toxigenic *C. diphtheriae* (4). However, it is estimated to reduce transmission by 60% (95% CrI, 51%–68%), likely through reduced symptomatic shedding (4).

Vaccination is highly effective at preventing symptomatic disease (>87% with 3 doses), yet has no effect on preventing infection, and while those with asymptomatic infections still transmit, they do so at only 24% the rate of symptomatic cases (4).

Truelove et al also found that widespread use of antibiotics may also play a role in maintaining herd immunity through accelerated clearance of colonisation, and, thus reduced secondary cases (4).

Education measures are important to inform the public, particularly those living with or caring for young children, of the hazards of diphtheria and the need for immunisation (1).

Special situations

Outbreak management

Evidence review

The evidence for the management of diphtheria outbreaks was reviewed. National and international guidelines, technical handbook and manual searches were conducted and stakeholder submissions reviewed.

Database searches were conducted on the 27 March 2026, using the search terms in the table below.

Table 5. Database search terms

Databases	Search terms
Pubmed, Ovid Embase, Cochrane library	Population – human Exposure – Diphtheria, Corynebacterium diphtheriae, C. diphtheriae, Corynebacterium ulcerans, C. ulcerans Comparator – no comparator terms used Outcome – disease outbreaks AND investigation, response, control, management Exclude – Reviews, Editorials, Comments

Screening of identified studies was conducted using the following inclusion and exclusion criteria:

Inclusion criteria	• Publications about toxigenic diphtheria
Exclusion criteria	• Publication types out of scope (opinion piece, editorial, commentary, conference abstracts) • Publication not in English • Withdrawn or superseded studies • Incomplete data (ongoing study, no outcomes of interest)

Evidence summary

Respiratory diphtheria

An outbreak of diphtheria as defined in the 'Field guide for preparedness and response to diphtheria outbreaks in the Western Pacific Region' is two or more locally acquired respiratory cases linked in time and place (85).

Outbreaks of respiratory diphtheria ranging in size from less than 10 cases in small settings to country-wide outbreaks of >5,000 cases per year have been reported since the introduction of diphtheria vaccination (5, 14, 86-106).

Historically, outbreaks have occurred across the world with outbreaks reported in the UK in the 1950's (92), the United States in the 1970s (103), and China in the 1980's (93). Throughout the 1990's, outbreaks of respiratory diphtheria occurred across the former Union of Soviet Republics (90, 91, 94-96, 100, 102, 104, 106-109), with >5,000 cases seen in some countries per year at its peak (102).

During these outbreaks, control measures across these countries included a range of interventions including:

- treating cases (90)
- screening of people with tonsilitis/pharyngitis for diphtheria (90, 95)
- isolating people with severe pharyngitis (95)
- identifying close contacts (90, 95, 104)
- testing close contacts (90, 95)
- treating close contacts(96)
- vaccinating contacts (104)
- treating carriers (90)
- introducing quarantine measures in institutions or workplaces in cases of exposure (95)
- screening for diphtheria before admission to institutional settings (95)
- changing childhood immunisation schedules (96, 106)
- modifying list of contraindications for vaccination (96)
- conducting routine childhood immunisation programs (91, 95, 100, 104)
- conducting targeted childhood immunisation programs (96, 100, 102)
- introducing booster doses for adults (90, 109)
- conducting targeted adult immunisation programs for adult occupational cohorts (94, 95, 102, 109)
- conducting mass immunisation programs for adults (90, 91, 95, 96, 100, 102, 104, 107).

An important lesson learned from the epidemic of diphtheria in the former Union of Soviet Republics is that an immunity gap in adults coupled with large numbers of susceptible children creates the potential for an extensive epidemic (102, 109). In the early years of the epidemic, investigation and control efforts centred on individual cases failed to control the spread of diphtheria until immunisation campaigns closed the population immunity gap (95, 102, 109). The success of the WHO/UNICEF strategy of "one dose for all" in the former Union of Soviet Republics and Baltic States demonstrates that successful control strategies

must raise immunity among all age groups to high levels (109). By the end of 1996, ≥95% of children were reported to be fully immunised (95, 100) and coverage of between 83-88% in adults, with at least one dose of diphtheria vaccine (94, 95, 102, 104). This rapid one-dose strategy was appropriate in the former Union of Soviet Republics and will be appropriate in other populations where the majority of the population has been immunologically primed (109).

The risk of spread of outbreaks to other countries was also present, with recommendations given during this outbreak that travellers to these regions ensure they are fully vaccinated and recommendations given to neighbouring countries to review population vaccination status and immunity (110).

Spread of outbreaks across countries has also been seen throughout the world in outbreaks in refugee or asylum seeker populations (5). Asylum seekers are particularly at risk of infectious diseases because of their generally low vaccination coverage, lack of hygienic conditions during travel, and crowded living conditions in refugee camps (111).

