Invasive meningococcal disease and vaccination in Belgium: a critical review of the current vaccination strategy

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Keywords

Neisseria meningitidis; invasive meningococcal disease; Belgium; vaccines; epidemiology

Abstract

In 2021, the World Health Organization issued a call to action to defeat meningitis by 2030. Neisseria meningitidis is a major cause of meningitis and septicaemia. Invasive meningococcal disease (IMD) is a severe and life-threatening disease but also vaccine-preventable. Monovalent serogroup C vaccines, quadrivalent meningococcal conjugate vaccines (MenACWY), and serogroup B vaccines (4CMenB, MenB-fHbp) have demonstrated safety and effectiveness in preventing IMD in infants through to young adults. Although the highest incidence of IMD is in infants <1 year of age, current recommendations in Belgium are not optimal and could be improved for this age-group. MenACWY is recommended for toddlers, adolescents, and risk-groups and 4CMenB on an individual basis for infants, adolescents and risk-groups. Neither MenACWY nor MenB vaccines are reimbursed. In this setting, low uptake of meningococcal vaccines is not unexpected, and meningococcal vaccines are conceivably less accessible to low-income families. A review and re-purposing of Belgium's meningococcal vaccination strategy is urgently needed. To this end we propose 6 readily achievable steps: 1) Increase awareness around disease and vaccine options amongst healthcare professionals and the public; 2) Encourage a proactive role for paediatricians and general practitioners; 3) Increase visibility of MenB vaccines in the calendar; 4) Consider reimbursement to increase coverage and avoid inequalities; 5) Learn from other countries that have successfully implemented meningococcal vaccination; 6) Optimise recommendations to protect age-groups/individuals at highest risk. The tools to prevent IMD in Belgium are available but under-utilised. Optimisation of the current meningococcal vaccination strategy could reduce the IMD burden in Belgium.

Introduction to invasive meningococcal disease

Neisseria meningitidis is a major cause of bacterial meningitis and septicaemia beyond the neonatal period and in all world regions (1). The human nasopharynx is the only known reservoir for the bacterium, and transmission occurs through droplet spread or via throat secretions. Nasopharynx colonisation rates are highest in adolescents reaching up to 30-40% (2, 3). Invasive meningococcal disease (IMD) occurs when a newly acquired *N. meningitidis* strain residing in the nasopharynx is able to enter the blood stream (4).

The initial symptoms of IMD are frequently 'flu-like' and non-specific, especially in young infants and in the early stages of disease. Thus, diagnosis may be difficult until the red flag symptoms of meningitis (headache, neck stiffness, photophobia, vomiting or altered mental status) and/or meningococcaemia (purpuric rash and/or symptoms of septic shock) occur (5). The disease course is rapidly fulminant and death can occur within 24-48 hours after symptom onset. The case fatality rate is approximately 10%, despite appropriate anti-microbial therapy and intensive supportive treatment, but can reach up to 40% when meningococcaemia is present (5, 6). Higher mortality rates (16%) are reported in cases caused by serogroup W (MenW) clonal complex (or "variant") 11 (cc11) (6). In developed countries, up to 20% of survivors suffer long-term sequelae including amputation, scarring, cognitive and behavioural deficits, vision, hearing and neurological deficits, with negative impacts on quality of life and life-time productivity (7, 8). While most cases can be prevented by vaccination, IMD has devastating consequences for patients, their families, and the broader public. Moreover, the treatment of IMD and its sequelae, and the management of outbreaks incur substantial direct and indirect costs (8).

