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Review Article **Open Access**

A review of the current diphtheria outbreaks

[1]Medugu, N., [2]Musa-Booth, T. O., [*1]Adegboro, B., [3]Onipede, A. O., [4]Babazhitsu, M., and [5]Amaza, R.

[1]Department of Medical Microbiology and Immunology, Nile University of Nigeria, Abuja, Nigeria
[2]1928 Woodlawn Drive, Woodlawn, Maryland 21207, USA
[3]Department of Medical Microbiology and Parasitology, Faculty of Health Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria
[4]Department of Medical Microbiology and Parasitology, Faculty of Basic Clinical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria
[5]Nigeria Center for Disease Control (NCDC), Jabi, Abuja, Nigeria
[*]Correspondence to: boazadegboro@gmail.com; boaz.adegboro@nileuniverity.edu.ng

Abstract:

Corynebacterium diphtheriae is responsible for both endemic and epidemic diphtheria. The predisposing factor for this disease is the failure to immunize during childhood. Humans are the only hosts of the organism and is present in the upper respiratory tract. The organism is transmitted via airborne route and can cause respiratory obstruction and heart failure because of the exotoxin it produces. There is presently a resurgence of diphtheria outbreaks in Nigeria. The Nigeria Center for Disease Control (NCDC) was notified of suspected diphtheria outbreaks in Lagos and Kano States, Nigeria, in December 2022 and has been issuing monthly reports since that time. This review of the diphtheria outbreaks following online database searches on PubMed and Google Scholar as well as the NCDC/WHO websites and grey literatures, describes the current trend of the outbreaks globally, elucidated the different strains of *Corynebacterium* responsible for the outbreaks, identified the recent vaccine formulation developed to tackle the outbreaks, and provide information on vaccine delivery and efficacy studies in the country and globally.

Keywords: Corynebacteria; outbreaks; DPT; immunization coverage

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Un examen des épidémies actuelles de diphtérie

[1]Medugu, N., [2]Musa-Booth, T. O., [*1]Adegboro, B., [3]Onipede, A. O., [4]Babazhitsu, B., et [5]Amaza, R.

[1]Département de Microbiologie Médicale et d'Immunologie, Université du Nil du Nigéria, Abuja, Nigéria
[2]1928 Conduire Woodland, Woodland, Maryland 21207, États-Unis
[3]Département de Microbiologie Médicale et de Parasitologie, Faculté des Sciences de la Santé, Université Obafemi Awolowo, Ile-Ife, Nigeria
[4]Département de Microbiologie Médicale et de Parasitologie, Faculté des Sciences Cliniques Fondamentales, Collège des Sciences de la Santé, Université Usmanu Danfodiyo, Sokoto, Nigéria
[5]Centre Nigérian de Contrôle des Maladies (NCDC), Jabi, Abuja, Nigéria
*Correspondance à: boazadegboro@gmail.com; boaz.adegboro@nileuniverity.edu.ng

Résumé:

Corynebacterium diphtheriae est responsable à la fois de la diphtérie endémique et épidémique. Le facteur prédisposant à cette maladie est l'absence de vaccination pendant l'enfance. Les humains sont les seuls hôtes de l'organisme et sont présents dans les voies respiratoires supérieures. L'organisme est transmis par voie aérienne et peut provoquer une obstruction respiratoire et une insuffisance cardiaque en raison de l'exotoxine qu'il produit. Il y a actuellement une recrudescence des épidémies de diphtérie au Nigeria. Le Centre Nigérian de Contrôle des Maladies (NCDC) a été informé des épidémies présumées de diphtérie dans les États de Lagos et de Kano, au Nigéria, en décembre 2022 et publie depuis lors des rapports mensuels. Cet examen des épidémies de diphtérie à la suite de recherches dans les bases de données en ligne sur PubMed et Google Scholar ainsi que sur les sites Web et les littératures grises du NCDC/OMS, décrit la tendance actuelle des épidémies dans le monde, a élucidé les différentes souches de *Corynebacterium* responsables des épidémies, identifié les récentes la formulation de vaccins développée pour lutter contre les épidémies et fournir des informations sur l'administration des vaccins et les études d'efficacité dans le pays et dans le monde.

Mots clés: Corynébactéries; les épidémies; TPD; couverture vaccinale

Introduction:

Corynebacteria are aerobic Gram-positive non-encapsulated, non-sporulating, and non-motile, pleomorphic granular rods, arranged in palisades. Many non-pathogenic species are members of the indigenous flora of the skin, oropharynx, urogenital and intestinal tracts where they are collectively known as diphtheroids (1). They produce polyphosphate volutin (metachromatic) granules, which stain red with Albert or methylene blue stain. The most pathogenic species, *Corynebacterium diphtheriae* has three strains identifiable on tellurite agar; the gravis (3-5m), mitis 2-4 mm and intermedius (1-2mm) strains. The gravis strain produces frosted metallic grey colonies with strained margins ("daisy head" colonies). On blood agar, some gravis and mitis strains are haemolytic, while the intermedius strain is non-haemolytic (1,2).

