Original Article

Diphtheria Outbreak During Covid-19 Pandemic in Katsina, North-Western Nigeria: Epidemiological Characteristics and Predictors of Death

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Abstract

Context: The impact of coronavirus disease 2019 (COVID-19) pandemic on vaccine-preventable diseases, including diphtheria, may hamper the previous gains made in the eradication of the disease. **Aims:** We report the epidemiological profile, clinical features, laboratory findings, and hospitalization outcomes amongst cases of diphtheria managed at Federal Medical Centre, Katsina, Nigeria during the first wave of COVID-19 pandemic. **Settings and Design:** This was a retrospective review of cases of diphtheria managed between July and December 2020. **Methods and Material:** We extracted the clinical (socio-demographics, clinical features, and hospitalization outcomes) and laboratory findings (full blood counts, electrolytes, urea and creatinine) from the record of the children. **Statistical Analysis Used:** Using SPSS, we carried out a descriptive analysis and applied binary logistic regression to determine factors associated with death. Level of statistical significance was set at $P < 0.05$. **Results:** A total of 35 cases of diphtheria were admitted and managed from 1 July to 31 December 2020. The mean age of the children was 7.6 ± 3.1 years. Males were 15 (42.9%). There were 24 deaths (case fatality of 68.6%). Clinical findings were comparable between survivors and non-survivors except the bull neck, which was more common among non-survivors ($P = 0.022$). The median duration of hospitalization was shorter in those that died ($P = 0.001$). The age, sex, immunization status, leukocytosis, and biochemical features of renal impairments were not predictive of deaths. Prescence of bull neck was predictive of death (adjusted odds ratio 2.115, 95% CI 1.270, 3.521). **Conclusions:** The study shows a high number of cases of diphtheria over a short period of six months with high mortality. Amongst the clinical and laboratory variables, only presence of bull neck was predictive of death.

Keywords: Children, diphtheria, outcomes, predictors of deaths

Introduction

Diphtheria is a highly infectious bacterial disease that is associated with significant morbidity and mortality.[1] It is a vaccine-preventable disease caused by the toxigenic strains of Corynebacterial species; mainly *Corynebacterium diphtheriae* and rarely *Corynebacterium ulcerans* and *Corynebacterium pseudotuberculosis* strains.[2] The *Corynebacterium diphtheriae*, a nonmotile, nonencapsulated, club-shaped, gram-positive bacteria typically causes a noninvasive infection of the upper airways (nasal cavities, oropharynx and rarely the larynx).[2] The pathogen multiplies on the mucosa, elaborates exotoxins that cause coagulative necrosis of the epithelium, ulceration, accompanied with fibrin and exudate which gives the characteristic gray-whitish, leathery appearance called pseudomembrane.[3] The exotoxin, a 62 kDa protein released is absorbed into the systemic circulation and causes damage (cell necrosis) to organs including the heart (myocarditis), kidneys (renal injuries), and nerves (neuropathy).[3] Cardiac involvement is the leading cause of death in children with diphtheria.[4]

Access this article online

Quick Response Code:

Website: www.njbcs.net

DOI: 10.4103/njbcs.njbcs_35_21

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Submitted: 27-Jul-2021 **Revised:** 11-Nov-2021
Accepted: 15-Nov-2021 **Published:** 12-Jul-2022

How to cite this article: Ibrahim OR, Lawal IM, Mohammed B, Abdullahi SB, Bello SO, Issa A, *et al*. Diphtheria outbreak during Covid-19 pandemic in Katsina, North-Western Nigeria: Epidemiological characteristics and predictors of death. Niger J Basic Clin Sci 2022;19:59-65.

Globally, cases of diphtheria have declined with the introduction of a vaccine in the 1950s with a successful elimination in many high-income countries. The number of diphtheria cases reduced from more than 1,000,000 cases per year (pre-vaccination era) to an average of 6,582 between 2013 and 2017[5,6] While the global burden appears to have reduced substantially, there have been outbreaks in Russia in the early 90s, and a series of outbreaks documented in India, Vietnam, Nepal, Indonesia and parts of Africa including Nigeria.[6]

In Nigeria, like most African countries, cases of diphtheria are under-reported with few reports of outbreaks.[7–10] The few reports highlight the country's susceptibility to vaccine-preventable diseases due to low immunization coverage.[11] The highest number of cases was documented in the northeastern region in 2011.[7] Besa *et al.*[7] reported 98 cases of diphtheria with a case fatality of 21% in Kimba Village, Borno State, northeastern Nigeria in 2011. The other studies reported few isolated cases without a detailed analysis.[8–10]

