A Large-Scale Outbreak of Diphtheria among Forcibly Displaced Myanmar Nationals in Bangladesh, 2017-2019

*Zaki QA,[1] Islam MS,[2] Rahman S,[3] Begum MS,[4] Yunus M,[5] Rashid HU,[6] Akhter F[7]

Abstract

Introduction: Ethnic violence in Myanmar in August 2017 resulted in the movement of over 700,000 Rohingya refugees to overcrowded camps in Cox's Bazar, Bangladesh. A large outbreak of diphtheria subsequently began among this immunologically naïve population, which continues to this day.

Methods: We collected data from nine Diphtheria Treatment Centres operated by national and international organizations, vaccination campaigns and contract tracing to describe the epidemiological and clinical features of the outbreak and measures to prevent and control transmission during the first two years of the outbreak.

Results: Between 10 November 2017 and 10 November 2019, 7064 cases were reported: 285 (4.0%) laboratory-confirmed, 3610 (51.1%) probable, and 3169 (44.9%) suspected cases. The crude attack ratio was 51.5 cases per 10,000 person-years. The median age was 10 years (range 0-85), 3126 (44.3%) were male. The typical symptoms were sore throat (93.5%), fever (86.0%), pseudomembrane (34.7%), and gross cervical lymphadenopathy (30.6%). Diphtheria antitoxin (DAT) was administered to 1064 (15.1%) patients, adverse reactions following among 231 (21.5%). There were 45 deaths with low diphtheria case fatality ratio of 0.6%. Vaccination coverage rates were ranged between 88.5% and 110.4% over three rounds. The number of traced close contacts was 6848 total chemoprophylaxis uptake and adherence was 87.7% (N=6007) and 49.5% (N=3393), respectively. Administrative coverage varied between 88.5% and 110.4% over the three rounds of the mass vaccination campaign.

Conclusion: This is the largest reported diphtheria outbreak in refugee settings. An adequate global DAT stockpile needs to be maintained. Crisis-affected populations must have access to health services and routine vaccination, mitigating such health crises.

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1. **Dr. Quazi Ahmed Zaki, Assistant Professor, Shaheed Syed Nazrul Islam Medical College, Kishoreganj. qazaki@gmail.com*
2. *Dr. Md. Saiful Islam, Assistant Professor, Directorate General of Health Services (DGHS), MOHFW.*
3. *Dr. Sabura Rahman, Specialist (Clinical Pathology), United Hospital Ltd, Gulshan, Dhaka.*
4. *Dr. Mosammat Shahina Akhter Begum, Assistant Professor, Institute of Health Technology, Mohakhali, Dhaka*
5. *Dr. Mohammad Yunus, Assistant Professor, Department of Medicine, Cox's Bazar Medical College, Cox's Bazar.*
6. *Dr. Harun Ur Rashid, Assistant Professor, Directorate General of Health Services (DGHS), MOHFW.*
7. *Dr. Fahmida Akhter, Assistant Professor, National Institute of Preventive and Social Medicine (NIPSOM).*

** For correspondence*

Introduction

On 25 August 2017, violence erupted in Rakhine state, Myanmar and resulted in the displacement of an estimated 706,000 refugees – mostly stateless Rohingya – from Rakhine state into the neighbouring district of Cox's Bazar, Bangladesh. Together with previously displaced refugees, the total number of forcibly displaced Myanmar nationals (FDMNs) in Bangladesh exceeds 919,000.[1]On 10 November 2017,*Médecins Sans Frontières* (MSF) reported a case of suspected diphtheria in a 30-year-old Rohingya woman from Ukhiya. Additional suspected cases were reported, and after laboratory confirmation on 4 December 2017, the Bangladesh Ministry of Health and Family Welfare (MoH&FW) officially declared an outbreak. We describe the epidemiological and clinical features of a diphtheria outbreak among FDMNs and local host population in Cox's Bazar district, Bangladesh during the first two years of the ongoing outbreak, from 10 November 2017 to 10 November 2019. Despite a decrease in worldwide incidence, diphtheria outbreaks still occur, particularly among populations with poor vaccination coverage. FDMN population was highly deprived of primary health care and most of the population was not vaccinated for any kind of vaccine preventable diseases (VPDs) in past decade in Rakhain region of Myanmar. Minor outbreaks in Latin and South America, India and South Asia, Thailand, Laos, and Nigeria have been reported in recent decades.[2,3]In 2017, outbreaks occurred in Yemen, Venezuela, and Indonesia, with an ongoing outbreak in Haiti.[4,5] However, the Cox's Bazar outbreak represents the largest outbreak since the 1990s.

