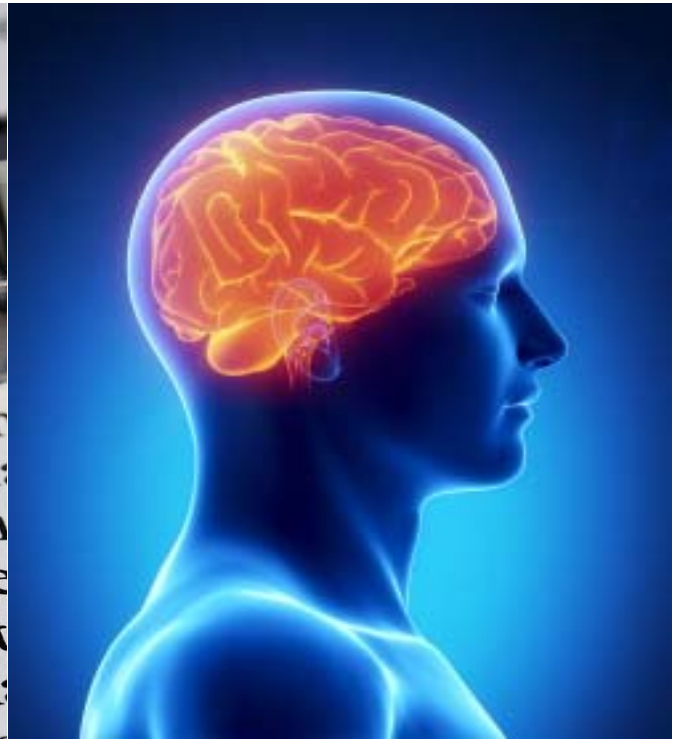
KCE REPORT 231Cs

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SYNTHESIS

A QUADRIVALENT VACCINE AGAINST SEROGROUP B MENINGOCOCCAL DISEASE: A COST-EFFECTIVENESS STUDY



Belgian Health Care Knowledge Centre

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HEALTH TECHNOLOGY ASSESSMENT

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Other reported interests:	All authors declare to have no conflict of interest specific to the subject; Caroline Trotter has received consultant fees from GSK for a critical review of a meningococcal vaccine health economic model (March 2013) but this vaccine was targeting other serogroups. All validators and external experts declare to have no conflict of interest specific to the subject of this study, except for the participation to a Meningococcal B Symposium sponsored by Novartis in 2013 (A. Vergison). David Tuerlinckx participated as co-investigator (Community-acquired pneumonia in children from Pfizer) and principal investigator (Measure of pneumococcal antibodies from Multigam) in two sponsored studies that were not related to this study, and received a travel grant from GSK to participate to the ESPID 2012 and ESPID 2013 conferences. The funds for research and grants were directly paid to his hospital and he received no personal remuneration for his work. Beatrice Swennen received a travel grant from GSK to participate to the ESPID 2013 and ESPID 2014 conferences. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health, United Kingdom.
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FOREWORD

The meningococcus is a very dangerous bacteria. It is currently one of the rare pathogens that can kill a young child in good health in a few hours. Moreover, the increased risk of transmission among the contacts of a case may generate great amounts of anxiety in the population involved. Meningococci are divided into several families or serogroups. In Europe, serogroup B is the most prevalent serogroup. In Belgium each year, around a hundred subjects will develop a meningitis or a septicaemia due to serogroup B meningococcus, the outcome of which will be quickly fatal in 5 to 10% of cases, or will result in serious sequelae in 10 to 20% of cases. The reasons why some people, generally in good health, develop such a disease are poorly understood. We know however that the victims are young, even very young, for the most part: one case in five is actually less than one year old.

When a disease may be fatal despite a treatment, the question of its prevention becomes particularly important. Although vaccines against other serogroups exist since a long time, for example against serogroup C, a vaccine against serogroup B has only been recently available in Europe. Should we therefore consider vaccinating all age groups of the population likely to develop the disease?

The answer is far from trivial. Which groups should be vaccinated? What vaccine coverage rates can be expected, and what effect will they have on disease transmission? Adverse events should also be accounted for, especially high fevers, which may worry parents. Finally, the cost of vaccination will also have an impact on the decision to finance it totally or partially by the society - and therefore its affordability. The potential benefits of a vaccination programme should indeed be weighed against all other preventive or curative measures that could potentially be funded by the health insurance.

However, when it comes to avoiding the loss of a child, the economic evaluation is only one of the factors guiding the choice of the decision makers. These models may, however, provide a better insight into the costs of the different options, the inevitable adverse events and the inability to prevent all infections and their consequences, as zero risk can never be achieved, at least for now. The current study is a contribution to the health care system construction. It was done rigorously with the best tools available today, and with the expertise of researchers from the University of Bristol and numerous Belgian experts. The choices do not become easier, but hopefully better informed.

Christian LÉONARD
Deputy general director

Raf MERTENS
General director

ABSTRACT

BACKGROUND

4CMenB (Bexsero), which is a new quadrivalent meningococcal vaccine with the capacity to protect against serogroup B disease, was licensed in the EU in January 2013.

Belgian decision-makers need to make decisions about whether and how best to use this vaccine. Mathematical and economic models which estimate the potential clinical impact and cost-effectiveness of different vaccine strategies are useful tools for informing these decisions.

The aim of this project is to evaluate the potential clinical impact and cost-effectiveness of 4CMenB vaccine programmes in Belgium.

METHODS

The only 4CMenB trial on carriage, looking at a possible reduction of transmission (through “herd” or indirect effects) failed to show a significant effect against serogroup B carriage. We therefore opted for base case analyses with no herd effect. However this trial lacked statistical power and some secondary endpoints suggest that an effect on carriage is possible; we thus also included a scenario assuming herd effects, in anticipation of further studies. Two types of model - a single cohort static model assuming direct protection only, and a transmission dynamic model incorporating herd effects - were thus developed to evaluate 4CMenB vaccination in different target groups (infants and/or adolescents).

The models were originally developed to examine the impact of a “generic” serogroup B vaccine in England. The models have been adapted here to address similar questions on the use of 4CMenB in Belgium.

Models are parameterised using a range of Belgian (to the largest extent possible) and contemporary data sources including: serogroup B-specific incidence, mortality and acute hospitalisation costs from the Belgian hospital discharge databases linked to the National Reference Centre dataset; sequelae, quality of life losses, vaccine efficacy and safety from the literature; cost data from the health care payer perspective; and for the dynamic model, age-specific carriage prevalence estimates from a systematic review and patterns of social contacts from a Belgian survey.

Uncertainty in these parameters is explored through scenario analyses in both models, and additional (partial) probabilistic analysis in the cohort model.

RESULTS

If 4CMenB has no effect on carriage (base case)

If the vaccine does not induce herd effects, the base case model predicts that infant vaccination could prevent 4 to 10% (i.e. 5 to 14 cases) of the serogroup B cases occurring over the lifetime of a birth cohort, depending on the vaccination option (i.e. vaccination included in the routine schedule, partly reimbursed or available in the private market only). Substantial numbers of vaccine-related adverse events are expected to occur, e.g. routine infant vaccination is predicted to generate 2757 and 976 adverse events requiring outpatient and inpatient care, respectively. These event are however expected to resolve rapidly.

All infant strategies considered would result in high costs per QALY gained, over €400 000 per QALY gained under the base case.

None of the scenarios explored in sensitivity analysis yielded cost-effectiveness ratios that are in the range of those estimated for recently introduced vaccinations in Belgium. The best case scenario combining the most vaccine favourable assumptions would prevent 20% (n=71) of serogroup B cases but would still cost €98 300 per QALY gained compared to no vaccination.

Vaccination of adolescents would prevent only 1-6% of all cases. Combined infant and adolescent vaccination averts the highest number of cases (5-16%). The costs per QALY gained of both strategies were higher than those of the infant strategies.

If 4CMenB has an effect on carriage

Greater health benefits are seen when the vaccine is assumed to generate herd effects in addition to affording direct protection. In this case strategies targeting adolescents (14 year olds), in which carriage prevalence is thought to be high, maximises case reduction.

Substantial reductions in cases (65%) can be achieved in the long term by routine vaccination of adolescents alone. Due to the lower number of doses required, the cost per QALY gained of this strategy falls below €25 000. However, this high impact would only be achieved 10 to 20 years after vaccine introduction, while infants would still be affected by the disease in the first decade. The highest reduction in cases (67%) is seen with combining routine infant and adolescent vaccination but this strategy would cost over €800 000 per QALY gained compared to adolescent vaccination. If we compare this combined strategy to no vaccination, i.e. if decisions are only guided by the highest clinical impact and thus reducing meningococcal disease in infants is especially valued (i.e. vaccinating adolescent alone would not be considered a plausible option), this strategy would still cost €83 000 per QALY gained, compared to no vaccination. And again this impact would only be achieved 10 to 20 years after vaccine introduction.

The cost per QALY gained of the combined routine infant and adolescent vaccination (compared to no vaccination) was most reduced under a high incidence and case fatality scenario (€22 500), if the vaccine price is reduced to ≤€5 per dose (€30 000) or in a best case scenario with parameters simultaneously set to their most vaccine-favourable estimates (€17 400).

CONCLUSIONS

These models have shown that the introduction of a routine immunisation programme with 4CMenB in Belgium has the capacity to reduce meningococcal disease. However, this vaccination will not prevent more than 16% of the cases if no herd effects are induced, and at a high cost. Greater number of cases would be averted and at a lower cost if the vaccine is able to induce herd effects.