COVID-19, declared a pandemic in March 2020 by the World Health Organization, remains unabated despite global efforts to contain it. As of 5 November 2021, the WHO dashboard indicated 248,467,363 confirmed cases with more than 5,027,183 deaths.[12] Nigeria also shares part of the global burden of the disease, with 212,641 confirmed cases and 2905 deaths as of 6 November 2021.[13] Besides the burden of the disease, COVID-19 negatively impacted health care deliveries, especially during the first wave of the pandemic. COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), reduced access to health care due to measures such as lockdown to curtail the disease, health care workers' attitude, shortage to non-availability of personal protective equipment (PPE), disruption of health care delivery and routine immunization services, especially in children.[14,15] The United Nations International Children's Emergency Fund (UNICEF), the Global Alliance for Vaccines and Immunization (GAVI), and WHO data showed substantial disruption of global vaccination affecting 68 countries with 80 million infants at risk of diseases such as diphtheria due to COVID-19 pandemic.[16] The impact of COVID-19 on childhood immunization programs may therefore reverse the gains in the global eradication of vaccine-preventable diseases including diphtheria.[17] Hence, we hypothesized that the COVID-19 pandemic may affect the burden and outcome of diphtheria cases at our facility. We report here the epidemiological profile, clinical features, laboratory findings, and hospitalization outcomes amongst cases of diphtheria managed at a tertiary health facility in North-western Nigeria between July to December 2020 during the first wave of COVID-19 pandemic.

Subjects and Methods

Study design and location

This study was a retrospective review of cases of diphtheria managed between July and December 2020 at Federal Medical Centre, Katsina, Nigeria. Katsina is one of the states in the northwestern geopolitical zone in Nigeria. The state has an estimated population of eight million people as of 2020. The hospital is the only tertiary health facility in the state, and serves as a referral center for the state and parts of the adjoining states. The health facility is a 500-bed hospital with a 20 bed-Isolation ward for managing highly infectious diseases such as diphtheria.

Study population

The study comprised of children and adolescents with diphtheria managed during the study period (from 1 July 2020 to 31 December 2020).

Case definitions

The case definition of diphtheria was based on the clinical descriptions of features of upper respiratory tract infections inclusive of pharyngitis, nasopharyngitis, tonsillitis or laryngitis and presence of pseudomembrane with or without bull neck.[2] For those that presented late with neuropathy or cardiac complications with clearance of pseudomembrane, the case definition of diphtheria was based on the preceding history of upper respiratory tract infection and a bull neck [Figure 1].[7,18]

All patients were managed based on the institution's protocols which comprised of administration of antibiotics (penicillin, and metronidazole) and intravenous fluids in those that did not tolerate oral intake. Despite efforts to secure anti-toxin, none of the children received it as the country does not stock it at the national level. In addition, children with symptoms of sepsis had a third-generation cephalosporin added to their medications. Those with cardiac toxicity with hypotension received vasopressor support (dopamine infusion). Most of the patients also had laboratory investigations done, which included throat swabs (samples taken from the edges of the pseudomembrane) and cultured using a blood agar plate.

Sample size

The sample comprises of all the cases of diphtheria that presented at the facility during the study period.

Inclusion criteria

This study included children and adolescents with a diagnosis of diphtheria.

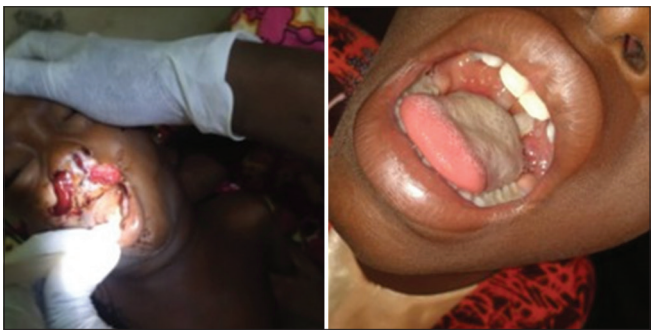

Figure 1: Picture of some of the cases of diphtheria showing bull neck and pseudomembrane

Exclusion criteria

We excluded children with other forms of diagnosis that was not diphtheria managed during the study period.