Methods

Population and data source and case definitions

All suspected cases were referred to nine Diphtheria Treatment Centres (DTCs), operated by the Bangladesh Red Crescent, International Organization for Migration, MSF, or Samaritan's Purse. DTCs collected daily data for demographic and clinical characteristics of cases and were reported electronically to the World Health Organization's Early Warning, Alert and Response System (EWARS) for consolidation and cleaning.[6] We extracted case and contact tracing data on cases with symptom onset from 10 November 2017 to 10 November 2019. We used the final iteration of the clinical case definition, introduced in July 2018, as per standard WHO and MoH&FW diphtheria surveillance case definitions of suspected, probable, or confirmed cases. Admission, treatment, and reporting of suspect cases remained at the discretion of clinicians.

Clinical management

Patients were triaged at arrival to the DTC by disease severity with a suspected or probable diagnosis of respiratory diphtheria to severe and non-severe patients (supplementary file). DAT was administered immediately to patients with probable, clinical diagnosis of respiratory diphtheria. Owing to the limited global supply of DAT, prioritization of DAT usage was based on *a priori* decisions by an ethical, transparent decision-making process involving key stakeholders.

Diagnostics

Confirmatory laboratory testing for toxigenic *C. diphtheriae* was performed by real time PCR with multiplex PCR assay for toxin, *rpo*B and cup *rpo*B. Initially, this was done at the Institute of Epidemiology Disease Control and Research national reference laboratory in Dhaka. A field laboratory in Cox's Bazar medical college hospital performed these analyses from April 2018 onwards.

Contact tracing, prophylaxis, and reactive and mass vaccination

Contact tracing was established in mid-December 2017. Close contacts of probable (and subsequent confirmed) cases were identified during the case investigation process and targeted for treatment and follow-up over the seven-day course of prophylactic antibiotic treatment. Contact tracers visited all contacts three times on days 0, 3-4 and 7. Additionally, diphtheria vaccine was offered for all contacts of confirmed and probable cases. Individuals were targeted for three doses of vaccination over three rounds of a mass reactive diphtheria vaccination campaign during 12-31 December 2017, 27 January – 10 February 2018, and 10-25 March 2018 including FDMNs and host community aged under 15 years and residing in Ukhia and Teknaf Upazilas. Vaccination coverage for all rounds was estimated using vaccine consumption monitoring data collected during the campaigns with population estimates provided by MoH&FW and UNHCR.

Statistical analysis

Continuous variables were described as median values with interquartile ranges (IQR). Frequencies for categorical variables were described and compared using Chi-square or Fisher's exact (cell values <5) tests, Odds Ratios (OR) or Incidence Risk Ratios (IRR). The overall attack rate was calculated by dividing the number of diphtheria infected FDMNs by the settlement population. We calculated time from illness onset to notification at a DTC. We fitted a simple linear regression against dates of illness onset for trend assessment.We bisected the outbreak into two phases separated by the median case for response activity evaluations. For age analyses, we divided cases to over and under 15 years at the time of disease onset. We calculated confidence intervals (CIs) of proportions assuming binomially distributed symptom occurrence. Case fatality ratios were calculated using observed deaths.

Results

Descriptive epidemiology

A total of 7064 cases with diphtheria were reported among FDMN. There were 285 (4.0%) laboratory-confirmed, 3610 (51.1%) probable, and 3169 (44.9%) clinically suspected cases (Table I; Figure 1) with an additional 1624 excluded, suspected diphtheria-negative cases.

The crude diphtheria attack rate over the first two years of the outbreak was 51.5 cases per 10,000 person-years; including only confirmed and probable cases, the attack rate was 28.4 cases per 10,000 person-years. Of all cases, 3126 (44.3%) were male, median age was 10 years (IQR 7-15; range 0-85) (Table I). Those aged 15 years and older represented 2020 (28.6%) of cases.

