MAJOR ARTICLE

Diphtheria Antitoxin Administration, Outcomes, and Safety: Response to a Diphtheria Outbreak in Cox's Bazar, Bangladesh

Nell Eisenberg,[1,2] Isabella Panunzi,[1] Anja Wolz,[1] Chiara Burzio,[1] Anna Cilliers,[1] Md Ariful Islam,[1] Waqar Mohammad Noor,[1] Oren Jalon,[1] Deanna Jannat-Khah,[2] and Julita Gil Cuesta[1]

[1]Médecins Sans Frontières, Operational Center Brussels, Brussels, Belgium, and [2]Division of Hospital Medicine, Weill Cornell Medical Center, New York, New York, USA

Background. Diphtheria has re-emerged over the past several years. There is a paucity of data on the administration and safety of diphtheria antitoxin (DAT), the standard treatment for diphtheria. The 2017–2018 outbreak among Rohingya refugees in Bangladesh was the largest in decades. We determined the outcomes of DAT-treated patients and describe the occurrence and risk factors associated with adverse reactions to DAT.

Methods. We conducted a retrospective study at the Médecins Sans Frontières Rubber Garden Diphtheria Treatment Center from December 2017–September 2018. Diphtheria was diagnosed based on the World Health Organization clinical case criteria. High-acuity patients were eligible for DAT. Safety precautions were meticulously maintained. We calculated the presence of adverse events by age, duration of illness, and DAT dosage using bivariate comparisons.

Results. We treated 709 patients with DAT; 98% (n = 696) recovered and were discharged. One-fourth (n = 170) had at least 1 adverse reaction. Common reactions included cough (n = 115, 16%), rash (n = 66, 9%), and itching (n = 37, 5%). Three percent (n = 18) had severe hypersensitivity reactions. Five patients died during their DAT infusion or soon afterwards, but no deaths were attributed to DAT.

Conclusions. Outcomes for DAT-treated patients were excellent; mortality was <1%. Adverse reactions occurred in one-quarter of all patients, but most reactions were mild and resolved quickly. DAT can be safely administered in a setting with basic critical care, provided there is continuous patient monitoring during the infusion, staff training on management of adverse effects, and attention to safety precautions.

Keywords. diphtheria; antitoxins; disease outbreaks; Bangladesh; drug-related side effects and adverse reactions.

Diphtheria antitoxin (DAT) was developed more than 100 years ago, when the blood of diphtheria-immunized animals was shown to have therapeutic potential [1]. Within several years it was mass produced in immunized horses and used successfully to treat sick children [2]. A recent systematic review found that DAT reduces mortality by 76% [3]. However, despite the long history of use, there are no scientific papers evaluating safety. Horse serum–derived immunotherapy is known to cause adverse effects in humans due to the presence of foreign proteins, which can cause hypersensitivity reactions [4]. Although textbooks suggest that the risk of adverse reaction to DAT is between 5% and 20% (with a 0.6% risk of anaphylaxis), there is little evidence to support this

number in the modern medical literature [5, 6]. In fact, none of major guidelines on diphtheria case management include data on DAT safety or adverse effects [7–11].

The re-emergence of diphtheria over the past several years in areas of poor vaccination coverage has led to renewed need for effective and readily available diphtheria treatment. There are still diphtheria epidemics in areas where vaccination coverage is low [12, 13]. The largest modern diphtheria epidemic was in the former Soviet Union in the 1990s [14], and there are ongoing outbreaks in Yemen, Venezuela, and Haiti [15, 16]. The supply of DAT has become increasingly complex [17, 18]. Most high-resource countries no longer produce the serum, and there is worldwide concern about obtaining stock and quality control [19].

A diphtheria outbreak in Bangladesh occurred in 2017, soon after 700 000 Rohingya migrants crowded into camps in Cox's Bazar [20]. In an attempt to control the outbreak, a mass 3-dose diphtheria vaccination campaign was initiated. Between November 2017 and September 2018 there were 8178 cases of diphtheria reported to the World Health Organization (WHO). Médecins Sans Frontières (MSF), a humanitarian medical nongovernmental organization, has gained considerable experience

with diphtheria case management during recent epidemics. This study describes outcomes of patients with diphtheria treated with DAT at the MSF Rubber Garden (RG) Diphtheria Treatment Center in Cox's Bazar during the outbreak. Specifically, we report the frequency and predictors of adverse effects of DAT among the treated cohort, an important addition to the literature on this therapy. Additionally, we document the feasibility of DAT administration in a low-resource setting.

