Alege et al. BMC Infectious Diseases (2025) 25:8
https://doi.org/10.1186/s12879-024-10401-4

BMC Infectious Diseases

RESEARCH

Open Access

Clinical presentation and predictors of hospital mortality of diphtheria in Nigeria, July 2023 to April 2024: a single-center study

Abdurrazzaq Alege[1*†], Olayinka Rasheed Ibrahim[2*†], Rasheedat Mobolaji Ibraheem[3], Olajide Aladesua[1], Abubakar Sani Lugga[1], Yunusa Yusuf Yahaya[1], Abdallah Sanda[4] and Bello Muhammed Suleiman[1]

Abstract

Background Despite recurrent outbreaks of diphtheria in Nigeria, there is a lack of in-depth analysis of hospitalization outcomes. Herein, we describe the sociodemographic, clinical, and laboratory features associated with hospitalization outcomes (defined as death or discharge) during the recent diphtheria outbreak in Nigeria.

Methods This prospective observational study included 246 confirmed diphtheria cases managed in a dedicated isolation ward of a health facility in northwestern Nigeria from July 1, 2023, to April 30, 2024. We analyzed clinical and laboratory features, immunization status, and socio-demographics in relation to hospitalization deaths using SPSS version 29.

Results The median age (interquartile range) was 7.00 (4–10) years and 49.6% (122) were aged 5–10 years. Common clinical features were fever (95.9%), sore throat (91.9%), painful swallowing (90.7%), pseudomembrane (93.1%), and cervical-submandibular lymphadenopathy (91.5%). Most children were unvaccinated (158; 64.2%), 199 (80.9%) received diphtheria antitoxin, and both were related to outcomes. Mortality rate was 23.5% (58/246). After adjusting for confounders, predictors of hospitalization deaths were neck swelling with an adjusted odds ratio (AOR) of 9.80 (95% CI 1.68–56.47), abnormal respiratory findings (AOR, 149.99 [95% CI, 15.60–1442.02]), hypoxemia (AOR, 37.79 [95% CI, 4.26–331.96]), and elevated serum creatinine above 1.5 mg/dL (AOR 107.78, 95% CI, 7.94–1462.38).

Conclusions Diphtheria is a significant burden in Nigeria, particularly among children. Neck swelling, hypoxemia, abnormal respiratory findings, and impaired renal function were predictive of hospitalization death. Although antitoxin and vaccination were related to outcomes, they did not predict hospitalization death.

Keywords Diphtheria, Clinical features, Laboratory findings, Outcomes, Nigeria

†Abdurrazzaq Alege and Olayinka Rasheed Ibrahim contributed equally to this work and shared first authorship.

*Correspondence:
Abdurrazzaq Alege
abdurrazzaqalege@gmail.com
Olayinka Rasheed Ibrahim
ibroplus@gmail.com

[1]Department of Pediatrics, Federal Teaching Hospital, Katsina, Nigeria
[2]Department of Pediatrics, Division of Clinical Medicine, University of Global Health Equity, Kigali, Rwanda
[3]Department of Pediatric and Child Health, University of Ilorin Teaching Hospital & University of Ilorin, Ilorin, Nigeria
[4]Department of Medical Microbiology, Federal Teaching Hospital, Katsina, Nigeria

Introduction

Diphtheria is a potentially life-threatening infectious disease caused by the bacterium *Corynebacterium diphtheriae* [1]. The re-emergence of the disease continues to cause significant morbidity and mortality, especially in low- and middle-income countries, including Nigeria [2–4]. Despite the availability of effective vaccines and antibiotics, it has remained a significant public health concern in Nigeria with recurrent outbreaks [4]. The vulnerability and spread of diphtheria in the country are due to various factors, including incomplete or lack of immunization, low levels of education, poor knowledge of the disease, poverty, misconceptions, and certain religious beliefs [5, 6]. Studies conducted in India and Nigeria found that 57.0% and 45.8% of children hospitalized with diphtheria, respectively, were completely immunized according to the national immunization schedule [2, 3]. The findings also suggest that vaccinated children can develop severe disease and highlight the importance of maintaining high vaccination coverage to prevent outbreaks.

Diphtheria, especially in severe cases, requires hospitalization because of potentially serious complications such as respiratory failure, cardiac arrest, and even death if left untreated [1, 7]. Hospitalization is also required for the administration of diphtheria antitoxin. Previous studies in Nigeria showed a complete lack of diphtheria antitoxin in the country, which partly accounts for the high mortality recorded in the past [8]. Besides the availability of antitoxin, there are other associated factors, including socio-demographics, the severity of the disease, and clinical and laboratory features, that may influence the hospitalization and outcomes of cases of diphtheria [9, 10]. Understanding the factors associated with outcomes in hospitalized diphtheria cases is critical for developing effective strategies to improve patient care and reduce mortality rates. Therefore, this study aimed to investigate the factors (socio-demographics, clinical features, and laboratory features) associated with outcomes in children hospitalized for diphtheria at a single Nigerian tertiary hospital. We reviewed 246 cases of prospectively gathered data on diphtheria managed during the recent outbreak in Nigeria from July 2023 to April 2024 to identify the factors influencing hospitalization outcomes (discharge or death). By understanding these factors, health care providers can develop targeted interventions to improve patient outcomes and reduce mortality rates in diphtheria.