An outbreak of respiratory diphtheria was reported in refugee camps in Bangladesh. In this outbreak, contact tracing was undertaken, with close contacts of all probable and confirmed cases identified during case investigation targeted for vaccination, treatment, and follow-up over the course of prophylactic antibiotic treatment. Chemoprophylaxis was initially given for seven days with follow-up on days 0, 3 and 7. This was changed to three days of chemoprophylaxis mid-outbreak, with follow-up on day 0 and 3. Due to concerns with compliance this later changed to chemoprophylaxis provided by contact tracers on visits on day 0, 1 and 2. Mass vaccination of pregnant women and children aged 6 weeks to 14 years was undertaken with one booster dose administered if documented evidence of having completed the primary vaccination schedule was available. Otherwise, 3 doses were administered, with at least 4 weeks interval between doses. It is noted that there may be a need for earlier launching of the mass vaccination campaign with an expanded (older) target age group, given a quarter of the cases were ages 15-29 years during this outbreak and its continuation despite the mass vaccination campaign (5). The authors identified that enhanced detection and isolation of new cases by active case finding using community health workers, and more effective contact tracing, with possibly a greater proportion of contacts vaccinated and provided with prophylactic antibiotics, might have brought the epidemic to an earlier end (5).

Outbreaks in Indonesia have affected multiple islands. These outbreaks were due to the accumulation of vulnerable groups to diphtheria, as these groups had received no vaccination or incomplete immunisation (87). Three important strategies were utilised to manage this outbreak; immunising children aged 1-19 years, early detection and proper handling of diphtheria cases, and identification of appropriate diphtheria contact or carrier

management procedures (14). Evaluation of these outbreaks demonstrated that the majority of cases recorded towards the end of this outbreak included children who were not immunised, were not reached by the immunisation program, or had a history of incomplete immunisation. People older than 19 years of age accounted for 24% of the cases (97).

Outbreaks as a result of decreased immunity in the community can be seen worldwide with sporadic outbreaks reported in South Africa (89) and Somalia (105). In South Africa, outbreak management focused on active case finding, contact tracing, chemoprophylaxis and immunisation of close contacts and suspected cases (89), alongside targeted vaccination programs of local community groups (89). In Somalia 79% of cases were in children under 15, and 87% had no vaccination history (105). This was due to an immunity gap with large susceptible cohorts, especially children aged 5–15 years who were born during periods of extremely low coverage and who never received booster doses. These groups then formed the backbone of the outbreak. The focus of control was on immunisation of children 5–14 years (105).

Outbreaks in communities such as the outbreak in the Wujal Wujal community in East Cape York have been managed through the use of contact tracing and management, community engagement and opportunistic vaccination in the community clinic. A week-long mass vaccination of people 14 years and older was then undertaken for anyone who had not had an immunisation in the previous year, increasing the coverage rate to 88% of the community who had a vaccination in the last 10 years. No further cases were identified in this community in the following 22 months (112).

In other situations of sporadic cases or small outbreaks, such as in the UK (98, 101), Thailand (99) and Malaysia (88), control measures all included active case finding (88, 98, 99, 101), contact tracing (88, 98, 99, 101), chemoprophylaxis (88, 98, 99, 101), monitoring and immunisation of high risk contacts (88, 98, 99, 101), with hospital staff excluded from work until they had received negative swab results (98) and medium risk contacts offered immunisation if >12 months since last immunisation and provided education on signs and symptoms (98).

Management of diphtheria in a hospital emergency department was reviewed during an outbreak in Indonesia, with measures being taken to vaccinate all hospital staff who may be exposed, screening patients during triage and identifying those at high-risk of disease. Isolation of suspected cases and use of set diagnostic packs containing one surgical mask with a face shield, a pair of non-sterile gloves, three cotton buds, one disposable apron, two disposable wooden tongue depressors, and a biohazard plastic bag, improved infection control procedures and facilitated the improvement of diagnostic processes in

the setting (86). This study highlights the importance of personal protective equipment (PPE) and isolation in reducing risk in healthcare settings.

A systematic review on respiratory diphtheria by Truelove et al reports that while vaccine is estimated to reduce transmission by 60% (95% CrI, 51%–68%), the effectiveness of vaccination for outbreak response is limited by the time required to deploy vaccine and develop immunity. Vaccinated individuals can also still become colonised and transmit; consequently, vaccination alone can only interrupt transmission in 27% of outbreak settings, making isolation and antibiotics essential (4).

Truelove et al note that to be most effective in controlling outbreaks, measures must either interrupt transmission earlier among symptomatic individuals or also target asymptomatic individuals (4). In a fully vaccinated population, antibiotic treatment of 25% of symptomatic cases an average of 5 days after fever onset can interrupt transmission when $R0 < 2.4$ (35% of estimated outbreak settings). Improving antibiotic treatment to 50% of cases within 2 days interrupts transmission when $R0 < 2.6$ (48% of settings), and with 90% treated within 1 day, transmission is interrupted when $R0 < 2.9$ (70% of settings) (4).

