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The Challenge of Eradicating Meningococcus Outbreaks Through Vaccines

Elijah Ige Ohimain*

Department of Biological Sciences, Niger Delta University, Medical and Public Health Microbiology Research Unit, Wilberforce Island, Bayelsa State, Nigeria.

Abstract

About 1.0-1.2 million cases of cerebrospinal meningitis infections are recorded each year, with a case fatality of about 70-90% without the use of antibiotics and 10% even with the use of antibiotics. Neisseria meningitidis (Meningococcus) is the major cause of bacterial meningitis all over the world. Due to the combined problem of antibiotics resistance and the development of long-term sequelae/ complications, the use of vaccines could provide the best option for the control of bacterial meningitis. This study reviewed the vaccine strategy for the control of meningococcus and found that three vaccine strategies have been commercialized. The strategy involved vaccine production using capsular polysaccharide, capsular polysaccharide-protein conjugate and outer membrane vesicles. The study also identified challenges of using vaccine to eradicate meningococcus. These problems include the presence of diverse serogroups, strains and clonal complexes of the bacteria inhabiting different geographic locations, lack of cross protection among different vaccines for the different serogroups and high costs of vaccination. More research is therefore required to develop a common vaccine that will protect against all serogroups, strains and clonal complexes of Neisseria meningitidis and possibly the other two species causing bacterial meningitis i.e. Haemophilus influenzaetype b and Streptococcus pneumoniae. Polyvalent vaccine produced using both capsular-protein conjugate and outer membrane vesicle is likely going to be the ideal candidate.

Keywords

Antibiotics; Conjugate Vaccines; Herd Immunity; Meningitis; Outer Membrane Vesicles Vaccine; Polysaccharide Vaccines

Introduction

Since the discovery in 1805 of Neisseria meningitidis (Nm) as the causative agent of meningococcal meningitis, the bacteria have spread globally with different serogroups predominating in different parts of the World. An estimated 1.0- 1.2 million cases are recorded each year [1,2] killing 50-70% of infected person if no treatment is administered [2]. The mortality rate could be reduced to 10% with the administration of antibiotics. Also, neurological complications often occur in over 10% of survivors, such as deafness, brain damage, paralysis, limb loss, learning disabilities [3, 4-7]. Even with adequate antibiotics treatment, about 10% of patients die within 48 hours of the onset of symptoms [6]. Holst et al. [8] reported that prior to the use of antibiotics, the fatality rate of the disease was 70-90%, but dropped to 5-15% with the use of antibiotics, with about 10-15% of survivors developing permanent disabilities. In non-epidemic setting, 10% of healthy individuals carry meningococcus perhaps as normal flora in their upper respiratory tract [7]. Many people may carry the disease in this way, because since 1960, three pandemics of meningitis caused by NmA have occurred in Asia [4]. Neisseria meningitidis A causes seasonal outbreaks of Cerebrospinal Meningitis (CSM) in African meningitis belt.

The attack rate varies with geographical area, being 0.1/100,000 in Mexico and Japan, <1/100,000 persons in USA, >2/100,000 persons in Chile, Brazil and Europe, 5/100,000 in the UK [9] and 20-1000/ 100,000 persons in the extended African meningitis Belt (AMB). The region comprising of 26 countries (Benin, Burkina Faso, Burundi, Cameroun, CAR, Chad, Cote d'Ivorie, DRC, Eritrea, Ethiopia, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Mali, Mauritania, Niger, Nigeria, Rwanda, Senegal, Sudan, South Sudan, Tanzania, Togo and Uganda) with about 450 million people at risk where endemic, epidemic and pandemic outbreaks of meningococcus occur frequently. Endemic rates in Africa is quite high circa 20/100,000, which could increase to 1000/100,000 persons during epidemics [4]. WHO defined epidemic as >100/100,000 population/year. Meningococcal infections often result in meningitis and less commonly meningococcal septicemia also known as meningosepticemia. The symptoms of meningococcal meningitis include headache, fever, photophobia, stiff neck, vomiting and lethargy, while septicemia symptoms include rash, fever, headache, vomiting and abdominal pains [6,7].

