NT Health Interim Guidelines v2

Clinical Management of Diphtheria in Primary Care in the Northern Territory

These interim guidelines are intended to support clinicians managing suspected and confirmed cases of diphtheria in the community. As the diphtheria outbreak evolves, guidance will be updated as necessary (1). Vaccination remains the most important measure to protect against severe diphtheria. Antibiotics are important to treat diphtheria and reduce transmission.

There are several different ways that a case of diphtheria might present or be detected in the primary healthcare setting in the Northern Territory. These include:

1. Respiratory diphtheria presentation
2. Cutaneous diphtheria presentation (most common)
3. Late complications of diphtheria, a significant contributor to diphtheria related mortality: cardiac (myocarditis, arrhythmias, dilated cardiomyopathy), renal failure, neuropathy.

1. Respiratory diphtheria

Respiratory diphtheria can present with slowly progressive pharyngeal symptoms initially signs and symptoms of **pharyngitis** or **tonsillitis** (2,3). The classic presentations of pseudomembrane formation and progressive neck swelling are characteristic of severe diphtheria.

Early pseudomembrane may be difficult to differentiate from standard pharyngeal or tonsillar exudate. Pseudomembrane development is due to direct toxin effects on tissue leading to cellular necrosis and classically is more fibrous and adherent to the tissue, rather than purulent exudate which is easily removed by a swab. It coalesces in later disease to form a well demarcated grey-white membrane. Disruption of significant pseudomembrane can cause bleeding and respiratory obstruction.

For any suspected respiratory case, follow *Appendix A: Suspected **respiratory** diphtheria algorithm.* Use standard, contact and droplet precautions.

2. Cutaneous diphtheria

Cutaneous diphtheria might be suspected in a non-healing wound or ulcer (>2 weeks), or an ulcer of any duration in someone who has had contact with a known case of diphtheria. These lesions can begin as a pustule, developing into a superficial, sloughy ulcer with well-demarcated edges. It may also be diagnosed coincidentally based on a swab culture of a skin sore where toxin gene-positive *C. diphtheriae* is isolated in the laboratory alongside other common pathogens like Strep A and *Staphylococcus aureus.* The role of *C. diphtheriae* in mixed co-infection is less clear; these cases are however still likely to contribute significantly to ongoing transmission.

Non-toxigenic strains of *C. diphtheriae* can also be isolated from wound swabs, however, these do not usually cause disease (4), and do not require directed treatment, or contact tracing.

Toxin-mediated (i.e. severe) disease from cutaneous diphtheria is rare (3), and most cases can be managed with antibiotics, without any need for hospital admission or administration of diphtheria antitoxin (DAT).

However DAT may be needed for progression of a large wound (>2cm diameter) or suspected toxin-mediated systemic features.

Please give empiric diphtheria treatment if cutaneous diphtheria is strongly suspected at the time of presentation due to the likely contribution of skin infection to diphtheria transmission to reduce the current outbreak.

Wounds should be swabbed, cleaned and covered with a dressing. Use standard and contact precautions. **See** *Appendix B: Suspected **cutaneous** diphtheria algorithm.*

3. Late complications of diphtheria

It is possible for late, toxin-mediated complications of diphtheria to present days, weeks or months after resolution of symptoms associated with untreated toxigenic *C. diphtheriae* infection. These presentations are likely to be rare but should be considered if someone presents with unexplained cardiac, renal or neurological disease (5–7). Discuss with (adult or paediatric) infectious diseases on-call and consider hospital admission for further investigations and management. Notify CDC.

Cardiac complications

Cardiac complications of myocarditis usually present 7-14 days after the onset of respiratory symptoms, and may manifest as dysrhythmias, conduction disturbances including heart block, and dilated cardiomyopathy presenting as congestive cardiac failure (2). People presenting with shortness of breath, chest pain, palpitations, unexplained tachycardia need a medical consult; perform clinical review including ECG and consider myocarditis in differential diagnosis if recent diphtheria infection.