In fully susceptible populations, containment requires immediate isolation of 68% (95% CrI, 50%–84%) of symptomatic cases (isolation immediately halts transmission, unlike antibiotics). Contact tracing with isolation or antibiotic prophylaxis of contacts would be similarly effective, depending on the capture rate. Alternatively, instead of a targeted approach, a novel approach that includes random, mass administration of antibiotics would interrupt transmission in all but the most extreme settings, with relatively low coverage (median required coverage of 27% [95% CrI, −69% to 95%]) (4).

Truelove et al conclude that full vaccination coverage is only sufficient to interrupt transmission in 27% of outbreak settings. However, this improves to 70% with rapid antibiotic treatment of 90% of symptomatic cases. Efforts that target cases earlier and target asymptomatic carriers demonstrate even greater effectiveness, with lower required coverage, including contact tracing, isolation, and antibiotic prophylaxis, and should be essential tools in routine outbreaks response. They also posit that mass administration of antibiotics, particularly azithromycin, which reaches both symptomatic and asymptomatic individuals, could be effective for diphtheria control. This could be particularly effective if coupled with other mass healthcare activities such as vaccination.(4).

Cutaneous diphtheria

Spread of outbreaks of cutaneous diphtheria across countries has also been seen throughout the world in refugee or asylum seeker populations (5, 23, 111, 113, 114). Outbreaks of cutaneous diphtheria have been reported in these settings in New Zealand (23) and in multiple setting in Europe (111, 113, 114).

In New Zealand, cases identified in a refugee resettlement centre were treated and isolated until two clearance swabs had been received. Contact tracing was undertaken with high and medium risk contacts undergoing testing of throat, nasopharynx and wound swabs, followed by chemoprophylaxis and offered immunisation. Any suspected cases were monitored daily until swab clearance was received. Low risk contacts were offered immunisation (23). Staff involved in the outbreak were provided vaccination if they had not been vaccinated in the previous 5 years. Additionally high-risk contacts were monitored daily for symptoms for 7 days, skin lesions were covered and assessed by public health nurses daily and education on transmission and cleaning was provided to contacts and staff (23).

In Europe, outbreaks have been reported across Belgium (111), Germany (113) and Switzerland (114), with human-to human transmission reported within these populations (113) and genetic sequencing revealing genetically related clusters across the countries (113).

In Belgium, the investigation and management of the outbreak in a population of unsheltered asylum seekers required adjustments to case finding, contact tracing and treatment procedures. Isolation and contact tracing of cases was not possible, with test and treat centres utilised and suspected cases being treated and having any wounds covered while awaiting confirmation. Chemoprophylaxis was provided to all suspected cases, any identified contacts with pharyngeal carriage, and to all minors living close to a confirmed case. Antimicrobial treatment was reduced to three days to increase compliance. Testing of clearance was not undertaken. Any identified close contacts with pharyngeal carriage confirmed were also treated. Vaccination centres were opened and mobile vaccination campaigns were utilised to vaccinate asylum seekers and staff. While these measures reduced the incidence, the identification of three respiratory cases in the following year suggests the presence of continued undetected transmission (111).

In Switzerland, a reported outbreak was managed through mass screening, treatment and immunisation of residents on floors with confirmed cases. Isolation and treatment of identified respiratory carriers was also undertaken. After the initial mass throat screening, a targeted case-finding approach was implemented and targeted vaccination was expanded to mass vaccination of all residents; vaccination was rarely included as a management component in close contacts and cases (114).

Spread of diphtheria through travel was identified as the cause of detection of cases of cutaneous diphtheria in the UK in 2002 (63). Management of this detection of diphtheria involved active case finding through testing of nose and throat swabs of contacts, followed by chemoprophylaxis and immunisation as appropriate. School aged people in this cluster

were also excluded from school until treatment was complete and two negative swabs were received 24 hours apart (63).

