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Impact of the Pentavalent Meningococcal Conjugate Vaccine(NmCV-5) Targeting Serogroups A,C,Y,W, and X on the Sub-Saharan Africa Region

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Abstract. Meningococcal disease poses a considerable public health burden in sub-Saharan Africa (SSA), particularly in the "meningitis belt". Although the rollout of the serogroup A meningococcal vaccine (MenAfriVac) has effectively contributed to a significant reduction in the incidence of group A meningitis, serogroups C, W, Y, and X are experiencing rising infection rates, highlighting the urgent need for new vaccines to address the threat posed by non-serogroup A Neisseria meningitidis. Considering this, Serum Institute of India Pvt Ltd., in partnership with PATH, developed a pentavalent conjugate vaccine (NmCV-5) containing capsular polysaccharides of meningococcal serogroups: A, C, W, X and Y, conjugated to a protein carrier, tetanus toxoid. In this paper, the epidemic trend of meningococcal and the development of NmCV-5 vaccine in SSA were analyzed by literature review. It has been shown that the NmCV-5 vaccine demonstrated good safety and immunogenicity against all serogars in clinical trials, especially significant protection against Neisseria meningitidis serogroup X. The single-dose schedule of the vaccine also improves roll-out feasibility in resource-limited Settings. However, the rollout of the vaccine still faces challenges such as poor infrastructure and insufficient public awareness.

Keywords: NmCV-5; Sub-Saharan Africa; Meningococcal disease.

1. Introduction

Meningitis continues to be a significant global public health issue.The darkest colors in Figure 1 are concentrated in sub-Saharan Africa (SSA), Notably within the region known as the "meningitis belt".This region, spanning nations from Senegal to Ethiopia, has an incidence of more than 100 cases per 100 000 population per year, Some localities saw over 300 cases every year.Climatic conditions and inadequate health resources, combined with low vaccine coverage, contribute to frequent outbreaks of meningitis. Countries with moderate incidence are mainly located in South America, central Asia, and Southeast Asia. The incidence in these places is between 10 and 100 cases per 100,000 persons per year. Despite lower incidence rates than in the African meningitis belt, these regions continue to face major public health issues.

In industrialized countries such as Europe, North America, and Australia, The rate of occurrence of meningitis is low, falling between 0 and 10 instances annually per 100,000 people. These countries have strong health systems, efficient vaccination programmes and well-developed health services, so the incidence of meningitis is effectively controlled. Although the incidence of meningitis is lower in high-income countries, meningitis remains a serious public health challenge from a global perspective, especially in areas with inadequate sanitation. The global uneven vaccination and lack of medical resources are important factors hindering the control of meningitis.

Meningitis can be caused by various bacteria, fungi,viruses and parasites. Most infections are transmitted between individuals. A small number of cases result from injuries, cancer, or medications. The most prevalent and serious type of meningitis is bacterial meningitis.Over half of all meningitis deaths worldwide are caused by the principal pathogens of acute bacterial meningitis, which are Neisseria meningitidis (meningococcus), Streptococcus pneumoniae (pneumococcus), Haemophilus influenzae, and Group B Streptococcus (GBS). Among them, Neisseria meningitidis is one of the

main culprits for meningitis epidemics around the globe, especially in the "meningitis belt" of sub-Saharan Africa, where meningococcal diseases claim thousands of lives every year.

Understanding and controlling this deadly disease is crucial for improving global public health. Originally to the meningococcal serogroup A conjugate vaccination (MACV) being distributed throughout sub-Saharan Africa (SSA), serogroup A was quite common [1]. Following the signing of the Yaoundé Declaration in 2008, the serogroup A conjugate vaccine was introduced and widely administered across Africa, significantly reducing NmA cases and eliminating NmA outbreaks. The establishment of MenAfriNet in 2014 further improved meningitis surveillance and advanced preventive measures, detection, and response to meningitis outbreaks in Africa [2].

