

REVIEW

Meningococcal serogroup B vaccine in Italy: state-of-art, organizational aspects and perspectives

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Key words

Meningococcal serogroup B vaccine • Meningococcal diseases • Regional immunization schedules

Summary

Neisseria meningitidis causes severe invasive meningococcal diseases (IMDs) in humans including meningitis and septicemia, responsible for serious clinical conditions and leading to life-long disabilities and death. Serogroup B dominates IMDs burden in Italy, accounting for over 60% of total cases. On January 2013 the European Medicine Agency (EMA) licensed the first serogroup B meningococcal (MenB) vaccine in Europe. A number of European countries and Regions have introduced the new MenB vaccine in their immunization schedule, including Italy. In this paper we present the state of art, related critical issues and future perspectives of MenB vaccine introduction in Italy, in the context of the most recent available epidemiological data. In particular, we systematically assess the ongoing

processes in the 8 Italian regions and one autonomous province that have already introduced MenB vaccine. With the new 2014-2018 National Vaccine Prevention Plan including active MenB vaccine offer about to be adopted, it is of fundamental importance to gather further evidence on MenB vaccine clinical effectiveness, duration of protection and cost-effectiveness. Italian regions are called to organize and manage MenB immunization programs. Careful consideration will need to be devoted on timing, doses, and co-administration with other vaccines but also to economic assessments and strengthened communication to the general public. Our data will help to plan, implement and evaluate MenB immunization programmes in other Italian and international settings.

Background

Neisseria meningitidis (meningococcus) causes severe invasive meningococcal diseases (IMDs) in humans including meningitis and septicemia, responsible for serious clinical conditions and leading to life-long disabilities and death [1]. It is estimated that between 10% and 14% of cases of IMD are fatal, and that up to 30% of survivors suffer from long-term sequelae [2, 3]. There are 13 identified serotypes of meningococcus, with six (A, B, C, X, W-135 and Y) being responsible for over 90% of severe meningitis and septicemia cases [4]. The distribution of meningococcus serotypes is setting-specific. Serogroup A is mainly distributed in the Sub-Saharan African countries of the *meningitis belt* where it causes around 85% of IMDs. Serogroup X, previously a rare cause of sporadic meningitis, has been responsible for outbreaks between 2006 and 2010 in the African region [5, 6]. The meningitis belt is the area where the highest burden of IMDs occurs with 14317 cases and 1304 deaths reported in 2014 [7].

In Europe, the USA and other industrialised regions, serogroups B and C are the major cause of IMDs [8]. In Europe good surveillance data is available in most countries and implementation of meningococcal immunization programs have largely contributed to decreasing endemic rates [9]. The most recent available surveillance data refers to 2012 with 3,463 reported IMDs, this corresponding to an incidence of 0.68 cases per 100,000

population, higher in children under one year of age (11.4/100,000) and between one and four years of age (3.7/100,000). The overall case fatality rate (CFR) was 7.9% and meningitis was the clinical presentation in 43% of cases [8].

Meningococcal disease is a vaccine preventable disease. There are several registered vaccines: a meningococcal A conjugate vaccine, C conjugate vaccines, tetravalent A, C, Y and W conjugate vaccines and meningococcal polysaccharide vaccines [10]. In Europe, serogroup C conjugate vaccination (MCC) implementation has had a major impact on the declining incidence of serogroup C meningitis [11]. In 2012, serogroups B and C were responsible for, respectively, 68% and 17% of confirmed IMDs cases in the EU [8]. Since the introduction of serogroup C conjugate vaccination (MCC) Meningococcus B had emerged as a relatively important cause of IMD in Europe, this due to the lack of preventative measures for this serogroup [12]. On 14 January 2013 the European Medicine Agency (EMA) licensed the first serogroup B meningococcal vaccine in Europe. A number of European countries and Regions have introduced the new MenB vaccine in their immunization schedule, including Italy. In the United States the first Meningococcal Group B vaccine was licensed by the Food and Drug administration in 2014 Vaccine [13].

General aim of the present study is to describe the introduction of the MenB vaccine in Italy, presenting the state of art, related critical issues and future perspectives.

tives. In particular, specific objectives are: i) to describe the technical documents, decisions and policies taken at the national level and ii) to systematically assess the ongoing processes in the 8 Italian regions and one autonomous province that have already introduced the MenB vaccine in the Regional immunization schedules.

