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Expert opinion on the introduction of the meningococcal B (4CMenB) vaccine in the EU/EEA

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Abbreviations

A&E	Accident and emergency
DALYs	Disability-adjusted life years
EU/EEA	European Union/European Economic Area
HEE	Health economic evaluation
hSBA	Serum bactericidal antibody assay utilising human complement
IMD	Invasive meningococcal disease
JCVI	Joint Committee on Vaccination and Immunisation
MATS	Meningococcal antigen typing system
MenB	Meningococcal group B
NFP	National focus points
NIP	National immunisation programme
NITAG	National immunisation technical advisory group
QALY	Quality-adjusted life-year
SBA	Serum bactericidal antibody
SgB IMD	Serogroup B invasive meningococcal disease
TESSy	The European Surveillance System
VENICE	Vaccine European New Integrated Collaboration Effort
VPD	Vaccine-preventable disease/s
4CMenB	Multicomponent meningococcal capsular serogroup B protein vaccine

The following country codes were used in this publication:

AT	Austria
BE	Belgium
BG	Bulgaria
HR	Croatia
CY	Cyprus
CZ	Czech Republic
DK	Denmark
EE	Estonia
FI	Finland
FR	France
DE	Germany
GR	Greece
HU	Hungary
IS	Iceland
IE	Ireland
IT	Italy
LV	Latvia
LT	Lithuania
LU	Luxembourg
MT	Malta
NL	The Netherlands
NO	Norway
PL	Poland
PT	Portugal
RO	Romania
SK	Slovakia
SI	Slovenia
ES	Spain
SE	Sweden
UK	United Kingdom

Executive summary

Aim

The multicomponent meningococcal B (4CMenB) vaccine Bexsero for the prevention of serogroup B invasive meningococcal disease (SgB IMD) has been available in the European Union/European Economic Area (EU/EEA) since 2013. Meningococcal serogroup B (SgB) is the most common cause of IMD in all age groups at the aggregated EU/EEA level. SgB IMD predominantly affects infants and young children and is the leading cause of mortality and morbidity related to IMD in children under five years of age.

The aim of this document is to provide an ECDC expert opinion on the introduction of the 4CMenB vaccine in the Member States of the EU/EEA. This expert opinion document is intended to support national decision-making by summarising the considerations and concerns of some EU/EEA countries when they discussed whether to introduce the 4CMenB vaccine into their national immunisation programmes. It also summarises the reasons behind national recommendations for the 4CMenB vaccine, points out data gaps, and presents options on how to introduce the vaccine.

Methods

The information provided in this report is based on a) data from The European Surveillance System (TESSy) platform at ECDC, b) data on the decision-making process in Member States on SgB IMD vaccination collected by the Vaccine European New Integrated Collaboration Effort (VENICE III) in March 2015, c) an ECDC expert consultation meeting with public health experts and researchers that took place in November 2015, and d) evidence from published peer-reviewed and grey literature.

The following information was collected:

- Burden of SgB IMD in the EU/EEA and current status of 4CMenB vaccine introduction in EU countries and globally
- General considerations for vaccine introduction, and specifically for 4CMenB vaccine introduction, including:
  - vaccine immunogenicity and efficacy
  - vaccine safety
  - vaccine effectiveness and impact, including strain coverage, effect on carriage and post-licensure studies
  - health economic evaluations
  - ease of implementation and acceptance
- Areas for country collaboration

Results

Burden of invasive meningococcal disease serogroup B in the EU/EEA and the current status of 4CMenB vaccine introduction

In 2015, EU/EEA countries reported to ECDC a total of 3 121 cases of IMD, with a notification rate of 0.61 confirmed cases per 100 000 population. Of the 3 121 cases reported, the serogroup was known for 2 780 cases (89%). Of these cases with known serogroup, 1 682 were caused by SgB. Data indicate that the EU IMD cases caused by SgB in 2015 were highest among infants younger than one year of age, followed by those 1–4 years of age and adolescents (aged 15–24 years). The epidemiology of SgB IMD across the EU/EEA varies between countries with regard to incidence, serogroup distribution and case fatality. All these factors and more were taken into account when countries considered the introduction of the 4CMenB vaccine into their national immunisation schedule.

SgB IMD has a high morbidity and case fatality. The first meningococcal B vaccine (Bexsero) was licenced in the EU in 2013, and since then twelve countries (AT, BE, CZ, ES, FR, DE, GR, IE, IT, LU, NO, and UK) have made an assessment of the vaccine and recommendations about its use.

The 4CMenB vaccine was introduced into the publicly funded national routine immunisation programme in the UK in September 2015 and in Ireland in October 2016. In Italy, the vaccine was introduced into the publicly funded national routine immunisation programme in January 2017. Vaccination advisory boards in Austria, the Czech Republic and Germany (in the state of Saxony) have all recommended the vaccine, but without funding.

In Belgium, France, Greece, Luxembourg and Norway, the vaccination advisory board has not recommended the inclusion of the vaccine in the publicly funded national routine immunisation programme.

Six countries have introduced the vaccine nationally for risk groups only (BE, ES, FR, LU, NO and PT). The recommendation for risk groups is also in place in the three countries that have introduced the vaccine in their publicly funded national routine immunisation programme (IE, IT and UK) and in countries which have recommended the vaccine without funding (AT, CZ, and one federal state of DE (state of Saxony) including a national recommendation for risk groups).

Considerations for 4CMenB introduction

Vaccine immunogenicity and efficacy

The level of protection offered by the 4CMenB Bexsero vaccine is primarily inferred from immune responses against the four main antigens of the vaccine. Due to the generally low incidence of meningococcal disease, vaccine efficacy studies are not practical, therefore the serum bactericidal antibody assay utilising human complement (hSBA) is considered the accepted serological correlate of protection for serogroup B meningococci [1,2]. Efficacy of outer membrane vesicle (OMV) vaccines correlate with the percentage of subjects with hSBA titres ≥4 and/or of subjects with ≥fourfold rises pre-to post-vaccination, therefore the hSBA titre ≥4 has been proposed as a tentative protective titre and was used as basis for licensure of Bexsero [3].

The immunogenicity of the 4CMenB vaccine was shown through the serological correlate of protection with immunisation in various schedules. In clinical trials, the vaccine has been shown to be immunogenic in young infants between two and five months and has been recommended for use in a three-dose primary series, followed by a booster between 12 and 15 months of age (3+1 dose schedule). In infants over six months of age and young children from 2 to 10 years of age, the vaccine has been shown to be immunogenic after at least two doses and has been recommended for use in a two-dose primary series, followed by a booster in the second year of life. In adolescents and adults, two doses led to protective antibodies against the vaccine antigens. In June 2017, results from a randomised open-label phase 3b trial were published and have shown the 4CMenB vaccine to be immunogenic and safe in young infants at a reduced infant schedule of 2+1 doses [4].

It has not been fully elucidated if a ≥4 hSBA cut-off is appropriate for other SgB IMD strains which cause disease in local areas [5], and it is not practical to predict vaccine strain coverage based on testing of many different meningococcal strains directly in hSBA. This has led to the development of MATS (meningococcal antigen typing system) as a typing system to predict the strain coverage for each of the four components in the 4CMenB vaccine [6].

4CMenB vaccine safety

Fever is a common adverse event, especially in infants and children. Its frequency is increased if the vaccine is co-administered with other routine vaccinations [7]. Bexsero is the first vaccine for which prophylactic use of antipyretic medication has been recommended in various countries. Thus far, there have been no serious adverse events observed in the two vaccination campaigns, one in a region of Quebec with elevated SgB IMD incidence [8] and after two university outbreaks in the United States when over 15 000 people were vaccinated [9]. In the UK, where the 4CMenB vaccine was introduced into the publicly funded national routine immunisation schedule in September 2015, no serious unexpected safety issues have been identified to date [10,11] .

4CMenB effectiveness and impact

There are preliminary results on vaccine effectiveness that have come out from the UK, where the vaccine has been universally introduced in infants. These results are based on the period 1 Sept 2015 – 30 June 2016, following the introduction of 4CMenB into the national immunisation schedule as a two-dose priming schedule. Two-dose vaccine effectiveness was 82.9% (95% CI 24.1–95.2) against all SgB IMD cases, which corresponds to a vaccine effectiveness of 94.2% against the highest predicted SgB IMD strain coverage of 88%. Compared with the pre-vaccine period, there was a 50% reduction in the incidence rate ratio (IRR) of SgB IMD cases in the vaccine-eligible cohort. Cases in vaccine-eligible infants halved in the first 10 months of the programme [12].

The predicted effect of the implementation of the 4CMenB vaccine is dependent on country-specific strain coverage. At this stage, the effect of 4CMenB vaccination on meningococcal carriage is not known. Data on the effect on carriage will be important for vaccination scheduling. Adolescents have the highest carriage, and if the 4CMenB vaccination is found to disrupt it, vaccinating adolescents may be an effective vaccination strategy. Many countries are waiting for post-licensure studies from those countries that have universally introduced the vaccine, such as the UK, before continuing or starting an assessment of the vaccine. These studies will be vital to filling the existing data gaps, especially around vaccine impact.

4CMenB cost-effectiveness

The calculation of cost-effectiveness of introducing the 4CMenB vaccine is highly dependent on the country-specific context, such as the epidemiology of SgB IMD and the healthcare structure, including the costs of services. All models predict that introducing the 4CMenB vaccine will reduce the number of invasive cases. In model

calculations, countries with low SgB IMD incidence which used the manufacturer's list price per dose, incurred costs per quality-adjusted life-year gained that were above internationally accepted threshold values for adoption.

Health economic assessments from the UK and Ireland showed the vaccine to be cost-effective because of the higher incidence of SgB IMD in these countries and by including costs such as cost of care, litigation costs and loss of quality of life from disease (including impacts on family and network members) and with a lower vaccine price than the manufacturer's list price.

Ease of implementation and acceptance

In the expert meeting, a few experts pointed out that some parents and healthcare professionals had reservations about adding the 4CMenB vaccine to the routine vaccination schedule. Some experts were concerned that the uptake of other vaccines might decrease if Bexsero were introduced to the vaccination schedule because of the high fever that infants may experience if vaccinated simultaneously with other vaccines funded by national routine immunisation programmes. Some experts also pointed out that the introduction of additional vaccination sessions into the vaccination schedule might lead to the non-completion of other routine vaccinations.

