Review Article

Understanding the Trend of Diphtheria Outbreak in Nigeria from 1941-2023: A Narrative Review

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ABSTRACT

Diphtheria is a contagious infection caused by *Corynebacterium diphtheriae* spread through respiratory droplets, typically from coughing or sneezing, and characterized by difficulty in breathing, heart rhythm challenges, and even death. Objective: This narrative review explored the trend of Diphtheria outbreaks in Nigeria and suggested a way to forestall reoccurrence. We search two bibliographic databases, PubMed and Scopus, to identify studies using the keywords "Diphtheria" and "Nigeria". Approximately eighty-two (82) years after isolating virulent strains of *Corynebacterium diphtheriae* in Nigeria, the country still suffers recurrent outbreaks of Diphtheria, a vaccine-preventable infection. Between the years 1974 to 2021, the World Health Organization (WHO) documented 40258 reported cases of diphtheria in Nigeria, although it missed 117 cases reported in Lagos, Benin, Katsina, and Borno between 2007 and 2017, where a 21.4% fatality was recorded in Borno alone. The current outbreak, labeled as one of the most severe outbreaks in Nigeria in recent years, so far, has 798 cases and 10% case fatality with the northern part of the country being particularly hard hit. The recurrence of the Diphtheria outbreak in Nigeria is attributed to incomplete vaccination exacerbated by poor vaccination coverage (e.g., < 50% in 2016), waning vaccine-induced immunity, maternal knowledge, and poverty. Incomplete immunization resulting from poor immunization coverage, poor sensitization, and lack of access to healthcare facilities is undoubtedly the single predominant determinant of Diphtheria outbreaks in Nigeria. There is an urgent need to promote complete immunization to prevent resurgence and re-emergence.

Keywords: *Corynebacterium diphtheriae*, Diphtheria, Nigeria Outbreak, Resurgence, Incomplete vaccination; Children.

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INTRODUCTION

Corynebacterium diphtheriae has been known to cause endemic and epidemic diphtheria disease. One of the main factors associated with the disease is the lack of immunization during childhood. *Corynebacterium diphtheria* affects only humans, and it affects the upper respiratory tract (1). The bacteria is contagious and transmitted through an airborne route. It causes respiratory obstruction accompanied by coughing or sneezing and is characterized by difficulty breathing, heart rhythm challenges, heart failure, and even death due to the exotoxin it produces. *Corynebacterium* are Gram-positive, non-encapsulated, non-sporulating, aerobic, and non-motile, pleomorphic granular rods organized in palisades. Most Corynebacterium non-pathogenic species are normal flora of the skin, oropharynx, urogenital and intestinal tracts (known as diphtheroids). *Corynebacterium diphtheriae* produces polyphosphate volutin (metachromatic) granules that stain red with Albert or methylene blue stain. The most pathogenic species, *Corynebacterium diphtheria*, is divided into three strains that can be identified and differentiated on tellurite agar (2). The *Corynebacterium diphtheriae gravis* (3-5m), *Corynebacterium diphtheriae mitis* 2-4mm, and *Corynebacterium diphtheriae intermedius* (1-2mm) strains.

Globally, the diphtheria mortality rate has been reported to range between 5-10%, with lack of immunization coverage being the major determinant of mortality rate. Children under five years and adults above 40 years could have higher death rates up to 20% higher. Diphtheria is known as a childhood disease, most common in children below 15 years; however, among the immunosuppressed and high population of unvaccinated individuals in countries with a lower prevalence of diphtheria, cases may be high among people above 40 years[1].

The clinical manifestation of Corynebacterium infection includes nasal diphtheria, anterior nasal diphtheria, bull-neck diphtheria, severe pharyngeal diphtheria, laryngeal diphtheria, tracheobronchitis, and cutaneous diphtheria. The clinical manifestation of the infection is influenced by the anatomic site affected, the immune status of the host, and the production and systemic distribution of the Diphtheria toxin. The Diphtheria toxin is easily absorbed in the surrounding tissues of the patient's throat, prompting a local inflammatory reaction in the nasopharynx and larynx (3).

