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Original article

Respiratory diphtheria in the time of Omicron

Annabeth Simpson, Paul Douglas, Jenny Draper, Vitali Sintchenko, Zoe Cutcher, Daniel Ashton

Abstract

Diphtheria is a potentially fatal bacterial infection caused by toxin-producing strains of corynebacteria, most often *Corynebacterium diphtheriae* and less commonly *Corynebacterium ulcerans*. Incidence of the disease has fallen significantly since the introduction of vaccination programs; it is now rare in countries with high vaccination coverage such as Australia.

This article presents the most recent respiratory cases of diphtheria in two children in New South Wales—the first locally acquired childhood cases in Australia in 30 years—and discusses potential contributing factors. These encompass the lack of clinical awareness and the delays in laboratory diagnosis in regional laboratories. The cases also highlight the problem of vaccine hesitancy and the role that primary carers play in addressing these anxieties.

While clinical management of the cases progressed well, factors in the public health responses were complicated by access to appropriate care and by delays in antibiotic sensitivity profiles.

The public health response to these cases raises important considerations for clinicians and public health practitioners, including preparedness for rare and re-emerging diseases, the need for culturally safe environments and the importance of addressing vaccine hesitancy. Preparedness requires consideration of the capacity of regional health systems with fewer resources and of how public health departments can support response to multiple crises. Preparedness also relies on access to necessary diagnostic laboratory resources, on up-to-date guidelines, and on maintaining awareness among clinicians for these rare infections.

Keywords: diphtheria; outbreak; vaccine preventable disease; vaccine hesitancy; re-emerging disease; preparedness; cultural safety

Introduction

Diphtheria is a potentially fatal bacterial infection caused by toxin-producing strains of corynebacteria, most often *Corynebacterium diphtheriae* and less commonly *Corynebacterium ulcerans*.[1] These bacteria can cause respiratory or cutaneous infection and produce toxins responsible for several clinical manifestations.

Diphtheria is transmitted by respiratory droplets and by direct contact with respiratory secretions or infected skin lesions from symptomatic individuals. Respiratory diphtheria is characterised by a sore throat, fever, swelling of the neck and growth of a pseudomembrane in the oropharynx, which can occlude airways. The toxin produced by the bacteria kills healthy tissues in the respiratory system and can cause cardiac, neurological and renal complications.[1] Case fatality rates vary from 5% to 20%, dependent on vaccination and on access to appropriate treatment.[2,3] Toxigenic diphtheria is an urgent, notifiable condition in New South Wales (NSW) under the *Public Health Act 2010 (NSW)*.[4]

Globally, the incidence of diphtheria has fallen significantly since the introduction of vaccination programs and it is now rare in countries with high

vaccination coverage, like Australia. A recent epidemiological review in Australia reported that there were eight notifications of respiratory diphtheria during 1999–2019.[2] All were in adults, five were locally acquired (four of these in Queensland) and two unvaccinated adults died.

In this article we present the most recent respiratory cases of diphtheria in two children in New South Wales, the first such cases in 30 years,[5] and discuss potentially contributing factors.

Case presentation

In June 2022, North Coast Population and Public Health (NCPPH) was notified of a suspected diphtheria case in an unvaccinated two-year-old male (Case 1) who presented to an emergency department (ED) two days earlier with a four-day history of runny nose, sore throat, decreased oral intake, vomiting, loose stool, fevers, lethargy, cough and decreased urine output. The case's family had relocated from Queensland earlier in the year. Nose and throat swabs were submitted alongside blood culture and plated onto standard culture media. The case was admitted with an initial diagnosis of tonsillitis. Given the child had a negative test for coronavirus disease 2019 (COVID-19), they were accommodated in the general paediatric area, with standard infection control precautions. The child was administered intravenous benzylpenicillin. Their condition deteriorated over 48 hours, with continuing high temperatures and moderate respiratory distress (with increasing dyspnoea, notable stridor and dysphagia). The child tested negative for COVID-19, respiratory syncytial virus and influenza virus, and there was no growth on blood culture. Review by the ear, nose and throat registrar identified a thick pseudomembrane extending from the tonsils to the epiglottis, leading to clinical diagnosis of respiratory diphtheria. Standard infection control plus droplet precautions were followed. NCPPH was notified in accordance with the *Public Health Act 2010 (NSW)*.[4] The child was intubated prior to transfer and additional throat swabs were collected. The child was transferred to the paediatric intensive care unit at the nearest referral hospital, where diphtheria anti-toxin was administered within six days of the original symptom onset, two days following admission. Anti-toxin is stored only at key hospitals in state capital cities, and remote areas may access from nearby interstate capitals.

