Epidemiological Update
Diphtheria

16 April 2018

Diphtheria in the Americas - Summary of the situation

In 2017, four countries in the Region of the Americas—Brazil, the Dominican Republic, Haiti, and the Bolivarian Republic of Venezuela—reported confirmed diphtheria cases. In 2018 as of epidemiological week (EW) 14 of 2018, four countries in the Region—Brazil, Colombia, Haiti, and Venezuela—have reported suspected and confirmed diphtheria cases.

The following is a summary of the situation in each country with reported suspected and confirmed cases in 2018.

In **Brazil** in 2017, there were 42 suspected cases reported in 14 states. Of the reported cases, 5 were confirmed in four states: Acre (1), Minas Gerais (2), Roraima (1 fatal case, imported from Venezuela), and São Paulo (1). The remaining 37 cases were ruled out. Three of the 5 confirmed cases (2 in Minas Gerais and 1 in São Paulo) had received the full vaccination scheme. The confirmed cases range from 4 to 66 years of age (median 19 years), and four are male and one is female. Additionally, in EW 14 of 2018, 6 suspected cases were reported in 6 states; one reported in the state of Roraima (imported from Venezuela) is currently under investigation. As of EW 14, none were confirmed.

In **Colombia** in EW 7 of 2018, a fatal confirmed case of diphtheria imported from Venezuela was reported in La Guajira Department. The case is a 3-year-old Venezuela national with an unknown vaccination history. Onset of symptoms was on 2 January 2018 and the case died on 8 January. The case was laboratory-confirmed based on clinical, epidemiological, and laboratory criteria (Gram-positive bacilli and RT-PCR positive for *Corynebacterium diphtheriae* with no identification of biotype or positive toxin).

In **Haiti**, since the beginning of the outbreak at the end of 2014 up to EW 6 of 2018, there have been 410 probable cases of diphtheria reported, including 75 deaths.[1] Reported case-fatality rates were 22.3% in 2015, 27% in 2016 and 10.7% in 2017 and 2018. During the first four epidemiological weeks of 2018, 2 to 5 probable cases per EW were reported similar to that observed during the last four weeks of 2017.

Females accounted for 57% of the total probable cases in 2015, 50% in 2016, 60% in 2017, and 47% in 2018 (up to EW 6). With respect to vaccination coverage, between 2015 and 2018 the unvaccinated cases accounted for 17% (2018) to 38% (2015) of the total cases. Children less than 10 years of age accounted for 64% of the probable cases reported between 2017 to EW 4 of 2018.

[1] Per the Haiti Ministry of Public Health and Population, a probable case is defined as any person, of any age, that presents laryngitis, pharyngitis or tonsillitis with false adherent membranes in the tonsils, pharynx and / or nasal pits, associated with edema of the neck.

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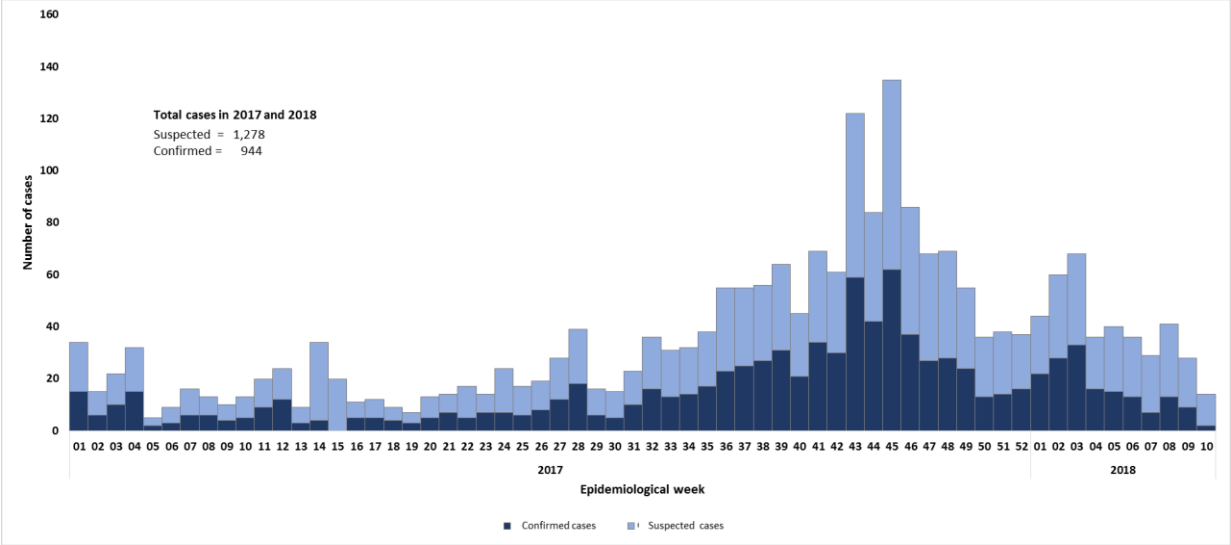
Since the beginning of the outbreak the departments reporting the highest number of probable cases are Artibonite, Centre, and Ouest.

