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Original Article

Putting Out the Fire before it becomes an Inferno: Responding to an Outbreak of Diphtheria in Edo State, Nigeria

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Abstract

Background: The recent outbreak of diphtheria in Nigeria, lasting over 18 months, is largely attributed to a lack of vaccination, but other factors may have been contributory. The study aims to describe the characteristics of cases and control measures of a localised outbreak of diphtheria in Edo State, Nigeria.

Methodology: This was a descriptive study of patients who met the case definition for suspected diphtheria in Edo state between May and September 2024. A multidisciplinary management strategy was instituted for sample collection, integrated disease surveillance, contact investigation, awareness creation and standard treatment protocols. Data (age, gender, immunization status, signs and symptoms, receipt of Diphtheria Antitoxin (DAT), laboratory results and outcomes) were extracted from the case notes, entered into an Excel spreadsheet and exported into an SPSS spreadsheet for analysis. Continuous data were expressed as median (IQR), categorical data were summarized as proportions, and the level of immunity was categorized into adequate and inadequate. Ethical approval for the study was obtained from the University of Benin Health Research Ethics Committee with Protocol Number: ADM/22/A/VOL.VII/4831141825 and dated May 28th 2025

Results: Of the19 suspected cases, 5(26.3%) were laboratory confirmed, and 4/5(80.0%) of the confirmed cases were older than 9 years. The commonest symptoms were catarrh12(63.2%), sore throat and neck swelling 11(57.9%) each, and fever and hoarseness 10(52.6%). The majority, 89.6% were vaccinated. Of the ten cases that had serology done, 7(70%) had inadequate immunity. No secondary cases were found on contact investigation.

Conclusion: A multidisciplinary team approach ensured this outbreak did not spread widely. With diphtheria occurring in almost 90% of previously vaccinated children, waned immunity was likely a major contributor to this outbreak. It is recommended that booster doses be included in the immunization schedule of Nigerian children.

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Introduction

Diphtheria is a life-threatening, vaccine-preventable disease caused by toxigenic strains of *Corynebacterium diphtheriae*.[1]In the pre-immunization era, diphtheria was one of the major contributors to under-five mortality.[2] With the advent of formal immunization programmesthe disease has become a rarity in many climes.[1]There have, however, been concerns about its reported reemergence in high-income countries with high vaccination coverage and the implications for countries with weak immunization structures.[3]

Diphtheria is spread from person to person through respiratory droplets released during speech, sneezing, crying and through contact with secretions from indolent ulcers caused by the organism. The principal sites affected are the pharyngotonsillar area, the larynx, nose and skin. *C. diphtheriae* releases an exotoxin which results in destruction of the epithelium and a superficial inflammation with the organism, necrotic cells and epithelium forming a thick coagulum of pseudomembrane. The pseudomembrane spreading over the tonsils, pharynx and larynx leads to airway obstruction. The exotoxin may also be disseminated haematogenously to other organs such as the heart, kidneys and neural tissue, leading to complications such as myocarditis, renal failure and polyneuropathy.

The major control strategy is vaccination. The World Health Organisation (WHO) recommends 3 doses of diphtheria toxoid-containing vaccine given at least 4 weeks apart in infancy, followed by booster doses given at 18 months, 4-7 years of age and at 9-15 years.[4]

Diphtheria is endemic in Nigeria. Althoughthere had been a decline in reported cases,[5] sporadic outbreaks and epidemics have been reported in the past.[6,7] Nigeria is currently just closing out a major outbreak, of which the first cases were seen in August 2022.[8] As of January 2025, 41,336 suspected cases of diphtheria had been reported,with 24,846 (60.1%) confirmed and 1,262 deaths among the confirmed cases, giving a case fatality rate of 5.1%.[8]Confirmed cases were reported from 26 states in the country. The majority (99.4%) of the confirmed cases were from 8 northern states(see figure 1), with the epicenter of the outbreak beingKano state, which reported 17,770cases.[8]

