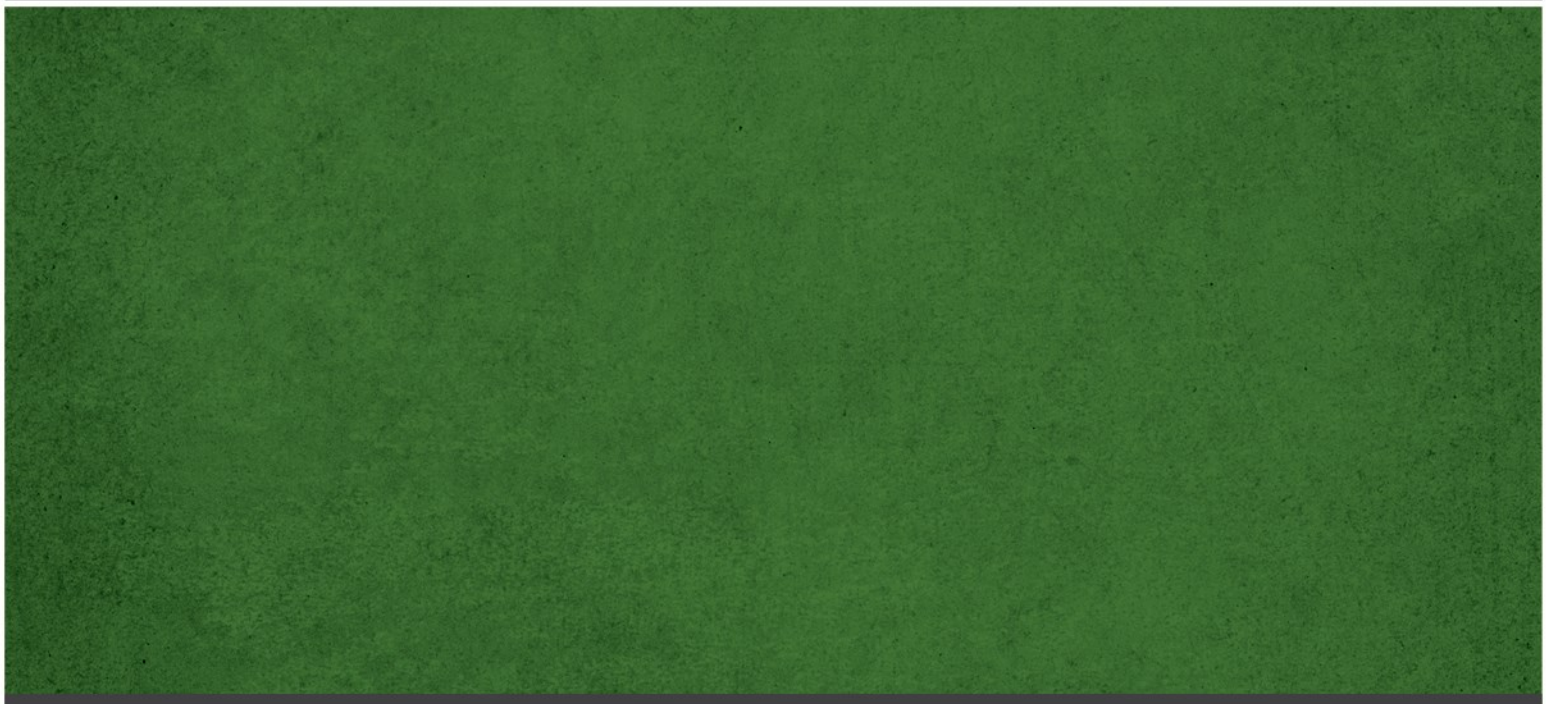
An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

The Use of Bivalent Factor H Binding Protein Meningococcal Serogroup B (MenB-fHBP) Vaccine for the Prevention of Meningococcal B Disease



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—Public Health Agency of Canada

Également disponible en français sous le titre : Utilisation du vaccin bivalent dirigé contre la protéine de liaison au facteur H (MenB-fHBP) pour la prévention de l'infection à méningocoque du sérogroupe B

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Over the coming years NACI will be refining methodological approaches to include these factors. Not all NACI Statements will require in-depth analyses of all programmatic factors. As NACI works towards full implementation of the expanded mandate, select Statements will include varying degrees of programmatic analyses for public health programs.

PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

The following highlights key information for immunization providers. Please refer to the remainder of the Statement for details.

1. What

Invasive meningococcal disease

Invasive meningococcal disease (IMD) usually presents as an acute febrile illness with rapid onset and features of meningitis or septicemia (meningococcemia), or both, and a characteristic non-blanching rash. Overall case fatality is approximately 10%, and up to a third of survivors may have long term sequelae, which include hearing loss, neurologic disabilities, and digit or limb amputations. From 2012 to 2016, a total of 353 of 583 (60.5%) reported cases of IMD in Canada were due to serogroup B. The highest rate of infection occurs in infants <1 year of age. The rates of IMD from other serogroups have been decreasing since the introduction of routine programs using conjugate polysaccharide vaccines. Additional information about IMD is available on the Government of Canada web site (https://www.canada.ca/en/public-health/services/immunization/vaccine-preventable-diseases/invasive-meningococcal-disease.html).

Bivalent factor-H binding protein meningococcal serogroup B (MenB-fHBP) vaccine (Trumenba®)

The bivalent factor-H binding protein meningococcal serogroup B (MenB-fHBP) vaccine was authorized for use in Canada in October 2017 for the prevention of IMD caused by *N. meningitidis* serogroup B in individuals 10–25 years of age. The MenB-fHBP vaccine is immunogenic, although its effectiveness, impact on carriage and herd immunity, and its duration of protection remain unknown.

2. Who

Groups recommended for immunization

NACI makes the following general recommendations and guidance and recommendations for public health program level and individual level decision-making.

General recommendations and Guidance

General guidance: ***NACI continues to recommend immunization against serogroup B IMD to all individuals who are at a higher risk of disease due to an underlying medical condition or at an increased risk of exposure. However, the two serogroup B meningococcal vaccines currently authorized for use in Canada (MenB-fHBP and 4CMenB) are not interchangeable, as they contain different antigens and there are no published studies on the immunogenicity resulting from a vaccination series combining the two products. Therefore, the same vaccine product should be used for all doses in a vaccination series. If, in a person with an incomplete vaccination series, it is unknown what vaccine product they initially received, the initial dose(s) should be discounted and***

the vaccination series repeated using the same vaccine product for all doses in the new, repeated series.

Recommendations for Public Health Program Level Decision-making (i.e., provinces/territories making decisions for publicly funded immunization programs)

Recommendation 1: **NACI recommends that the MenB-fHBP vaccine should not be offered in routine universal immunization programs in Canada at this time. (Strong NACI Recommendation)**

- **NACI concludes there is insufficient evidence to recommend routine universal immunization (Grade I Evidence).**

Recommendation 2a: **NACI recommends that a serogroup B meningococcal vaccine (MenB-fHBP or 4CMenB) should be offered in jurisdictions experiencing serogroup B meningococcal disease outbreaks or with the emergence of hyperendemic *N. meningitidis* strains that are predicted to be susceptible to the vaccine. (Strong NACI Recommendation)**

- **NACI concludes there is fair evidence to recommend vaccine use during outbreaks (Grade B Evidence).**

Recommendation 2b: **NACI recommends that the MenB-fHBP vaccine may be considered as an option for use in individuals 10 years of age and older in such circumstances. (Discretionary NACI Recommendation)**

- **NACI concludes there is insufficient evidence of the MenB-fHBP vaccine use in such circumstances (Grade I Evidence); therefore, this recommendation is based on expert opinion.**

Recommendation 3a: **NACI recommends that a serogroup B meningococcal vaccine (MenB-fHBP or 4CMenB) should be offered, in addition to chemoprophylaxis, for protection of individuals who are close contacts with a case of invasive meningococcal disease caused by serogroup B *Neisseria meningitidis*. (Strong NACI Recommendation)**

- **NACI concludes there is insufficient evidence of vaccine effectiveness in close contacts of cases of IMD (Grade I Evidence); therefore, this recommendation is based on expert opinion.**

Recommendation 3b: **NACI recommends that the MenB-fHBP vaccine may be considered as an option for use in individuals 10 years of age and older who are close contacts with a case of IMD caused by serogroup B *Neisseria meningitidis*. (Discretionary NACI Recommendation)**

- **NACI concludes there is insufficient evidence of the MenB-fHBP vaccine use in close contacts (Grade I Evidence); therefore, this recommendation is based on expert opinion.**

Recommendation 4a: **NACI recommends that a serogroup B meningococcal vaccine (MenB-fHBP or 4CMenB) should be offered for the active immunization of individuals**

with underlying medical conditions that would put them at higher risk of meningococcal disease than the general population to reduce the risk of invasive serogroup B meningococcal disease. (Strong NACI Recommendation)

- **NACI concludes there is insufficient evidence of vaccine use in high-risk populations (Grade I Evidence); therefore, this recommendation is based on expert opinion.**

Recommendation 4b: **NACI recommends that the MenB-fHBP vaccine may be considered as an option for use in high-risk individuals 10 years of age and older, in a 3-dose schedule (0, 1–2, 6 months), to reduce the risk of invasive serogroup B meningococcal disease. (Discretionary NACI Recommendation)**

- **NACI concludes there is insufficient evidence of the MenB-fHBP vaccine use in high-risk populations (Grade I Evidence); therefore, this recommendation is based on expert opinion.**

For Individual Level Decision-making (i.e., individuals wishing to prevent serogroup B IMD or clinicians wishing to advise individual patients about preventing this outcome with vaccines that may not be currently included in publicly funded immunization programs; and organizations or decision makers responsible for programs offering vaccine services to various groups including individuals at risk of acquiring this outcome)

Recommendation 5a: **NACI recommends that a serogroup B meningococcal vaccine (MenB-fHBP or 4CMenB) should be offered for the active immunization of individuals at higher risk of exposure to serogroup B meningococcal isolates than the general population to reduce the risk of invasive serogroup B meningococcal disease. (Strong NACI Recommendation)**

- **NACI concludes there is insufficient evidence of vaccine use in high-risk populations (Grade I Evidence); therefore, this recommendation is based on expert opinion.**

Recommendation 5b: **NACI recommends that the MenB-fHBP vaccine may be considered as an option for use in such high-risk individuals 10 years of age and older, in a 2-dose schedule (0, 6 months), to reduce the risk of invasive serogroup B meningococcal disease. (Discretionary NACI Recommendation)**

- **NACI concludes there is insufficient evidence of the MenB-fHBP vaccine use in high-risk populations (Grade I Evidence); therefore, this recommendation is based on expert opinion.**

Recommendation 6: **NACI recommends that the MenB-fHBP vaccine may be considered as an option for individuals 10-25 years of age who are not at higher risk of meningococcal disease than the general population, in a 2-dose schedule (0 and 6 months), to reduce the risk of invasive serogroup B meningococcal disease. (Discretionary NACI Recommendation)**

- **NACI concludes there is fair evidence of vaccine immunogenicity to recommend the MenB-fHBP vaccine when given according to the schedule used during clinical trials (Grade B Evidence).**

3. How

The vaccine is supplied in a single-dose, prefilled syringe. Doses of MenB-fHBP should be administered as intramuscular injections only, preferably in the deltoid muscle.