Methods

Study design and setting

This prospective observational study involved cases of diphtheria managed from July 1, 2023, to April 30, 2024, at a tertiary health facility in northwestern Nigeria. The hospital is the only tertiary health facility in the state with a dedicated 15-bed isolation ward for highly infectious diseases. The facility receives and manages diphtheria cases in the state, with an estimated population of 9.3 million (2024), and members of the infectious disease unit include consultants, resident doctors, nurses, and attendants.

Study population

This study included all cases of diphtheria (pediatrics and adults) that presented and were admitted to the isolation ward of the hospital during the study period (July 1st 2023 to April 30th 2024). We excluded patients admitted with other forms of diagnoses that did not have confirmed diphtheria during the study period.

Sample size

The minimum sample size was estimated by using an online calculator (http://www.raosoft.com/samplesize.html*)*. Using an incidence of 3.1% of diphtheria cases reported earlier at the study site, we obtained a minimum sample size of 183 at a 95% confidence level and 2.5% margin of error [3] However, all cases (246) of diphtheria managed in the 10 months were included in the study.

Laboratory case confirmation

Laboratory case confirmation was carried out at the Nigeria National Reference Laboratory, situated at the Nigeria Centre for Disease Control and Prevention (NCDC) Headquarters in Abuja, Nigeria. In brief, all patients that fit the case definition of suspected diphtheria adopted from the Nigeria Centre for Disease Control and Prevention had throat samples collected at admission [11]. The samples were transported in Amies Charcoal Media and subsequently cultured on Tellurite blood agar at the reference laboratory. Those with positive culture growth were further subjected to a modified Elek test (demonstration of toxin production using an immunoprecipitation reaction). Throat samples were also subjected to real-time polymerase chain reaction to detect the presence of the A and B subunits of the diphtheria toxin gene (tox).

Study outcomes

The primary outcomes were factors (socio-demographics, vaccination history, antitoxins, and clinical and laboratory features) associated with hospitalization outcomes (defined as death or discharge). Secondary outcomes included a description of the epidemiology (demographics) and complications associated with diphtheria.

Data collection

At the onset of the outbreak, a register (an Excel spreadsheet) was opened at the isolation center to capture the following variables at the point of admission: age, sex, address, symptoms, immunization status, signs, complications, laboratory parameters (full blood count, electrolytes, serum urea and creatinine, and throat swab for pathogen identification), treatments received, including antitoxins, and hospitalization outcomes (defined as death or discharge). The spreadsheet was updated regularly and at the time of discharge.

For each case, we also obtained immunization history as a component of the history at the admission, and it was based on recall by most of the caregivers (184), while (62) the caregivers provided the national immunization cards. Nigerian childhood immunizations follow the World Health Organization (WHO) expanded program on immunizations, and at present, children receive three doses of vaccines administered at the 6th, 10th, and 14th weeks as a component of pentavalent vaccines [12]. However, children (less than five years old) with missed doses are expected to receive three doses of pentavalent at a four-week interval. Children aged five and above with missed doses received the Tetanus-Diphtheria (Td) vaccine at four weekly intervals for a total of three doses. The country does not routinely administer booster doses to children and adults, which are recommended at 12–23 months, 4–7 years, and 9–15 years of age by WHO; however, as part of the outbreak responses, mop-up doses were administered in the affected areas [13].

Sociodemographic for each patient were determined using 'Oyedeji's social classification [14]. In brief, socioeconomic classes were derived from the mean scores of the parents' highest educational attainment and occupations. For educational status, those with a degree and masters were scored as 1, while those without formal education were scored as 5. For occupation, professional and large business-class individuals were scored as 1, while full-time housewives and the unemployed were scored as 5. The scores of education and occupation were determined and further ranked as mean scores of 1 and 2 as upper, mean score of 3 as middle, and mean scores of 4 and 5 as low socioeconomic class [14].

As part of the case management, all patients received 40,000 I.U of diphtheria antitoxin in 250 ml normal saline over 2 h after a test dose. However, patients with severe manifestations, including upper airway obstruction, nasopharyngeal diphtheria, or bleeding, received 60,000 I.U of diphtheria antitoxin after a test dose. It is worth noting that 41 (19.1%) of the admitted patients did not receive diphtheria antitoxin due to non-availability.

Data analysis

We cleaned the data and exported to IBM Statistical Package for the Social Sciences (version 29) for analysis. The age was summarized as the median with interquartile range (IQR). The discrete variables, sex, clinical and laboratory features were summarized with percentages and frequency tables and compared using the chi-square test, whereas continuous variables (not normally distributed) were compared using the Mann-Whitney U test. Variables that were significant (p value less than 0.05) in two-by-two tables were entered into a multiple logistic regression to identify factors predicted hospitalization deaths. The results of multiple logistic regression were presented as adjusted odds ratios with 95% confidence intervals. For all levels of statistical significance, we set the p-value at less than 0.05.