References

1. Heymann DL (ed.). 'Control of Communicable Diseases Manual 21st edition'. American Public Health Association, 2022.
2. Howes M, Menouhos D, et al. 'Characterisation of Corynebacterium diphtheriae isolates in the Northern Territory of Australia'. Communicable Disease Intelligence (2018). 2023;47, doi: 10.33321/cdi.2023.47.31.
3. Chen W, Chen Y, et al. 'Global patterns of syphilis, gonococcal infection, typhoid fever, paratyphoid fever, diphtheria, pertussis, tetanus, and leprosy from 1990 to 2021: findings from the Global Burden of Disease Study 2021'. Infectious Diseases of Poverty. 2024;13(1):66, doi: 10.1186/s40249-024-01231-2.
4. Truelove SA, Keegan LT, et al. 'Clinical and Epidemiological Aspects of Diphtheria: A Systematic Review and Pooled Analysis'. Clinical Infectious Diseases. 2020;71(1):89-97, doi: 10.1093/cid/ciz808.
5. Polonsky JA, Ivey M, et al. 'Epidemiological, clinical, and public health response characteristics of a large outbreak of diphtheria among the Rohingya population in Cox's Bazar, Bangladesh, 2017 to 2019: A retrospective study'. PLOS Medicine. 2021;18(4):e1003587, doi: 10.1371/journal.pmed.1003587.
6. Exavier MM, Paul Hanna M, et al. 'Diphtheria in Children in Northern Haiti'. Journal of Tropical Pediatrics. 2019;65(2):183-7, doi: 10.1093/tropej/fmy021.
7. Gidding HF, Burgess MA, et al. 'Diphtheria in Australia, recent trends and future prevention strategies'. Communicable Disease Intelligence. 2000;24(6):165-7, doi: 10.33321/cdi.2000.24.26.
8. Acosta A. 'Diphtheria. In: Ryan E HD, Solomon T, Aronson N, Endy T, editor, Hunter's Tropical Medicine and Emerging Infectious Diseases', Elsevier; 2020. p. 439-45.
9. Sutter RW. 'Diphtheria and Other Corynebacterium Infections. In: Goldman L, editor, Goldman-Cecil Medicine. 26th ed', Elsevier; 2020. p. 1881-4.
10. Hempenstall A, Short J, et al. 'Clinician alert: toxigenic diphtheria cases across North Queensland are on the rise'. The Medical Journal of Australia. 2023;218(5):238, doi: 10.5694/mja2.51858.
11. Armstrong P. 'Alert for Kimberley, Pilbara and Goldfields Clinicians – Outbreak of diphtheria in the Kimberley'. Perth: Department of Health, Government of Western Australia; 2026 [Available from: https://www.health.wa.gov.au/~/media/Corp/Documents/Health-for/Infectious-disease-alerts/2026/Clinician-alert-Diphtheria-March-2026.pdf]
12. Draper AD, Sistrom M, et al. 'Diphtheria outbreak, Northern Territory of Australia, 2025 to 2026'. Eurosurveillance. 2026;31(23):2600443.

13. Tetteh-Ocloo G, Odoom A, et al. 'Global trends in travel-related antimicrobial resistance: a systematic review, 2020-2024'. International Health. 2025, doi: 10.1093/inthealth/ihaf071.
14. Karyanti MR, Nelwan EJ, et al. 'Diphtheria Epidemiology in Indonesia during 2010-2017'. Acta Medica Indonesiana. 2019;51(3):205-13.
15. Gower CM, Scobie A, et al. 'The changing epidemiology of diphtheria in the United Kingdom, 2009 to 2017'. Eurosurveillance. 2020;25(11), doi: 10.2807/1560-7917.ES.2020.25.11.1900462.
16. De Zoysa A, Hawkey PM, et al. 'Characterization of toxigenic Corynebacterium ulcerans strains isolated from humans and domestic cats in the United Kingdom'. Journal of Clinical Microbiology. 2005;43(9):4377-81, doi: 10.1128/JCM.43.9.4377-4381.2005.
17. Ottolini M, Cirks B, et al. 'Pediatric Infectious Diseases Encountered During Wartime-Part 1: Experiences and Lessons Learned From Armed Conflict in the Modern Era'. Current Infectious Disease Reports. 2021;23(12):27, doi: 10.1007/s11908-021-00770-1.
18. Li L, Ross D, et al. 'Two cases of imported respiratory diphtheria in Edinburgh, Scotland, October 2019'. Epidemiology & Infection. 2020;148:e143, doi: 10.1017/S0950268820001028.
19. Klouche M, Lühmann D, et al. 'Low prevalence of diphtheria antitoxin in children and adults in northern Germany'. European Journal of Clinical Microbiology & Infectious Diseases. 1995;14(8):682-5, doi: 10.1007/bf01690874.
20. Ahmed AA, Omar NMS, et al. A complex case of diphtheria in a pediatric patient: complications of renal failure and myocarditis'. International Journal of Emergency Medicine. 2026;19(1), doi: 10.1186/s12245-026-01146-9.
21. Finger F, Funk S, et al. 'Real-time analysis of the diphtheria outbreak in forcibly displaced Myanmar nationals in Bangladesh'. BMC Medicine. 2019;17(1):58, doi: 10.1186/s12916-019-1288-7.
22. Fraga M, Angst FA, et al. 'The Burden and Risk Factors Associated with Infectious Diseases among Refugees in a Camp for Migrants in Porto Alegre: A Cross-Sectional Survey'. Annals of Global Health. 2024;90(1):48, doi: 10.5334/aogh.4242.
23. Reynolds GE, Saunders H, et al. 'Public health action following an outbreak of toxigenic cutaneous diphtheria in an Auckland refugee resettlement centre'. Communicable Disease Intelligence Quarterly Report. 2016;40(4):E475-e81, doi: 10.33321/cdi.2016.40.53.
24. Jones CE, Danovaro-Holliday MC, et al. 'Routine Vaccination Coverage – Worldwide, 2023'. Morbidity and Mortality Weekly Report. 2024;73(43):978-84, doi: 10.15585/mmwr.mm7343a4.
25. NSW Health. 'Diphtheria – NSW Control Guideline for Public Health Units'. New South Wales Government; 2024.