The vaccine is authorized for use in two immunization schedules. The standard schedule for routine immunization is two doses (0.5 mL per dose) administered at 0 and 6 months. For persons at increased risk of IMD, there is a three-dose schedule (0.5 mL per dose) administered at 0 month followed by a second dose at least one month later, followed by a third dose at least 4 months after the second dose. The need for a booster dose following the primary immunization series has not been established.

MenB-fHBP should be refrigerated at 2 °C to 8 °C. The vaccine should be discarded if it has been frozen.

Contraindications to administration of the vaccine include hypersensitivity to the vaccine or any of its components. A severe allergic reaction to any previous dose of the vaccine or to any of its components is also a contraindication to MenB-fHBP administration. There are no data available on the use of MenB-fHBP in immunocompromised individuals or in pregnant women. It is also not known whether MenB-fHBP is excreted in human breast milk.

The safety and efficacy of the vaccine have not been established in children less than 10 years of age. The vaccine has also not been studied in older adults (>65 years).

The vaccine can be given concomitantly with quadrivalent human papillomavirus vaccine; meningococcal serogroup A, C, Y, W conjugate vaccine; and tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed. The concomitant administration of MenB-fHBP has not been studied with other vaccines. If MenB-fHBP is to be administered concomitantly with another vaccine, a separate injection site and a different syringe must be used for each injection.

4. Why

Although the incidence of IMD is low, outbreaks can occur and people with certain medical conditions are at greater risk of disease than the general population. Serogroup B is now responsible for the majority of IMD cases in Canada. The overall case fatality rate of invasive meningococcal disease (IMD) is approximately 10% and up to a third of survivors may have long term sequelae, which include hearing loss, neurologic disabilities, and digit or limb amputations.

I. INTRODUCTION

I.1 Objectives of this statement

The need for this National Advisory Committee on Immunization (NACI) Advisory Committee Statement on the Use of the Bivalent Factor H Binding Protein Meningococcal Serogroup B (MenB-fHBP) vaccine for the Prevention of Meningococcal B Disease was triggered by the receipt of a Notice of Compliance (NOC) for the MenB-fHBP vaccine on October 5, 2017. The primary objectives of this statement are to review the evidence on the efficacy, effectiveness, immunogenicity and safety of the MenB-fHBP vaccine for the prevention of IMD caused by *Neisseria meningitidis* serogroup B in individuals 10–25 years of age. A literature review was also undertaken to identify cost-effectiveness studies of serogroup B protein-based meningococcal vaccines in developed countries. This evidence was used to develop recommendations for the use of the MenB-fHBP vaccine in Canada. The scope of this statement does not include comparative recommendations on the use of the MenB-fHBP vaccine (Trumenba®) and the 4CMenB vaccine (Bexsero®).

I.2 Background on meningococcal serogroup B vaccines, immunization programs and recommendations in Canada

In December 2013, Bexsero® [1], a multicomponent meningococcal serogroup B (4CMenB) vaccine, received a NOC authorizing its use in Canada in individuals 2 months through 17 years of age. In August 2018, Bexsero was authorized for use in individuals 2 months through 25 years of age.

In April 2014, NACI released an Advisory Committee Statement for the use of Bexsero® (http://publications.gc.ca/site/eng/463960/publication.html). The vaccine is recommended for use in individuals at high risk of meningococcal disease and for use in controlling outbreaks due to serogroups that would be predicted to be covered by the vaccine. The recommendations also state the vaccine should be considered in addition to chemoprophylaxis for close contacts of a case of IMD caused by serogroup B *Neisseria meningitidis.*

There are currently no established national disease reduction targets or vaccination coverage goals for the prevention of invasive meningococcal serogroup B disease. There are also no publicly funded, routine meningococcal serogroup B immunization programs in Canada.

II. METHODS

In brief, the broad stages in the preparation of a NACI Advisory Committee Statement are:

1. Knowledge synthesis – individual studies are retrieved and key data abstracted, the level (i.e., study design) and quality of the evidence assessed, and this information is summarized in Summary of Evidence Tables (Appendix A, B)
2. Synthesis of the body of evidence of benefits and harms, considering the quality of the evidence and magnitude of effects observed
3. Translation of evidence into recommendations

Further information on NACI's evidence-based methods is available in: Evidence-Based Recommendations for Immunization: Methods of the NACI, January 2009, CCDR at:

http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-1/index-eng.php).

NACI reviewed the key questions for the literature review as proposed by the Meningococcal Disease Working Group, including such considerations as the burden of illness of the disease to be prevented and the target population(s); the safety, immunogenicity, efficacy, and effectiveness of the vaccine; vaccine schedules; and other aspects of the overall immunization strategy. The knowledge synthesis was performed by two medical specialists, and supervised by the Working Group. Following critical appraisal of individual studies, proposed recommendations for vaccine use were developed. The Working Group chair and the Public Health Agency of Canada medical specialist presented the evidence and proposed recommendations to NACI on June 6, 2018 and June 6, 2019. Following thorough review of the evidence and consultation, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text.

II.1 Burden of illness

Basic epidemiological data on probable and confirmed IMD cases, as per the national case definition (https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2009-35/definitions-communicable-diseases-national-surveillance/invasive-meningococcal-disease.html), are routinely collected through the Canadian Notifiable Disease Surveillance System. The Enhanced Invasive Meningococcal Disease Surveillance System (EIMDSS) also captures additional epidemiological and laboratory-linked data using probabilistic matching. However, data are not available on vaccination status or risk factors (e.g., comorbidities).

II.2 NACI literature review (efficacy/effectiveness, immunogenicity, safety)

The research question addressed in this statement is: *What is the efficacy, immunogenicity and safety of Trumenba® in reducing the risk of invasive meningococcal serogroup B disease in persons 10 years of age and older?*

Population: individuals 10 years of age and over
Intervention: vaccination with MenB-fHBP vaccine
Comparator: placebo or other vaccines in controlled trials
Outcomes: efficacy/effectiveness, immunogenicity and safety parameters

MEDLINE, the Cochrane Database of Systematic Reviews and Health Technology Assessment (which is included in MEDLINE) and EMBASE electronic databases were searched from 1974 until July 3, 2017 using search terms and strategies developed with the assistance of a Health Canada library specialist. Studies retrieved from the database searches were initially screened by title and abstract for potential eligibility by a single reviewer and the full-text of studies deemed potentially eligible after title and abstract screening, or for which insufficient information was available to determine eligibility (e.g., no abstract), were obtained and further reviewed for eligibility by two independent reviewers. Hand-searching of the reference lists of included articles was performed by one reviewer to identify additional relevant publications. Potential articles identified through hand-searching were then subjected to eligibility screening by two reviewers as described above. One reviewer extracted data from the studies included for review into an evidence table using a piloted data abstraction template designed to capture information on study design, population and outcomes of interest. A second reviewer independently

validated the abstracted data with any disagreements or discrepancies resolved by discussion and consensus. The level of evidence (i.e., study design) and methodological quality of included studies was assessed independently by two reviewers using the design-specific criteria by Harris et al. 2001 adopted by NACI for rating the internal validity of individual studies (Tables 2, 3).

A synthesis of the information extracted from the included studies was used to explore the efficacy/effectiveness, immunogenicity and safety of the MenB-fHBP vaccine, including summaries of the direction, size and statistical significance of reported effect estimates for various study-defined outcomes.

Data identified in the NACI literature review was supplemented by the manufacturer's presentation of unpublished data to the Meningococcal Working Group.

II.3 Literature review (cost-effectiveness)

A comprehensive literature review was undertaken to identify, characterize and critically appraise published cost-effectiveness studies of serogroup B protein-based meningococcal vaccines in developed countries. The main objectives of the literature review were to assess the cost-effectiveness of serogroup B protein-based meningococcal vaccines in Canada and comparable healthcare settings, to determine the factors influencing the vaccine's cost-effectiveness, and to identify conditions under which the vaccine would be considered cost-effective. The components of the research question are summarized as:

> Population: General population or high-risk groups defined by age from developed countries
> Intervention: Licensed serogroup B protein-based meningococcal vaccines
> Comparator: "No vaccination" or different vaccination strategies (i.e., dose regimen/schedule)
> Outcomes: Measures of cost-effectiveness (incremental cost per quality-adjusted life year, incremental cost per disability-adjusted life year, and cost per life year, etc.)