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*Corresponding author:

Elijah Ige Ohimain
Medical and Public Health Microbiology Research Unit, Biological Sciences Department
Niger Delta University, Wilberforce Island
Bayelsa State, Nigeria
E-mail: eohimain@yahoo.com

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Serial No.	Serotype	Location recording outbreaks
1	A	Africa, Europe, Middle East
2	B	North and Central America, South America, Europe, Middle East, Australia, New Zealand
3	C	Africa, North and Central America, South America, Europe, Middle East, Australia
4	W-135	Africa, Middle East
5	X	Africa
6	Y	North and Central America

Table 1: Global spread of meningococcal strains by serotype and region

Cerebrospinal Meningitis (CSM) is caused mostly by microbial infections, but non-infectious CSM occur rarely due to cancer or the use of drugs that affects the meninges. Different types of microbes have been linked to CSM including bacteria, fungi, yeast, parasites and viruses. Among bacteria, three species have been commonly reported to cause CSM, Neisseria meningitidis, Streptococcus pneumonia and Haemophilus influenza. Recently the WHO ranked H. influenzae (ampicillin resistant) and S. pneumoniae (Penicillin susceptible) as medium priority pathogens requiring the development of new antibiotics [10]. Neisseria meningitidis account for over 80% cases of bacterial meningitis, hence the focus on this organism. Before the use of antibiotics, the fatality of bacterial meningitis was 70-90%, which have reduced to 5-15%, with about 10-20% of survivors developing complications [8], such as hearing impairment, brain damage, and paralysis. Antibiotics resistance has been reported in Neisseria meningitidis. Rouphael and Stephens [9] cited cases of resistance of Nm to sulfonamides, penicillin and Ciprofloxacin. Resistance to Chloramphenicol has also been reported. However, ceftriaxone is currently being used for treatment in the current outbreak of NmC in Nigeria. Due to the combined problem of antibiotics resistance and the development of long-term sequelae/complications, the use of vaccines could provide the best options for the control of bacterial meningitis. Hence, this paper is aimed at presenting updates on meningococcal vaccines and the challenge of using vaccine for the control of meningococcal meningitis.

Neisseria Meningitidis

Neisseria meningitidis also known as meningococcus is the major cause of bacterial meningitis. This organism is a fastidious gram-negative diplococcus, aerobic and naturally inhabiting the nasopharynx of humans. The bacterium is either capsulated or non-capsulated. Capsulation appears to have increased the virulence of capsulated strains over the non-capsulated ones. Based on the structure and chemical composition of the polysaccharide (PS) capsule and attendant immunological reactivity, Neisseria meningitidis (Nm) can be classified into 13 distinct serogroups (A, B, C, E29, H, I, K, W-135, X, Y, Z and Z') of which only six (A, B, C, W-135, X and Y) have been implicated in CSM [9, 11]. Different serogroups of Nm predominate in different parts of the world (Table 1) with serogroup A responsible for 80 – 85% of bacterial meningitis in African meningitis belt [6], with serogroups X, W135 and C accounting for the rest [12]. Padron et al. [11] citing WHO, reported that about 500,000 cases of bacterial meningitis are reported each year, with about 90% of the cases caused by serogroups A, B and C. Bacterial meningitis vaccines do not exhibit cross-protection. Hence, the specific vaccines used by different countries is highly dependent on the predominate serogroup, cost and availability [3].

The capsule which is one of the most important virulence factor of the bacteria is also important as a site for the drug attack and forms the basis of most of the licensed meningococcal vaccines. Like most bacteria, Nm has outer membrane, which is the site for the development of Outer Membrane Vesicles (OMV) vaccines specific for NmB.

Meningococcal Vaccines

There are at least three different types of vaccines used against Neisseria meningitidis. They are Polysaccharide Vaccines (PV), polysaccharide-protein conjugate vaccine (CV) and Outer Membrane Vesicle Vaccines (OMV). Table 2 present a list of licensed meningococcal vaccines including their manufacturers/ developers, types of vaccines, vaccine development status/ licensure, valence, route of administration and the target serogroup. Several polysaccharide vaccines have been marketed globally including Bivalent AC (A + C meningococcal vaccine by Sanofi Pasteur), trivalent (ACW-135 by GSK) and tetravalent /quadrivalent ACW-135Y (Menomune by Sanofi Pasteur). Polysaccharide vaccines are produced from purified, lyophilized capsular polysaccharide of the respective Nm serogroup [13]. Polysaccharide vaccines have been on use for over 40 years. They are safe and immunogenic and highly effective in close population such as in military barracks and camps [3]. Nevertheless, polysaccharide vaccines have several challenges because they are poorly immunogenic especially among infants and children <2 years old, do not induce herd immunity, fail to induce immunological memory and provide only protection for only 2-3 years [3,6,13]. Goldblatt [14] reported that polysaccharide vaccines fail to induce significant and sustained immunity in children and infants, perhaps because the antibody induced is dominated by IgM and IgG2. Notwithstanding its limitations, WHO [15] reported the use of trivalent (ACW) vaccine for the control of epidemic meningococcal disease outbreaks in countries of the Africa meningitis belt.