SYNTHESIS

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1. MENINGOCOCCAL DISEASE AND VACCINES

1.1. Invasive meningococcal disease and serogroup B

Invasive meningococcal disease (IMD) is defined as the isolation or detection of *Neisseria meningitidis* from a normally sterile site. In Europe, IMD is relatively rare, affecting around 1/100 000 persons per year and up to 10/100 000 <5 years of age.[1] But IMD can cause severe disease, especially in young children, such as meningitis and septicaemia, which may lead to septic shock, death (5-10% of cases) and long-term sequelae (10-20% of cases).[1-4]

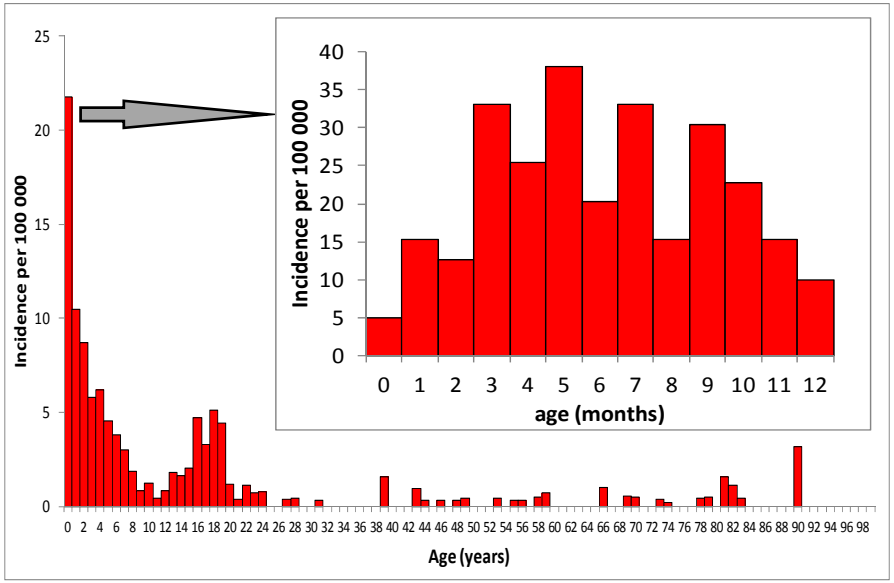
Most disease transmission occurs through asymptomatic carriage of *N. meningitidis*. Carriage leads to IMD in a small proportion of subjects, but the relationship between carriage and disease is not yet fully understood. While disease incidence is highest among young children, prevalence of carriage is low among this group but highest in adolescents and young adults, with peaks at 20-30%.[5, 6] Adolescents are thus playing a key role in transmission.

Although the disease is rare, IMD is considered a public health concern, because it is a severe disease that can kill young children, and also because it can potentially lead to small outbreaks within closed communities such as schools. This is related to the increased transmission among contacts of a case through increased carriage: attack rates as high as 4-7/1000 among contacts sharing the same household or day-care nursery as IMD cases were reported by an older Belgian study (1971-76).[7] IMD may thus generate significant amounts of anxiety in the population. Public health management around an IMD case in Belgium involves the tracing of close contacts and the administration of antibiotic prophylaxis to eradicate carriage.

Six serogroups of *N. meningitidis* principally cause disease worldwide but serogroup B has been the most prevalent in Belgium, with the exception of a peak of serogroup C around 2001.[1] Serogroups are known to differ in terms of disease severity, mortality, clinical picture and age distribution.[1-4] For instance, the serogroup C that was predominant in part of Europe in the early 2000's, led to more severe forms of disease and a higher mortality than serogroup B.

In Belgium, an estimated 179 IMD cases occurred per year (incidence at 1.7 per 100 000) in 2009-10, including 139 serogroup B cases. Around 6 deaths per year were attributed to serogroup B (5.4% of the cases). Children below five years of age account for half of serogroup B cases and a third of all deaths (Figure 1). The highest peak in disease is observed at five months of age.

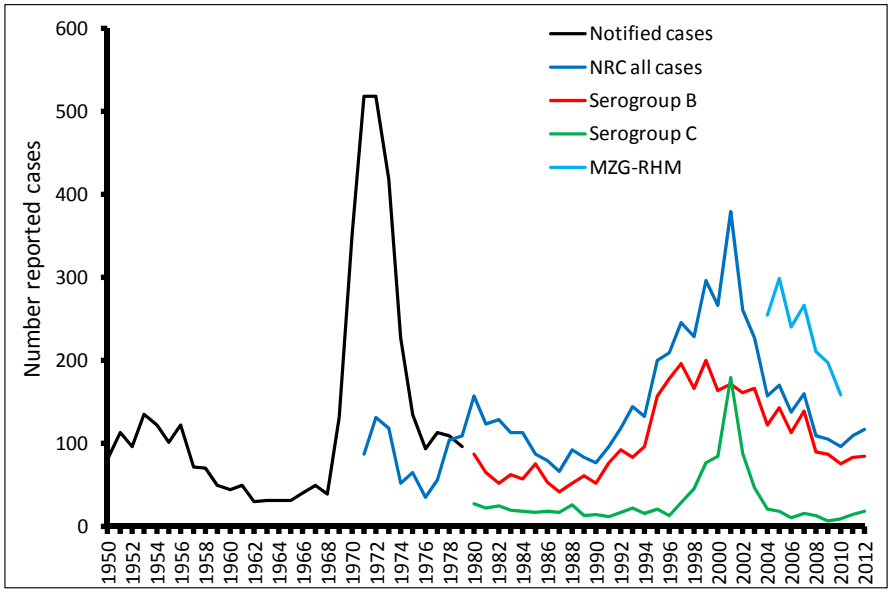
Figure 1 – Incidence of serogroup B cases by year of age, average 2009-10



Source: MZG-RHM new stays with ICD-9 code 036 and NRC database for proportions of serogroup B and age distribution <5 years. MZG-RHM: Minimale Ziekenhuisgegevens - Résumé Hospitalier Minimum. ICD: International Classification of Disease. NRC: National Reference Centre.

Large fluctuations in IMD incidence and mortality over time make predictions of future trends difficult. In Belgium according to data from the National Reference Centre for meningococcus, serogroup B showed two marked increases in the last 50 years, related to the expansion of specific clones (Figure 2), with a large peak in 1970-75 and a new rise in the nineties.[8-10] In 2004-10, serogroup B incidence showed a progressive decline, which was observed in all age groups. The factors involved in these changes are still unknown, but similar declining trends were observed in most other EU countries, suggesting the role of secular trends.[11]

Figure 2 – Annual numbers of reported invasive meningococcal cases by serogroup, 1950-2012



Based on National Reference Centre (NRC) for Neisseria meningitidis, De Maeyer et al. J of Infection 1981,[9] Carion et al. Eurosurveillance 1997.[10] NRC activities started in 1971 and the national notification system ended around 1980 (caution: case definitions differ). MZG-RHM: Minimale Ziekenhuisgegevens - Résumé Hospitalier Minimum.

1.2. The 4CMenB vaccine

A number of vaccines against meningococcal serogroups A, C, W-135 and Y are today available. The conjugate vaccine against serogroup C was introduced into the Belgian infant vaccine schedule in 2002, after the rise in serogroup C incidence. The inclusion of this vaccine, together with large catch-up campaigns among children, led to a dramatic decline of serogroup C IMD in all age groups.[12] Widespread programmes using this vaccine generated an important indirect effect (herd effects) in the population at large, as shown by the drops in incidence among unvaccinated individuals and the significant reduction in serogroup C carriage in the United Kingdom. This is an important finding because indirect effects were found to be a very influential factor in cost-effectiveness analyses.[13-15]

Development of a serogroup B vaccine has been difficult because serogroup B capsule shares similarities with components of human neurones and are poorly immunogenic.[16] After decades of research, 4CMenB (Bexsero) became the first multicomponent vaccine against serogroup B, produced by Novartis by a new technique ("reverse vaccinology") in which studying the genome of the pathogen allows identification of components that play a role in the immune response. 4CMenB received its market authorization from the European Commission in January 2013,[17] and contains four components: three proteins (fHbp, NadA, and NHBA) and an outer-membrane vesicle (OMV) component derived from an epidemic New Zealand strain.[17] OMV-derived vaccines, used for decades, are directed against a very variable component of the pathogen and therefore have only been used to control specific epidemic strains. These four vaccine components of 4CMenB are expressed in a high proportion of European serogroup B strains (78% of 1052 European strains in 2007-08),[18] but there are no Belgian data of this proportion.

Because the disease is rare, this vaccine has been approved based on a surrogate of protection, the serum bactericidal antibody (SBA) titres. Evidence from serogroup C and OMV vaccines indicates that SBA titres $\geqslant$1:4 (measured with human complement) confer clinical protection against IMD. This has not been established for the three other components of 4CMenB at the time of finalizing this report.

1.3. Research question

Following the authorisation of 4CMenB in Europe, the vaccine became available in some EU countries. Belgian decision-makers need to determine its potential utilisation.

The research question is: What would be the clinical impact and the cost-effectiveness of introducing 4CMenB in Belgium, according to different vaccination scenarios (i.e. vaccination schedules and target groups such as infants and/or adolescents) and according to the following vaccination policies:

- Inclusion in the universal routine schedule, free of charge ("routine")
- Partial reimbursement by the RIZIV-INAMI ("partial reimbursement")
- Vaccine only available in pharmacies, at full charge ("private market")

These analyses must take into account the potential vaccine effects on transmission if these are demonstrated.

The vaccination scenarios proposed for the cost-effectiveness analyses have been selected in deliberation with experts, stakeholders (Communities) and the Health Council Vaccination Working Group, and are described in Table 1. Because the concomitant administration of 4CmenB with routine vaccines resulted in particularly high rates of fever in clinical trials, most selected schedules involve 4CMenB administration at different times from other vaccines. Selected scenarios and schedules represent a compromise between age-specific disease burden, immune response to a given schedule, current vaccine calendar, risk of adverse events when given concomitantly and population acceptability of injections per visit. In particular, it was decided that the number of injections should not exceed two per visit, in line with recent research on vaccination acceptability.[19] Vaccine decision makers plan to schedule 4CMenB, not at 2 months (as usually indicated) because two injections are already scheduled at that age, but at 3 months because only one other injectable vaccine (hexavalent) is given at that age. Other infant doses are scheduled separately from other vaccines. Adolescent doses are provided at the same time as HPV vaccination in girls. Catch up vaccination in other age groups is not considered due to the low burden in these groups and high number of doses required. Vaccination limited to risk groups has not been included, in the absence of relevant vaccine trials providing immunogenicity and safety data for this group.

The use of 4CMenB to control clusters and outbreaks has also been considered, but has not been included as a full research question. No formal analysis has thus been conducted, but the relevance of this strategy in a Belgian setting is discussed below.

Table 1 – Proposed vaccination scenarios

Target group	Number of doses	Age at doses
Infants alone	3+1	3, 5, 6 months, booster at 14 months
Adolescents alone	2	Around 13 years (2 doses 2 months apart, together with HPV vaccination for girls)†
Infants + adolescents	As above	As above

† This occurs in the second year of the secondary school in Wallonia (i.e. 13-14 years of age, see http://www.sante.cfwb.be/index.php?id=4295) and in the first year in Flanders (i.e. 12-13 years, see http://www.zorg-en-gezondheid.be/hpv/). HPV: Human Papilloma Virus. Note: in order to avoid a long recoding process of the models that would delay the study, the schedules presented in Table 1 vary slightly with those applied in the models (see below).