Studies were included if they described a full economic evaluation of a protein-based meningococcal vaccine targeting serogroup B licensed for use in the general population in a developed country (countries with "Advanced Economies" according to the International Monetary Fund data for 2017). As per definition, full economic evaluations include cost-effectiveness analysis (CEA), cost-benefit analysis (CBA) and cost-utility analysis (CUA). All studies that provided comparisons with "no vaccination", current vaccination or different vaccination strategies were included. No language restrictions were applied. Studies were excluded if they met one or more of the following exclusion criteria: they were not full economic evaluations (e.g., cost-analyses), the full text was not available, the studies were conducted in a developing country (countries not included in "Advanced Economies"), and the target population was a high-risk group not defined by age.

Four journal-indexing databases were searched with the help of a librarian (PubMed, Embase, Scopus and Web of Science) from inception to November 2017 and subsequently updated on June 23, 2018, using key words and index terms related to the vaccine, disease (meningitis, meningococcal disease or infection, *Neisseria meningitidis*), and economic assessments. This was complemented by a manual search in public health agencies' websites of 10 developed countries, reference tracking, and information provided by vaccine manufacturers. Two

independent reviewers conducted title and abstract screening, as well as full-text screening. Disagreements were resolved by consensus. A preliminary list of studies selected for analysis was reviewed by vaccine manufacturers to verify completeness of the search results and to obtain information on other economic evaluations currently under development. A standardized data extraction tool was used to record study characteristics, methods and findings of included studies.

Studies were summarized qualitatively. All cost data were converted to 2017 Canadian dollars based on Consumer Price Indices and official exchange rates to allow for comparisons across countries over time. A quality appraisal was not conducted.

III. EPIDEMIOLOGY

N. meningitidis (meningococcus) is a potentially serious pathogen that can cause IMD. It colonizes up to 10% of healthy individuals without causing harm. Meningococci can be classified based on the immunologic reactivity of the polysaccharide capsule into 12 different serogroups, of which six (A, B, C, W, Y and X) are associated most frequently with IMD around the globe. Further classification into serotypes and serosubtypes can be made based on the immunologic reactivity of meningococcal outer membrane proteins. Characterization using nucleotide sequence-based methods such as genetic sequencing of porA and porB genes is used to substitute or supplement serology-based classifications.

IMD usually presents as an acute febrile illness with rapid onset and features of meningitis or septicemia (meningococcemia), or both, and a characteristic non-blanching rash. Overall case fatality is approximately 10%, and up to a third of survivors may have long term sequelae, which can include hearing loss, neurologic disabilities, and digit or limb amputations[2, 3].

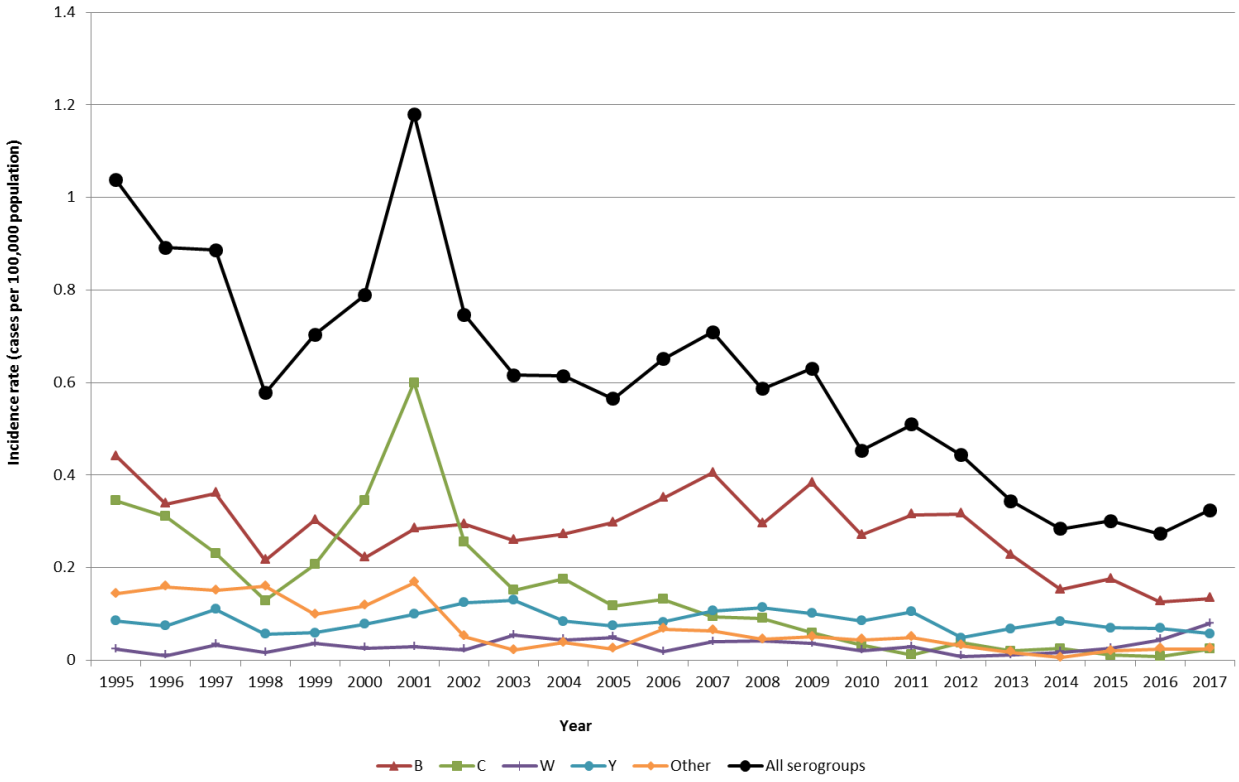
IMD is a reportable communicable disease in all provinces and territories. All probable and confirmed cases are reported to provincial/territorial public health authorities and the Public Health Agency of Canada (PHAC) enhanced IMD surveillance system. Provincial/Territorial public health and/or hospital laboratories send all meningococcal isolates to PHAC's National Microbiology Laboratory for strain characterization, including confirmation of serogroup and determination of serotype, serosubtype and sequence type/clonal complex.

There is currently no routine immunization program against IMD caused by serogroup B in Canada. However, the 4CMenB vaccine has been used in a hyperendemic region in Quebec and in an outbreak in Nova Scotia. For more information on the various vaccination programs for IMD in Canada, please refer to Canada's provincial and territorial routine vaccination programs.

III.1 Disease distribution by serogroup

Since the implementation of various meningococcal immunization programs, starting in 2001, an important decline in the overall incidence of IMD in Canada has been observed (1.2 cases per 100,000 population in 2001 to 0.3 cases per 100,000 population in 2017) (Figure 1). Since the early 2000s, the yearly incidence of IMD by serotype was highest for Serogroup B compared to other serotypes. In 2017, the incidence of IMD due to Serogroup B was 0.13 cases per 100,000 population.

Figure 1: Reported invasive meningococcal disease incidence in Canada by serogroup, 1995–2017*

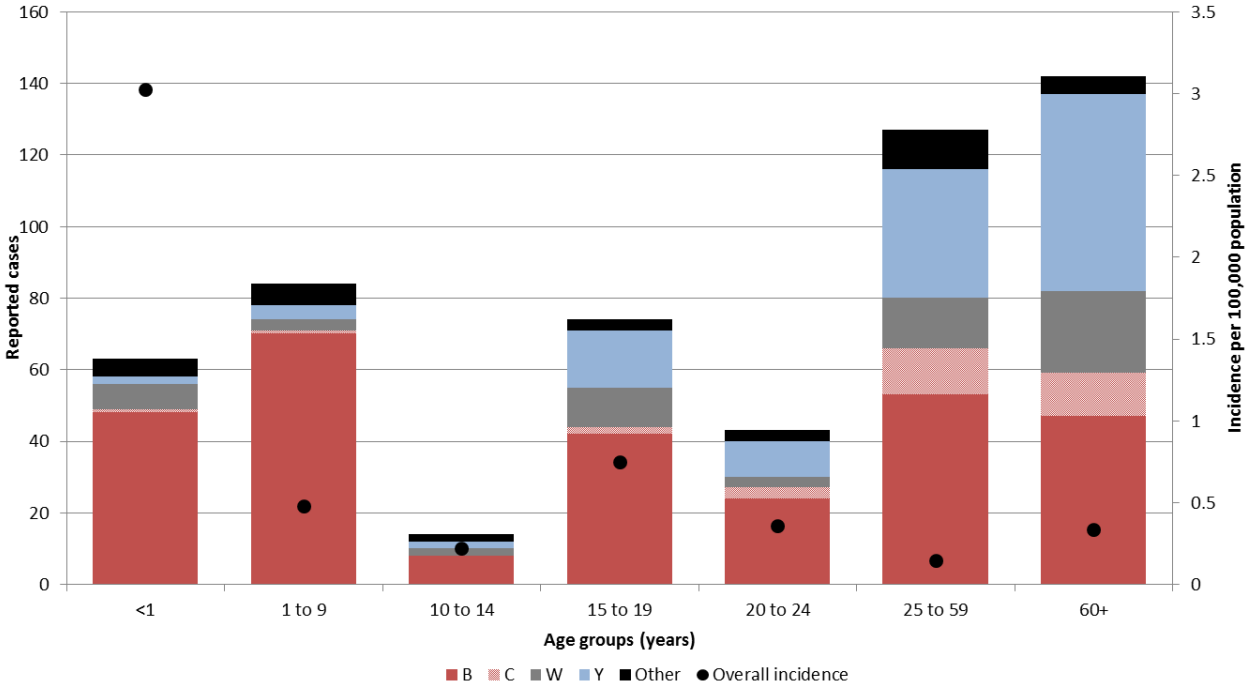


*Other includes serogroup A, 29E, X, Z, non-groupable and unknown

III.2 Disease distribution by age and serogroup

From 2013 to 2017, a total of 548 IMD cases were reported. Infants less than 1 year of age had the highest incidence rate at 3.0 cases per 100,000 population (Figure 2) and ranged from 0.1 to 0.7 per 100,000 population for the other age groups. The majority of cases were associated with serogroup B (53%) and accounted for the largest proportion of cases in all age groups except in adults 60 years and older. In infants and young children, serogroup B accounted for 80% of all IMD cases in those age groups. Overall, the proportion of serogroup B cases declined with decreasing age groups. Conversely, the proportion of serogroup Y cases increased with age with adults added 60 years and older reporting the largest proportion of serogroup Y cases.