The new Meningococcal B vaccine

As introduced above, a new vaccine for the prevention of serogroup B meningococcal (MenB) disease is now available in Europe (4CMenB) [14, 15]. In the past, the antigenic diversity of the meningococcal surface proteins had been the main limitation in the design of broadly protective meningococcal vaccines, as well as the fact that the polysaccharide of serogroup B fails to stimulate the production of antibodies (phenomena of immune tolerance). MenB vaccine was developed through the 'reverse vaccinology' technique, which has been applied for the first time to develop the MenB vaccine [16] and allows the production of vaccines from genome-derived antigens. In fact, it applies bioinformatic tools to comprehensively screening of pathogens' genome data for surface-expressed proteins, in order to select candidate vaccine antigens. Proteins likely to be used as vaccine antigens are identified and further tested for immunogenicity on animal models [17]. In the case of MenB, the genome sequence of the virulent MenB strain MC58 was analysed (i.e. The MenB genome was sequenced). Nearly 600 open reading frames were selected; from these, 350 candidate antigens were expressed in *Escherichia coli*, purified and used to immunize mice. Subsequent screening of the mice sera revealed 91 surface-exposed proteins that induced bactericidal antibodies in vivo [18]. This step-by-step elimination, based on the ability to induce broad protection in infant rat or mouse models, led to the identification of the antigens now included in the 4CMenB vaccine formulation. In other words, the reverse vaccinology strategy identified a set of proteins that had the characteristic for being effective vaccines' antigens: accessible to the immune system, immunogenic, inducing a protective response, present in all strains, and with minimal sequence variation [18, 19]. The 4CMenB contains the following four components [19]:

- The Neisseria adhesion protein (NadA);
- The Neisseria Heparin Binding Antigen (NHBA) fused with the Neisseria Antigens GNA1030;
- The factor H binding protein (fHbp) fused with the Neisseria Antigens GNA2091;
- Outer membrane vesicles (OMV)

4CMenB is indicated for active immunisation of individuals from 2 months of age and older, against invasive meningococcal disease caused by *Neisseria meningitidis* group B. It was licensed in Europe (European Medicine Agency - EMA, 2013) [20], in Australia (Therapeutic Goods Administration - TGA, 2013), in USA (Food and Drug Administration - FDA, 2015) in Canada (2013) and Chile [14, 15]. In the United States, also another

MenB vaccine was licensed by FDA in 2014 (rLP2086 vaccine) [21].

Clinical trials have been carried out in the context of the vaccine registration process and some data are available on 4CMenB immunogenicity and safety. No studies have been conducted so far to test clinical efficacy and vaccine efficacy has been inferred by demonstrating the induction of serum bactericidal antibody response to vaccine antigens [20, 22-25].

MenB vaccine introduction in other countries: an update

As the new MenB vaccine has been licensed in several countries and scientific evidence is accumulating on its efficacy and safety, a number of countries are in the process of evaluating the introduction of MenB vaccine in their immunization schedule (Tab. I).

To our knowledge, the United Kingdom is the only country where universal 4CMenB vaccination has been recommended. The Joint Committee on Vaccination and Immunization (JCVI) published a document in March 2014 recommending to offer to offer the MenB vaccine to children at 2, 4 and 12 months (2+1 doses schedule). As the JCVI states, this recommendation depends on securing a cost-effective price for the vaccine [26].

In France, Germany, Spain, the USA as well as the UK, MenB vaccine is recommended on an individual basis to high-risk subjects and during outbreaks [26-29].

Other countries including Canada, Ireland and Belgium National Immunization Committees have not yet produced recommendations and are waiting to gather relevant epidemiological and economic data to support their decisions.

National Immunization Committees in Spain and Germany have recently concluded that there is not enough available data on vaccine efficacy and economic analysis to support the introduction of universal MenB immunization in national immunization schedules, this also considering that MenB meningitis incidence is decreasing in those countries [28, 29].

Setting-specific predictive models on the epidemiological impact of MenB vaccine introduction and cost-effectiveness analysis have been carried out in France, this model allowed to evaluate different vaccine strategies [27].

In decentralized health systems – as we will outline for Italy – some regions but not others have introduced MenB vaccine in their immunization schedule, including Saxony in Germany and Quebec in Canada [30].

The Italian setting

EPIDEMIOLOGY OF MENINGOCOCCAL DISEASES IN ITALY

To describe IMDs epidemiology in Italy, two sources of data are used: i) the National Surveillance System of Invasive Bacterial Diseases (MIB), coordinated by the

Tab. I. Recommendations and positions of selected European countries on MenB Vaccine.