Corynebacterium diphtheriae produce diphtheria toxin, which is a lethal exotoxin produced under the influence of a temperate bacteriophage. The exotoxin is a heat-labile coagulable protein sensitive to denaturation by solutions at pH < 6, and by moderate heat. The addition of formalin will turn the toxin into a toxoid which is highly immunogenic (1,2). Only three *Corynebacterium* species (*C. diphtheriae, C. pseudotuberculosis*, and *C. ulcerans*) are known to produce the lethal exotoxin called diphtheria toxin. The diphtheria toxin gene (*tox*) is donated by corynebacteriophages and are produced by the bacteria through lysogenisation, which allows the corynephage carrying the *tox* gene to be stably integrated into the chromosome (2). During the diphtheria epidemic in Eastern Europe in the 1990s, a new strain called non-toxigenic *tox* gene-bearing (NTTB) strain, was identified (2,3). They however did not express the gene protein, but are believed to be potentially toxigenic. It is therefore possible that the new resurgent outbreaks of diphtheria in different parts of the world could be due to these NTTB strains of *C. diphtheriae*.

The clinical spectrum of infection includes nasal diphtheria, anterior nasal diphtheria, "bull-neck" diphtheria, severe pharyngeal diphtheria, laryngeal diphtheria, tracheabronchitis and cutaneous diphtheria (1). The manifestations of *C. diphtheriae* infection are influenced by the anatomic site of infection, the immune status of the host, and the production and systemic distribution of toxin (4). Diphtheria toxin is easily absorbed in the surrounding tissues of the patient's throat, where it induces local inflammatory reaction in the nasopharynx and larynx. There is a serocellular exudate which forms a grayish membrane across the larynx, causing severe acute respiratory obstruction.

Corynebacterium diphtheriae is responsible for both endemic and epidemic diseases, and is communicable for 2-6 weeks without antibiotic treatment (4). The predisposing factor for this disease is the failure to immunize during childhood. Humans are the only hosts of the organism and are present in the upper respiratory tract. The organisms are transmitted via airborne droplets (4,5). Blockage of the recurrent laryngeal nerve by exotoxin is an important part of the pathogenesis of diphtheria because it leads to respiratory failure. The toxin also blocks the bundle of His, leading to atrio-ventricular block and heart failure. Patients could quickly die from acute respiratory obstruction, and/or heart failure (1, 4,5).

There is presently a resurgence of diphtheria outbreaks in Nigeria. The Nigeria Center for Disease Control (NCDC) was notified of suspected diphtheria outbreaks in Kano and Lagos States on December 1, 2022. From January to March 2023, the NCDC reported a total of 733 suspected cases, including 89 deaths, with children between the ages of 5 and 18 years mostly afflicted, with overall case fatality rate (CFR) of 12.3%. There have been reports that *Corynebacterium ulcerans* and some other species are now capable of elucidating exotoxin (2,6).

The aims of this review therefore are to; (i) provide information on the epidemiology and current trend of diphtheria outbreaks globally and in Nigeria; (ii) elucidate the different strains of *Corynebacterium* responsible for the outbreaks; (iii) describe the response and identify the recent vaccines developed to tackle the outbreaks; (iv) provide information on diphtheria, pertussis and tetanus (DPT) vaccine delivery and DPT efficacy studies in the country; and (v) to suggest recommendations on how the current diphtheria outbreaks can be speedily controlled.

Methodology and Results:

Electronic databases including PubMed and Google Scholar were searched for primary source articles including original reports, case series studies, case reports, seroprevalence studies and epidemiologic investigation reports on diphtheria in Nigeria from 2015 to 2023. The websites of the NCDC and World Health Organization (WHO), including other grey literatures, were equally searched for information relevant to diphtheria outbreaks. Secondary search was also conducted using references of primary articles reviewed.

Inclusion criteria for selecting studies for the review were studies that provided information on strains of *C. diphtheria* responsible for outbreaks, recent diphtheria vaccines developed, DPT vaccine delivery, and DPT effi-

cacy studies in Nigeria. Search words used include "diphtheria" AND/OR "*Corynebacterium diphtheria*" AND/OR "*C. diphtheria*" AND "diphtheria outbreak in Nigeria" AND "*C. diphtheria* vaccine" AND/OR "DPT vaccine" AND "DPT vaccine delivery" AND "DPT efficacy". Publications on systematic and narrative reviews on diphtheria were excluded.

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guide, initial search produced 2240 articles from Google Scholar and 1139 articles from PubMed. Following de-duplication, 495 article titles and abstracts were screened, followed by assessment of 70 full articles to determine eligibility, and 53 articles were further excluded. Following primary and secondary searches, 23 articles were included (17 from primary search and 6 from secondary search), in addition to 16 publications from the grey literatures (Fig 1).