2. MODELS AND ECONOMIC EVALUATION – METHODS

2.1. Models structure

The clinical impact and cost-effectiveness of 4CMenB vaccination is explored through two types of models, exploring different target groups:

- a single cohort static model, which assumes direct protection only and in which infant vaccination alone is simulated;
- a dynamic model, which allows inclusion of an effect on carriage, and thus potential indirect effects to be estimated; and in which infant and adolescent schedules are simulated, alone or in combination.

The only 4CMenB trial on carriage, assessing whether 4CMenB can reduce transmission (herd effects), failed to show a significant effect on carriage of serogroup B strains (see section 3.2 below). We thus assumed no effect on carriage in the base case analyses. These analyses are conducted using the static model for infant vaccination, and the dynamic model (set at no effect on carriage) for adolescent vaccination strategies. However, the carriage study lacked power and some of the secondary endpoints suggest that an effect on carriage acquisition is possible; we thus also included a scenario assuming herd effects in anticipation of further studies, using the dynamic model.

Infant strategies are thus simulated by both the static (base case) and the dynamic models. Adolescent strategies are simulated by the dynamic model only as these were a priori considered relevant only under the assumption of an indirect effect.

2.1.1. Details common to both models

The models were originally developed to examine the potential clinical impact and cost-effectiveness of a "generic" serogroup B vaccine in England.[20] The models have been adapted and updated here to address similar questions on the use of 4CmenB in Belgium.

The models are structured into 100 single year of age classes. After disease, individuals may survive with sequelae, survive without sequelae, or die due to the disease. Survivors with sequelae are assumed to have a reduced quality of life. Those dying from the disease were assumed to lose the average life expectancy for the age at which they died. The base case models considered serogroup B meningococci only, as the vaccine has received authorisation from the European Medicines Agency for immunisation against serogroup B only. Individuals may die due to causes other than meningococcal disease; published mortality rates (2011 Belgian estimates) were adjusted to remove deaths due to meningococcal disease as these are explicitly modelled. Based on available literature, vaccinated individuals were assumed to acquire immunity one month following their second dose of vaccine and have a reduced risk of disease. Immunity wanes over time, in which case individuals then have the same risks of infection as unvaccinated individuals.

2.1.2. Static model specific details

The static model is constructed using a Markov model, with monthly time steps. Individuals are born susceptible and cases arise by multiplying the age-specific probability of disease by the susceptible population. We assumed that individuals only have disease once and are removed from the susceptible pool. Years of life are weighted by the age-specific quality of life. The cohort size was based upon Belgian population figures for 2011 and a single birth cohort of 128 605 individuals was considered.

2.1.3. Dynamic model specific details

A Susceptible-Infected-Susceptible (SIS) model was used to represent the transmission of meningococcal carriage. This structure was chosen because individuals are expected to have multiple episodes of asymptomatic carriage of meningococci in their lifetimes.[6] Individuals are born susceptible, may become carriers of a meningococcal strain which is covered (thus preventable) by the vaccine or not, and after a period of time clear carriage to return to the susceptible state. Population mixing is based on mixing patterns from self-reported leisure contacts in Belgium (POLYMOD).[21] Cases are generated by applying an age-specific case-carrier ratio to the number of new carriage acquisitions.[6, 22] Vaccinated individuals with immunity may have protection against carriage acquisition (if any) as well as against disease. The demographics (single year of age population) were based on the living population from the static model, to aid comparisons between the static and dynamic results.

2.2. Clinical impact and economic evaluation

Key outputs of the models include: averted cases, averted cases with sequelae and deaths averted; life years saved, quality adjusted life years (QALY) gained and incremental cost-effectiveness ratios (ICER).

The economic evaluation was performed from the perspective of the health care payer, as recommended by the Belgian guidelines on economic evaluations.[23] Costs included were direct medical costs paid out of the health care budget (be it the federal government or the three federated entities) and the patients' out-of-pocket expenses for health care. Societal costs such as productivity losses and direct non-health care costs such as personal travel expenses were not accounted for. All costs are expressed in Euro 2012. The base case time horizon of the models was 100 years. Future costs and benefits were discounted back to their present value using a discount rate of 3% for costs and 1.5% for benefits.[23]

The main outcome for the cost-effectiveness analysis is the incremental cost per QALY gained. Results are compared to the situation without vaccination (i.e. the current situation without 4CMenB vaccination, and cases are treated as they arise), and to the next best alternative when relevant (i.e. in the dynamic model where different target groups can be opted for, i.e. infant and/or adolescent).

Uncertainty around the model parameters was handled in two ways:

- by running both models under a number of different scenarios (univariate and multivariate scenarios, including best and worst case scenarios);
- by making the cohort model (partially) probabilistic.[a]

In the univariate scenario analyses, the base case models were run considering higher and/or lower values for a large range of uncertain parameters, separately. Best (favouring vaccination) and worst (against vaccination) case scenarios were run by simultaneously varying several parameters to their high or low estimate.

The base case analyses assumed 4CMenB is effective against serogroup B IMD only, because it has been authorized for the prevention of that serogroup only. However, 4CmenB is a vaccine targeting meningococcal proteins that may be expressed by other serogroups and it may therefore provide protection against other serogroups (no data are yet available). An alternative scenario therefore explores the possibility that the vaccine might also be effective against all serogroups (multivariate "all serogroup" scenario).

In the probabilistic analysis, distributions (instead of point estimates) were used to represent the uncertainty around the quality of life (QoL) loss and all cost parameters, with the exception of the vaccine costs per dose. Other parameters were less well described or their uncertainty was too large to inform a plausible probability distribution so were considered using scenario analyses. One thousand simple random samples of the distributions were then propagated through the model to provide a distribution in the output parameters.

It should be noted that ICERs alone do not allow conclusions to be made about an intervention's cost-effectiveness. Such conclusions require a comparison with a reference ("threshold") value for the ICER, above which an intervention would not be considered cost-effective (because the additional cost for an additional unit of effect is considered too high) and below which it would be considered cost-effective. However Belgium does not use such a threshold.[24]

As a guide for interpretation, the ICERs reported in the current study are compared to the ICER estimates from past KCE reports for the recently implemented routine pneumococcal and HPV vaccinations in Belgium.

However, caution should be taken when comparing the results of the current study with other interventions since it is not clear whether economic or other factors (e.g. therapeutic value, ethical and organisational issues) have been considered or played a decisive role in the decision-making process. Decisions are rarely made on the basis of cost-effectiveness considerations alone. Moreover comparison with ICERs calculated in the past is only warranted if the ICERs are obtained in the same way, i.e. using the same methodology and under the same conditions (costs, existing technologies, experience, etc.).

[a] In the dynamic model uncertainty was not handled probabilistically due to computational limitations.

3. INPUT PARAMETERS

Belgian data were used to the largest extent possible, including the latest available data, based on several complementary sources. As serogroup B disease differs from other serogroups in severity and age distribution, we intended to derive serogroup B specific data to the largest extent possible for the base case analyses. In particular, cases from the Belgian hospital discharge databases (MZG-RHM: Minimale Ziekenhuisgegevens - Résumé Hospitalier Minimum and AZV-SHA: Anoniem Ziekenhuis Verblijf - Séjour Hospitalier Anonyme) were linked to those from the dataset of the National Reference Centre (NRC) to derive serogroup-specific parameters. Hospital database records were selected based on ICD-9-CM diagnostic code "036" (Meningococcal infection) as principal or any diagnosis.[b] Other parameters were derived based on the literature.

The parameters used in the base case and in the scenario analyses are summarized in Table 4, together with the corresponding section in the main report for further details.

3.1. Epidemiological and clinical parameters

Age-specific serogroup B incidences were estimated based on 2009-10 MZG-RHM and NRC (for proportion of serogroup B) datasets.

The proportions of deaths among cases (case fatality ratio or CFR) were based on 2004-10 NRC confirmed serogroup B cases completed with MZG-RHM outcome data on linked cases, to avoid small numbers. The "all serogroup" parameters were estimated using the same method and time period. Table 2 indicates that children bear the highest incidence and an increased CFR; the CFR is highest among the elderly but incidence is low in this group.

The proportion of strains that are covered by the 4CMenB vaccine is usually estimated by a test owned by the vaccine producer, the meningococcal antigen typing system (MATS). This test predicts the proportion of strains that would be killed (in vitro) by the serum of vaccinated infants[18] as a proxy for strain coverage. In 2007-08, 78% of 1052 European strains tested positive by MATS. However, the MATS technique was not made available to Belgium by the vaccine producer before this study and the proportion of Belgian strains covered by 4CMenB is thus unknown. We used the average European estimates from that study as proxy (using unpublished age-specific data provided by Novartis for the static model).[18] We thus assumed that 78% of Belgian serogroup B strains would be covered by 4CMenB in the base case analysis (85% as high estimate and 50% as low estimate for the scenario analyses).

Table 2 – IMD incidence rates and case fatality ratio by age (base case)

	IMD incidence per 100 000[a]	Serogroup B incidence per 100 000[b]	Serogroup B case fatality ratio[c] (%)
<1 year	24.1	21.8	5.6%
1-4 years	8.5	7.9	4.7%
5-9 years	3.0	2.8	1.2%
10-19 years	2.9	2.6	4.1%
20-64 years	0.5	0.3	8.8%
65+ years	0.9	0.3	12.8%
Total	1.7	1.3	5.4%

a: IMD (all serogroup) is not used in the base case but serogroup B incidence is derived from it. Based on 2009-10 MZG-RHM data. b: based on 2009-10 IMD incidence and age-specific % of serogroup B from NRC. c: based in 2004-10 NRC cases and outcome from MZG-RHM on matched cases.

Because Belgian data on sequelae following IMD are not available, parameters were extracted from literature reviews of studies in comparable settings. On average, we estimated that at least one sequelae was found in 15% of the serogroup B cases (range 3-19%), with the highest frequency in children and lowest in adolescents (Table 4). The most frequent sequelae included hearing loss, scar and/or necrosis, amputation, epilepsy or seizures and renal failure, with varying frequency by age. Other sequelae involved neurological consequences such as speech and communication disabilities and psychological disorders.

[b] Note that carriage of *N. meningitidis* is not included and that only codes referring to invasive meningococcal disease were considered.

