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Seasonal Meningococcal Meningitis Outbreaks in Nigeria: A Need for an Accelerated Introduction of a Conjugated Meningococcal Vaccine into the National Routine Immunization Schedule

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ABSTRACT

Epidemic meningococcal meningitis affects huge populations annually in sub-Saharan Africa with differentially higher death rates among children. Nigeria is one of the twenty-six countries that lie in 'African meningitis belt'. This paper briefly describes the epidemiology of seasonal recurrent meningococcal meningitis, current efforts to address the epidemics, and then argues for an accelerated introduction of conjugated meningococcal vaccine into routine immunization in Nigeria. This paper also highlights the nature of the epidemics with its attendant impacts on the population; the weaknesses of the current strategies; the emergence of mixed pathogens; the challenges and potential opportunities associated with an introduction of routine vaccination against meningococcal meningitis. The quick introduction of the conjugated meningococcal vaccine into expanded program on immunization (EPI) schedule will mitigate the risk of future massive outbreaks and its attendant morbidity, mortality and larger societal cost. Furthermore, authors suggest the introduction of polyvalent conjugated meningococcal vaccine rather than monovalent (targeting only serotype A), as this will potentially prevent emerging outbreaks of other serotypes such as NmC and W135.

Keywords: Seasonal meningococcal meningitis, Outbreaks, Conjugated meningococcal vaccine, Routine immunization, Nigeria

INTRODUCTION

Nigeria is one of the twenty-six countries that lie in 'African meningitis belt' that spans from Senegal in the west to Ethiopia in the east of the African continent [1]. The seasonal epidemic of meningococcal meningitis usually starts in December when the weather condition is hot, dry and dusty, and ends in June when the weather condition seems unfavorable (higher humidity, reduced temperature, and rainy) to the spread of the epidemic [1-3]. There are other factors such as living conditions, vaccination status, social mixing pattern, health-seeking behaviors etc. that may also predict the recurrent seasonal meningococcal meningitis epidemics reported in this region of the world [4].

Historically, the yearly epidemics have been occurring with different magnitude for more than a century, particularly in West Africa as far back as 1905, and it has been predominantly caused by *Neisseria meningitidis* type A (NmA) [5]. There are other serotypes of *Neisseria meningitis* that have caused outbreaks in Africa such as NmC, NmX and W135, especially in West Africa [6-8]. Epidemic meningococcal meningitis affects hundreds of thousands of people annually in sub-Saharan Africa with differentially higher death rates among children [9]. The West African sub-region has been ravaged by this deadly bacterial pathogen (*Neisseria meningitidis*) for many decades [10]. The 'meningitic belt' suffered its worst outbreak in 1996/97 epidemic season affecting over 250,000 people and causing 25,000 deaths [11].

In this paper, we focus on Nigeria using Kebbi State and other northwestern States surveillance data, the literature and in-country experience to briefly describe the epidemiology, current efforts to address this public health challenge, and then build a case for an accelerated introduction of routine vaccination, specifically, the introduction of conjugated meningococcal vaccine into routine immunization in order to halt the recurrent seasonal epidemics and sustain population immunity.

Current Epidemiology in Nigeria

The recurrent seasonal epidemics of meningococcal meningitis are essentially a northern phenomenon with the northwest region of Nigeria appearing to be differentially more affected [12]. It is indeed the "hub" of seasonal meningococcal meningitis outbreaks.

In recent years, there is an expansion in the 'meningitic belt' in Nigeria (a similar trend observed within the African region at large), as the outbreaks seem to be moving southwards [13]. This finding may be explained by increasing desertification, increasing population, and faster means of transport which aids the spread of infection, and climate change (rising temperature and reduced rainfall) in Nigeria [14-17].

In Nigeria alone, a total of 109,580 cases with 11,717 deaths and a case fatality rate (CFR) of 10.7% were reported during the 1996 meningococcal meningitis outbreak [18]. In 2017, there was a fourth sequential outbreak (from 2014-2017) of NmC in Nigeria starting from Zamfara (a Northwestern State) resulting in 14,518 cases, 1,166 deaths and a CFR of 8% [6]. Generally, case fatality rates in the last four consecutive outbreaks range from 6.8% and 10%, with Northern Nigeria most-affected [6].