Discussion:

Global epidemiology of diphtheria:

According to the WHO data, there has been a gradual rise in the global diphtheria cases from 4,535 in 2015 to almost 23,000 in 2019. There was a decline in reported cases in 2020 (10,137 cases) possibly due to the COVID-19 pandemic but the downward trend continued in 2021 with just over 8,500 cases reported (5). Ethiopia accounts for the highest number of cases with over 50% of reported cases. Other countries with a high number of cases include India, Nigeria and Yemen (7). The incidence rate in recent times was lowest in 2015 at 0.7/1,000,000 population and highest in 2019 at 3.4/1,000,000 population. The incidence rate currently stands at 1.3/1,000,000 population (7).

Global diphtheria mortality rate has been reported to range between 5-10% with vaccination coverage being a major determinant of mortality rate. Children under five years and adults above 40 years may have higher death rates, which can be as high as 20% (8). Diphtheria is known as a childhood disease, most common in children below 15 years, but with waning immunity and increase in unvaccinated individuals in countries with low diphtheria prevalence, there has been an increase in case detection among people above 40 years (5). Diphtheria is not associated with any race. Incidence is similar in both males and females, with some studies showing higher incidence in males below 15 years and adult females over 40 years (9). Mortality may be higher among females in endemic regions as vaccination is higher in male children in these regions.

Global DPT 1st dose vaccine coverage has remained high. It increased by 1% in 2016 and reached its peak coverage of 90% where it remained till 2020 when it declined by 3% and by 2021, it declined to 86%. DPT 3rd dose coverage also followed a similar trend from 86% in 2016 down by 3% in 2020 and at 81% in 2021 (10).

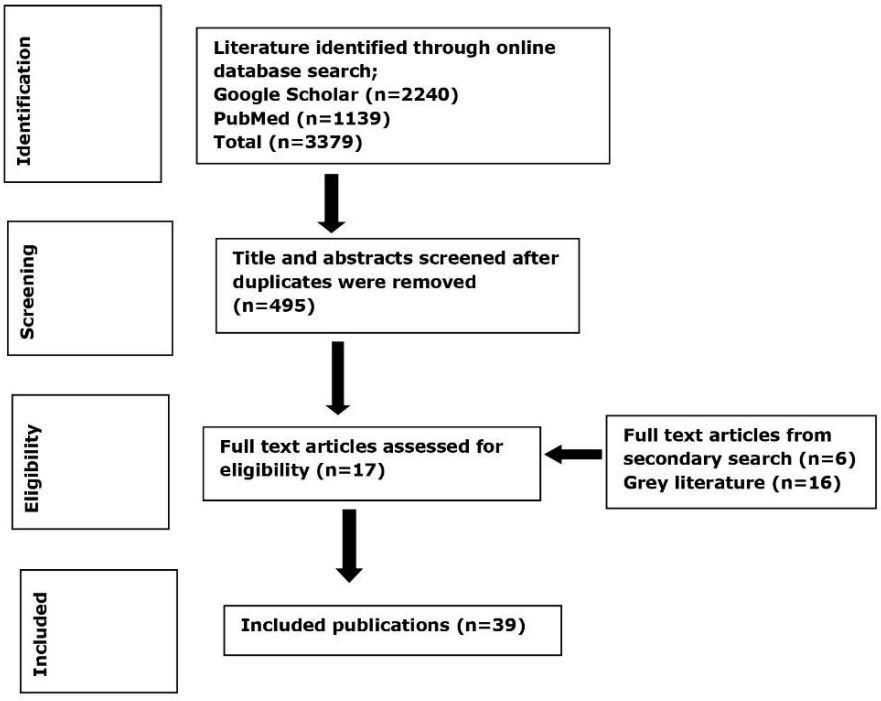


Fig 1: Process of selection of publications (PRISMA guide) used for the review

Epidemiology of diphtheria in Nigeria from 2015 to 2023:

The diphtheria outbreak in Nigeria in 2023 has been concerning, with 216 reported cases and 40 deaths across four States as of February 2023 (11). The outbreak is believed to have started in late December in Kano State, but cases have also been reported in Lagos, Osun, and Yobe States (12-15). Reports had Kano with 172 of 216 cases (91.0%), Katsina with 9 cases (4.8%), and Lagos with 8 cases (4.2%). Among the suspected cases that were reported, 111 cases, accounting for 42.1% of the total, were confirmed. Out of these confirmed cases, 8 were confirmed through laboratory testing, while 103 were determined to be clinically compatible with the disease. Additionally, 18 cases (7.1%) were discarded as not being related to the disease, while 40 cases (15.3%) are pending classification, and 84 cases (33.2%) had unknown status.