Outcome measures

The primary outcome of this study was the epidemiological description (age, sex, clinical and laboratory features) of cases of diphtheria, while the secondary outcomes were hospitalizations outcomes (defined as discharge or death), and factors (clinical and laboratory variables) that were predictive of death.

Data extraction

Two co-authors extracted the data (age, sex, symptoms, immunization status, examination findings), laboratory findings (laboratory investigations included full blood counts, electrolytes, urea, creatinine, and blood culture in those associated with sepsis), duration of hospitalization and outcomes (discharged or death) for each child from the electronic health records into an excel spread sheet. The extracted data were verified by another co-author for accuracy of information.

Data analysis

The data was entered into the SPSS version 25 software. The age was summarized as means with standard deviations and compared (survivors vs non-survivors) with an independent *t* test. The discrete variables (sex, clinical features and immunization status) were summarized as frequency and percent tables. We compared the variables between the survivors and non-survivors. Variables with a *P* value that was less than 0.2 (hoarseness of voice, bull neck, serum potassium, serum chloride, serum urea) on the cross-tabulation and those variables (age, sex, vaccination status, symptoms duration, length of hospitalization, serum creatinine and total white blood cell count) from the literature that were previously reported to be associated with outcomes in diphtheria were entered into a binary logistic regression to generate predictors of a poor outcome (death). The level of statistical significance was set at a $P < 0.05$.

Ethical consideration

The Ethical Review Committee approved the study (FMCNHREC.REG.N003/083012), and being a retrospective study, waived informed consent. Data was also anonymous during extraction and analysis. We also observed absolute confidentiality while handling the data.

Results

Age and sex distribution of the study children

Of the 1137 admissions into the Emergency Paediatric Unit (EPU) during the study period, 35 cases (3.1%) were diphtheria [Figure 2]. The mean age of the 35 cases was 7.6 ± 3.1 years with a range of 1.7–14 years. There were 15 males (42.9%), with a male to female ratio of 1:1.3. Most of the admitted children were in the age group of 5–10 years (21; 60.0%) as shown in Table 1.

Outcomes of cases of diphtheria

There were 24 deaths out of the 35 children that were admitted, with a case fatality of 68.6%. The highest mortality occurred amongst children less than five years (5 out of 7) and those above 10 years of age (5 out of 7; 71.4.0%). Also, mortality was high amongst females (75.0%; 15 out of 20) [Table 2].

Clinical and laboratory findings in children with diphtheria

The commonest symptom was fever (30; 85.7%). The other symptoms included painful swallowing (21; 67.7), hoarseness of voice (11; 31.4%), and bull neck (23; 65.7%) as shown in Table 3. Table 3 also shows that less than half (40.0%; 14 out of 35) were fully vaccinated. The median [interquartile range (IQR)]

Table 1: Age distribution of children in the study

Age group (Years)	Total	Male	Female
<5	7 (20.0)	2 (13.3)	5 (25.0)
5-10	21 (60.0)	12 (80.0)	9 (45.0)
> 10	7 (20.0)	1 (6.7)	6 (30.0)
Total	35 (100.0)	15 (100.0)	20 (100.0)

Table 2: Outcomes of cases of diphtheria based on the age group and sex

Variables	Frequency (*n*=35)	Death (*n*=24)	Case fatality rate (%)
Age group (years)			
<5	7	5	71.4
5-10	21	14	66.7
>10	7	5	71.4
Sex			
Male	15	9	60.0
Female	20	15	75.0

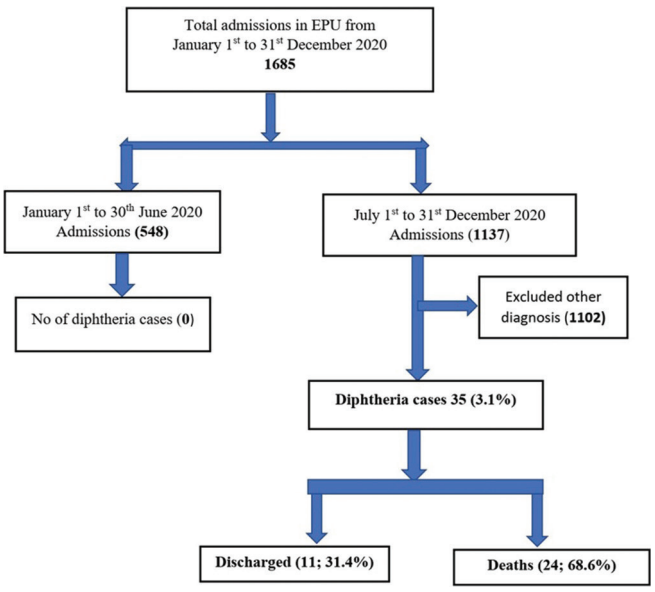

Figure 2: Flow chart of the patients in the study

duration of symptoms before presentation was 4 (2–5) days. The median (IQR) length of hospital stay was 3 (1–9) days.