Before 2013, the predominant serotype in Nigeria, similar to other countries within the meningitic belt, was NmA [19]. However, with the implementation of a preventive mass vaccination campaign in 2013 in Northern Nigeria, there was a disappearance of serotype A and emergence of serotype C in the following years [6,20]. Recent studies from Kebbi State, in the northwestern region of Nigeria, indicated the dominance of serotype C following the preventive mass vaccination campaign [6]. Further, the most recent outbreak data from the World Health Organization (WHO) Kebbi State Field Office during a period from December 2017 to June 2018 (epidemic season) enlisted a total of 25 confirmed cases; 12 of these cases were NmA, a serotype that has previously disappeared for four consecutive epidemics in Kebbi State, and most of Northern Nigeria. In the same vein, there was a massive outbreak of serotype C in the same epidemic season (2017/18) in neighboring Zamfara and Sokoto States, with Sokoto State being the most affected.

Kebbi State has a projected population of 4,671,594 based on 2006 census with a growth rate of 3.2% [21]. Kebbi State is bordered by Zamfara State in the east, Sokoto State in the north and Niger State in the South [22]. These are all practically Sahelian states with similar environmental/climatic characteristics. It also has international borders with Republics of Niger and Benin [22]. This geographical proximity with these bordering countries has implications on the epidemiology of seasonal meningitis and control efforts within West African meningitis belt.

The re-emergence of serotype A in the States within northwestern Nigeria, as demonstrated above, may be due to an increasing number of susceptible individuals, which is large enough to propagate the epidemic. The other States in Northern Nigeria have also reported a mixed epidemic-NmA and NmC cases in 2017/2018 epidemic season [23,24]. Could the resurgence of NmA have been averted?

Current and Immediate Past Control Efforts

The recurrent seasonal epidemic of meningococcal meningitis has been a chronic public health challenge in most of Northern Nigeria with relatively high case fatality rate [2-4,6]. Various public health interventions such as health education focusing on avoidance of overcrowding and living in well-ventilated rooms, isolation and chemoprophylaxis using oily chloramphenicol and treatment with ceftriaxone (antibiotics) had been adopted to manage the seasonal epidemics [25]. Sadly, not much progress has been made in mitigating some of the drivers of the recurrent seasonal epidemics, such as poor nutrition, housing condition, cooking method- use of firewood, weather condition, poor health-seeking behavior and low immunization uptake in Nigeria and within the 'African meningitic belt' in general [4].

WHO's recommended a strategy for the control of epidemic meningitis is built on three key pillars: surveillance, treatment and care and vaccination [26]. In the last twenty years, efforts have been directed at conducting reactive vaccinations which are usually ill-timed (usually taking place more than 4 weeks after the attainment of an epidemic threshold) [2,5,21,27]. In recent past, polysaccharide vaccines against type A had been used with less impact because of late delivery and limited scope of vaccination. Also, the inherent protective value of the polysaccharide meningitis vaccine is limited- offers protection for two years, does not reduce nasopharyngeal carriage, and does not elicit an immune response in children that are less than two years [28]. This science and technology of vaccine development against meningococcal meningitis was revolutionized with the development of meningococcal conjugate vaccines which could be monovalent or polyvalent (covering more than one serotypes) [29]. The development of meningococcal vaccine has potentially brought succor to the meningitic belt as the likelihood of eradication increased. However, this vaccine is limited in supply due to cost and the fact that most of the countries in this belt are low-and-lower-middle-income countries (LLMICs), and cannot afford the cost of the vaccine [30]. Therefore, there is no real commercial value for a large-scale vaccine production by the pharmaceutical industry. In the light of the above, the International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control (ICG) has a global stockpile of vaccines to assist these LLMICs (developing countries) often ravaged by the outbreak [31]. However, the rationed supplies are often too little to make any real impact during outbreak. The Meningitis Vaccine Project (MVP) funded by Bill and Melinda Gates Foundation (BMGF) incentivized the commercial manufacture of Men-Afrivac (conjugated meningococcal vaccine against type A) by Indian Pharmaceutical for the supply of vaccines that were used for preventive mass vaccination campaign across the 'African Meningitic belt' from 2011-2014 [32]. The impact of this intervention was palpable as NmA serotype disappeared for about 4 years [33]. Unfortunately, this was not complemented by the introduction of Men-Afrivac into routine immunisation (RI) schedule that could have sustained population immunity [20,33].