Notably, the majority of confirmed cases (91.9%) occurred in the age group of 2 to 14 years. Sadly, a total of 22 deaths were recorded among the confirmed cases, resulting in a case fatality rate (CFR) of 19.8%. It is concerning to note that only 12 out of the 111 confirmed cases (10.8%) had received full vaccination with a diphtheria toxin-containing vaccine (11,15). All confirmed cases were reported from nine local government areas (LGAs) in Kano State, and four deaths were recorded among these confirmed cases, resulting in CFR of 7.4% (11,13,14).

There were no reported cases of diphtheria in 2022 although in general, data are sparse with many years not having records of diphtheria officially reported (7). According to the NCDC, there were 160 reported cases of diphtheria in Nigeria in 2021. Most of the cases were reported in the northern part of the country, with Kano, Bauchi, and Yobe States having the highest number of cases. Other States with reported cases include Borno, Gombe, Jigawa, Kaduna, Katsina, Kebbi, Sokoto, and Zamfara (11,16,17). In Kano State, majority of the cases were reported in the Kumbotso, Gwale, and Tarauni LGAs. In Bauchi State, majority of the cases were reported from Bauchi, Ganjuwa, and Tafawa Balewa LGAs, and in Yobe State, majority of cases were reported from Damaturu, Fika, and Potiskum LGAs.

In 2020, there were 245 reported cases from 25 States of the country (11,18), the highest number of cases were reported in the northwest region of Nigeria, with Katsina and Kano States recording the highest number of cases. Other States with significant number of cases included Jigawa, Sokoto, and Zamfara. However, cases were reported across the country, including the southern States.

In 2019, a total of 2,289 cases were reported, of which 157 were confirmed (11, 18). The outbreak was reported in 24 States in the country, with the highest number of cases reported in Kano (41 cases) followed by Zamfara (33 cases). Other affected States in 2019 included Kaduna, Plateau, Bauchi, Jigawa, and Lagos, among others. At the LGA level, 80 LGAs in the affected States reported cases of diphtheria.

In 2018, Nigeria experienced a large outbreak of diphtheria, with a total of 1,870 suspected cases reported (7). Of these, 176 were confirmed, and 22 were fatal. The outbreak was mainly concentrated in four States; Adamawa, Bauchi, Borno, and Kano, which accounted for more than 80% of the total suspected cases. The outbreak affected several LGAs, including Gombi, Yola North, Yola South, Jama'are, Katagum, and Damban in Bauchi State; Jere, Konduga, Maiduguri Metropolitan, and Mafa in Borno State; Nasarawa, Tarauni, and Kano Municipal in Kano State; and Song in Adamawa State.

In 2017, there were 782 suspected cases of diphtheria reported in Nigeria, with 213 confirmed cases and 22 deaths. Reports were from 24 of the 36 States of the Federation (11,19), with the highest number of cases reported in Kano State, accounting for 36% of the confirmed cases. A total of 80 LGAs were affected with the highest number reported in Kano Municipal LGA, followed by Gwale LGA, Tarauni LGA, and Dala LGA.

In 2016, there were 29 confirmed cases of diphtheria reported, a significant increase from the 12 cases reported in the previous year. The cases were reported from 11 States across the country including Bauchi, Borno, Kano, Katsina, Sokoto, Yobe, Zamfara, Delta, Ebonyi, Enugu, and Rivers. Bauchi State had the highest number of reported cases (10 cases), followed by Kano State (6 cases). The cases were reported from 16 LGAs across the 11 States, with the highest number of cases reported from Bauchi LGA (6 cases), followed by Kano Municipal LGA (4 cases).

In 2015, there were 5,959 suspected cases of diphtheria with a case fatality rate of 7.5% (7). The outbreaks were reported in 16 States of the country, with the highest number of cases recorded in Kebbi, Sokoto, and Zamfara States. The other States include Bauchi, Borno, Gombe, Jigawa, Kaduna, Kano, Katsina, Nasarawa, Niger, Plateau, Taraba, Yobe, and the Federal Capital Territory. The outbreaks occurred in several local government areas in the affected States. The overall cases reported by Nigeria officially to the WHO are shown in Table 1.

Case fatality rate of diphtheria in Nigeria:

The CFR for diphtheria in Nigeria has shown significant variability in recent years (20). In 2016, there were four reported deaths,

Table 1: Diphtheria cases in Nigeria reported to the World Health Organization

Period	Diphtheria cases reported to WHO by Nigeria
2015-2019	4159
2010-2014	0
2005-2009	312
2000-2004	7253
1995-1999	2724
1990-1994	9479
1985-1989	11551
1980-1984	2144
1975-1979	2144
1970-1974	129
Total	**39895**

with a CFR of 13.8%. The CFR decreased in 2017 to 10.3%, although males were slightly more affected, accounting for 54% of the confirmed cases. In 2018, out of the 2,360 suspected cases, 22 were fatal, resulting in a CFR of 0.93%. However, in 2019, the number of deaths increased significantly to 21, with a CFR of 13.4%. In 2020, CFR was not reported, while in 2021, it was reported as 5%. These trends suggest that while efforts to combat diphtheria in Nigeria have been effective in reducing the CFR, there is still a need for continued vigilance to prevent and manage outbreaks. Fig 2 shows the CFR trend over this period.