Country collaboration in the assessment process

In order to reduce duplication of work during the assessment of the 4CMenB vaccine, countries have pointed out areas of potential collaboration. Countries could consider leveraging and adapting previously used mathematical models of disease transmission and economic evaluations. It is also possible to jointly conduct or share systematic reviews on context-free aspects (vaccine efficacy, safety, and impact). Strain coverage laboratory support is already an area of collaboration between countries [13,14].

Summary conclusions

The twelve Member States (AT, BE, CZ, ES, FR, DE, GR, IE, IT, LU, NO and UK) that have already assessed the 4CMenB vaccine have taken various considerations into account during the decision-making process on the introduction of the vaccine. Two Member States, UK and Ireland, introduced the vaccine into their publicly funded national routine immunisation programmes for infants (vaccination at two and four months of age, with a booster at 12 months). Italy also added the 4CMenB vaccine to its publicly funded national immunisation programme for infants (vaccination at three, four and six months of age, with a booster at 13 months).

Other Member States (AT, BE, CZ, FR, GR, LU and NO) which have assessed the potential introduction of the 4CMenB vaccine, have reported a number of factors which led to the decision to not recommend the routine vaccination of infants, children or adolescents in the publicly funded national routine immunisation programmes at this point in time. Reasons cited by these Member States were the low incidence of SgB IMD in their country, the difficulties of integrating a three-dose series into the infant vaccination schedule, the increased likelihood of fever, the unfavourable cost-effectiveness in the country's epidemiological context, and a lack of data (on efficacy, duration of protection, and the effect of the vaccine on meningococcal carriage). Some Member States such as Germany and Spain which conducted a preliminary assessment are waiting for post-licensure studies from the countries which have introduced the vaccine into the national immunisation schedules before continuing the assessment of the vaccine.

There are different policy options to be considered for the introduction of the 4CMenB vaccination, including: recommendation for inclusion of the vaccination in the national schedule for children below one year of age; recommendation of the vaccination in different age groups; recommendation of the vaccination for individuals at increased risk for SgB IMD; and finally recommendation of the vaccination for individuals in an outbreak setting based on country-specific evaluation and analysis.

Background

Introduction

Invasive meningococcal disease (IMD) is a severe disease that has a high probability of related sequelae and death. It is caused by the bacterium *Neisseria meningitidis* (meningococcus) which can be classified into 12 different serogroups. Of these 12 serogroups, six (A, B, C, W, X and Y) are most associated with IMD globally.

Group B invasive meningococcal disease (SgB IMD) is a significant cause of septicaemia and meningitis in EU/EEA countries and is one of the major causes of childhood death from infectious disease in high-income countries. The burden of SgB IMD is highest among infants under one year of age and young children, with a secondary peak during adolescence. The onset and progression of infection is rapid and can be difficult to diagnose early. Even if diagnosed early, survivors have a high likelihood of long-lasting disability, which can include deafness, neurological problems, and amputations [15]. Close and prolonged contact or living in close quarters with an infected person facilitates spread of the disease. Other factors for increased risk for meningococcal disease include certain medical conditions such as asplenia, complement component deficiency, being infected with HIV, and/or travel to countries where meningococcal disease is endemic or hyperendemic [16]. Due to the rapid onset, high morbidity and high case-fatality, prevention is essential.

There are two SgB IMD vaccines, Bexsero (approved by EMA, the European Medicines Agency) in January 2013 for use from the age of two months [17]) and Trumenba (approved by the in June 2017 for use from the age of 10 years [18]). Since approval of the Bexsero 4CMenB vaccine, several EU/EEA countries have considered the introduction of the vaccination into routine immunisation schedules, and some have actually introduced it.

In the EU, most vaccines are evaluated by the EMA Committee for Medicinal Products for Human Use (CHMP). The decision to grant marketing authorisation is then made by the European Commission [19]. The timing of new vaccination recommendations by national immunisation technical advisory groups (NITAGs) and the introduction of new vaccines into vaccination schedules can differ widely from country to country. This is mainly due to differences in national decision-making processes, available resources, epidemiology and burden of disease, availability of data, and national priorities.

Scope of the expert opinion document

The aim of this document is to provide an ECDC expert opinion on the introduction of the multicomponent meningococcal B (4CMenB) vaccine (trade name *Bexsero*) in the Member States of the EU/EEA. This document is intended to support Member States that consider introducing the vaccine by describing the steps some countries have already taken, pointing out barriers to vaccine introduction, and summarising lessons learnt from the assessment and introduction process in some Member States. A similar approach can be applied when discussing the introduction of other vaccines in Member States.

Target audiences for this document are national policymakers, regulatory authorities, civil society organisations with an interest in SgB IMD, and those involved in the decision-making process for the introduction of 4CMenB vaccine at the national level (e.g. paediatricians, epidemiologists, specialists in infectious diseases, and primary care physicians).

This expert opinion does not substitute any international or national guidelines for the introduction of the 4CMenB vaccine. It should be read in the context of wider guidance and policy documents.

Methods

The information provided in this report was collected from the following sources:

European Surveillance System (TESSy) data

The surveillance of IMD in the EU/EEA was first coordinated by the European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS) at Public Health England from 1999–2007 and subsequently transferred to ECDC.

Since then, the annual data collection from 30 Member States has been carried out through the European Surveillance System (TESSy) platform at ECDC [20]. Case-based data on IMD are received from 30 Member States. IMD surveillance data up to 2015 are available online from the interactive ECDC Surveillance Atlas of Infectious Diseases [21].

VENICE III survey and report

The Vaccine European New Integrated Collaboration Effort (VENICE III) is a network dedicated to vaccine-preventable diseases, funded by an ECDC grant, with the objective of collecting, sharing and disseminating

information on national immunisation programmes. It consists of consortium members and a network of national experts from all EU/EEA Member States [22].

In March 2015, VENICE III collected data on the current situation of the decision-making process in EU/EEA Member States on the introduction of the SgB IMD vaccination [23]: the survey asked whether an assessment was planned, whether it was ongoing, or whether a decision had already been taken. The survey also collected additional information about the assessment, e.g. whether the assessment took into account systematic reviews, used disease transmission modelling, or conducted a health economic evaluation.

Parts of the final VENICE III report were used for this expert opinion. The full report (unpublished) can be requested from: vpd@ecdc.europa.eu.

Consultation meeting

The Vaccine-Preventable Diseases team at ECDC held an expert consultation meeting on meningococcal B vaccine introduction on 9–10 November 2015. The 18 experts who participated in this meeting consisted of European public health experts and researchers and one Canadian public health expert. For a list of experts please refer to p. ii.

The objectives of the expert consultation were to:

- provide available evidence about the 4CMenB vaccine
- provide an overview of country recommendations for 4CMenB vaccine
- analyse steps taken in considering introduction of the vaccine in national immunisation programmes
- review lessons learned
- foster an expert discussion.

The first section of the meeting consisted of a review of the epidemiological situation of IMD; 4CMenB vaccination in the EU/EEA; available evidence including MATS, predicted strain coverage, mathematical modelling and post marketing studies. The second section of the meeting focused on experiences in Member States that assessed the introduction of 4CMenB vaccination.

To ensure the independence of ECDC's output, declarations of interest were collected from all meeting participants.

Following the expert consultation meeting, an ECDC editorial group drafted a report which was shared for reviews and feedback with the meeting participants and the national focal points (NFPs) for the ECDC Vaccine-Preventable Diseases Programme.

Evidence from published peer-reviewed and grey literature

Evidence from published peer-reviewed and grey literature was gathered, including publications suggested by internal and external experts who were involved in the ECDC consultation meeting. Additional literature was discovered through a review of vaccination plans from EU/EEA countries.

Results

Invasive meningococcal disease serogroup B in the EU/EEA

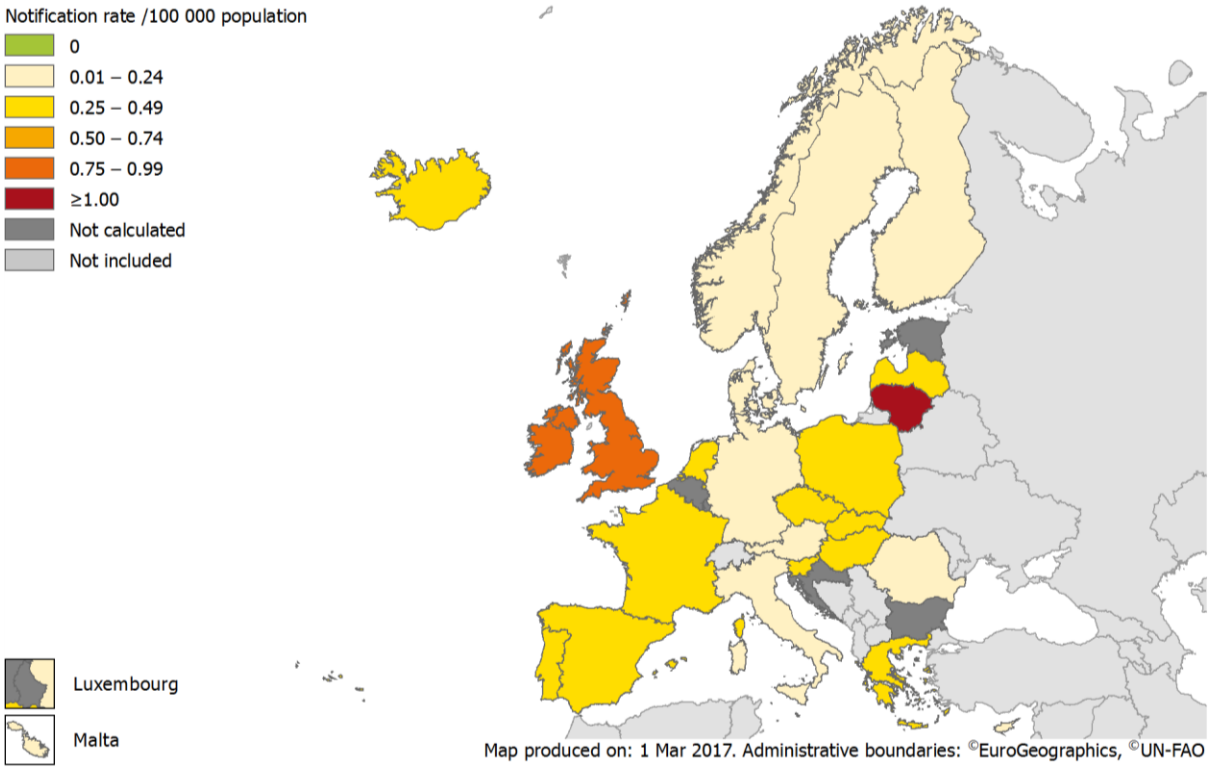
In 2015, 3 121 confirmed cases of invasive meningococcal disease were reported by 30 EU/EEA Member States to ECDC. The notification rate was 0.6 cases per 100 000 population [20]. Of the 3 121 cases reported, the serogroup was known for 2 780 (89%). Of the cases with known serogroup, 1 682 (61%) were serogroup B (Table 1). Despite a decreasing trend, serogroup B meningococcal disease has been predominant in the EU/EEA since the beginning of the surveillance in 1999.