METHODS

Study Setting
Rubber Garden is a makeshift 200-bed facility constructed from bamboo and plastic sheeting (Supplementary Figure 1). There are 7 wards built with infection-control stations at the entrance for handwashing and face-mask distribution. The DAT ward was staffed 24 hours per day by doctors, medical assistants, and nurses. Each nurse had only 1 or 2 patients receiving DAT infusion at any time.

Study Population
Case Definition
All patients with diphtheria presenting to RG between 27 December 2017 and 11 September 2018 who were treated with DAT are included in this study. Patients with suspected diphtheria were referred to RG from health facilities throughout the camp or self-presented to the center. Diagnosis of diphtheria was by clinical case definition. Patients who met WHO's case definition for a probable case were admitted for treatment. The WHO case definition, adopted by RG, defined a probable case as "a person with an illness characterized by laryngitis or pharyngitis or tonsillitis, AND an adherent membrane of the tonsils, pharynx and/or nose OR gross lymphadenopathy" [8].

Criteria for Diphtheria Antitoxin Treatment
The WHO triage algorithm for Cox's Bazar divided diphtheria cases into high-acuity and low-acuity. At RG, high-acuity cases were defined as patients presenting with the following: (1) an upper respiratory tract infection (URI) and a pseudomembrane or (2) an URI and anterior cervical lymphadenopathy ("bull neck") or (3) any diphtheria case with clinical warning signs. (Clinical warning signs were those defined by the Cox's Bazar WHO guidelines: stridor, tachypnea, chest indrawing, restlessness or lethargy, bull neck, delayed capillary refill, tachycardia, cold extremities, cyanotic). All patients in the high-acuity group—including infants, the elderly, and pregnant women—were eligible for DAT unless the patient was moribund on arrival. These patients were stabilized, treated with antibiotics, and then treated with DAT immediately. Patients with low-acuity diphtheria were those who had an early pseudomembrane and did not have clinical warning signs. These patients were admitted to a separate ward where they were treated with antibiotics and supportive care, then observed with serial exams. While under observation, all low-acuity patients who evolved to meet the high-acuity definition were transferred to the high-acuity ward for DAT administration. Only patients in the high-acuity group were treated with DAT and are the subjects of this report.

Treatment Protocol
Antibiotic Administration
Patients who could swallow were given oral weight-based azithromycin; those who could not swallow received penicillin G intravenously. A 14-day course of antibiotics was standard through February 2018. Starting in March 2018, the course was shortened to 5 days based on changes in WHO recommendations.

Diphtheria Antitoxin Dose Determination
Diphtheria antitoxin dosing is not standardized worldwide. At RG, DAT dose was consistent with dosing recommendations of the Centers for Disease Control and Prevention [7] and WHO guidelines for Cox's Bazar [6, 8]. Patients with pharyngitis with limited pseudomembrane were administered 20 000 IU DAT. Patients with extensive pseudomembranes were administered 40 000 IU DAT. Patients with cervical edema (bull neck) or who appeared critically ill received 60 000 to 80 000 IU. Dosing did not vary by age or weight of the patient.

Diphtheria Antitoxin Administration Protocol
Diphtheria antitoxin that was administered in this outbreak was manufactured in India by Premium Serums and Vaccines Pvt Ltd, purchased and imported by MSF, and stored in refrigeration at RG [21]. (MSF-Belgium also received a small donation of antitoxin from WHO [~2% of the total stock used at RG]. The manufacturer of these vials cannot be verified. However, the rate of adverse effects from the months that the donated stock was used was not significantly different from the several months immediately preceding this period.) Each 10-mL ampule contained 10 000 IU diphtheria antitoxin immunoglobulin fragments preserved in phenol (Supplementary Figure 2). The antitoxin was administered in a specialized ward staffed by MSF providers who were trained in the protocol and in how to recognize and treat adverse effects. Informed consent was obtained from all patients. Nurses used a checklist to ensure all safety steps were taken prior to the infusion. Protocols for DAT sensitivity testing, DAT desensitization, and premedication evolved over the course of the epidemic according to gained experience (see Supplementary Methods). For example, in the first 2 weeks of operation, the Besredka skin-sensitivity testing method was used to determine which patients were at high risk for hypersensitivity. Within 2 weeks, clinicians noted that skin-test results were poorly predictive of which patients got adverse reactions, and skin testing was stopped.