Within the African meningitis belt, serogroup A Neisseria meningitidis outbreaks have been eradicated in twenty-one nations since the serogroup A conjugate vaccine was developed. However, non-serogroup A meningitis remains a significant burden in the region and is largely unpredictable. As serogroup A cases have declined, other serogroups such as C, W, Y, and X have emerged as significant pathogens. While serogroup X meningococcus is less common compared to other serogroups, it remains a major cause of meningitis outbreaks in some areas of sub-Saharan Africa [3, 4]. This underscores the critical importance of developing a pentavalent vaccine.

This paper will review the existing literature to explore the role of the pentavalent meningococcal conjugate vaccine NmCV-5, which targets serogroups A, C, Y, W, and X, in reducing disease burden and improving public health. It will analyze the effectiveness of this vaccine in lowering disease burden and discuss the challenges encountered during its rollout, as well as potential future improvements.

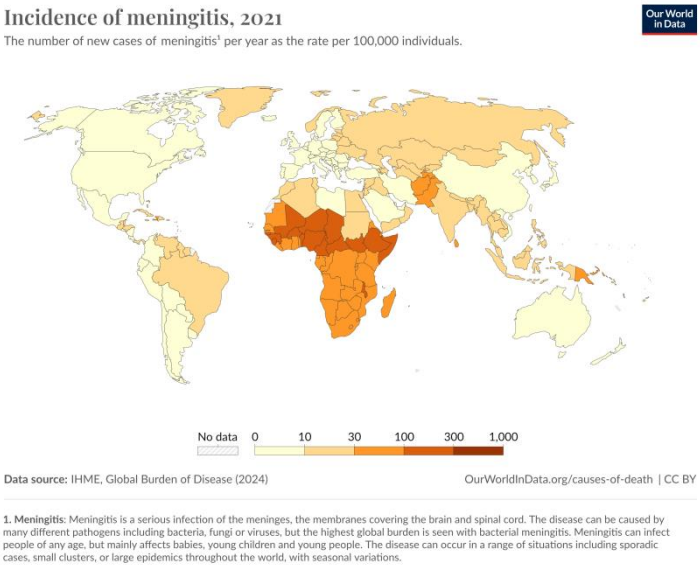

Figure 1. Incidence of meningitis, 2021 May 20, 2024 IHME, Global Burden of Disease (2024). https://ourworldindata.org/grapher/incidence-of-meningitis?time=latest

2. The Epidemiological Trends of Meningococcal Disease in Sub-Saharan Africa (SSA)

Particularly in the "meningitis belt," which stretches from eastern Senegal to Ethiopia, SSA has one of the highest rates of meningococcal illness worldwide.Each year, from January to May, during the 'dry season,' when much of sub-Saharan Africa experiences dry, windy, and dusty conditions, meningitis epidemics spread across multiple countries [5]. For much of the 20th century, serogroup A Neisseria meningitidis was the most common pathogen in this region. Large-scale epidemics of serogroup A meningitis occurred every 8 to 12 years, resulting in tens of thousands of infections and significant mortality. To address this severe public health issue, the introduction of the serogroup A

meningococcal conjugate vaccine (MenAfriVac) in the late 2000s successfully controlled the outbreak of this serogroup.

Serogroup C Neisseria meningitidis has caused significant outbreaks in certain countries, such as Nigeria and Niger. Serogroup W Neisseria meningitidis initially gained attention during the Hajj in Saudi Arabia and later spread to SSA, causing multiple outbreaks. Although serogroup Y Neisseria meningitidis has been relatively less common, there are emerging trends of increasing infections in some regions. Serogroup X Neisseria meningitidis caused localized outbreaks in the late 2000s, particularly in Burkina Faso and Niger, demonstrating its potential to spread among unprotected populations [6].

The epidemiological patterns of these diverse serogroups suggest that effective control of meningococcal disease in the region necessitates a vaccine targeting multiple serogroups. The development and implementation of the pentavalent meningococcal conjugate vaccine (ACYWX) are intended to address this increasingly intricate epidemiological challenge.

