Re-emergence of diphtheria and pertussis: Implications for Nigeria

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Abstract

In the prevaccine era pertussis and diphtheria were responsible for significant morbidity and mortality in children. In the United States of America more than 125,000 cases of diphtheria with 10,000 deaths were reported annually in the 1920s. In the same period about 1.7 million cases of pertussis with 73,000 deaths were also reported. Vaccination against these two diseases has caused remarkable reduction in the morbidity and mortality from these diseases both in developed and developing countries. The initial vaccines were the combined diphtheria toxoid and whole cell pertussis vaccine.

The recent reported increases in the incidence of these two diseases in countries which maintain high childhood vaccination coverage is a source of concern not only to these countries but also for developing countries with weak immunization programmes. Nigeria for example reported 11,281 cases of pertussis, the second highest number of cases worldwide in 2009.

Waning immunity in adult and adolescent populations has been reported and epidemiologically, more cases are being reported in adults and adolescents. Also a high proportion of pertussis cases are being reported in infants and most of these infant cases are linked to adult/adolescent sources.

Recent approaches to control of these diseases include booster doses of combined diphtheria, tetanus and acellular pertussis vaccine while the cocooning strategy (which is immunizing every person who is likely to have contact with a given infant such as mother, father, grandparents and health care workers) is being used in a number of countries.

For developing countries including Nigeria where the capacity for making the diagnosis of both diseases is limited, strengthening of routine immunization as well as diagnostic capacity is imperative. Research to determine current levels of immunity in children, adolescents and adults is required. This will enable the determination of the need for booster doses and the age at which such boosters should be administered. Improved surveillance will be needed to delineate current epidemiological profiles of both diseases.

1. Introduction

Diphtheria and pertussis are two vaccine preventable infectious diseases, which caused a lot of morbidity and mortality among children aged below 14 years in the pre-vaccine era in industrialized countries [1,2]. In the United States, more than 125,000 cases of diphtheria with 10,000 deaths were reported annually in the 1920s [3]. In England and Wales, diphtheria was second only to pneumonia among all causes of death in children with an annual death rate of 32 per 100,000 in children younger than 15 years [1]. Approximately 1.7 million cases of pertussis were reported in the United States between 1922 and 1931 of which 73,000 deaths occurred [4]. With the introduction of vaccines against these two diseases their incidence reduced and also did mortality attributable to them [2,5]. The incidence of pertussis reduced by 99% in the United States while diphtheria reduced to 0–5 per year [3,6]. The initial vaccines were the whole cell pertussis vaccine combined with diphtheria and tetanus toxoid, which was recommended in the 1940s [7]. Acellular pertussis vaccine became the preferred vaccine in the 1990s because they were less reactogenic and were not associated with neurologic complications as was observed with the whole cell pertussis vaccines [7].

In recent years there have been reports of increasing morbidity and mortality from these two diseases in countries with very high vaccination coverage and where the diseases had been under control. Epidemics of diphtheria have been reported from the Newly Independent States of the former Soviet Union [8]. Pertussis is also re-emerging and has become a public health concern. WHO estimated 16 million cases in 2008 world wide with 195,000 deaths [9]. The incidence of pertussis has also been increasing in several developed countries including United States of America and Canada [10,11].

Nigeria is the most populous country in Africa with about 50% of her population aged below 18 years [12]. With current globalization
and the poor immunization indices in Nigeria, Nigeria may be at risk for epidemics from these two diseases. The recent reports of probable diphtheria from three centres in Nigeria lend credence to such concerns [13–15]. Nigeria does not stock diphtheria antitoxin (DAT), which is the mainstay of management of diphtheria. Thus an epidemic of diphtheria will portend grave consequences. Similarly an epidemic of pertussis in Nigeria will be challenging especially in infants as facilities for critical care of young infants are inadequate. In addition, the capacity for diagnosis of both diseases is limited. In the African region Nigeria is strategic as seen from the global eradication efforts for poliomyelitis. Nigeria is the only African country of the countries still endemic for the wild polio virus and there have been reports that Nigeria has also been re-infecting neighbouring countries [16]. An epidemic of pertussis or diphtheria in Nigeria will thus have serious public health consequences not just for her teeming population but also for neighbouring countries in the sub-region. This review aims to describe the epidemiology of these two diseases and the current strategies for their control while examining the possible implications for Nigeria.

