REVIEW

Meningococcal B vaccination strategies and their practical application in Italy

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Summary

Immunisation against meningococcal meningitis has a long history, which has passed through several phases: the studies by Flexner, extraction of the polysaccharide capsule, the development of monovalent and multivalent conjugate vaccines, the outer membrane vesicle vaccines up to the development of effective and safe vaccines for meningococcal B invasive disease through the application of the techniques of molecular biology and reverse vaccinology.

The new available vaccines are Bexsero® and Trumenba®. Bexsero® has been approved and is available in Europe, the USA, Canada, Australia and Chile, and is currently under review in Brazil for the prevention of MenB invasive disease in subjects ≥ 2 months.

Trumemba® is currently approved only in the USA, for use in adolescents and young adults.

At present, the greatest obstacle to the extensive use of these vaccines in industrialised countries is the high cost and the need administer multiple doses in infants. However, in some European countries and in some Italian Regions, strategies (free and active call) to fight the disease through vaccination (Bexsero®) are already in place.

Introduction

Conjugate vaccines against *Haemophilus influentiae* type b, *Streptococcus pneumoniae* and *Meningococcus* C have dramatically reduced cases of bacterial meningitis in the industrialised nations. However, meningitis type B continues to be a threat to children and adolescents worldwide.

Unlike other serogroups, *Neisseria meningitidis* B (MenB) disease cannot be prevented by polysaccharide vaccines. The reason for this lies in the chemical structure of the MenB capsule, which contains units are identical to some human polysaccharides (human foetal neural cells) and, therefore, determine immunological tolerance [1]. Consequently, research into an effective MenB vaccine has focused on subcapsular antigens, outer membrane vesicles (OMVs). OMVs were successfully used to control specific outbreaks. OMVs are proteoliposomes that contain several different molecular components out of which the porin protein, PorA, is the principle antigenic source of bactericidal antibodies. The limitations of these vaccines are that effectiveness tends to be limited to strains containing the same PorA protein (serosubtype-specific), limiting its use to strain-specific outbreaks and they often elicited a scant immune response in young children [2].

In the last years, the vaccine industry has overcome this difficulty, and a MenB multicomponent vaccine – 4CMenB – Bexsero® – has been developed. This vaccine has been licensed in Europe and other developed countries for the prevention of MenB invasive disease in subjects ≥2 months. In addition, a vaccine containing two variants of factor H binding protein (fhbp) of the complement has been approved by the Food and Drug Administration in the USA (Trumemba®) for use in individuals 10 through 25 years of age.

These advances have prompted some authors to wonder whether we are witnessing "the beginning of the end for invasive MenB disease" [1].

In order to eliminate an infectious disease, the first essential requirement is undoubtedly the availability of safe and effective vaccines. However, strategic planning of the application of the vaccines which have become available is equally important.

This overview examines the policies of vaccination with new meningococcal B vaccines, particularly 4CMenB, in Italy.

Natural history of MenB infections

Meningococci have their natural and unique survival niche in humans. This fundamental biological fact implies that *N. meningitis* has acquired several mechanisms for cohabitation with the human organism [3]. Only in particular conditions of frailty of the human host or in certain environmental situations is the microorganism able to manifest its aggressiveness, leading to meningococcal diseases and even death [4, 5].

From sero-epidemiological studies [6, 7] we have learnt much about the biology of this microorganism. In the blood of infants, bactericidal antibodies against Neisseriae are present as a result of the passage of maternal antibodies through the placenta during pregnancy. However, as this protection wanes early, infants are soon exposed to the risk of infection. Indeed, the percentage of infants and children who show bactericidal antibodies grows until the age of about four years. Subsequently, antibody titres decline until adolescence, before increasing again. This pattern is in line with the fact that the two main peaks of morbidity of the disease are seen in subjects under 4 years of age (particularly in infants under 1 year) and in young adults. These epidemiological observations are of primary importance in understanding the spread of the microorganism in the environment around the infant and adolescent. The greatest risk to the infant is engendered by premature contact with virulent strains of *N. meningitidis*, as has been shown by mathematical modelling [8]. Indeed, the risk of MenB invasive disease has been calculated to be 400 times higher in such cases than in the case of non-early contact.
The situation changes during adolescence, when a more promiscuous social life (kissing, sexual contact, frequenting recreational premises such as pubs, etc) exposes subjects to more frequent contact with the microorganism. Indeed, it is precisely in these subjects that *Neisseriae* find their ideal niches for survival, as demonstrated by studies on carriers [9, 10].