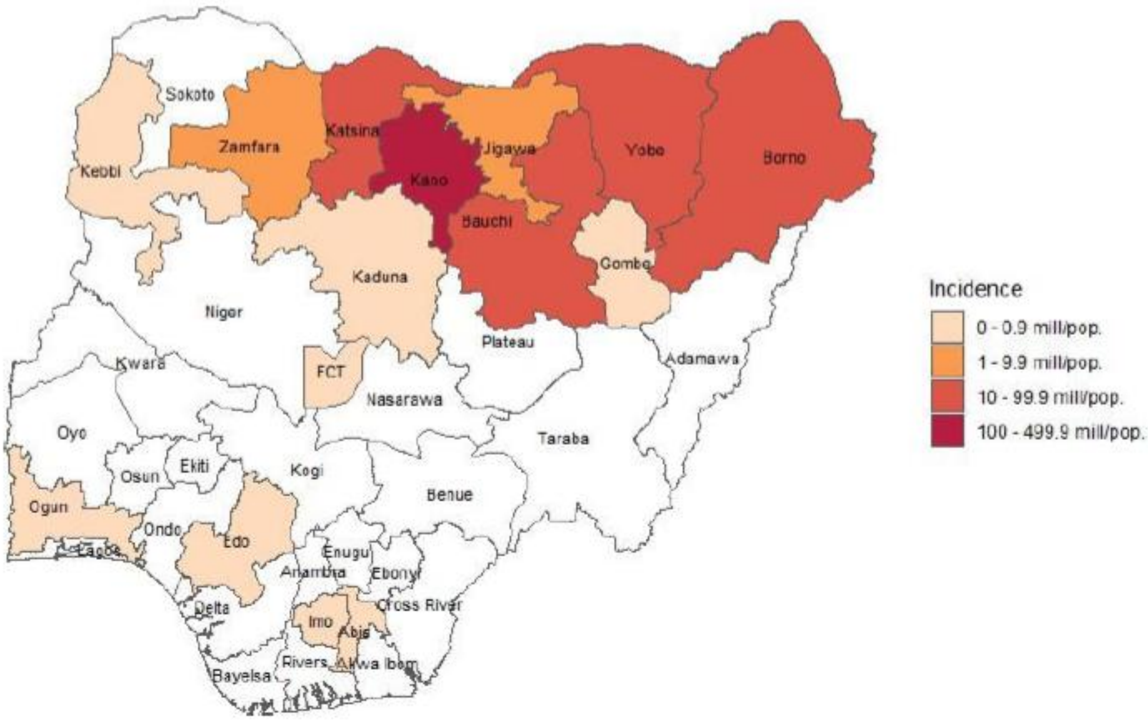

Figure 1 showsthe incidence (per million population) of confirmed diphtheria cases by state, epi week 19, 2022 to epi week 35, 2024. Source Nigeria Centre for Disease Control and Prevention[8]

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This prolonged diphtheria outbreak required several strategies to control,including mass vaccination of children, as it was identified thatthe majority of the affected children were not vaccinated. Abdulrasheed et al[9] have opined that the recurrent outbreaks of diphtheria are due to low vaccination coverage, delayed diagnosis and management, barriers to the supply of diphtheria antitoxin, environmental factors and lack of political will.