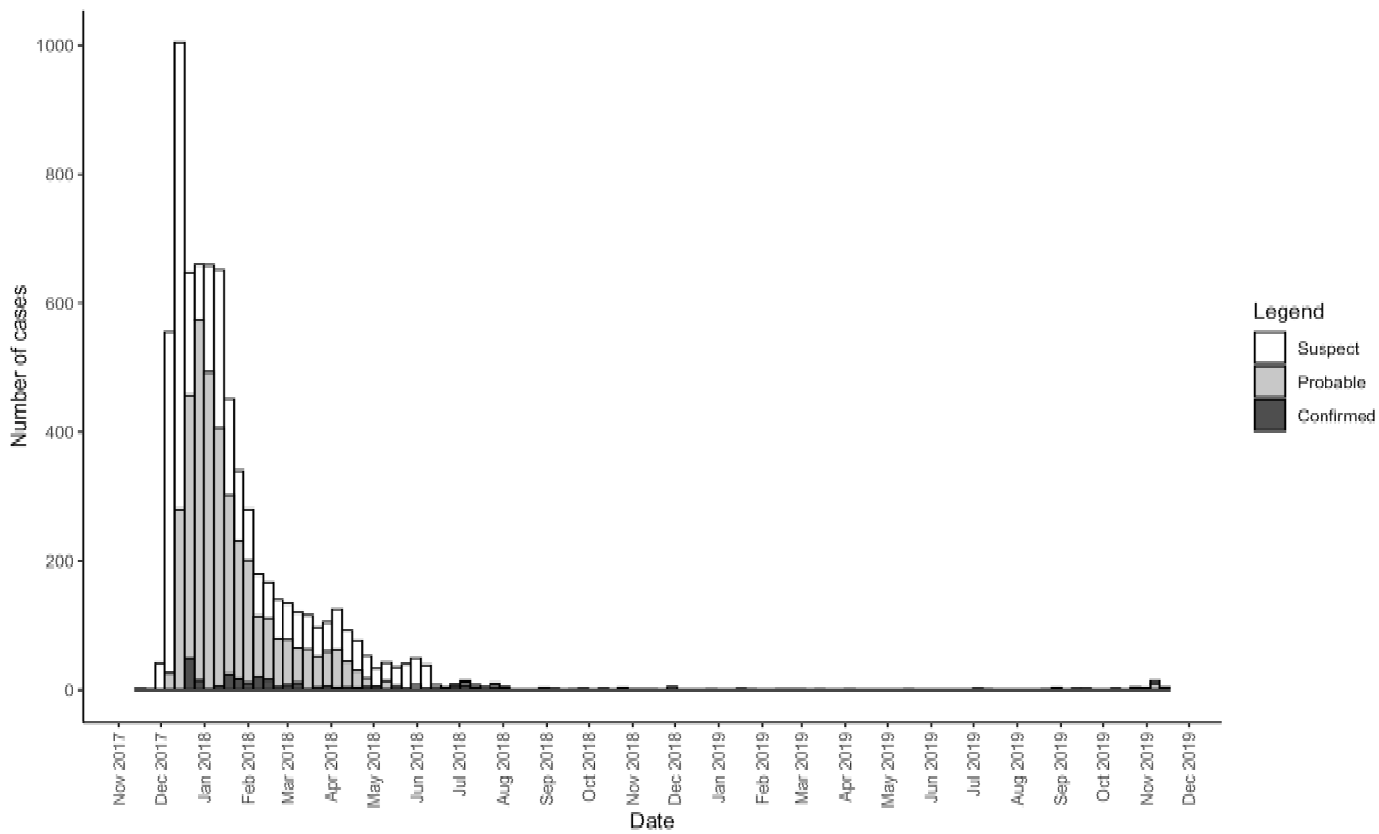

Figure 1. Epidemic curve of diphtheria cases (confirmed, probable and suspected) among forcibly displaced Myanmar nationals, Cox's Bazar, Bangladesh, 10 Nov 2017 - 10 Nov 2019

Table I. Characteristics of diphtheria cases by case definition among forcibly displaced Myanmar nationals, Cox's Bazar, Bangladesh, 10 Nov 2017 - 10 Nov 2019

		Case definition			
Characteristic		Confirmed	Probable	Suspect	Total
Age	<7	59	873	797	1729
	7-14	136	1743	1430	3309
	15-29	83	784	693	1560
	30-44	4	158	170	332
	45+	3	48	77	128
	Missing	0	4	2	6
Sex	Male	118	1632	1376	3126
	Female	167	1978	1793	3938
Total		285	3610	3169	7064

The age and sex distribution of the cases evolved during the course of the outbreak: after 4 Jan 2018 (the median date of onset in the population and approximately two weeks post-first vaccination campaign; cases were more likely to be 15 years or older (Odds ratio (OR) = 1.6, 95% CI: 1.43 – 1.79) and female (OR = 1.13, 95% CI: 1.02 – 1.25). Most patients (5850, 82.8%) recovered, while a substantial proportion (1075, 15.2%) were lost to follow-up (Table 2). There were 45 reported deaths among cases (CFR 0.6%).