The Need for Accelerated Introduction of Men a Conjugate Vaccine into National EPI Schedule

The Global Vaccine Action Plan (GVAP) is a framework adopted at the 65th World Health Assembly in May 2012 to realize the Decade of Vaccines vision by ensuring universal access to immunization [34]. One of the objectives of Global Vaccine Action Plan (GVAP), a 10-year global strategic plan for immunization is to sustain the gains of the past decade in the area of immunization and expanding the successes by introducing new vaccines with the overall aim of protecting people from vaccine-preventable diseases, especially in low-and-middle-income countries [34].

Nigeria had planned to introduce Men A conjugate vaccine into it expanded program on immunization (EPI) as far back as 2016 to complement the impact of the successful 2013 mass vaccination campaign. Sadly, the country is yet to include the antigen (vaccine) into routine immunization as at the time of writing this paper. The failure of health system governance to implement the policy has led to the re-emergence of NmA as mentioned above (creating a mixed epidemic) which may likely be due to waning immunity and increasing (large) number of susceptible population [33,35-37]. Credence to this epidemiological finding was noted in the conclusion of Lydon and colleagues in a perspective published in WHO Bulletin, stating that failure of low and lower-middle income countries to mobilize resources to finance the non-vaccine component will severely compromise their ability to meet the objectives of the Global Vaccine Action Plan [38].

Challenges to Vaccine Introduction

New vaccine introduction is typically associated with additional costs apart from the cost of the vaccine [39]. The traditional EPI vaccines are cheaper and stable in supplies, due to a suitable funding mechanism that guaranteed supply and encouraged multiple manufacturers [40]. However, newer vaccines such as human papillomavirus (HPV) vaccine, yellow fever, conjugated CSM vaccine are relatively expensive with unpredictable supply chain, mainly owing to pricing and profitability issues [39-43].

The health system inputs such as human resources, vaccine supplies and logistics infrastructure far outweigh the cost of vaccines even for the more expensive newer vaccines, particularly in low and lower-middle income [27,44]. To better understand the resources requirement for the Global Vaccine Action Plan (2011-2020), notably, the non-vaccine health system costs, the WHO and United Nations Children Fund (UNICEF) undertook a needs-cost exercise [45]. The report of this constituted group of experts calculated the investment requirement for 19 diseases across 94 low and lower-middle income countries relative to 2010 as the baseline [45]. The exercise made use of ingredients-based approach and use of approximations based on the previous spending to generate vaccine and non-vaccine delivery costs to routine and supplementary immunization programs. Funding projections are based primarily on supports from national governments and GAVI. Cumulative total costs for the decade are estimated to be US$57.5 billion, with

85% for the routine vaccination program and the remaining 15% for supplementary immunization activities (SIAs) [45]. Of these costs, delivery costs account for 54% of the total cumulative costs while the vaccines cost accounts for the remainder. The estimated non-vaccine cost of delivering the routine vaccination program to the health system in this decade is US$25.4 billion [34]. Furthermore, it was projected that the average health system cost per child will increase from US$18.1 (2010) to US$24.9 (2011-2015), and to US$32.6 from 2016-2020 [5,45]. This cost has almost tripled relative to cost in the previous decade. The cost of vaccine may reduce with the advent of newer technologies in vaccine production, however, the cost of non-vaccine health system inputs may likely continue to rise. This warrants innovative strategies in new vaccine delivery, especially in high-disease burden settings, which are mainly developing countries.