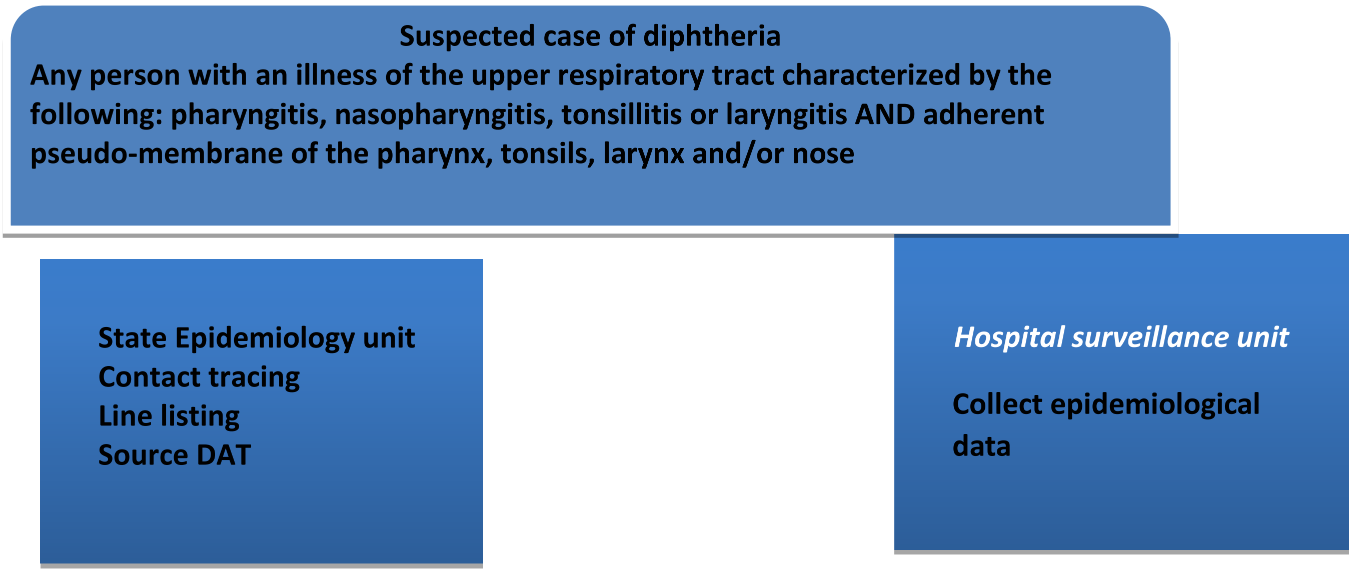
While this recent epidemic seemed to have mainly affected the northern states, the potential for similar outbreaks occurring in other parts of the country remains a public health concern. Although low vaccination coverage was a major factor in this epidemic,there are likely to be others, as other states with relatively better immunization coverage have developed outbreaks.[8]This means that the mechanisms and epidemiological realities of outbreaks may be locale-dependent.Moreover, limited epidemiological data and descriptions of outbreak dynamics have been reported from southern Nigeria.This report aimed to describe the characteristics of the cases,highlighting key features and the response in combating the outbreak. The Edo state experience may provide useful insights into the understanding of diphtheria outbreaks and their control in low- and middle-income countries.

Methodology

Study design: This was a descriptive, chart review study.

Setting:

Edo State is one of the 6 states in the South-South geopolitical zone of Nigeria. It is made up of 18 local government areas, each of which has at least 10 wards. It is home to two major teaching hospitals, and each local government area has at least a secondary care facility. Primary health care centres are located in every ward, and there are many private hospitals, clinics and maternities in the state. The first two suspected cases of diphtheria were managed inperipheral hospitals. Subsequently,19suspected cases were seen in the University of Benin teaching hospital (one of the two major teaching hospitals in the state)between May and September 2024,and these were the subjects of this report. The first case in the teaching hospital was managed in the Ear, Nose, and Throat (ENT) department following presentation for severe membranous tonsillitis with suspected diphtheria. Two weeks later, the sibling of the index case presented with classic features of diphtheria that required a tracheostomy. At this point, a system of management was put in place, as shown in the flow chart in Figure 2.