Country	Reccomendations	MenBIMDI Incidence (by age of group)	Country	Reccomendations	MenBIMDI Incidence (by age of group)
Belgium	Currently not recommended. The Superior Health Council is currently assessing the available evidence on the topic	Relative to 2011	Total: 0.8/100,000	<1 year: 10.8/100,000	1-4 years: 4.3/100,000
France	Not routinely recommended for children and adolescents. Recommended for high-risk subjects and during outbreaks	Relative to 2011	Total: 0.6/100,000	<1 year: 8.4/100,000	1-4 years: 2.8/100,000
Germany	Currently not recommended. It may be recommended for people at increased risk of IMD, but the decision to vaccinate should be based on individual considerations of risk/benefit	Relative to 2012	Total: 0.3/100,000	<1 year: 5.9/100,000	1-4 years: 1.7/100,000
Ireland	Ongoing evaluation. Cost effectiveness study in progress	Relative to 2012	Total: 1.3/100,000	<1 year: 23.5/100,000	1-4 years: 17.9/100,000
Portugal	Assessment in progress	Relative to 2011	Total: 0.3/100,000	<1 year: 17.8/100,000	1-4 years: 2.7/100,000
United Kingdom	Recommended conditional on the vaccine being available at low cost. the vaccine should also be offered to the same high-risk groups who are offered the ACWY vaccine.	Relative to 2011	Total: 1.3/100,000	<1 year: 25.3/100,000	1-4 years: 8.6/100,000
Spain	Currently not recommended. Health authorities may consider whether to use the vaccine in case of outbreaks and for immunocompromised patients.	Relative to 2011	Total: 0.7/100,000	<1 year: 13.1/100,000	1-4 years: 4.4/100,000
Canada	Currently not recommended	Relative to 2012	Total: 0.23/100,000	<1 year: 6.2/100,000	1-4 years: 0.4 to 1.4/100,000
United States	Currently it is recommended for individuals identified as being at greater risk of contracting IMD during outbreaks	Relative to 2012	Total: 0.06/100,000	<1 year: 1.24/100,000	1-4 years: 0.13/100,000

Translated and adapted from: Istituto Superiore di Sanità (ISS): *Vaccinazione anti-meningococco B: dati ed evidenze disponibili per l'introduzione in nuovi nati e adolescenti*. 2015 [33].

Italian Institute of Health [31] and ii) the National hospital discharge records administrative register (SDO). Surveillance IMDs data in Italy is available from the MIB system for the periods 1994-2006, 2007-2010 and 2011-2015 [32]. The most recent MIB data were updated in March 2015 [32]. In 2013 in Italy 172 cases of invasive meningococcal disease were reported, this corresponding to an incidence rate of 0.29 cases per 100,000, slightly higher as compared to previous years (0.23/100,000 in 2012 and 0.25/100,000 in 2011). IMD incidence in Italy is among the lowest in Europe [8]. IMDs' incidence is higher in the age group 0-4 years (1.75/100,000 in 2013) and in particular in the first year of life (4.01/100,000 in 2013), this mirroring IMDs epidemiology of most high-income countries. Nearly 50% of IMDs cases are sepsis or meningitis/sepsis, the per-

centage being higher children under 5 years of age (76% in 2013). A relatively stable trend is reported in 2011-2013 in all regions apart from 4 regions (Apulia, Lombardy, Marche, Tuscany) where number of cases slightly increased over the years and the Veneto region where it decreased. IMDs' Mortality data is derived from national mortality data and available for the period 2003-2010 where 122 IMDs deaths were reported [33].

In Italy Meningococcus B is the most common notified serogroup (46, 50 and 63% of the total of strains typed in 2011, 2012 and 2013), followed by meningococcus C (33, 17 and 17% of the strains typed in 2011, 2012 and 2013) and meningococcus Y (16, 17 and 13% of the strains typed in 2011, 2012 and 2013), this distribution remaining constant over the years. Of concern, the percentage of notified infection for which serogroup info

is not available, is high (33% in 2013) and increased as compared to 2011 (23%) and 2012 (21%). Although with fluctuations in incidence, serogroup B IMDs distribution over time (1994-2013) has been constantly greater as compared to serogroup C IMDs (except in the years 2004 and 2005), this being in line with the data from other European countries [8] from the literature, presents clear fluctuations of incidence over time. The number of cases of serogroup B between 1994 and 2012 has always been greater than the number of cases by serogroup C, except that in the years 2004 and 2005. Comparing hospital discharge records data with National IMDs' surveillance system register allow to assess the latter's detection rate, which is estimated to slightly underestimate IMDs' burden in Italy [33]. In addition, the percentage of IMDs with no serotyping data, remains high at 20%. Furthermore, in 2013 the proportion of typified cases (67%) is lower than 2012 (79%) and 2011 (77%).