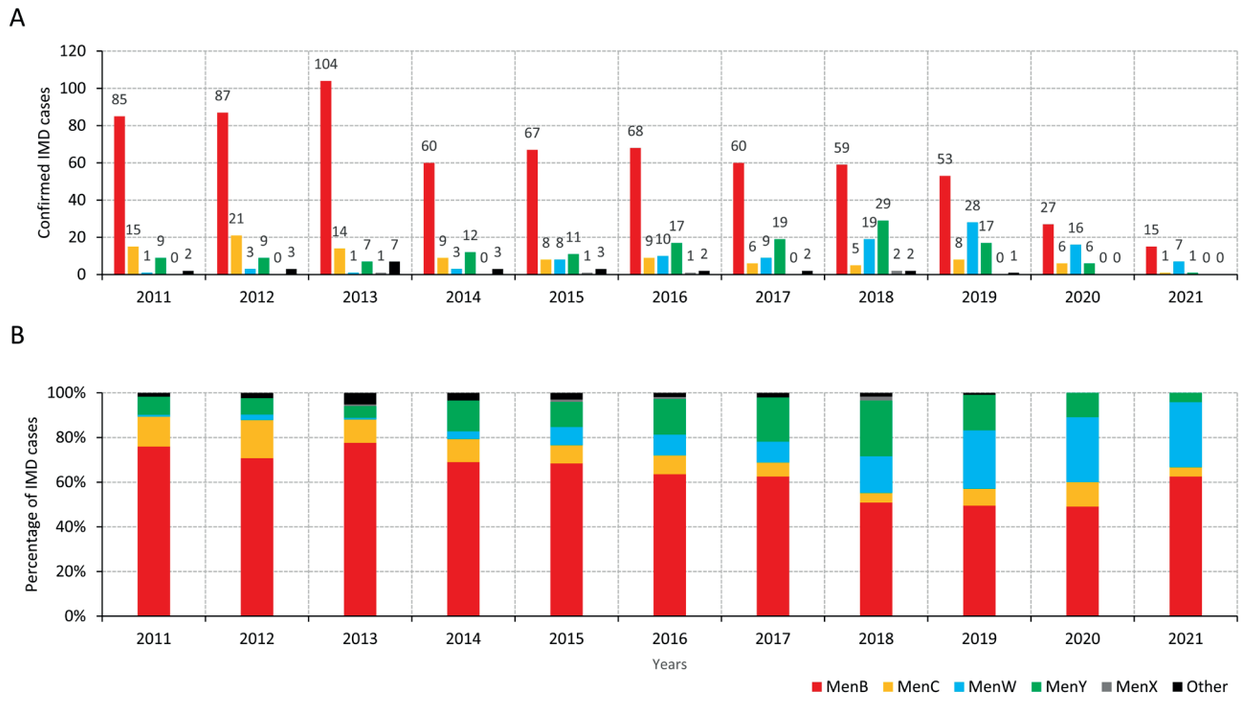
Epidemiology of IMD

Six meningococcal serogroups cause the majority of IMD: MenA, MenB, MenC, MenW, MenY and MenX, with marked temporal and regional differences in their distribution (1). According to the European Centre for Disease Prevention and Control, the number of cases caused by MenB overall decreased during the decade of 2009-2019 while cases of MenW and MenY progressively increased during the same time period. Moreover, reported cases decreased for all meningococcal serogroups for the year 2020 impacted by the SARS-CoV-2 pandemic (9). The highest incidence of IMD is in infants less than 1 year of age, with a second disease peak during adolescence, although IMD can occur at any age, including adults.

Belgian surveillance data mirror the picture across Europe (Figure 1) (10-12). From 2011 until 2021, the percentage of IMD caused by MenB progressively decreased in Belgium, plateauing at approximately 50% to 62.5% of cases since 2018. In line with trends observed elsewhere in

Figure 1 : *A) Number B) percentage of cases of invasive meningococcal disease in Belgium from 2011 until 2021 by serogroup (11, 12). Men(B/C/W/Y/X): meningococcal serogroup (B/C/W/Y/X).*

Note the continued increased in serogroup W and serogroup Y cases from 2015. Fewer cases were observed overall in 2020 and 2021 due to social distancing and hygiene measures secondary to the SARS-CoV-2 pandemic.