Table II: Number (%) of signs and symptoms, complications, and treatment outcomes among diphtheria cases, by case definition, among forcibly displaced Myanmar nationals, Cox's Bazar, Bangladesh, 10 Nov 2017 - 10 Nov 2019

Characteristic		Confirmed	Probable	Suspected	All cases
Sign/symptom	Sore throat	282 (98.9)	3551 (98.4)	2771 (87.4)	6604 (93.5)
	Fever	259 (90.9)	3246 (89.9)	2573 (81.2)	6078 (86.0)
	Pseudomembranes	195 (68.4)	2258 (62.5)	0	2453 (34.7)
	Difficulty in swallowing	183 (64.2)	1269 (35.2)	1026 (32.4)	2478 (35.1)
	Lymphadenopathy	125 (43.9)	2040 (56.5)	0	2165 (30.6)
	Tonsillitis	45 (15.8)	284 (7.9)	154 (4.9)	483 (6.8)
	Nasal regurgitation	15 (5.3)	159 (4.4)	208 (6.6)	382 (5.4)
	Nasal blood	13 (4.6)	34 (0.9)	41 (1.3)	88 (1.2)
	Lethargy	2 (0.7)	39 (1.1)	45 (1.4)	86 (1.2)
Complications	Neuropathy	4 (1.4)	21 (0.6)	3 (0.1)	28 (0.4)
	Respiratory distress	3 (1.1)	19 (0.5)	4 (0.1)	26 (0.4)
	Cutaneous necrosis	1 (0.4)	2 (0.1)	1 (<0.1)	4 (0.1)
	Irregular heart rhythm	0 (0.0)	3 (0.1)	2 (0.1)	5 (0.1)
	Shock	0 (0.0)	5 (0.1)	1 (0.1)	6 (0.1)
	Kidney damage	0 (0.0)	2 (0.1)	0 (0.0)	2 (<0.1)
Treatment outcomes	Recovered	241 (84.6)	3143 (87.1)	2466 (77.8)	5850 (82.8)
	Death	2 (0.7)	19 (0.5)	24 (0.8)	45 (0.6)
	Transferred	2 (0.7)	53 (1.5)	29 (0.9)	84 (1.2)
	Lost to follow up	40 (14.0)	389 (10.8)	646 (20.4)	1075 (15.2)
	Other	0 (0.0)	6 (0.2)	4 (0.1)	10 (0.1)

We estimated epidemic doubling time as 3.6 days (95% CI 3.0 – 4.5) during the first 30 days of the epidemic with 561 cases, confirmed by sensitivity analysis with confirmed and probable cases as 3.9 days (95% CI 3.3–4.6). The MVC launch coincided with a decrease in transmissibility for the first two rounds, with no effect observed following the third MVC, Figure 2.

Diagnostic

Multiplex PCR assay was performed on 1329 cases, 271 (20.4%) tested positive for toxigenic *C. diphtheriae*. Laboratory confirmed cases were more likely to be aged <15 years (OR = 2.81, 95% CI 1.92 – 4.13), have pseudo-membrane (OR = 4.78, 95% CI 3.33 – 6.97) and not received diphtheria vaccine (OR = 0.64, 95% CI 0.44 – 0.94) than test negative cases (Table 3).