1.1. Pertussis

Pertussis is classically caused by *Bordetella pertussis* an organism with predilection for the ciliated cells of the respiratory epithelium. It is a natural pathogen of humans only [6]. A pertussis-like illness is also seen with infection by *Bordetella parapertussis*, Adenovirus types 1, 2, 3 and 5 [6].

Pertussis is highly communicable and in the absence of immunization all children would have suffered it by the age of 16 years [17].

Pertussis is an exhausting illness that can persist for several months. The incubation period is 7–13 days. The clinical course of the illness is in three phases – the catarrhal or prodromal phase, the paroxysmal phase and the convalescent phase. During the catarrhal phase mild symptoms – rhinorrhea, conjunctivitis, lacrimation, cough and low grade fever are seen. These features are indistinguishable from those of an uncomplicated upper respiratory tract infection. This phase lasts 1–2 weeks. Clinical diagnosis in this phase except in a setting of an epidemic is often impossible [17].

The paroxysmal phase is characterized by repetitive series of paroxysmal cough during a single expiration followed by a sudden massive inspiratory effort that produces a whoop as air is forcefully inhaled against a partially closed glottis. The synonym for pertussis “whooping cough” is derived from this characteristic whoop [18]. Normal activity such as eating and drinking often provokes paroxysms of cough. Other features which include facial redness, cyanosis, bulging eyes, protruding tongue, salivation, lacrimation, haemoptysis, subconjunctival haemorrhages (Fig. 1) and hernias may result from severe paroxysms [17]. The paroxysmal cough may lead to vomiting of sufficient severity to cause weight loss and malnutrition. Young infants may experience apnoea but often they do not produce the characteristic whoop. The paroxysmal phase lasts 2–4 weeks but may persist for up to 20 weeks.

In the convalescent phase of the disease, the paroxysms gradually reduce in frequency and severity. Coughing may persist for months and in subsequent respiratory infection paroxysmal cough may be present. Infections may occur in immunized individuals but the disease is usually atypical and the severity is reduced. Reinfection of those previously infected can occur but the disease is also milder [18,19].

Pertussis can result in respiratory, neurological and nutritional complications. The most frequent complications are atelectasis and bronchopneumonia. Pulmonary complications are age dependent being more among younger children. The most common neurological complications are convulsions and altered consciousness. Others include hemiplegia, paraplegia, blindness and decerebrate rigidity. The neurological complications are secondary to anoxia and/or cerebral haemorrhages caused by raised intracranial pressure during episodes of paroxysmal coughing or encephalitis. The risk of neurological morbidity is also higher in young infants. Nutritional problems are related to the repeated vomiting.

Typical cases of pertussis with the characteristic whoop are diagnosed clinically. In infants where the presentation may be atypical (absence of whoop) and in previously vaccinated individuals where the disease is milder clinical diagnosis may be difficult.

Isolation of the organism from nasopharyngeal swabs is the gold standard [11,20]. This may provide suboptimal yield in those who have been on antibiotics, in those who were previously vaccinated but have waning immunity and if samples are not taken within the first 2 weeks of symptoms [19]. Samples taken during the catarrhal phase provide greater yield [19]. Although, culture has a high specificity, it has low sensitivity [11,20]. This means that culture will not identify all cases of pertussis while being able to identify cases that are not pertussis.

Fluorescent antibody testing offers more rapid results but is less sensitive and specific [17]. Measurement of IgA and IgG antibodies to pertussis toxin and filamentous haemagglutinin is useful in diagnosis among unimmunized children. It however poses difficulty in previously immunized children as it is unable to distinguish between antibodies acquired from natural infection and that acquired through vaccination [17]. Polymerase chain reaction on the other hand though sensitive and rapid is not well standardized between laboratories [11].

Management of pertussis is mainly supportive. Hypoxia and pulmonary complication are prevented through oxygen supply and gentle suctioning to remove viscid secretions. Erythromycin is the drug of choice for treatment and prophylaxis given at 40–50 mg/kg per day in four divided doses for 14 days. Antibiotic therapy may prevent disease if given early in the incubation period [17]. It may also modify the disease making it milder and reducing its duration. It also prevents the spread of infection [17]. However, once the paroxysmal stage has begun; antimicrobial therapy has little effect on the course of the illness and is indicated primarily to limit the spread of the organism to others.