Ethical consideration and approval

The Federal Teaching Hospital Katsina Human Research Ethical Review Committee approved this study (FTH-KTNHREC. REG.24/06/22 C/173). This study was conducted in conformity with the declaration of Helsinki. We obtained informed consent from the adult participants and the caregivers/parents of the recruited children. We anonymously extracted the data from the spreadsheet and de-identified them before the analysis. All the data were stored on a password-secured computer with absolute confidentiality.

Results

Socio-demographic characteristics of the study subjects

This study included a total of 246 patients (pediatric and adult) with a median age (IQR) of 7.0 (4–10) years, a minimum age of 11 months, and a maximum age of 36 years. Approximately half of the patients were children aged 5–10 years (49.6%) (Table 1). Overall, there were more females (138; 56.1%) and a higher median age (IQR) of 8.00 (4.00–8.00), $p=0.044$. In addition, most patients were from lower and middle socioeconomic classes (219; 89.0%).

Laboratory confirmation and form of diphtheria

All 246 patients had respiratory diphtheria and comprised pharyngeal (229; 93.1%), nasal (15;6.1%), and laryngeal diphtheria (2;0.8%). Of the 246 cases with samples analyzed, 55 (22.4%) yielded toxigenic strains of corynebacterium on modified Elek's tests, 183 (74.4%) yielded non-toxigenic strains, while 8 (3.3%) did not yielded any growth [attributed to insufficiency samples].

Clinical and Laboratory features of the study population

The age groups and sex were comparable between those who survived and those who did not. The most common symptoms were fever (95.9%), sore throat (91.9%) and painful swallowing (90.7%). Symptoms at presentation associated with hospitalization outcomes included inability to swallow, drooling of saliva, cough, difficulty breathing, nasal discharge, nasal blockade, voice changes, and nasal regurgitation (Table 2). The most common signs at presentation were pseudomembrane (93.1%) and

Table 1 Relationships between clinical features, laboratory features, and outcomes of hospitalization among the study patients ($n = 246$)

Variable	Subgroup	Survivor *n* (188; 76.4%)	Non-survivor *n* (58; 23.6%)	*P* value
Age (years)	< 5	47	19	0.318
	5 to 10	93	29	
	> 10	48	10	
Sex	Male	87	21	0.177
	Female	101	37	
SEC	Upper	22	5	0.026
	Middle	74	13	
	Lower	92	40	
Symptoms	Fever	179	57	0.302
	Sore throat	173	53	0.876
	Painful swallowing	170	54	0.827
	Inability to swallow	111	51	< 0.001
	Drooling of Saliva	46	25	0.006
	Cough	25	21	< 0.001
	Breathing difficulty	20	38	< 0.001
	Nasal discharge	26	19	0.001
	Nasal blockade	11	13	< 0.001
	Voice changes	64	34	< 0.001
	Nasal regurgitation	10	9	0.011
Signs	Cerv-sub. Lymp.	171	54	0.609
	Neck swelling	84	47	< 0.001
	Pseudomembrane	172	57	0.075
	Exudates	26	5	0.296
	Tonsillar enlargement	75	32	0.040
	Bloody nasal discharge	9	13	< 0.001
	Added HS	11	13	< 0.001
	Abn. chest findings	9	34	< 0.001
	Temp ≥ 38.5	31	11	0.661
	Hypoxemia	7	31	< 0.001
Contact Hx	Yes	102	34	0.559
Immunization status	No vaccination	111	47	0.008
	Partially vaccinated	26	5	
	Fully vaccinated	51	6	
Antitoxin*	Yes	158	41	0.024
WBC (x 10^9/L)	≤ 10	101	18	**0.003**
	> 10	87	40	
Lymphocyte (%)	≤ 40	96	40	**0.017**
	> 40	92	18	
Neutrophils (%)	≤ 60	116	25	**0.012**
	> 60	72	33	
PCV (%)	≤ 20	3	3	0.057
	21–30	50	22	
	> 30	135	33	
Platelets (x 10^9/L)	< 100	21	11	0.296
	100–400	141	39	
	> 400	26	8	
Bicarbonate (mmol/L)	≤ 15	44	25	**0.004**
	> 15	144	33	
Sodium (mmol/L)	≥ 135	130	27	**0.002**
	< 135	58	31	
Potassium (mmol/L)	≤ 4.5	160	39	**0.002**
	> 4.5	28	19	

Table 1 (continued)

Variable	Subgroup	Survivor *n* (188; 76.4%)	Non-survivor *n* (58; 23.6%)	*P* value
Serum Cr (mg/dL)	≤ 1.5	182	38	**< 0.001**
	> 1.5	6	20	

SEC-Socioeconomic class; Cer-sub lymph-Cervical-submandibular lymphadenopathy; HS-Heart sounds, Abn-Abnormal; Temp-Temperature, Hx-History. WBC-white blood count. *Diphtheria antitoxin- 41 admitted cases did not receive vaccines due to non-availability at of their admission and management