Europe, IMD caused by MenW and MenY has increased. The percentage of cases caused by MenY peaked in 2018 (25.0%) and appears to be reducing, whereas IMD caused by MenW has increased annually since 2014 (3.4% to 29.2% in 2021) (11, 12). The hypervirulent MenW cc11 strain originating in South America and responsible for outbreaks in the Netherlands and the United Kingdom (UK), was first observed in Belgium in 2016, and continues to cause IMD with high mortality to this day, more frequently in older age groups (6, 11). Another virulent MenW clone circulating in France (ST-9316) since 2013 was also identified in Belgium in recent years (11, 13-15). The emergence of virulent MenW clones prompted re-evaluation of meningococcal vaccination strategies in the Netherlands, UK and Belgium, with the adjustment of the vaccination calendar to reflect the changing serogroup distribution (16-18).

In 2019 the overall incidence of IMD in Belgium was approximately 1 case per 100,000 population. However, the incidence was 5-fold higher in children <5 years of age, and 15-fold higher in infants <1 year of age (19). As a result of social distancing and hygiene linked to infection mitigation strategies associated with the SARS-CoV-2 pandemic, the number of cases and incidence rate (IR) progressively decreased in all age-groups from 107 cases in 2019 (IR = 0.94 per 100,000) to 55 cases in 2020 (IR = 0.48 per 100,000) then 24 cases in 2021 (IR = 0.21 per 100,000) (11, 12). A return to previous levels is likely unless preventative actions are taken to uphold the current gains in IMD control. Furthermore, changes in serogroup circulation, emergence of more virulent meningococcal strains, potentially reduced carriage, and delays in routine vaccination related to lockdown periods may have caused a decline in meningococcal herd immunity, and an increase in the number of individuals susceptible to meningococcal infection (20). Early evidence from the UK has substantiated these concerns. There has been a sharp increase in MenB IMD observed in adolescents and young adults following relaxation of pandemic containment measures, to levels that have surpassed pre-pandemic rates (21). Post-pandemic mitigation surges in other infectious disease, such as respiratory syncytial virus infection in young children, have also been observed, leading to calls to maximise routine vaccination programs to prevent infection (22).

Meningococcal vaccines and the Belgian meningococcal vaccination calendar

Currently available meningococcal vaccines fall into 2 groups: polysaccharide-protein conjugate vaccines and multi-component protein vaccines that include several highly expressed surface proteins as antigens (23).

Polysaccharide-based meningococcal conjugate vaccines

The first meningococcal conjugate vaccines were monovalent MenC vaccines initially developed and licensed in response to a protracted MenC epidemic in the UK. These vaccines proved to be highly efficacious and also induced strong herd effects that reduced the incidence of IMD in unvaccinated cohorts (24, 25).

Multi-component conjugate vaccines targeting meningococcal serogroups A, C, W, and Y (MenACWY), were subsequently developed and are now used widely in many countries in infants, adolescents, individuals at high risk of IMD, and travellers to endemic regions (26). Available evidence points to high effectiveness of MenACWY vaccines against IMD, with reductions demonstrated in nasopharyngeal carriage of vaccine serogroups (27-29). The immune response to MenC induced by quadrivalent MenACWY has been shown to be similar to responses induced by monovalent MenC vaccines, suggesting that they confer similar protection (30, 31).

Monovalent MenC vaccine was recommended in Belgium from 2002 for use as a single dose at 15 months of age until 2019 (32). In 2019, the Belgian Superior Health Council replaced the monovalent vaccine with the quadrivalent MenACWY conjugate vaccine and added an additional dose at 15-16 years of age into the vaccination calendar, with catch-up vaccination in 15-19 year-olds until 2024 (32). This decision was based on several factors: 1) increasing MenW disease incidence in Belgium due to the hypervirulent cc11 strain; 2) evidence of increasing MenY disease; 3) data from studies showing waning immunity in adolescents against MenC 10 years after primary vaccination; 4) the age distribution of IMD caused by MenW and MenY; and 5) the potential for herd effects on unvaccinated individuals (17, 32, 33). According to their respective Belgian labels, the MenACWY

tetanus toxoid conjugate vaccine (*Nimenrix*, Pfizer) can be administered as 2 primary doses from 6 weeks to 5 months of age or a single primary dose as of 6 months of age, followed by a booster dose at 12 months (with at least 2 months interval between the last primary dose and booster), while the MenACWY diphtheria CRM_{197} conjugate vaccine (*Menveo,* GSK) can be administered as a single dose from the age of 2 years (34, 35).