The following day, the laboratory reported that *C. diphtheriae* was not identified from the initial nose/throat swabs: the appropriate selective culture medium (Hoyle's medium) is not routinely available in regional settings, and diphtheria was not specifically requested at the time despite clinical suspicion. Since diphtheria is rarely seen by clinicians and microbiologists, and in view of the lack of selective medium in regional areas, this likely contributed to the limited knowledge of the necessary processes to ensure isolation of diphtheria. Two days after collection of the initial specimen, both the initial and subsequent respiratory specimen were transferred to another laboratory for plating onto selective Hoyle's medium. Two days later (five days after presentation, nine days after symptom onset), *C. diphtheriae* was isolated, toxin was detected by polymerase chain reaction (PCR) testing, and subsequent sensitivity testing demonstrated resistance to penicillin.

The case remained hospitalised for seven weeks. Recovery was complicated by vocal cord palsy and toxin-mediated myocarditis, in addition to a healthcare-associated COVID-19 infection. During their stay, the child received a two-week course of antibiotic therapy, consisting of intravenous benzylpenicillin, oral azithromycin and amoxicillin. The patient was negative for *C. diphtheriae* on three clearance swabs collected 8, 11 and 15 days after symptom onset (4, 7 and 11 days following admission), and discharged in mid-August 2022, seven weeks after the original symptom onset and admission to hospital.

Nine days after Case 1's onset, their five-year-old sibling (Case 2) developed loss of appetite and a sore throat. Case 2 was partially vaccinated, having received three out of five recommended doses of diphtheria vaccine,[3] and had previously received benzathine penicillin intramuscularly in community. They were admitted with exudative tonsillitis and commenced on intravenous benzylpenicillin then azithromycin with a presumptive diagnosis of diphtheria. The following day, *C. diphtheriae* was isolated from an oropharyngeal swab collected one day prior to their symptom onset during contact tracing, five days following their sibling's (Case 1) hospital admission. Treatment was changed to erythromycin following identification of resistance to penicillin in Case 1's pathology results. Diphtheria anti-toxin was administered to the patient later that day. Case 2 did not progress to severe toxin-mediated disease, remained stable during admission and was discharged after three days, continuing antibiotics.

Public health response and contact tracing

NCPPH commenced an urgent public health investigation following notification of Case 1. This entailed providing advice on droplet and transmission precautions to contacts, and escalating laboratory investigations. Initially, ten contacts were identified from Case 1 and a further four following the second case. Due to limitations on managing acute respiratory cases in general practice under COVID-19 restrictions, along with already limited general practitioner (GP) availability in the region, all contacts were directed to ED to facilitate public health management. All contacts were swabbed, offered post-exposure prophylaxis (PEP) antibiotic therapy and vaccinations. One close contact had an initial swab incorrectly collected onto viral transport media and did not re-present for a second collection. Ten contacts received PEP booster vaccines and four declined. All commenced a course of PEP antibiotic therapy, and 12/14 completed the course. Eight contacts who initially received benzathine penicillin PEP were recalled when penicillin resistance was identified and directed to ED for alternate PEP antibiotics (doxycycline, azithromycin or erythromycin); however, due to extended waiting times during heightened pressure on EDs amid a surge in COVID-19 cases in the region, one contact left before receiving updated therapy.

All contacts' swabs were negative except one collected from Case 1's sibling, who later became Case 2. Sixteen hours after Case 2's admission, *C. diphtheriae* was isolated from their swab.