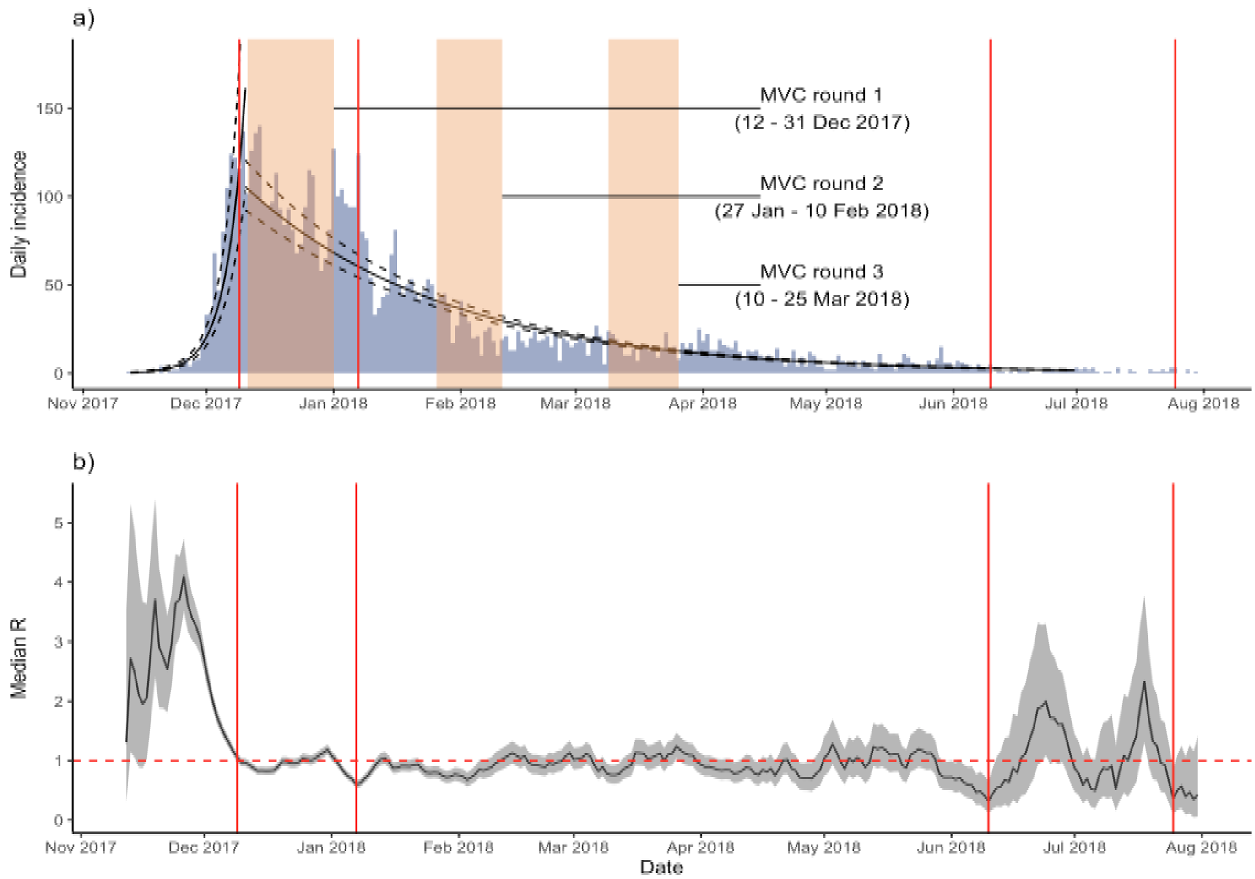

Figure 2.

a) Log-linear models fitted to daily incidence over time, with optimal split date (10 December 2017) automatically determined, Cox's Bazar, Bangladesh, 10 Nov 2017 - 31 Jul 2018. The timing of three rounds of mass vaccination campaign are shown in shaded bars, while the results of changepoint analysis for automatic detection of dates of change in daily incidence are shown as solid red lines.

b) Estimates of time-varying reproduction number (Rt) for diphtheria cases, Cox's Bazar, Bangladesh, 10 Nov 2017 - 31 Jul 2018. The results of changepoint analysis for automatic detection of dates of change in daily incidence are shown as solid red lines.

Contact tracing, prophylaxis and reactive and mass vaccination

Since 1 January 2018, 6848 close household contacts were identified, 1,180 (17.2%) of whom were <5 yr, with a median of 3 contacts per case (IQR 0 - 7; range 0 - 30). A majority of contacts (87.7%; N=6007) consented to begin chemoprophylaxis; adherence was 49.5% (N=3393) and 50.0% (N=3424) at 3-day and 7-day follow-up respectively. The proportion of household contacts vaccinated was 64.7% overall. The administrative coverage of the mass vaccination campaign was 88.5%, 110.4%, and 104.0% for the first, second, and third rounds, respectively.