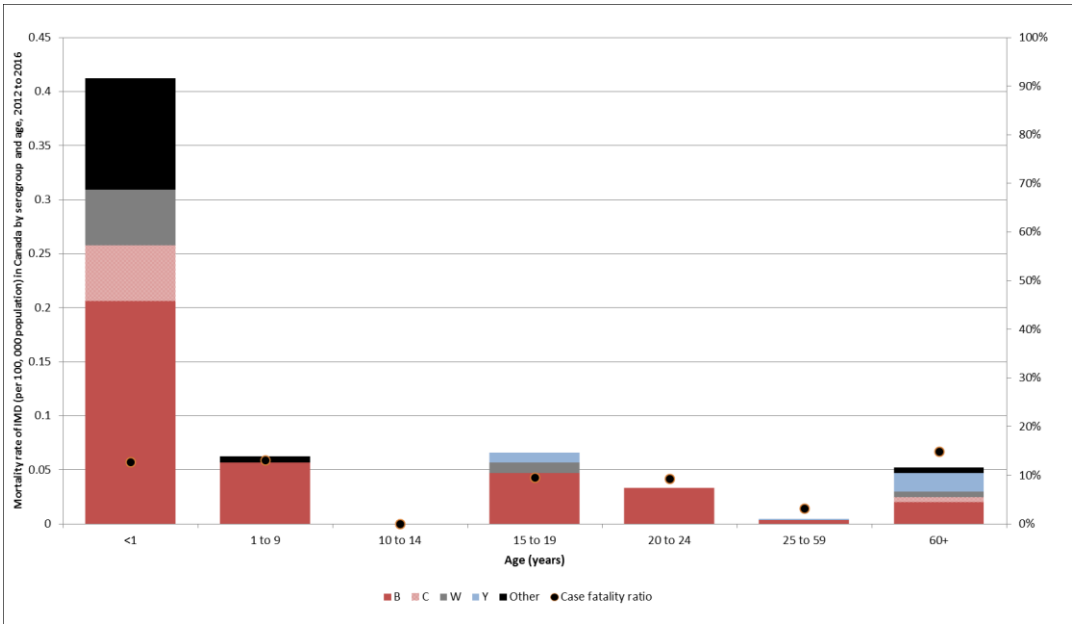
Figure 2: Invasive meningococcal disease cases in Canada by serogroup and age and overall incidence by age group, 2013–2017 (n=548)



III.3 Deaths associated with invasive meningococcal disease

From 2013 to 2017, a total of 55 deaths associated with IMD were reported resulting in a mortality rate of 0.03 per 100,000 population. Serogroup B accounted for the majority (62%) of deaths during this period (Figure 3). The mortality rate was highest in infants under 1 year of age (0.41 per 100,000) and ranged from 0 to 0.07 per 100,000 population in the other age groups. The overall case fatality ratio (all ages) for IMD cases was 10% and ranged from 0% to 15% by age group.

Figure 3: Mortality rate and case fatality ratio of Invasive meningococcal disease by age and serogroup, Canada, 2013–2017



IV. VACCINE

IV.1 Preparation(s) authorized for use in Canada (e.g. description, composition)

Differences in the chemical composition of the capsular polysaccharides of *Neisseria meningitidis* differentiate the meningococcal serogroups. The capsular polysaccharide was used as the basis for vaccines developed against meningococcal serogroups A, C, W and Y. However, this method is not feasible for producing a vaccine against MenB, because the capsular polysaccharide is comprised of repeating units of polysialic acids that are structurally similar to adhesion molecules found on human neuronal cells, thus resulting in poor immunogenicity and the theoretical risk of creating auto-antibodies[4, 5]. Therefore, development of a vaccine against MenB focused on identifying surface-exposed proteins prevalent in the majority of circulating strains with limited immunologic variability across diverse MenB isolates and the ability to elicit an appropriate immune response to MenB strains homologous and heterologous to the vaccine strains.

The 4CMenB vaccine[1], the first serogroup-B specific vaccine authorized for use in Canada in December 2013, is a multicomponent vaccine consisting of four antigens: a detoxified outer membrane vesicle (consisting primarily of major porin protein, PorA, P1.4), neisserial heparin binding antigen (NHBA), factor-H binding protein (fHBP) and Neisseria adhesin A (NadA)[1]. In contrast, the MenB-fHBP vaccine[6] is a vaccine consisting of two purified *N. meningitidis* serogroup B recombinant lipoprotein 2086 (rLP2086) antigens (MenB-fHBP), one from each of the two immunologically distinct fHBP subfamilies (A and B). The fHBP is used by *N. meningiditis* to evade complement-mediated bactericidal activity and is expressed by a large majority (>95–97%) of serogroup B isolates[4, 6]. There is high sequence identity (83–99%) between variants within each fHBP subfamily, but only 60–75% sequence identity between

subfamilies. These characteristics suggest a vaccine based upon fHBP would require fHBP antigens from each subfamily to provide broad protection[4].

The MenB-fHBP vaccine was authorized for use in Canada in October 2017 for the prevention of IMD caused by *N. meningitidis* serogroup B in individuals 10–25 years of age[6]. The vaccine is supplied in a single-dose, prefilled syringe with each dose (0.5 mL) of vaccine containing 60 µg of purified *N. meningitidis* serogroup B recombinant rLP2086 antigen from subfamily A (fHBP variant A05) and 60 µg of rLP2086 antigen from subfamily B (fHBP variant B01), as well as aluminum phosphate, histidine, polysorbate 80, sodium chloride and water for injection[6].

IV.2 Efficacy and Effectiveness

A systematic review of the literature did not identify any published studies on the efficacy or effectiveness of MenB-fHBP. It should be noted that in non-epidemic settings, pre-licensure efficacy studies for meningococcal vaccines are not considered feasible due the low annual incidence of meningococcal disease. Demonstration of vaccine efficacy for the purposes of licensure was based on immunogenicity using vaccine-elicited bactericidal activity as a surrogate marker of efficacy, as measured *in vitro* by the serum bactericidal assay using human complement.

IV.3 Immunogenicity

A systematic review of the literature identified 10 randomized controlled trials (RCTs) and 6 observational studies that examined the immunogenicity of MenB-fHBP (Appendix A). Study participants were primarily adolescents (11–18 years) and young adults (18–25 years of age) who were either healthy or did not have any significant underlying diseases that might be expected to impair immune response. Although the number of individuals over 25 years of age participating in studies involving adult age groups (e.g., adults 18–40 years) was not specifically reported in many of these studies, the number and the reported mean age of adults participating in these published studies suggests there were few individuals over 25 years of age (n<150) and no participants greater than 65 years of age. All studies excluded pregnant women. The identified studies were conducted in the United States of America (USA), Europe, Australia and Canada. Information on the studies' characteristics, key results and assessments of study design and quality are contained in the summary tables (Appendix A).

IV.3.1 Measures of immunogenicity

In the absence of efficacy studies, the effectiveness of MenB vaccines is inferred from immunologic measures of protection derived from immunogenicity studies. For MenB-fHBP, these immunogenicity tests are based on the functional ability of serum antibodies to kill meningococcal test strains containing various subfamily A and B fHBP variants in a complement-mediated process. The functional ability of these bactericidal antibodies is measured using a human serum bactericidal assay (hSBA), where the hSBA titre for a specific MenB test strain is calculated as the highest serum dilution that kills >50% of the target bacteria, with results reported as step titres (e.g., 1:4, 1:8, 1:16)[7]. In studies of MenB-fHBP, immunogenicity was assessed primarily by two clinical endpoints: (1) the proportion of study participants who achieved a four-fold or greater increase in hSBA titre (seroconversion), which is the accepted correlate of protection against IMD based on studies of meningococcal serogroup C disease, for each of the primary MenB test strains and (2) the proportion of study participants who achieved an hSBA titre greater than the lower limit of assay quantitation

(seroprotection) for all of the primary MenB test strains (composite response). Some studies also assessed the proportion of MenB-fHBP recipients who achieved seroprotection against various supplementary MenB test strains. In the majority of MenB-fHBP immunogenicity studies, seroprotection was defined as an hSBA titre of ≥1:8 (and ≥1:16 for fHBP variant A22). Another aspect of immunogenicity assessed in a number of studies was whether there was any evidence of immunogenic interference when MenB-fHBP was concomitantly administered with other vaccines routinely administered to adolescents. In such studies, the hSBA geometric mean titre (GMT) ratio had to meet a non-inferiority criterion (e.g., the lower limit of the two-sided 95% confidence interval for the GMT ratio was >0.67) for each of the antigens of interest as evidence of a lack of immunologic interference.

IV.3.2 MenB test strain selection

Serogroup C meningococcal strains all express an identical serogroup-specific capsular polysaccharide. Therefore, hSBA titres generated against a representative meningococcal C test strain can be inferred to apply to all meningococcal strains of the serogroup[7]. In contrast, although >97% of MenB strains express fHBP on their surface[4], the variant of fHBP present and its level of expression can vary. Therefore, assessment of the breadth of protection afforded by MenB-fHBP vaccines requires demonstration of immunogenicity against a representative sample of disease causing MenB test strain isolates[7].