Patients were premedicated with weight-based steroids and antihistamines 30 minutes prior to DAT infusion. Nurses sat at the bedside while monitoring for adverse reactions for the duration of the infusion. The entire dose was administered continuously over to 2 to 4 hours, starting slowly, and then increasing the rate if no adverse effects were observed. Vital signs, including oxygen saturation, were measured and recorded every 5 minutes for the first 15 minutes, then every 15 minutes, then every 30 minutes. Bedside nurses responded to mild adverse reactions (cough, itching) by slowing down the rate of infusion. More serious adverse reactions were reported to the doctor, who could respond by giving medication (eg, adrenaline, steroids, promethazine, salbutamol, ondansetron, oxygen, acetaminophen, intravenous fluids), changing the rate of infusion, or stopping the infusion altogether.

After the DAT infusion was completed, patients were observed closely in the DAT ward for at least an additional 6 hours. If stable, they were transferred to a standard ward. For patients who tolerated the infusion without reaction and showed signs of improvement, the typical length of stay was 48 hours. Severely ill patients stayed longer. Patients who developed severe complications were transferred elsewhere for more advanced care.

Data Collection and Analysis

This study is a retrospective analysis from an Excel (Microsoft Corporation) line list that was abstracted from individual patient files. The line list was updated daily on site as part of the case-management protocol by data encoders and an epidemiologist. The variables collected included the following: demographic information, date of admission and exit, symptoms and signs of illness and duration, vaccination history, exposure history, comorbid conditions, complications, medications administered, DAT dose received, adverse reactions, management/outcomes of adverse reactions, samples taken, exit outcome, and length of stay. Adverse reactions were defined as the presence of 1 or more of the following signs and symptoms appearing during or within 6 hours after the DAT infusion: anaphylaxis, angioedema, other facial edema, cough, oxygen desaturation, wheeze, generalized rash, localized rash, itching, agitation/restlessness, nausea/vomiting, or other (free text). For a comprehensive list of variables, see Supplementary Table 1.

We calculated the presence of adverse events by age group, duration of illness, and DAT dosage. Bivariate comparisons were performed using chi-Square or Fisher's exact test when required. *P* values less than .05 were considered statistically significant. Data were analyzed using Stata version 16.0 (StataCorp).

Sensitivity Analysis

Criteria were defined to diagnose anaphylaxis on retrospective review of the line list, as there were no prespecified criteria in the case-management protocol. The criteria used were based on those recommended by the National Academy of Allergy and Infectious Diseases [22]: 2 or more of the following occurring minutes to several hours after exposure to DAT: (1) involvement of the skin-mucosal tissue (eg, hives, itch/flush, swollen lips or tongue), (2) respiratory compromise (eg, dyspnea, wheeze, stridor, or hypoxemia, or (3) gastrointestinal symptoms. A criterion using blood pressure was not included because pediatric sphygmomanometers were not always available at RG. Cases in which the research team was uncertain whether anaphylaxis was present were included in the anaphylaxis group.

Ethical Considerations

This study obtained an exemption from full review from the MSF Ethical Review Board, as data were routinely collected as part of the case-management protocol. Bangladesh approvals in Cox's Bazar were obtained from the Civil Surgeon and the Office of the Refugee Relief and Repatriation Commissioner.

RESULTS

A total of 5080 patients presented for care from 27 December 2017 to 11 September 2018. Of the 5080 patients, 3097 were diagnosed as cases and were admitted: 2388 were low-acuity and were treated with antibiotics and supportive care and 709 patients (23%) were high-acuity and were treated with antibiotics plus DAT.