Multi-valent protein-based MenB vaccines

Prevention of MenB IMD required a different strategy because of poor immunogenicity of the MenB antigen and the potential for cross-reactivity with human neural proteins (36). Two protein-based vaccines were developed that use conserved surface proteins to induce protective immune responses.

Bexsero (4CMenB, GSK), contains 4 antigens: 3 surface proteins; factor H binding protein (fHbp), Neisserial Heparin Binding Antigen (NHBA), *Neisseria* adhesin A; and an outer membrane vesicle containing the Porin A P1.4 antigen previously used as a vaccine during an IMD epidemic in New Zealand (37). 4CMenB has been used in epidemic control in Canada and is implemented in 9 National Immunisation Programmes (NIPs) in the UK, Ireland, Italy, Lithuania, Malta, Czech Republic, Portugal, Andorra and San Marino, and in 3 regional programs in Spain and Australia and in a United States vaccination programme for adolescents (38). A solid body of observational studies and real-world evidence has demonstrated the safety, impact and effectiveness of 4CMenB in infants and young adults in several countries (38).

According to the Belgian product label, 4CMenB is indicated from 2 months of age (39). 4CMenB is administered in a 2+1 or 3+1 schedule in children aged 2 to 5 months of age at first dose; as a 2+1 schedule from 6 to 23 months of age at first dose; and as a 2-dose schedule from 2 years of age and older, with consideration of a booster dose for individuals at continued risk of exposure to meningococcal disease (39). In Belgium, vaccination is recommended on an individual basis for children from 2 months to 5 years of age, adolescents aged 15-19 years, and risk groups (32).

Trumenba, (MenB-fHbp, Pfizer) includes 2 fHbp variants. MenB-fHbp was immunogenic and well tolerated in clinical trials. MenB-fHbp was used in outbreak control in France and the United States (40-42), but real-world estimates of effectiveness are lacking.

According to the Belgian product label, MenB-fHbp is approved for use in a 2-dose or 3-dose schedule from the age of 10 years (43). In Belgium, MenB-fHbp is recommended on an individual basis for adolescents aged 15-19 years (32).

Vaccination against MenB is recommended by many countries for a large number of risk groups that include persons with asplenia, complement deficiency, complement inhibitors, or humoral immunosuppression (Table 1) (44, 45). A limited number of risk groups for MenB vaccination were listed in the 2017 Belgian MenB vaccine recommendations (46), but were not specifically defined in the 2019 updated recommendations (32).

Obstacles to IMD control in Belgium

The tools to prevent the majority of IMD are available in vaccines that have been demonstrated to be safe and highly effective (24, 25, 28, 29, 38).

Currently available meningococcal vaccines target 5 of the 6 serogroups that cause most IMD in humans. MenW IMD has been effectively controlled in the Netherlands using a dose of MenACWY in toddlers and adolescents where coverage of 93% in toddlers and 86% in adolescents was achieved (47). While the move to MenACWY in young children and the introduction of an adolescent dose of MenACWY into the Belgian NIP is a strong step forward, the current strategy in Belgium is unlikely to achieve similar results because of sub-optimal vaccine uptake in some regions, especially in adolescents who are the main carriers of *N. meningitidis*. Additionally, the current vaccination calendar does not include MenB vaccines, and visibility and awareness of MenB vaccines is low.

Neither MenACWY nor MenB vaccines are reimbursed in Belgium for any age group and the full cost (52.60 euro for MenACWY vaccines, 86.52 euro for 4CMenB, and 76.98 euro for MenB-fHbp) is incurred by patients (48). Cost is a well-recognised barrier to meningococcal vaccine uptake and leads to health case discrimination when vaccination is only affordable for higher income families (49). A study in France showed that low household income and social disadvantage are risk factors for childhood IMD (50). Therefore, high vaccine costs can put meningococcal vaccination out of reach for families known to be at higher risk of IMD.