Age group and gender distribution of diphtheria in Nigeria:

The diphtheria trend in 2020 and 2021 showed that the highest number of reported diphtheria cases in Nigeria occurred in children under 15 years of age, with the most affected age group being children between 5 and 14 years, accounting for 54% of the reported cases. In 2019, the age distribution of confirmed cases showed that 61% were between the ages of 5 and 14 years, followed by those aged 15-24 years, which accounted for 23% of the cases.

There was equal distribution of diphtheria cases among both sexes in 2020 and 2021. In 2019, however, males accounted for the majority (56%) of reported cases (18). Similarly, in 2018, a slightly higher proportion of males (53%) were affected compared to females (47%). In 2015, there was a slightly higher number of diphtheria cases reported among males compared to females. Fig 3 shows the general trend as reported by WHO for diphtheria cases in Nigeria.

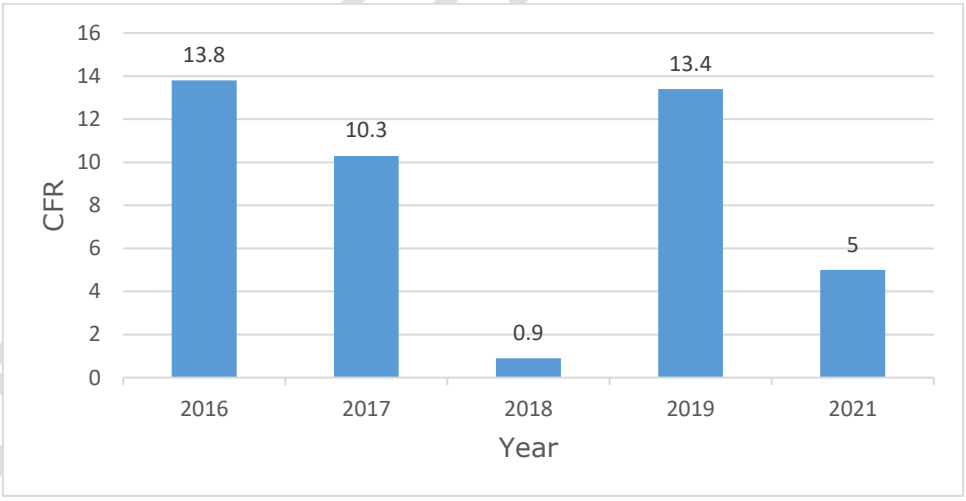


Fig 2: Case fatality rate (CFR) of diphtheria in Nigeria over 5 years

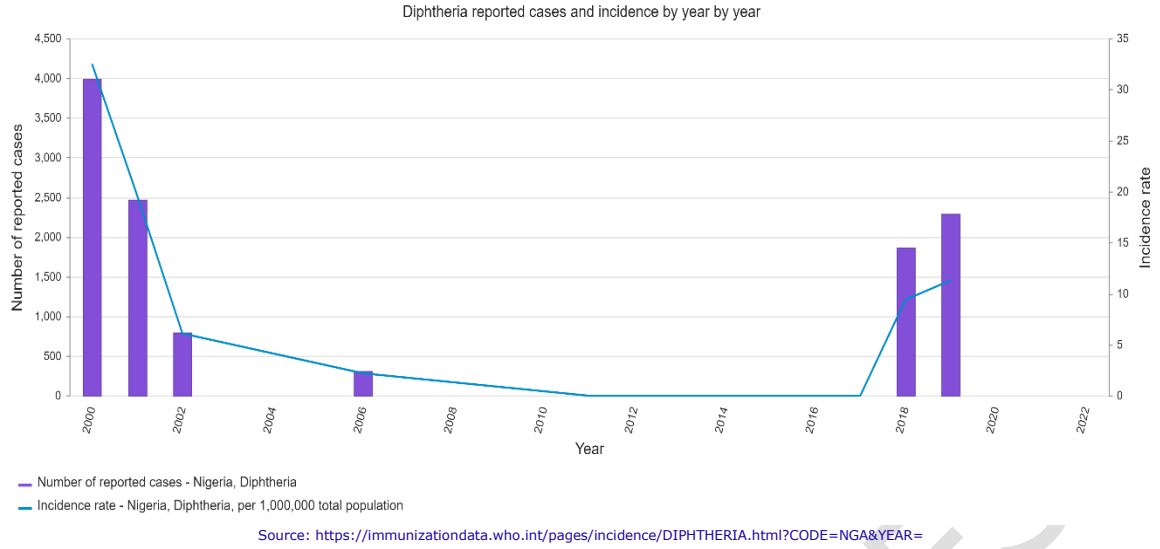


Fig 3: Trend of diphtheria cases in Nigeria as reported to the World Health Organization