Patient Characteristics

Table 1 displays the characteristics of the 709 patients treated with DAT. Two-thirds were female and nearly half were under the age of 15. All patients received antibiotics. Table 1 also includes the DAT dose prescribed and the infusion completion rate. Sixty percent of patients were prescribed 20 000 IU and the remaining patients were prescribed 40 000 IU or more. Of the 709 patients treated with DAT, 601 (85%) completed the infusion without the need to adjust the rate, 74 (10%) completed the infusion with slowing of the rate because of an adverse reaction, and 34 (5%) had their infusion stopped before completion.

Adverse Reactions to Diphtheria Antitoxin Treatment

Table 2 describes the types of adverse reactions experienced by the 170 patients (24%) who had 1 or more adverse effects from DAT infusion. Mild adverse reactions were not unusual, including cough in 115 patients (16%), skin reactions in 66 patients (9%), and itching in 37 patients (5%). Eighteen (3%) patients were retrospectively identified as having reactions consistent with anaphylaxis. For all patients with an adverse reaction, the mean time of onset after beginning the infusion was 57.4 minutes (range, 5–255 minutes). Table 2 also includes the treatments used to manage adverse reactions, including epinephrine for 3 patients, glucocorticoids for 47 patients, and antihistamines for 35 patients. Among

Table 1. Characteristics of Patients Treated With Diphtheria Antitoxin at Rubber Garden Diphtheria Treatment Center, 27 December 2017–11 September 2018

	n	%
Age		
12–59 months	42	6
5–14 years	295	42
15–29 years	286	40
≥30 years	86	12
Gender		
Male	228	32
Female	481	68
Pregnant[a]	1	0
Self-reported vaccine (no. of doses)		
0	189	27
1	82	12
2	81	11
≥3	68	10
No data	289	40
Clinical symptoms[b]		
Fever	694	98
Sore throat	125	18
Difficulty swallowing	123	17
Nasal regurgitation	9	1
Swollen neck	3	0
Cough	18	3
Duration of illness		
0–2 days	470	66
3–4 days	186	26
>4 days	53	8
Clinical signs[b]		
Pseudomembrane	705	100
Tonsillar enlargement	97	14
Lymphadenopathy	80	11
Bull neck	3	0
Stridor	6	6
Indication for DAT[c]		
Stridor or other clinical warning signs	13	2
Pseudomembrane	705	100
Bull neck	3	3
Antibiotics received		
Yes	709	100
No	0	0
DAT dose prescribed		
20 000 IU	427	60
40 000 IU	222	38
60 000–80 000 IU	10	1
DAT infusion completion		
Infusion completed as planned	601	85
Infusion completed with slowing of rate	74	10
Infusion stopped before completion	34	5
Adverse reactions (see Table 3)		
Total	170	24

N = 709. Abbreviation: DAT, diphtheria antitoxin.

[a]Self-reported.

[b]Not mutually exclusive; patients may have more than 1 symptom or sign.

[c]Not mutually exclusive; patients may have more than 1 indication.

Table 2. Adverse Reactions in Diphtheria Antitoxin–Treated Patients at Rubber Garden Diphtheria Treatment Center, 27 December 2017–11 September 2018

	n	%
Adverse reaction[a] (N = 709)		
Documented anaphylaxis in patient file	3	0
Anaphylaxis by retrospective adjudication	18	3
Angioedema	1	0
Other facial edema	5	1
Cough	115	16
Oxygen desaturation	31	4
Wheeze	19	3
Generalized rash	51	7
Localized rash	15	2
Itching	37	5
Agitation/restlessness	8	1
Nausea or vomiting	6	1
Total (any adverse reaction)	170	24
Adverse reaction management[b] (N = 170)		
Adrenaline	3	2
Hydrocortisone	47	28
Promethazine	35	21
Salbutamol Nebulization Solution (neb)	8	5
Oxygen	17	10
IV fluid	2	1
Ondansetron	3	2
Time to resolution (N = 170)		
Within 1 hour	99	58
1–6 hours	56	33
>6 hours	1	1
Data missing	14	8

Abbreviation: IV, intravenous.

[a]Not mutually exclusive; patients may have more than 1 adverse reaction.

[b]Not mutually exclusive; patients may have more than 1 therapy.

(3%) who had a desensitization attempt are presented in the Supplementary Results.