Table 2 Multiple logistic regression of baseline variables associated with in-hospitalization deaths

Variable	Categories	*n*	β	Std error (β)	Adjusted OR	(95% CI)	*P* value
Age (years)	< 5	66			Ref		
	5 to 10	122	1.26	0.88	3.54	0.64, 19.68	0.149
	> 10	58	1.56	1.02	4.77	0.65, 35.25	0.126
Sex	Female	138			Ref		
	Male	108	0.03	0.73	1.03	0.25, 4.28	0.973
SEC	Upper	27			Ref		
	Middle	87	-0.76	1.54	0.47	0.02, 9.65	0.623
	Lower	132	0.80	1.39	2.23	0.15, 34.05	0.565
Inability to swallow	Yes#	162	0.55	0.95	1.73	0.27, 11.06	0.561
Drooling of Saliva	Yes#	71	-0.38	0.75	0.68	0.16, 2.96	0.611
Cough	Yes#	46	-0.13	0.94	0.87	0.14, 5.53	0.886
Difficulty in breathing	Yes#	58	-0.76	0.94	0.47	0.07, 2.96	0.420
Nasal discharge	Yes#	45	-0.69	1.00	0.50	0.07, 3.56	0.491
Nasal blockade	Yes#	24	0.06	1.20	1.06	0.10, 11.23	0.961
Voice changes	Yes#	98	0.29	0.77	1.34	0.30, 6.04	0.707
Nasal regurgitation	Yes#	19	1.18	0.81	2.88	0.29, 29.00	0.369
Immunization status	Fully vaccinated	57			Ref		
	Partially vaccinated	31	0.04	0.84	1.04	0.20, 5.38	0.963
	No vaccination	158	0.39	1.30	1.48	0.12, 18.77	0.762
Neck swelling	Yes#	131	2.28	0.90	9.76	1.69, 56.47	**0.011**
Tonsillar enlargement	Yes#	107	1.82	0.81	6.19	1.26, 30.54	0.025
Bloody nasal discharge	Yes#	22	0.12	1.16	1.12	0.12 10.85	0.921
Heart sounds	Added sounds**	24	0.45	0.92	1.57	0.26, 9.53	0.626
Chest	Abnormal findings**	43	5.01	1.16	149.99	15.60, 1442.02	**< 0.001**
Hypoxemia	Yes#	38	3.63	1.11	37.59	4.26, 331.96	**0.001**
WBC (x 10^9/L)	≤ 10	119			Ref		
	> 10	127	0.37	0.76	1.45	0.33 6.37	0.626
Lymphocyte (%)	≤ 40	136			Ref		
	> 40	110	1.35	1.32	3.85	0.29, 51.07	0.307
Neutrophils (%)	≤ 60	141			Ref		
	> 60	105	1.86	1.29	6.43	0.51, 80.67	0.150
Bicarbonate	> 15	177			Ref		
	≤ 15	69	-1.07	0.88	0.34	0.70, 16.18	0.130
Sodium	≥ 135	157			Ref		
	< 135	89	0.73	0.72	2.07	0.50, 8.48	0.313
Potassium	≤ 4.5	199			Ref		
	> 4.5	47	1.21	0.80	3.37	0.70, 16.18	0.130
Serum Cr (mg/dl)	≤ 1.5	220			Ref		
	> 1.5	26	4.68	1.33	107.78	7.94, 1462.38	**< 0.001**
***Antitoxin**	No***	47	1.25	0.81	3.48	0.71, 16.99	0.124

SEC-Socio-economic class; *Diphtheria antitoxin; β- Beta coefficient; Std-Standard CI-Confidence interval, OR-Odds ratio, ref-reference value for the odds ratio; #References were "no" **References were normal findings; ***Reference was Yes cervical-submandibular lymphadenopathy (91.5%). Neck swelling, exudates, tonsillar enlargement, blood nasal discharge, third heart sounds, abnormal chest findings, and hypoxemia were associated with hospitalization outcomes (Table 1).

Most children were unvaccinated (158; 64.2%), and vaccination status was related to hospitalization outcomes (Tables 1 and 1S). Of the 246 patients managed during the study period, 199 (80.9%) received diphtheria antitoxin, which was associated with hospitalization outcomes (Table 1).

The laboratory findings at presentation associated with outcomes included white blood cell counts, lymphocytes, neutrophils, serum bicarbonate levels, serum sodium levels, serum potassium levels, and serum creatinine levels (Table 1).

Predictive factors of in-hospital mortality

Of the 246 patients with diphtheria admitted during the study period, 58 in-hospital deaths occurred with a crude mortality rate of 23.6%. After adjusting for confounders including age and sex, variables that predicted hospitalization deaths were the presence of neck swelling with an adjusted odd ratio (AOR) of 9.80 (95% CI 1.69 to 56.47), abnormal chest findings on physical examination at presentation with an AOR of 149.99 (95% CI 15.60 to 1442.02), the presence of hypoxemia (AOR 37.79, 95% CI 4.26 to 331.96), and elevated serum creatinine above 1.5 mg/dL (AOR 107.78, 95% CI 7.94 to 1462.38) (Table 2).