Polysaccharide – protein Conjugate Vaccine (CV) have been developed to overcome the limitation of polysaccharide vaccines. Conjugate vaccines are highly immunogenic, they confer longtime protection not only to those that receive it, but also to their close associates (herd immunity). It induces immunological memory, effective in the protection of children <2 years, and it elicit high response to booster doses and the quality of the antibodies produced is quite high [3, 6].

Several monovalent (A and C), bivalent (AC, BC) trivalent (ACW-135) and several brands of tetravalent/quadrivalent (ACW-135Y) conjugate vaccines are currently being marketed (Table 1). In December 2010, a new monovalent NmA conjugate vaccine MenAfricVac was introduced in the Africa meningitis belt and about 235 million individuals of age 1 – 29 years were immunized [6,13,16], which resulted in the near elimination of NmA until recently when novel strains of Nm C emerged in Nigeria and Neighboring Niger Republic [12,17,18]. MenAfricVac A have other advantages including, it can be administered outside cold chain, promotes community/herd immunity, provides long time protection and relatively inexpensively (circa $ 0.5/dose) [5,16]. Conjugate vaccines have also been developed for Haemophilus influenzae type b and Streptococcus pneumoniae [14]. The global sales of conjugate vaccines have increased astronomically in recent times, approaching $ 10 billion in annual sales, with pneumococcus, meningococcus and H. influenzae vaccines accounting for 60%, 25%, 15% respectively, whereas other conjugate vaccines accounted for <1% of the vaccines administered [19].

Borrow et al. [20] did a comparative study among conjugate C vaccines and found Neis Vac-C has the longest longevity among currently licensed NmC conjugate vaccines. Generally, conjugate vaccines are produced by covalently bonding a poor antigen, in this case, polysaccharide with a strong antigen, in this case, proteins in order elicit a strong immunological response. Antibody responses, unlike polysaccharides which are dominated by IgM and IgG2 that are relatively short lived, responses to polysaccharide protein

S.No	Vaccine	Manufacturer	Type of vaccine	Valence	NM serogroup	Development status	Age groups	Cost per dose, $	Adm route	Remarks
1	MenAfri Vac A	Indian Serum Institute*	CV	Monovalent	A	Approved for use in Africa	-	0.5	-	Successful in Africa
2	Trumenba	Pfizer	OMV	Mono valent	B	FDA licenced 2014	10-25 yr	-	IM	-
3	Bexsero	GSK	OMV	Mono valent	B	FDA licenced 2015	-	50	IM	-
4	MeNZB	Chiron, GSK	OMV	Mono valent	B	Licenced in New Zealand	-	-	-	Successful in New Zealand
5	MenBVac	NIPH^	OMV	Mono valent	B	Licenced in Norway	-	-	-	Successful in Norway
6	Meningitec	Neuron Bio-tech	CV	Mono valent	C	Licenced	-	-	-	-
7	Menotirix	GSK	CV	Mono valent	C	Licenced	-	-	-	-
8	Menjugate	Novartis	CV	Mono valent	C	Licenced	-	-	-	-
9	Neisvac-C	GSK/Pfizer	CV	Mono valent	C	-	-	-	IM or SC	-
10	HibMenC	-	CV	Mono valent	C**	-	-	-		-
11	DTPw-HBV/ Hib-MenAC	GSK	CV	Bivalent	A, C***	-	-	-	IM	-
12	VA-MEN-GOC-BC	Finlay Insti-tute	OMV	Bivalent	B, C	Licensed in Cuba in 1989	-	-	IM	Successful in Cuba
13	A+C menin-gococcal vaccine	Sanofi Pasteur Formerly Mérieux	PS	Bivalent	A, C	-	-	-	-	Successful in Brazil
14	Trivalent ACW vac-cine	GSK	PS	Trivalent	A, C, W-135	Licensed in Belgium in 2003	-	1	-	WHO used in in Burkina-Faso in 2003-2004
15	Menhibrix	GSK	CV	Bivalent	C & Y**	FDA licenced 2012	6 wk-18 mt	-	-	-
16	Menomune	Sanofi Pasteur	PS	Tetravalent	A, C, W-135 & Y	-	-	-	SC	-
17	Nimenrix	Pfizer	CV	Tetravalent	A, C, W-135 & Y	-	-	-	-	-
18	Menactra	Sanofi Pasteur	CV	Tetravalent	A, C, W-135 & Y	FDA licenced 2005	9 mt-55yr	-	IM	-
19	Menveo	Novartis	CV	Tetravalent	A, C, W-135 & Y	FDA licenced 2010	2 mt-55yr	-	IM	-
20	Mencevax	GSK	CV	Tetravalent	A, C, W-135 & Y	-	-	-	-	-
21	NmVac4	JN-Interna-tional Medical Corporation	CV	Tetravalent	A, C, W-135 & Y	-	-		IM	-