Nigeria has faced many Diphtheria outbreaks since 2018, with the most recent in 2023. The Nigeria Centre for Disease Control (NCDC) reported the most recent, where they observed an increase in the suspected number of cases (733), 89 deaths with a case fatality rate (CFR) of 12.3% affecting children of 5 and 18 years old[2]. Nigeria's current diphtheria outbreak is a major public health threat to the neighboring countries and the world in general, being the most populous nation in Africa. Vaccination coverage of at least 90% has been known to give protection to about 60% population at risk. However, there is limited coverage of vaccination in the country (4).

Despite the incessant recurring trend of Diphtheria outbreaks, there remains a lack of comprehensive understanding of the epidemiology of Diphtheria outbreaks in Nigeria. This narrative review seeks to bridge this knowledge gap by synthesizing existing literature and analyzing past outbreak patterns to put forward the determinants of the Diphtheria outbreak in Nigeria and the way forward.

MATERIALS AND METHODS

Search Strategy

We used two bibliographic databases, PubMed and Scopus, for studies that reported the incidence, prevalence, or epidemiology of Diphtheria in Nigeria. The search query was formulated using the key concepts “Diphtheria” and “Nigeria” combined with the Boolean operator (AND). The search was executed without filters on the 5th of June 2023 at 2:45 pm East African Time.

Study Selection Criteria

We included studies that reported the prevalence, incidence, or outbreaks of Diphtheria in Nigeria. Studies were excluded if they lacked relevant data or accessible full texts. The selection of studies included in this review is shown in (**Figure 1**).

Data Extraction and Critical Appraisal

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Data extraction, deduplication, and title and abstract screening was performed by two independent authors (DM and PPD).Following title and abstract screening, two authors (DM and TP) screened the eligible studies' fulfillment of the inclusion criteria and extracted relevant data into a standardized Microsoft Excel (2019) spreadsheet columns labeled as follows: author name, year of publication, article title, and article type.

Statistical Analysis

All study characteristics were analyzed descriptively using Microsoft Excel version 2019 and presented as percentages.

RESULTS

Study Selection and Characteristics

We systematically searched PubMed and Scopus databases and retrieved 230 studies. Another four (4) studies not indexed in the databases we searched were retrieved from Google search, bringing the total number of studies retrieved to 234 studies. Fifty-six (56) duplicates were removed, and one hundred and seventy-eight (178) studies were subjected to title and abstract screening. One hundred and sixty-three (163) were ineligible and excluded. The remaining fifteen (15) eligible studies were further screened for all components of the inclusion criteria. One inaccessible study and two (2) studies lacking relevant data were excluded. Figure (1) below shows the study selection process. Twelve (12) studies made the inclusion criteria out of which 50% (n= 6) were letters to editor, 16.7 % articles and case reports respectively. Reviews and editorials each constituted 8.3% of the studies. **Table 1** below presents this information. Notably, most studies focused on providing insights and perspectives through letters to the editor, indicating a notable emphasis on discussing and addressing the diphtheria outbreak in Nigeria from various viewpoints.

DISCUSSION

Historical Perspective of Corynebacterium diphtheriae Outbreak in Nigeria

According to the World Health Organization, Nigeria reported 40258 cases of Diphtheria between 1974 and 2021 **(Figure 2**). According to this report, cases of diphtheria have been reported since the first report in 1974 except for the years: 1995, 1997, and 1999, 2003-2005, 2007-2017, and 2020-2021. Extrapolating from this report, it is clear that the most significant outbreak occurred between 1984-1993, followed by the period between 1994-2003, after which we saw a massive decline between 2004-2013. The decline can partly be explained by vaccination uptake (5).

While the WHO report dates back to 1974, a case report from 1941 is the earliest published scholarly piece that provided valuable insights into the existence of diphtheria in Nigeria by isolating and identifying virulent strains of Corynebacterium. Following the 1941 case report, Sadoh & Oladokun (6) published the re-emergence of diphtheria and pertussis. In their opinion, there is a surveillance challenge for Diphtheria in Nigeria, evidenced by the lack of data for a complete decade, as highlighted in the WHO reports. The authors' opinion of a resurgence culminated from the emergence of reports of four cases of diphtheria from Lagos, five from Benin, and ten cases from Katsina state, all between the years 2007-2010, underscoring the need for continuous surveillance and consistent vaccination coverage [6]. Notably, these cases emerged between 2007 and 2017, yet the WHO had no such data.