Table III. Multivariable linear regression for predictors for diphtheria patients testing positive for toxigenic C. diphtheriae strain by PCR, Cox's Bazar, Bangladesh, 10 Nov 2017 - 10 Nov 2019

			Unadjusted		Adjusted	
Independent variable	Level	N	RR (95% CI)	p-value	RR (95% CI)	p-value
Age group	0-6	1942	*Reference*	-	*Reference*	-
	7-14	3968	0.88 (0.66 - 1.19)	0.393	0.96 (0.62 - 1.53)	0.849
	15+	2971	0.44 (0.32 - 0.60)	<0.001	0.48 (0.30 - 0.79)	0.003
Sex	Female	5124	*Reference*	-	*Reference*	-
	Male	3764	1.34 (1.07 - 1.67)	0.011	1.20 (0.87 - 1.64)	0.261
Vaccination status	Unvaccinated	2097	*Reference*	-	*Reference*	-
	Vaccinated	2211	0.82 (0.61 - 1.10)	0.177	0.81 (0.57 - 1.15)	0.229
Period	Pre-campaign	3091	*Reference*	-	*Reference*	-
	Campaign era*	5205	0.41 (0.32 - 0.55)	<0.001	0.55 (0.31 - 1.05)	0.059
Pseudomembrane	False	5856	*Reference*	-	*Reference*	-
	True	2981	3.93 (3.11 - 4.99)	<0.001	3.48 (2.49 - 4.95)	<0.001
Gross cervical lymphadenopathy	False	5820	*Reference*	-	*Reference*	-
	True	3017	0.91 (0.73 - 1.14)	0.443	1.28 (0.94 - 1.74)	0.111

*Patients were divided into two periods, according to the date of symptom onset relative to the completion of the first round of mass vaccination campaign.

Discussion

This diphtheria outbreak with more than 7000 cases is the largest reported diphtheria outbreak occurring among refugees. This outbreak was and still is a direct consequence of sub-optimal vaccine coverage among the FDMNs, reflecting a long history of under-provision of health services in Rakhine state, including routine vaccinations. Concurrent large diphtheria outbreaks in Yemen, Indonesia, and Venezuela led to shortages in vaccine and DAT availability 17 potentially further hampering the outbreak response. Approximately half of the cases were probable, with only a small fraction of cases test-positive. Overall, two thirds of the cases were children <15 years of age, however, there was a shift of cases towards older and predominantly female after the MVCs. The age distribution, with older cases than expected for a disease that typically affects young children, likely reflects low diphtheria vaccination coverage in this population. Similar findings have been reported for diphtheria elsewhereas well as measlesand mumpsamong refugee and other populations lacking adequate routine vaccine coverage.[7-10] The female predominance likely reflects the practice of nursing of small infants by female household members; a similar effect was observed in a large outbreak in the former Soviet Union. The majority of FDMN cases (90%) were unvaccinated, consistent with other recent diphtheria outbreaks reported from South Africa, 75 %, Lao People's Democratic Republic, 88 % (Lao PDR), Nigeria, 98% and Norway, 100%.[11-13] The clinical presentation of the cases in the current outbreak was typical of diphtheria. Complications were rare.We observed a low CFR for this outbreak. One explanation could be effective treatment provided by the national and international healthcare professionals surged to respond to this outbreak.[14,15] The deaths occurred more commonly among children, there was also a longer lag-time between onset to admission among fatal cases. These highlight the importance of adequate medical attention in the initial phase of diphtheria. The low observed CFR was likely due to low specificity of the case definitions applied, a substantial proportion of suspect cases may not have been cases of diphtheria. The findings that both transmissibility and the delay from disease onset to presentation at health facilities decreased during the early phase of this outbreak suggest that implemented interventions were effective. We found that vaccinated cases had a longer delay from disease onset to presentation at health facilities, possibly as a result of reduced severity among vaccinated individuals, or of different health-seeking behavior among older individuals. The limited global supply of both vaccineand DATwere important considerations during this outbreak, particularly as there were multiple concurrent outbreaks.[16,17]

Conclusions

This outbreak reminds us that diphtheria may still cause large, rapidly expanding outbreaks among susceptible populations in the vaccine era. An adequate global DAT stockpile needs to be maintained by an independent body, as for yellow fever, meningitis and cholera vaccines.Moreover EPI surveillance in Bangladesh need to be strengthened to early detect any suspected diphtheria case in FDMN as well as host population to effectively contain any potential outbreak.

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