Neuropathy

Neuropathy can develop weeks to months after onset of diphtheria (2). Presentation of demyelinating polyneuropathy has clinical features similar to Guillain-Barre syndrome. Specific findings may include: bulbar dysfunction (impaired swallowing, coughing, nasal voice and nasal regurgitation), other cranial nerve palsies, limb weakness, diaphragmatic weakness and autonomic dysfunction.

4. Follow up of confirmed diphtheria cases

For all confirmed cases of cutaneous or respiratory diphtheria, advise regarding symptoms of late complications, and to present if concerns. Arrange recall/follow-up:

Approximately 1-2 weeks:

- **Symptom check**- myocarditis (chest pain, shortness of breath, palpitations) or neuropathy (numbness, tingling sensations, loss of feeling or function).
- **Perform HR/RR/BP/O2 saturations, ECG**. If signs or symptoms concerning for myocarditis are present: perform troponin, and refer for specialist review and echocardiogram if clinically indicated, as per usual management of acute coronary syndrome. Notify CDC.
- **For patients with confirmed respiratory diphtheria,** complete a post-treatment swab for m/c/s 1-2 weeks after starting antibiotic treatment. **For patients with confirmed cutaneous diphtheria,** repeat skin swab for m/c/s if wound not healed at time of follow-up, and ongoing signs of infection. Check

and document reported adherence to treatment. Ongoing isolation/precautions are not required whilst awaiting the result. However, if the repeat swab returns positive on **culture and PCR**, an antibiotic treatment course should be repeated.

- **Give diphtheria toxoid containing vaccine if not yet received post diagnosis, and if not febrile or unwell.** See NT diphtheria outbreak vaccination schedule.
- **Approximately 1, 3 and 6 months** following onset of symptoms: Assess for symptoms/signs of neuropathy e.g. numbness, tingling sensations, loss of feeling or function. Consider performing UEC if underlying risk factors for renal disease. Refer as per usual clinical care pathways. Notify CDC if suspected late complications from diphtheria.

5. Antibiotic treatment

Empiric antibiotic recommendations in this guideline are based on the antimicrobial susceptibility patterns observed in the current diphtheria outbreak to date. Antibiotic resistance may emerge, and treatment should be guided by antimicrobial susceptibility testing results when these are available.

Azithromycin is the preferred first-line treatment for cases of confirmed cutaneous diphtheria and suspected/confirmed respiratory diphtheria. The additional azithromycin dosing option of 30mg/kg as a single dose in children is based on local expert opinion, and use in other indications including acute otitis media (7,14,15).

Alternative antibiotics for allergy or long QT

Alternate effective antibiotics include amoxicillin and doxycycline. These can be used in the case of allergy to azithromycin, contraindication (e.g. long QT). The multi-dose per day dosing requirements of these regimens may impact on treatment adherence and completion.

Amoxicillin has been included in version 2 of these guidelines as **empiric treatment for suspected cutaneous diphtheria.** Amoxicillin will cover both strep A and diphtheria. Strep A is a primary driver of skin infection, particularly impetigo; however, strep A isolates in the Northern Territory are not always susceptible to azithromycin (10).

Doxycycline provides empiric coverage for *S. aureus* (including community acquired MRSA) and diphtheria but requires bd dosing, and the side effect and tolerability profile result in it being less preferred compared to azithromycin. For children, if *S. aureus* co-infection suspected (e.g. boil), use amoxicillin to cover diphtheria PLUS antibiotic of choice for *S. aureus* e.g. trimethoprim/sulfamethoxazole.

IM benzathine penicillin is not recommended for treatment of diphtheria in this current outbreak, though it can still be used as first-line treatment for impetigo (skin sores) and suspected strep throat as per CARPA. Diphtheria outbreak strain isolates to date have been reported by the laboratory as 'penicillin susceptible increased exposure' meaning that higher than usual doses of penicillin are required (i.e. high dose IV penicillin), and low dose penicillin (such as in IM benzathine penicillin) is unlikely to be adequate for treatment (3).