Adverse reactions by antitoxin dose received are presented in Table 3. There was no statistically significant difference in the percentage of patients who had an adverse reaction in the group who received relatively low-dose DAT (≤25 000 IU) compared with the group who received relatively high-dose DAT (26 000–80 000 IU) ($P = .825$). The probability of having an adverse reaction was also not significantly associated with gender

Table 3. Adverse Reactions in Diphtheria Antitoxin–Treated Patients at Rubber Garden Diphtheria Treatment Center by Diphtheria Antitoxin Dose Received

	DAT Dose Received, No. of Patients (%)		
	Lower Dose (≤25 000 IU)	Higher Dose (>25 000 IU)	Total
No adverse reaction	349 (76)	190 (77)	539 (76)
Adverse reaction	111 (24)	58 (23)	169 (24)
Total	460 (100)	248 (100)	708 (100)

N = 708. Chi-square $P = .825$. Abbreviation: DAT, diphtheria antitoxin.

[a]Data for DAT dose received are missing for 1 patient.

the 170 patients with adverse reactions, 99 (58%) had complete resolution within 1 hour and only 1 patient had symptoms that persisted beyond 6 hours. Results for the 18 patients

Table 4. Adverse Reactions in Diphtheria Antitoxin–Treated Patients at Rubber Garden Diphtheria Treatment Center by Patient Age

	Number of Patients (%)				
	12–59 Months	5–14 Years	15–29 Years	≥30 Years	Total
No adverse reaction	24 (57)	196 (66)	242 (85)	77 (90)	539 (76)
Adverse reaction	18 (43)	99 (34)	44 (15	9 (10	170 (24)
Total	42 (100)	295 (100)	286 (100)	86 (100	709 (100)

N = 709. Chi-square *P* < .001.

or duration of illness. The proportion of adverse events was significantly smaller with the increase in age (*P* < .001), as described in Table 4.

Exit Outcomes

Of the 709 patients treated with DAT, 696 (98%) recovered and were discharged from the hospital. The average length of stay was 2.5 days (range, 0–10 days). Of the remaining 13 patients, 5 died (all of whom presented in critical condition), 1 left the hospital against advice, and 7 were transferred to another facility for additional inpatient care. All 5 deaths were children (mean age, 5 years; range, 2–6 years) who were critically ill on admission. One patient died prior to starting the DAT infusion, and 4 died during the infusion or soon after. The senior physicians on site thought the cause of death was likely to be advanced diphtheria rather than an adverse reaction in each of these cases.

DISCUSSION

This study describes case management of the largest contemporary cohort of patients treated with DAT in an outbreak setting. Although the outbreak in the Soviet Union was approximately 20 times larger, the published literature does not describe case management in detail, nor does it include data on DAT-treated patients from a large cohort at a single treatment site [23, 24]. As described above, approximately one-quarter of the patients in the RG cohort had symptoms during or after DAT administration. The symptoms were clinically consistent with hypersensitivity reactions, which are not unexpected from horse serum therapy. However, some of isolated symptoms during infusion (such as cough) are nonspecific and may in fact have been due to the underlying disease itself rather than from the treatment. Most symptoms were easily managed by slowing down the infusion and treating with symptom-directed therapy, although 3% of patients had severe adverse reactions that were consistent with anaphylactic reactions. Even though most of these patients were not diagnosed as having anaphylaxis at the time, and were not treated as such, all but 1 of the patients recovered quickly. For comparison, in the 1993–1996 outbreak in the Republic of Georgia, 2% of DAT-treated patients (n = 8) had anaphylactic shock [24].

One of the important unanswered questions about DAT is whether the dose received is associated with adverse reactions. Our data show that there is no statistical difference in frequency of adverse reactions in the group who received lower-dose DAT versus the group who received higher-dose DAT (Table 3). This is consistent with the hypothesis that most reactions are hypersensitivity related, which are expected to occur soon after the infusion is started and are not dependent on total dose. Our findings show an association between younger age and adverse effects, but we are cautious to interpret this as it is opposite to the expected trend in medication-related anaphylactic reactions (which are generally more common in older patients) [25].

Mortality in the RG cohort was less than 1%. A recent systematic review reported that case fatality rates (CFRs) for outbreaks in resource-limited settings range from 3% to 33% [3].