Most of the clinical findings were comparable between survivors and non-survivors except bull neck which was more amongst those that died (P = 0.022). The median duration of stay was shorter in those that died compared with the survivors (P = 0.001) as shown in Table 3.

The median (IQR) white blood cell count and platelet count were 17.4 (13.2–23.6) X 10^9/L and 129.0 (650–216.0) X 10^9/L respectively. The mean packed cell, serum sodium, serum potassium, and serum chloride were 33.7 ± 6.5%, 132 ± 7.4 mmol/L, 4.4 ± 1.1 mmol/L, and 97.4 ± 8.3 mmol/L respectively. The median (IQR) serum urea and creatinine were 7.2 (4.9–17.1) mmol/L and 82.0 (64.0–168.0) µmmol/L respectively [Table 4]. Mean serum potassium level was lower among survivors compared to non-survivors (3.8 ± 0.8 vs 4.7 ± 1.1 mmol/L, P = 0.034). Also, serum chloride was higher among survivors compared to non-survivors (102.1 ± 9.2 vs 96.0 ± 7.1 mmol/L, P = 0.034). There were no significant differences in the mean serum sodium, mean hematocrit, mean platelet counts, mean white cell counts, mean serum urea and mean serum creatinine between the survivors and non-survivors [Table 3].

Predictors of deaths among children with diphtheria

The age, sex, status of immunization, leukocytosis, and biochemical features of renal impairments were not predictive of deaths. However, presence of bull neck was predictive of death (adjusted odds ratio 2.115, 95% CI 1.270, 3.521) as shown in Table 4.

The spectrum of diphtheria cases

The most common form of presentation was respiratory diphtheria (20; 57.1%), while the least common was diphtheria with sepsis (2; 6.0%) as shown in Figure 3.

Table 3: Clinical and laboratory findings on children with diphtheria

Variables	Total (%)	Survivors	Non-survivors	*P*
Age (Years)*	7.60±3.1	7.9±2.8	7.6±3.3	0.653[t]
Sex				
Males	15 (42.9)	6 (40.0)	9 (60.0)	0.467[f]
Females	20 (57.1)	5 (25.0)	15 (75.0)	
Fever	30 (85.7)	9 (30.0)	21 (70.0)	0.640[f]
Throat pains	24 (68.6)	7 (29.2)	17 (70.8)	0.709[f]
Painful swallowing	21 (67.7)	6 (28.6)	15 (71.4)	0.685[f]
Poor feeding	3 (8.6)	3 (100.0)	0 (0.0)	0.025[f]
Noise breathing	2 (5.7)	0 (0.0)	2 (100.0)	1.000[f]
Body weakness	5 (14.7)	2 (40.0)	3 (60.0)	1.000[f]
Difficult swallowing	9 (25.7)	4 (44.4)	5 (55.6)	0.416[f]
Vomiting	5 (14.3)	2 (40.0)	3 (60.0)	0.640[f]
Hoarseness of voice	11 (31.4)	5 (45.5)	6 (54.5)	0.263[f]
Nose bleeding	3 (8.6)	0 (0.0)	3 (100.0)	0.536[f]
Drooling of saliva	6 (17.1)	1 (16.7)	5 (83.3)	0.640[f]
Bull neck	23 (65.7)	4 (17.4)	19 (82.6)	0.022[f]
Cough	5 (14.3)	1 (20.0)	4 (80.0)	1.000[f]
Breathing difficult	10 (28.6)	1 (10.0)	9 (90.0)	0.120[f]
Immunization status				
Completed	14 (40.0)	3 (21.4)	11 (78.6)	0.461[f]
Uncompleted/Unvaccinated	21 (60.0)	8 (38.1)	13 (61.9)	
Hypoxemia	7 (20.6)	1 (14.3)	6 (85.7)	0.384[f]
Weight (Kg)*	19.3 (6.4)	19.28 (5.5)	19.25 (6.9)	0.989[t]
Symp.' duration (days)[≠]	4 (2-5)	3 (1.75-4.25)	4 (2-5)	0.287[u]
LOH (days)[≠]	3 (1-9)	11 (7-15)	1 (1-5)	0.001[u]
WBC (×10^9/L)[≠]	16.5 (13.2-22.8)	16.1 (11.0-18.7)	17.6 (13.2-26.6)	0.276[u]
PCV (%)*	33.6±6.3)	31.9±6.4	34.6±6.2	0.277[t]
Platelets (×10^9/L)[≠]	134.0 (65.7-192.8)	134 (75.8-209.8)	119.5 (59.0-177.0)	0.359[u]
Sodium (mmol/L)*	132.0±7.2	134.0±5.8	130.7±7.6	0.131[t]
Potassium (mmol/L)*	4.4±1.1	3.8±0.8	4.7±1.1	0.034[t]
Chloride (mmol/L)*	98.0±8.2	102.1±9.2	96.0±7.1	0.034[t]
Urea (mmol/L)[≠]	7.2 (4.9-15.5)	5.7 (4.7-13.3)	7.3 (5.0-22.2)	0.145[u]
Creatinine µmol/L[≠]	82.0 (64-161.5)	84 (54.3-117.3)	79.5 (64.0-251.5)	0.500[u]