3. Background and Development of ConjugatePentavalent (ACYWX) Vaccines

3.1. Mechanism of Conjugate Vaccine

ACYWX vaccines belong to conjugate vaccines, the basic principle of which is to stimulate the immune system to respond to the weak antigen by linking the weak antigen by conjugating it with a more robust antigen.This is achieved by chemically linking a weak antigen (commonly a polysaccharide) to a carrier protein that acts as a strong antigen. The immune system recognizes and responds to carrier proteins and weak antigens.This promotes the development of antibodies capable of recognizing and neutralizing weak antigens, thereby providing protection against the disease. The immune memory effect of conjugate vaccine in infants and young children means that after vaccination with conjugate vaccine, the immune system of infants and young children can produce a memory response to the polysaccharide antigen in the vaccine [7,8].Conjugate vaccines have demonstrated greater efficacy compared to traditional polysaccharide vaccines, particularly in the immunization of young children

3.2. Development and Approval of the Pentavalent ACYWX Vaccine

3.2.1. Dvelopment

Meningitis caused by Neisseria meningitidis is a a principal cause of epidemic meningitis, particularly in the region known as the 'meningitis belt' of sub-Saharan Africa. Traditionally, serogroup A of Neisseria meningitidis was the most predominant pathogen in this area, however with the control of Group A meningococcal meningitis, the prevalence of other serogroup such as C, W, Y and X began to increase. To meet this new challenge, it became necessary to develop A vaccine capable of covering the five major serogroup A, C, Y, W, and X.

Pentavalent meningococcal conjugate vaccine (A, C, Y, W, X). The development of is designed to provide broad protection. The vaccine combines polysaccharide antigens from multiple serogroups with carrier proteins, thereby improving immunogenicity, especially in children and those with weakened immune systems. The development of the pentavalent vaccine was based on substantial epidemiological data demonstrating a significant increase in the incidence of Group X meningococcal meningitis in SSA and the need for more comprehensive preventive measures [9]. In response to the various difficulties posed by meningococcal illness in Sub-Saharan Africa, NmCV-5 was created.

3.2.2. Clinical Trials and Safety

In 2017, NmCV-5 vaccine completed phase 1 trials, This study focuses on the phase I study of a pentavalent meningococcal conjugate vaccine targeting serogroups A, C, Y, W, and X (NmCV-5). The objective of the investigation was to assess the safety and immunogenicity of the NmCV-5 vaccine. The results showed that NmCV-5 vaccine was well tolerated in healthy adults and produced

serum antibodies predicted to provide protection against all five serogroups. Further clinical trials will help to confirm the safety and immunogenicity of NmCV-5 in the target population. The vaccine holds promise for further elimination related to meningococcal disease in sub-Saharan Africa and for prevention in travellers and during the Hajj in other regions [10]. The phase 2 trial was completed in 2018 and addressed the safety and immunogenicity of MenACWYX conjugate vaccine in Malian toddlers aged 12-16 months. The local reactivity of non-adjuvanted and adjuvanted NmCV-5 was found to be similar to MenACWY-D, and no safety concerns were identified. It was also found that NmCV-5 did not require an adjuvant, as the immune response to all serogold was similar in both formulations at all time points. In addition, NmCV-5 is also highly immunogenic against group X, for which no licensed vaccine is currently available. The findings suggest that single-dose NmCV-5 may provide protection in vaccinated children aged 12 to 16 months and that NmCV-5 is noninferior to MenACWY-D in immune response [11]. Phase III trials conducted in Mali and The Gambia with healthy individuals aged 2 to 29 years demonstrated that the NmCV-5 vaccine was immunologically non-inferior to the licensed quadrivalent meningococcal conjugate vaccine, MenACWY-D. The study's findings suggested that the NmCV-5 vaccination was non-inferior in all three age categories, whether measured by seroresponse or geomertric mean titer (GMT). The safety assessment of the NmCV-5 vaccine was comparable to that of other licensed vaccines. These data are expected to support the classification of NmCV-5 as a pentavalent meningococcal conjugate vaccine, which includes protection against serogroup X.