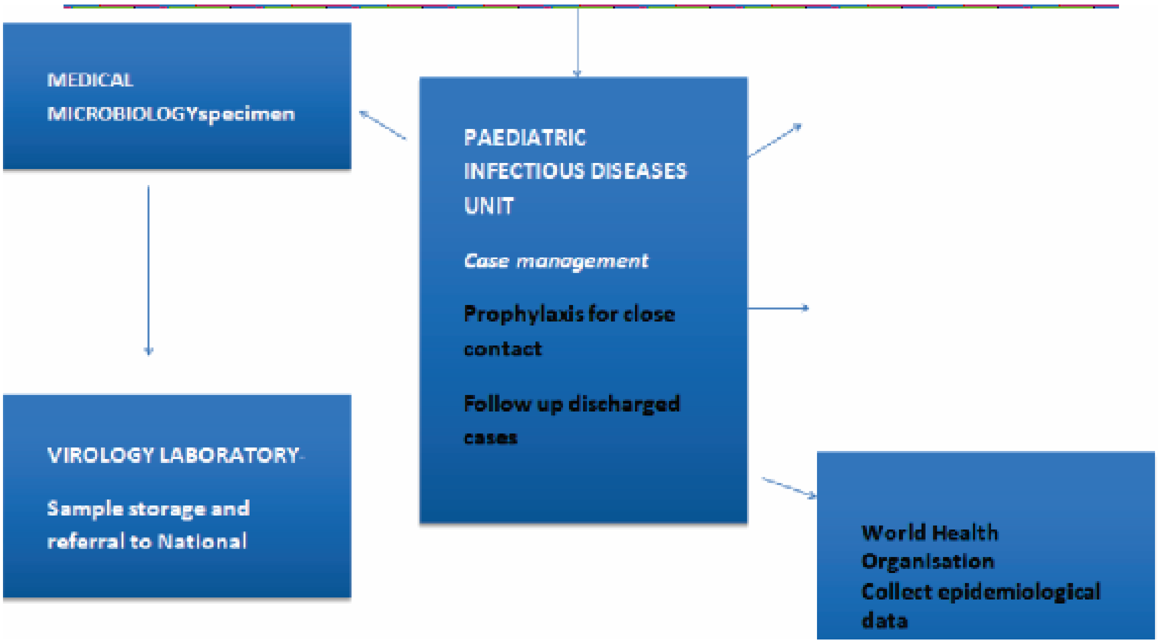


Figure 2-Flow chart of Diphtheria control activities in Edo state

Case definition

The established case definition for suspected diphtheria was "Any person with an illness of the upper respiratory tract characterized by the following: pharyngitis, nasopharyngitis, tonsillitis or laryngitis AND adherent pseudo-membrane of the pharynx, tonsils, larynx and/or nose". A confirmed case was "A person with *Corynebacterium* spp. isolated by culture and positive for toxin production, regardless of symptoms."[10]

Multidisciplinary team responsibilities

Following the identification of any suspected case, the Paediatric Infectious Diseases(PIDs) unit was notified. The PIDs unit would activate the cascade, which included

- inviting medical microbiologists for appropriate sample collection. At least two samples were taken from each patient, one of which was processed locally, while the other, transported in Amies medium, was sent to the National Reference Laboratory via the virology laboratory, as specific media for bacteriological culture and toxigenicity testing were not available on-site.
- Notification of the surveillance unit in the hospital,the State Epidemiology Unit and the WHO team.Public healthphysicians and infection control specialists of the hospital surveillanceunitprovided integrated Disease Surveillance in the facility.The State Epidemiology Unit was tasked with contact tracing and sensitising healthcare workers about diphtheria. Line-listed contacts were followed up for 2 weeks.
- The ENT unit was notified and was on hand for patients needingsurgical airway management.

The PIDs unit institutedcase management according to the WHO protocol, which included intravenous antibiotics (amoxicillin/clavulanic acid or erythromycin, Diphtheria antitoxin (DAT) and hydrogen peroxide gargle)[11]. The dose of DAT was based on the WHO protocol.[11] In addition, 5mls of blood was obtained aseptically from an accessible peripheral vein and stored in a plain sample bottle free of anticoagulant. This was sent to the Chemical Pathology laboratory within 30minutes of collection. The sample was spun and separated, and the serum was stored at -20^{o}C until analysis. Samples were analysed using commercially available ELISA test kits according to the manufacturer instructions.The PIDs unit also prescribed oral erythromycin for close family contacts.