Table 1. Serogroup distribution of confirmed cases of invasive meningococcal disease, EU/EEA, 2015

Serogroup	Cases	%
B	1 682	61
C	403	14
Y	290	10
W	317	11
Other	88	3
Total	2 780	100

'Other' refers to all cases reported as serogroup A, X, 29E, non-groupable or 'other'.
Source: Country reports from Austria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, the United Kingdom.

Figure 1. Notification rate of SgB IMD disease in EU/EEA countries, 2015



EU IMD cases caused by serogroup B in 2015 were highest among infants younger than one year of age (6.97 cases per 100 000 population), followed by 1–4 year-olds (2.00 cases per 100 000 population) and 15–24-year-olds (0.45 cases per 100 000 population).

Current status of 4CMenB vaccine introduction in EU/EEA countries and globally

The information in the paragraph below is based on data collected by the VENICE III network in 2015 [23] and through further ad hoc consultations with Member States in 2016 and 2017.

As of March 2015, 12 Member States (AT, BE, CZ, ES, FR, DE, GR, IE, IT, LU, NO and UK) have made an assessment on the introduction of the 4CMenB vaccine into the national immunisation programme (NIP) (see Figure 2 and Table 2).

The 4CMenB vaccine was introduced into the publicly funded national routine immunisation programme in the UK in September 2015; in October 2016, it was introduced in Ireland. In Italy, the vaccine was introduced into the publicly funded national routine immunisation programme in January 2017.

Vaccination advisory boards in Austria, the Czech Republic and Germany (in the state of Saxony) have all recommended the vaccine, but offer no reimbursement. In Greece, Portugal (which has made an initial assessment) and Spain, the national paediatric societies recommend the vaccination, which is available for purchase in the private sector. The 4CMenB vaccine can also be purchased privately in most other countries in the EU. Many parents purchase the vaccine and get their infants vaccinated through the private health sector (outside of the routine vaccination schedule), but administered doses are currently not monitored in the majority of Member States. Spain has started monitoring vaccinations provided through the private health sector. For many Member States, not monitoring these vaccinations may be a missed opportunity for assessing the vaccine and its impact.

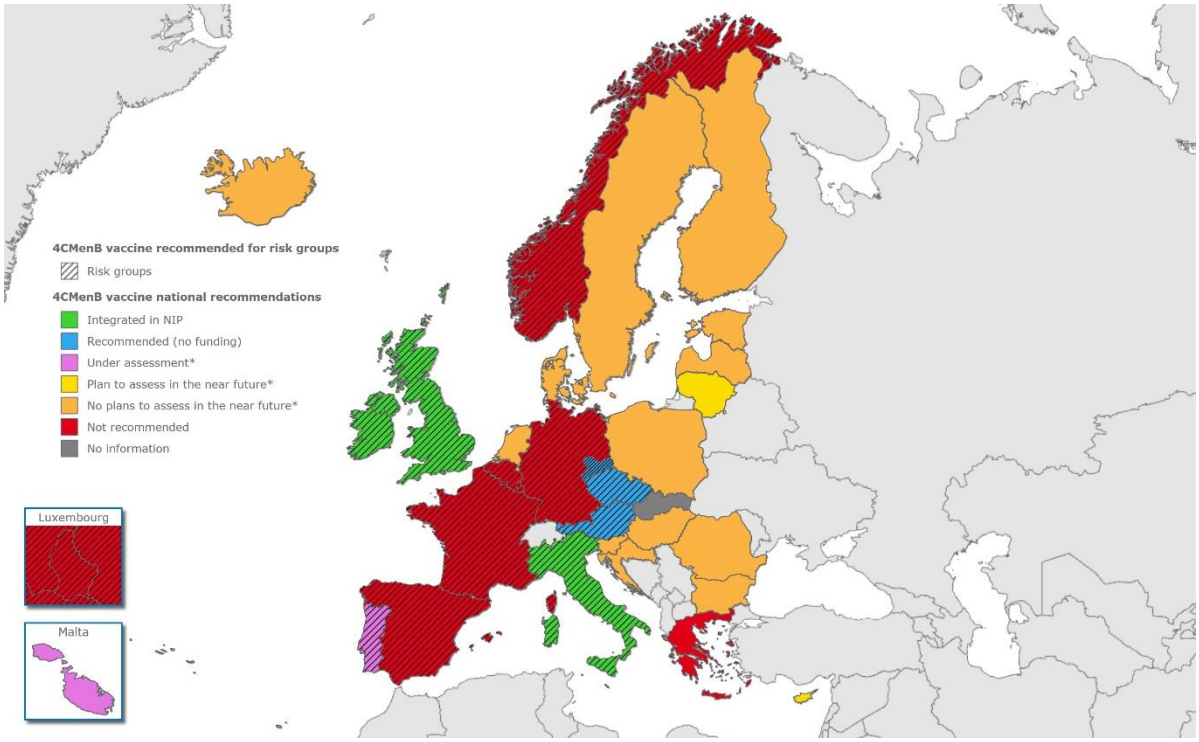
In Belgium, France, Greece, Luxembourg and Norway the vaccination advisory boards have not recommended the inclusion of the vaccine in their publicly funded national routine immunisation programmes.

Six countries have introduced the vaccine nationally for risk groups only (BE, ES, FR, LU, NO and PT). A recommendation for risk groups is also in place in the three countries that have introduced the vaccine in their publicly funded national routine immunisation programme (IE, IT, UK) and in countries which have recommended the vaccine without funding (AT, CZ and DE (state of Saxony) including a national recommendation for risk groups).

According to VENICE III, five countries (BE, IE, IT, MT and PT) stated that they were assessing vaccine introduction at the time of the survey. Belgium, Ireland and Italy have since made an assessment. At the time of the survey, three countries (CY, LT and LU) stated that they were planning to assess the vaccine in the next six months, and sixteen countries had no plans to assess the 4CMenB vaccine in the near future (BG, HR, DK, EE, FI, DE, IS, HU, LV, LI, NL, PL, RO, SI, ES and SE). Since then Luxembourg has conducted an assessment (April 2016), and Germany and Spain have preliminary assessed the vaccine and plan to resume their assessment once further data on safety and vaccine effectiveness become available. There is no current information on the status of vaccine assessment in Slovakia.

Of the 16 countries which had no plans to start an assessment at the time of the survey, 11 (BG, DK, EE, FI, IS, LV, NL, PL, RO, SI and SE) reported that the vaccine was considered not relevant for public health in their country (incidence was too low or declining), or that there were other public health priorities. Four countries (DK, DE, HU, and ES) stated that they wanted to wait until new/better data regarding the vaccine characteristics or experience of programme implementation from other countries were available. Croatia stated that the vaccine was not available in the country. In communication with Member States in September 2017, Slovenia and the Netherlands reported that poor availability of the vaccine was also an issue.

Figure 2. Decision-making status of 4CMenB vaccine introduction in the national immunisation programmes in EU/EEA countries



** Defined as 'assessment within the next six months from March 2015' (based on VENICE III survey, 2015)*

Note: Adapted from VENICE III survey (2015), presentations from country experts and ad hoc consultation with Member States

As of March 2017, there are no countries outside of the EU/EEA that have thus far introduced the 4CMenB vaccine into their publicly funded national routine immunisation programmes. Australia [24], Canada [25] and the United States [26] have made assessments of introducing the vaccine.

In April 2014, the members of the Canadian Immunisation Committee recommended immunisation of persons living in the Saguenay-Lac-Saint-Jean region in Quebec to control an enduring 'hyperendemic' situation. The 4CMenB immunisation campaign started in May 2014 and ended in December 2014. It targeted 57 000 people between the ages of 2 months and 20 years. Overall vaccination coverage was 82% for one dose and 70% for two doses. Active surveillance for adverse reactions was in place. Acetaminophen was recommended for children below 2 years of age, and antipyretics were used by 70% of all vaccinees. Around 10% declared having fever the week after vaccination; fever was less frequent in older age groups and in persons taking antipyretics. Fifty per cent reported local reactions. As of January 2016, no SgB IMD cases were observed among the 47 115 vaccinated residents, whereas two cases occurred among the 230 444 unvaccinated residents in the same region [27].

Outbreaks occurred at Princeton University in 2013 and the University of California in 2014. Even though the 4CMenB vaccine had not yet been licenced in the US at this point in time, the vaccine was authorised to control the outbreaks. A total of 13 confirmed cases was reported, including one fatality. Over 15 000 people were vaccinated, and more than 28 000 doses of the vaccine were administered. Causal association of adverse events following immunisation with 4CMenB was suspected for two events, one case of rhabdomyolysis, which was possibly related [9], and one case of anaphylaxis, which was related [28]. No cases of SgB IMD disease were reported among vaccinated individuals [29].