The rationale for many countries, including Belgium, not to include MenB vaccines in NIPs was based at the time on 1) the low incidence of MenB

Table 1 : *Specification of risk groups for vaccination against invasive meningococcal disease (IMD) caused by serogroup B (MenB)* versus Belgium recommendations.*

Populations at high risk of IMD caused by MenB	Belgian MenB vaccination recommendations (46)
Complement disorders (including properdin deficiency)	✓
Receiving complement inhibitor therapy (eculizumab or ravulizumab therapy)	✓
Asplenia/hyposplenism/ splenic dysfunction	✓
Immunocompromised individuals	✓
Primary immunodeficiency (including hypogammaglobulinemia)	✓
Autologous or allogeneic hematopoietic stem cell transplantation	×
Solid organ transplant	×
After bacterial meningitis and septicaemia	×
Human immunodeficiency virus infection	×
Down Syndrome	×
Professionally exposed (i.e., laboratory workers)	×
During clusters/outbreaks	×
Close contacts of cases	×
Travellers to hyperendemic or epidemic countries	×
Adolescents or adults exposed in big groups (universities, residence halls, military recruits)	×
Men who have sex with men	×

*based on recommendations from the United States Centers for Disease Control and Prevention and the European Centre for Disease Control

IMD; 2) the difficulties of integrating a 3-dose series into infant vaccination calendars; 3) the increased likelihood of fever when co-administered with routine vaccines; 4) unfavourable cost-effectiveness; and 5) lack of data on efficacy, duration of protection and carriage (32, 44).

Incidence and the under-recognised disease burden

In Belgium, the incidence of IMD in children less than 1 year of age is 15 per 100,000 population, of which approximately 50% is due to MenB (2019) (19). This incidence rate is not far from the 2014 incidence in infants in the UK immediately prior to the introduction of routine 4CMenB vaccination (19 per 100,000 population of which 80% was due to MenB), and to the incidence of MenB IMD in the Saguenay-Lac-Saint-Jean region of Quebec of 11.4 per 100,000 (≤20 year olds) that triggered a mass-immunisation programme (19, 51, 52). When IMD cases occur, the direct and societal costs are substantial and prolonged, lasting well past the acute treatment phase and often for a lifetime (8). It is thus regrettable that in 2019, most IMD cases in infants and children up to 5 years of age in Belgium were vaccine-preventable in a country where vaccines are readily available.

Successful introduction into routine infant immunisation programmes has been demonstrated

Countries that have introduced 4CMenB into their routine infant vaccination programmes have experienced high rates of acceptance and achieved high coverage rates. 4CMenB has been well accepted in the UK since its introduction in 2015, with 92.5% uptake of the primary immunisations in 2018 and no impact on compliance with other routine vaccinations (53, 54). 4CMenB can be co-administered with other routinely recommended vaccines (55). Concerns around acceptance of a third injection and of a higher rate of fever following co-administration have not proven to be major hurdles to implementation. A recommendation for prophylactic paracetamol administration prior to vaccination is associated with reduced rates of fever, with no clinical impact on the immune response of MenB and routine vaccines (56). Analysis of consultation rates of fever after 4CMenB vaccination found only a small increase compared to earlier years (57). In summary, the UK experience illustrates that initial concerns that were considered impediments to successful infant 4CMenB vaccination were unfounded.