Following the emergence of diphtheria in Lagos, Benin, and Katsina between 2007-2010, for which Sadoh & Oladokun (6) opined that there was a resurgence, Besa *et al*. (7) reported an outbreak that happened in February 2011 in a village in Borno state. Their retrospective outbreak investigation revealed 98 predominantly children cases and a 21.4% case fatality ratio. They also revealed poor vaccination uptake, as 98% of the cases were never immunized. Goni et al. (8) also reported a 7-year-old child with a diphtheria case in Yobe, northeastern Nigeria. When the world was grappling with Covid-19, Ibrahim *et al*. (9) reported 35 cases of diphtheria managed at the federal medical Center in Katsina, North-western Nigeria, which presented with a 68% case fatality.

The character of the current outbreak suggests a resurgence. Some regions of the country are more vulnerable than others. Specifically, more outbreaks

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with high fatalities have been reported in the Northern part of the country. Reasons for this disparity could be multifactorial. Socioeconomic factors such as poverty, limited access to healthcare services, and inadequate immunization coverage may contribute to these regions' higher susceptibility and severity of diphtheria outbreaks. Factors such as overcrowding, poor sanitation, and limited awareness about preventive measures also play a role.

Spread of Diphtheria in Nigeria as of June 2023.

The first report on the current Diphtheria outbreak in Nigeria was made by the Nigeria Centre for Disease Control and Prevention (NCDC) in December 2020. It was said to be affecting several states. Six months after the first reports, the number of confirmed cases has risen to 798 across 33 local government areas in 8 states, including Kano, Lagos, Yobe, Katsina, Cross River, Kaduna, Osun, and the Federal Capital Territory (FCT). Children between the ages of 2-14 constitute 71.7% of the cases, with 10% case fatality.

Determinants of Diphtheria Outbreak in Nigeria

Low Immunization Coverage

Diphtheria is a vaccine-preventable disease, and the effectiveness of the vaccines, especially in children between 5-9 years, exceeds 75% (10). However, over the years, the World Health Organization and other researchers have pointed to the direction of low vaccine coverage or lack of vaccination as the leading determinant of the Diphtheria outbreak in Nigeria. According to WHO, Nigeria was among the eight countries which did not meet 50% coverage with DTP3 in 2016, alongside Ukraine, Somalia, Chad, Central African Republic, Equatorial Guinea, South Sudan, and the Syrian Arab Republic. By 2019, Nigeria was listed as contributing to the over 60% of children that did not get the DPT vaccine (11). This trend saw a change through 2021, but it was still described as suboptimal, with 57% coverage for a third dose of the vaccine (12). In light of the current outbreak, the 40% case fatality rates associated with settings with poor access to the diphtheria antitoxin corroborates the importance of this vaccine. A "57% coverage for third does of DPT" underscores a clear definition of "low vaccine coverage" and "incomplete vaccination". While the Center for disease control recommends a 5-dose DTaP series, administered at 2, 4, and 6 months, 15 through 18 months, and 4 through 6 years. The widely implemented series is the 3-dose diphtheria-tetanus-pertussis (DTP3) given at 6, 10-14, and 14-18 weeks of age13. With these numbers of doses, all spread across 4-6 apart, the likelihood of incomplete immunization is high. In a study by Eze *et al*. (11), only 55.5% of children in rural communities are fully immunized compared with 94.5% in urban communities. The study further highlighted the determinants of incomplete immunization, including single motherhood, absence of skilled birth attendants during delivery, maternal lack of postnatal care, maternal knowledge of routine immunization, poverty, and distance to health facilities (11). While incomplete immunization may be the best explanation in the Nigerian context, the country also houses over 3 million (14%) of the global 27 million zero-dose or missed-dose children (14). However, the reasons might be similar to those reported by Eze *et al*. (11)

Waning of vaccine-induced immunity

Another potential driver of the outbreak is the waning of vaccine-induced immunity associated with age (6). The working principle of vaccines explains this phenomenon. A vaccine introduces one's body to a weakened or killed version of the bacteria that causes the disease. This part of the bacteria cannot make one sick but is enough to grab the immune system's attention. The immune system now memorizes the features of the bacteria so that if the real bacteria ever enter one's body later, the immune system will recognize it as a threat. After recognizing the vaccine's part, the immune system builds an army of antibodies designed to fight off that specific bacteria. Even after the immune system defeats the fake virus from the vaccine, it keeps some of the trained antibodies ready (15).