To achieve this goal, the manufacturer of the MenB-fHBP vaccine worked in collaboration with reference laboratories in the USA and Europe (Czech Republic, France, Germany, Norway, Spain, United Kingdom) to systematically assemble a collection of invasive meningococcal serogroup B isolates from 2000–2006 representative of the diversity of MenB invasive disease strains circulating in the USA and Europe at that time (the Extended MenB SBA strain pool). The diversity of fHBP variants in the Extended MenB SBA strain pool was also found to be comparable to more contemporary strains in the USA collected between 2006 and 2012[8]. Based on this exploratory work four primary MenB test strains possessing fHBP variants heterologous to the MenB-fHBP vaccine (A22, A56, B24, B44) and a variety of secondary test strains (e.g., A06, A07, B03, B09) were selected for subsequent immunogenicity studies. A comparative analysis of MenB isolates from the Extended MenB SBA strain pool and disease causing strains collected by the Canadian Immunization Monitoring Program Active (IMPACT) from 2006–2012 found similar fHBP variants to be prevalent in the two collections; however, the most prevalent fHBP variant in the IMPACT collection (B44) was the 5th most prevalent fHBP variant in the Extended MenB SBA strain pool and the most prevalent fHBP variant (B24) in the USA strain pool was the 9th most prevalent variant found in the Canadian collection[8]. This difference in the relative prevalences of fHBP variants in Canada compared to the USA and Europe should be kept in mind when assessing the applicability to the Canadian context of MenB-fHBP vaccine immunogenicity results conducted in the US and Europe. The immunogenicity of the MenB-fHBP vaccine against the meningococcal serogroup B ST269 clone which circulated in Quebec and led to an increased incidence of serogroup B IMD cases in one region of the province is also not known.

IV.3.3 Adolescents

The immunogenicity of a three-dose regimen (0, 2, 6 months) of MenB-fHBP in adolescents (10–18 years) was demonstrated in a Phase 3 study in which 78.8–90.2% of adolescents achieved seroconversion to each of the four primary MenB test strain fHBP antigen variants (A22, A56, B24, B44) and 82.7% (95% confidence interval, CI: 80.4–84.7%) achieved a composite response to all four MenB test strains[9]. The proportion of three-dose recipients demonstrating seroprotection against 10 supplementary MenB test strain fHBP variants (A06, A07, A12, A15, A19, A29, B03, B09, B15, B16) ranged from 75.3–98.7%. After two doses of the vaccine, 56.0–85.3% of adolescents achieved seroconversion to each of the four primary MenB test strain fHBP antigen variants (A22, A56, B24, B44) and 53.7% (95% confidence interval, CI: 50.9–56.5%) achieved a composite response to all four MenB test strains. The corresponding proportions of participants achieving seroprotection to the 10 secondary MenB test strains ranged from 58.8–99.0%. The hSBA GMT against the four primary (two doses: 14.3–130.0 vs. three doses: 23.7–218.4) and 10 secondary (two doses: 13.1–68.1 vs. three doses: 21.4–93.6) MenB test strains also varied by the number of doses of MenB-fHBP received. In a Phase 2 RCT, a sub-analysis of sera obtained from a small sample (n=15) of healthy adolescents (11–18 years of age) immunized with MenB-fHBP (120 µg; 0, 2, 6 month dosing regimen) found seroconversion and seroprotection against MenB strains [A22, B03, B24(x 2), B44, B228] isolated from each of six outbreaks in France between 2011 and 2015 increased with increasing number of vaccine doses received[10]. In this study, the proportion of participants achieving seroconversion for each MenB outbreak strain after two doses of MenB-fHBP increased further with receipt of a third dose of the vaccine: 40% vs. 73% (A22), 33–47% vs. 60–73% (B24), 80% vs. 100% (B44), 67% vs. 100% (B03) and 53% vs. 100% (B228). Similarly, compared with receipt of two doses of MenB-fHBP, the proportion of adolescents achieving seroprotection increased with receipt of a third dose of the vaccine: 47% vs. 73% (A22), 40–60% vs. 73–87% (B24), 93% vs. 100% (B44); 67% vs. 100% (B03), and 60% vs. 100% (B228). A Phase 2 RCT assessed the immunogenicity of three formulations (60 µg, 120 µg, 200 µg) of MenB-fHBP, in a three-dose series (0, 2, 6 months), against a panel of eight MenB test strains (A04, B03, A56, B44, A22, B24, A05, B02)[11]. The study found that the immune response did not increase in proportion to an increase in vaccine dose: 67.9–100.0% of participants (n=349) who received three doses and 35–100% of participants who received two doses of MenB-fHBP (either 120 µg or 200 µg) demonstrated seroprotection against MenB test strains containing fHBP antigens A04, A05, A56, B02, B03, B44. Seroconversion against fHPB variants A05 and B02 (homologous or near-homologous to vaccine strains) was assessed in a subset of participants (n=40) who received three doses of MenB-fHBP (120 µg). The seroconversion rates were 88.0% (95% CI: 68.8–97.5%) (A22) and 83.9% (95% CI: 66.3–94.5%) (B24).

In a study which conducted a secondary analysis of data from two previously published studies, serum samples from adolescents (11–18 years of age) immunized with MenB-fHBP (120 µg) in a three-dose regimen (0, 2, 6 months) were assessed for seroprotection against fHBP variants determined to be prevalent among MenB carriage isolates (A04, A05, A22, A56, B02, B03, B09, B16, B24, B44) in US high school students and college students in the United Kingdom[12]. The study found that 75–100% of immunized adolescents had seroprotective hSBA titres (≥1:4) against each of the fHBP variants common in IMD isolates. In another study, sera from adolescents (11–18 years of age) who were immunized with MenB-fHBP (120 µg) in a three-dose regimen in three other clinical studies were selected in an unbiased fashion[13]. The study assessed the proportion of participants with seroprotective hSBA titres (≥1:8) against 14 prevalent fHBP variants (A04, A05, A07, A12, A19, A22, A56, B02, B03, B09, B16, B24, B44, B153), including strains from two MenB outbreaks at US colleges in 2013 (B24, B153), in the US and Europe. The proportion of adolescents exhibiting seroprotective hSBA titres against the

four primary MenB test strains (A22, A56, B24, B44) differed by fHBP variant after two or three doses of MenB-fHBP, respectively: A22 (88.7% vs. 88–95%), A56 (94.9% vs. 87.5%), B24 (55.6–77.8% vs. 88.9–100%), B44 (68.7% vs. 88.7%). Seroprotection against the remaining fHBP variants ranged from 33.3–100% after two doses of MenB-fHBP and 61.7–100% after three doses, depending on fHPB variant.

An early Phase 1 RCT assessed the immunogenicity of three doses of MenB-fHBP (20 µg, 60 µg, or 200 µg) in a three-dose series (0, 1, 6 months) in children (8–14 years of age) against five MenB test strains (A05, A22, B02, B09, B24). The study results suggested that compared to two doses of the vaccine, three doses of MenB-fHBP increased the proportion of children achieving seroconversion (A05,B02: 68.8–95.3% vs. ~20–82% and A22,B09,B24: 39.5–66.7% vs. ~5–50%) and seroprotection (A05,B02: 68.8–97.7% vs. ~25–85%; A22,B09,B24: <60% vs. <30%), but only for some fHBP antigens and only at the higher vaccine doses[14]. The study also found IgG-specific GMTs (not hSBA GMTs) to be higher (>1000) for each MenB test strain after three doses of the vaccine than after two doses (approximately 500–1000). However, it is difficult to compare these results to other studies, as the doses examined were different than the dose in the licensed vaccine.

The immunogenicity of two-dose (0, 6 months; 0, 2 months; and 0, 4 months) versus three-dose (0, 1, 6 months and 0, 2, 6 months) series of MenB-fHBP (120 µg) was assessed in healthy adolescents (11–18 years of age) in a Phase 2 RCT[15]. The study found the majority of participants achieved seroprotection (≥1:8) against the four MenB test strains (A22, A56, B24, B44) after receipt of the two-dose (A22: >90%, A56: >98%, B24: >69%, B44: >70%) or the three-dose vaccine series (A22: 91.7–95.0%, A56: 98.9–99.4%, B24: >69%, B44: 86.1–88.5%). The hSBA GMTs increased with each dose of MenB-fHBP and were highest among participants who received three compared to two doses of vaccine (A22: 55.1–56.3 vs. 37.1–48.4; A56: 152.9–155.6 vs. 104.9–125.6; B24: 25.6–29.1 vs. 14.7–20.6; B44: 35.0–40.3 vs. 17.8–22.5). In addition, in two-dose regimens, GMTs were trended numerically higher with longer intervals between the first and second dose (i.e., six months between doses as opposed to two or four months).

IV.3.4 Adults

The immunogenicity of a three-dose regimen (0, 2, 6 months) of MenB-fHBP in young adults (18–25 years) was demonstrated in a Phase 3 study in which 78.9–89.7% of adults achieved seroconversion to each of the four primary MenB test strain fHBP antigen variants (A22, A56, B24, B44) and 84.5% (95% CI: 82.7–86.1%) achieved a composite response to all four primary MenB test strains[9]. The same study found the proportion of participants demonstrating seroprotection against 10 supplementary MenB test strain fHBP variants (A06, A07, A12, A15, A19, A29, B03, B09, B15, B16) ranged from 71.5–99.3% in young adults after three doses of vaccine. In contrast, after two doses of the vaccine 54.6–85.6% of adults achieved seroconversion to each of the four primary MenB test strain fHBP antigen variants and 63.3% (95% CI: 61.1–65.5%) achieved a composite response. The proportion of participants demonstrating seroprotection against the 10 supplementary MenB test strains after two doses of rLP2086 was 51.5–98.0%. The hSBA GMT against the four primary MenB test strains for two doses versus three doses of rLP2086, respectively were 21.7–113.3 and 46.3–175.3. The corresponding hSBA GMT against the 10 secondary MenB test strains were 11.8–87.4 and 20.7–97.0[9]. In an open label, Phase 2 study of MenB-fHBP (120 µg; 0, 1, 6 month dose regimen) in healthy adults (18–40 years of age), the proportion of participants achieving seroconversion against MenB test strains (A05, B02, A22, B44, B24) increased from 58.3–