Updated cost-effectiveness analyses are needed

In 2014, the Belgian Health Care Knowledge System published a cost-effectiveness analysis for MenB control in Belgium and concluded that vaccination would prevent no more than 16% of cases at high cost (58). The models' assumptions were based on a 3+1 schedule for infants whereas a 2+1 schedule is commonly employed, and the most recent real-world effectiveness and persistence data were not considered. The model also included rather low primary vaccination coverage of 55%; high rates of medical consultation and hospital admission for fever investigation; and the costs of ongoing disease surveillance. While some impacts of preventing long-term sequelae were included, the model did not include other potential benefits of 4CMenB vaccination that have since emerged, such as an impact on preventing IMD caused by other serogroups, and preliminary evidence suggesting a potential effect on preventing *Neisseria gonorrhoea* infections (38). Additionally, more precise estimates of the rates of post-vaccination fever consultations and hospitalisations are now available (57, 59). A new cost-effectiveness evaluation conducted for the UK using updated assumptions based on contemporary data and comprehensive disease burden inputs including long-term sequelae, found that 4CMenB infant vaccination at £75 per dose, can be cost-effective at a threshold of £20 000 per quality-of-life-year gained (60). Vaccine price is an important underlying assumption that has a major impact in cost-effectiveness models. On the other hand, a meta-analysis of data that did not include the updated UK analysis, did not demonstrate cost-effectiveness of MenB vaccination strategies (61). In view of the contradictory results published so far, updated health technology assessments in the Belgian context are warranted.

Real-world evidence of effectiveness and impact, carriage, and safety is now available

The published evidence demonstrating the effectiveness and impact of 4CMenB in preventing MenB IMD was collated in a review by Martinon-Torres et al, 2021 (38). Vaccine effectiveness in fully vaccinated cohorts ranged from 59%-100%, with evidence of continued protection up to 4 years after vaccination. Vaccine effectiveness was demonstrated across different age-groups and settings, including NIPs, observational studies and in outbreak control.

A prospective population-based study in Australian adolescents conclusively demonstrated that 4CMenB has no impact on nasopharyngeal carriage of meningococci, including MenB strains (62). This means that vaccination only protects the vaccinee, reinforcing the need for direct protection of at-risk groups such as infants and adolescents through individual vaccination.

Reviews of vaccine safety have not identified any safety concerns following the widespread use of 4CMenB in infants and adolescents (54, 63-65).

Towards a meningitis-free Belgium by 2030.

In 2021, the World Health Organization (WHO) issued a call to action and published a road map to defeat meningitis by 2030, with the main goal to increase vaccination coverage (66). The 2030 objective is to reduce cases of vaccine-preventable bacterial meningitis by 50% and deaths by 70% compared to 2015 levels. In response to the WHO's mission, we propose the following strategy made up of 6 readily achievable steps with the aim of promoting an IMD-free Belgium by 2030 (Figure 2).

Step 1: Increase awareness about disease and vaccine options amongst healthcare professionals and the public

Educating healthcare professionals and the public about diseases and the options available to prevent them is an important step in reducing hesitancy and improving uptake of all vaccines (67). Efforts to improve general knowledge about IMD and the available vaccine options need to employ all available communication means, including the regular media, social media, and influencers to increase reach and relevance to parents and young people.

Step 2: Encourage a proactive role among paediatricians and general practitioners to engage in discussion with patients/parents

More awareness is needed about meningococcal vaccines and their pros and cons among vaccine providers in Belgium. General practitioners and paediatricians (supported by their professional organisations and medical societies) are a critical information gateway in recommending vaccines. Their role in informing their patients about vaccine options and encouraging their uptake is essential, particularly in the current setting of non-reimbursement.

Step 3: Increase visibility of meningococcal vaccines currently not present in the vaccination calendar

Vaccines that are recommended by authorities, even if not reimbursed, should be clearly mentioned and made visible to healthcare professionals and the public via the vaccination calendar, which is considered to be the most reliable source of information for vaccinations. Including MenB vaccination as an option in the vaccination calendar, along with guidance on implementation such as the timing of vaccination with respect to other vaccines is a simple strategy that would provide a prompt, and a reminder to vaccine providers who might otherwise neglect or fail to remember this option.

Step 4: Consider vaccine reimbursement to increase vaccination coverage and avoid inequalities

Requiring full out-of-pocket payment for all meningococcal vaccines is a disincentive to uptake and leads to inequalities in health care among the economically and socially disadvantaged who are at higher risk of IMD, and least able to afford preventative measures (50). The issue of reimbursement is critical to success, with meningococcal vaccines currently out of reach for many families.