While the DPT vaccine has been effective at conferring immunity with over 75% efficacy, a recent meta-analysis has reported the potential of such immunity to wan off and thus recommends a booster dose (16). Waning of vaccine-induced immunity refers to the gradual decrease in the protective effect of a vaccine over time. In the Nigerian context, Cummings et al. (17) recommended vaccinating parturient women with

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booster doses of the diphtheria toxoid vaccine because significant proportions of Nigerian mothers and newborns are at risk of developing diphtheria.

Inadequate Outbreak Surveillance

Poor surveillance systems' role in Nigeria's disease outbreaks cannot be downplayed. According to the WHO, the number of diphtheria cases in the country is under-reported (18). It can be recalled that for the period between 2007 and 2017, the WHO data repository had no data on Diphtheria outbreak yet there were with over 100 cases. Aborode et al. (19) and Agrawal et al. (20), in their letters to the editor, also highlighted the need for an adequate surveillance system for disease outbreaks.

According to the WHO, Diphtheria surveillance entails a regular monthly report detailing probable or confirmed cases and prompt investigation of any outbreaks with thorough case-based data collection. Monitoring the administration of the third dose of diphtheria toxoid-containing vaccine (DPT3) to infants holds significant importance. In regions with low incidence, where coverage typically exceeds 85%–90%, immediate case-based data reporting of probable or confirmed cases is advised, spanning from peripheral to intermediate and central levels.
Given such a vivid standard for diphtheria surveillance provided by the WHO, the question arises: where does Nigeria go wrong in implementing effective surveillance mechanisms? The evidence suggests that there is a need for significant improvements in data collection, reporting accuracy, and a better-coordinated approach to ensure comprehensive outbreak monitoring and control. Addressing these deficiencies would be critical in mitigating the impact of disease outbreaks and protecting public health in Nigeria.

Conclusion

Low immunization coverage and incomplete immunization, exacerbated by lack of awareness, access and distance from health facilities, poor hygiene, and waning vaccine-induced immunity, are significant drivers of the current outbreak. There is a need to address this public health concern; promoting vaccine coverage and implementing comprehensive surveillance efforts are crucial for preventing further occurrence in Nigeria. Also, increased scholarly articles and the adoption of scholarly recommendations are invaluable.