Compiled from several sources

*In partnership with SynCo Bio Partners, US Centre for Biologics Evaluation and Research

**Also protects against and Haemophilus influenzae type b.

*** Heptavalent DTPw–HBV/Hib–MenAC (diphtheria, tetanus, whole cell pertussis-hepatitis B virus/Haemophilus influenzae type b-Neisseria meningitidis serogroups A and C) vaccine.

^NIPH= Norwegian Institute of Public Health

OMV=Outer Membrane Protein; Nm= Neisseria meningitides; GSK = Glaxo Smith Kline; CV = Conjugate Vaccine; PS= Polysaccharide Vaccine

Table 2: Meningococcal vaccines for the prevention of CSM

conjugates are dominated by IgG1 and IgG3 that confer prolonged immunity [14]. As a result, majority of the commercially available meningococcal vaccines are conjugates. Therefore, many conjugate vaccines are produced using various protein carriers such as Tetanus Toxoid (TT) e.g. MenAfriVac-A, Menitorix, NeisVac-EC, Menhibrix, Nimenrix; diphtheria toxoid e.g. Menactra or a non-toxic derivative/ mutant of diphtheria toxoid called cross reacting material (CRM 197) e.g. Mengitec, Menveo, Menjugate among others [3, 14, 20]. It appears that tetanus toxoid is more effective than CRM 197. Due to the success of conjugate vaccines, research has now focused on the development of polyvalent vaccines that could protect against Neisseria meningitidis and other pathogens. Gatchalian et al. [4] reported the development of heptavalent diphtheria-tetanus-pertussis-hepatitis B-Haemophilus influenzae type b-Neisseria meningitidis serogroup A and C conjugate vaccine, which was immunogenic, safe, had persistence of antibodies and demonstrated immune memory.

A type of meningococcal vaccine that cannot be produced via polysaccharide or conjugates are produced via Outer Membrane Vesicles (OMV). OMV are specific for NmB. For a long time, it was quite challenging producing polysaccharide or conjugate vaccines for NmB for several reasons. The capsular polysaccharide of NmB is poorly antigenic/ immunogenic and is similar or homologous to human fetal neural tissues [1,2,11].

Protein from the outer membrane vesicle of Nm B has been developed for specific outbreaks, which was successfully used in the control of epidemics in Cuba, Norway and New Zealand [1,2,11]. Few OMV based vaccines are in the market including Bexsero, Trumemba, MENZB and VA-MENGOC- BC (bivalent) vaccines. The Norwegian government has discontinued the use of MenBvac. The VA-MENGOC-BC vaccine, which was registered in 1989, was among the first safe, effective and commercially available vaccine against NmB in the world. Over 55 million doses of this vaccine have been administered in Cuba and 15 other countries in Latin America and the Caribbean over a period of 30 years [11].

Challenges of Eradicating Epidemic/ Invasive Meningococcus Using Vaccine Strategy

Due to antibiotic resistance, vaccines have become the plausible strategy for eradicating invasive bacterial meningitis globally. The first sets of meningococci vaccines, which were produced from the capsular polysaccharide, had some limitations. Polysaccharide vaccines are poorly immunogenic in infants (infants are among the most vulnerable to bacterial meningitis), short duration of protection and lack of herd/community immunity. Polysaccharide- protein conjugate vaccines were developed to overcome the aforementioned limitations of polysaccharide vaccines. About 30 years ago, different type of vaccines based on OMV technology specific for NmB was developed. There is no doubt, that all of these three different vaccine approaches along with antibiotics have help to reduce the global burden and death resulting from bacterial meningitis, but there are some challenges that must be addressed before vaccines strategy can effectively eliminate meningococcal meningitis.