Carriage data were included in the dynamic model only and were based on the meta-analysis of a systematic review of 82 studies, as no recent Belgian carriage data were available. In this meta-analysis, prevalence of *N. meningitidis* carriage increased from 4.5% in infants to 7.7% in 10-year olds and peaked at 23.7% in 19-year olds before decreasing in older adults.[5] The proportion of serogroup B in carried strains (32%) was derived from an old Belgian carriage study measured in a period with similar incidence and similar proportion of serogroup B among all IMD as observed in 2009-11.[25] Duration of carriage was assumed to average 6 months.

3.2. Vaccination parameters

Expected vaccine uptakes per selected vaccination strategy were determined in consultation with experts and based on Belgian data on similar vaccines, similar visit time and similar policies (Table 4). For infant routine doses that were given separately from other vaccines, uptakes were based on the proportion of regular medical visits to physician or child clinics from regional surveys and thus assumed to be lower than uptakes of current routine vaccines (i.e. for four doses: 50% vs. >90% for hexavalent). 4CMenB uptake in the partial reimbursement policy was based on those of reimbursed vaccines at the same ages (e.g. hepatitis B vaccine in 1999) and ranged between 25-65%. Uptake in the private market policy was based on PCV7 in 2004-06 and MenC vaccination before it was funded (range 10-30%).

No efficacy trial involving clinical outcomes has been conducted on 4CMenB. Efficacy against strains covered by the vaccine was based on a surrogate of protection, i.e. the proportions of vaccinated subjects with protective SBA titres per antigen, dose and schedule, adjusted for the pre-existing immunity (i.e. protective titres) in controls. Four trials involving more than 3000 subjects were retrieved, three trials among infants (2562 subjects) and one trial among adolescents (660 subjects). Pooling of SBA values by antigen took into account the proportion of antigens found in circulating strains, from EU MATS data (Table 4). Overall, 95% and 100% efficacy against the strains covered by 4CMenB was assumed for infants and adolescents, respectively.

Likewise, the duration of vaccine protection was based on persistence of SBA responses after the last dose of each schedule in follow-up studies of the above trials, assuming an exponential decline of immunity after vaccination. Immunity declined rapidly after the primary schedule (mean duration of 22 months) and lasted slightly longer after the booster dose (27 months); the need of further booster is not yet established by the manufacturer. Immunity lasted longer after adolescent vaccination (73 months).

Efficacy on carriage (for the dynamic model) is based on data of a British trial on efficacy against carriage of serogroup B strains among new university students. This study showed no efficacy against the primary endpoint (carriage of virulent serogroup B strains at 1 month after 2 doses), and no significant efficacy against serogroup B carriage at any later sampling point. However, significant efficacy was demonstrated against carriage of any *N. meningitidis* strains and the efficacy against new acquisition of serogroup B strains was around 30%, although not statistically significant (28.6%, 95%CI -12.0 to 54.4). The study also lacked power, partly due to a very rapid acquisition of carriage among new students. We thus selected 30% for the scenario analysis assuming an effect on transmission.

The risk of adverse event (AE) following 4CMenB was based on trial data. Only AE that were attributable to 4CMenB were included, by using the rate difference between 4CMenB and controls (e.g. controls receiving routine vaccines when concomitant) or by restricting them to severe AE that were possibly or probably related to 4CMenB. The rates of mild AE requiring outpatient visits per dose were based on trial data when available or by applying Belgian rates of medical visits for high fever following routine vaccines (from regional studies) to the proportion of 4CMenB doses resulting in high fever. To estimate the rate of severe AE requiring hospitalisation, we assumed that severe conditions (possibly, probably or definitely related to the 4CMenB), as well as children “observed in the hospital” for fever would all be hospitalised in a Belgian setting, at least for a short observation period. Trials show that 4CMenB administration is followed by fever in a high proportion of vaccinees, especially when administered concomitantly to routine vaccines (temperature >38°C and >39°C in 58% and 12% doses respectively when 4CMenB was given concomitantly to routine vaccines). This explains the high estimated rates of AE attributed to 4CMenB requiring outpatient visits or hospitalisation (e.g. 8 and 4 per 1000 doses for the three primary infant doses). However, most AE were of short duration and resolved spontaneously.

3.3. Cost parameters

Inpatient costs due to acute IMD were obtained by coupling the MZG-RHM/AZV-SHA data to the NRC database for the period 2004-2010. Based on NRC data, average acute hospitalisation costs were computed separately for all IMD cases (i.e. any serogroup, 698 episodes) and for serogroup B IMD cases only (597 episodes), the latter being used in the base case analyses (Table 4).

Costs of follow-up care for patients with no sequelae or for patients with sequelae/complications persisting after the acute hospitalisation were estimated from several Belgian sources: literature, former KCE reports, the Belgian reimbursement scheme which contains the unit costs of all health care services reimbursed by the Belgian health care insurance, the database of drug prices in Belgium (BCFI-CBIP[c]) and the publicly available data from the Belgian Technical Cell for hospital data management. The type and frequency of the resources consumed to treat each sequelae were revised by two independent medical experts.

The costs of managing contacts of an IMD case were estimated by region, based on available data, literature and information from regional public health officers, as well as the prices of prophylactic drugs in Belgium. Two hours of public health professional's time (1 hour for a nurse and 1 hour for a doctor) were included per IMD case for contacts tracing and for arranging prophylaxis.

The costs of one dose of the vaccine are the prices set at the Federal Public Service Economy. These prices are not explicitly reported as they are not yet public at the time of writing the report. The reduction obtained through mass purchase for routine vaccination was estimated from a study reporting negotiated price reductions obtained for Prevenar in Belgium in 2004-07.

The costs of vaccine administration per dose were based on the proportions of vaccinators (i.e. general practitioner, paediatrician or under-5 clinics[d] for infants; general practitioner or the school for adolescents) reported from regional studies for current vaccines under similar policy (i.e. fully funded, partly reimbursed or private market). Regional proportions were weighted with their respective population to derive Belgian proportions. Vaccine doses given along with another vaccine (Hexavalent at 3 months and HPV for adolescent girls) or during regular medical visits were only attributed the cost of the extra time required to explain and administer the injection.

The costs of an outpatient visit due to mild AE attributable to the vaccine was estimated from regional surveys reporting the type of carer consulted (general practitioner or paediatrician) for sick children. The cost of a hospitalisation due to AE attributable to 4CMenB were obtained by computing the average cost of the 1002 hospital stays with a principal diagnosis of febrile convulsion in patients aged 0-18 years from the coupled MZG-RHM/AZV-SHA data of the Belgian Technical Cell (2007-2010), as proxy.

The additional costs required for epidemiological surveillance post-vaccination (i.e. costs of introducing new typing techniques) were estimated from data from the Scientific Institute of Public Health.

3.4. Quality of life

The health-related quality of life (QoL) loss for survivors of meningococcal serogroup B disease with any sequelae was estimated from the best study identified through a systematic review of the literature performed up to September 2013 (Table 4).

The review did not identify studies valuing the quality of life lost by patients during the acute IMD phase. This was thus not included in the base case. QoL loss for adverse events resulting from vaccination were not included, nor were the QoL losses for caregivers (e.g. the parents) of sick patients.

[c] Belgisch Centrum voor Farmacotherapeutische Informatie - Centre Belge d'Information Pharmacothérapeutique.

[d] Kind en Gezin and Office National de l'Enfance (K&G-ONE).

3.5. Parameters combined for best and worst case scenarios

The combination of parameters simultaneously varied in the best and worst case scenarios are presented in Table 3.

Table 3 – Parameters combined for the best and worst case scenarios

Parameter	Static model		Dynamic model	
	Best case	Worst case	Best case	Worst case
Disease incidence - serogroup B	High	Low	High	Low
Case fatality rate - serogroup B	High	Low	High	Low
Proportion of survivors with sequelae	High	Low	High	Low
Vaccination uptake	High	Low	High	Low
Vaccine strain coverage	High	Low	High	Low
Average duration of vaccine protection	High	Low	High	Low
Cost of follow-up care in those with no sequelae	Probabilistic		High	Low
Sequelae treatment cost – serogroup B	Probabilistic		High	Low
Cost of public health management of contacts	Probabilistic		High	Low
Acute care hospitalization costs – serogroup B	Probabilistic		High	Low
Frequency AE (mild and serious)	Low	High	Low	High
Cost per vaccine dose	Low	High	Low	High
Costs of vaccine administration	Probabilistic		Low	High
Costs AE (mild and serious)	Probabilistic		Low	High

AE: adverse event. Best case: favours vaccination. Worst case: against vaccination. Values for low and high estimates to be found in Table 4.

Table 4 – Summary of input parameter values

Parameter	Base case	Sensitivity analysis	Low scenario	High scenario	Reference section in main report
Epidemiological and demographical parameters					
Carriage prevalence†	Variable by age	High scenario	-	Variable by age	See 6.6.1.[5, 25, 26]
Disease incidence (per 100 000) - all serogroups‡	1.7 (variable by age)	-	-	-	See 3.1.1 and 6.2.1.
Serogroup B incidence (per 100 000)	1.3 (variable by age)	High and low scenarios	0.9 (Variable by age)	3.2 (Variable by age)	See 6.2.1.
Case fatality ratio (%) - all serogroups‡	7.0 (Variable by age)	-	-	-	See 6.2.3.
Case fatality ratio (%) - serogroup B	5.4 (Variable by age)	High and low scenarios	1.5 (Variable by age)	6.1 (Variable by age)	See 6.2.3.
Mixing patterns†	Polymod	Alternative scenario	Preferential mixing		See 6.6.2.[21, 22]
Years of life lost	Variable by age	-	-	-	See 5.6.[27]
Natural mortality rates	Variable by age	-	-	-	See 5.6.[27]
Population birth cohort	128 605	-	-	-	See 5.6.[27]
Proportion of IMD survivors with sequelae (serogroup B and all serogroups)					See 3.1.7 and 6.2.4.[3, 4, 28, 29]
- **≤4 years**	0.215	High and low scenarios	0.102	0.267	
- **5-19 years**	0.086	High and low scenarios	0.066	0.106	
- **20+ years**	0.116	High and low scenarios	0.089	0.144	
QALY utilities					
QALY utility for susceptibles and survivors of IMD without sequelae	0.86 (Variable by age)	-	-	-	[30]
QALY loss for survivors with sequelae	0.074	Probabilistic γ (5.94, 0.01) High scenario	-	0.30	See 6.4.[29, 31, 32]
Vaccination parameters					
Vaccination uptake – Routine vaccination, free of charge (%)					Assumptions, see 6.1.2.
- **Infant immunisation priming course**	55	High and low scenarios	49	93	
- **Infant immunisation booster**	50	High and low scenarios	43	91	
- **Adolescent immunisation**	60	High and low scenarios	42	82	
Vaccination uptake – Partly reimbursed vaccination (%)					
- **Infant immunisation priming course**	50	High and low scenarios	34	65	
- **Infant immunisation booster**	40	High and low scenarios	25	52	
- **Adolescent immunisation**	30	High and low scenarios	21	39	
Vaccination uptake – Private market vaccination (%)					
- **Infant immunisation priming course**	20	High and low scenarios	10	30	
- **Infant immunisation booster**	10	High and low scenarios	10	30	
- **Adolescent immunisation**	10	High and low scenarios	10	30	