In lower-middle income countries, like Nigeria, with low budgetary expenditure on health (4% of the total proposed budget for 2018) [46], it is often difficult to cope with the cost of non-vaccine inputs. Some of these non-vaccine health system inputs are as cold chain requirements (slow and fast cold chain); infrastructure such as power supply; other logistics for service delivery such as updating of routine immunization (EPI) data tools [30,35]. Others are the cost of training of personnel and health workers at various operational levels; production cost of training manuals and guidelines; inadequate human resource for health; funding for outreaches and mobile strategies for vaccine delivery to underserved populations [2,30,35]. Lastly, the additional cost implication of the need to strengthen clinical and laboratory surveillance for new vaccines, in this case, conjugate vaccine against meningococcal meningitis upon introduction into EPI schedule.

Potential Opportunities from New Vaccine Introduction

The introduction of new vaccine such as Men A conjugated vaccine may not be entirely a burden to EPI or health system; however, it could potentially be leveraged upon to strengthen the EPI and by extension the health system, especially in countries with fragile health system such as Nigeria. Suggestions from the literature indicate that new vaccine introduction could increase uptake of other vaccine antigens, raise awareness about immunization service due to increased social mobilization efforts accompanying new vaccine introduction [47]. Furthermore, experiences, competencies and structures acquired from previous vaccine introduction do serve future vaccine introduction as well as general support to RI services [2]. The gaps found during the assessment of the readiness of administrative level and facilities would potentiate advocacy to government and relevant stakeholders to provide resources towards addressing such gaps such as infrastructural deficit, which will serve or strengthen the EPI and possibly the entire health system [26]. Other EPI goals could be strengthened such as the Logistics Sub-committees, etc. at various administrative levels (national, state and local government). The broader health system goal, for example, the sentinel surveillance site in place provides information about the epidemiology, better understanding of the pathogen and more importantly, provides a basis or empirical evidence for vaccine introduction. The laboratory networks are often well-managed and equipped, and could serve the general health system, or upgraded, even in the event of disease outbreaks for other VPDs or infectious diseases. The laboratory network often harbor a pool of well-trained laboratory scientists, technicians and pathologists whose wealth of knowledge and experience could serve the general health systems beyond the EPI. The laboratory also provides the opportunity of providing empirical evidence regarding the impact of introducing a new vaccine into the population.

CONCLUSION

The realization of GVAP goals and Sustainable Development Goals may be seriously under threat in many low-and-lower-middle income countries, including Nigeria, as the cost of newer vaccines (such as Men A conjugate vaccine, HPV, Rota vaccine) and non-vaccine costs appear overwhelming. Therefore, there is an urgent need for all stakeholders including donors and international agencies, such as UNICEF, WHO, GAVI and BMGF, to support the government of Nigeria through the National Primary Health Care Development Agency (NPHCDA) to accelerate the introduction of conjugated meningococcal vaccine against serotype A as conceived. The introduction of the conjugated meningococcal vaccine into EPI schedule without further delay will mitigate the risk of future massive outbreaks and its attendant morbidity, mortality and larger societal cost. Furthermore, authors suggest the introduction of polyvalent conjugated meningococcal vaccine rather than monovalent (targeting only serotype A), as this will potentially prevent emerging outbreaks of other serotypes such as NmC and W135.

Take Home Points

- The value of vaccination in combating vaccine preventable diseases has been well-established, however, low-and-lower-middle-income countries (LLMICs) such as Nigeria, are yet to fully benefit from the myriads of new vaccines available such as conjugated meningococcal vaccine for routine vaccination
- The realisation of Global Vaccine Action Plan goals and Sustainable Development Goals may be threatened due to overwhelming costs of new vaccine introduction and health system challenges in Nigeria
- The introduction of meningococcal meningitis vaccine into the Expanded Programme on Immunisation (EPI) schedule is long overdue, and will potentially mitigate the risk of massive outbreaks and its attendant morbidity, mortality and larger societal cost
- The authors suggest the introduction of polyvalent conjugated meningococcal vaccine rather than monovalent type (against serotype A) being planned, as indicated by the current epidemiology in Northern Nigeria

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Authors' Contributions

SAO conceived and designed the framework of the paper, participated in literature search, wrote the first draft of the manuscript and critically reviewed all the drafts of manuscript. KKK participated in the literature search, reviewed and edited the drafts of the manuscript. All the authors read and approved the final draft of the manuscript before submission.

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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