Licensure and World Health Organization prequalification. This study demonstrates that meningococcal ACWYX conjugate vaccine is safe and effective in the population of African countries and can provide an important tool for the prevention of meningococcal infection [12].

3.2.3. Vaccine Introduction and Implementation

NmCV-5 was prequalified by WHO in July 2023 and was included in the third pentavalent vaccine. The vaccine has been approved by the WHO Strategic Advisory Group of Experts on Immunization (SAGE). SAGE has recommended that the vaccine be licensed for use in the African meningitis belt.The state will target serogroups A, C, Y, W, and X (Men5CV, novel pentavalent meningococcal conjugate vaccine (NmCV-5) was included in the routine immunization program.In high-risk countries and regions, catch-up vaccination efforts should also target all individuals aged 1 to 19 years at the time of NmCV-5 introduction [13-15]. As NmCV-5 is still in the process of development and promotion, its impact on disease burden, public health and social economy in SSA has not yet been shown. For SSA regions with frequent meningitis outbreaks, a single-dose regimen of NmCV-5 vaccine may be more cost-effective because there is no need for people to return for a second dose. Therefore, NmCV-5 vaccine is expected to play A role in outbreaks of meningitis caused by serogroups A, C, W, Y, or X in the meningitis belt areas of SSA and achieve similar success to MenAfriVac [11]. At the same time, the World Health Organization (WHO) and national governments are collaborating to roll out NmCV-5 vaccine in additional high-risk countries by 2024. This includes mass immunization campaigns and research that continues to monitor vaccine efficacy and safety [14].

4. Possible Challenges and Recommendations for NmCV-5 Vaccines in SSA

4.1. Lack of Public Awareness

The barriers to lack of public awareness mainly included misconceptions about vaccines, vaccine hesitancy, lack of awareness about the importance of vaccination, concerns about side effects of vaccination, and lack of knowledge about vaccination services. These factors influence public decision making and behavior regarding vaccination.

In order to overcome these barriers, health education to the public is needed to improve their knowledge and trust in vaccines. At the same time, parents or guardians may hesitate or refuse to vaccinate their children due to concerns about the safety and efficacy of vaccines, fear of vaccine side

effects, and misconceptions about vaccination or the impact of misinformation.In order to overcome vaccine hesitancy, it is necessary to strengthen public education and publicity on vaccines, provide accurate and reliable information, support the safety of vaccines through more experimental data, and increase trust and recognition of vaccination. In addition, it is necessary to strengthen communication with parents and communities to understand and address their doubts and concerns, provide personalized health education and counseling services to address their concerns about vaccine side effects, and provide clear information about vaccination services. In addition, socio-cultural contexts, including attitudes and decision-making power of male partners, need to be considered to ensure successful implementation of vaccination programs.

4.2. Poor Infrastructure

There are a number of infrastructure barriers in the vaccination process that affect vaccine coverage. First of all, the vaccine cold chain system is not perfect, and the vaccine refrigerator often fails to ensure the cold storage temperature of the vaccine. Second, some remote areas lack adequate health service points, parents have to travel long distances to bring their children for vaccination, and some vaccination points are understaffed, often with only one staff member responsible for a wide range of vaccinations. In addition, health workers need to travel long distances for vaccination services due to inconvenient transportation, and parents are also unable to complete the full vaccination due to distance. Moreover, vaccine supply was low, and staff had to wait until enough children were seen before they could start using multi-dose vials. These problems combine to make vaccination difficult, especially in remote and low-resource Settings.

To overcome these barriers, infrastructure needs to be strengthened to improve the stability and reliability of the vaccine supply chain, provide appropriate storage and transportation conditions, and increase medical facilities and transportation convenience in remote areas. In addition, health system management and supervision need to be strengthened to ensure the sustainability and quality of vaccination services.