Table 2. Decision-making status of 4CMenB vaccine introduction in the national immunisation programme in EU/EEA countries

Country	Decision on introduction of 4CMenB vaccine	Target age groups and schedule	SgB IMD notification rate, 2015 (n/100 000)	SgB IMD notification rate among <1-year-olds, 2015 (n/100,000)	MATS strain coverage
Austria	Recommended (not funded); risk groups	2–5 months to 2 years (3 doses)	0.20	8.70	68% (95% CI: 59%–76%)
Belgium	Not recommended in NIP; risk groups	--	-	-	.
Bulgaria	No plans to assess in the near future*	--	-	-	.
Croatia	No plans to assess in the near future*	--	0.46	17.5	.
Cyprus	Plan to assess in the near future*	In children	0.24	10.83	.
Czech Republic	Recommended (not funded); risk groups	2–5 months (3 doses), 6 months – 10 years (2 doses), 13–15 years (2 doses)	0.29	10.01	74% (95% CI: 8%–87%)
Denmark	No plans to assess in the near future*	--	0.18	5.25	.
Estonia	No plans to assess in the near future*	--	-	0.00	.
Finland	No plans to assess in the near future*	--	0.15	1.73	.
France	Not recommended in NIP; risk groups	--	0.36	5.22	85% (95% CI: 69–93%)
Germany	Recommended only in the state of Saxony (not funded); not recommended in NIP (preliminary assessment); risk groups	2–5 months (3+1 doses), 1 year olds (2+1 doses), older children (2 doses)	0.22	4.61	82% (95% CI: 69–92%)
Greece	Not recommended in NIP	--	0.37	5.45	88% (95% CI:60–96%)
Hungary	No plans to assess in the near future*	--	0.27	9.69	.
Iceland	No plans to assess in the near future*	--	0.30	22.95	.
Ireland	Introduced into NIP Oct 2016; risk groups	2,4 and 12 months (2+1)	0.95	16.40	68% (95% CI:61–83%)
Italy	Introduced into the NIP Jan 2017; risk groups	3,4,6 and 13 months (3+1)	0.08	2.01	87% (95% CI:70–93%)
Latvia	No plans to assess in the near future*	--	0.30	18.46	.
Liechtenstein	No plans to assess in the near future*	--	.	.	.
Lithuania	Plan to assess in the near future*	In children	1.30	13.18	.
Luxembourg	Not recommended in NIP; risk groups	--	-	0.00	.
Malta	Under assessment*	< 5 years	0.23	0.00	.
Netherlands	No plans to assess in the near future*	--	0.38	5.15	.
Norway	Not recommended in NIP; risk groups	--	0.15	0.00	85% (95% CI:76–98%)
Poland	No plans to assess in the near future*	--	0.38	10.63	.
Portugal	Under assessment*; risk groups	In children	0.45	9.72	67.9%(95% CI:56–81%)
Romania	No plans to assess in the near future*	--	0.09	-	.
Slovakia	-	--	0.28	9.01	.
Slovenia	No plans to assess in the near future*	--	0.44	14.19	.
Spain	Not recommended in NIP (preliminary assessment); risk groups	--	0.31	6.33	69% (95% CI: 48–85%)
Sweden	No plans to assess in the near future*	--	0.13	-	.
UK	Introduced in NIP Sept 2015; risk groups	2,4 and 12 months (2+1)	0.81	16.09	73% (95% CI: 57–87%)

** Defined as 'assessment within the next six months from March 2015' (based on VENICE III survey, 2015)*
0.00: no cases
-- not applicable
- not calculated (when the information was known for less than 30% for the age and outcome, or less than 50% for the serogroup of cases, the corresponding indicator was not calculated for the geographical region and time period)
. no information
Note: Adapted from VENICE III survey (2015), TESSy 2015 data, presentations from country experts, ad hoc consultation with Member States, and published, peer-reviewed and grey literature [30-33].

Recommendations for risk groups

Twelve Member States have recommended the 4CMenB vaccine for use in risk groups (Table 3). These 12 countries recommended the vaccine for complement disorders and asplenia, due to the higher incidence of disease following colonisation in these groups. On the other hand, there are limited data available about the impact of 4CMenB vaccine in the elderly, in immunosuppressed individuals or in those with other chronic medical conditions. Data are equally limited on whether the vaccine mounts a protective antibody response or whether there are safety differences in the risk groups mentioned above.

The majority of countries also recommend the vaccine for those who are at increased risk of infection due to their profession, such as laboratory workers, for use during outbreaks, clusters and in close contacts. One country recommends the vaccine for adolescents and young people, in particular for those in environments with a high degree of social contact, such as universities or boarding schools and for persons travelling to hyperendemic areas.

The ECDC expert consultation meeting also discussed the relevance of temporary recommendations of the 4CMenB vaccine for certain groups. For example, as of 2016, Norway recommends 4CMenB vaccination for men who have sex with men after an individual evaluation and in line with the ACWY conjugate vaccine recommendations. However, this is not a permanent recommendation and will be reviewed after a review of the epidemiological data.

Some Member States, such as Sweden [34], which has not assessed the introduction of the 4CMenB vaccine to its NIP, may have included vaccination with the 4CMenB vaccine in their recommendations for the prevention of IMD for special risk groups.

Table 3. Specification of risk groups that are recommended for routine 4CMenB vaccination in EU/EEA countries

Risk groups	AT	BE	CZ[1]	FR	DE[2]	IE	IT[3]	LU	NO	PT	ES	UK
Complement disorders (incl. properdin deficiency)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Receiving complement inhibitor therapy (eculizumab therapy)	x	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓
Asplenia/hyposplenism/ splenic dysfunction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Immunocompromised individuals	x	✓	✓	x	✓	✓	✓	✓	x	✖	x	x
Primary immunodeficiency (incl. hypogammaglobulinemia)	✓	✓	✓	x	✓	✓	✓	✓	x	x	x	x
Autologous or allogeneic hematopoietic stem cell transplantation	x	x	✓	✓	x[10]	✓	x	✓	x	x	x	x
Solid organ transplant	x	x	x	x	x[10]	✓	✓	✓	x	x	x	x
After bacterial meningitis and septicaemia	x	x	✓	x	x	✓	x	x	x	x	✓	x
HIV infection	x	x	x	x	x[10]	✓	✓	✓	x	x	x	x
Down syndrome	x	x	x	x	x[10]	✓	x	x	x	x	x	x
Professionally exposed (i.e. laboratory workers)	✓	x	✓	✓	✓	x[8]	x	x	✓	✓	✓	✓
Clusters*	✓	x	✓	✓[13]	✓	✓	x	✓	✓	x	✓	✓[11]
Outbreaks	x	x	✓	✓[12]	✓	✓	x	✓	✓	✓[7]	✓	✓[12]
Close contacts*	x	x	✓	x	✓	✓	✓	✓	✓[5]	x	✓	✓[9]
Travellers to hyperendemic or epidemic countries	x	x	✓	x	✓	x	x	x	x	x	x	✓
Residency in countries with mandatory/recommended vaccination	x	x	x	x	✓	x	x	x	✓	x	x	x
Adolescents or adults exposed in big groups (university)	x	x	✓	x	x	x	x	x	x	x	x	x
Men who have sex with men	x	x	x	x	x	x	x	x	✓[6]	x	x	x

✓ *Yes*
x *No*
** Definitions of cluster and close contact may differ between countries*
[1] Vaccine recommended in persons with underlying health conditions
[2] Immunocompromised individuals with disorders other than those checked here would be eligible for the vaccine based on an individual risk assessment by their physician.

[3] Recommended in four regions. Recommended nationally on an individual basis.
[4] Individual evaluation, not for routine use
[5] Together with antibiotics (carrier eradication)
[6] After an individual evaluation and with a focus on ACWY–conjugate vaccine
[7] In the scope of public health procedures
[8] Considered for those in higher risk settings (e.g. reference laboratories or working in infectious disease units or with other clinical contact)
[9] Only at-risk household contacts; all household contacts after a second SgB IMD case occurs in same family
[10] These risk groups would be covered under the broader recommendation for vaccination of IMD cases
[11] Two or more cases within a four-week period offered to same group that would be considered for antibiotic prophylaxis
[12] Based on the calculated age-specific attack-rate
[13] At least two SgB IMD cases within four weeks interval if strains were covered by the vaccine
Note: Adapted from VENICE III survey (2015), presentations from country experts, feedback from VPD NFPs, and country vaccination plans [35-46]

General considerations for vaccine introduction in the EU/EEA

Each country has its own mechanism for an informed decision-making process, usually through the NITAG or expert groups. NITAGs are independent advisory bodies that provide evidence-based recommendations to policy makers in order to guide vaccination policies and strategies. NITAGs review existing evidence and guide policy and programmatic work. They take into account the purely medical benefits and risks of the evaluated vaccine ('context-free' factors such as vaccine effectiveness and safety), consider the local disease burden, and appraise cultural values and preferences about vaccination [47] ('context-specific' factors) (See Table 4).

The final decision to introduce a new vaccine into the national vaccination schedule/programme is most often taken by the ministry of health, sometimes in combination with other stakeholders (i.e. ministry of finance or public health institutes). In the UK, the ministry of health is obliged to introduce the vaccine if it is recommended by the NITAG, provided it is also cost-effective. The national processes on vaccine policymaking and the role of the Member States' NITAGs have been described elsewhere [47].

Table 4. Key factors in the decision-making process for adopting vaccines in the national immunisation programme

Key factor	Number of countries considering the factor (N=25)	
Vaccine efficacy/effectiveness	**25**	Largely context-free aspects
Vaccine safety at population level	**25**	
Severity of disease	**25**	
Vaccine safety at individual level	23	
Method of vaccine administration	14	
Disease burden in home country	**25**	Context-sensitive aspects (i.e. country specific)
Disease burden in neighbouring country	7	
Feasibility of recommendation	23	
Priority of vaccine related to other VPDs	21	
Results from economic evaluations	20	
Results from mathematical modelling	11	
Public perception about the disease	10	

Note: Adapted from VENICE III survey on characteristics and roles of NITAGs in EU/EEA, 2013 [48]

Specific considerations for introducing the 4CMenB vaccine in the EU/EEA

Key considerations taken into account in the 4CMenB vaccine assessment included: pathogen characteristics; disease burden; vaccine characteristics such as efficacy, predicted strain coverage and safety; impact of the vaccine as estimated through transmission modelling and health economic/cost-effectiveness evaluations; ease of implementation; and acceptance of the vaccine [23] (Table 5).