Data collection and analysis

Information on the age, gender, clinical features, immunization status,and laboratory results of the suspected cases were obtained from their case notes, de-identified and entered into a Microsoft Office Professional Plus 2010 Excel spreadsheet and then exported into an IBM Statistics SPSS version 21 spreadsheet. The data was cleaned, double-checked for correctness and stored in a password-protectedcomputer with access only to the first author. Age, number of persons in households and number of symptoms per case were summarized as medians with interquartile range. Cases with various attributes (gender, symptoms, complications, outcomes) were summarized as simple proportions. Missingdata were reported as such, and for variables in which data were missing, analysis was based on available data.

The level of protection from diphtheria (immunity) was categorized according to level of serum IgG antidiphtheria antibody titres as follows: titre<0.01IU/ml, no protection; 0.01-0.09IU/ml, minimal protection; 0.1-0.9IU/ml, full protection; and >1IU/ml, long-term protection.[12] All subjects with no protection and minimal protection were further categorized as inadequate protection, while those with full protection and long-term protection were classified as adequate protection.

Ethics Statement

Research activities were carried out in compliance with international and national guidelines.

Ethical clearance and waiver of consent was obtained from the University of Benin Teaching Hospital Research and Ethics committee withProtocol Number: ADM/22/A/VOL.VII/4831141825 and dated May 28th 2025.

Results

Nineteen children met the case definition for suspected diphtheria, of which 5(26.3%) were confirmed through bacteriological culture. There were 11/19(57.9%) females with a male-to-female ratio of 0.7:1. The affected children were aged 3 to 14 years, with the majority being older than 9 years(Table 1). Also, 4/5(80%) of the confirmed cases were aged 10 years and older(Table 2). All but two of the children lived in urban areas,and all were from contiguous local government areas, with the majority of the cases being from the 3 local governments (Egor, Oredo, Ikpoba-Okha) that constitute Benin City, the state capital. The median(IQR)number of persons living in thehousehold of cases was 6(5,6) with a range of 4 to 8 persons. History of contact was elicited in two families (in one family, 2 siblings were affected, both of whom presented to the hospital while in the other family, 3 children were affected, of which one died before the others presented in our hospital).Vaccination status was available for all but one child, who was adopted. All except one child were said to have been vaccinated in infancy.

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Table1 Sociodemographic characteristics of children with suspected diphtheria

Characteristics	n	%
Sex		
Male	8	42.1
Female	11	57.9
Age		
<5	4	21.0
5-9	6	31.6
>9	9	47.4
Local Government of residence		
Egor	4	21.0
Ikpoba-Okha	5	26.3
Oredo	7	36.8
Ovia North East	1	5.3
Ovia South West	1	5.3
Undocumented	1	5.3
Number of Persons living in household		
4	2	10.5
5	6	31.6
6	6	31.6
7	3	15.8
8	1	5.3
Undocumented	1	5.3

Table 2: Demographic profile, vaccination status and outcome of confirmed cases of diphtheria

Case	Gender	Age in years	Vaccination	Complications	Outcome
I	Female	10	Yes	Yes	Discharged
2	Female	11	Yes	Yes	Discharged
3	Male	6	Yes	No	Discharged

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4	Female	14	Yes	Yes	Discharged
5	Male	12	Yes	Yes	Discharged

The children presented with multiple symptoms (the median number of symptoms was 5 with a range of 2-8 symptoms per child) and all of them presented with features of respiratory tract infection. The commonest symptoms were catarrh (63.2%), sore throat and neck swelling (57.9% each), hoarseness and fever (52.6% each). (Table 3). The duration of symptoms ranged between 1 and 8 days with 5(26.3%) presenting within 3 days of onset of symptoms and 6(31.6%) presenting at ≥ 6 days. All the children presented with membranes, the commonest sites being the tonsils and pharynx. Only one child had a nasal membrane..