Immunization is the cornerstone for the prevention of pertussis. Efforts should be made to maintain coverage with three doses of the pertussis vaccine at 90% or higher [21]. The role of immunization in the prevention of pertussis is better appreciated from the scenario in Sweden. Immunization against pertussis was discontinued in Sweden in 1979 following which there was an upsurge
of cases between 1980 and 1985 [17]. The age distribution was similar to that of the pre-vaccine era with majority of cases being among those aged 1–6 years [17]. With the introduction of acellular pertussis vaccine in 1996 the incidence of pertussis reduced from 80 to 150/100,000 before its introduction to <10/100,000 after its introduction [22].

1.2. Global epidemiological trends in pertussis

The worldwide total number of cases reported to the World Health Organization ranged from 2.1 to 2.8 million cases per year at the end of the 1970s [17]. This reduced to 600,000 by the end of the 1980s and further decreased to 220,000–440,000 at the beginning of the 1990s [17]. This represents a global decrease of 85–90% over a 15-year period [12]. In sub-Saharan Africa the decrease reported over the same period is 77% [17]. It is pertinent to note that global completion of reporting is about 1–2% [17].

The peak age incidence in the pre-vaccine era in developed countries was 1–4 years. With the introduction of vaccination the incidence of pertussis reduced while there was abolition of the endemic pattern [17]. Also, the peak age incidence has shifted to infants [17].

Similarly in the prevaccine era in developing countries majority of cases occurred in children below the age of 6 years as seen in epidemics reported from Kenya, Cote d’Ivoire and Indonesia [23–25]. Few studies abound on the epidemiology of pertussis since the introduction of immunization in developing countries. One such study on the epidemiology of pertussis before and after introduction of widespread immunization in Senegal showed a drop in incidence of 46% after 6 years of the programme [26]. The greatest drop was observed in children younger than 2 years. More (62%) children aged 5–14 years accounted for the cases of pertussis in the post immunization period of the study compared to 40% in the pre immunization period.

In the recent past some developed countries with high immunization coverage have reported increasing incidence of pertussis and there have been observed changes in the epidemiology of the disease [10,19]. In the United States for example more cases were being reported among infants (>6 fold increase) and in persons older than 10 years compared to the pre-vaccine era [10]. The reasons suggested for these changes include waning immunity among adolescents and adults who become a source of infection for young infants and a greater awareness of pertussis as well as availability of better laboratory tests; the latter resulting in better diagnosis even amongst adolescents and adults with atypical disease.

1.3. Pertussis in Nigeria

Nigerian reports to the WHO have shown trends similar to global trends with 42,929, 38,910 and 11,281 cases reported in 1990, 2000 and 2005, respectively [27]. Although the decreasing reports of cases from Nigeria over the years suggest reduction in the incidence of pertussis, Nigeria nevertheless reported the second largest number of pertussis cases in 2009 [28]. It is however likely that there is underreporting in Nigeria due to misdiagnosis especially in atypical cases in infants (no whoop), poor reporting of diseases generally, poor diagnostic facilities (inability to culture the organism), possible lack of awareness and lack of active surveillance. Due to these inadequacies increase in incidence may not be easily recognized. The reports to WHO do neither show age specific prevalence nor the geographical distribution within Nigeria.

Few studies have described pertussis in Nigeria. One of the most comprehensive reports in Nigeria involved a longitudinal study of 405 children in a village called Imesi in South Western Nigeria [29]. The study was in the prevaccine era in Nigeria. In that study it was observed that majority of the children developed pertussis before the age of 5 years during an epidemic in the 1960s and the introduction of immunization completely removed the infection from the village at the time [29]. Of the 405 children 206 (50.9%) developed pertussis before their fifth birthday. The diagnosis of pertussis was made on clinical grounds. Thus, the prevalence of pertussis may have been underestimated.

The median age of children affected was 2.2 years with a mortality rate of 6.3%. Young infants were shown to have a high frequency of pertussis. The reasons adduced for this were the carrying of young infants on the backs of their mothers and dwelling within extended families. The carrying of the young infant on the mothers back to the market, church, mosque, etc. offers opportunity for the child to be exposed to infection by droplets at an early age. In the extended family several families with small children live in close proximity; thus the infants contacting with other children is continuous. This was contrasted in the study with what obtains in developed settings where the infant lives in nuclear families with few opportunities for contact with other children.

In the Nigerian study the authors did not consider overcrowding to be a contributor to the spread of pertussis. Perhaps this is because this study was in a rural setting. This is likely different from situations in urban slums where several families with several young children live in close proximity in rented single room apartments. However, the cultural practice of carrying babies on the backs of their mothers still obtains while communal living still occurs in rural areas of present day Nigeria. These demographic conditions would be conducive to the spread of pertussis in the event of an epidemic.