Table 1: Antibiotic regimens used for treatment of suspected or confirmed diphtheria

ANTIBIOTIC REGIMEN	INDICATION			
	Suspected or confirmed respiratory diphtheria	Suspected cutaneous diphtheria	Confirmed cutaneous diphtheria	Azithromycin contraindicated
ADULT & CHILD **Azithromycin 500mg (child 10mg/kg) oral daily for 7 days**	✓		✓	
CHILD ONLY Azithromycin (children up to age 18) 30mg/kg (max 2g) single dose oral	✓ PLUS repeat dose on day 5 if ongoing symptoms of respiratory diphtheria		✓	
ADULT & CHILD Amoxicillin 1g (child 30mg/kg/dose max 1g) oral tds for 7 days*	✓	✓	✓	✓
ADULT & CHILD Doxycycline 200mg for first dose, then continue 100mg (child 2mg/kg/dose rounded to nearest 25mg) oral bd for 7 days	✓	✓	✓	✓

* Higher dose amoxicillin 2g (child 50mg/kg/dose max 2g) oral BD for 7 days may be used on a case-by-case basis, but may be less effective than tds dosing.

Chemoprophylaxis is recommended for high risk contacts of diphtheria. Please see the diphtheria contact management matrices to determine risk-level.

Antibiotic options for contact prophylaxis:

- azithromycin 500mg (children 10mg/kg/dose max 500mg) oral daily for 5 days OR
- azithromycin (children up to age 18yrs) 30mg/kg (max 2g) oral single dose OR
- amoxicillin 1g (children 30mg/kg/dose max 1g) oral tds for 7 days

6. Importance of immunisation

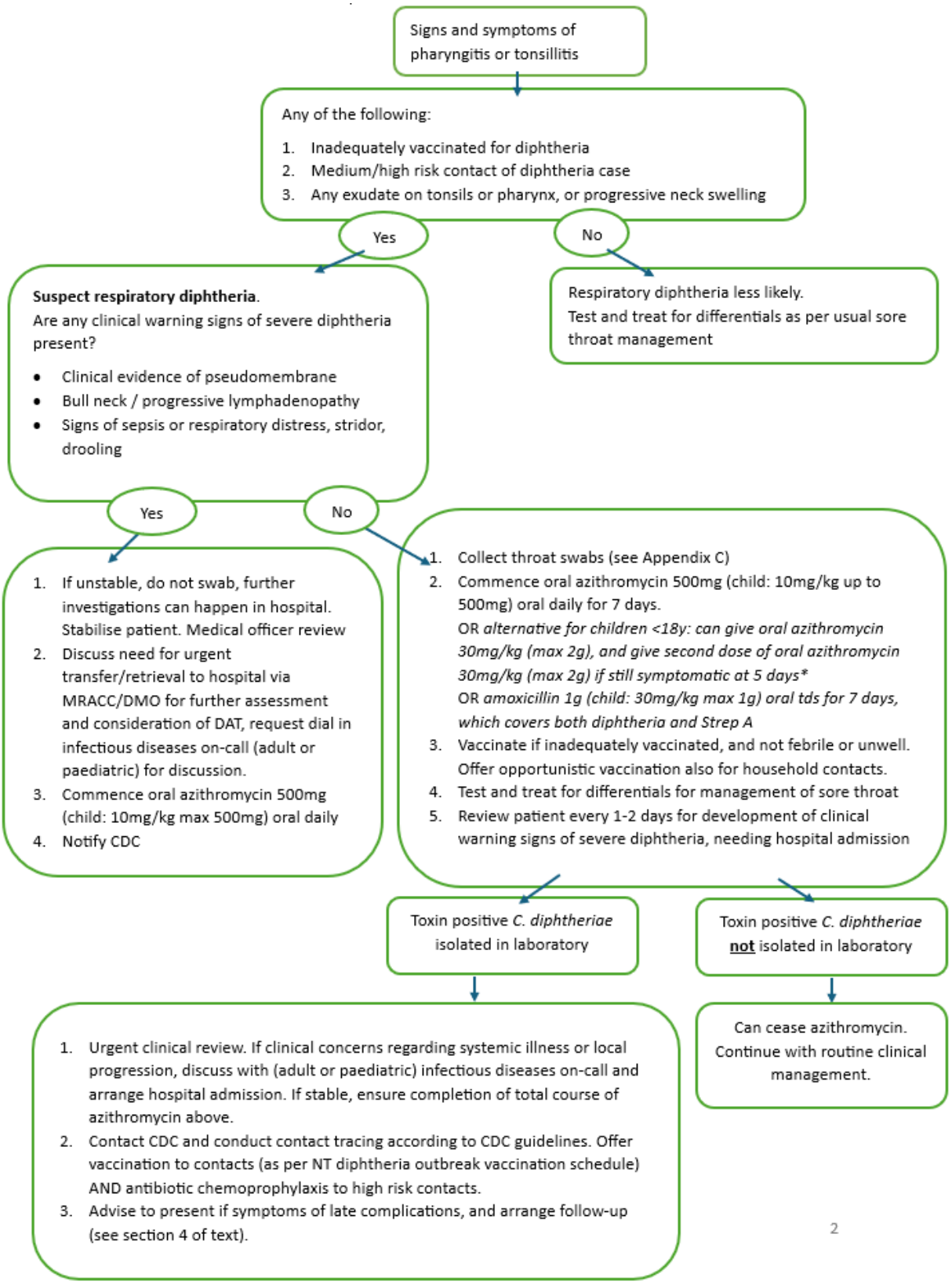
"Inadequately vaccinated" applies to children who are not up to date with childhood immunisation recommendations (diphtheria toxoid containing vaccine at 2, 4, 6, 18 months, 4 years, 12 years) or an adult who has had less than 3 diphtheria toxoid containing vaccines in their life or is more than 5 or 10 years (depending on their risk level) since their last diphtheria toxoid containing vaccine dose. See the NT diphtheria outbreak vaccination schedule.