Complications of diphtheria

Of the 246 patients in this study, 83 (33.7%) developed at least one complication. Further analysis showed that 59 patients had a single complication (59; 24.0%). The most common complications were cardiac complications ($n=42$; 17.1%), followed by neuropathy ($n=31$; 12.6%), and the least common was airway obstruction ($n=15$; 6.1%), as shown in Fig. 1a and b.

Discussion

Nigeria has experienced recurrent outbreaks of diphtheria due to low immunization coverage and healthcare challenges [8]. This study included 246 cases of diphtheria over 10 months, perhaps one of the largest hospital-based data from Nigeria, and highlighted the significant threat posed by this re-emerging disease. This finding translated to an average of 25 cases per month and far exceeded the total of 35 cases reported at the same facility during the COVID-19 pandemic (July to December 2020) [3]. The cases recorded at the facility also exceeded the 233 diphtheria-related cases reported from acute care hospitals in Canada from 2006 to 2017 [15]. Comparatively, the average monthly cases also exceeded the average of 20 cases per month reported from six hospitals in Indonesia (389 cases over 20 months) from January 2017 to August 2018 [9]. In contrast, cases from this study are far fewer than 2,925 cases (average of 60 cases per month) reported from January 2008 to December 2012 at a referral hospital in India [16] and less than 527 cases reported in the northern Kerala region of India in 2016 [17]. Although less than 656 epidemiologically reported cases of diphtheria by the NCDC for epidemiological week 42 (2024) and cumulative 22,293 suspected cases and 13,387 (60.1%) confirmed cases from Epi-week 19 (2022) to Epi-week 51 (2023) in the country [18], which comprise both admitted and non-admitted cases, our data support the continuous unabating burden of diphtheria and a call to re-appraise the current strategies towards curbing the disease.

Clinical features associated with hospitalization outcomes at presentation included inability to swallow, drooling of saliva, cough, difficulty breathing, nasal discharge, nasal blockade, voice changes, nasal regurgitation, neck swelling, exudates, tonsillar enlargement, bloody nasal discharge, added heart sounds, abnormal chest findings, and hypoxemia. These features were among the variables similarly identified to be associated with outcomes in a cohort of 283 cases of diphtheria in Indonesia [9]. However, the present study's findings contrast with an earlier Nigerian study [3], where most of the clinical features were comparable between survivors and non-survivors, probably due to the sample size effect, as the present study had 246 cases compared with the earlier study, which had 35 cases. Other reasons that could account for the differences in the present study compared with the earlier study may be due to the study methods; the present study is prospective and includes pediatrics and adults compared with previous studies, which were retrospective and limited to the pediatric age group. The clinical features are evidence of disease progression and disease severity, which have been identified to be related outcomes of the disease [19]. The findings of these clinical features also reinforce their continuous relevance as part of the case definition, especially in resource-constrained settings, where there is limited access to diagnostic facilities.

The laboratory findings associated with hospitalization outcomes were white blood cell counts, lymphocytes, neutrophils, serum bicarbonate levels, serum sodium levels, serum potassium levels, and serum creatinine levels. Similarly, in Indonesia, white blood cells and thrombocytes were associated with hospitalization outcomes, although electrolytes were not among the variables evaluated in their study [9]. In contrast, our previous study only found a relationship between outcomes and serum potassium and chloride [3]. Further comparison of the current laboratory data is limited, as most studies did