Age is a determinant of severity and prognosis of pertussis [17]. Case fatality is highest in infants. Hospitalization is also more likely for younger patients who tend to have more severe disease. The duration of hospital stay is also longer for younger children [17]. This was also the finding in the Nigerian study with children under 1 year accounting for more than 60% of the observed mortality [29].

In the Nigerian study it was observed that the epidemics of pertussis were not seasonal and that the community that was being studied was never free of pertussis at any given time. This was comparable to findings in England in the prevaccine era. The disease was responsible for considerable loss of weight among the children and it took many months for one quarter of them to regain their previous weights. Other complications like convulsions, pneumonia, haemoptysis and oedema of the upper eyelids were seen in the studied children.

The EPI in Nigeria was introduced in 1974 [30]. Six diseases were targeted and these included pertussis and diphtheria. The DPT which contained the whole cell pertussis has been utilized until a few months ago when the pentavalent vaccine containing DPT, hepatitis B and Haemophilus influenza was introduced. Three doses of DPT are administered at 6, 10 and 14 weeks. Although Nigeria’s immunization programme has been present for over 30 years it has been dogged with low to moderate coverage of the different vaccines [31]. Nigeria had achieved the Universal Child Immunization coverage of 80% at the end of the 1980s following intense drives for immunization. Analysis of mortality data covering that period had shown reduction in mortality attributable to pertussis [30,32]. Immunization coverage gradually reduced subsequently reaching an all time low in 2003 [33]. Using WHO data shown in Table 1 cases of reported pertussis seemed to correlate with DPT 3 coverage with increased incidences in years when the DPT 3 coverage dropped.

Current coverage for the third dose of Diphtheria Pertussis Tetanus (DPT 3) vaccine is 34.9% based on data from the Multiple Indicator cluster survey in 2011 while the WHO reported coverage is 71% [27,34]. This highlights the problem of reliability of reported data. However neither of the reported coverages is high enough to break transmission as the herd immunity threshold is 92–94%.
for pertussis [35]. Thus the observed changes in epidemiology for areas with high immunization coverage may not be seen in Nigeria. Nigeria may actually still be endemic rather than being at risk for epidemics.

The drop out rate between DPT 1 and DPT 3 in Nigeria is 16.5% [34]. Studies have shown that some protection does accrue from even a single dose of DPT [36]. Some studies showed reduced severity of disease while others showed reduction in the need for hospitalization [36]. This may in fact explain the reduction in cases despite unsustained high immunization coverage.

Adults and adolescents may be at increased risk of pertussis and may actually have higher incidence due to the fact that their vaccine-derived immunity may have waned. Infections in adults are also more likely to be unrecognized as they are more likely to have atypical disease. These adults and adolescents may then be sources of infection to children who are unimmunized or yet to complete their immunization. The Nigerian infant may thus be more susceptible for longer periods as they tend to commence immunization late and therefore complete the DPT schedule later than usual. The average age at receipt of the third dose of DPT was 126.8 days as against the recommended of 98 days (14 weeks) in a Nigerian study while in another study about 41.4% were delayed for receipt of DPT 3 [37,38].

More recently a study on adults and adolescents showed that HIV infected adolescents were more likely to have pertussis than HIV negative adolescents [39]. The subjects of the study had received 3 doses of DPT in infancy suggesting that waned immunity is a contributory factor and that waned immunity is more in HIV infected adolescents whose specific immunity may have been compromised by the HIV infection.

Although the prevalence of HIV is reducing (5.8% in 2001 to 4.6% in 2008) [40], Nigeria has a large population of persons living with HIV. Of pregnant women needing antiretroviral therapy only 9% received 3 doses of DPT in infancy suggesting that waned immunity has been compromised by the HIV infection. Although the prevalence of HIV is reducing (5.8% in 2001 to 4.6% in 2008) [40], Nigeria has a large population of persons living with HIV. Of pregnant women needing antiretroviral therapy only 9% have access [28]. There is also a high prevalence of tuberculosis, which is being fuelled by the HIV pandemic [41]. The combination of HIV and TB may thus have a large impact on population immunity.

There are no current reports on the epidemiology of pertussis in Nigeria and the reports to WHO do not show age and geographical distribution of cases. Currently pertussis is reported as part of the routine disease reporting system. Diagnosis is clinical and most laboratories do not have the capacity to isolate the organism. Although the recommended treatment for pertussis is erythromycin, most children who have cough in Nigeria would have received various over the counter cough mixtures in addition to a variety of antibiotics including erythromycin which is available in most chemist and pharmacy shops before presenting to the hospital. Also children are more likely to be investigated for tuberculosis when they present with chronic cough.