Combining data on IMD cases derived from hospital discharge records with the serogroup distribution reported by the IMD surveillance system, it is estimated that serogroup B IMD incidence in the period 2007-2012 was 0,23/100,000, higher in the first year of life (3,44/100,000 in 2013) and in the 1-4 years age group (1,07/100,000 in 2013). In particular, 133 serogroup B IMDs were reported in 2007, of which 43 in children <5 years and 19 in children <1 year. The average impact of serogroup B IMDs in Italy in 2007-2012 is estimated to be 5,194 DALY per year, with an average mortality impact of 4,817 years of life lost per year and average sequelae impact of 376 years with disabilities per year [33].

NATIONAL-LEVEL IMMUNIZATION POLICES AND GUIDANCE DOCUMENTS

In Italy, The National Vaccine Prevention Plan (PN-PV) is the guidance document issued by the Ministry of Health that establishes immunization recommendations at the national level and sets national coverage targets with the overall aim of harmonizing immunization strategies among Italian regions. The 2012-2014 PNPV, published in February 2012 does not include recommendations on 4CmenB [34].

In 2014 it was published the second edition of the "Lifetime immunization schedule" [35], a joint proposal for an immunization schedule issued by the four Italian scientific societies, historically involved in the study of vaccines and vaccination policies, namely: the Italian Society of Hygiene, Preventive Medicine and Public Health (SIIt), the Italian Society of Paediatrics (SIP), the Italian Federation of Family Paediatricians (FIMP), and the Italian Federation of General Practitioners (FIMMG). The 2014 "Lifetime immunization schedule" recommends the introduction of universal 4CmenB immunization with the 3+1 doses schedule at 3°-4°-6° months of age with a booster dose after 13 months of age. The "Lifetime immunization schedule" recommends also the use of MenB vaccine on an individual basis in at-risk subjects as specified in the vaccine's summary of

product characteristics [20] and raises awareness on the importance of routinely vaccinating also adolescents against meningococcal disease [35].

While recommending the introduction of universal MenB immunization in Italy with a 3+1 doses schedule, the 2014 "Lifetime immunization schedule" leaves to regional health authorities the final decision on the best setting-specific immunization schedule to adopt. As for now the decision to include MenB vaccine in the immunization schedule is taken at the regional-level in a context where several regions are coping with deficit-reduction plans.

INTRODUCTION OF MENINGOCOCCAL B VACCINE IN ITALIAN REGIONAL IMMUNIZATION SCHEDULES

Currently there are three types of meningitis vaccine available in Italy: the meningococcal polysaccharide tetravalent (A, C, Y and W-135) vaccine, the meningococcal conjugate tetravalent (A, C, Y and W-135) vaccine and the Monovalent serogroup C conjugate vaccine. Since 4CmenB was licensed by EMA and became available in Italy, eight Italian regions and one autonomous province have introduced it in their regional immunization schedules as active immunization offer – free of charge for all children under one year of age. The eight regions are Apulia, Basilicata, Calabria, Friuli Venezia Giulia, Liguria, Sicily, Tuscany and Veneto [36]. Of them, five have implemented the 3+1 doses MenB immunization schedule and two the 2+1 doses one. The Autonomous Province of Bolzano has also implemented the 2+1 schedule [36, 37]. The MenB vaccine schedules in different Italian regions are schematized in Table II.

In particular, the region Apulia has been the first region to include the 3+1 doses universal MenB vaccine offer in the regional immunization schedule, legally formalized in January 2014, added to the updated edition of the regional lifetime immunization schedule and implemented starting with the 2014 birth cohort [38].

Similarly, the Basilicata and Tuscany regions adopted in February and October 2014, respectively, the 3+1 doses universal MenB vaccine [39-41] and implemented the new immunization programme starting from the 2014 birth cohort. More recently, in January 2015, the regions Sicily and Liguria adopted the 2014 "Lifetime immunization schedule" and introduced the MenB vaccine within the regional immunization schedules [42-44].