This study has several limitations. First, diagnosis of diphtheria was by clinical case definition rather than by laboratory testing. Whenever there was any doubt about whether a patient truly had diphtheria—as opposed to another respiratory illness with pharyngitis—the patient was treated for diphtheria. Based on this practice, we suspect that our cohort included some patients who may have had another disease. Because confirmatory laboratory testing was not done on all specimens, we cannot assess whether diphtheria was overdiagnosed, and to what degree. Other outbreaks in low-resource settings have been subject to the same limitation [26, 27]. Second, the majority of patients were discharged 48 hours after receiving DAT. This limits complete evaluation for delayed reactions, such as serum sickness, which generally occurs approximately 1 week after infusion. All patients were encouraged to return if they had new symptoms, however, and follow-up was done (publication forthcoming). Third, criteria for diagnosing anaphylaxis were not explicitly defined in advance. This led to an underdiagnosis of this syndrome at the time of care. In an effort to conservatively assess the prevalence of anaphylaxis, we identified 18 cases retrospectively. However, unless a clinician is at the bedside actively monitoring a patient, it is difficult to be certain of this diagnosis.

Conclusions and Recommendations

Diphtheria is a re-emerging disease in settings with poor vaccination coverage, which is often associated with political conflict and poverty. Our results confirm that a low CFR is possible in an outbreak setting where DAT is readably available and is combined with optimal case management. One-quarter of the patients who received DAT had adverse reactions, most of which were mild; yet, 3% had severe adverse reactions that were consistent with hypersensitivity reactions typical for horse serum therapies. Diphtheria antitoxin can be safely administered in settings where modern critical care facilities are not available, provided that trained staff are present to rapidly detect and treat adverse reactions.

Given the conclusions described above, we have recommendations for future outbreaks. First, DAT administration in an outbreak setting requires basic critical care: a high-enough clinician-to-patient ratio to allow for continuous observation during DAT infusion, staff training for management of adverse reactions, and readily available emergency drugs and equipment. Second, rapid point-of-care diagnostics are necessary for optimal case management in order to avoid over- and underdiagnosis of diphtheria and unnecessary use of DAT in patients who may have an alternate diagnosis. Third, consensus needs to be reached on eligibility criteria for antitoxin should rationing become necessary in future outbreaks. There was adequate DAT supply in Bangladesh, but this may not always be the case given the global supply limitations. Finally, further research and advocacy are needed for the development of alternate therapies for diphtheria, such as monoclonal antibodies, which have had promising results in preliminary studies [28].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Note