### 1.4. Diphtheria

Diphtheria, a disease caused by *Corynebacterium diphtheriae* and its exotoxin is characterized by high case fatality [1,3,42]. It is spread by airborne respiratory droplets. The organism may be harboured asymptomatically by 3–5% of healthy individuals in endemic areas [3]. Reported carriage rates among household contacts of cases is 0–25%. The risk of developing diphtheria after a household exposure to a case is 2% and 0.3% if the exposure is to a carrier [3]. Diphtheria commonly affects the tonsils, pharynx and larynx. The *diphtheria* remains in the superficial mucosa or skin and elaborates its exotoxin. The diphtheria exotoxin, a potent 62 kDa polypeptide inhibits protein synthesis leading to local tissue necrosis [1]. The exotoxin is absorbed into the mucous membranes and causes destruction of epithelium and a superficial inflammatory response [3]. The necrotic epithelium becomes embedded in exuding fibrin and red and white cells, resulting in a dense necrotic coagulum of organisms, epithelial cells, fibrin, leukocytes, and erythrocytes [3,43]. This advances – commonly over the tonsils, pharynx, or larynx, and becomes a grey-brown, leather-like adherent pseudomembrane (*Diphthera* is Greek for leather). With increase in the concentration of toxin, it is spread to other tissues through haematogenous dissemination [1].

Pharyngotonsillar diphtheria is the most common form of diphtheria presenting with sore throat, fever and malaise. The membrane is seen over the pharynx, tonsils and uvula. Oedema of the underlying tissues and enlargement of lymph nodes leads to swelling of the neck giving the characteristic bull neck appearance. Laryngeal involvement, which may occur on its own or as a result of membrane extension from the nasopharynx, presents as hoarseness, stridor, croupy cough and dyspnoea [3]. These patients are at significant risk for suffocation because of local soft tissue oedema and airway obstruction by the diphtheritic membrane [3]. Nasal diphtheria, which is common in infants is characterized by the presence of serosanguinous, purulent, erosive rhinitis with membrane formation. Shallow ulcerations of the external nares and upper lip may occur.

Cutaneous diphtheria may occur at one or more sites often localized to areas of previous mild trauma. Characteristically it presents with an indolent ulcer (lasting weeks to months) with sharply defined borders and formation of brownish grey membrane.

There may be toxin-mediated paralysis of soft palate, posterior oropharynx and hypopharynx [43]. Although the toxin has no target organs the myocardium and peripheral nerves are most affected [1]. Other toxin-mediated complications of diphtheria are toxic cardiomyopathy, which occurs in 10–25% of patients with respiratory diphtheria and is responsible for 50–60% of deaths [3]. Neurotoxicity and renal damage can also occur. Some of these features may present up to 6 weeks after the onset of the illness suggesting an immunological basis for the pathophysiologic mechanism for these delayed features of diphtheria [1].

A high index of suspicion is required especially when patients present with pharyngotonsillar disease. Confirmation of the diagnosis by culture of the organism and testing for toxigenicity is carried out [1]. Nasopharyngeal specimens from patients and close contacts are sent for culture. The organism requires special media enriched with Tellurite for culture. Toxicity testing is done using the Elek’s test.

Diphtheria antitoxin is the mainstay of management and it is administered as soon as the clinical diagnosis is made [3]. The antitoxin neutralizes free toxin and its efficacy diminishes as time elapses. If DAT is administered within the first day of the illness, mortality is 1% but if delayed to the fourth day mortality is 20% [1]. It has no effect on bound toxin. Antibiotic therapy (penicillin and erythromycin are the recommended) serves to halt toxin formation, treat localized infection and prevent transmission of the

### Table 1

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<th>Year</th>
<th>DPT 3 coverage (%)</th>
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<td>Pertussis</td>
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<td>1980</td>
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<td>72</td>
<td>10,997</td>
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<td>2009</td>
<td>71</td>
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Data were obtained from WHO preventable diseases monitoring system. Global summary 2012. Available at: http://apps.who.int/immunization_monitoring/en/globalsummary/timeseries/tsincidencecbycountry.cfm
organisms to susceptible individuals. Ear, nose and throat evaluation is required as tracheostomy may be needed for severe airway obstruction.