Epidemiology of MenB infections

The distribution of the various serogroups of meningococcal pathogens fluctuates considerable. However, serogroup B currently predominates over the other serogroups in Europe, Australia, Canada and Japan. One reason for this predominance is attributable to extensive vaccination with conjugate vaccine against meningococcal serogroup C [11-16]. Of a total of 3463 confirmed cases of invasive meningococcal disease (IMD) reported in 28 EU/EEA countries in 2012, 2078 were caused by serogroup B; this predominance of serogroup B was most pronounced in infants (83% of cases, 8.9 per 100,000) and 1-4-year-olds (9% of cases, 2.9 per 100,000) [17].
The Italian surveillance system of invasive bacterial infections detected 991 cases of invasive meningococcal disease from 2007 to 2012, with an average of 165 cases per year. Information on typing is available for 764/991 cases (77.1%). Serogroup B was the most frequent (455 cases), constituting 59.6% of the cases typed, followed by serogroup C (220 cases) and serogroup Y (59 cases). During the reporting period, a decrease was observed in cases of meningococcal B (from 81 cases in 2007 to 52 in 2012) and C (from 43 cases in 2007 to 34 in 2012), while cases of serogroup Y gradually increased (from 3 in 2007 to 17 in 2012). Furthermore, on analysing the distribution of serogroups by age-group, it was observed that serogroup B was the most frequently isolated in the younger age-groups. Indeed, considering the 762 cases for which age information was available, serogroup B accounted for 81.1% (77/95) of all cases occurring in the first year of life, 66.2% (92/139) of cases in 1-4-year-olds and 70.1% (54/77) in 5-9-year-olds; in the other age-groups it accounted for about 50% of cases [18]. However, as demonstrated by Azzari et al. [19] by means of real-time PCR, in those countries (such as in Italy) [20] where only positive-isolate samples are counted as meningococcal cases, the incidence is largely underestimated. Furthermore, it is well known that culture-based methods have even lower sensitivity than molecular methods when the patient has been treated with antibiotics [21]. In addition, Azzari et al. found in their study that the case fatality rate was 13.2%, which is higher than the 5% rate recently reported in MenB in patients of any age [19, 22].

History of meningococcal vaccines against MenB

In the early 1900s, several attempts at using inactivated vaccines containing whole bacterial cells were made [23-27]. However, both these studies and subsequent clinical trials revealed that whole inactivated vaccines were excessively reactogenic. Later vaccines obtained from meningococcal culture filtrate also yielded contradictory results [28, 29]. The first successful meningococcal vaccines were obtained as a result of studies by Gotschlich et al., who were able to extract and purify high-molecular-weight meningococcal polysaccharides at the Walter Reed Army Institute [30, 31]. However, unlike the polysaccharides of serogroups A and C, the polysaccharide of serogroup B did not raise the production of antibodies on account of phenomena of immune tolerance. Thus, studies to prepare a vaccine against meningococcal B shifted to subcapsular antigens. The first and simplest approach was to use the meningococcal outer membrane vesicles containing membrane proteins (OMVs) and lipopolysaccharide (LPS). Four different formulations of these vaccines were used in Cuba, Chile, Norway, New Zealand and France [32].
However, as subcapsular proteins are very variable, these vaccines proved to be of limited use in containing clonal epidemics. Therefore, in order to identify antigens for development of universal MenB vaccine, studies were oriented towards the determination of the entire genome of a pathogenic strain of *N. meningitidis* type B (MC 58 strain) [33]. Thus, thanks to remarkable advances in bioinformatics and molecular biology, along with the knowledge acquired over the entire genome of MenB, a new science was born – "reverse vaccinology". Indeed, the computer-assisted screening of the genome of the microorganism enabled the proteins that were the best candidates for a vaccine against MenB to be identified [34]. It was thus possible to identify about 600 open reading frames that were believed to express surface or exported proteins of MenB. Starting from these 600 proteins, it was possible to express 350 in *E. coli*, which, after being purified, were able to elicit bactericidal an-