In **Venezuela**, the diphtheria outbreak that began in July 2016 remains active (**Figure 1**). Since the start of the outbreak until EW 10 of 2018, a total of 1,602 suspected diphtheria cases were reported (324 cases in 2016, 1,040 in 2017, and 238 in 2018), of which 976 were confirmed by laboratory (314) or epidemiological-link (662), and 142 died (17 in 2016, 103 in 2017, and 22 in 2018). The cumulative case fatality rate is 14.5%.

Figure 1. Suspected and confirmed diphtheria cases by epidemiological week based on symptom onset. Venezuela, EW 1 of 2017 to EW 10 of 2018



Source: Data from the Venezuela Ministry of Popular Power for Health and reproduced by PAHO/WHO

In 2016, cases were reported in five states (Anzoátegui, Bolívar, Delta Amacuro, Monagas, and Sucre), while in 2017, 22 states and the Capital District reported confirmed cases. In 2018, 9 federal entities have reported confirmed cases. Cases have been reported among all age groups; however, the majority of cases occurred among the 1-49 year age group while the highest incidence rate occurred among the 5-19 year age group.

Health authorities are intensifying epidemiological surveillance, investigations, medical care, and vaccinations. In addition, they are maintaining continuous training of healthcare workers (based on the updated manual of standards, guidelines, and procedures for the management of the disease) as well as health education.

Advice for Member States

The Pan American Health Organization / World Health Organization (PAHO/WHO) advises Member States to continue their efforts to maintain high vaccination coverage with the full 3-dose primary series and booster doses in all territorial entities.

PAHO/WHO stresses that the populations at greatest risk are unvaccinated children under 5 years of age, schoolchildren, healthcare workers, military service personnel, prisoner

community, and persons who, due to the nature of their occupation, are in contact with a large number of persons on a daily basis.

Although travelers do not have a special risk of diphtheria infection, it is recommended that national authorities remind travelers going to areas with diphtheria outbreaks to be properly vaccinated in accordance with the national vaccination scheme established in each country prior to travel. If more than five years have passed since their last dose, a booster dose is recommended.

PAHO/WHO recommends Member States strengthen their surveillance system for the early detection of suspected cases in order to initiate the timely treatment of cases and follow-up of contacts, and ensuring the supply of diphtheria antitoxin.

Vaccination is key to prevent cases and outbreaks, and adequate clinical management reduces complications and mortality. Below are some guidelines for health authorities regarding clinical management.

Clinical management

Initial clinical management

The clinical management of patients with suspected diphtheria includes the administration of antibiotics and diphtheria antitoxin (DAT), and implementation of infection prevention and control measures. The following is recommended:

- Place the patient in a room or isolation area and apply standard droplet and contact precautions.
- Administer DAT as soon as possible.
- Administer antibiotics (penicillin, erythromycin, or azithromycin) as soon as possible in accordance with national protocols.
- Continuously monitor and provide supportive therapy in case of severe complications (i.e., airway management and cardiac, neurological, or renal failure).

Antibiotic treatment

Antibiotics should be administered as soon as possible once a case is suspected, without waiting for laboratory confirmation.

- For patients who cannot swallow or who are in serious condition, intravenous (IV) or intramuscular (IM) administration of antibiotics should be used. However, once the patient improves clinically, oral administration can be carried out.
- Oral therapy can be used from the start in patients with mild or moderate symptoms.
- Before initiating treatment, inquire whether the patient has an allergy history to penicillin.

Antibiotic treatment
• **Procaine benzyl penicillin (penicillin G)**: administer IM All persons: 50,000 IU/kg once daily (maximum 1.2 MIU a day). Treat for a total of 14 days.
• **Aqueous benzyl penicillin (penicillin G)**: administer IM or slow IV All persons: 100,000 units/kg/day administer in divided does of 25,000 IU/kg every 6 hours. Maximum does is 4 MIU or 2.4 grams per day.
• **IV Erythromycin** All persons: 40-50 mg/kg/day (máximum, 2gm/day). Administer in divided dose, 10-15 mg/kg every 6 hours, maximum 500 mg per dose. Treat for a total of 14 days.