Prognosis depends on the virulence of the organism, the age of the patient (the very young and the elderly have higher mortality), the immunization status of the patient and the timeliness of administration of the antitoxin.

1.5. Global epidemiologic trends in diphtheria

Diphtheria was one of the most common causes of death among children in the prevaccine era [1]. Although there was a gradual decline in death from diphtheria in most industrialized countries in the early 20th century (associated with improving living standards) it remained one of the leading causes of death until widespread vaccination was implemented [1]. The incidence of diphtheria continued to decline steadily throughout the vaccine era and by the beginning of the 1980s many countries were progressing towards elimination of diphtheria [5]. But by the end of the 1980s, there was resurgence of epidemic diphtheria in the former Soviet Union. This epidemic extended from 1990 to 1995 with about 47,000 reported cases and 1700 deaths in 1994 alone [3].

Changes in the age pattern of acquisition of immunity have been documented [8]. In the prevaccine era, the incidence of diphtheria was high and there was exposure to toxigenic strains of C. diphtheriae which provided natural boosts to the development and maintenance of immunity against diphtheria [8]. Most newborn infants passively acquired antibodies from their mothers [8]. This immunity waned and was gradually replaced by active immunity which was acquired through increasing exposure to natural infection [8]. By 15 years about 80% of children had acquired immunity against diphtheria [8]. During this prevaccine era diphtheria was mostly a disease of children.

The introduction of vaccination, led to marked decrease in the incidence of the disease and the subsequent reduction of the reservoir of the toxigenic strains of the organisms [8]. In the post vaccine era children have high levels of diphtheria immunity due to childhood immunization. Following the primary series of immunization 94–100% of infants develop protective antibody levels higher than 0.01IU/ml, the level considered to be protective [21]. This immunity wanes in later childhood and adolescence due to reduced exposure to natural boosting by exposure to circulating organisms and also if booster vaccinations are not given [21]. Thus there is absence of immunity in large proportions of the adult population [5]. The proportion of adults with antibody titres below levels considered to be protective ranges between 23% and 53% in different industrialized countries [5].

In the epidemics during the post vaccine era, changes in the age distribution of diphtheria cases have been observed with more cases being among adults [8]. However, it has been argued that this change in epidemiology antedated the widespread use of immunization. Other factors such as socioeconomic factors are thought to have contributed to this change [8]. The general increase in the standard of living, smaller families and less overcrowding created an environment in which children were not subjected to the same intensity of infection in their preschool years as they had been previously [8]. More recent outbreaks of diphtheria in Europe and United States have occurred in poor, socioeconomically disadvantaged groups living in overcrowded conditions [8].

In developing countries a high rate of skin infections with C. diphtheriae and high circulation of the organism still appears to be an important factor in the early development of immunity [8]. However, the introduction of mass immunization programmes, socioeconomic changes and changing lifestyles may result in epidemiologic changes [8]. In epidemics reported since the introduction of mass immunization epidemiologic changes were observed. There was a shift to older age groups as shown in outbreaks that occurred in Yemen, Jordan and Sudan [8].

1.6. Diphtheria in Nigeria

According to the WHO reporting system, there has been a steady decline of reported diphtheria cases from 5039 in 1989 to 2468 in 2001 and 312 in 2006 [27]. The absence of data for years beyond 2006 probably reflect the incomplete reporting system and poor surveillance for diseases in Nigeria. It is pertinent to note that a decrease in incidence of diphtheria was documented in some of the developed countries before outbreaks of diphtheria started [44,45]. The reports of probable diphtheria from three centres in three different geographic areas in Nigeria may suggest that perhaps there is resurgence of the disease. Four cases were reported from Lagos (2007–2008), five from Benin (2008–2009) while 10 cases were reported from three contiguous local governments of Katsina state (2009–2010) [13–15]. This is against the backdrop of inconsistent immunization coverage, which has ranged from low to moderate for DPT 3. Current DPT 3 coverage in Nigeria is 34.9% [34].

In all three reports the children were aged below 15 years [13–15]. Most of the children presented with pharyngotonsillar symptoms. Majority of the children 63.2% did not receive any dose of DPT. A common feature of all three reports is the high case fatality rate (50% in Lagos, 40% in Benin and 80% in Katsina) and also the absence of definitive management (diphtheria antitoxin). In one of the studies it was noted that all the affected children were from overcrowded environments and from families of low socio economic status [13]. More recently in 2011 an epidemic of diphtheria occurred in the Borno state in northern Nigeria [46]. It required the assistance of Medecin Sans Frontiere to investigate the epidemic. A total of 107 probable diphtheria cases were identified with 24 deaths giving a case fatality ratio of 22.4%. Majority of the cases (62.4%) were aged below 10 years and 38.5% of cases aged below 5 years died. 98% of the probable cases had never received any childhood immunization. In addition there were delays in seeking medical care as well as absence of antitoxin and adequate antibiotic therapy.