Table 5. Items for the assessment process for 4CMenB vaccination in EU/EEA Member States

Identified assessment process items
1. Considered aspects for literature reviews: ▪ Disease burden ▪ Immunogenicity ▪ Vaccine safety outcomes ▪ Strain coverage of 4CMenB vaccine ▪ Values and preferences
2. Disease transmission modelling
3. Health economic evaluations
4. Ease of implementation and acceptance

Note: Adapted from VENICE III report [23]

Each country considering introducing the 4CMenB vaccine into the vaccination schedule has made a national assessment of the epidemiology and burden of IMD (Table 2). Assessing the burden of meningococcal incidence by serogroup, age group, case-fatality, quality-adjusted life-years (QALYs), and disability-adjusted life-years (DALYs) provides a clear country-specific picture of the burden of SgB IMD and its level of prioritisation.

Vaccine immunogenicity and efficacy

The 4CMenB vaccine consists of subcapsular antigens including New Zealand strain outer membrane vesicles (NZ OMV) with PorA 1.4 antigenicity and recombinant antigens which include NadA (neisserial adhesion A), NHBA (*Neisseria* heparin binding antigen) and fHbp (factor H binding protein) [49,50]. These are expressed on circulating meningococci in various variants that are recognised by vaccine-induced antibody to a certain degree [5].

Protection afforded by the 4CMenB Bexsero vaccine is primarily inferred from immune responses against the four main antigens of the vaccine. Certain levels of circulatory bactericidal antibody are required to provide protection against invasive disease (immunological memory alone is not sufficient).

Due to the generally low incidence of meningococcal disease, vaccine efficacy studies are not practical, therefore the accepted serological correlate of protection for serogroup B meningococci is the serum bactericidal antibody assay utilising human complement (hSBA) [1,2] (referred to the 'accepted surrogate' of protective immunity against *N meningitidis* as there is no verification of the SBA level that is protective [51]). The hSBA determines functional activity (lysis) through formation of membrane attack complex [1,2]. Efficacy of OMV vaccines correlate with the percentage of subjects with hSBA titres ≥4 and/or of subjects with ≥ fourfold rises pre- to post-vaccination [3]. Therefore, hSBA titre ≥4 has been proposed as a tentative protective titre and was used as basis for licensure of Bexsero [3].

Based on initial published studies and licensure application, the vaccine has been shown to be immunogenic in infants between two and five months of age and has been approved for use in a three-dose primary series followed by a booster between 12 and 15 months of age (3+1 dose schedule), and in infants six months to 11 months a two dose primary series followed by a booster in the second year of life.

Young children between two and 10 years of age have been shown to be immunogenic after at least two doses, and the vaccine has been recommended for use in this age group in a two-dose primary series.

In adolescents and adults, two doses led to protective antibodies against the vaccine antigens [52-55]. A 2017 clinical trial has shown the vaccine to be immunogenic and safe in young infants at a reduced primary schedule of two doses (2+1) [4].

It has been demonstrated that a hSBA titre ≥4 against the strain 44/76-SL correlates with protection against the 'Norwegian' outbreak strain (also 44/76-SL). It has not been fully elucidated if a ≥4 hSBA cut-off is appropriate for other SgB IMD strains other than the reference strains used in clinical trials. Immunogenicity data against the three/four Bexsero indicator strains may not be representative of local representative strains due to difference in protein expression and protein variation [5]. This has led to the development of MATS (meningococcal antigen typing system) as a typing system to enable prediction of the strain coverage for each of the four components in the 4CMenB vaccine [6].

An article from Basta et al. based on a seroprevalence survey to quantify the individual immune responses induced by 4CMenB among students during a university outbreak in 2013 where 4CMenB vaccine was used before licensure found that eight weeks after the administration of the second dose of the 4CMenB vaccine there was no evidence of an hSBA response against the outbreak strain in 33.9% of vaccinees [56]. This shows the need for further post-licensure serologic studies to assess immunity against diverse meningococcal B strains and to better understand the breadth of 4CMenB-induced immunity [56].

There are also uncertainties about the long-term immunogenicity of the 4CMenB vaccine and the need for a booster. There are some signs of waning immunity which require further long-term research [57,58].

Safety

In clinical trials, 26–41% of infants experienced fever after receiving Bexsero with no other routine vaccinations [7]. Studies have also shown that the co-administration of 4CMenB vaccine with other routine vaccinations significantly increased the probability of fever [7]. Bexsero is the first vaccine for which prophylactic use of antipyretics is recommended. In Canada, acetaminophen was recommended during the vaccination campaign. In the UK, health authorities recommend prophylactic paracetamol with infant doses when the 4CMenB vaccine is administered concomitantly with routine vaccines [59]. Studies have shown that acetaminophen treatment does not compromise the immunogenicity of the vaccine [60], however more research is ongoing to examine this.

No worrisome safety signals have been observed in connection with the two vaccination campaigns carried out so far. In Québec, more than 46 000 persons aged between two months and 20 years were vaccinated [8], and more than 15 000 Princeton University students received the 4CMenB vaccine [9]. The spectrum of reactogenicity observed was similar to that described in published clinical trials and no further cases of SgB IMD disease occurred in the vaccinated population.

Further studies on reactogenicity in both adults and adolescents showed that severe local pain, myalgias and arthralgias were commonly reported after administration of Bexsero compared to a placebo or MenACWY-vaccination [61]. Other pre-approval studies in infants/toddlers observed cases of Kawasaki disease (which may affect up to 1 in 1 000 people) and febrile and non-febrile seizures (these may affect up to 1 in 100 people), which were considered as at least possibly related to the 4CMenB vaccination [62].

Since the introduction of the 4CMenB vaccine in the UK NIP, several studies looking into accident and emergency admissions following 4CMenB vaccination in infants have been conducted [63,64]. Nainai et al. found an increase in emergency department attendances, investigations and antibiotic use for AEFIs following vaccination with 4CMenB [63]. Additional studies are necessary to provide further information of specific adverse events.

Concerns have been raised about the risk posed by rare, potentially severe adverse events. This risk could not be adequately evaluated due to the insufficient size of the conducted clinical trials. The safety database for infant vaccination will be much enhanced following the implementation of routine vaccination with Bexsero in the first year of life in a number of countries, including the UK, Ireland and Italy.

Effectiveness and impact

Preliminary evidence on the effectiveness and impact of the 4CMenB vaccines is available from the UK experience. By the end of February 2017, preliminary 4CMenB vaccine coverage estimates from Public Health England are 96.8% for one dose and 87.9% for two doses by six months of age, and 96.3% for one dose and 93.1% for two doses by 12 months of age [65]. Promising preliminary results of the effectiveness and impact of the 4CMenB in the UK have also been published [12]. These results are based on the period 1 Sept 2015 – 30 June 2016 following the introduction of 4CMenB into the national immunisation schedule as a two-dose priming schedule. Two-dose vaccine effectiveness was 82.9% (95% CI 24.1–95.2) against all SgB IMD cases, which corresponds to a vaccine effectiveness of 94.2% against the highest predicted SgB IMD strain coverage of 88%. Compared with the pre-vaccine period, there was a 50% reduction in the incidence rate ratio (IRR) of SgB IMD cases in the vaccine-eligible cohort. Cases in vaccine-eligible infants halved in the first 10 months of the programme. It should be noted, however, that these results are preliminary and may change downwards (accumulation of higher numbers and infants nearer one year of age with waned immunity) or upwards (higher numbers and increased protection post boost at 12 months of age).

Strain coverage

The predicted effect of the implementation of the 4CMenB vaccine is dependent on country-specific strain coverage. The only practical way to predict vaccine strain coverage is by using the meningococcal antigen typing system (MATS). MATS is based on an enzyme-linked immunosorbent assay (ELISA) that determines the minimum amount of recognisable antigen needed to result in bacterial killing for each of fHbp, Nad A and NHBA (PorA characterised by sero/genotyping) [6]. For a strain to be 'covered', at least one antigen must be expressed at a level greater than the positive bactericidal threshold or possess homologous PorA (P1.4).

MATS has allowed for estimation of 4CMenB coverage for any particular region. It has been standardised and transferred to different countries [13,14]. A study by Vogel et al. [30] found that the predicted strain coverage for Bexsero using MATS was 78% (95% CI 63–90%), with coverage varying between countries. The study analysed 1 052 strains from six European countries (UK (England and Wales), France, Germany, Italy and Norway) between

2007 and 2008. The study also found that results from the Czech Republic and Spain were consistent with those for the other countries (Table 8).

MATS coverage estimates must be carefully interpreted considering the conservative nature of assays and additional issues concerning the positive bactericidal threshold and the binary nature of results. Under certain conditions, MATS can either underestimate or overestimate the strain coverage afforded by Bexsero [51]. Deriving the positive bactericidal threshold from pooled infant sera (in order to ensure a conservative estimate) and applying this threshold to all age groups can result in an underestimation of 4CMenB coverage, primarily so in older age groups [13, 66]. MATS might also overestimate the breadth of an infant's antibody repertoire, potentially leading to an overestimate of vaccine efficacy if pooled infant sera samples are used [51]. Also, using a binary measure (i.e. each strain classed as covered/not covered) does not consider vaccine non-responders.

Surveillance post-Bexsero implementation will provide a better understanding of SgB IMD correlates of protection. Current correlates relate to individual protection. Conjugate vaccines have shown to impart indirect protection.

Since only a few reference laboratories in Europe have been accredited to perform MATS, it would be helpful if these laboratories could offer MATS testing services for selected isolates on request – both for their own country and for neighbouring countries. MATS kits can be requested from GlaxoSmithKline by accredited laboratories.

Further developments in sequencing may make it possible to predict coverage from sequence data.

Effect on bacterial carriage

The effect of 4CMenB vaccination on meningococcal carriage is not well known; current accepted correlates of protection to assess response to 4CMenB vaccines relate only to individual protection against *Neisseria meningitidis*, and the only study on this topic yielded inconclusive results [67]. In addition, there are no data available on the effect on carriage of harmless *Neisseria* strains such as *N. lactamica*, which may induce immunity to *N. meningitidis*.

Post-licensure surveillance studies

Ongoing post-licensure follow-up studies include several studies in the UK and one study in the USA. A multi-centre study has been completed (Table 6).