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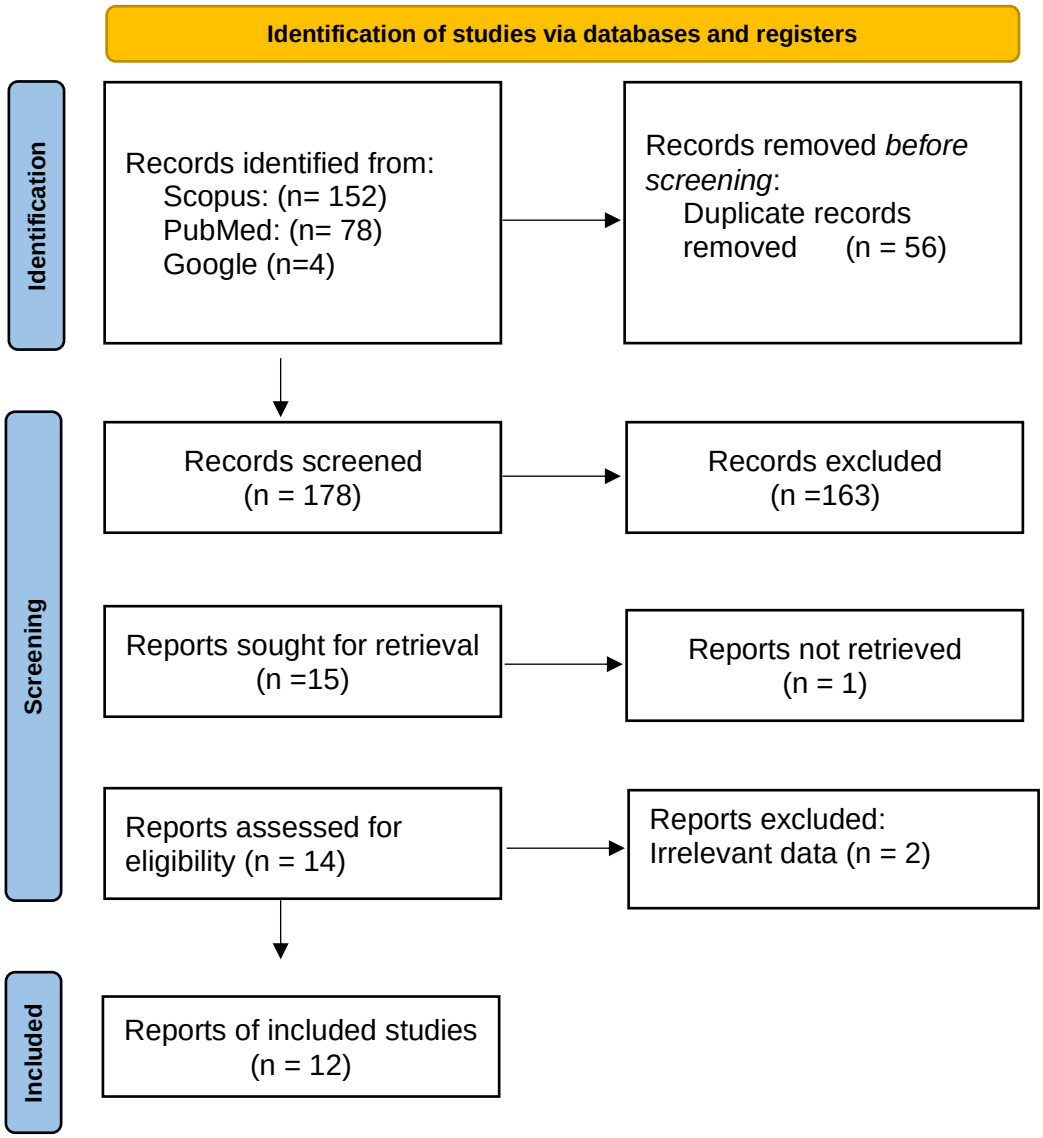

Figure 1: Study Selection Framework. **Source** (21)

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Table 1: Scholarly Publications Reporting Outbreaks of Diphtheria in Nigeria

Authors	Title	Year	Article Type
Goni et al. (8)	Diphtheria in a 7-year-old child in northeastern Nigeria – management in a resource-poor setting	2014	Case Report
Gulumbe et al. (22)	The outbreak of meningitis amidst Lassa fever and diphtheria crisis in Nigeria: An urgent call for action	2023	Letter to Editor
Aborode et al. (19)	The resurgence of a diphtheria outbreak in Nigeria	2023	Letter to Editor
Besa et al.(7)	Diphtheria Outbreak with high mortality in Northeastern Nigeria	2013	Article
Agrawal et al. (20)	"Nigeria on alert: Diphtheria outbreaks require urgent action" - A critical look at the current situation and potential solutions	2023	Letter to Editor
Adegboye et al. (23)	A resurgence and re-emergence of diphtheria in Nigeria, 2023	2023	Letter to Editor
Elmes (24)	The isolation of virulent strains of Corynebacterium diphtheriae in Nigeria	1941	Case Report
Sadoh & Oladokun (6)	Re-emergence of diphtheria and pertussis: Implications for Nigeria	2012	Review
Gulumbe et al.(12)	Diphtheria outbreak in Nigeria: What do we know so far?	2023	Letter to Editor
Shariff et al.(2)	Diphtheria outbreak in Nigeria: Lessons from the past for the challenges ahead	2023	Editorial
Adepoju(25)	An Epidemic in the Making: The Urgent Need to Address the Diphtheria Outbreak in Nigeria	2023	Letter to Editor
Ibrahim et al. (9)	Diphtheria outbreak during Covid-19 pandemic in Katsina, North-Western Nigeria: Epidemiological characteristics and predictors of death	2022	Article