Table 3 Clinical and laboratory features of cases of suspected diphtheria

Symptoms	n	%	Duration of Symptoms
Catarrh	12	63.2	1-8
Sore throat	11	57.9	1-8
Neck swelling	11	57.9	<1-6
Hoarseness	10	52.6	1-5
Fever	10	52.6	<1-6
Cough	9	47.4	3-8
Odynophagia	8	42.1	1-2
Dysphagia	4	21.1	1-5
Drooling	3	15.8	2
Difficult breathing	5	26.3	1-3
Location of membrane			
Tonsils	15	78.9	
Pharynx	12	63.2	
Nose	1	5.3	
Vaccination Status			
Complete	17	89.6	
Incomplete/Nil	1	5.3	
Unknown	1	5.3	

Culture result			
Positive	5	26.3	
Negative	12	63.2	
No result	2	10.5	

Anti-diphtheria IgG antibody wasassessed for 10 children; 7(70%) had inadequate protective levels of <0.01 IU/ml while the others had adequate protection at levels >0.1 IU/ml. Of the 17 children for whom culture results were available 5(29.4%) had positive cultures of toxigenic *Corynebacterium diphtheria.*Seven of the 14 children with negative cultures were adjudged to be probable cases of diphtheria (one was epidemiologically linked to a confirmed case while 6 hadclinical courses and complications that were compatible with diphtheria).

Three children received 40,000 IU of DAT while 7 received 80,000IU. One child was not given DAT due to a low index of suspicion of diphtheria; another died before DAT could be given while the others did not get DAT because it was not available

Complications of diphtheria occurred in 10 (52.6%) children as shown in Figure 3.Figure 4 shows the outcome of the illness. The three children with neurologic deficits at discharge eventually recovered fully on follow up.

There were 231 contacts line listed and followed up. No secondary cases were found.

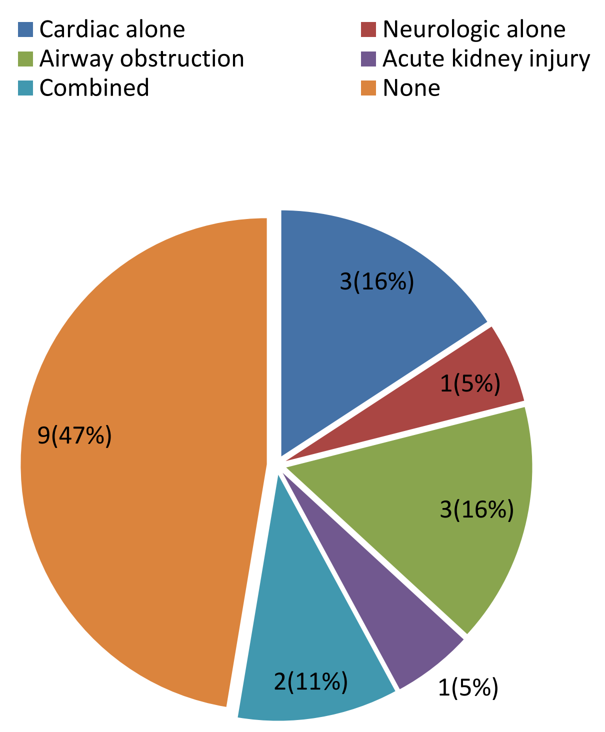

Figure 3: Distribution of complications among children with suspected diphtheria

Cardiac complications were myocarditis, congestive cardiac failure and arrhythmias while neurologic complications included polyneuropathy (cranial nerve palsies, ataxia). Combined was cardiac and neurologic