Laboratory diagnosis and strains of corynebacteria responsible for the outbreaks:

In general, advancements in laboratory diagnostics have revolutionized the diagnosis of diphtheria. Serological diagnosis, utilizing the detection of specific antibodies in the patient's blood serum against the diphtheria toxin, remains a critical tool in confirming cases, assessing immune status, and monitoring vaccine effectiveness especially in low-and-middle-income-countries (LMICs) because of its relatively lower cost. The classic Elek test is one such method, known for its simplicity, affordability, and suitability for resource-limited settings, it has been widely utilized for serological diagnosis (21). It does have the limitation of only being useful for diagnosis and not strain typing. However, newer serological methods such as enzyme-linked immunosorbent assay (ELISA) have emerged, offering improved sensitivity and specificity (22,23).

The biochemical differentiation of *C. diphtheriae* strains into biovars have been relegated to historical significance only due to its lack of reliability, low reproducibility, false-negative results due to variations in biological expression, and its moderate to high complexity (24). In addition to serological methods, various molecular genotyping methods such as ribotyping, amplified fragment length polymorphism (AFLP) or random amplified polymorphic DNA (RAPD), pulse-field gel electrophoresis (PFGE), clustered regularly interspaced short palindromic repeat (CRISPR)-based spoligotyping, and multilocus sequence typing (MLST), have been utilized to investigate the molecular epidemiology and diversity of *C. diphtheriae* (25,26).

In particular, the MLST scheme has shown clinical correlation with severity of disease with most of the >300 strains identified up to date being clinically and epidemiologically relevant (26,27). The MLST strains causing outbreaks are largely country specific with the only literature report from Africa being the MLST ST-375 which caused the diphtheria epidemic of 2015 in South Africa (28).

The molecular approach provides valuable insights into the genetic characteristics and population dynamics of the bacterium, allowing for a better understanding of its transmission patterns, evolution, and spread in different populations and geographic regions (22). Of these advanced methods, PCR is the most available in developing economies. PCR allows for rapid and highly sensitive detection of *C. diphtheriae* and its toxin gene, enabling faster turnaround times and more accurate identification of toxigenic strains. Other cutting-edge technologies like whole-genome sequencing and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry have been used in limited settings but have also shown promise in enhancing the accuracy and speed of diphtheria diagnosis (29).

A relatively new *C. diphtheriae* strain called non-toxigenic tox gene-bearing (NTTB) strain, has been identified (30). Molecular characterization of the NTTB strain revealed that it carries the *tox* gene, which traditionally encodes for the diphtheria toxin, but lacks the ability to produce the toxin. These strains are genotypically *tox*-positive but do not express the toxin. However, the level of their involvement in current outbreaks has not yet been investigated. The significance of the NTTB strain has been highlighted in numerous reported cases, and its epidemic potential even in countries with high vaccination rates has been well-documented (30). While there is at yet no reported NTTB strain in West-Africa, the strain has been linked to severe clinical manifesta-

tions, including myocarditis, polyneuritis, and bacteraemia (30). The MLST-212 has been one of the more common NTTB strains reported globally (31).

Surveillance data have shown that the NTTB strains have been identified in both toxigenic and non-toxigenic strains, and its presence has been associated with variable clinical manifestations (5). While traditionally diphtheria cases present with respiratory symptoms, including sore throat, difficulty breathing, and hoarseness, cases caused by the NTTB strain have shown a wider spectrum of clinical presentations, ranging from mild respiratory symptoms to severe systemic manifestations, including myocarditis and neuritis (31,32). This has therefore posed challenges in clinical diagnosis and management of diphtheria caused by the NTTB strain.

Limited data suggest that similar risk factors associated with diphtheria outbreaks caused by toxigenic strains, such as low vaccination coverage, poor sanitation and hygiene practices, overcrowded living conditions, and limited access to healthcare services, may also play significant roles in the transmission of the NTTB strains (5). However, further research is needed to better understand the unique epidemiology and risk factors associated with this strain. The advancements in laboratory diagnostics play a pivotal role in confirming diphtheria cases, identifying outbreaks, monitoring vaccine effectiveness, and guiding timely intervention strategies to prevent the spread of diphtheria. They offer improved accuracy, efficiency, and rapidity, empowering healthcare providers to promptly diagnose and manage diphtheria cases, and ultimately contribute to better patient outcomes.