Antibiotic treatment for patients who can receive oral treatment
• **Oral phenoxymethyl penicillin V** All persons: 50 mg/kg/day, administer in divided dose 10-15 mg/kg/dose administered every 6 hours. Maximum is 500 mg per dose. Treat for 14 days.
• **Oral erythromycin** All persons: 40-50 mg/kg/day (maximum, 2gm/day). Administer in divided dose, 10-15 mg/kg every 6 hours. Maximum 500 mg per dose. Treat for total 14 days.
• **Oral azithromycin** For children: 10-12 mg/kg once daily (maximum 500 mg/day). Treat for 14 days. For adults: 500 mg once daily. Treat for 14 days. Note: There is no data to support the exact duration required for azithromycin.

Diphtheria antitoxin (DAT) therapy

DAT is highly efficient for the treatment of diphtheria and should be administered immediately without waiting for laboratory confirmation.

- Diphtheria toxin, once it enters the host cells, is not neutralized by DAT. Therefore, to reduce complications and mortality, DAT should be administered as soon as possible after clinical onset.

- Because there is a risk of severe allergic reaction to the administration of DAT, a sensitization test (i.e., Besredka test) must be performed prior to its administration.

- DAT must be administered in a closely monitored setting with appropriate medical interventions available if needed.

- The amount of recommended antitoxin varies, depending on the severity of the clinical picture (persons with extensive pseudomembrane, neck swelling, systemic signs). The dose is the same for children and adults and it is not necessary to repeat.

Clinical presentation	Dosage for adults and children
Laryngeal or pharyngeal of 2 days duration	20,000 - 40,000 IU
Nasopharyngeal disease	40,000 - 60,000 IU
Extensive disease of 3 or more days of duration or any patient with diffuse swelling of the neck (respiratory distress, hemodynamic instability).	80,000 - 100,000 IU
Cutaneous diphtheria (there is no consensus regarding the usefulness of DAT against cutaneous diphtheria)	20,000 – 40,000 IU

- Pregnant women should not receive DAT.

Since the disease does not confer immunity, immunization should be completed once the clinical picture is over.

Infection prevention and control measures

- Vaccinate, according to age, with a diphtheria toxoid-containing vaccine.
- Apply standard precautions at all times.
- Keep the isolation area separate from other patient-care areas.
- Maintain one meter of distance between patients, when possible.
- After discharge, restrict contact with others until completion of antibiotic therapy (i.e., remain at home, do not attend school or work until treatment course is complete).

Care of close contacts

Close contacts include: household members (all persons who slept in the same house during the **last 5 nights** before onset of disease of the case); any persons with a history of direct close contact (**less than one meter**) for a prolonged time (**over 1 hour**) during the **5 days prior to onset of disease** of the case (e.g. caretakers, relatives, or friends who regularly visit the home); and healthcare workers exposed to oral or respiratory secretions of a case-patient.

All close contacts should be assessed for signs and symptoms compatible with diphtheria and kept under daily supervision for 7 days from the last contact with the case. Adult contacts should avoid contact with children and should avoid handling food until it is proven they are not a carrier.

All contacts should receive a single dose of benzathine benzylpenicillin intramuscularly (600,000 units for children under 6 years and 1.2 million units for those 6 years and older). If the culture is positive, antimicrobial treatment should be started.

Laboratory diagnosis

The best specimens for bacteriological cultures are pharyngeal swabs obtained by swabbing the edge of the mucosal lesions or directly under the membrane. In general, Gram staining is not recommended, as other *Corynebacterium* can normally colonize the throat.

Once *C. diphtheriae* is isolated, its biotype can be determined. It is recommended to verify whether the isolated *C. diphtheriae* strain is toxigenic; therefore, the toxin production test or Elek immunodiffusion test must be performed.

Additionally, there are several protocols for detection of the A portion of the diphtheria toxin gene (*tox*) using polymerase chain reaction (PCR), which allow for results to be obtained in a few hours. However, detection of the *tox* gene does not confirm the production of toxin, and therefore, PCR techniques should be considered as complementary tests and not a substitute for bacteriological culture.

References

1. Diphtheria vaccine: WHO position paper – August 2017. Available at: http://bit.ly/2CCN7UW

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3. Faulkner A, Acosta A, Tejpratap S.P, Tiwari. Manual for the Surveillance of Vaccine-Preventable Diseases, 5th Edition, 2011. Diphtheria: Chapter 1. Available at: http://bit.ly/2oFCA5j