Prevention of diphtheria in Nigeria has been through the use of DPT immunization, which was introduced as part of the EPI in 1974 [30]. Between 1979 and 1983 no reduction in morbidity from diphtheria was observed [30]. An apparent reduction in mortality due to diphtheria occurred in the 1988–1991 period [32] and this coincided with when Nigeria attained the Universal Child Immunization target of 80% for all EPI vaccines. The epidemiology of diphtheria in Nigeria may show different patterns in different geographical areas to reflect the performance of immunization activities. For example the immunization coverage in northern Nigeria is lower than that in Southern Nigeria.

Waning immunity has been documented in adolescents and adults in developed countries and this has been thought to contribute to the increased incidence of diphtheria in these countries [5]. In developing countries on the other hand it is believed that the continuing presence of cutaneous diphtheria may serve as continuous boosters thereby maintaining immunity in adults and adolescents. This assertion may in fact not be correct. In an earlier study in 1980 Kriz et al. [47] found that 85–90% of Nigerians between the ages 15 and 40 years had adequate diphtheria immunity. In a recent study in 2010 on Nigerian parturients, it was found that a significant proportion 29.9% did not have protective antibodies and infants born to them did not also have adequate immunity [48]. It was suggested that improving socioeconomic status may have reduced the presence of cutaneous diphtheria and therefore mothers lacked the opportunity of boosting by this means.
Currently only routine reporting of diphtheria is done in Nigeria. Most laboratories do not have the capacity to identify the organism beyond gram stain. Cultures are not done and test for toxin production are also not done. Like in other African countries reporting is incomplete and the likelihood that diphtheria may be reported as non-specific upper respiratory tract infection is high [49].

Since pharyngotonsillar disease is the most common presentation many children will receive antibiotics purchased from chemist shops often at suboptimal doses. Care seeking is often delayed as observed in the epidemic in Borno state, Nigeria [46]. Patients presenting with airway obstruction are unlikely to receive the expert care required to relieve the obstruction as medical personnel with such expertise and are more likely to be found in secondary and tertiary care facilities. DAT is unavailable in Nigeria.

2. Current approaches to the control of pertussis and diphtheria

Immunization remains the mainstay of prevention for both pertussis and diphtheria. A combination of various forms of diphtheria and pertussis vaccine is recommended. Most of the developing world including Nigeria utilizes the WHO Expanded Programme on Immunization (EPI) schedule which prescribes three doses of DPT given at 6 weeks, 10 weeks and 14 weeks of age [19]. In most developed countries a four-dose schedule is utilized with the first three doses given in the first year of life while the fourth is given in the second year of life [21]. Many developed countries now recommend boosters for adults and adolescents [9]. Boosters are not recommended in the EPI schedule.

For immunization to be effective in preventing diphtheria and pertussis, coverage has to be high. It is recommended that coverage be at least 90% with the third doses of DPT as herd immunity for diphtheria is 85% while that for pertussis is 92–94% [35]. In Nigeria there has been and continue to be challenges to achieving and maintaining high coverage for vaccines [31]. These challenges include provider problems such as vaccine not being available, missed immunization opportunities, more emphasis on supplemental immunization activities rather than strengthening of routine immunization. Consumer factors such as lack of confidence, rumours, lack of motivation and high drop rate also contribute to the difficulties with the immunization programme. These challenges are surmountable if there is political will and commitment, restructuring to eliminate corruption, community mobilization, community participation and community empowerment.

In Nigeria there are no routine immunizations for children beyond infancy or any other group of persons other than tetanus toxoid for pregnant women. A recent study in Nigeria had shown that a significant proportion of parturient women did not have protective diphtheria antibodies and infants born to them did not also have adequate immunity to diphtheria [48]. The report suggested that vaccine immunity may have waned while the opportunity for boosting from cutaneous infections may have reduced due to improving socioeconomic milieu. Thus an epidemic in Nigeria may affect both adults and children emphasizing the need to introduce booster doses for the Nigerian populace.