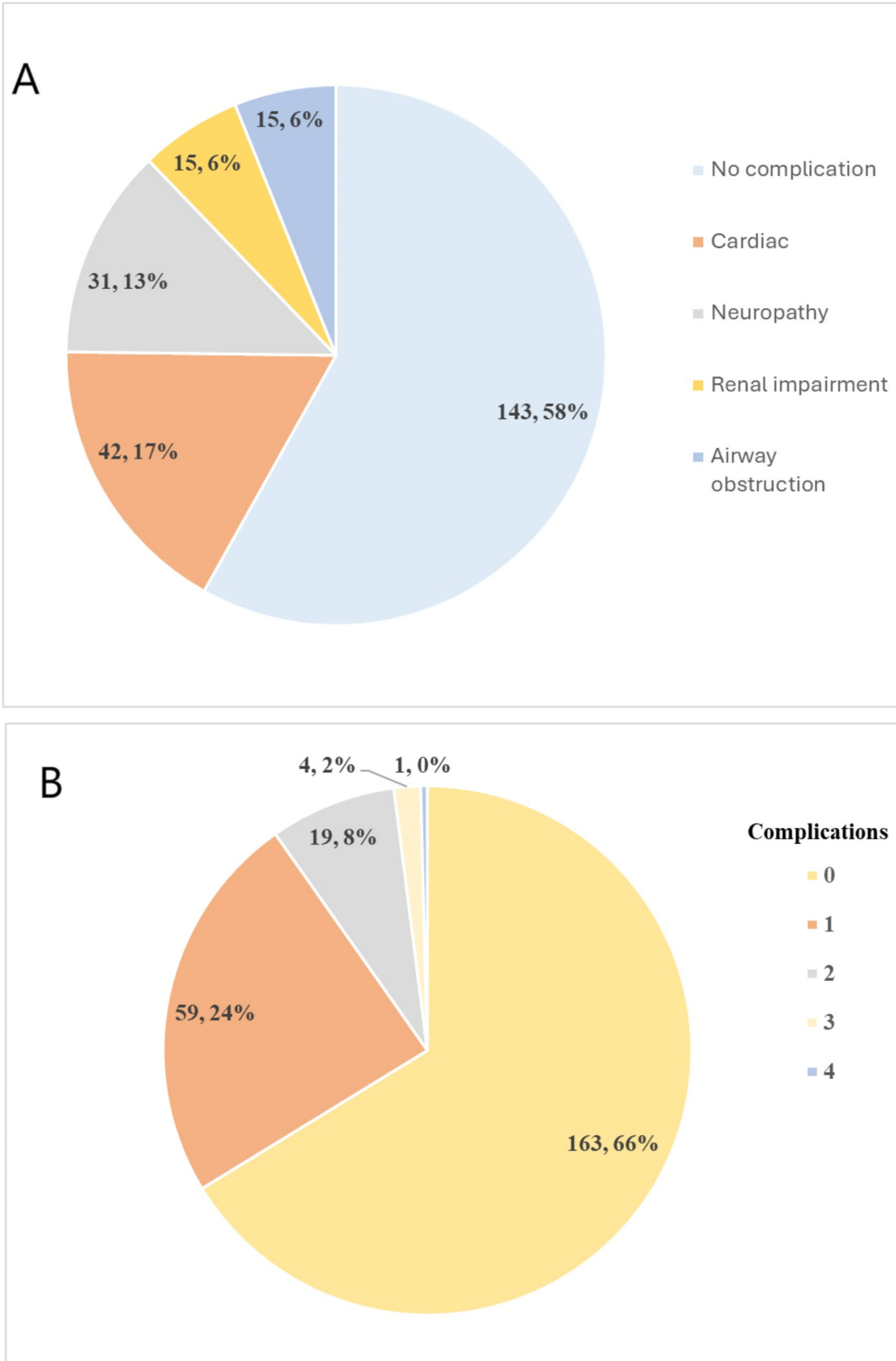

Fig. 1 Complications among the admitted patients and No of Complications among the admitted patients

not report laboratory features that impact outcomes in diphtheria [2, 4]. These laboratory features are probably reflective of ongoing pathogenic responses to toxin-mediated cellular damage, with electrolyte imbalance also reflecting reduced intake due to respiratory pathologies, such as pseudomembrane and an enlarged neck [7].

Immunization remains a key strategy for curbing and preventing the spread of diphtheria, while the administration of antitoxins has also been documented to improve clinical outcomes, both of which are supported by the findings of this study [20]. Studies have documented that immunization levels are critical in preventing outbreaks, with a higher coverage rate for diphtheria, reducing the chance of an outbreak [20, 21]. The uptake of the third dose of Pentavalent vaccine across Nigeria is low (about 50% of coverage for children aged 12 months to 23 months), with northwestern Nigeria having one of the lowest coverage rates (42%), which may have been part of the reasons for the continuous re-emergence of diphtheria in the region [22]. This calls for a re-appraisal of vaccination campaign strategies, ensuring rapid scale-up of routine immunization and possibly regular supplemental vaccination in the affected regions besides the outbreak immunization response. Approximately 81% of the cohort in this study received antitoxin along with other standards of care for case management, with improved outcomes, which is consistent with observations in other studies [5, 23]. Antitoxin, when administered early, bind diphtheria toxins and prevent tissue damage, the main pathogenic mechanism associated with various complications.

The mortality rate in this study was 23.6%, although still high, which is less compared to studies in Nigeria [24] and India [21]. This relatively low mortality rate compared with the aforementioned studies is probably due to the impact of the administration of antitoxin (previously not available in Nigeria) and to the improved standard of care, as the patients were managed in dedicated isolation wards with adequate supportive care. All admitted patients received free treatments, and adequate laboratory support and admission costs were waived, which ensured optimal care for all cases, all of which may have contributed to the reduction in mortality. The number of complications in this study is also low and comparable to other countries, probably a reflection of the impact of the administration of antitoxin and improved standards of care [19, 25].