Table 6. Post-licensure studies

Country and study number	Study details	Study time
UK (V72_36OB)	Observational registry-based safety study in infants to assess potential associations between specific adverse events, e.g. febrile seizure and Kawasaki's disease, using self-controlled case series design	Start at launch of the UK vaccination programme in September 2015; duration: three years
UK (V72_38OB)	Observational registry-based effectiveness study on the impact on IMD and effectiveness in infants using a screening method	Study is in collaboration with Public Health England and will last three years; start: September 2015
UK (V72_39OB)	Monitoring the use of vaccine during pregnancy study, using data from *Vaccines in Pregnancy* surveillance system	Starting one year from the launch of the UK vaccination programme in September 2015, with the final study report planned for December 2017
USA (V72_82OB)	Observational registry-based study of safety of Bexsero in pregnancy	Started in January 2016, lasting three years
Multi centre (V72_62)	Phase IIIb, open label, controlled study to evaluate the safety, tolerability and immunogenicity of two doses of meningococcal Group B vaccine when administered to immunocompromised patients from 2 to 17 years of age who are at increased risk of meningococcal disease because of complement deficiency or asplenia compared to matched healthy controls	From May 2014 to trial end date on 22 October 2015

Many countries are waiting for results from post-licensure studies which will provide essential vaccine safety and effectiveness data that were not possible to determine in pre-licensure studies. A number of countries depend on data from these studies to carry out, or continue with, their assessment of the 4CMenB vaccine.

Mathematical transmission modelling and health economics

Setting-specific disease transmission modelling uses mathematical concepts and language to describe real-world systems and can be used to combine all available evidence relating to a vaccine, the disease it protects from, and the characteristics of the health system in order to make predictions about a vaccine's impact. A number of different models have been developed to predict the impact of a vaccine against SgB IMD (Table 7). Modelling approaches vary in structure, data used, model fitting and assumptions made. Two modelling types have been used: cohort models, which cannot appropriately account for herd effects, and transmission dynamic models, which can.

Table 7. Papers/reports and types of models considering the impact of the 4CMenB vaccine

Paper/report	Country	Modelling type	Herd effects	Probabilistic (base case)	Costs
Hanquet et al. 2013 [68]	Belgium	Markov	No	Yes (cohort)	Yes
		Transmission dynamic	Yes	No	Yes
Lecocqa et al. 2013 [69]	France	Markov	[Approx]	Yes	Yes
Christensen et al. 2016 [70]	Germany	Markov	No	Yes (cohort)	Yes
		Transmission dynamic	Yes	No	Yes
di Pietro et al. 2013 [71]	Italy	Markov	No	No	Yes
Tirani et al. 2015 [72]	Italy	Markov	No	No	Yes
Gasparini et al. 2016 [73]	Italy	Markov	No	Yes (cohort)	Yes
Pouwels et al. 2013 [74]	Netherlands	Markov	No	Yes	Yes
Tu et al. 2014 [75]	Canada	Markov	[Approx]	No	Yes
Christensen et al. 2013 [76]	England	Markov	No	Yes (cohort)	Yes
		Transmission dynamic	Yes	No	Yes
Christensen et al. 2014 [77]	England	Transmission dynamic	Yes	No	Yes
Huels et al. 2014 [78]	UK	Transmission dynamic	Yes	No	No

Note: Adapted from presentation by Hannah Christensen

Economic and mathematical modelling are highly dependent on the local country context, which includes factors such as disease epidemiology and healthcare structure. A number of vaccination strategies have been considered in these models, with different assumptions regarding the possibility of inducing indirect protection. Models can take into account programmatic issues relating to vaccination schedules already in place in the country. Incidence and case fatality from disease are highly influential in these models, and incidence varies considerably from country to country.

Relevant factors for models considering cost-effectiveness, or health economic evaluations are, for example, the prevalence of sequelae following disease and the associated loss of quality of life. There are a number of approaches for their inclusion in the models, ranging from case-control studies on SgB IMD survivors to using utilities from related conditions. There are, however, major differences in the health economic approach taken by different countries with regard to discount rates and thresholds used for cost-effectiveness.

All models predict that introducing the 4CMenB vaccine will reduce the number of invasive cases, but countries with a low incidence of SgB IMD which used the manufacturer's list price for their model calculations found that the costs per QALY gained were higher than the internationally accepted threshold values for adoption.

In models based on the situation in the UK, Ireland and Italy, the vaccine has been found to be cost-effective.

In 2013, the UK Joint Committee on Vaccination and Immunisation (JCVI) published an interim position statement advising against the introduction of the vaccine on grounds of unfavourable cost-effectiveness [79]. This decision was challenged by charities, clinicians, academics and politicians. In 2014, a second model was carried out by Christensen et al. [77] including updated new evidence on the vaccine characteristics and disease burden but also cost of care, litigation costs, and loss of quality of life from disease for family and network members. The results from this model indicate that the vaccine could be cost effective in the UK with a vaccine price lower than the manufacturer's list price and a reduced two-dose infant priming schedule [77]. Following this, the JCVI issued a position statement recommending the use of the 4CMenB vaccine with the immunisation schedule at 2, 4 and 12 months of age (2+1) [59].

In Ireland, a health technology assessment on introducing 4CMenB vaccination into the national immunisation programme found the 4CMenB vaccine cost-effective when taking into account the epidemiology of SgB IMD, applying societal parameters similar to those used in the UK assessment, and with a lower vaccine price.

In Italy, the vaccine was shown to be cost-effective when the possible underestimation of the disease incidence was considered and the evaluation of possible sequelae and their cost was included [73].

Recent modelling by Christensen et al. [80] provided information on the cost-effectiveness of catch-up 4CMenB vaccination in England for children too old to receive the vaccine under the current infant programme. The study estimated that catch-up vaccination of 1-year-old children could be cost-effective, incremental to the existing infant programme, if the vaccine could be procured at a lower cost. Extending vaccination to 2-year-olds was found to be less cost-effective or not cost-effective with conservative vaccine assumptions. Extending the vaccination to 3–4 year olds was not found to be cost-effective [80].

Ease of implementation and acceptance

In the expert meeting, a few experts pointed out that some parents and healthcare professionals had reservations about adding the 4CMenB vaccine to the routine vaccination schedule. Reportedly, practitioners expressed concerns about a possible negative impact of adding the 4CMenB three-dose vaccine plus booster to an already complicated vaccination schedule for young children. In a survey of more than 3 000 paediatricians in Germany, over a third of the responders were concerned that the uptake of other vaccines might decrease if Bexsero were introduced [81]. Concerns were also raised around parental acceptability of the vaccine due to the increase of fever, especially when co-administered with routine infant vaccines. Less than half of the surveyed paediatricians were willing to accept the 4CMenB vaccine administered concomitantly with other routine vaccines, and over half favoured administration at ≥ six months of age. Despite these issues, the majority of participating healthcare workers would recommend Bexsero to parents of infants eligible for vaccination.

Other surveys carried out among physicians in France [82], Austria [83], and Italy [84] showed similar reservations regarding implementation in infants. Several studies suggested moderate to high parental acceptance for the 4CMenB vaccine [84-87] and acceptance of more than three vaccinations at a visit if recommended by a physician [88,89].

In the UK, where the vaccine was introduced into the vaccine schedule as a reduced 2+1 schedule, healthcare workers and public acceptance of 4CMenB vaccine appears to be high and supported by information materials [90] and a communication plan run by Public Health England.

Outbreak, cluster and hyperendemic situations

A major area of application for the 4CMenB vaccine could be mass vaccinations during SgB IMD outbreaks or the vaccination of contacts of sporadic cases to prevent late/later disease occurrence due to continued circulation of the outbreak strain – at least in countries where the vaccine is not already used universally. Guidance on the use of Bexsero in outbreaks have been produced in various countries.

In France, an analysis was carried out by Santé Publique France (at the time of analysis still called the French Institute for Public Health Surveillance, InVS) regarding the potential use of Bexsero for contacts of sporadic cases and for the control of SgB IMD clusters, outbreaks or hyperendemic situations. All clusters identified within the last 15 years by the French surveillance system were reviewed and analysed retrospectively. Factors which were taken into account included the number of cases, the interval between disease onsets, the attack rates, and the delay between outbreak detection and launch of an alert. 'Alert criteria' in France do not automatically lead to vaccination. Based on the results, Bexsero was not recommended for close contacts of sporadic cases. The vaccine was recommended to control SgB IMD outbreaks (three cases due to the same strain, within three months, attack rate ≥10/100 000) and clusters of at least 2 SgB IMD cases within four weeks if strains were covered by the vaccine. For other situations, particularly localised increases in the incidence of group B disease, ad hoc expert advice should be sought. Criteria to detect these situations include: clonal cluster with ≥ four cases within 52 weeks, incidence ≥3/100 000 [91,92].

The UK have produced guidance material for the use of Bexsero in outbreak and cluster situations. In order to manage clusters in the wider community, the age-specific attack rate should be calculated. Bexsero may be considered in the community if the age-specific attack rate for a vaccine-preventable SgB IMD strain exceeds 40/100 000 within a defined geographical boundary over a three-month period [93].

In Spain, no threshold is used to consider the use of Bexsero by the Regional Public Health Authorities. Its use is recommended in cases and close contacts in clusters (two or more cases in same institution and in ≤ four weeks) and outbreaks (three or more cases in a given community in ≤ three months). In sporadic cases, the use of Bexsero is recommended. It is also recommended for close contacts belonging to risk groups; contacts in risk

groups will receive Bexsero together with chemoprophylaxis. In healthy close contacts, only chemoprophylaxis is recommended.

In Germany, the recommendations for MenB vaccination are similar to the longstanding recommendations for the use of MenACWY vaccines in outbreak or hyperendemic situations: two or more cases of the same serogroup in day-care facilities for children, schools, dormitories or similar facilities within a four-week period; three or more cases of the same serogroup over a three-month period in a circumscribed segment of the population (e.g. adolescents) of a certain region or with a resulting incidence ≥10/100 000 inhabitants.

ECDC published a guidance document on public health management of sporadic cases of invasive meningococcal disease in 2010 [94]. The guidance pointed out that if a case of meningococcal disease is caused by a strain that is preventable by an available licensed vaccine, an appropriate course of vaccination – in addition to chemoprophylaxis – is recommended for household contacts who are not already immune (strong recommendation with a very low level of evidence). This was suggested, however, at a time when there was no 4CMenB vaccine available [94].