Giving Tdap to pregnant women instead of tetanus toxoid will at least improve the immunity of a segment of adult population while also providing the added advantage of improving the immunity of newborns who will receive transplacental transfer of antibodies from such immunized mothers. Young infants are known to have more severe disease and increased mortality from both diphtheria and pertussis. This option is feasible in Nigeria as it only requires a change of vaccine as the infrastructure for accessing pregnant women is already in place. The only draw back is the less than optimal utilization of antenatal care services in many parts of the country.

The content of the diphtheria pertussis vaccines differ between countries; while most developed countries utilize acellular pertussis vaccines (Tdap) for children most developing countries still utilize whole cell pertussis vaccine [19]. For booster doses the requirement for diphtheria containing vaccines is a reduced dose of the diphtheria component for vaccines to be used in adults and adolescents (Tdap) as this is less likely to cause side effects while being adequately immunogenic. The whole cell pertussis containing vaccine is more likely to cause side effects with increasing age and number of doses hence acellular pertussis containing vaccines are the recommended choice for boosters [9].

It is important to consider the use of boosters in populations with low DPT 3 coverage. The factors that are responsible for low coverage may also affect coverage for the boosters. However, the boosters may serve as an opportunity to immunize those who missed their primary immunization while boosting those who had only one or two doses of the primary series. This also should be a subject for research.

Following the resurgence of pertussis and the observation that adults and adolescents were increasingly being affected and that most infant cases were traceable to adult or adolescent household members the concept of “cocooning” emerged. Cocooning is a targeted vaccination strategy [50]. Cocooning is defined as the strategy of vaccinating pregnant women immediately post partum and all other close contacts of infants age <12 months with Tdap to reduce the risk of transmission of pertussis to infants [51]. The recommendations are that everyone who has contact with an infant should get a Tdap booster. These include brothers, sisters, mother, father, grandparents, caregivers and health care workers [51]. In this way the infant is cocooned in a circle of protection both in the family and community.

Several countries recommend cocooning. These include the United States of America, Germany, Australia, France and Costa Rica [9]. There are several reports from some of these countries that have documented the effectiveness of the cocooning strategy. The World Health Organization, however, does not recommend it on the grounds of inadequate evidence [9]. The challenges to the use of cocooning in Nigeria include the cost and the fact that antenatal care coverage is only moderate. In addition most deliveries occur outside health care setting. Achieving high coverage with this intervention may thus not be feasible. Research on the acceptability of such a strategy will also be needed.

For optimal control of diphtheria and pertussis a good surveillance system is essential. This will entail stipulating case definition, case identification and reporting, building capacity for diagnosis, building capacity for investigating outbreaks as well as appropriate case management including the provision of DAT for diphtheria. Training and re-training of medical personnel on case identification, reporting and case management will be required. The facilitation of a fast and reliable referral system will be needed. General health education to ensure that communities are aware of these two diseases and therefore present early when symptoms are observed will also be useful.

2.1. Implications of current increase in diphtheria and pertussis for developing countries

The current increase in incidence of pertussis and diphtheria in developed countries may spread to developing countries considering current globalization with easy movement of people from one place to another. The lack of preparedness for such eventualities as evidenced by the poor levels of routine immunization in some countries (like Nigeria), the documented lack of diphtheria immunity in large proportions of adult Nigerians, absence of booster
doses in the immunization programmes for adults and adolescents may in fact lead to epidemics in such countries. This is particularly of importance in Nigeria where there has been non-availability of the DPT vaccines for varying periods in the past few years leading to a cohort of susceptible children who can readily propagate an epidemic. The poor reporting system, lack of diagnostic capacity for both diseases and the lack of specific therapy (diphtheria antitoxin for cases of diphtheria) may portend grave outcomes in the event of an epidemic.

However, the possibility that natural boosting effect for diphtheria through cutaneous infections still exists may serve to mitigate the spread of the organism.

Continuing education of health care workers to create awareness of current epidemiological realities (the continued presence of diphtheria in children, increasing incidence of pertussis in infants, adults and adolescents as well as its atypical presentation in these age groups) will improve early case identification and reporting. Building capacity for the confirmation of these diseases is needed. Stocking of DAT is mandatory as long as cases of diphtheria abound. Strengthening of routine immunization is essential. Research to establish current levels of immunity in children, adolescents and adults is required. This will enable the determination of whether booster doses are required and at what age these should be administered.

3. Conclusion

Diphtheria and pertussis are two diseases with potential for mortality. The possibility of epidemics in countries with poor immunization systems is real. Efforts to build capacity for the diagnosis, management and control of these diseases should be paramount in every society.

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