Symp: symptoms; *Mean with standard deviation; [≠]Median with Interquartile range; Kg: Kilogram; LOH: Length of hospitalization; WBC: White blood count; PCV: Packed cell volume; *t*: independent *t* test, f: Fischer's exact test; u: Mann-Whitney U test

All the children tested negative for SARS-CoV-2. Electrocardiogram was done in some of the children, and findings were consistent with diphtheria cardiotoxicity.

Of note is that out of the 35 cases, 21 had throat samples cultured but only two grew diphtheroid species. The Elek plate test was not carried out due to the non-availability of test kits. The polymerase chain reaction on one of the two positive samples was positive for the Detox gene.

Discussion

The COVID-19 pandemic disrupted health care services across the world including Nigeria. Of significant impact on childhood health indices is the effect on routine immunization especially in areas where there is relatively low immunization coverage.[11] In this study, we observed an average of 5 to 6 cases of diphtheria per month between July and December 2020. The number of cases far exceeds the most recent reports from Nigeria.[8,10] However, the cases were less than 98 cases reported in Borno State (Northeastern Nigeria), a decade ago.[7] The cases were also far less than what was reported from Indonesia, India and some east Asian countries.[19–21] The relatively high number of cases over the six-month duration may have been due to certain reasons. Routine immunization could not be carried out in most vaccination centers during the lockdown, creating a further gap in the vaccination coverage.[17] Besides, due to fear of COVID-19, most people avoided early presentation at a health facility, thus causing delayed diagnosis and intervention.[17] The sudden increase in the incidence of diphtheria seen in this study highlights the great susceptibility of the country to vaccine-preventable diseases, and the need for continuous surveillance while strengthening routine immunization.

The mortality rate in this study was higher than those reported in some low-middle income countries such as Indonesia (3.5%),[19] Bangladesh (0.9%),[20] and India (2.2%).[21] It was also higher than 33.3% in Benin, Edo State, southern Nigeria[10] but was less than 88% in Kaduna.[8] The poor outcomes in children with diphtheria in Nigeria remain unacceptably high. The high mortality observed in this study

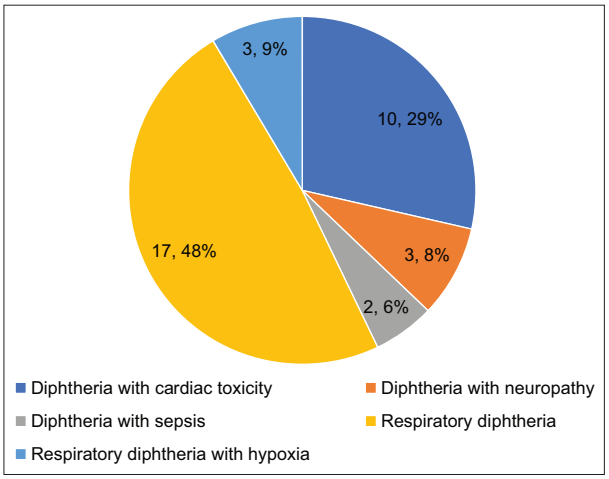

Figure 3: Spectrum of diphtheria cases

Table 4: Factors that are Predictive of poor outcome (death)