65.5% after two doses of MenB-fHBP to 70.0–94.7% after three doses of the vaccine, but with overlapping 95% confidence intervals[16]. The point estimates of the proportion of participants achieving seroprotection after three doses of MenB-fHBP were relatively high (A05, B02, A22, B44: >94%; B24: 81%) and greater than after two doses of the vaccine (A05, B02, A22, B44: 70–85%; B24: 75%), but again the confidence intervals around the estimates overlapped. The level of hSBA GMTs after three doses of MenB-fHBP ranged from 37.8–109.6 across all MenB strains tested. In contrast, levels after two doses could not be calculated for some fHBP antigens (A05, B02, B24), but were ranged from approximately 50–60 (B44) to 100 (A22) for the other antigens. In another study, sera from adults (18–25 years of age) who were immunized with MenB-fHBP (120 µg) in a three-dose regimen in three other clinical studies were selected in an unbiased fashion[13]. The study assessed the proportion of participants with seroprotective hSBA titres (≥1:8) against 14 prevalent fHBP variants (A04, A05, A07, A12, A19, A22, A56, B02, B03, B09, B16, B24, B44, B153), including strains from two MenB outbreaks at US colleges in 2013 (B24, B153), in the US and Europe. The proportion of adults exhibiting seroprotective hSBA titres against the four primary MenB test strains (A22, A56, B24, B44) differed by fHBP variant after two or three doses of MenB-fHBP, respectively: A22 (60–75% vs. 88.2–94.7%), A56 (87.5% vs. 100%), B24 (68.0% vs. 81.0%), B44 (63.6–78.3% vs. 83.3–94.7%). Seroprotection against the remaining fHBP variants ranged from 31.8–95.8% after two doses of MenB-fHBP and 55.6–100% after three doses, depending on fHPB variant. In a study which conducted a secondary analysis of data from two previously published studies, serum samples from young adults (18–40 years of age) immunized with MenB-fHBP (120 µg) in a three-dose regimen (0, 1, 6 months) were assessed for seroprotection against fHBP variants determined to be prevalent among MenB carriage isolates (A04, A05, A22, A56, B02, B03, B09, B16, B24, B44) in US high school students and college students in the United Kingdom[12]. The study found that 75–100% of immunized young adults had seroprotective hSBA titres (≥1:4) against each of the fHBP variants common in IMD isolates.

An early Phase 1 RCT in healthy adults (18–25 years of age) assessed seroconversion, seroprotection and GMTs elicited by three different doses of MenB-fHBP (20 µg, 60 µg, or 200 µg) in a three-dose schedule (0, 1 and 6 months) against 6 MenB test strains (A05, A17, A22, B01/B02, B09, B24)[11, 17]. There was a suggestion of generally greater immune responses (i.e., proportion of participants achieving seroconversion, seroprotection, GMT) against the 6 MenB test strains with higher vaccine dose formulations and with increasing number of doses received (i.e., after dose 3 versus dose 2), but responses varied by fHBP variant and there was considerable overlap in the confidence intervals around the proportions. It is also difficult to interpret these results, as the study did not use the dosage of MenB-fHBP (120 µg) subsequently authorized for use. A small Phase 1 open-label RCT assessed the immunogenicity of MenB-fHBP given in one of three dosages (60 µg, 120 µg, 200 µg) to healthy adults (18–40 years) (n=8–11 participants/group)[18]. Immunogenicity was assessed as IgG-specific GMTs (not hSBA GMTs) at one month after doses 2 and 3 against vaccine homologous fHBP antigens (A05, B02). There was a trend towards an increase in IgG GMTs between dose 2 and dose 3 of the vaccine, but the differences were not statistically significant: >1000 for both dose 2 and 3 (A05) and ~1000 for dose 2 versus >1000 for dose 3 (B02). However, it is difficult to compare these results to other studies, as the study measured IgG-specific GMTs and not hSBA GMTs.

There have also been two small studies investigating the immunogenicity of MenB-fHBP in microbiologists/laboratory workers[19, 20]. The first involved adults (range: 24–66 years of age; median: 40 years) immunized with MenB-fHBP (120 µg) in a three-dose schedule (0, 2, 6 months)[19]. Immunogenicity was assessed after two (n=17) and/or three (n=15) doses of the vaccine against 15 MenB test strains comprising eight different fHBP variants [A19(x3), A23,

A25, A76, B01(x3), *m*B01, B15(x3), B276, B510] obtained from recent university outbreaks in the US (n=6), jurisdictions in Canada and Norway with hyperendemic disease (n=3), US states with endemic disease (n=5) and a B01 mutant with low fHBP expression (*m*B01). After two doses of MenB-fHBP, ≥70% of subjects achieved seroconversion against 3/6 subfamily A fHBP variants (A19[x1], A23, A76) and 2/9 subfamily B fHBP variants [B01(x1), B510]. After three doses of the vaccine, ≥70% of subjects had seroconversion to all six subfamily A fHBP variants and to 7/9 subfamily B fHBP variants [B01(x3), B15(x2), B276, B510]. There was no obvious relationship between seroconversion to a fHBP antigen variant and its sequence relatedness to either vaccine variant (A05, B01). A high proportion of participants (94–100%) achieved seroprotective titres (≥1:4) against all 15 MenB test strains after three doses of MenB-fHBP. After three doses of MenB-fHBP, hSBA GMTs ranged from 33 to <151 for the six subfamily A fHBP variants and 22–76 against the nine subfamily B fHBP variants. The corresponding ranges after two doses of vaccine were approximately 15–70 and 8–25, respectively. The second study is a single-arm, open label Phase 2 study of adult (range: 24–62 years; mean: 44 years) laboratory workers (n=6) who worked directly with pathogenic *N. meningitidis*[(20)]. Immunogenicity was assessed against four MenB test strains expressing vaccine heterologous fHBP variants (A22, A56, B24, B44) after two and three doses of MenB-fHBP (120 µg) given in a three-dose regimen (0, 2, 6 months). The proportion of participants achieving seroprotective hSBA titres (1:16 for A22, 1:8 for A56, B24, B44) one month after two and three doses of the vaccine, respectively were: A22 (60%, 100%), A56 (100%, 100%), B24 (100%, 100%) and B44 (50%, 50%). The proportion of participants achieving seroconversion after dose 3 varied by fHBP variant: A22 (83%, 5/6), A56 (100%, 5/5), B24 (67%, 4/6) and B44 (50%, 3/6). The proportion of participants achieving seroprotection against all four fHBP variants (composite response) was the same after two or three doses of the vaccine (60%, 3/5).

IV.3.5 Persistence of immune response

A Phase 2 RCT assessed the persistence of hSBA antibody titres against four MenB test strains (A22, A56, B24 and B44) at 6, 12, 24 and 48 months after adolescents (11–18 years) received the third dose of MenB-fHBP (120 µg) in a three-dose regimen (0, 2, 6 months)[(21)]. At one month after dose 3, 93–100% of participants, depending on the fHBP variant, had seroprotective (1:8 for A56, B24, B44; 1:16 for A22) levels of antibodies compared to 0–35% of controls. The proportions of participants demonstrating seroprotection against fHBP variants A22, A56 and B24 declined from month 6 (57–89%) to month 12 (54–69%) after dose three of the vaccine and then remained fairly stable from month 24 (53–54%) to month 48 (51–59%). The corresponding proportions of participants demonstrating seroprotection for fHBP variant B44 was 37%, 29%, 22% and 20%, respectively, at 6, 12, 24 and 48 months after the third dose of MenB-fHBP. Overall, after three doses of the vaccine 19% (8/42) of participants achieved a composite seroprotective response against all four MenB test strains at 48 months. The hSBA GMT for all MenB test strains remained stable from 6 to 48 months after the third dose of rLP2086 (A22: 19.3–21.6, A56: 16.2–49.8; B24: 11.3–12.6; B44: 6.6–8.5). The other study identified that assessed the persistence of seroprotection after immunization with MenB-fHBP was in a small number of adult (range: 24–66 years of age; median: 40 years) microbiologists and health care workers immunized with MenB-fHBP (120 µg) in a three-dose schedule (0, 2, 6 months)[(19)]. In this study, 94–100% of participants (n=15) achieved seroprotective titres (≥1:4) against all 15 MenB test strains at one month after the third dose of MenB-fHBP. In contrast, at 9–11 months after dose 3, 27–80% of participants (n=12) demonstrated seroprotection against a subset of subfamily A fHBP variants [A19(x2), A25] and 33–85% demonstrated seroprotection against a subset of subfamily B fHBP variants [B01(x2), *m*B01, B15(x3), B276]. Of the 10 MenB test strains, for only 6 of these strains did ≥50% of subjects maintain seroprotective hSBA titres [A19(x2), B01(x1), B15(x2), B276].

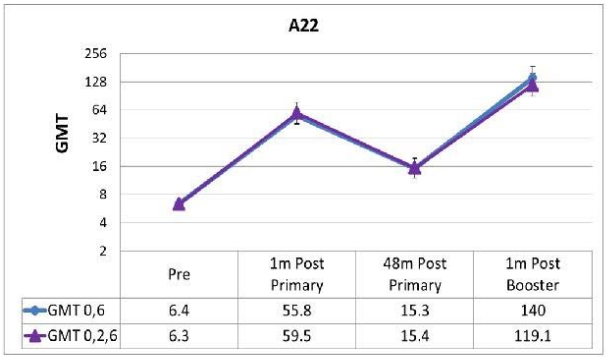
The persistence in seroprotective (≥1:4) hSBA antibody titres against four MenB test strains (A22, A56, B24, B44) at 12, 18, 24, 36 and 48 months after the last dose of vaccine was compared in adolescents (10–18 years of age) immunized with MenB-fHBP (120 µg) in either a two-dose (0, 6 months) or a three-dose (0, 2, 6 months) regimen[22, 23]. The study found no significant difference in the proportion of participants with seroprotective hSBA titres against each of the four MenB test strains one month after the last dose in either a two-dose or three-dose MenB-fHBP regimen (Table 1). The composite response against all four MenB test strains in the three- and two-dose recipients was 81.7% (95% CI: 77.3–85.7%) and 73.5% (95% CI: 68.5–78.1%), respectively[23]. In both the two-dose and three-dose regimens, the proportions of participants demonstrating seroprotection hSBA titres for each fHBP variant declined from one month to 12 months after the last vaccine dose, but remained stable between 12 and 48 months (Table 1).