Three clinical isolates of *C. diphtheriae* (two isolates from Case 1, one from Case 2) associated with this outbreak were submitted for sequencing. All three isolates carried the diphtheria toxin gene tox and belonged to sequence type (ST) 381, an uncommon type reported in New South Wales and Papua New Guinea.[6,7] The outbreak isolates, all available ST381 sequences[6,7] and all available New South Wales sequences[6] were compared using Nullarbor v2.0 and Snippy v4.6.3,[8,9] with *C. diphtheriae* biovar Mitis ISS 3319 (ST6) as the reference, and the Snippy core single-nucleotide-polymorphism (SNP) alignment used to generate a phylogeny with IQ-Tree (Figure 1).[10] The phylogenetic tree (Figure 1) presents genetic distances between a subset of historical isolates of *C. diphtheriae* in New South Wales. The outbreak sequences were identical to each other (0 SNPs), 28–31 SNPs from the other ST381 sequences, and > 1,300 SNPs from their nearest non-ST381 sequences (Figure 1), indicating similarity between isolates from Cases 1 and 2 and an emerging cluster in Papua New Guinea.

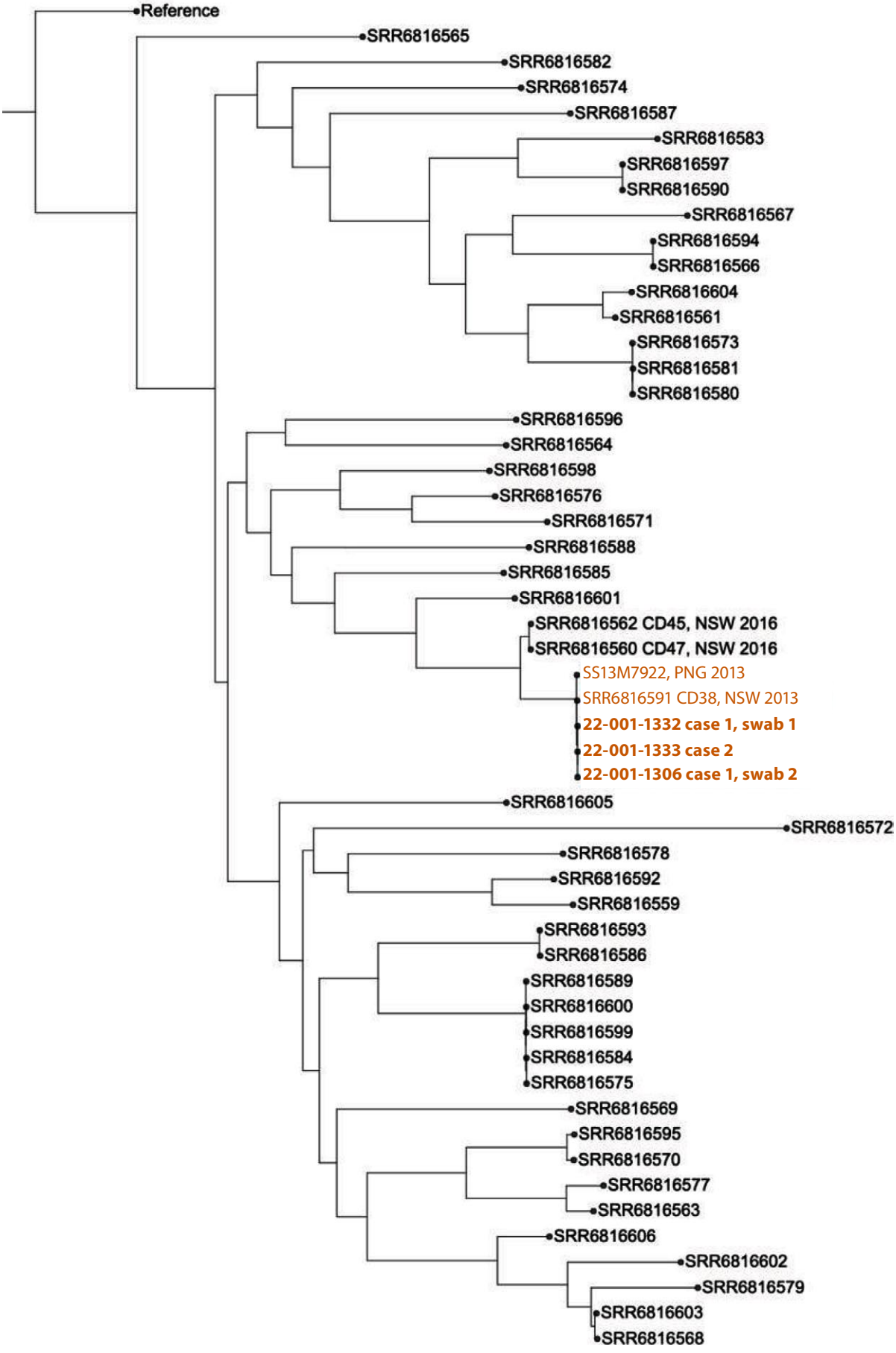
Discussion

These cases highlighted several challenges of managing serious, life-threatening vaccine preventable diseases at the time of a pandemic. Diphtheria remains rare in Australia due to high vaccination coverage, with only eight respiratory cases notified during 1999–2019.[2] In recent years we have seen notable outbreaks across different countries in the Asia-Pacific region, including in Bangladesh, Indonesia, Pakistan and Vietnam.[11–16]

Due to its rarity in Australia, diphtheria has never been seen by most healthcare practitioners.[5,17] Lack of familiarity with diphtheria can lead to low clinical suspicion, resulting in missed or late diagnosis and poor outcomes.[5,17] In this instance, while diphtheria was not suspected on admission, the clinical suspicion of the specialist was key to diagnosis and life-saving intervention. Clinical symptoms of respiratory diphtheria are sore throat, mild fever, loss of appetite, swollen glands in the neck and a greyish-white membrane forming over the throat and tonsils which can cause difficulty in swallowing and breathing.[1] Maintaining clinical awareness of rare and re-emerging diseases, like diphtheria, particularly in general practice and EDs, is critical for prompt diagnosis, timely administration of anti-toxin and immediate public health response to limit disease transmission.