However, there continue to be gaps in laboratory confirmation of diphtheria as well as other diseases of public health importance in Africa. These gaps include limited laboratory capacity to determine toxigenicity, challenges in availability of culture media, and difficulties in accessing diphtheria antitoxin. As a result, only a limited number of African countries report national, case-based surveillance for diphtheria with laboratory confirmation, indicating the need for increased laboratory capacity to effectively detect and manage diphtheria outbreaks in the region.

Response to diphtheria outbreaks:

The NCDC, Primary Health Care Development Agency (PHCDA), and WHO collaborated to respond to the 2019 diphtheria outbreak in Nigeria. They provided technical support for case management, laboratory testing, and active surveillance, while also improving routine immunization coverage and surveillance systems. In addition, they conducted public awareness campaigns to educate the populace about the disease and the importance of vaccination. While the response helped control the outbreak, sustained efforts are needed to improve routine immunization coverage and disease surveillance in Nigeria. The NCDC is supporting States in increasing diagnostic capacity and supply of antitoxins for the treatment of diphtheria.

Diphtheria vaccine delivery and coverage:

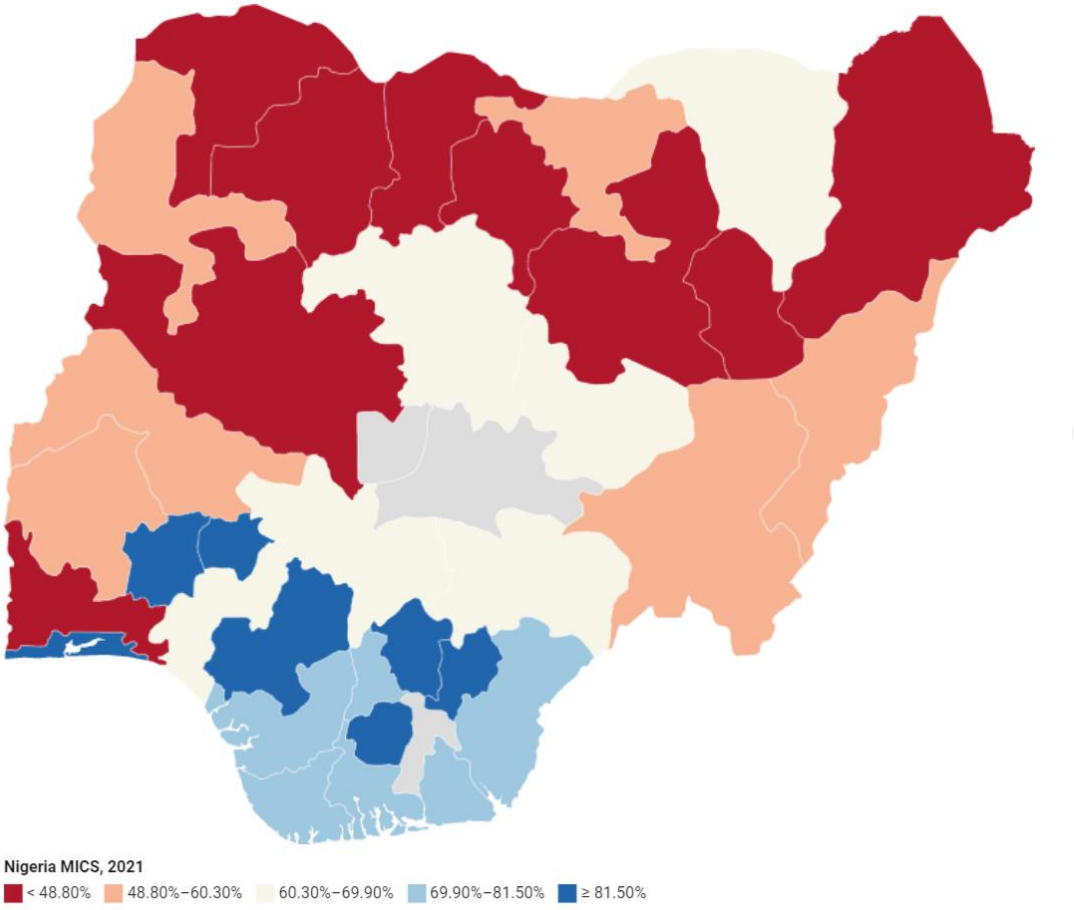
According to recent data, immunization rate for diphtheria was reported to be lowest in the northeast region of Nigeria, with only 41.7% of children receiving the vaccine. In the northwest region, the rate was slightly higher at 42.9%, while the north-central region had the highest rate at 57.2%. When considering urban versus rural areas, a higher percentage of children living in urban areas (72.7%) had received the third dose of the diphtheria, pertussis, and tetanus (DPT) vaccine compared to those in rural areas (47.5%). Additionally, vaccination rates were found to be higher (88.9%) among children whose mothers had higher or tertiary education compared to those whose mothers had no education (36.2%). In terms of household income, the data showed that diphtheria vaccination rates were higher (84.6%) among children from households considered to be rich compared to those in the poor households (38.7%). Fig 4 shows the vaccination coverage rates of diphtheria in Nigeria.