Parameter	Base case	Sensitivity analysis	Low scenario	High scenario	Reference section in main report
Vaccine strain coverage (%) [e]	78	High and low scenarios	50	85	See 6.2.2.[18]
Vaccine efficacy against disease, infant schedule 3+1 doses (%)	95	Low scenario	77	-	See 6.3.1.[33-36]
Vaccine efficacy against disease, ado (%)	100	Low scenario	73	-	
Vaccine efficacy against carriage (%) †	0	High scenario	-	30	See 6.3.3.[37]
Average duration of vaccine protection (months)					See 4.1.2.[35, 36, 38 17]
- **Infant immunisation primary doses**	22	High and low scenarios	16	26	
- **Infant immunisation booster**	27	High and low scenarios	17	36	
- **Adolescent immunisation**	73	High and low scenarios	69	105	
Rate of adverse events (number of vaccine doses resulting in 1 reaction)					See 4.3 and 6.3.4.[34-36, 39-41]
- **Mild, requiring outpatient visit, infants**	100	High and low scenarios	225	38	
- **Mild, requiring outpatient visit, ado**	868	High and low scenarios	1429	370	
- **Serious, requiring hospitalisation, infants**	282	High and low scenarios	643	118	
- **Serious, requiring hospitalisation, ado**	719 790	High and low scenarios	0	1208	
Cost of treatment					See 6.5.1 and 6.7.1.
Acute care hospitalization costs (mean cost per stay in hospital, €) – Serogroup B					
- **<1 year**	7320.26	Probabilistic γ (2.25, 3247.07) High and low scenarios†	4254.49	8066.55	
- **1-4 years**	6228.36	Probabilistic γ (3.38, 1842.24) High and low scenarios†	4163.19	6814.24	
- **5-9 years**	5510.99	Probabilistic γ (9.39, 586.88) High and low scenarios†	4162.36	6498.02	
- **10-19 years**	7934.41	Probabilistic γ (2.50, 3169.29) High and low scenarios†	4562.10	8607.59	
- **20+ years**	9989.20	Probabilistic γ (2.26, 4422.53) High and low scenarios†	5660.07	11 642.21	
Acute care hospitalization costs (mean cost per stay in hospital, €) – All serogroups ‡					See 6.5.1 and 6.7.1.
- **<1 year**	7195.07	Probabilistic γ(2.28, 3161.41)	-	-	
- **1-4 years**	6242.73	Probabilistic γ(3.36, 1856.83)	-	-	
- **5-9 years**	5959.91	Probabilistic γ(4.77, 1250.40)	-	-	
- **10-19 years**	7917.83	Probabilistic γ(2.50, 3163.16)	-	-	
- **20+ years**	10 516.10	Probabilistic γ(1.76, 5962.90)	-	-	

[e] Age-specific proportions were used for the static model, but are not provided here (unpublished data).

Parameter	Base case	Sensitivity analysis	Low scenario	High scenario	Reference section in main report
Cost of follow-up, all ages, for those without sequelae (€)	97.14	Probabilistic γ (100, 0.97) High and low scenarios†	79.03	117.08	See 6.5.2.
Cost of support/care for those with sequelae (€)					See 6.5.3.[42-47, 48, 49]
- **One off, serogroup B**	Variable by age	Probabilistic γ (variable by age) High and low scenarios†	Variable by age	Variable by age	
- **One off, all serogroups‡**	Variable by age	Probabilistic γ (variable by age) High and low scenarios†	Variable by age	Variable by age	
- **Annual, serogroup B**	Variable by age	Probabilistic γ (variable by age) High and low scenarios†	Variable by age	Variable by age	
- **Annual, all serogroups‡**	Variable by age	Probabilistic γ (variable by age) High and low scenarios†	Variable by age	Variable by age	
Cost of public health response					
Cost of public health response per case (€)	86.89 (Variable by age)	Probabilistic γ (variable by age) High and low scenarios†	Variable by age	Variable by age	See 6.5.4.
Cost of post vaccine surveillance (€)	25 000	Probabilistic γ (44.44, 562.50)	-	-	See 6.5.5.4.
Cost of vaccination					
Cost per vaccine dose (€)					See 6.5.5.1.[50]
- **Routine vaccination, free of charge**	Not public	High and low scenarios	Not public	Not public	
- **Partly reimbursed vaccination**	Not public	Low scenario	Not public	-	
- **Private market vaccination**	Not public	-	-	-	
Vaccine administration costs – Routine vaccination free of charge (€)					See 6.5.5.2 and 6.7.1.[40, 41, 47, 48, 51, 52]
- **Infant priming course**	34.22	Probabilistic γ (44.44, 0.77) High and low scenarios†	24.91	44.99	
- **Infant booster**	16.26	Probabilistic γ (44.44, 0.37) High and low scenarios†	11.84	21.38	
- **Adolescent**	9.58	High and low scenarios	6.97	12.59	
Vaccine administration costs – Partly reimbursed vaccination (€)					
- **Infant priming course**	32.16	Probabilistic γ (44.44, 0.72) High and low scenarios†	23.40	42.27	
- **Infant booster**	16.26	Probabilistic γ (44.44, 0.37) High and low scenarios†	11.84	21.38	

Parameter	Base case	Sensitivity analysis	Low scenario	High scenario	Reference section in main report
- **Adolescent**	9.58	High and low scenarios	6.97	12.59	
Vaccine administration costs – Private market vaccination (€)					
- **Infant priming course**	48.20	Probabilistic γ (100.00, 0.48) High and low scenarios†	39.21	58.09	
- **Infant booster**	23.53	Probabilistic γ (100.00, 0.24) High and low scenarios†	19.14	28.35	
- **Adolescent**	23.05	-	-	-	
Cost of vaccine-attributable adverse event (per event, €)					See 6.5.5.3 and 6.7.1.[49, 53]
- **Mild adverse event, requiring outpatient visit, infants**	29.96	Probabilistic γ (5.43, 5.52) High and low scenarios†	10.30	59.92	
- **Mild adverse event, requiring outpatient visit , adolescents**	23.05	High and low scenarios†	7.93	46.10	
- **Severe adverse event, requiring hospitalisation, all**	2135.63	Probabilistic γ (4.11, 519.92) High and low scenarios†	595.14	4642.23	

† Used in the dynamic model only. ‡ Simultaneously varied in the 'all serogroup' scenario analysis. γ: gamma distribution.

4. CLINICAL IMPACT AND COST-EFFECTIVENESS OF 4CMENB VACCINATION

4.1. Current burden of serogroup B invasive meningococcal disease

In the current situation of no vaccination against serogroup B disease, the static model predicts that 139 cases of serogroup B IMD, resulting in 20 cases with sequelae and 7 deaths (490 quality adjusted life years lost), would occur over the lifetime of a single birth cohort (128 605 individuals) with the costs of treatment and long term care totalling €5.8 million.

4.2. 4CMenB vaccination – if no effect on carriage

The base case analyses assumed no vaccine effect on carriage and vaccine effects limited to serogroup B IMD.

4.2.1. Infant vaccination

Under the routine infant vaccination policy (i.e. at 3, 5, 6 and 12 months[f] with a 50% uptake for the booster, assuming a 95% vaccine efficacy against covered strains and 27 months protection after the booster), the model predicts that 14 cases (10% of the total 139 cases), including 3 cases with sequelae and 1 death, could be prevented per year. Routine vaccination is predicted to generate 2757 and 976 adverse events requiring outpatient and inpatient care, respectively.

If the vaccine was offered in the private market only (i.e. fully charged) the model predicts that only 5 cases would be averted, due to the low assumed vaccine uptake (i.e. uptake 10% for booster) under this policy; an extra 8 cases (i.e. 13 cases) are predicted to be averted if the vaccine was partly reimbursed (i.e. uptake 40% for booster).

Introducing routine infant vaccination with 4CMenB is expected to cost €16.4 million annually (including the patient share) which would include the costs of the vaccine itself, its administration and the treatment of the adverse vaccine reactions. Only €0.8 million would be averted through reductions in cases if 4CMenB vaccination is introduced. This results in a net cost of €15.6 million for routine infant vaccination (Table 5). Given the high vaccination costs, the three infant vaccination policies (free of charge, partly reimbursed, private market) resulted in very high mean costs per quality adjusted life year gained (QALY), over €400 000, under the base case. Results from the 1000 probabilistic simulations were all above €250 000 per QALY gained.

Table 5 – Cost-effectiveness of infant vaccination options, assuming no effect on carriage (compared with no vaccination)

	Cases averted (%)	Deaths averted (%)	QALYs gained[a]	Net cost of vaccination[b]	ICER: cost per QALY gained[c]
Base-case analyses – Infants vaccination at 3, 5, 6 + 12 months					
Routine	14 (10)	1 (10)	65	€15.6M	€422 700
Partly reimbursed	13 (9)	1 (9)	58	€22.3M	€663 600
Private market	5 (4)	0 (3)	23	€8.7M	€667 800
Selected scenario analyses on the routine vaccination strategy					
Increased incidence and case fatality ratios	34 (10)	2	158	€14.5M	€167 000
Higher vaccine uptake	24 (18)	1	110	26.9M	€427 400
Higher MATS coverage	15 (11)	1	70	€15.5M	€391 100
Alternative assumption for QoL loss for survivors with sequelae	14 (10)	1	115	€15.6M	€239 100
All serogroups	16 (9)	1	77	€15.5M	€355 000
Best case	71 (20)	4	284	€17.0M	€98 300

Undiscounted values, except ICER. ICER: incremental cost-effectiveness ratio. M: million. QoL: quality of life. a: QoL lost during the acute phase of the disease and for the adverse events are not included. b: additional cost of vaccination less costs averted through reduction in cases. c: discounted figures rounded to nearest 100.

[f] The selected vaccination schedules and scenarios presented in Table 1 were slightly adapted to fit with the existing model structure and avoid a long recoding that would delay the study. The models simulated the booster dose at 12 months instead of 14 months, and adolescent vaccination at 14 years instead of around 13 years.