Notably, the cases had relocated to New South Wales from Queensland earlier in the year; where a marked increase in diphtheria cases was reported:[18] Queensland Health reported 24 (20 cutaneous, four respiratory) diphtheria notifications in 2022, more than four times the five-yearly average, with all notifications arising from the north-east region.[19] During 2017–2021, the annual number of diphtheria cases across Queensland was much lower, ranging from four to nine cases.[18] In this context, it is essential that clinicians maintain an index of suspicion for diphtheria, particularly where there is an epidemiological link to areas with an increased incidence.

Figure 1: Phylogenetic tree of *C. diphtheriae* sequences from New South Wales and Papua New Guinea[a]



a ST381 sequences are highlighted in orange.

Maintaining diagnostic capability for rare and unexpected pathogens can be a challenge for the clinician and the routine microbiology laboratory, especially in regional areas. Often, specific diagnostic tests are only available in reference laboratories, thus further delaying efficient therapy and outbreak management. For Case 1, selective culture media (Hoyle's medium) was not readily available and required sample transfer to another laboratory, delaying the isolation of *C. diphtheriae* and the identification of resistance to penicillin. This resulted in changes to Case 1's treatment regimen and delayed administration of correct PEP antibiotics for close contacts, with several contacts having to re-commence different antibiotic therapies. A consideration of access to specialised culture media in regional laboratories is important to ensure a timely, comprehensive, and correct PEP response.

Management of these cases was complicated by the impact of the COVID-19 pandemic on the healthcare system in regional Australia. When these cases occurred, the region was experiencing a significant increase in COVID-19 cases and hospitalisations. Emergency Departments were experiencing high demand, and in a region where access to GPs was already limited, high COVID-19 case numbers made accessibility more difficult.