One major challenge is the bacteria themselves, which exhibit different phenotypic expressions based on the composition of their capsular polysaccharide. To date, there are about 13 different serogroups (A, B, C, E-29, H, I, K, L, W-135, X, Y, Z and Z') of which only six (A, B, C, W-135, X and Y) are currently clinically significant. The vaccines developed thus far, are serogroup specific. Hence, despite causing epidemic in Africa and some parts of China, there are no currently licensed vaccines that could tackle Nm X. Moreover, any of the other serogroups that are benign now could become virulent in the future due to several factors such as evolution, acquisition of plasmids, and horizontal gene transfer and capsular-switching, which has been reported among meningococcus [1,9]. There is also the phenomenon of epidemiological shift [18] /serogroup replacement [17]. For instance, because of the mass vaccination with MenAfriVac-A conjugate vaccine in 2010 – 2012, NmA which used to be the dominant serogroup reduced drastically, almost virtually eliminated, but other serogroups are now becoming dominant including NmC [17] causing current outbreaks in northern Nigeria and Niger and NmX and NmW-135, which have also caused infections in Burkina Faso and Mali. Meningococcal vaccines are serogroup specific, MnB vaccines are specific to the type of strain, sequence and clone. Hence, cross protection does not occur among different serogroups. This problem probably explains the reason for carrying out reactive vaccination based on the epidemic serogroup or strain rather than preventive vaccination.

Another challenge is that the epidemiology of bacterial meningitis can be unpredictable with the prevailing Nm serogroup changing sporadically [1]. Besides, there are different strains, variants, Clonal Complexes (CC) and Sequence Types (ST). For instance, Shao and Zhu [1] reported CC1, CC4 and CC5, ST-3, ST-5 and ST-7 belonging to serogroup A. They also reported that CC4821 belonged to both serogroups B and C due to capsular switching. In addition, Nm B has a few hyper invasive CC including CC32, CC11 and CC41/44.

One of the main challenges of controlling NmB via vaccines is that there are no broad-based vaccines that can protect against all strains of B serogroup. Only tailor-made OMV B vaccine from the strain causing the outbreak can be used. Hence, NmB Strain Cu 385/83 (B:4: PI-15) and NZ 98/204 (B:4: PI 7-2, 4) were used for the development of vaccines that was used to control the respective epidemics in Cuba in the 1980s and New Zealand in the 1990s [1].

Another major challenge especially of the polysaccharide vaccines is that they lack immune memory, coverage is relatively short (circa 2-3 years) and they respond poorly to booster doses. Notwithstanding these limitations, polysaccharide vaccines are still used in several countries including China, where PS is still present in their routine vaccination. Also, reactive vaccination using polysaccharide AC vaccine is being used to fight the current meningococcal outbreak in Nigeria.

Another problem is that meningococcal vaccines elicit different levels of response among different age groups. Hence, the vaccines were licensed for different age groups. Most of the vaccines require more than one dose to be effective. Vaccines are quite expensive, which many poor countries are unable to afford. International agencies such as WHO and PATH have intervened to reduce the cost. For example, MenAfriVac – A was supplied at about $0.5 per dose.

Conclusion

Meningococcal meningitis is a deadly disease caused by Neisseria meningitidis with several serogroups predominating in different countries or regions. About 1 million cases are reported annually with about 60- 65% in the African meningitis belt. Meningitis caused about 135,000 death each year and even 10-20% of survivors develop longtime complications such as brain damage, paralysis, deafness, and learning impairment. Antibiotics have been quite effective in the treatment of patients. Also, their emerging resistance to antibiotics has necessitated the use of vaccines as a strategy for the control and possible eradication of the disease. Three different types of vaccines have been developed and used globally including polysaccharides, conjugate and OMV vaccines. The use of these vaccines along with antibiotics has resulted in the global reduction in the cases and fatality of the disease. There are several challenges that must be addressed for the vaccine strategy to be able to eliminate the disease. More research is therefore needed to be able to develop a common vaccine that will protect against all strains of NmB, all pathogenic serogroups of Nm and possibly two other species causing bacterial meningitis i.e. H. influenzaeand S. pneumoniae. Polyvalent vaccine produced using both capsular-protein conjugate and outer membrane vesicle is likely going to be ideal candidate. Optimization of carrier proteins could permit the conjugation of more than one capsular polysaccharide, which could permit the development of broad spectrum polyvalent vaccines.

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