26. Queensland Health. 'Diphtheria – Queensland Health Guidelines for Public Health Units'. Queensland Government; 2023.
27. Aboriginal Health Council of Western Australia. 'COVID-19 Response Review by the WA Aboriginal Community Controlled Health Sector'. Highgate: Aboriginal Health Council of Western Australia; 2025.
28. Massey PD, Miller A, et al. 'Australian Aboriginal and Torres Strait Islander communities and the development of pandemic influenza containment strategies: community voices and community control'. Health Policy. 2011;103(2-3):184-90, doi: 10.1016/j.healthpol.2011.07.004.
29. Nous. 'Evaluation of the Aboriginal Community Controlled Health sector's COVID-19 initiatives'. National Aboriginal Community Controlled Health Organisation; 2025.
30. Graham S, Kamitsis I, et al. 'A Culturally Responsive Trauma-Informed Public Health Emergency Framework for Aboriginal and Torres Strait Islander Communities in Australia, Developed during COVID-19'. International Journal of Environmental Research and Public Health. 2022;19(23):15626, doi: 10.3390/ijerph192315626.
31. NSW Health Public Health Preparedness. 'Public Health Emergency Preparedness and Response with Aboriginal Communities'. NSW Government; 2024.
32. Crooks K, Taylor K, et al. 'Engage, understand, listen and act: evaluation of Community Panels to privilege First Nations voices in pandemic planning and response in Australia'. BMJ Global Health. 2022;7(8), doi: 10.1136/bmjgh-2022-009114.
33. Crooks K, Taylor et al. '"No one ever comes back and asks us how could we do it better": findings from First Nations community panels about ways to keep First Nations peoples safe from COVID-19'. AlterNative: An International Journal of Indigenous Peoples. 2025;21(2):392-405, doi: 10.1177/11771801251334916.
34. Crooks K, Law C, et al. 'Embedding Aboriginal cultural governance, capacity, perspectives and leadership into a local Public Health Unit Incident Command System during COVID-19 in New South Wales, Australia'. BMJ Global Health. 2023;8(7), doi: 10.1136/bmjgh-2023-012709.
35. Ralph AP, Noonan S, et al. 'The 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease'. The Medical Journal of Australia. 2021;214(5):220-7, doi: 10.5694/mja2.50851.
36. Fowler F, Einsiedel L. 'A Qualitative Study Exploring Perceptions to the Human T Cell Leukaemia Virus Type 1 in Central Australia: Barriers to Preventing Transmission in a Remote Aboriginal Population'. Frontiers in Medicine. 2022;9:845594, doi: 10.3389/fmed.2022.845594.
37. Massey PD, Pearce G, et al. 'Reducing the risk of pandemic influenza in Aboriginal communities'. Rural Remote Health. 2009;9(3):1290, doi: 10.22605/RRH1290.
38. Ward J, Costello-Czok M, et al. 'So far, so good: Maintenance of prevention is required to stem HIV incidence in Aboriginal and Torres Strait Islander communities in

Australia'. AIDS Education and Prevention. 2014;26(3):267-79, doi: 10.1521/aeap.2014.26.3.267.
39. Jones SA, Miller HJ, et al. 'An experience of diphtheria in Westminster'. Public Health. 1984;98(1):3-7, doi: 10.1016/S0033-3506(84)80053-0.
40. Rousseau C, Belchior E, et al. 'Diphtheria in the south of France, March 2011'. Eurosurveillance. 2011;16(19).
41. Montenegro-Idrogo JJ, Resurrección-Delgado C, et al. 'Oligosymptomatic diphtheria infection in adults: two contacts of the Peruvian index case after 20 years without disease report'. InfezMed. 2021;29(2):268-71.
42. Saleeb P. 'Corynebacterium diphtheriae (diphtheria). In: Bennett J. E.; Dolin RB, M. J., editor. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases'. Philadelphia: PA: Elsevier; 2020.
43. MacGregor R . 'Corynebacterium diphtheriae. In: Principles and Practice of Infectious Diseases. Seventh edition', Saunders Elsevier; 2009.
44. Sears A, McLean M, et al. 'Cases of cutaneous diphtheria in New Zealand: implications for surveillance and management'. The New Zealand Medical Journal. 2012;125(1350):64-71.
45. de Benoist A-C, White JM, et al. 'Imported Cutaneous Diphtheria, United Kingdom'. Emerging Infectious Disease Journal. 2004;10(3):511, doi: 10.3201/eid1003.030524.
46. Edwards D, Kent D, et al. 'Transmission of toxigenic Corynebacterium diphtheriae by a fully immunised resident returning from a visit to West Africa, United Kingdom, 2017'. Eurosurveillance, 2018;23(39), doi: 10.2807/1560-7917.ES.2018.23.39.1700681.
47. Wagner KS, White JM, et al. 'Diphtheria in the United Kingdom, 1986-2008: the increasing role of Corynebacterium ulcerans'. Epidemiology and infection. 2010;138(11):1519-30, doi: 10.1017/S0950268810001895.
48. Monaco M, Sacchi AR, et al. 'Respiratory diphtheria due to Corynebacterium ulcerans transmitted by a companion dog, Italy 2014'. Infection. 2017;45(6):903-5, doi: 10.1007/s15010-017-1040-1.
49. Konrad R, Hörmansdorfer S, et al. 'Possible human-to-human transmission of toxigenic Corynebacterium ulcerans'. Clinical Microbiology and Infection. 2015;21(8):768-71, doi: 10.1016/j.cmi.2015.05.021.
50. Lartigue MF, Monnet X, et al. 'Corynebacterium ulcerans in an immunocompromised patient with diphtheria and her dog'. Journal of Clinical Microbiology. 2005;43(2):999-1001, doi: 10.1128/jcm.43.2.999-1001.2005.
51. Berger A, Huber I, et al. 'Toxigenic Corynebacterium ulcerans in woman and cat'. Emerging Infectious Diseases. 2011;17(9):1767-9, doi: 10.3201/eid1709.110391.
52. Hoefer A, Herrera-León S, et al. 'Zoonotic Transmission of Diphtheria from Domestic Animal Reservoir, Spain'. Emerging Infectious Diseases. 2022;28(6):1257-60, doi: 10.3201/eid2806.211956.