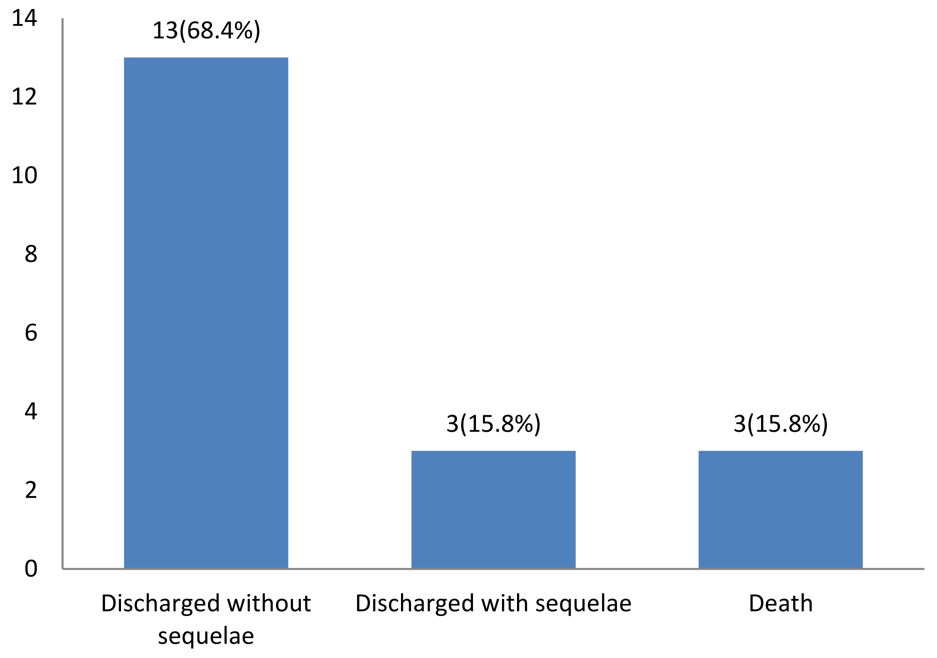

Figure 4: Outcome of diphtheria cases

Discussion

The recent diphtheria outbreak in Nigeria which is the largest and most protracted in recorded history occurred mostly in the northern part of the country. Our report is the first to provide an account from southern Nigeriathat reveals key epidemiological differences that could influence diphtheria control strategies.

The children with confirmed diphtheria in this outbreak report were mostly in the early adolescent age group. This is different from national and regional data as reported by the Nigeria Centre for Disease Control (NCDC)[8] and Alegeet al.[13]in north western Nigeria in whichmajority of the cases were in the age group 5-9 years. Older age amongst casesasin this report from Edo state may reflect previously documented observations; following the introduction of the primary series of diphtheria vaccination in an endemic area there is an initial shift in the population most affected from preschool to school-age children followed by a transition to adolescents and young adults.[4]

Also, in contrast to previous reports[8,13,14] where over 60% of the cases were unimmunized, majority of the children in the Edo state outbreak had received the primary diphtheria vaccination series in infancy. Recent immunization coverage data shows that Edo state has higher immunization coverage than most of the affected northern states.[15] Thus, the outbreak in Edo state could have been due to waned immunity which may be more pronounced in the adolescents than in the school-aged children. This hypothesis was corroborated by the serological evaluation which showed that a good number of suspected caseshad inadequate immunity despite having been vaccinated.This finding requires urgent policy action as it not only has implication for long term control strategies and surveillance but also for

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vaccine promotion in general. The occurrence of vaccine preventable diseases in vaccinated children may exacerbate the already significant vaccine hesitancy amongst care givers who may erroneously conclude that vaccinating children is not useful since they may still acquire the target diseases. Nigeria currently does not offer booster doses as recommended by WHO.[4]To prevent recurrent outbreaks of diphtheria, vaccination coverage needs to improve and the resultant immunity must be maintained by administering boosters. Longitudinal serological surveys among under-fives, school aged children, adolescents and even adults are needed to provide the evidence establishing the need and timing of these boosters.