Table 1: Persistence of hSBA responses (≥1:4) against MenB test strains (A22, A56, B24, B44) at 1, 12, 18, 24, 36 and 48 months in adolescents (10–18 years) receiving either two doses (0, 6 months) or three doses (0, 2, 6 months) of MenB-fHBP

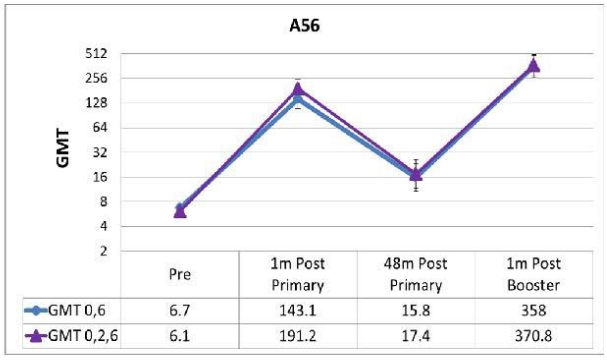
	Baseline	1 month	12 months	18 months	24 months	36 months	48 months
A22							
2-dose	26.4%	94.0%	38.9%	49.5%	46.8%	47.2%	39.6%
3-dose	23.9%	92.0%	48.6%	50.0%	43.0%	46.1%	45.0%
A56							
2-dose	25.1%	98.9%	68.9%	63.7%	61.5%	61.6%	61.6%
3-dose	22.1%	99.1%	80.7%	80.2%	69.6%	73.9%	60.6%
B24							
2-dose	14.4%	83.0%	38.8%	32.4%	31.8%	36.4%	31.4%
3-dose	15.4%	86.5%	49.1%	50.5%	44.9%	46.0%	41.8%
B44							
2-dose	7.8%	78.9%	19.1%	23%	19.4%	23.9%	24.5%
3-dose	7.8%	89.2%	26.1%	25.5%	24.8%	25.2%	24.0%

The hSBA GMT responses to the primary MenB test strains measured at baseline, one month and 48 months after the primary series were not significantly different between the two- and three-dose MenB-fHBP regimens[22, 23]. A booster dose given at 48 months elicited a greater hSBA GMT response in both the two- and three-dose regimens than in either regimen after the primary series; however, again there was no significant difference in the GMT response to the booster dose between the two-dose and three-dose regimens (Figure 4).

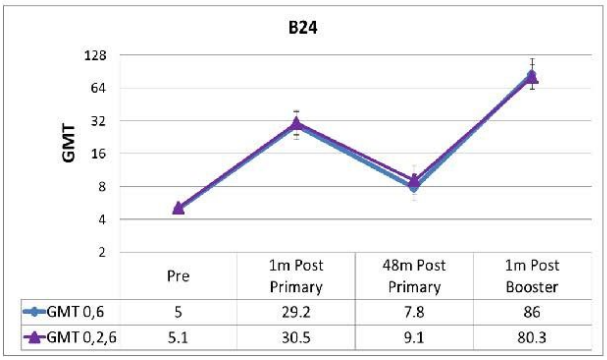
Figure 4: hSBA GMT responses to a booster dose 4 years following two (0, 6 month) or three (0, 2, 6 month) primary doses of MenB-fHBP in adolescents (10–18 years of age)



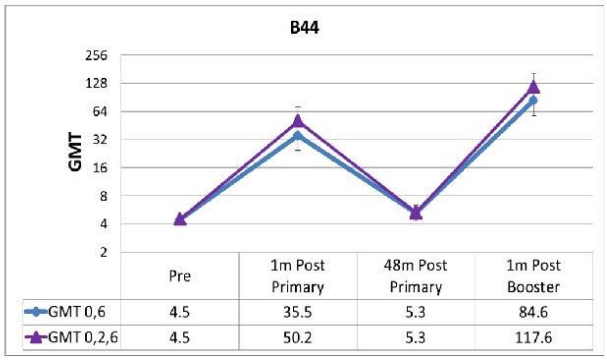
	Pre	1m Post Primary	48m Post Primary	1m Post Booster
GMT 0,6	6.4	55.8	15.3	140
GMT 0,2,6	6.3	59.5	15.4	119.1



	Pre	1m Post Primary	48m Post Primary	1m Post Booster
GMT 0,6	6.7	143.1	15.8	358
GMT 0,2,6	6.1	191.2	17.4	370.8



	Pre	1m Post Primary	48m Post Primary	1m Post Booster
GMT 0,6	5	29.2	7.8	86
GMT 0,2,6	5.1	30.5	9.1	80.3



	Pre	1m Post Primary	48m Post Primary	1m Post Booster
GMT 0,6	4.5	35.5	5.3	84.6
GMT 0,2,6	4.5	50.2	5.3	117.6

IV.3.7 Conclusions

There are currently no published studies on the efficacy or effectiveness of MenB-fHBP in preventing IMD or carriage of *N. meningitidis*. As a consequence, studies have assessed measures of immunogenicity (e.g., seroconversion, seroprotection, GMT) as proxies of the vaccine's effectiveness. However, the definition of seroprotection for a given fHBP variant can differ between studies, which may make it challenging to compare findings across studies. To demonstrate the breadth of protection afforded by the vaccine against invasive disease caused by meningococcal serogroup B strains, studies have assessed the immunogenicity of the vaccine against vaccine-heterologous fHBP variants commonly circulating in Europe and the US (as well as against strains having caused outbreaks in some jurisdictions). However, some caution must be taken in extrapolating these findings to the Canadian context; in the limited comparisons performed to date of the common fHBP variants present in Europe and the US compared to Canada, it appears the fHBP variant B44 is more common in Canada. The studies identified in the current NACI literature review have found the immune response against fHBP B44 elicited by MenB-fHBP appears in general lower than for the other fHBP variants present in the primary MenB test strains assessed in the studies.

In the studies identified in the present literature review, MenB-fHBP elicited protective levels of immunogenicity in a substantial proportion of both healthy adolescents and healthy young adults (or adults with stable chronic illnesses not likely to affect immune response). However, it should be noted that the identified studies included few adults greater than 25 years of age and only one adult greater than 65 years of age. In addition, the studies did not include pregnant or

lactating women or persons with underlying health conditions that would put them at high-risk for IMD.

In general, the proportion of study participants demonstrating seroprotection, seroconversion and a composite response against the fHBP variants present in the MenB test strains was greater with three compared to two doses of the vaccine. However, the persistence of the immune response was not significantly different between two- and three-dose recipients up to 48 months after receipt of the last vaccine dose in the respective two- and three-dose vaccine series. In addition, both two- and three-dose vaccine recipients had a comparable immune response measured one month after a booster dose given at 48 months post last-dose in the respective primary vaccination series.

IV.4 Vaccine Administration and Schedule

The vaccine is supplied in a single-dose, prefilled syringe. Doses of MenB-fHBP should be administered as intramuscular injections only, preferably in the deltoid muscle. Please see the product monograph for details.

The vaccine is authorized for use in two immunization schedules. The standard schedule for routine immunization is two doses (0.5 mL per dose) administered at 0 and 6 months. For persons at increased risk of IMD, there is a three-dose schedule (0.5 mL per dose) administered at 0 months followed by a second dose at least one month later, followed by a third dose at least 4 months after the second dose[6].

The need for a booster dose following the primary immunization series has not been established.

IV.5 Serological Testing

Serological testing is not recommended before or after receiving meningococcal vaccine.

IV.6 Storage Requirements

The MenB-fHBP vaccine should be refrigerated at 2 °C to 8 °C. The pre-filled syringes should be stored horizontally (lying flat on the shelf) in the refrigerator to minimize redispersion time.

The vaccine is stable at temperatures up to 25 °C for four days. The vaccine should be discarded if it has been frozen[6].

IV.7 Simultaneous Administration with Other Vaccines

There were three studies identified in the NACI literature review that examined the effect on immunogenicity of concomitant administration of MenB-fHBP with other vaccines[24-26].

The first study was a Phase 2 RCT that compared the immune responses induced by MenB-fHBP (120 µg; 0, 2, 6 months) co-administered with meningococcal conjugate ACWY vaccine (MCV4) and tetanus, diphtheria and acellular pertussis vaccine (Tdap) in healthy adolescents (10–12 years of age) (n=2648, ~880/group)[24]. The study found that for participants who

received MCV4 + Tdap + MenB-fHBP compared to those of received MCV4 + Tdap, the GMT ratios for all six Tdap and four MCV4 antigens (rGMT=0.88–1.02) met the criteria for a non-inferior immune response. In addition, 68.1–98.6% of subjects receiving MCV4 + Tdap + MenB-fHBP and 72.7–98.3% of subjects who received MCV4 + Tdap alone had seroconversion to all MCV4 + Tdap antigens (composite response). The immune response against the two MenB test strains (A22, B24) induced by MenB-fHBP + MCV4 + Tdap was also non-inferior to the immune response induced by MenB-fHBP alone (A22: rGMT=0.92, 95% CI: 0.84–1.02; B24: rGMT=0.90, 95% CI: 0.82–1.00). The study also found that the majority of participants who received MCV4 + Tdap + MenB-fHBP exhibited seroprotection (B24: ≥1:8; A22: ≥1:16) against the two MenB test strains after two doses (A22: 68.0%, B24: 64.2%) and three doses (A22: 89.4%; B24: 91.3%) of MenB-fHBP (similar responses were found for rLP2086 alone). A similar trend was observed in the proportion of participants who had seroconversion after two doses (A22: 64.0%; B24: 57.4%) and three doses (A22: 86.3%; B24: 86.7%) of MenB-fHBP in combination with MCV4 + Tdap (similar responses were found for MenB-fHBP alone).