53. Wake K, Kikuchi J, et al. 'Transmission of toxigenic Corynebacterium ulcerans infection with airway obstruction from cats to a human'. Acute Medicine & Surgery. 2021;8(1):e705, doi: 10.1002/ams2.705.
54. Taylor J, Saveedra-Campos M, et al. 'Toxigenic Corynebacterium ulcerans infection in a veterinary student in London, United Kingdom, May 2010'. Eurosurveillance. 2010;15(31).
55. Berger A, Boschert V, et al. 'Two cases of cutaneous diphtheria associated with occupational pig contact in Germany'. Zoonoses and Public Health. 2013;60(8):539-42, doi: 10.1111/zph.12031.
56. Efstratiou A, George RC. 'Microbiology and Epidemiology of Diphtheria'. Reviews and Research in Medical Microbiology. 1996;7(1):31-42.
57. Dazas M, Badell E, et al. 'Taxonomic status of Corynebacterium diphtheriae biovar Belfanti and proposal of Corynebacterium belfantii sp. nov'. International Journal of Systematic and Evolutionary Microbiology. 2018;68(12):3826-31, doi: 10.1099/ijsem.0.003069.
58. Clarridge J. 'Diphtheria and other corynebacterial and coryneform infections, in Topley and Wilson's microbiology and microbial infections. Tenth edition'. New York : Oxford University Press. 1998.
59. Tiwari TS, Golaz A, et al. 'Investigations of 2 cases of diphtheria-like illness due to toxigenic Corynebacterium ulcerans'. Clinical Infectious Diseases. 2008;46(3):395-401, doi: 10.1086/525262.
60. Dangel A, Berger A, et al. 'Geographically Diverse Clusters of Nontoxigenic Corynebacterium diphtheriae Infection, Germany, 2016-2017'. Emerging Infectious Diseases. 2018;24(7):1239-45, doi: 10.3201/eid2407.172026.
61. Ganeshalingham A, Murdoch I, et al. 'Fatal laryngeal diphtheria in a UK child'. Archives of Disease in Childhood. 2012;97(8):748-9, doi: 10.1136/archdischild-2011-300272.
62. Farizo KM, Strebel PM, et al. 'Fatal respiratory disease due to Corynebacterium diphtheriae: case report and review of guidelines for management, investigation, and control'. Clinical Infectious Diseases. 1993;16(1):59-68, doi: 10.1093/clinids/16.1.59.
63. de Benoist AC, White JM, et al. 'Imported cutaneous diphtheria, United Kingdom'. Emerging Infectious Diseases. 2004;10(3):511-3, doi: 10.3201/eid1003.030524.
64. Maegrath B. 'Skin Conditions in Clinical Tropical Diseases. Ninth edition'. Oxford: Blackwell Scientific Publications; 1989.
65. Bowler IC, Mandal BK, et al. 'Diphtheria--the continuing hazard'. Archives of Disease in Childhood. 1988;63(2):194-5, doi: 10.1136/adc.63.2.194.
66. Harnisch JP, Tronca E, et al. 'Diphtheria among alcoholic urban adults. A decade of experience in Seattle'. Annals of Internal Medicine. 1989;111(1):71-82, doi: 10.7326/0003-4819-111-1-71.