At baseline, variables that predicted hospitalization deaths were neck swelling, abnormal chest findings, hypoxemia, and elevated serum creatinine above 1.5 mg/dL. The finding of neck swelling has been well documented as a strong predictor of death in the literature and is due to enlarged cervical lymphadenitis along with soft tissue swelling [26]. Neck swelling, otherwise referred to as "bull neck," should be considered a sign of severe disease and calls for closer monitoring. We also observed abnormal chest findings [tachypnea, crackles, and reduced breath sounds], which are signs of respiratory complications at presentation and are predictors of death. Respiratory complications with respiratory failure have been identified as a leading cause of death in cases of diphtheria [19] A few studies have also identified hypoxemia as a cause of death, suggesting that respiratory diphtheria, the most common form of the disease, may impair airflow, necessitating closer monitoring [27, 28]. Hypoxemia may be an indication for early airway support such as mechanical ventilation and tracheostomy as part of the standard of care, as documented in a few studies [28]. This study also identified elevated creatinine at baseline as a predictor of death, which contradicts our previous publication [3]. Elevated creatinine level, a sign of renal impairment, is an independent predictor of poor outcomes in many clinical conditions, including infectious diseases, suggesting that the renal system plays a significant role in the outcomes of diphtheria cases [29]. Diphtheria toxin has been shown to be lethal to renal tubular cells and subsequent kidney impairment.

Strengths and limitations of this study

The strength of this study is that it is one of the largest hospital-based datasets from Nigeria and evaluates three core areas that have been documented to impact the outcomes of diphtheria: socio-demographics, clinical features, and laboratory features. Secondly, most of the cases received antitoxin (previously unavailable in Nigeria), and improved standard of care, allowing us to see the potential impact on the decline in mortality compared with the previous case fatality rate in Nigeria. Thirdly, unlike other Nigerian studies that relied on retrospective methods, we collected data prospectively. Despite these plausible reasons, this study has some limitations: it is a single-center study and may represent the tip of the iceberg on the actual burden of the diphtheria outbreak in the country. In addition, nutritional assessment among the cohort was not analyzed, which may also have impacted some of the outcomes. In addition, the mortality rate in this study does not reflect the actual case fatality rate in the country, as the hospital data only reflects admitted moderate-to-severe cases of the disease.

Conclusion

Diphtheria is a re-emerging disease that constitutes a significant burden in Nigeria, particularly among children. The presence of neck swelling, hypoxemia, respiratory findings at presentation, and impaired renal function (creatinine levels above 1.5 mg/dl) are highly predictive of in-hospital death. Despite the availability of antitoxin, the hospital-based case fatality rate remains high, which calls for a re-appraisal of the present case management strategies of diphtheria in the country.

Abbreviations

CI	Confidence interval
COVID	19 Coronavirus disease 2019
IQR	Interquartile range
NCDC	Nigeria centre for disease control and prevention
Td	Tetanus-diphtheria
WHO	World health organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-10401-4.

Supplementary Material 1

Acknowledgements

We thank the staff of Isolation ward for their care of the patients during hospitalization.

Author contributions

A.A conceptualized this work, was involved in study design, data curation, literature review, data visualization, draft and approved the final version. O.R.I. was involved in conceptualization, data curation, data visualization, data analysis, literature review, draft and critically appraised the manuscript. R.M.I was involved in study design, data visualization, data analysis, literature review, draft and critically appraised the manuscript. O.A was involved in study design, data curation, literature review, data visualization, draft and approved the final version. A.S.L was involved in study design, data curation, literature review, data visualization, draft and approved the final version. Y.Y.Y was involved in study design, data curation, literature review, data visualization, draft and approved the final version. A.S was involved in study design, data curation, literature review, data visualization, draft and approved the final version. B.M.S was involved in study design, data visualization, data analysis, literature review, draft and critically appraised the manuscript. All authors reviewed the manuscript.

Funding

This research has no grant or external funding.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Federal Teaching Hospital Katsina Human Research Ethical Review Committee approved this study (FTHKTNHREC. REG.24/06/22 C/173). This study was conducted in conformity with the declaration of Helsinki. We obtained informed consent from the adult participants and the caregivers/parents of the recruited children. We anonymously extracted the data from the spreadsheet and de-identified them before the analysis. All the data were stored on a password-secured computer with absolute confidentiality.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 25 August 2024 / Accepted: 23 December 2024
Published online: 02 January 2025