Among the univariate scenario analyses performed on the routine policy, the most effective is the high incidence and case fatality ratio scenario, with a reduction of 34 (10%) cases and 2 deaths (Table 5), followed by a scenario of high vaccine uptakes (91-93% similar to other routine vaccines, resulting in 24 cases averted or 18%). A higher and lower proportion of strain coverage (MATS) would result in 11% and 6% prevented cases, respectively. The cost-effectiveness ratio was also improved under the high incidence and case fatality ratio scenario, as well as when the quality of life loss for survivors was assumed to be 0.30 instead of 0.074 in the base case. However, the cost-effectiveness ratios under those scenarios remained above €167 000 per QALY gained.

The best case scenario combining the most vaccine favourable assumptions would prevent 71 cases (20%) and 4 deaths, at a cost of €98 300 per QALY gained. To reach a cost-effectiveness ratio of €40 000 per QALY under this best case scenario, the price of the vaccine would have to be as low as €6 per dose.

4.2.2. Adolescent vaccination

The base case analysis of adolescent strategies run in the dynamic model (with no effect on carriage) shows that only 6% of cases are averted over a 100 year period under routine vaccination, and this proportion decreases to 3% and 1% under the partial reimbursement and private market policies.[g] Likewise 5%, 3% and 1% of deaths would be averted under the routine, partial reimbursement and private market policies, respectively. The incremental cost-effectiveness ratios (ICERs) of the adolescent strategies were higher than those of the infant strategies (simulated in the dynamic model with no effect on carriage, results not shown). Combined infant and adolescent vaccination strategies avert the highest number of cases (16%, 12% and 5% for the routine, partial reimbursement and private market policies) and deaths (15%, 11% and 4% for the routine, partial reimbursement and private market policies) but still resulted in ICERs above those of the infant strategies (simulated in the dynamic model with no effect on carriage, results not shown).

4.3. 4CMenB vaccination – if effect on carriage

Analyses performed under this scenario assume the vaccine is able to prevent a proportion (30%) of serogroup B carriage, simulated in the dynamic model.

The absolute numbers reported in Table 6 and Table 7 from the dynamic model are very different from the absolute numbers reported in Table 5 for the static model. This is due to a difference in model structure. The dynamic model follows 100 births cohorts over a 100 year period to catch the interactions across the cohorts, while the static model follows only one cohort over a 100 year period.

4.3.1. Infant vaccination

Assuming an effect on carriage acquisition slightly increases the number of cases averted under the infant vaccination policies, with 12%, 11% and 4% of cases averted under the routine, partly reimbursed and private market vaccination policies, compared to 10%, 9% and 4% respectively in the base case. The number of deaths averted also slightly increases when an effect on carriage is assumed (Table 6).

Given the higher number of cases and deaths averted, infant vaccination appears more cost-effective than in the base case analysis without herd effect, when compared to no vaccination. However, the model assuming an effect on carriage shows further that infant vaccination strategies would cost more and produce fewer QALYs gained compared to adolescent vaccination strategies (Table 6). Infant vaccination strategies are thus dominated by adolescent vaccination strategies when herd effects are assumed.

[g] As the dynamic model computes cases and deaths prevented for multiple cohorts over a 100 year horizon, the health impact explored by the dynamic model cannot be directly compared to results from the cohort model that only considers a single cohort.

4.3.2. Adolescent vaccination

If the vaccine reduces carriage acquisition by 30%, the model predicts that sustained reductions in case numbers could be achieved in the long term through vaccination of adolescents, in whom carriage is high, and through combined infant and adolescent vaccination in the short term (Table 6).

In this scenario, adolescent vaccination is predicted to avert up to 65%, 43% and 15% of cases in the routine, partly reimbursed and private market policies. Due to the lower number of doses required for such strategies (compared with infant vaccination) and the sustained reduction in cases achieved in the longer-term with herd effects, the cost per QALY gained for vaccinating adolescents amount to €24 400, €34 600 and €37 700 for the routine, partly reimbursed and private market vaccination policies, compared to no vaccination.

Table 6 – Cost-effectiveness of infant, adolescent and combined vaccination options, assuming an effect on carriage (compared with no vaccination)

	Cases averted (%)	Deaths averted (%)	QALYs gained[a]	Net cost of vaccination[b]	ICER: cost per QALY gained[c]
Routine vaccination policy, free of charge					
Infant	1699 (12)	85 (12)	5015	€1589.5M	€260 700
Adolescent	8904 (65)	476 (65)	21353	€518.0M	€24 400
Infant + adolescent	9180 (67)	490 (67)	22596	€2151.7M	€83 000
Partly reimbursed vaccination policy					
Infant	1532 (11)	77 (11)	4525	€2252.8M	€407 500
Adolescent	5925 (43)	317 (43)	13910	€496.2M	€34 600
Infant + adolescent	6676 (49)	354 (48)	16360	€2772.3M	€146 300
Private market vaccination policy					
Infant	604 (4)	30 (4)	1788	€877.3M	€402 000
Adolescent	2090 (15)	112 (15)	4992	€198.1M	€37 700
Infant + adolescent	2592 (19)	137 (19)	6499	€1076.4M	€142 800

Undiscounted values, except ICER. ICER: incremental cost-effectiveness ratio. M: million. a: QoL lost during the acute phase of the disease and for the adverse events are not included. b: additional cost of vaccination less costs averted through reduction in cases. c: discounted figures rounded to nearest 100.

Combining adolescent vaccination with infant vaccination has the greatest impact on averted case numbers: reductions of 67%, 49% and 19% of cases are achieved in the routine, partly reimbursed and private vaccination policies. However the gain in effectiveness in vaccinating infants on top of adolescents appears limited in view of the substantial additional vaccination cost required. As a consequence, the strategies combining infants and adolescents resulted in higher incremental cost per QALY gained than the adolescent strategies alone, i.e. €83 000, €146 300 and €142 800 when compared to no vaccination. Further, compared to adolescent vaccination, adding infant vaccination over adolescent vaccination results in a very high cost. Each additional QALY gained by infant vaccination, above those already gained by adolescent vaccination, costs €879 500, €711 800 and €470 700 for the routine, partly reimbursed and private vaccination respectively when herd effects are assumed.

Among the univariate scenario analyses performed on the combined (infant and adolescent) routine strategy (Table 7), the cost-effectiveness ratio was most improved under the high incidence and case fatality ratio scenario and with a higher quality of life loss assumption (0.30), from €83 000 in the base case to €22 500 and to €54 200 per QALY gained compared to no vaccination, respectively. The best case scenario was predicted to cost €17 400 per QALY gained. Increased strain coverage averted 5% point more cases compared to the base case, at a cost of €76 500 per QALY gained. Other scenarios did not improve the cost-effectiveness of this strategy to such extent. Altering the time horizon of the model from 100 to 20 years had a detrimental effect on the cost-effectiveness ratio (over €800 000 per QALY gained compared to no vaccination) showing that vaccination strategies involving adolescents would only be cost-effective in the long run.

Threshold analysis further revealed that combined adolescent and infant routine vaccination would be below €40 000 per QALY gained if the vaccine would cost less than €12 per dose, or below €30 000 per QALY gained if the vaccine would cost less than €5 per dose. Under partial reimbursement policy, it would be below €30 000 per QALY gained if the vaccine price was €4 per dose.

Table 7 – Selected scenario analyses on the combined infant and adolescent routine vaccination strategy, assuming an effect on carriage (compared with no vaccination)

	Cases averted (%)	Deaths averted	QALYs gained[a]	Net cost of vaccination[b]	ICER: cost per QALY gained[c]
Increased incidence and case fatality ratios	23606 (67)	1677	74661	€1764.7M	€22 500
Alternative assumption for QoL loss for survivors with sequelae	9180 (67)	490	34712	€2151.7M	€54 200
All serogroups	6416 (36)	425	18691	€2213.6M	€98 800
Best case	27644 (79)	1962	93262	€1546.2M	€17 400
20 year time horizon	1097 (40)	58	549	€467.3M	€803 600

Undiscounted values, except ICER. ICER: incremental cost-effectiveness ratio. M: million. QoL: quality of life. a: QoL lost during the acute phase of the disease and for the adverse events are not included. b: additional cost of vaccination less costs averted through reduction in cases. c: discounted figures rounded to nearest 100.

5. DISCUSSION

5.1. 4CMenB vaccination

This study explored the potential clinical impact and cost-effectiveness of vaccination strategies using 4CMenB (Bexsero) in Belgium and targeting two age groups (infants and adolescents), alone or combined.

Considerable uncertainty remains around a number of parameters, especially around vaccine properties (i.e. clinical efficacy against disease and carriage, duration of protection and proportion of strains covered by the vaccine), but also around future evolution of IMD and expected vaccine uptake. For instance, our vaccine parameters combine sparse data on correlates and surrogates of protection (MATS and SBA) from a limited number of trials. These results should thus be taken with caution in the absence of robust data on efficacy/effectiveness and vaccine waning. For that reason, uncertainty was extensively explored through probabilistic analyses - when possible - and through scenario analyses, considering higher and/or lower assumptions for a range of uncertain parameters. It is possible however, that we did not cover the entire uncertainty around some parameters.

5.1.1. If 4CMenB has no effect on carriage (base case)

In the base case analyses, we assumed no vaccine effect on carriage (no herd effect), 4CMenB effect limited to serogroup B disease and relatively low vaccine uptakes (e.g. 50% for booster dose) as the vaccine must be administered separately from other vaccines and has a high reactogenicity. In this conservative base case, vaccinating infants would only prevent 4-10% of the total predicted cases over the lifetime of a cohort and 0-1 deaths per year, depending on the vaccination policy. This low proportion of averted cases is due to a late protection of infants (at around 6 months of age, after the incidence peak) which is assumed to be of short duration. Routine infant vaccination is expected to result in a large number of adverse events with subsequent high costs due to the high numbers of vaccinated, although most reactions are assumed to be mild and of short duration. Due to the high costs of vaccination (i.e. vaccine doses, administration and side effects) and the limited IMD treatment costs avoided, the three infant vaccine policies would present unfavourable cost-effectiveness ratios, all above €400 000 per QALY gained in this base case. The price reduction needed to reach

cost-effectiveness ratios of €20 000, €30 000 and €40 000 per QALY gained was explored. However, even with a free vaccine, those values were never reached, due to the other vaccination costs (administration costs related to separate visits and costs of adverse events).