67. Sing A, Heesemann J. 'Imported cutaneous diphtheria, Germany, 1997-2003'. Emerging Infectious Diseases. 2005;11(2):343-4, doi: 10.3201/eid1102.040560.
68. UK Health Security Agency. 'Public health control and management of diphtheria in England'. London: UK Government; 2025.
69. World Health Organization. 'Clinical management of diphtheria: guideline'. Geneva: World Health Organization; 2024.
70. Zakikhany K, Neal S, et al. 'Emergence and molecular characterisation of non-toxigenic tox gene-bearing Corynebacterium diphtheriae biovar mitis in the United Kingdom, 2003-2012'. Eurosurveillance. 2014;19(22), doi: 10.2807/1560-7917.ES2014.19.22.20819.
71. Ramsay M (editor). 'Immunisation against infectious disease (Green Book)'. London: UK Health Security Agency; 2021.
72. Public Health England. 'Immunoglobulin Handbook: Guidance on the use of Diphtheria Anti-toxin (DAT)'. London: Public Health England; 2018.
73. Eisenberg N, Panunzi I, et al. 'Diphtheria Antitoxin Administration, Outcomes, and Safety: Response to a Diphtheria Outbreak in Cox's Bazar, Bangladesh'. Clinical Infectious Diseases. 2021;73(7):e1713-e8, doi: 10.1093/cid/ciaa1718.
74. de Silva HA, Pathmeswaran A, et al. 'Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial'. PLoS Medicine. 2011;8(5):e1000435, doi: 10.1371/journal.pmed.1000435.
75. World Health Organization. 'Infection prevention and control and water, sanitation and hygiene measures for diphtheria in health-care settings: operational guide'. Geneva: World Health Organization; 2024.
76. National Health and Medical Research Council. 'Australian Guidelines for the Prevention and Control of Infection in Healthcare'. Canberra: Commonwealth of Australia; 2019.
77. Coia JE, Ritchie L, et al. 'Guidance on the use of respiratory and facial protection equipment'. Journal of Hospital Infection. 2013;85(3):170-82, doi: 10.1016/j.jhin.2013.06.020.
78. United States Centre for Disease and Prevention Control. 'Expanded Access Investigational New Drug (IND) Application Protocol: Use of Diphtheria Antitoxin (DAT) for Possible Diphtheria Cases. In: United States'. Atlanta: Centre for Disease and Prevention Control; 2022.
79. Blue SR, Hahn C, et al. 'Notes from the field: Respiratory diphtheria-like illness caused by toxigenic corynebacterium ulcerans --- Idaho, 2010'. Morbidity and Mortality Weekly Report. 2011;60, doi: 10.15585/mmwr.mm7323a3.
80. Centers for Disease Control and Prevention. 'Respiratory diphtheria caused by Corynebacterium ulcerans--Terre Haute, Indiana, 1996'. JAMA. 1997;277(21):1665-6.

81. World Health Organization. 'Diphtheria vaccine: WHO position paper'. Weekly Epidemiological Record. 2017;92(31):417-35, doi: 10.1016/j.vaccine.2017.08.024.
82. Begg N. 'Manual for the management and control of diphtheria in the European region'. Copenhagen: WHO Regional Office for Europe; 1994.
83. Northern Territory Health. 'NT Centre for Disease Control – Diphtheria contact management, Respiratory Diphtheria'. Northern Territory Government; 2026.
84. Northern Territory Health. 'NT Centre for Disease Control – Diphtheria contact management, Cutaneous Diphtheria'. Northern Territory Government; 2026.
85. World Health Organizaion Western Pacific Region. 'Field guide for preparedness and response to diphtheria outbreaks in the Western Pacific Region'. Manila: World Health Organization Regional Office for the Western Pacific; 2023.
86. Habib H, Kurniawaty H. 'Triage in the Time of Diphtheria'. Western Journal of Emergency Medicine. 2020;21(5):1156-9, doi: 10.5811/westjem.2020.6.46094.
87. Tosepu R, Gunawan J, et al. 'The outbreak of diphtheria in Indonesia'. Pan African Medical Journal. 2018;31:249, doi: 10.11604/pamj.2018.31.249.16629.
88. Tok PSK, Jilani M, et al. 'A diphtheria outbreak in Johor Bahru, Malaysia: Public health investigation and response'. Journal of Infection in Developing Countries. 2022;16(7):1159-65, doi: 10.3855/jidc.16076.
89. Mahomed S, Archary M, et al. 'An isolated outbreak of diphtheria in South Africa, 2015'. Epidemiology & Infection. 2017;145(10):2100-8, doi: 10.1017/S0950268817000851.
90. Magdei M, Melnic A, et al. 'Epidemiology and control of diphtheria in the Republic of Moldova, 1946-1996'. The Journal of Infectious Diseases. 2000;181 Suppl 1:S47-54, doi: 10.1086/315538.
91. Jõgiste A, Ching P, et al. 'Diphtheria in Estonia, 1991-1996'. The Journal of Infectious Diseases. 2000;181 Suppl 1:S65-8, doi: 10.1086/315541.
92. Lycett CD, George JT. 'An outbreak of diphtheria; influence of immunization'. British Medical Journal. 1953;1(4817):964-8, doi: 10.1136/bmj.1.4817.964.
93. Youwang Y, Jianming D, et al. 'Epidemiological features of an outbreak of diphtheria and its control with diphtheria toxoid immunization'. International Journal of Epidemiology. 1992;21(4):807-11, doi: 10.1093/ije/21.4.807.
94. Vitek CR, Brisgalov SP, et al. 'Epidemiology of epidemic diphtheria in three regions, Russia, 1994-1996'. European Journal of Epidemiology. 1999;15(1):75-83, doi: 10.1023/a:1007558601804.
95. Filonov VP, Zakharenko DF, et al. 'Epidemic diphtheria in Belarus, 1992-1997'. The Journal of Infectious Diseases. 2000;181 Suppl 1:S41-6, doi: 10.1086/315537.
96. Kembabanova G, Askarova J, et al. 'Epidemic investigation of diphtheria, Republic of Kazakhstan, 1990-1996'. The Journal of Infectious Diseases. 2000;181 Suppl 1:S94-7, doi: 10.1086/315546.

