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Review

Meningococcal vaccines: Current state and future outlook

Les vaccins méningocciques : état des lieux et perspectives

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ABSTRACT

Neisseria meningitidis infections are a major public health problem worldwide. Although conventional approaches have not led to development of a serogroup B meningococcal vaccine, a new technique based on genome sequencing has created new perspectives. Recently, a universal serogroup B meningococcal vaccine, Bexsero®, was licensed in Europe, Australia and United States, following several clinical studies demonstrating its immunogenicity and safety. Availability of this vaccine could contribute positively to human health, by significantly reducing the incidence of meningococcal infections. However, unfavorable cost-effectiveness analysis means that routine vaccination is not currently recommended. Another serogroup meningococcal vaccine, Trumemba®, was also recently licensed in United States. Like any drug, Bexsero® and Trumemba® will require close observation to assess their impact on meningococcal epidemiology.

Mots clés :
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RÉSUMÉ

Les infections à *Neisseria meningitidis* sévissent dans le monde entier et restent un véritable problème de santé publique. Toutefois, la vaccinologie conventionnelle n'a pas permis le développement d'un vaccin contre le méningocoque de sérogroupe B. Une nouvelle technique, la vaccinologie inverse, a alors ouvert de nouvelles perspectives. Récemment, un vaccin universel antiméningococcique B, Bexsero®, a été autorisé en Europe, en Australie et aux États-Unis, suite à des études cliniques d'immunogénicité et d'innocuité concluantes. La mise à disposition d'un tel vaccin peut apporter une réelle contribution à l'amélioration de la santé humaine, pouvant réduire significativement l'incidence des infections méningococciques. Cependant, la vaccination systématique n'est pas recommandée actuellement, en raison d'une analyse coût–efficacité défavorable. Un second vaccin antiméningococcique B, Trumemba®, a également été récemment autorisé aux États-Unis. Comme tout médicament, ces deux vaccins nécessiteront une surveillance étroite, permettant d'étudier leur impact sur l'épidémiologie méningococcique.

Invasive meningococcal disease (IMD) is perceived as a serious threat by the public, who are very influenced both by the media, and by the medical professions [1]. These infections have different clinical consequences (meningitis, septicemia, arthritis, pneumonia, and pericarditis), which can occur simultaneously, sometimes inducing misdiagnosis [2,3].

Meningococcal infections remain a public health problem throughout the world [2,4]. Indeed, in the context of the development and accessibility of relatively new vaccines (especially against *Haemophilus influenzae* type b and *Streptococcus pneumoniae*), *Neisseria meningitidis* is considered one of the most frequent infectious causes of death outside the neonatal period [5–7]. The diversity of meningococcal strains is correlated to the antigenic variability of the bacterial capsule [8,9].

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In accordance with serological methods based on the composition of the polysaccharide capsule, an international nomenclature was established to identify and to monitor precisely epidemic clones [10]. This classifies *Neisseria* into 13 distinct serogroups, of which 6 (A, B, C, W135, X and Y) are distinguished by their high virulence for humans [3,8,9,11].

Since the introduction of polysaccharide conjugate vaccines against serogroups A, C, W-135 and Y, serogroup B has emerged as the basic cause of IMD, particularly in Europe and North America, where it creates hyperendemic or epidemic situations, especially due to the lack of prophylaxis for this serogroup [4,11].

Thus, the best strategy against IMD remains primary prevention via meningococcal vaccination, including the development of a vaccine targeting serogroup B [3,10,12,13].

1. Development of a meningococcal group B vaccine

1.1. The need for meningococcal group B vaccine

The epidemiology of meningococcal disease is dynamic: all serogroups vary temporally and geographically [6,10,14]. This marked disparity can mainly be explained by differences in immunity among ethnic groups, and by the influence of environmental factors [3,6].

Each year, IMD estimates rise by 1.2 million cases worldwide, including 135,000 deaths [12]. In response to these alarming statistics, the World Health Organization (WHO) has for example introduced specific vaccination campaigns against serogroup A in Africa where it is predominant to limit large meningococcal epidemics [14,15].

However, the threat persists, especially in industrialized countries where serogroup B is involved in most cases of IMD (84% of IMD in Australia, 83% in New Zealand, 76% in Europe and 35% in the United States). In Europe, the annual incidence of serogroup B is 1 case per 100,000 population [14].

According to epidemiology data, some populations are more sensitive to infection. In the United States, nearly 60% of IMD in infants under the age of 59 months is caused by serogroup B [16].