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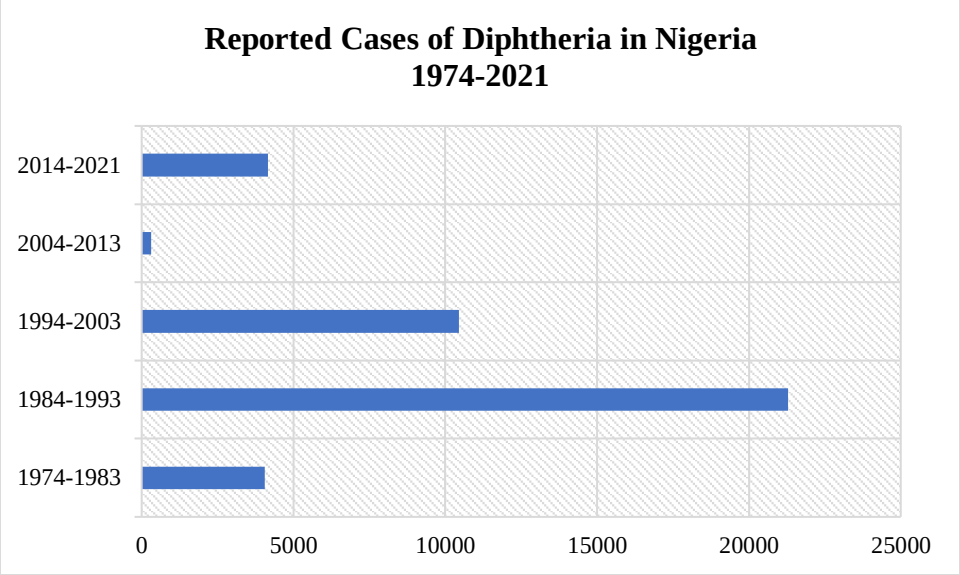

Figure 2: Cases of Diphtheria Outbreak in Nigeria from 1974-2021 *Source: (5)

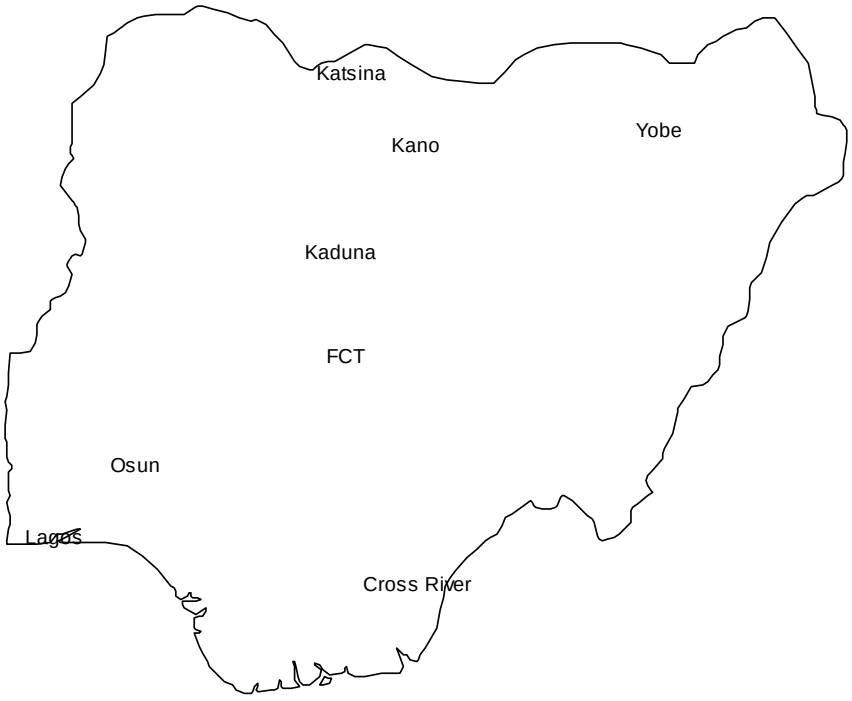

Figure 3. Nigerian States Affected by the Current Diphtheria Outbreak

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