tibodies in mice. Finally, through successive studies on rat and mouse models, the best components were found: Neisserial heparin binding antigen (NHBA), factor H binding protein (fHbp), Neisseria adhesion A (NadA) [32]. The new universal MenB vaccine (4CMenB – Bexsero®) also contains the OMVs of the New Zealand strain NZ98/254.
Contemporarily, other researchers developed another new-generation MenB vaccine (rLP2086 – Trumemba®), a preparation containing two representative variants of subfamilies A and B of fHbp [35-39].
Another approach pursued by scientists in order to develop a vaccine for meningitis B was to improve vaccines containing antigens of the outer membrane. This approach is based on the ability of genetically modified MenB to express different subtypes of porin A. The latest development of this vaccine contains 9 subtypes of PorA [40].

Availability of new MenB vaccines

Bexsero® has been approved and is available in Europe, the USA, Canada, Australia and Chile, and is currently under review in Brazil [41]. Trumemba® is currently approved only in the USA, for use in adolescents and young adults [42].

MenB vaccination policies

Vaccination strategies should be considered in terms of both collective prevention and individual prevention.
The natural history of meningococcal infections and invasive disease epidemiological trends clearly suggest that: a) it is necessary to protect infants as early as possible; b) it is important to vaccinate adolescents and young adults, who are a risk group, as they constitute the reservoir of the microorganism and can transmit the pathogen to infant siblings. Moreover, in the individual perspective, it is important to reach vulnerable subjects.
The best policy would be to vaccinate all subjects from 0 to 18 years of age through an extensive campaign, as suggested by the results achieved in the UK with the conjugate vaccine for meningococcus C [43]. When this is not economically sustainable, it is very important to study the conditions which regulate the spread of the disease. Mathematical models with simplified algorithms can provide the key to obtaining the maximum yield with the minimum of resources. The first question concerns how many subjects the sick person is able to infect [44]. Naturally, this will depend on the characteristics of diffusivity of the pathogen, the number of subjects with whom the patient comes into contact, the number of susceptible, partially susceptible or protected individuals, and the period of time during which the subject is able to spread the disease. It is logical to imagine that, if a large number of subjects are protected, for example through vaccination, the pathogen will have difficulty spreading in the healthy population. If the proportion of vaccinees is high enough, it may be assumed that the patient can infect only a small number of people; if this number falls below 1, there is hope that the disease can be eliminated, as it will be impossible for the microrganism to circulate among humans. The mathematical modellers call this proportion the critical percentage of vaccination coverage. The higher the critical percentage is, the harder it will be to eliminate the disease. Now, in the case of meningitis, this critical percentage is estimated to be not very high. Indeed, to calculate the critical percentage of coverage, it is necessary to know the value of the basic reproductive number (R_0), which has been estimated to be approximately 1.36-1.4 [45] for meningococcal type C. It may be even lower for meningococcal type B [46]. If, however, we imagine that the value of R_0 is between 1.26-1.4 for MenB, we can calculate [47] that the critical percentage of coverage ranges from 26.5 to 28.6%. Furthermore, during our recent study [9], we did not find the carriage state for meningococcus C among young adults in a setting where a coverage rate for the conjugate vaccine against *N. meningitidis* of serogroup C is 87% among children and 49% among adolescents [48].
It is also important to consider that herd immunity against *N. meningitis C* has been substantially achieved through vaccination with the conjugate vaccine. Indeed, Trotter et al. found that, although the protection provided by the vaccine is, theoretically limited in British infants immunised with conjugate vaccine this protection persisted over time. This was also in agreement with the decrease in meningococcal C carriers among young British adults after the 1999-2000 vaccination campaign [49, 50]. It could therefore be surmised that herd immunity can be effectively induced by MenB vaccine, too.
Recently, the World Health Organization (WHO) drew up some criteria for the introduction of a new vaccine. The basic criteria concern: disease burden, efficacy, safety and quality of the vaccine, comparison with other interventions against the disease, economic and financial issues, fiscal impact, financial sustainability, vaccine presentation, supply availability, and programmatic strength [51].
The guidelines defined by the WHO are in line with the criteria of Health Technology Assessment (HTA), which can obviously be applied to vaccines, too. Indeed, HTA is a method of multidisciplinary assessment that deals with analysing the technical, scientific, economic, ethical, legal, social and organizational issues arising from the application of new technologies [52]. Thus, in order to insert a new vaccine into the vaccination schedule (free and active offer by National Health Service), it is necessary to conduct an HTA study [53]. Indeed, vaccines are to be regarded as any other medical technology [52]. In HTA evaluations, cost-effectiveness studies assume great importance. In the specific case of Bexsero®, these have yielded contrasting results and there is still uncertainty as to whether MenB vaccination by means of the 4CmenB vaccine should be introduced in developed countries. Indeed, on evaluating the introduction of Bexsero® in England,