The high number of adverse events attributable to 4CMenB deserves consideration: according to our assumptions, routine vaccination of infants would generate 976 hospitalisations per year, while preventing 14 IMD hospitalisations from the expected 139 ones. However, IMD is a devastating disease requiring long hospital stay (mean length of stay 12 days) and with potential severe sequelae while most adverse events are expected to resolve rapidly.

Vaccination of adolescents (14 year olds) in the absence of indirect effects, explored through a dynamic model, would prevent only 1-6% of all cases. Combined vaccination of infants and adolescents would avert the highest number of cases (5-16%). Both strategies resulted in worse cost-effectiveness ratios than those of the infant strategies alone.

When no effect on carriage is assumed, routine infant vaccination would prevent the highest number of cases if incidence rises to the highest values observed in the last 35 years, followed by a scenario of high vaccine uptakes (range 91-93%). A higher 4CMenB coverage of strains (85% as in France) would only prevent one additional case. The highest number of cases would be averted by routine vaccination of infants under a hypothetical best case scenario. However, none of these scenarios yielded favourable cost-effectiveness ratios: the best case scenario is the most favourable but would still cost €98 000 per QALY gained compared to no vaccination.

Other cost-effectiveness studies from England, France and the Netherlands found similar results and unfavourable cost-effectiveness ratios when no effects on transmission are assumed,[20, 54, 55] even though parameters for costs and vaccine adverse events differed substantially.[h] In the English study published in 2013,[i] routine vaccination of 91% of infants would prevent 28% of cases and cost £164 000 per QALY gained with a similar vaccine price.[20] However, this study estimated that routine infant strategies could be considered cost-effective in England (i.e. <£30 000 per QALY) if the vaccine would cost around £9 per dose.

5.1.2. If 4CMenB has an effect on carriage

In a scenario assuming a 30% reduction in carriage acquisition (dynamic model), routine infant vaccination would not prevent many more cases compared to the base case (12% vs. 10%). The herd effects seen under infant vaccination alone are limited because meningococcal carriage prevalence is low in young children. Infant vaccination is however dominated (costs more and results in fewer QALYs gained) by adolescent vaccination.

Substantially greater decreases in cases could be achieved through adolescent vaccination in routine and partly reimbursed policies (65% and 43% respectively) with favourable cost-effectiveness ratios, because carriage is high in this age group and vaccinating them is assumed to reduce transmission. Costs per QALY gained of these adolescent strategies would be in the range of those estimated for recently introduced vaccines in Belgium: €24 400 and €34 600 per QALY gained for routine and partly reimbursed 4CMenB vaccination policies, respectively, compared to €10 000 per QALY gained for routine infant PCV7 vaccination (2+1 doses assuming no replacement) and €33 000 per QALY gained for Human Papillomavirus vaccination of 12 year-old girls (3+1 doses[j]), respectively.[56, 57] Caution should be exercised however when comparing the results of the current study with other introduced interventions since it is not clear whether economic or other arguments have been considered or played a decisive role in the decision-making process previously. Adolescent vaccination would also result in a long term reduction in cases due to an assumed sustained reduction of transmission. However, the assumed reduction of transmission would not result in substantial reductions of cases until after 10-20 years from the start of vaccination. In the short-term, routine infant vaccination prevents more cases.

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h The base case results of the Belgian study were estimated by the cohort static model, but our dynamic model predicted the same proportion of cases prevented for multiple cohorts over a period of 100 years, which are thus totally comparable to those of France.

i An update of this study was conducted in 2013-14 but was unpublished at the time of writing this report

j 3 doses at €0 marginal administration costs, and a booster dose every 10 years administered by GPs.

Adding infant to adolescent routine strategies (i.e. in a combined routine infant and adolescent strategy) would reduce cases in both the short term and the long term, but would cost over €800 000 per QALY gained compared to adolescent vaccination alone. However, other considerations may prevail in the choice of a vaccination strategy, e.g. if the combined vaccination of infants and adolescent is preferred because avoiding meningococcal disease in young children in the short-term is especially valued and cost-effectiveness is not the main criteria. In this case this strategy should be compared to 'no vaccination' but would still result in high cost-effectiveness ratios (€83 000 per QALY gained). In the scenario analysis, this combination strategy would cost ≤€30 000 per QALY gained (compared to no vaccination) only if the incidence and case fatality ratio were substantially increased, if the vaccine price is reduced to ≤€5 per dose or in the best case scenario (€22 500, €30 000 and €17 400 per QALY gained respectively). Varying other assumptions did not result in favourable cost-effective ratios for routine combined strategies. The other policies (partly reimbursed or private market) for this combined vaccination would cost more than €140 000 per QALY gained. In the partial reimbursement policy, the price of the vaccine would need to be as low as €4 per dose to reach an ICER of €30 000 per QALY gained.

Studies in France and England used other assumptions but found similar patterns under scenarios of herd effects. The French study also found that vaccinating adolescents is the most favourable option but cost-effectiveness ratios are systematically higher than our estimates.[54] The English study published in 2013 also indicates that adolescent vaccination is the most cost-effective strategy, with slightly higher cost-effectiveness ratios than in our study at a similar vaccine price despite an assumed 60% effect on carriage (£40 200 per QALY gained). Routine infant vaccination and other combined strategies are all unfavourable (above £80 000 per QALY gained).[20, k]

Our analyses thus suggest that 4CMenB would only prevent a substantial number of cases and be reasonably cost-effective if efficacy on carriage can be assumed and large proportions of adolescents are vaccinated. However, this would only be achieved in the long term while meningococcal disease would keep affecting young children. If this is not an acceptable option, the combined vaccination of adolescents and infants would result in attractive cost-effectiveness ratio only if the vaccine price could be dramatically reduced. These predictions however assume a 30% efficacy on serogroup B carriage which has not been demonstrated. This parameter is thus a key factor to determine if 4CMenB vaccination could be cost-effective in a Belgian setting. Future studies are necessary to produce the evidence required on carriage.

5.1.3. Use of 4CMenB in control of clusters and outbreaks

No 4CMenB vaccination as public health response to clusters of cases or limited outbreaks is proposed, as this strategy has the following disadvantages: immune response is only documented 30 days after vaccination – a period after which only few subsequent cases occur, at least two doses (up to four in infants) are required to mount sufficient immunity, waning occurs rapidly and identification of the strains covered by the vaccine is currently not possible in Belgium and would require additional time if strains were to be tested in another country. Antibiotic prophylaxis is considered as an effective and efficient strategy in these situations, and the advantage of 4CMenB vaccination in addition to chemoprophylaxis seems thus limited based on current knowledge. Likewise, no meningococcal C vaccination has been included in the regional guideline to control clusters and outbreaks, although the vaccine is known to be very effective. However, the relevance of implementing 4CMenB vaccination could be considered in the case of large outbreaks or protracted high incidence in defined groups. But the decisions on strategies would require refined analysis per age group and time and better information on the duration of protection conferred by one or two doses of 4CMenB.

5.2. Strengths and limitations of this analysis

The strengths of this analysis include the following aspects:

- Two different types of model were used to assess the potential impact of the new vaccine, allowing for herd effects.

[k] An update of this study was conducted in 2013-14 but was unpublished at the time of writing this report.

- These models use Belgian data to the largest extent possible, including the latest available data, based on several complementary sources. It is the first time in Belgium that the Reference Laboratory dataset and hospital discharge databases have been linked to derive serogroup-specific parameters.
- Extensive sensitivity analyses were performed to assess the importance of uncertainty around the model parameters. We opted for univariate and multivariate (including best and worst case) scenario analyses in both models instead of a probabilistic sensitivity analysis on all parameters, due to the lack of robust evidence to properly inform the distributions around many parameters

The limitations of this work include:

- The full vaccine characteristics are not yet known: the vaccine licensure was based on surrogates of protection, the true vaccine efficacy and duration of protection are unknown, and responses to each of the four 4CMenB components wane at different rates. Furthermore, results from long-term follow-up are not yet available. However, the uncertainty around these parameters was explored through scenario analyses in both models. Although we varied vaccine parameters based on available study data, it is possible that we did not cover the entire range of possibilities in the scenario analyses.
- The proportion of serogroup B strains that will be prevented by this multi-component vaccine is also unknown in Belgium as no MATS testing could be performed. Interestingly, the scenario analyses using large range of values of strain coverage (50-85%) did not yield very different results.
- Quality of life losses to patients during the acute phase of the illness have not been included in the models due to lack of data at the time of the study. Although the impact on QoL loss is likely to be considerable during the acute phase of the disease, its overall impact on the total QoL is likely to be small because of its short duration compared to the time horizon of the model. Quality of life losses to caregivers were not included either. Although IMD serogroup B sequelae in children will have a substantial impact on their caregivers for many years, inclusion of carer QALYs is thought to have limited impact on the cost-effectiveness results due to the small number of cases in this study. A substantially higher quality of life loss for persons with IMD sequelae (from 0.074 to 0.30) was simulated in sensitivity analyses. Although this favoured the cost-effectiveness results, the ICERs of the vaccination strategies simulated remained high. Quality of life losses for adverse events resulting from vaccination have not been included; including these would only make vaccination less attractive because vaccine adverse events, though relatively mild and transient, are expected to affect a large number of subjects.
- In this study, the treatment costs of adverse event attributed to vaccination and requiring hospitalisation (€2135, 95%CI €595 to €4642) were higher compared to other studies. These costs were derived based on all Belgian hospital stays with a principal diagnosis of febrile convulsion in patients aged 0-18 years. Hospitalisation costs were £421 for anaphylactic reaction in the UK,[20] and €1329, €2097 and €2716 for febrile convulsion, juvenile arthritis and Kawasaki disease in France.[54] This higher cost may simply reflect true differences in clinical practice and organization of the health care sector.
- We estimated a higher proportion of doses leading to hospitalisation for adverse reaction in Belgian practice compared to other studies. For instance the French model was based on the same studies but assumed that cases of “fever observed in the hospital” would be seen at hospital outpatient visits in France, while we assumed that they would be admitted to a hospital in Belgium (short observation stay).[54] We believe that our choice corresponds to the Belgian health care system. The English model used much lower rates from the serogroup C vaccine and OMV serogroup B vaccines, because 4CMenB safety data were not yet available at that time. This factor also influences the total cost of treating vaccine adverse events.
- The dynamic model structure does not allow for the potential negative effects of meningococcal carriage reduction, such as the loss of natural boosting or replacement by other serogroups or other pathogens, as observed for the 7-valent pneumococcal conjugate vaccine.
- No catch-up vaccination was considered in this study as this strategy was not deemed relevant by Belgian decision-makers in vaccination, due to a relatively low disease burden and the need of two or three doses at ages at which no vaccination or medical visit is planned.