Variables	Categories	Deaths *n*=24 (%)	Beta coef.	Adjusted OR	95% CI	*P*
Age (years)	≥5	19 (79.2)	-0.121	1		
	<5	5 (20.8)		0.886	0.515, 1.524	0.662
Sex	Male	9 (37.5)	0.195	1		
	Female	15 (62.5)		1.216	0.756. 1.956	0.421
Bull neck	No	5 (20.8)	0.749	1		
	Yes	19 (79.4)		2.115	1.270, 3.521	0.004
Vaccination status	Completed	11 (45.8)	-0.034	1		
	Uncompleted/Unvaccinated	13 (54.2)		0.967	0.612, 1.528	0.885
Duration of symptoms (days)	≥48 h	16 (66.7)	-0.053	1		
	<48 h	8 (33.3)		0.948	0.582, 1.546	0.831
LOH (days)	≥24 h	14 (58.3)	0.150	1		
	<24 h	10 (41.7)		1.162	0.728, 1.854	0.528
Potassium (mmol/L)	<4.5	11 (45.8)	-0.159	1		
	≥4.5	13 (54.2)		0.853	0.536, 1.357	0.502
Chloride (mmol/L)	<95	10 (41.7)	-0.075	1		
	≥95	14 (58.3)		0.928	0.586, 1.470	0.749
Urea (mmol/L)	<6.5	8 (33.3)	0.078	1		
	≥6.5	16 (66.7)		1.081	0.663, 1.764	0.755
Creatinine (mg/dL)	<1.5	14 (58.3)	-0.202	1		
	≥1.5	10 (41.7)		0.817	0.518, 1.288	0.384
WBC ($\times 10^9$/L)**	<15,000	8 (36.4)	0.122	1		
	≥15,000	14 (63.6)		1.129	0.696, 1.834	0.622

LOH: Length of hospitalization; WBC: White blood count; ***n* (33); Beta coef: beta coefficient; OR: odds ratio; CI: confidence interval. Overall percentage of prediction model 73.3%; Nagelkerke R^2=0.039

may be due to delayed presentation; moreover, none of the children received diphtheria antitoxin (DAT) as Nigerian, as a country, does not stock DAT. Thus, children with diphtheria hardly received the DAT which was shown to reduce mortality especially if administered early in the course of the disease. This calls for an pragmatic approach from the Nigerian government to urgently ensure the availability of DAT at the national level and make this available for cases of diphtheria since the country has been experiencing frequent resurgence and outbreaks. It is worthy of note that countries such as Indonesia and other Asian countries with a frequent outbreak of diphtheria do have DAT, which has had a significant impact on the reduction of mortality.[22]

We observed in this study that age, sex, status of immunization, leukocytosis, and biochemical features of renal impairments were not predictive of death. However, presence of bull neck was highly predictive of death. A study in Jakarta, Indonesia showed that incomplete immunization, stridor, bull neck, leukocytosis and thrombocytopenia were associated with deaths.[19] Also, a study from India found only myocarditis as a predictor of death amongst children with diphtheria in the intensive care unit (ICU).[23] The bull neck remains one of the main features of diphtheria. This should be emphasized during public awareness programs, and requires early presentation and referral from the primary health care level. Early presentation will allow for early intervention and possible prophylaxis for the immediate contact and reduce further spread of the disease.

Our study shows that the most common complications are cardiotoxicity and neuropathy. This is similar to the findings from the Republic of Georgia.[23] Cardiac complications remain a leading cause of death in children with diphtheria and are due to the effect of diphtheria toxin on the heart. The clinical features of the cases observed in this study are also similar to previous reports. However, it is worthy to note that most cases in this study presented late with complications, which may have contributed to the poor outcomes. This further calls for public awareness on the common symptoms of diphtheria, the need for early presentation, and more importantly, completion of routine immunization in children as this study shows that less than half of the patients completed routine childhood immunization.

Though we retrieved all the records of cases seen over the study period, two of the 35 cases had no full blood counts. In addition, our sample is small (35), and our facility is a referral center; hence our findings may not be generalizable to the whole state.

Conclusion

The study noted a high number of cases of diphtheria over a six-month period with a high mortality. The clinical features are similar to previous studies from Nigeria with preponderance of fever and bull neck. Amongst the clinical and laboratory findings, only the presence of bull neck was predictive of death. We recommend strengthening of public awareness on common symptoms of diphtheria, and presence of bull neck should warrant further evaluation.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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