Two regions, Veneto and Friuli Venezia Giulia have introduced MenB vaccine starting with the 2015 birth cohort and recommending the 2+1 doses schedule [45-47]. The Autonomous Province of Bolzano has introduced the MenB vaccine in the immunization schedule with the 2+1 dose approach for subjects between 3 and 15 months of age [36, 37].

Also Calabria recently decided to introduce the vaccine against meningococcus B: since May 2015 the vaccine was included in the vaccination schedule with the scheme 3 + 1 doses, but timing of the third dose it is not clearly specified [48].

Tab. II. MenB Vaccine schedules implemented in different Italian regions [36-48].

Region	3° Month	4° Month	5° Month	6° Month	7° Month	8° Month	9° Month	13° Month	14° Month	15° Month
SCHEDULE 2 DOSES+ 1 BOOSTER										
Autonomous Province of Bolzano	Still to be decided (2 doses+1 booster)									
Friuli Venezia Giulia					1° MenB dose		2° MenB dose			MenB booster dose
Veneto					1° MenB dose		2° MenB dose			MenB booster dose
SCHEDULE 3 DOSES + 1 BOOSTER										
Apulia	1° MenB dose 76° day (after 15 days from the administration of hexavalent + PCV13)	2° MenB dose 106° day (after 1 month from the 1° dose of MenB vaccine)		3° MenB dose 151° day (after month from the 2° dose of MenB vaccine)						MenB booster dose (in co-administration with MenC)
Basilicata	1° MenB dose 75°-90° day		2° MenB dose 135°-150° day		3° MenB dose 181°-210° day				MenB booster dose after the 13° month	
Calabria	1° MenB dose 76° day	2° MenB dose 106° day		3° MenB dose						MenB booster dose
Liguria	1° MenB dose 76° day	2° MenB dose 106° day		3° MenB dose 151° day						MenB booster dose
Sicily		1° MenB dose (after 1 month from the administration of hexavalent, PCV13 and Rota)		2° MenB dose (after 1 month from the administration of hexavalent, PCV13 and Rota)	3° MenB dose at 7° or 8° month (after 1 month from the administration of 2° MenB dose)	3° MenB dose at 7° or 8° month (after 1 month from the administration of 2° MenB dose)				MenB booster dose at 15°-18° month (after 1 month from the administration of MRRV)
Tuscany	1° MenB dose 76° day (15 day after the administration of hexavalent + pneumo)	2° MenB dose 106° day (1 month after the 1° MenB vaccine)		3° MenB dose 151° day (after 1 month from the 2 dose of hexavalent + pneumo)				MenB booster dose		

Data derived from regional immunization schedules [36-48]

Discussion

The introduction of MenB vaccine in Italian regional immunization schedules rises several issues around: 1) the organization and management of immunization programmes; 2) health education and communication to the general population and, in particular, parents; 3) economic sustainability in a context of deprived resources for the national health system.

ORGANIZATION AND MANAGEMENT OF IMMUNIZATION PROGRAMMES

In the 2012-2014 National Vaccine Prevention Plan (PNPV) some general principles are outlined: a) the need of concentrating as much as possible the number of immunization sessions; b) the importance of avoiding that vaccines' co-administrations increase the risk of adverse effects; c) the urge of avoiding more than 2 injections in the same immunization session and d) the importance of guarantying the economic sustainability of immunization offers [49]. In this context, it is easy to understand the organisational problems related to the introduction of the MenB vaccine in children's immunization schedule. In fact, not only it requires to perform 4 doses in a limited and early-in-life period (3-4 doses during the first year of age), but also there is some evidence that MenB co-administration with other vaccines increase the risk of moderate to high fever [20].

As mentioned, the 2014 "Lifetime immunization schedule" recommends the introduction of universal 4CmenB immunization with the 3+1 doses schedule at 3°-4°-6° months of age with a booster dose after 13 months of age [35]. This schedule, although has the unavoidable disadvantage of adding three additional immunization sessions in the first year of age, has the following advantages [35]:

- administration of the first 3 doses in a short time;
- no changes to the current schedule for the other children routine vaccinations;
- administration of no more than two vaccines in a single session, minimizing the possibility of adverse events (fever);
- it allows to separately monitor any adverse events of the new vaccine;
- it makes it easier for parents to remember the next appointment.