Although catch-up strategies showed high and rapid reduction of cases in other studies, number of cases increased afterwards to return to the same incidence as reached without catch-up vaccination.[20, 54]

5.3. Implications for practice

Whatever decision on 4CMenB is taken, i.e. to include it in the routine calendar, to reimburse it or to leave it simply available to those who agree to pay for it, it will have a number of implications that must be taken into account.

Regardless of any cost-effectiveness criteria, if it is decided to include 4CMenB in the routine vaccine schedule, there are two main options for infant vaccination. The first one is to administer 4CMenB at different visits than the one planned for routine vaccines to avoid the high rates of adverse events in concomitant administration. In that case, the infant vaccine schedule will become crowded, from three to five vaccination visits before 12 months of age, involving higher costs. In addition, under 5 clinics (ONE and K&G) and school services (CLB-PMS[l]) will face operational challenges to organize these additional visits (or add vaccination to existing visits). Even in this option, the rate of high fever seems higher than for other vaccines, i.e. 3% with fever >39°C for routine vaccines vs. 6% for 4CMenB administered alone.[34] The other option is to administer 4CMenB together with routine vaccines, but the higher rates of high fever will necessitate informing and educating parents on how to manage fever (or administer prophylactic paracetamol) and this may undermine the confidence in the vaccination programme overall.

If it is decided to reimburse 4CMenB partially, accessibility will be lower compared to the routine schedule option as parents would have to pay between around €50 to €150 per infant for 3+1 doses.[m] If vaccination remains at the choice of parents on clinician advice (private market), the cost would be much higher obviously.[m] In both options, inequity will occur, as seen for PCV7 before it was introduced (2004-2006). In both cases, it is also important to advise parents that high fever may occur.

If no universal (routine) vaccination is decided, a question remains as to whether groups at high risk should be targeted for vaccination. Although there are no SBA data in this group so far, it is known that some groups may be at higher medical risk of developing IMD, such as those with complement deficiency and asplenia. Vaccination should be considered on a case by case basis, in discussion between clinicians and parents. In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) interim decision not to introduce 4CMenB generated many reactions from clinicians, academics and meningitis charities. It is unclear whether such reactions would occur in Belgium. The pressure to use the vaccine in case of clusters or outbreaks would certainly be high, although evidence of its effectiveness in such situations is lacking or questionable.

So far (up to July 2014), there are no possibilities to monitor vaccine failures nor vaccine effectiveness as the MATS test - which should allow the strains covered by the vaccine to be distinguished from other strains – has not been made available by the vaccine manufacturer to Belgium. Other options (e.g. to get suspected vaccine failures tested in another country) have not been considered thus far. In addition to this problem of availability, it is not totally clear to what extent the MATS test is reliable in identifying vaccine-preventable strains as this test is not totally transparent, and it is still owned and managed by Novartis only. Health authorities should seek possibilities to obtain the MATS technology or explore other solutions such as collaboration with other countries or investment in other tests.

And finally, whatever decisions will be taken, it should be noted that meningococcal disease is a devastating disease that can be rapidly fatal and has important long-term impact on the life of the survivors and their parents/caregivers. This cost-effectiveness study took into account some of the consequences of this disease on the health care costs and the quality of life of cases, but does not integrate the full extent of human suffering following disease. It should also be clear that decisions on vaccine policies are based on several factors, including impact on individuals and the society, and that cost-effectiveness is only one of these factors.

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[l] Centrum voor Leerlingenbegeleiding - Centre psycho-médico-social (CLB-PMS).

[m] Depending on the reimbursement category (B, C, Cs or Cx). The computation cannot be provided as the vaccine prices are not published at the time of writing this report.

5.4. Future perspectives

This study is based on a high number of assumptions due to a current lack of data on the vaccine effect on clinical disease and on carriage, on the persistence of protection and on the proportion of strains covered by the vaccine in Belgium. As of June 2014, no country has yet introduced universal vaccination with 4CMenB at national level. However, vaccination is being implemented locally in a few countries, whether as universal infant vaccination in some regions or as response to an increase in incidence or to outbreaks. England and Wales are also planning to introduce it providing that vaccine prices are lowered to reach their cost-effectiveness criteria. It is thus expected that some national programmes will include it in the future and that further trials may explore the 4CMenB effect on carriage. We can thus expect that new evidence will be generated in the future, and the predictions of this study may need to be revisited based on new data. However, the scenario analyses indicate that the main parameter that may significantly change the results of this study would be a positive effect on meningococcal serogroup B carriage.

This study did not include vaccination strategies using a 2+1 dose schedule as immunogenicity data are not available at the time of this study (study data due in 2015 at the earliest), and the rapid waning after the three doses primary schedule suggest that a 2-dose primary schedule may provide even less protection in an age of high incidence (before booster). However, the 2+1 schedule has been selected for future implementation in England and Wales. It is thus likely that the first available and robust effectiveness data will be based on a 2+1 vaccination status in that country. Although this schedule was not simulated in our study, an indication of the potential difference in cost-effectiveness results between the 3+1 schedule of this study and a 2+1 schedule can be provided by England and Wales prediction: moving from a 2, 3, 4 and 12 month to a 2, 4 and 12 month strategy in the England base case dynamic model (30% vaccine efficacy against carriage acquisition) reduced the cost per QALY gained by 26%.

Other vaccines to prevent serogroup B meningococcal disease are being developed. The next expected vaccine is the bivalent recombinant lipoprotein 2086 vaccine from Pfizer, which entered in Phase III in 2012, and showed favourable SBA results.[58] Our study is only based on characteristics of the 4CMenB vaccine and cannot be extended to other serogroup B IMD vaccines.

6. CONCLUSIONS

Meningococcal disease is a devastating disease, which can be rapidly fatal and has important long-term impact on the life of those affected and their parents/caregivers. This cost-effectiveness study did not integrate the full extent of human suffering due to IMD. Decisions on vaccine policies are obviously based on several factors, including impact on individuals and the society, and cost-effectiveness is only one of these factors. Nevertheless, cost-effectiveness models throw a useful light on the opportunity (if any) of the different vaccination options.

These models have shown that the introduction of a routine immunisation programme with 4CMenB can reduce meningococcal disease in Belgium, but involves a high frequency of adverse events, though principally mild and transient, following vaccination.

In the base case assuming no effect on serogroup B carriage, the highest number of cases are averted through routine combined infant and adolescent vaccination policy. However, this strategy would only reduce 16% of all cases and 15% of all deaths, and the cost per QALY gained of such a strategy is extremely high. Routine infant vaccination is the most cost-effective option but would prevent even less cases, still at a high cost (over €400 000 per QALY gained).

If the vaccine can disrupt carriage acquisition, substantial decreases in cases can be achieved in the long term through vaccination of adolescents, at a more favourable cost-effectiveness ratio (€24 000 per QALY gained). To obtain a short term effect, infant vaccination could be added but involves a very high cost. Vaccination of infants alone has a limited impact, impact, compared to adolescent vaccination over the long term, due to low carriage in this group.

Most of the strategies considered (even when the most favourable parameters are included) result in high costs per QALY gained, over €100 000. Only the most optimistic analyses assuming 30% vaccine efficacy against carriage acquisition result in a cost-effectiveness ratio that is comparable to other recently introduced vaccines in Belgium. However these results are based on a hypothetical 4CMenB effect on carriage, which is not yet demonstrated, and substantial reductions in disease would not be observed before 10 to 20 years after vaccine introduction.

In conclusion, our results suggest that 4CMenB vaccination could only prevent a limited number of cases and deaths in Belgium. Infant strategies alone, assuming or not indirect effect, have limited impact and cannot be considered cost-effective. Some of the vaccination strategies involving adolescents could be more effective and yield more favourable cost-effectiveness ratios but only if 4CMenB is able to reduce transmission, which is not shown to date, and if we consider long term effects. There remains considerable uncertainty around a number of the vaccine properties.

The results of this study may need to be revisited when new evidence will be generated, in particular on the effect on carriage.

RECOMMENDATIONS[n]

To the vaccine decision-makers:

- **Universal vaccination of infants with the new quadrivalent vaccine against meningococcal B disease (4CMenB) cannot be recommended as of today, because it would only have a small impact on the number of cases and deaths, generate a substantial number of adverse events and be much less cost-effective than other vaccines recently introduced in the vaccine calendar, even under the most optimistic assumptions (including low vaccine prices). Moreover, there is still a large uncertainty around vaccine properties and future evolution of meningococcal disease.**
- **Universal vaccination of adolescents cannot be recommended either, for the same reasons as described above. If new data would show that 4CMenB can effectively reduce carriage (i.e. by 30% or more), vaccinating adolescents could substantially reduce the number of cases (up to 65%) and become as cost-effective as other vaccines recently introduced in the vaccine calendar. However, this impact would only be achieved 10 to 20 years after vaccine introduction, while infants would still be affected by the disease in the first decade.**
- **Vaccine policy makers and advising bodies should inform clinicians on the risks and benefits of 4CMenB. Messages should include the 4CMenB capacity to protect against meningococcal B disease, the uncertainties around this vaccine protection and its coverage of circulating strains, and the high frequency of adverse events following vaccination among infants, especially if administered together with other routine vaccines.**
- **Any decision on introducing 4CMenB should be informed on the potential coverage of circulating strains in Belgium. Policy makers should seek possibilities to obtain the technology to determine strain coverage (currently owned by the vaccine manufacturer) or explore other solutions (e.g. collaboration with other countries; development of other tests).**

[n] The KCE has sole responsibility for the recommendations.

To the clinicians:

- **As meningococcal disease is a devastating and potentially rapidly fatal disease, some parents may choose to vaccinate their infant with 4CMenB. In those situations, co-administration with other vaccines should be avoided as much as possible, but vaccination should be started as soon as possible after two months of age, as the risk of disease is highest between three and seven months.**
- **Clinicians should inform parents on the known benefits and risks of the vaccine. This information should include the uncertainties around vaccine protection and the risk of high fever. If the parents opt for vaccination, clinicians should explain to them how to manage the occurrence of high fever.**
- **There are no data on the vaccination of children at higher risk of meningococcal disease, and recommendations are thus difficult to establish. Clinicians and parents should weigh the risks and benefits of meningococcal disease and of vaccination in these subjects.**

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