Christensen et al. concluded that vaccination would be cost-effective from the National Health Service (NHS) perspective at a cost of £9-£17 per dose [54]. Subsequently, however, after re-evaluating the cost-effectiveness of universal vaccination with Bexsero® in England could be cost-effective with a low vaccine price [55]. By contrast, the results of a study conducted in Italy by Capri et al. demonstrated the cost-effectiveness of vaccination at a cost of € 60 per dose, from the societal perspective [56]. However, a study conducted by Tirani et al. in Italy concluded that, from the NHS perspective, the immunisation programme was unlikely to be cost-effective [57].

We recently carried out a cost-effectiveness study of this issue (article submitted to Human Vaccines & Immunotherapeutics). Our results confirmed that, especially from the societal perspective, the vaccination of Italian infants is cost-effective; the study considered various scenarios and also took into account the fact that cases occurring in Italy are underestimated [19].

It is important to consider that economic studies on vaccinations can have some limitations and they often adopt conservative estimates as not considering the underestimation of cases of illness and considering a short-term duration of protection. It is certain that 4CmenB stimulates the immune memory as it is made from MenB surface proteins. Indeed, it is well known that the protein antigens are much more immunogenic in comparison with the polysaccharidic ones even if the latter are conjugated.

Fig. 1. Italian Regions where MenB vaccine is offer free vaccination (February 2015).

The offer of MenB vaccination against in Italy

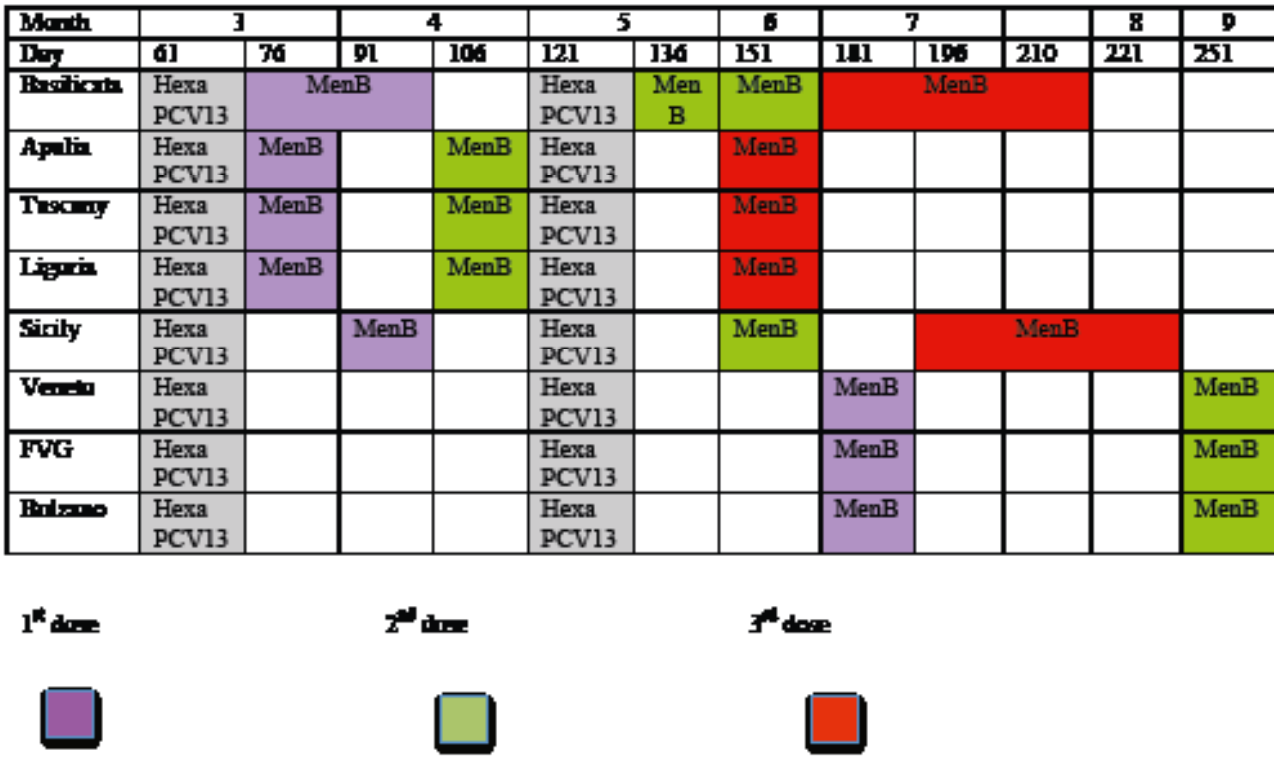
Eight Italian Regions and one Autonomous Province currently offer free vaccination for MenB to certain groups of people (Fig. 1). While Piedmont and Emilia Romagna offer it only to subjects at risk [58, 59], seven Regions and one autonomous Province offer it actively and free of charge for infants. Basilicata was the first Region to insert it into the childhood vaccination calendar [60]. Subsequently, Puglia, Veneto, Friuli Venezia Giulia, Tuscany, Liguria, Sicilia and the Autonomous Province of Bolzano included it in their vaccination schedules [61-67].