Step 5: Learn from other countries that have successfully implemented NIPs

Countries such as the UK, the Netherlands, Portugal, Italy, and South Australia have successfully implemented mass vaccination programmes and

Figure 2 : *Steps towards an IMD-free Belgium by 2030.*
IMD, invasive meningococcal disease; NIP, national immunisation programme secondary to the SARS-CoV-2 pandemic.

have accumulated multiple years of experience with MenB or MenACWY vaccines in their NIPs. This knowledge can be harnessed to help optimise Belgium's meningococcal vaccine program.

Under a similar epidemiological setting to that currently existing in Belgium (10, 51), the UK included 4CMenB for infants in their NIP. The UK subsequently observed a 75% reduction in MenB disease incidence as well as an indirect impact of 69% on MenW disease in fully-eligible cohorts (53, 68). In the Saguenay-Lac-Saint-Jean region of Quebec, a mass vaccination campaign was initiated in <20 year olds and achieved a 100% reduction in the first 2 years of the programme (52). In both countries, success followed high vaccine uptake of 87.9% and 82%, respectively (52, 53). If higher coverage of MenB vaccines in combination with ACWY vaccinations can be achieved in the context of an improved NIP in Belgium, there is the potential for a direct impact on the burden of IMD, including the indirect and long-lasting consequences and costs of the disease.

Step 6: Optimise meningococcal vaccine recommendations to protect age-groups with the highest incidence and persons at highest risk

The peak incidence of IMD is in infants and most IMD is caused by MenB in this age-group. However, the vaccination recommendation for this age-group is only on an individual basis, with low public visibility (32). The MenACWY conjugate vaccines administered to adolescents in whom carriage and transmission is highest could reduce *N. meningitidis* transmission and protect other age-groups including infants and other age-groups via herd effects (69). By contrast, MenB vaccines do not induce herd protection and require a different strategy, that of direct protection to age-groups at risk. Consideration needs to be given to a recommendation for MenB vaccination in infants, and adolescents or young adults who are also at higher risk of MenB IMD. In infants, the additional benefit of cross-protection against MenW disease could be important in Belgium where the first MenACWY vaccine is not given until the second year of life.

On the other hand, revised advice for vaccine recommendations for people in special risk groups is warranted (Table 1) (45).

Conclusion

Achieving the WHO's goal to defeat meningitis by 2030 requires a review and re-purposing of Belgium's meningococcal vaccination strategy. The existing recommendations for MenACWY are unlikely to achieve their stated goal unless coverage in different age groups can be substantially improved through enhanced visibility, awareness, and reimbursement. MenB remains the most common cause of IMD in all age-groups, with the highest burden in infants. An effective vaccine for infants is available in Belgium, but achieving high uptake is challenging due to its cost and lack of visibility in the vaccination calendar. The concerns that steered many European authorities away from recommending and implementing MenB vaccination are no longer relevant and a re-evaluation of the role of MenB vaccines in the NIP as well as revised recommendation for persons at risk are warranted. In 2021, representatives of several scientific societies in France sent a strong call for the introduction of free MenB vaccination for infants, arguing that early reasons for not including MenB vaccines in the French calendar were no longer justified, and that it is unethical to offer protection against a potentially fatal disease only to families who can afford the vaccine (70).

The tools to prevent IMD in Belgium are available but under-utilised. A series of readily achievable steps could markedly reduce IMD, contributing to the WHO's goal of defeating meningitis by 2030.

Conflicts of interest

DT, MR, MW, WM, LD, and JV declare no financial and non-financial relationships and activities and no conflicts of interest. JMH and KB are employed by the GSK group of companies. The authors declare no other financial and non-financial relationships and activities.

Funding

GlaxoSmithKline Biologicals SA took in charge all costs associated with the development and the publishing of the present manuscript.

Acknowledgements

The authors thank Anne Meulemans, employed by the GSK group of companies, for her contribution to the manuscript review. The authors also thank Business & Decision Life Sciences platform for editorial assistance, writing support, manuscript coordination and design support for the digital illustrations, on behalf of GSK. Joanne Wolter provided writing support. Diego Collin and Elena Chaves Rodriguez coordinated manuscript development and editorial support.

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