Table 8. Some considerations and reasons behind decisions for introduction/non-introduction of 4CMenB vaccine into the national vaccination programmes (NIP) in EU/EEA countries based on input from country experts during the ECDC consultation meeting in November 2015 and further feedback from NFPs for vaccine-preventable diseases

Country	NIP decision	Key considerations	Reasons behind decision
Austria	Recommended (not funded)	• SgB IMD epidemiology and microbiology data • Vaccine safety and immunogenicity	• Decreasing trend of SgB IMD • Require mathematical modelling and economic analysis • Data limitations: effect on carriage, vaccine coverage, no contact pattern data
Belgium	Not recommended	• SgB IMD epidemiology and microbiology data • Impact of vaccination • Indirect protection • Data on theoretical coverage • Side effects • Preliminary data on effectiveness	• Low incidence of SgB IMD • Impact of vaccination: limited duration of protection • Data limitations: effect on carriage, vaccine coverage
Czech Republic	Recommended (not funded)	• SgB IMD epidemiology and microbiology data • Vaccine safety and immunogenicity	• Low incidence and decreasing trend of SgB IMD • Require mathematical modelling and economic analysis
France	Not recommended	• SgB IMD epidemiology and microbiology data • Vaccine safety and immunogenicity • Impact and cost-effectiveness analysis • Use for contacts of sporadic cases, clusters and outbreaks	• Low incidence and decreasing trend • Lack of clinical efficacy data • Limited duration of seroprotection • Difficulty integrating three-dose series into schedule • Safety profile – reactogenicity leads to separate administration from other vaccines • Lack of data about effect on carriage • Not cost-effective • Uncertainties about efficacy on non-serogroup B
Germany	Recommended only in the state of Saxony	• Pathogen characteristics • Disease burden • Vaccine characteristics • Impact of vaccine • Cost-effectiveness • Implementability and acceptance	• Low and decreasing SgB IMD incidence • Reactogenicity comparatively high • Herd immunity and possible replacement effects uncertain • Very high cost/QALY gained based on modelling • Acceptance for vaccine high but implementability challenging (based on multiple injections)
Greece	Not recommended	• Literature review • SgB IMD epidemiology • Strain coverage • Vaccine safety and immunogenicity	• Low incidence of SgB IMD • Additional data needed: • (persistence of antibodies, effect on carriage, safety, cost-effectiveness) •
Ireland	Introduced into NIP (Oct 2016)	• SgB IMD epidemiology and microbiology data • Vaccine safety and immunogenicity • Health technology assessment (HTA)	• SgB IMD incidence amongst highest in EU • HTA shown to be cost effective when including revised parameters for assessment used by UK • Vaccine made available at cost-effective price • Strong push for introduction from the public, charities, clinicians and politicians
Italy	Introduced into the NIP (Jan 2017)	• SgB IMD epidemiology and microbiology data • Efficacy and safety • Economic sustainability Cost-effectiveness analysis • Public health prioritisation	• Underestimated incidence of SgB IMD • Public demand • Concerns raised by ministry about equity of implementing in some regions and not others
Luxembourg	Not recommended	• SgB IMD epidemiology analyses	• Low incidence of SgB IMD • Additional data needed on effect on carriage, and safety • Lack of clinical efficacy data

Country	NIP decision	Key considerations	Reasons behind decision
			• No data concerning circulating strains in Luxembourg or in neighbouring countries •
Norway	Not recommended	• SgB IMD epidemiology and microbiology data • WHO recommendations for meningococcal vaccinations (WHO position paper, November 2011)	• Low incidence of SgB IMD • No universal introduction based on WHO recommendation of only risk groups in countries with low incidence.
Spain	Not recommended	• SgB IMD epidemiology and microbiology data • Vaccine effectiveness and safety • Impact of modifications to immunisation programme • Ethical aspects • Economic evaluation	• Low incidence of SgB IMD and decreasing trend • Stopped assessment of introduction into national schedule after step 2 due to lack of data on vaccine efficacy and safety profile • Plan to resume assessment when new data available
UK	Introduced into NIP (Sept 2015)	• Epidemiological analyses • Safety and efficacy • Impact and cost-effectiveness study • Comments received on the interim statement July 2013 • Health economic analyses	• SgB IMD incidence <1 year among highest in EU • Declining incidence of SgB IMD but could possibly rise again (historic fluctuations of the disease) • Used strain coverage from SBA activity 88% (rather than MATS 73% (95% CI: 57%–87%) • Health economic model with revised parameters for assessment and a low vaccine price showed vaccine could be cost-effective • The public, charities, clinicians, academics and politicians push for introduction
Portugal	Currently under assessment by NITAG for inclusion in NIP	• Epidemiology • Efficacy and safety • Cost-effectiveness • Duration of protection	• Recommended by Portuguese Society of Paediatrics (not reimbursed)

Identified areas for country collaboration

According to the 2015 VENICE III survey on NITAGs in the EU/EEA [23] there is potential for country collaboration between those countries that have assessed the introduction of the 4CMenB vaccine and those that are currently assessing or planning an assessment. Based on the VENICE III survey, the majority of countries that required disease transmission models (Appendix 1) and health economic evaluations (Appendix 2) were interested in utilising an existing evaluation and adapting it to their own settings, which is essentially what Germany did with the UK model. Some countries were interested in jointly commissioning an evaluation which would provide country-specific results. Another option would be to jointly conduct or share systematic reviews for context-free aspects (vaccine efficacy, safety, and impact) (Appendix 3). Results from strain coverage research can also be adapted for those countries that have limited laboratory support.

Although some countries pointed out that collaborating in this area could be difficult due to differences in healthcare systems and vaccine delivery structures, lack of funding and resources, and language barriers/cultural differences, the majority were still interested in working together with other countries.

Summary considerations

There is still a need for more and better data on the 4CMenB vaccine for all countries, regardless of whether they are currently in the assessment process, plan to conduct an assessment, or have already decided to recommend the 4CMenB vaccine.

The UK, Ireland and Italy have introduced the 4CMenB vaccine into their publicly funded national routine immunisation programmes. The decision in the UK and Ireland was mainly taken because of their higher incidence of SgB IMD, especially in younger age groups. For Italy, the incidence appeared somewhat lower than in the UK and Ireland, but an underestimation of disease incidence was assumed and taken into account. In all three countries, the rapid nature of the disease and a supportive cost-effectiveness analysis contributed to adding the 4CMenB vaccine to the national immunisation programme. Austria, the Czech Republic and Germany (state of Saxony) all recommend the vaccine, but offer no funding/reimbursement.

Six countries have introduced the vaccine nationally, but only for risk groups (BE, ES, FR, LU, NO and PT). A recommendation for risk groups is also in place in the three countries that introduced the vaccine to their publicly funded national routine immunisation programme (IE, IT and UK) and in countries which have recommended the vaccine without funding/reimbursement (AT, CZ, and in DE (state of Saxony) including a national recommendation for risk groups).

The decision of other Member States to not introduce the vaccine universally were based on various considerations, e.g. the low incidence of SgB IMD, the high price of the vaccine, busy immunisation programmes, combined with uncertainties around strain coverage, vaccine safety, and a lack of data about the duration of protection, the need for boosters, and overall vaccine effectiveness. Some Member States reported that they require key data on the impact of the vaccine in order to adequately assess effectiveness and cost-effectiveness before introducing the vaccine into their funded immunisation programmes. Other Member States reported that they have deferred a decision but will continue with the assessment, or start an assessment, once experiences from programme introduction in other countries are made available and missing information is provided. In Croatia, the Netherlands and Slovenia, the unavailability of the vaccine in their countries was stated as one of the reasons for non-introduction.

Ad hoc expert group, expert meeting, VENICE III survey, and literature: key findings

The burden of SgB IMD

The burden of SgB IMD and the circulating strains varies between countries. Although some countries have no plans to assess the 4CMenB vaccine because the incidence of SgB IMD in their country is low, this could change in the future if case numbers start to increase. Historical data have shown that the serogroup distribution and incidence of IMD within a geographical area can change due to an epidemic or a shift over time [95]. This could be explained by secular trends, population immunity, host and environmental factors, and the emergence of new clones.

Predicting strain coverage

In order to measure the effectiveness of the 4CMenB vaccine, it is not practical to predict vaccine strain coverage based on testing of many different meningococcal strains directly in hSBA. For this reason, MATS is currently the best tool for predicting strain coverage. However, MATS coverage estimates must be carefully interpreted considering the conservative nature of assays and additional issues concerning the positive bactericidal threshold and the binary nature of results. Under certain conditions, MATS can either underestimate or overestimate the strain coverage afforded by Bexsero [13,51].

MATS is considered a standardised method to predict 4CMenB strain coverage [13,14] but would need to be performed on a representative strain collection to estimate country-specific strain coverage. Since only a few reference laboratories in Europe can perform MATS, it would be helpful if these laboratories could offer MATS testing services for selected isolates on request – both for their own country and for neighbouring countries. MATS kits can be requested from GlaxoSmithKline by accredited laboratories.

Use of antipyretics and safety

High fever has been observed following vaccination with 4CMenB, especially when co-administered with other vaccines included in the national immunisation schedules for children. The 4CMenB vaccine is the first vaccine for which prophylactic use of antipyretic is recommended. Further studies on the effects of antipyretics on immunogenicity are currently being conducted. Post-implementation surveillance is also essential to gain information on AEFI. Several studies looking at AEFIs following 4CMenB introduction are ongoing [63,64].

Effect on bacterial carriage

At this stage is it not clear if the vaccine can disrupt carriage transmission and induce herd protection. Interrupting transmission improves the public health profile of the vaccine and its cost-effectiveness. It is vital that carriage studies are carried out in all populations where the vaccine is introduced (as part of a universal programme or to control an outbreak) in order to provide critical information on herd protection induced by the vaccine. If the vaccine is effective against carriage in addition to invasive disease, the indirect effects of a vaccination programme could be considerable if the vaccine is targeted towards those with high carriage prevalence.

Duration of protection

There are uncertainties about the duration of protection of the 4CMenB vaccine and whether boosters are required. There are ongoing studies looking at two doses versus three doses for priming in infancy and catch-up vaccinations in children [4].