The above-mentioned seven Regions and the Autonomous Province of Bolzano, following the possible vaccine schedules (Tab. I), display slight variations in the age at which vaccination is administered. Indeed, as can be seen in figure 2, most of the Regions start vaccination early, as most cases of MenB invasive disease occur within the first year of life; only Veneto and Friuli Venezia Giulia schedule vaccination to begin at 7 months. With regard to the booster dose, most of the Regions schedule this at the 15th month, while Basilicata and Tuscany provide a booster at the13th month. For the moment, there is no plan to offer active and free vaccination for teenagers.

Tab. I. Authorized vaccination schedules of Bexsero® (Novartis Vaccines and Diagnostics Limited. Bexsero® Prescribing information. Document available at: http://www.bexsero.co.uk/healthcare-professional/pdfs/Bexsero%20PI.pdf. Accessed on 1st July 2015)

Age of administration	Primary immunisation	Time interval between doses	Booster dose
From 2 to 5 months	3 doses (0.5 ml)	At least 1 month	One dose from 12 to 23 months after primary immunisation
From 6 to 11 months	2 doses (0.5 ml)	At least 2 months	One dose in the 2nd year of life (at least 2 months after primary immunisation)
From 12 to 23 months	2 doses (0.5 ml)	At least 2 months	One dose (from 12 to 23 months after primary immunisation)
From 2 to 10 months	2 doses (0.5 ml)	At least 2 months	
From 11 months	2 doses (0.5 ml)	At least 2 months	

Fig. 2. Meningococcal B vaccination schedules of the Italian Regions that offer active, free vaccination for infants (primary immunisation).



Legend: Hexa: Hexavalent vaccine (diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and Haemophilus influentiae b); PCV13: Pneumococcal 13-valent conjugate vaccine; FVG: Friuli Venezia Giulia; MenB: Meningococcal B vaccine).

Conclusions

Strategically, infants constitute the first class of subjects to be vaccinated, and the Regions which offer free vaccination are rightly oriented in this direction. Indeed, the incidence rate of meningococcal meningitis in Italian infants under 1 year of age is 3.7 per 100,000, i.e. more than 10 times higher than the overall rate of invasive meningococcal diseases observed in Italy. Furthermore, serogroup B is more frequently detected among infants aged under 1 year, accounting for 65% of the total [68]. Moreover, both in order to better protect (indirectly) new-borns and to achieve the best herd immunity, it would be very useful to vaccinate young adults. It is likely that a similar multicohort strategy, even with relatively low coverage rates, could prevent the circulation of MenB.

Finally, the vaccination plans of the Italian Regions that offer vaccination for infants are appropriate to epidemiological reality, although Veneto and Friuli Venezia Giulia should bring forward the time of vaccination.

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