References

1. World Health Organization (WHO). Diphtheria. 2024. https://www.who.int/news-room/fact-sheets/detail/diphtheria. Accessed 13 Jul 2024.
2. Mohan V, Chandrasekaran V, Sistla S. Clinical profile and risk factors for mortality in children admitted with diphtheria: an observational study. Infect Dis (Auckl). 2023;55:431–8.
3. Ibrahim O, Lawal I, Mohammed B, Abdullahi S, Bello S, 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.
4. Murhekar M. Epidemiology of Diphtheria in India, 1996–2016: implications for prevention and control. Am J Trop Med Hyg. 2017;97:313–8.
5. Ikejezie J, Adebusoye B, Ekezie W, Langley T, Lewis S, Phalkey R. Modifiable risk factors for diphtheria: a systematic review and meta-analysis. Glob Epidemiol. 2023;5 July 2022:100100.
6. Olulaja ON, Anjorin ET, Ekerin O, Afolabi OT, Inuojo JM. A looming epidemic: combating the recurrent outbreaks of diphtheria in Nigeria. Pan Afr Med J. 2023;45:186.
7. Sharma NC, Efstratiou A, Mokrousov I, Mutreja A, Das B, Ramamurthy T, Diphtheria. Nat Rev Dis Prim. 2019;5:81.
8. Abdulrasheed N, Lawal L, Mogaji AB, Abdulkareem AO, Shuaib AK, Adeoti SG et al. Recurrent diphtheria outbreaks in Nigeria: A review of the underlying factors and remedies. Immunity, Inflamm Dis. 2023;11.
9. Arguni E, Karyanti MR, Satari HI, Hadinegoro SR. Diphtheria outbreak in Jakarta and Tangerang, Indonesia: epidemiological and clinical predictor factors for death. PLoS ONE. 2021;16:1–11.
10. Polonsky JA, Ivey M, Anam Mazhar MK, Rahman Z, le, Polain de Waroux O, Karo B et al. Epidemiological, clinical, and public health response characteristics of a large outbreak of diphtheria among the Rohingya population in Cox's Bazar, Bangladesh, 2017 to 2019: A retrospective study. PLoS Med. 2021;18:1–22.
11. NCDC. Nigeria Centre for Disease Control and Prevention. Nigeria Centre for Disease Control and Prevention. 2023. https://ncdc.gov.ng/ncdc.gov.ng/. Accessed 5 Apr 2024.
12. UNICEF. Nigeria Immunization Schedule. UNICEF Nigeria. 2021;:2021. https://www.unicef.org/nigeria/documents/nigeria-immunization-schedule. Accessed 5 May 2024.
13. World Health Organization. Diphtheria vaccine: WHO position paper, August 2017 – Recommendations. 2018.
14. Oyedeji GA. Socio economic and cultural background of hospitalized children in Ilesha. Niger J Paediatr. 1985;12:111–7.
15. Lin D, Ho Mi Fane B, Squires SG, Dickson C. Describing the burden of diphtheria in Canada from 2006 to 2017, using hospital administrative data and reportable disease data. Can Commun Dis Rep. 2021;47:414–21.
16. Meera M, Rajarao M. Diphtheria in Andhra Pradesh–a clinical-epidemiological study. Int J Infect Dis. 2014;19:74–8.
17. Sangal L, Joshi S, Anandan S, Balaji V, Johnson J, Satapathy A et al. Resurgence of Diphtheria in North Kerala, India, 2016: Laboratory supported case-based surveillance outcomes. Front Public Heal. 2017;5.
18. Nigeria Centre for Disease Control and Prevention. Weekly Epidemiological Report-Diphtheria. NCDC. 2024. https://ncdc.gov.ng/reports/weekly. Accessed 3 Aug 2024.
19. Kadirova R, Kartoglu HÜ, Strebel PM. Clinical characteristics and management of 676 hospitalized diphtheria cases, Kyrgyz Republic, 1995. J Infect Dis. 2000;181:S110–5.
20. Truelove SA, Keegan LT, Moss WJ, Chaisson LH, Macher E, Azman AS, et al. Clinical and epidemiological aspects of Diphtheria: a systematic review and pooled analysis. Clin Infect Dis. 2020;71:89–97.
21. Bist SS, Kumar L, Dhasmana G, Gupta A, Agarwal VK, Pant S. Clinical Profile and predictors of Outcome in patients with Diphtheria in a Tertiary Care Center. Int J Otorhinolaryngol Clin. 2022;13:77–81.
22. National Bureau of Statistics and United Nations Children's Fund. Multiple Indicator Cluster Survey 2021, Survey findings Report. Abuja, Nigeria; 2022.
23. Eisenberg N, Panunzi I, Wolz A, Burzio C, Cilliers A, Islam MA, et al. Diphtheria Antitoxin Administration, outcomes, and Safety: response to a Diphtheria Outbreak in Cox's Bazar, Bangladesh. Clin Infect Dis. 2021;73:e1713–8.
24. Sadoh AE, Sadoh WE. Diphtheria mortality in Nigeria: the need to stock diphtheria antitoxin. Afr J Clin Exp Microbiol. 2011;12:82–5.
25. Meshram RM, Patil A. Clinical profile and outcome of diphtheria in central India: a retrospective observational study. Int J Contemp Pediatr. 2018;5:1600.
26. Nawing HD, Pelupessy NM, Alimadong H, Albar H. Clinical spectrum and outcomes of pediatric diphtheria. Paediatr Indones. 2019;59:38–43.

27. Traugott MT, Pleininger S, Inschlag-Tisch S, Eder B, Seitz T, Merrelaar A, et al. A case of fulminant respiratory diphtheria in a 24-year-old Afghan refugee in Austria in May 2022: a case report. Infection. 2023;51:489–95.
28. Lai Y, Purnima P, Ho M, Ang M, Deepak RN, Chew KL, et al. Fatal case of Diphtheria and Risk for Reemergence, Singapore. Emerg Infect Dis. 2018;24:2084–6.
29. Prasad N, Patel MR. Infection-Induced kidney diseases. Front Med. 2018;5 NOV:1–11.

Publisher's note