Timely access, administration of PEP and swabbing of contacts are key public health measures that limit further transmission of diphtheria. These measures are typically arranged through a GP. Due to a lack of availability of GPs, contacts were directed to busy EDs for management, creating further challenges. In the overburdened hospital during the pandemic, nursing staff were so accustomed to collecting swabs for viral PCR, that one contact's throat swab was placed into viral transport media. This resulted in an inability to test for bacterial infections such as diphtheria and led to loss of the contact to follow-up. Additionally, in EDs faced with higher acuity cases, diphtheria contact screening and PEP was not prioritised, resulting in a contact leaving the ED after an extended wait for a change in antibiotics. Proper public health management requires testing and administering correct PEP to all identified contacts to prevent further disease transmission. These two lost contacts, amid heightened pressure on EDs and prolonged wait times due to the COVID-19 surge in the region, posed a risk of further diphtheria transmission.

While not reported as an issue in this instance, some COVID-19 guidelines instructed clinicians to avoid oral cavity examinations; this could potentially have further delayed diagnosis if the child had presented to a GP.

Australia offers highly effective, safe and free vaccination to protect against diphtheria as part of the National Immunisation Program. Despite this, the cases reported here were unvaccinated (Case 1) and partially vaccinated (Case 2). In some areas of the world there has been a rise in vaccine-preventable diseases including diphtheria, in part due to vaccine hesitancy.[20–22] Drivers of vaccine hesitancy are multifaceted and include complex perceptions, attitudes and behaviors influenced by sociocultural factors, experiences and relationships with providers.[23,24] An increase in vaccine acceptance can be achieved by tailoring immunisation programs to specific populations and communities; by listening to individual concerns; and by clearly communicating the risk of vaccine side effects.[21,22,25] In this instance, the family reported they perceived their oldest child experienced an adverse event following immunisation, prompting them to discontinue vaccinations for all siblings. On later review of medical records, it appeared possible the perceived adverse event may have been caused by an unrelated infection, and the family may not have had the opportunity to discuss and understand this with a health professional.

The cases were Aboriginal children, and the family members reported differential treatment in their interactions with the health system during the response. Such negative experiences in health services can lead to distrust of health staff and dissuade people from accessing treatment and vaccinations.[26] This reported experience between the family and health staff complicated the public health response; previous experiences with other healthcare providers may have played a role in the family's earlier decision to cease vaccination. The perceptions from the family highlight the need to ensure health services are culturally safe, respecting of cultural values, strengths, and differences, and free of racism and inequity.[26] Cultural safety can be achieved by: providing cultural training for all health workers; increasing the Aboriginal health workforce; and integrating evidence-based, culturally-considerate models of care, such as the Agency for Clinical Innovation's co-design toolkit and shared decision-making framework.[27] The impact of Aboriginal Health Workers is demonstrative of how support, respectful treatment, good communication and empowerment in decision-making can greatly improve patient experiences.[26–28]

Conclusion

The public health response to these cases raises important considerations for clinicians and public health practitioners, including preparedness for rare and re-emerging diseases, the need for culturally safe environments and the importance of addressing vaccine hesitancy. Preparedness requires consideration of the capacity of regional health systems with fewer resources, and of how response to multiple crises can best be supported. Preparedness also relies on access to necessary diagnostic laboratory resources, on up-to-date guidelines and on maintaining awareness among clinicians of these rare infections.

Everyone has the right to feel culturally safe when accessing health care, free of racial discrimination. This requires engagement in critical reflective practice to address racist attitudes and unconscious biases.

These two cases of childhood respiratory diphtheria are the first reported childhood cases in Australia since 1992. It is important to note that, while diphtheria vaccination rates in Australian children sit at 95%, both these cases were in unvaccinated or partially vaccinated children. Maintaining high vaccination rates remains the safest and most effective way to minimise disease, hospitalisations and deaths. Health providers are the most trusted influencer of vaccination decisions and must be supported to provide credible vaccine information to address vaccine-related concerns from patients.

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