When formulating a vaccine schedules some factors are to be taken into consideration, this including the age-specific distribution of diseases, age group with the highest disease incidence, the disease's clinical symptoms and complications, the vaccine's indicated doses and duration of protection [31]. In light of this reasoning the 2014 "Lifetime immunization schedule" also presents the MenB 2+1 doses immunization schedule with vaccine administration at 7°-9° months of age with a booster dose at two years of age [35]. The 2+1 doses immunization schedule had the advantage – as compared to the 3+1 doses immunization schedule – of adding only two additional vaccine sessions in the first year of age. However, if the 2+1 schedule is not combined with the

effect of herd immunity and – ultimately – decreasing MenB incidence, it would fail to prevent IMDs in the first months of age which is when the highest burden of IMDs is concentrated [35].

HEALTH EDUCATION AND COMMUNICATION

Challenges related to motivating parents to have their children vaccinated against MenB is a threat to the success of MenB immunization programmes. Low compliance to 4CmenB vaccination by parents might be associated on one hand by the introduction of additional immunization sessions in the first year of age and on the other by lack of information [50] around the new MenB vaccine. The Italian Center for Social Studies and Policies (CENSIS) has recently conducted a survey on a representative sample of 1,100 Italian parents (550 mothers and 550 fathers aged 22 to 55 years) with children from 0 to 12 years (target population for MenB vaccine) to assess parents' knowledge and attitudes towards IMDs and available vaccines, in particular MenB vaccine [51]. As emerges from the survey, 85.5% of parents report to be aware of meningococcal disease; among these 30% consider themselves to be adequately informed, especially parents with an high level of education. The main sources of information about meningitis and meningococcal vaccination are paediatricians (48.8% and 33.9%, respectively). However, 33% of respondents report not to have received proper health education on the topic. In addition, although one third of parents consider to have accessed to all needed information, almost half (45%) wants to be more informed. The majority of respondents (95%) believe that immunization campaigns targeting the general populations are necessary to educate and raise awareness on the benefits of MenB vaccination and to allow parents to take informed decisions. When specifically focusing on the new MenB vaccine, almost 70% of parents is not aware of its existence, this percentage being higher among parents with lower education. When asked about MenB vaccine population target, 23% report not to know it. Of crucial importance, half of the respondents do not know if MenB vaccine is available in their region of residence. More than half of the parents report their intention to vaccinate their children against meningococcus B, and if we add to this percentage 37.6% being 'undecided', the percentage of Italian parents not opposed to this new vaccine rises to about 90% [51].

ECONOMIC ISSUES

The introduction of new vaccines needs to follow transparent criteria of efficacy, safety, economic sustainability and public health prioritization [52]. Immunization schedules are proposed by experts in the field of clinical medicine, epidemiology and public health on the basis of the available scientific evidence and are then implemented by policy makers also taking into consideration resources allocation and financial sustainability [53]. In context of deprived resources for the Nation Health system, economic sustainability of new immunization programmes should be carefully assessed. Taking into

consideration both the fact that serogroup B IMD incidence is relatively low and that 4CMenB does not protect against all circulating strains (around 87% [33], the estimated cost per IMD case prevented is very high [54]. This consideration has stimulated a lively debate in the scientific community and among health authorities. As for now, Italian setting-specific cost-effectiveness and cost-benefit analysis on the introduction of 4CMenB are still scant [55].

Conclusions

The new National Vaccine Prevention Plan (PNPV) has been drafted in close consultation with Italian scientific societies and is about to be approved. It will likely include MenB immunization with an offer active and free of charge. This is a relevant step towards a comprehensive immunization offer and a significant sign at the national level. The implementation of MenB immunization programmes, the organizational details such as the calling methods and the organization of the vaccination services are still to be discussed and will be planned at the level of individual regions considering the overall resources needed, the workforce of health services and the availability of different healthcare professionals groups (family paediatricians).

Compared to other vaccine-preventable diseases, the IMDs incidence in Italy is low; however, IMDs are associated with a high lethality rate and high risk of complications. Serogroup B accounts for the vast majority of meningococcal infections in Italy. 4CMenB vaccine has good immunogenicity profile against invasive meningococcal disease B. Further evidence are needed and are currently being collected on the vaccine clinical effectiveness, duration of protection and cost-effectiveness. 4CMenB is under additional monitoring for the next five years and this will allow to collect detailed data on suspected adverse reactions. We present updated data on the eight Italian regions that have already implemented 4CMenB for the 2014 and 2015 birth cohorts taking into consideration IMDs burden in Italy. Our data will help to plan, implement and evaluate 4CMenB immunization programmes in other Italian setting. This will require careful consideration on timing, doses, and co-administration with other vaccines but also further economic assessments and strengthened efforts by institutions and scientific societies to promote health education and good communications among the population [56-59].

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