4.3. Policy and Governance Challenges

In some countries, despite well-developed vaccination policies, the implementation challenges such as bureaucracy, corruption, and misallocation of resources often undermine the effectiveness of vaccine roll-out. Especially in countries in sub-Saharan Africa (SSA), vaccination programs are highly dependent on assistance from international organizations and nongovernmental organizations. As a result of this dependence, any reduction or delay in international assistance may lead to interruption of the vaccination program, further affecting vaccination coverage and effectiveness.

Factors affecting childhood immunization coverage and effectiveness are multifaceted at the country level. First, the development and implementation of immunization policies and plans is critical to coverage. Governments need to develop clear, feasible policies and ensure their effective implementation and monitoring. Second, the capacity of health systems is another key factor. This includes adequate human resources, appropriate facilities and equipment, effective cold chain management, and adequate vaccine supply. In addition, health education and publicity are essential to improve public awareness of immunization, dispense with misconceptions and concerns, and increase the willingness to vaccination. In addition, sociocultural factors such as religious beliefs, cultural practices and social concepts also affect parents' attitudes and behaviors towards vaccination.

To overcome these challenges, countries need to adopt a combination of measures. First of all, we need to strengthen the capacity of policy formulation and implementation, ensure that policies are scientific and feasible, and supervise the implementation effect by establishing a sound monitoring and evaluation mechanism. Second, enhance health system capacity, including by increasing human resources, improving facilities and equipment, and strengthening vaccine cold chain management and supply security. At the same time, the state should also strengthen the publicity and education of vaccination to improve the public's awareness of vaccination. In addition, while international

cooperation remains important, SSA countries need to build more autonomous and sustainable health systems to reduce dependence on foreign aid fluctuations and ensure stability and continuity of vaccination programs.

Through these multipron-based strategies, countries can effectively address current vaccination challenges, further improve childhood immunization coverage and effectiveness, and protect children's health [16].

5. Conclusion

The formulation and advancement of promotion of pentavalent meningococcal conjugate vaccine (NmCV-5) provides an important opportunity aimed at the prevention and management of meningococcal disease in sub-Saharan Africa (SSA). The successful control of meningitis attributable to Neisseria meningitidis serogroup A shows that vaccination is a key tool to effectively contain epidemics, The introduction of NmCV-5 will help to cope with the epidemic trend of Neisseria meningitidis serogroups C, W, Y, and X. Several studies have confirmed the safety and immunogenicity of the NmCV-5 vaccine. The favorable safety profile of NmCV-5 has been confirmed in clinical trials and is similar to that of other multivalent meningococcal vaccines. Common adverse reactions are usually mild or moderate and mainly include localized reactions at the injection site, such as pain, redness, or induration and systemic responses(such as mild fever, fatigue, or muscle soreness). These reactions usually resolve spontaneously within 24 to 48 hours after vaccination. The incidence of Serious Adverse Events (SAEs) was very low, and there was no evidence of a causal association between the vaccine and severe adverse events, indicating that the vaccine was well tolerated. In terms of immunogenicity, NmCV-5 vaccine was able to elicit a robust humoral immune response, and the levels of specific antibodies against five serogars A, C, Y, W, and X were significantly increased. The study demonstrated that the serum bactericidal antibody (SBA) titer of the subjects increased significantly after vaccination, indicating the ability of the subjects to induce protective immunity. The vaccine shows high immunogenicity in people of different ages, including infants, children, adolescents and adults, and the antibody response lasts for a long time after multiple doses, providing broad protection against a variety of circulating serogroups.

Nevertheless, challenges to rollout remain, including poor infrastructure, unstable vaccine supply chains, and lack of public awareness. To ensure the successful rollout of NmCV-5, governments and international organizations need to strengthen cooperation in policy development, infrastructure development, and health education. In conclusion, the introduction of NmCV-5 vaccine is expected to significantly reduce the disease burden of meningitis in SSA, promote public health progress in the region, promote the optimal use of vaccine, and improve the coverage of vaccination in appropriate age groups and key populations.

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