Efficacy studies on diphtheria vaccine platform in Nigeria and globally:

The pentavalent (D, P, T, Hib, HepB) vaccine is now replacing the DPT vaccine in Nigeria and indeed, globally. The DPT and pentavalent vaccines have demonstrated equal efficacy in inducing IgG antibodies in vaccinated children (33,34). The pentavalent vaccine has been shown to be as effective as the previous individual DPT, Hib, and HepB, with associated fewer injections and similar tolerability (35,36). A meta-analysis by Truelove et al., (37) reported that receiving a full vaccination of at least three doses of the DTP vaccine is associated with 87% effectiveness in preventing symptomatic diphtheria.

On the other hand, they demonstrated that incomplete vaccination with just one or two doses is still associated with 71% effectiveness in preventing symptomatic disease (37). Very importantly, they demonstrated that full vaccination provided 93% protection against death and partial vaccination provided 68% protection against death (37). These findings highlight the importance of completing the recommended vaccination schedule to maximize protection against diphtheria and safeguard against its harmful effects.

Administering diphtheria antitoxin after



Source: https://africacheck.org/fact-checks/factsheets/factsheet-what-you-should-know-about-diphtheria-outbreak-nigeria

Fig 4: Diphtheria vaccination coverage rate (%) of Nigerian children aged 12–23 months by geographical regions of Nigeria

infection has been shown to significantly reduce mortality by 76%. However, it is important to note that the effectiveness of the antitoxin depends on prompt administration, as it only neutralizes circulating and not intracellular toxin. Delay in administering the antitoxin can have serious consequences, as mortality rate doubles with each day of delay (37), underscoring the critical importance of timely intervention to prevent adverse outcomes in diphtheria cases. The efforts towards ensuring zero missed dose of childhood vaccinations in Nigeria have been largely successful although there are still significant gaps especially in northern Nigeria where the overall vaccination rates are lowest (38,39).

Recommendations for control of diphtheria outbreaks:

Ensuring that laboratories have the necessary resources and capabilities for diagnosis of diphtheria is of utmost importance. Laboratory testing plays a critical role in confirming cases of suspected diphtheria, tracking the circulation of toxin-producing strains, and evaluating the effectiveness of vaccines. The availability and functionality of reliable laboratory surveillance system in place enables generation of timely and reliable data to make informed decision for appropriate treatment, and implementation of public health interventions. It is therefore vital to prioritize and invest in strengthening laboratory diagnostics for diphtheria, ensuring that laboratories have the necessary tools and support to effectively contribute to diphtheria control and prevention efforts.

We recommend that pentavalent (DPT, HiB and HepB) vaccine be continued as the primary childhood vaccination schedule for diphtheria in Nigeria, and in other priority settings where diphtheria is a public health issue. The advantages of the pentavalent vaccine, such as immune-protection, fewer injections and similar tolerability, can potentially help to streamline the vaccination process and increase vaccine coverage, leading to better protection against diphtheria. Furthermore, the importance of completing the full vaccination schedule for diphtheria cannot be over emphasized. Full vaccination provides higher protec-

tion against symptomatic diphtheria and its complications compared to partial vaccination. Thus, healthcare providers and policy makers should prioritize efforts to ensure that children receive the full complement of diphtheria-containing vaccines according to the recommended schedule, and address any barrier to completion.

In addition, timely administration of diphtheria antitoxin is crucial in cases of suspected or confirmed diphtheria. Healthcare providers should be educated about the importance of early recognition of diphtheria symptoms and immediate administration of antitoxin to neutralize the circulating toxin and prevent severe outcomes. Strengthening the healthcare system to ensure availability of diphtheria antitoxin and improving surveillance and reporting of diphtheria cases can aid in timely intervention and reduce mortality associated with diphtheria.

Finally, continued research are essential in guiding vaccination policies and strategies. Regular monitoring of diphtheria epidemiology, vaccine coverage and effectiveness can provide valuable insights. Further research can also assess the long-term impact of pentavalent vaccine implementation on diphtheria incidence, evaluate vaccine safety and effectiveness in different populations, and identify strategies to improve vaccine uptake and completion rates.

Contributions of authors:

AB conceived the review, designed the outline, wrote the introduction, efficacy of vaccines and recommendations, and reviewed and edited the manuscript; AO reviewed articles, wrote the introduction, and reviewed the drafts; TMB reviewed articles, wrote the global diphtheria and reviewed the manuscript; MN wrote the epidemiology of diphtheria in Nigeria, strains of diphtheria, and vaccine coverage, and reviewed the manuscript; MB reviewed the manuscript; and AR supplied some data from NCDC.

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