Determining the target populations and vaccination strategy

In accordance with the national recommendations and EMA's European Public Assessment Report (EPAR) on Bexsero which provides information on the indicated posology for the age groups 2–5 months, 6–11 months, 12–23 months, 2–10 years, and adolescents (from 11 years of age) and adults [62], the ECDC expert group considered infants under one year of age as the primary target group for 4CMenB, with optimal timing of vaccination prior to the peak of SgB IMD incidence at five months of age. According to published studies and licensure application, the vaccine has been shown to be immunogenic in infants between two and five months of age with a 3+1 dose schedule or a 3-dose schedule in infants at age 6–8 months at first vaccination. In young children, the vaccine has been shown to be immunogenic after at least two doses. A June 2017 study has shown the 4CMenB vaccine to be immunogenic and safe in infants at a reduced infant schedule of 2+1 [4].

In adolescents and adults, two doses led to the presence of protective antibodies against the vaccine antigens [52-55]. The aim of an adolescent programme would be to prevent acquisition of the infection rather than to disrupt carriage (at the time of writing there is no information on the effect of the vaccine on carriage). Vaccinating adolescents could be a very effective vaccination strategy; it should, however, be noted that strain replacement is a potential risk for adolescent programmes if the prevalence of bacterial carriage is high.

Cost-effectiveness

Due to competing health priorities and financial considerations, health economics (including cost-effectiveness analysis) play a central role in the decision to introduce a vaccine to a country's vaccination programme. Cost-effectiveness assessments depend on specific factors in a country such as the current epidemiology of SgB IMD or the structure of its public health system. The 4CMenB vaccine has been shown to be cost-effective in countries where there is a higher incidence of SgB IMD, where societal costs were taken into account, e.g. litigation costs and loss of quality of life from disease on family and network members and at a lower vaccine price.

Country collaboration

Collaboration with other countries in the assessment process could be beneficial for those countries that are currently assessing, or plan to assess, the vaccine. Collaboration related to strain coverage analysis and mathematical/health economic models was found to be highly useful.

Vaccination on the private market

In many Member States, the vaccine is not included in the national programme but is available for purchase in the private market. Monitoring of the number of doses administered in the private sector should be encouraged in order to capture crucial data on vaccine effectiveness and safety. During the ECDC expert consultation meeting it was mentioned that vaccination in the private sector may not be given at the optimal age when the child needs the most protection (infants under 12 months); instead, it may be given to older children because they require fewer doses or because the vaccine became available too late for the child to be vaccinated at a younger age. The availability of the vaccine only for those that can afford it may also raise issues around equity.

Stakeholders

It is important to closely coordinate with the various stakeholders when considering the introduction of the 4CMenB vaccine. Some countries have very strong advocacy groups supporting the universal introduction of the 4CMenB vaccine, particularly because SgB IMD affects mainly infants and the disease can cause negative long-term health sequelae.

Acceptability

It is important that a well-planned communication strategy is in place to educate parents and healthcare workers about the vaccine and how to manage the increased likelihood of fever. This is particularly important for countries where the vaccine has been introduced in the schedule, in order to increase its acceptability by healthcare workers and the public. Parents should be properly informed in order to provide them with facts to make an informed decision.

Conclusions

During the decision-making process for the introduction of the 4CMenB vaccine, a number of considerations were taken into account. Countries which have made a decision or are considering the introduction of the vaccine mostly cited the following factors:

- Epidemiology of SgB IMD B in the country, the age group most affected by SgB IMD, case-fatality, disease burden (e.g. expressed in QALYs or DALYs)
- Vaccine characteristics including immunogenicity, strain coverage, safety and efficacy
- Impact of the vaccine estimated through transmission modelling, health economic evaluations (e.g. cost-effectiveness studies)
- Ease of implementation and acceptance of the vaccine

Twelve EU/EEA Member States (AT, BE, CZ, ES, FR, DE, GR, IE, IT, LU, NO and UK) have made a formal assessment of the introduction of the 4CMenB vaccine. The UK and Ireland are among the Member States with the highest incidence of SgB IMD in children under one year of age in the EU/EEA. Reducing SgB IMD has been a priority in both countries, and both have introduced the vaccination into their funded national immunisation schedules for children below one year of age. Italy also decided to introduce the 4CMenB vaccine into the funded national immunisation schedule for children under one year.

Other Member States which have made an assessment did not recommend the routine vaccination of infants, children or adolescents because of the low burden of SgB IMD in their country, the difficulty of integrating a 3-dose series into the infant vaccination schedule, and the increased likelihood of fever after vaccination. Other reasons given included an unfavourable cost-effectiveness in the country's epidemiological context, the lack of data on efficacy, insufficient information on the duration of protection, and the effect of the vaccine on carriage. Some countries are waiting for post-licensure studies from the UK, Ireland and Italy.

Notwithstanding and recognising the above-described limitations and gaps in the currently available knowledge, the following options can be taken into account by countries that are considering the introduction of the 4CMenB vaccine:

- **Consider a recommendation for the universal vaccination of infants below one year of age,** based on the observed incidence and economic considerations. This option is currently pursued by countries with a high incidence of SgB IMD in infants if the vaccine was also cost-effective based on vaccine price and country- and context-specific considerations (e.g. IE, IT and UK, see Table 1). Pursuing this option could improve the short-term impact of the 4CMenB vaccine by targeting infants prior to the peak of disease incidence at five months of age. Based on the available evidence, the vaccine has been shown to be immunogenic in infants between two and five months of age with a primary series of three doses and a booster between 12 and 15 months. Results from a 2017 clinical trial have shown the vaccine to be immunogenic and safe at a reduced infant schedule of 2+1 doses [4]. In young children, the vaccine is shown to be immunogenic after at least two doses.
- **Consider a recommendation for the vaccination of different age groups,** based on incidence of IMD B across different age groups. A limited number of countries are currently adopting this approach by recommending the vaccine for use in infants, children and/or adolescents (e.g. Austria, the Czech Republic, and the German state of Saxony, see Table 1). The EMA's European Public Assessment Report on Bexsero provides further information on the indicated posology for the age groups 2–5 months, 6–11 months, 12–23 months, and adolescents (from 11 years of age) and adults [62]. The aim of pursuing an adolescent programme would be to prevent acquisition of the infection rather than to disrupt carriage. At this stage, the effect of 4CMenB vaccination on carriage is not known. Vaccinating adolescents could be a very effective vaccination strategy; it should, however, be noted that strain replacement is a potential risk for adolescent programmes if the prevalence of bacterial carriage is high.
- **Consider a recommendation for the vaccination of individuals at increased risk for SgB IMD;** this is currently the case in 12 EU/EEA Member States (Table 1). Main risk groups are:
  - Individuals with underlying medical conditions such as those affected by complement disorders and asplenia, due to the higher incidence of disease following colonisation in these groups
  - People exposed professionally to the risk of infection (e.g. laboratory workers)
- **Consider a recommendation for the vaccination of individuals in an outbreak setting,** which should be based on country-specific evaluations and analyses of the number of cases, the interval between disease onsets, the population at risk, the attack rate, etc.

These expert opinions should be considered as options and represent important aspects that Member States can take into account in order to facilitate the decision-making process for the introduction of the 4CMenB vaccine.

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Appendix 1

European Union and European Economic Area Member States that have not assessed the introduction of meningococcal B vaccination and which have a data need for literature/evidence review and their interest in collaborating with other countries in a 4CMenB vaccination assessment process, February 2015 (n=6).

Need for literature/evidence review and collaboration interest	Country	n	%
Review of literature/evidence	CY, GR, MT, PT, ES, SE	6	100
Collaboration interest			
Contribution or active participation in joint systematic review possible	CY, GR, ES	3	50
Due to limited resources/expertise no contribution or active participation possible	MT, PT, SE	3	50
Interest in teaming for systematic review with a country with more expertise	MT	1	17

Appendix 2

EU/EEA Member States which have not assessed the introduction of meningococcal B vaccination and which have a data need for disease transmission modelling and their interest in collaborating with other countries in a 4CMenB vaccination assessment process, February 2015 (n=9).

Need for disease transmission modelling and collaboration interest	Country	n	%
Disease transmission modelling	AT, CY, DK, FI, IT, MT, PT, ES, SE	9	100
Collaboration			
Interest in utilizing existing model	AT, CY, IT, ES, SE	5	56
Can do adaption to own settings themselves	AT, IT, ES, SE	4	44
Need adaption to own setting be conducted by others	CY	1	11
No ability/willingness to financially compensate for adaption (e.g. max. EUR 30 000)	CY	1	11
Interest in participation in a joint commissioning of a model (with specific results for each country)	FI, PT	2	22
Ability/willingness to contribute to the required budget for model development (e.g. max. EUR 30 000) per country	FI	1	11
No ability/willingness to contribute to the required budget for model development (e.g. max. EUR 30 000) per country	PT	1	11
No interest/ability to collaborate	DK, MT	2	22

Of the countries that are not interested or do not have the ability to collaborate in transmission modelling, Denmark stated that it is still awaiting the experience from the United Kingdom before proceeding with transmission modelling, whereas Malta explained that it is unable to develop a transmission model due to small population and consequently a limited number of cases.

Appendix 3

EU/EEA Member States which have not assessed the introduction of meningococcal B vaccination and which have a data need for health economic evaluation and their interest in collaborating with other countries in a 4CMenB vaccination assessment process, February 2015 (n=9).

Need for health economic evaluation and collaboration interest	Country	n	%
Health economic evaluation	CY, FI, GR, IT, MT, PT, ES, SE	8	100
Collaboration			
Interest in utilizing existing evaluation	CY, GR, IT, ES, SE	5	63
Can do adaption to own settings themselves	GR, IT, ES, SE	4	50
Need adaption to own setting be conducted by others	CY	1	13
No ability/willingness to financially compensate for adaption (e.g. max. EUR 30 000)	CY	1	13
Interest in participation in a joint commissioning of an evaluation (with specific results for each country)	FI, MT, PT	3	38
Ability/willingness to contribute to the required budget for evaluation (e.g. max. EUR 30 000) per country	FI	1	13
No ability/willingness to contribute to the required budget for evaluation (max. EUR 30 000) per country	MT, PT	2	25
No interest/ability to collaborate	-	0	0

Three (CZ, FI, IT) of the countries that have already implemented or planned to implement a meningococcal B vaccination within the next 12 months plan post-authorization research or enhanced surveillance projects. All three countries indicated that those projects include active surveillance regarding safety, effectiveness against clinical outcomes and effect on carriage. Italy has not implemented or decided yet on the concrete surveillance project and Finland is estimating preliminary results in 2019.

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