References

1. Kleinman LC. To end an epidemic. N Engl J Med **1992**; 326:773–7.
2. Park W. The clinical use of diphtheria antitoxin. N Engl J Med **1895**; 133:255–60.
3. Truelove SA, Keegan LT, Moss WJ, et al. Clinical and epidemiological aspects of diphtheria: a systematic review and pooled analysis. Clin Infect Dis **2019**. Available at: http://www.ncbi.nlm.nih.gov/pubmed/31425581. Accessed 10 September 2019.
4. Chippaux JP, Goyffon M. Venoms, antivenoms and immunotherapy. Toxicon **1998**; 36:823–46.
5. Mandell G, Douglas G, Bennett J. Mangell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia, PA: Elsevier, **2015**.
6. Kimberlin DW, Brady MT, Jackson MA, Long SS; American Academy of Pediatrics Committee on Infectious Diseases. Red book: 2018–2021 report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics, **2018**.
7. Centers for Disease Control and Prevention. Expanded access investigational new drug (IND) application protocol: use of diphtheria antitoxin (DAT) for suspected diphtheria cases IND sponsor: centers for disease control and prevention (CDC) protocol CDC IRB # 4167 BB IND 11184. **2016**. Available at: https://www.cdc.gov/diphtheria/downloads/protocol.pdf. Accessed 20 January 2019.
8. World Health Organization. Operational protocol for clinical management of Diphtheria Bangladesh, Cox's Bazar. **2017**. Available at: https://www.who.int/health-cluster/resources/publications/WHO-operational-protocols-diphtheria.pdf?ua=1. Accessed 12 January 2019.
9. World Health Organization. Surveillance guide for vaccine-preventable diseases in the WHO South-East Asia Region. **2017**. Available at: https://apps.who.int/iris/bitstream/handle/10665/277459/Module4-Diphtheria.pdf?sequence=16&isAllowed=y. Accessed 1 September 2020.
10. Public Health England. Guidance on the use of diphtheria antitoxin (DAT): October 2020. London: 2020. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/923670/18026_IMW025.04_immunoglobulin_handbood_diphtheria_update_2020_BUTANAN_product_FINALa.pdf. Accessed 1 September 2020.
11. NCID. Diphtheria: NICD recommendations for diagnosis, management, and public health response. **2018**. Available at: http://www.nicd.ac.za/assets/files/Guidelines_diphtheria_20160322_v2_3.pdf. Accessed 12 January 2019.
12. Martinez M, Shukla H, Wadood MZ, et al. Diphtheria vaccine: WHO position paper- August 2017. Weekly Epidemiol Rec **2017**; 92:417–35. Available at: https://apps.who.int/iris/bitstream/handle/10665/258681/WER9231.pdf;jsessionid=78F897586FAA1DB3D3729268DBB6FD58?sequence=1.
13. Galazka A, Dittmann S. The changing epidemiology of diphtheria in the vaccine era. J Infect Dis **2000**; 181:S2–9.
14. Dittmann S, Wharton M, Vitek C, et al. Supplement 1. Control of epidemic diphtheria in the newly independent states of the former Soviet Union. **2000**. Available at: https://www.jstor.org/stable/30109967. Accessed 21 October 2018.
15. Pan American Health Organization/ World Health Organization. Epidemiological update: diphtheria. 15 August 2019, Washington D.C.: PAHO/WHO, **2019**. Available at: https://www.paho.org/en/documents/epidemiological-update-diphtheria-15-august-2019.
16. Dureab F, Al-Sakkaf M, Ismail O, et al. Diphtheria outbreak in Yemen: the impact of conflict on a fragile health system. Confl Health **2019**; 13:1–7.
17. Blumberg LH, Prieto MA, Diaz JV, et al. The preventable tragedy of diphtheria in the 21st century. Int J Infect Dis **2018**; 71:122–3.
18. Both L, White J, Mandal S, Efstratiou A. Access to diphtheria antitoxin for therapy and diagnostics. Eurosurveillance **2014**; 19:1–6.
19. Wagner KS, Stickings P, White JM, et al. A review of the international issues surrounding the availability and demand for diphtheria antitoxin for therapeutic use. Vaccine **2009**; 28:14–20.
20. Chan EYY, Chiu CP, Chan GKW. Medical and health risks associated with communicable diseases of Rohingya refugees in Bangladesh 2017. Int J Infect Dis **2018**; 68:39–43.
21. Premium Serums and Vaccines Pvt Ltd. Diphtheria antitoxin product. Available at: https://www.premiumserums.com/product13.html.
22. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second Symposium on the Definition and Management of Anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. Ann Emerg Med **2006**; 47:373–80.
23. Kadirova R, Kartoglu HU, Strebel PM. Clinical characteristics and management of 676 hospitalized diphtheria cases, Kyrgyz. J Infect Dis **2000**; 181(Suppl 1):S110–15.
24. Quick ML, Sutter RW, Kobaidze K, et al. Epidemic diphtheria in the Republic of Georgia, 1993–1996: risk factors for fatal outcome among hospitalized patients. J Infect Dis **2000**; 181(Suppl 1):1993–6.
25. Simons FER. Anaphylaxis. J Allergy Clin Immunol **2010**; 125:S161–81.
26. Garib Z, Carolina Danovaro-Holliday M, Tavarez Y, Leal I. Diphtheria in the Dominican Republic: reduction of cases following a large outbreak. Rev Panam Salud Publica, **2015**; 38:292–29.
27. Sein C, Tiwari T, Macneil A, et al. Diphtheria outbreak in Lao People's Democratic Republic, 2012–2013. Vaccine **2016**; 34:4321–6.
28. Sevigny LM, Booth BJ, Rowley KJ, et al. Identification of a human monoclonal antibody to replace equine diphtheria antitoxin for treatment of diphtheria intoxication. Infect Immun **2013**; 81:3992–4000.