The clinical features presented by the cases are in tandem with documented literature.[13,14]However, the proportion of children with complicationsis higher compared to that reported by Alege et al.[13] it is not immediately clear as to why this is so.Despite the higher complication rate,the mortality in this series is lower than reported by Alege et al.[13]This may be due to , the residual immunity from infant vaccination being enough to mitigate the disease severity. It may also reflect differences in quality of care offered considering the multidisciplinary consultations offered in our centre. The mortality was however much higher than reported by the NCDC[8] and Denue et al.[14]One of the mortalities died before DAT could be administered as he presented late with airway obstruction while the other developed acute renal injury and died before DAT could be administered; the third death was from complications of the tracheostomy. These deaths highlight the severity of the disease and support the need for prevention.

The duration of symptoms of the cases presented ranged between 1 and 8 days with the majority presenting after 3 days of onset of symptoms.This suggestsless than optimal care-seeking behavior since diphtheria is an acute, life-threatening event. Late presentation was associated with poorer outcomes in Denue et al's[14] report. Delayed healthcare-seeking behaviour, often driven by low community awareness, remains a critical barrier to early case detection and intervention. Thus, strengthening public health education initiatives as was done in the Edo state outbreak is an important strategy for control.

While clinical acumen is required in early diagnosis and treatment of diphtheria, bacteriological confirmation of diagnosis using culture and antibiotic susceptibility profiling are important for outbreak characterization. At 26.3%, the laboratory confirmation rate in our series was slightly higher than the rate of 22.4% reported in a study in northwestern Nigeria.[13] Negative microbiological results especially in cases clinically adjudged to be diphtheria may be attributable to receipt of antibiotics in some of the cases prior to reporting to the hospital. While antibiotic treatment is essential to reduce the chances of spread of the organism as well as limit continued elaboration of toxin, it is important to note that DAT is the mainstay of management.

The efforts of the state epidemiology unit and WHO in the sourcing of DAT remain commendable but irregular supply of DAT constituted a major challenge to combatting the outbreak. It is well recognized that if cases present late such that the toxin is already bound, outcomes may not be as good as when cases present early.[14]The use of DAT was a significant determinant of a good outcome in the study by Alege et al.[13] The need for a sustainable source of DAT has been previously highlighted..[4,13,14]The availability of DAT contributed in changing the narrative for the national outbreak as case fatality in the early phase of the outbreak was high due to non-availability of DAT.

In all but two families there was no history of contact and contact tracing did not yield secondary cases. The absence of secondary cases may have been due to the prophylaxis instituted for close contacts and the observation of contact precaution as taught to family members. It is also possible that there may be reasonable population immunity which may have helped to break transmission. It has been shown that diphtheria vaccine requires about 85% coverage to generate herd immunity which is lower than for some highly contagious diseases such as measles.[16]The coverage for the third dose of diphtheria toxoid-containing vaccine in Edo state is 84.5%.[15]

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Sensitisation of health care workers may have also contributed to the outbreak being contained as early recognition and referral by peripheral and private hospitals meant that children were seen in the tertiary facility that had the capacity to manage the complications associated with diphtheria.

Another key contributor to the control of diphtheria in the statewas the adoption of a multidisciplinary approach. In the hospital setting the cases had access to emergency room physicians, paediatric infectious disease experts, paediatric cardiologists, ENT surgeons and experienced laboratory staff. The public health aspect of control was expertly managed by the State epidemiology unit as well as the Public Health Physicians and infection control specialists, who had the mandate to provide integrated Disease Surveillance and Response (IDSR) activities in the facility.Seamless communication facilitated information sharing including investigation results. Other strengths of the outbreak response were the incorporation of serological studies to investigate the level of protection amongst suspected cases and the meticulous follow-up of cases leading to observation of late complications which have otherwise been sparsely documented in the Nigerian literature. The study is however limited by the small size, the retrospective design incomplete serological data and lack of molecular characterization of isolates. This may affect the generalizability and applicability of the findings.

In conclusion, the Edo state diphtheria outbreak underscores the need to introduce boosters to prevent waning immunity while sustaining high vaccination coverage.A multidisciplinary response with strengthened laboratory capacity and stockpiling of DAT are vital for effective outbreak containment.

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