While colonisation or infection with toxigenic *Corynebacterium diphtheriae* is possible in both fully vaccinated and inadequately vaccinated people, the risk of severe diphtheria disease is higher in people who have missed doses on the NT immunisation schedule or whose last dose was more than 5 years ago. Immunosuppressed patients may have impaired immunity despite vaccination and be at increased risk of severe disease, and should also be considered for administration of diphtheria antitoxin (DAT) (3).

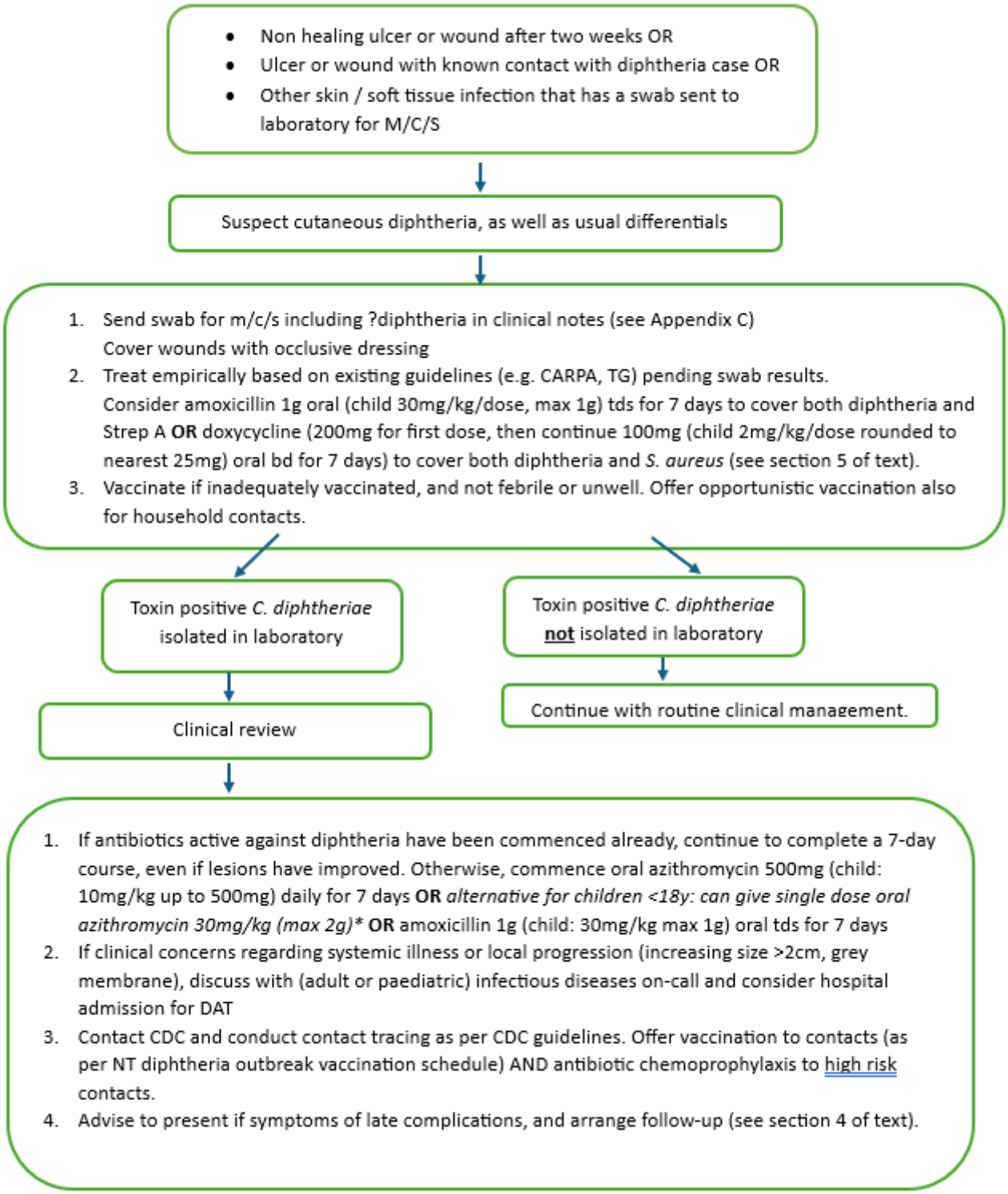
Cases	Additional dTpa# dose once clinically well OR 4 weeks after Diphtheria Antitoxin (DAT) administration	Greater than10 years old Boostrix® or Adacel® Children under 10 years old, give DTPa - Tripacel® / Infanrix®)
High and medium risk contacts	Additional dTpa# dose if more than 12 months since last dose	Boostrix® or Adacel® (Children under 10 years old, give DTPa - Tripacel® / Infanrix®) Low risk contacts
Low risk contacts	Additional dTpa# dose if more than 5 years since last dose	Boostrix® or Adacel® (Children under 10 years old, give DTPa - Tripacel® / Infanrix®) Low risk contacts
Aboriginal and Torres Strait Islander or frontline worker	Additional dTpa# dose if more than 5 years since last dose	Boostrix® or Adacel® (Children under 10 years old, give DTPa - Tripacel® / Infanrix®) Low risk contacts
All children < 10 years	NIP doses as per NT immunisation schedule at 6 weeks, 4 months , 6 months, 18 months, 4 years and 12 years	As per schedule

Please see the diphtheria contact management matrices to determine risk-level.

Appendix A: Suspected respiratory diphtheria algorithm



Appendix B: Suspected cutaneous diphtheria algorithm



Appendix C: Swabs for laboratory diphtheria testing

Suspected <u>cutaneous</u> diphtheria

Wound swab – M/C/S
x1 bacterial swab in gel transport, often **blue / purple** topped, with site labelled

Suspected <u>respiratory</u> diphtheria

Throat/Nose swab – M/C/S
x1 bacterial swab in gel transport, often **blue / purple** topped – **priority**

AND

x1 dry swab, often red topped, for direct diphtheria toxin PCR

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National Safety and Quality Health Service standards

National Safety and Quality Health Service standards							
Clinical Governance	Partnering with Consumers	Preventing and Controlling Healthcare Associated Infection	Medication Safety	Comprehensive Care	Communicating for Safety	Blood Management	Recognising & Responding to Acute Deterioration
☐	☐	☐	☒	☐	☐	☐	☐