In France, the highest incidence is observed in infants aged 0–12 months, with the annual incidence reaching 11.1 cases per 100,000 population. This rate is correlated to the immaturity of their immune system.

A high incidence is also observed later, in young adults aged 15–24: at 19 years, the incidence rises to 2.89 cases per 100,000 population [17,18]. The social behavior of young adults can facilitate exposure to strains against which they have no immunity [17,19].

IMDs are characterized by their global distribution, their epidemic potential, their unpredictability (their potential to alter the health of a healthy individual without any history of illness), their rapid progression and their minor and non-specific symptoms [3,6,8,20,21]. All these factors explain the severity of these infections, and why rapid diagnosis and immediate initiation of treatment are vital [2].

Despite technical and therapeutic advances, the overall mortality rate remains between 10% and 15%, and up to 19% of survivors have disabling sequelae such as hearing loss, cognitive dysfunction, motor nerve deficits, seizure disorders, amputation [16,20].

Given the severity of meningococcal infections, developing a meningococcal B vaccine that can control the most of these devastating epidemics has become a real priority for medical research [17,22].

1.2. Special features of serogroup B

Meningococcal vaccines targeting serogroups A, C, W-135 and Y have demonstrated their effectiveness [6,23]. However, there are a number of reasons why the immunological approach to traditional vaccine development, conjugate or polysaccharide, is out of the question for serogroup B [6,13,24,25].

First, the heterogeneity of intra-serogroup proteins, especially the dominant protein, Porin A (PorA), seriously complicates universal vaccine design [26,27].

Up to now, only specific vaccines prepared from vesicles on the bacterium surface, outer membrane vesicle (OMV), were developed and used as the need arose. They were used for disease control in epidemic situations in Brazil, Chile, Cuba (VaMencog-BC®), Norway (MenBVac® vaccine), New Zealand (MenZB® vaccine) and recently in France (Norwegian MenBVac® vaccine because of epidemic strain similarity) [4,22,28–35]. The composition of these vaccines was determined by a particular bacterial clonal strain, so their effectiveness was limited to certain epidemic conditions [24,27]. For example, the Cuban vaccine, which showed an effectiveness rate of about 83% in Cuban children aged above 4, was less effective in Brazilian children, with an effectiveness rate of 74% [28,31,36]. Moreover, Cuban vaccine effectiveness in Brazilian newborns appeared to be considerably lower than that reported for Cuba newborns [28]. These vaccines, termed *tailor-made*, are poorly immunogenic in children less than 4 years old, and the duration of protection is limited [4,10,37]. These protein vaccines do not therefore constitute a global vaccination strategy against serogroup B [25,28,38].

Secondly, the polysaccharide capsule of serogroup B contains polysialic acid, as do all the capsules of meningococcal virulent serogroups, with the exception of serogroup A, which is composed mainly of N-acetyl mannosamine-1-phosphate [3]. The main difference between serogroups B and C is their linkage patterns: the group B capsule has 2-8 linkage while group C has 2-9 linkage [38].

The final structure is sufficiently different to induce specific antibodies for each serogroup [6]. The derivative of the polysialic acid contained in the serogroup B capsule is found in many human tissues, especially in the central nervous system, and particularly in adhesion cells (neural cell adhesion molecule [N-CAM]), highly expressed in the fetus and the young child in development [26,39,40]. Cross-reactivity between N-CAM embryonic isoforms and sera from patients with serogroup B meningococcus was also demonstrated while this reaction was absent in healthy subjects [39]. Molecular mimicry induces low immunogenicity, attributed to immunological tolerance by the host to the sialylated glycopeptides, physiologically contained in some body zones [25]. Consequently, if this antigen was included in a vaccine, T-cells, particularly T-lymphocytes, might recognize the self-antigen [25,39]. Antibodies secreted by the immune system would be directed against a molecule physiologically present in the human body, and might cause autoimmune disorders, particularly in the brain. Despite various attempts, particularly chemical modification of the N-acetyl group, there has been no real success [41].

The real challenge is therefore to develop a multivalent vaccine to expand vaccine coverage and to avoid the risk of selecting for vaccine escape variants against a pathogen that mimics host molecules [27].

1.3. Reverse vaccinology, an innovative and promising technique

The conventional approach to vaccine development proceeds via the in vitro culture of the pathogenic organism, allowing potential antigenic components to be individually identified by biochemical, immunological and microbiological methods [37,42]. Finally, each isolated antigen is analyzed to determine its ability to induce protective immunity. Although this long and tedious technique, termed "classical vaccinology", has led to many vaccines commonly used today, it still presents some limitations