97. Husada D, Puspitasari D, et al. 'Impact of a three-dose diphtheria outbreak response immunization in East Java, Indonesia, 6 months after completion'. Human Vaccines & Immunotherapeutics. 2020;16(9):2144-50, doi: 10.1080/21645515.2020.1778918.
98. Perkins S, Cordery R, et al. 'Investigations and control measures following a non-travel-associated case of toxigenic Cornyebacterium diphtheriae, London, United Kingdom, December 2009-January 2010'. Eurosurveillance. 2010;15(16), doi: 10.2807/ese.15.16.19544-en.
99. Centers for Disease Control and Prevention. 'Diphtheria outbreak--Saraburi Province, Thailand, 1994'. Morbidity and Mortality Weekly Report. 1996;45(13):271-3, doi: 10.1111/j.1708-8305.1996.tb00741.x.
100. Niyazmatov BI, Shefer A, et al. 'Diphtheria epidemic in the Republic of Uzbekistan, 1993-1996'. The Journal of Infectious Diseases. 2000;181 Suppl 1:S104-9, doi: 10.1086/315548.
101. Booth LV, Ellis C, et al. 'An atypical case of Corynebacterium diphtheriae endocarditis and subsequent outbreak control measures'. Journal of Infection. 1995;31(1):63-5, doi: 10.1016/S0163-4453(95)91519-2.
102. Nekrassova LS, Chudnaya LM, et al. 'Epidemic diphtheria in Ukraine, 1991-1997'. The Journal of Infectious Diseases. 2000;181 Suppl 1:S35-40, doi: 10.1086/315536.
103. Pedersen AH, Spearman J, et al. 'Diphtheria on Skid Road, Seattle, Wash., 1972-75'. Public Health Reports. 1977;92(4):336-42.
104. Khetsuriani N, Imnadze P, et al. 'Diphtheria epidemic in the Republic of Georgia, 1993-1997'. The Journal of Infectious Diseases. 2000;181 Suppl 1:S80-5, doi: 10.1086/315544.
105. Siad AS, Yusuf AM, et al. 'Diphtheria Outbreak in Somalia: An Alarming Public Health Crisis, Challenges, and Solutions'. Infection and Drug Resistance. 2026;19:563822, doi: 10.2147/IDR.S563822.
106. Balasanian M, McNabb SJ. 'Epidemic investigation of diphtheria in the Republic of Armenia, 1990-1996'. The Journal of Infectious Diseases. 2000;181 Suppl 1:S69-72, doi: 10.1086/315542.
107. Markina SS, Maksimova NM, et al. 'Diphtheria in the Russian Federation in the 1990s'. The Journal of Infectious Diseases. 2000;181 Suppl 1:S27-34, doi: 10.1086/315535.
108. Centers for Disease Control and Prevention. 'Update: diphtheria epidemic--New Independent States of the Former Soviet Union, January 1995-March 1996'. Morbidity and Mortality Weekly Report. 1996;45(32):693-7.
109. Dittmann S, Wharton M, et al. 'Successful control of epidemic diphtheria in the states of the Former Union of Soviet Socialist Republics: lessons learned'. The Journal of Infectious Diseases. 2000;181 Suppl 1:S10-22, doi: 10.1086/315534.

110. Hardy IR, Dittmann S, et al. 'Current situation and control strategies for resurgence of diphtheria in newly independent states of the former Soviet Union'. Lancet. 1996;347(9017):1739-44, doi: 10.1016/S0140-6736(96)90811-9.
111. Jacquinet S, Martini H, et al. 'Outbreak of Corynebacterium diphtheriae among asylum seekers in Belgium in 2022: operational challenges and lessons learnt'. Eurosurveillance. 2023;28(44), doi: 10.2807/1560-7917.ES.2023.28.44.2300130.
112. Hempenstall A, Neville J, et al. 'Community-led diphtheria vaccination campaign to manage a diphtheria outbreak in a remote Aboriginal community'. Communicable Disease Intelligence. (2018). 2024;48, doi: 10.33321/cdi.2024.48.49.
113. Badenschier F, Berger A, et al. 'Outbreak of imported diphtheria with Corynebacterium diphtheriae among migrants arriving in Germany, 2022'. Eurosurveillance. 2022;27(46), doi: 10.2807/1560-7917.ES.2022.27.46.2200849.
114. Brockhaus L, Urwyler P, et al. 'Diphtheria in a Swiss Asylum Seeker Reception Centre: Outbreak Investigation and Evaluation of Testing and Vaccination Strategies'. International Journal of Public Health. 2024;69:1606791, doi: 10.3389/ijph.2024.1606791.