Another Phase 2 RCT examined the immune response induced by co-administration of quadrivalent human papillomavirus vaccine (HPV4) and MenB-fHBP (120 µg; 0, 2, 6 months) in healthy adolescents (11–17 years of age)[25]. The study found the immune response induced by HPV4 + MenB-fHBP was non-inferior to immune response to HPV4 alone against the two MenB test strains after three doses of MenB-fHBP: A22 (rGMT=0.92, 95% CI: 0.85–1.00), B24 (rGMT=0.92, 95% CI: 0.84–1.01). The immune response induced by HPV4 + MenB-fHBP also met non-inferiority criteria for three of the four HPV4 antigens: HPV6 (rGMT=0.82, 95% CI: 0.72–0.94), HPV11 (rGMT=0.82, 95% CI: 0.74–0.91), HPV16 (rGMT=0.78, 95% CI: 0.68–0.88), but not for HPV18 (rGMT=0.71, 95% CI: 0.62–0.81). However, 99% of participants receiving HPV4 vaccine achieved seroconversion to all four HPV antigens. The study also compared recipients of MenB-fHBP + HPV4 or MenB-fHBP alone in the proportion of participants achieving hSBA seroprotective (A56, B24, B44: ≥1:8; A22: ≥1:16) and seroconversion titres to each of 4 MenB test strains (A22, A56, B44, B24) and a composite response to all 4 MenB test strains after two and three doses of MenB-fHBP. The rates of seroprotection achieved in the MenB-fHBP + HPV4 or MenB-fHBP alone recipients after two doses of MenB-fHBP were similar, but varied by fHBP antigen (A22: 83.0–85.8%; A56: 97.5–98.5%; B24: 70.6–74.2%; B44: 54.5–57.1%). The rates of seroprotection increased after three doses of MenB-fHBP for both groups of vaccine recipients, but again varied by fHBP antigen (A22: 94.0–96.3%; A56: 98.9–99.4%; B24: 90.5–92.6%; B44: 82.7–85.7%). A composite response to all 4 MenB test strains was obtained by 49.9% and 51.9% of MenB-fHBP + HPV4 and MenB-fHBP alone recipients, respectively after two doses of MenB-fHBP vaccine, increasing to 81.0% and 83.9%, respectively after 3 doses. The proportion of participants from both groups of vaccine recipients who achieved seroconversion increased from dose 2 to dose 3 of MenB-fHBP for each of the 4 fHBP antigens: A56 (92% vs. 95%) and A22, B24, B44 (46–74% vs. 77–86%).

And finally, a Phase 2 RCT examined the immune response in healthy adolescents (11–18 years of age) who received diphtheria, tetanus, acellular pertussis and inactivated polio vaccine (DTaP/IPV) + MenB-fHBP (120 µg; administered at 0, 2, 6 months) compared to DTaP/IPV alone[26]. The study found a non-inferior percentage difference (differences ranged from –1.3 to 0) in the proportion of participants who achieved pre-specified levels of antibodies to all nine DTap/IPV antigens one month after the DTap/IPV dose in both groups. In addition, GMTs of antibody levels to DTaP/IPV antigens measured one month after DTaP/IPV vaccination were similar between vaccine groups for each DTaP/IPV antigen. The study also found participants receiving DTaP/IPV + MenB-fHBP had substantial seroprotective hSBA responses (≥1:8 for A56, B24, B44 and ≥1:16 for A22) against four MenB test strains (A22, A56, B24, B44) one month after dose 2 and dose 3, respectively: A22: 81.8% and 95.6%; A56: 97.3% and 100%;

B24: 81.0% and 96.8%; B44: 55.5% and 81.5%. The GMTs for each of the four MenB test strains were substantially higher in the DTaP/IPV + MenB-fHBP group than in the DTaP/IPV alone group after dose 2 (A22: 35.5 vs. 11.2; A56: 91.1 vs. 8.3; B24: 15.9 vs. 4.8; B44: 14.6 vs. 4.7) and dose 3 (A22: 63.4 vs. 11.0; A56: 151.5 vs. 8.5; B24: 28.3 vs. 4.8; B44: 36.5 vs. 4.7).

In the three studies examining the concomitant administration of vaccines in adolescents, using vaccines that are part of routine adolescent immunization schedules (MCV4, Tdap, HPV4, DTaP/IPV) there was no significant impairment in immune response found for the antigens in the co-administered vaccines (with the exception of HPV18) or for the MenB test strain fHBP variants. The assessment of immunogenicity occurred after concomitant administration of the vaccines in these studies and, therefore, did not allow for an assessment of any potential impact on immunogenicity of prior administration of Men-fHBP and another vaccine, such as MCV4. Therefore, there is no evidence for safe intervals between these vaccines if they are not administered concomitantly.

However, based upon NACI expert opinion, MenB-fHBP may be administered concomitantly with other vaccines in individuals 10 years of age and older. If MenB-fHBP is to be administered concomitantly with another vaccine, a separate injection site and a different syringe must be used for each injection.

IV.8 Vaccine Safety

Of the 18 studies identified in the NACI literature review, 14 studies (11 RCTs and 3 observational) examined the safety of MenB-fHBP as a study objective (Appendix B). Study participants were primarily adolescents (11–18 years of age) and young adults (18–25 years of age) who were either healthy or did not have any significant underlying diseases that might be expected to impair immune response. There were few individuals over 25 years of age (n<150) and no participants greater than 65 years of age. All studies excluded pregnant women. The identified studies were conducted in the US, Europe, Australia and Canada. Information on the studies' characteristics, key safety findings and assessments of study design and quality are contained in a summary table (Appendix B).

IV.8.1 Solicited local and systemic reactions

Recipients of MenB-fHPB had higher rates of local and systemic events than placebo, but most of these reactions were of mild to moderate severity and of short duration (1–3 days). The rates of local and systemic reactions also did not increase with subsequent doses.

IV.8.1.1 Children and adolescents

There were eight RCTs identified in the NACI literature review that examined the safety and tolerability of MenB-fHBP vaccine in healthy adolescents[9, 11, 14, 15, 24-27]. The adolescents in the studies were primarily 11–18 years of age, but one study enrolled children as young as 10 years of age and another study included children as young as 8 years of age.

There were two early phase RCTs that each investigated the safety and tolerability of MenB-fHBP using different dose levels of MenB-fHBP and different three-dose immunization schedules: 20 µg, 60 µg, and 200 µg in a 0, 1, and 6 month schedule in children 8–14 years of age[14] and 60 µg, 120 µg, and 200 µg in a 0, 2 and 6–9 month schedule in adolescents 11–18 years of age[11]. The differences in vaccine dose levels used in these studies makes it difficult to

directly compare findings to those of other studies which used the final, authorized dose formulation (120 µg) of MenB-fHBP. However, both studies found the majority of local and systemic reactions to be mild to moderate in severity and of limited duration. For example, in the Richmond et al. study[11], the duration of injection site pain was 2–3 days, induration was 1–4.5 days and erythema was 2–4 days, with systemic reactions resolving in 1–3 days. The most common local reaction in both studies was injection site pain in MenB-fHBP and placebo/control recipients (44.5-72.7% and 14.4-15.1%, respectively)[11] and (88.3–100% and 61.9–70.0%, respectively)[14]. The Richmond et al. study reported headache, fatigue and myalgia as the most common systemic events in MenB-fHBP and placebo recipients (7.9–37.5% and 0.8–31.9%, respectively)[11]. Similar rates were also reported in the Nissen et al. study in which individuals that received either MenB-fHBP or Twinrix (control) reported headache (18.8–58.1% and 30.0–52.4%, respectively) and fatigue (6.3–51.1% and 25.0–33.3%) as the most common systemic reaction following immunization[14]. Compared to the placebo/control groups, MenB-fHBP recipients had a higher frequency of local reactions, but a comparable frequency of systemic reactions. Reports of local and systemic reactions were also more frequent at the higher dose level (200 µg) of the vaccine. For example, in the study by Richmond et al.[11], the frequency of fever was greater in MenB-fHBP recipients than in placebo recipients (60 vs. 5 episodes) and increased with higher MenB-fHBP dose level (i.e., 200 µg > 120 µg > 60 µg). However, no participant had a fever of >40 °C.

Later Phase 2 and 3 studies using the final, authorized dose level (120 µg) of MenB-fHBP found similar safety and tolerability results to the early dose escalation studies.

A recent Phase 3 study, which included healthy adolescents 10–18 years of age, found in both MenB-fHBP and control (HAV) recipients, injection site pain was the most common local reaction, reported in 92.6% of adolescents[9]. Injection site pain was most frequently reported after the first dose of vaccine, with the majority of reactions assessed as mild to moderate and resolving in a median of 1–3 days. However, six adolescents (all recipients of MenB-fHBP) withdrew from the study due to local reactions. In a Phase 2 study investigating various two- and three-dose schedules for MenB-fHBP in healthy adolescents 11–18 years of age, the most commonly reported local reaction in MenB-fHBP recipients was injection site pain followed by erythema and induration, with the majority of local reactions being mild to moderate in severity and of short duration (2.1–3.2 days)[15]. Similarly, another Phase 2 study comparing safety and tolerability of MenB-fHBP when concomitantly administered with DTap/IPV, found a greater proportion of participants who received MenB-fHBP reported local reactions after each dose of vaccine compared to saline recipients. Injection site pain was the most commonly reported local reaction[26]. The majority of local reactions were mild to moderate in severity and the duration of reactions were comparable between MenB-fHBP and saline recipients[26]. Compared to healthy children (10–12 years of age) receiving MCV4+Tdap, children who received MenB-fHBP vaccine more commonly experienced local reactions (20.1–46.5% vs. 86.5–95.6%), with injection site pain being the most commonly reported local reaction[24]. However, most local and systemic reactions were mild to moderate in severity and transient. Another Phase 2 study assessing the safety of MenB-fHBP concomitantly administered with HPV4 in healthy adolescents 11–17 years of age again found injection site pain to be the most commonly reported local reaction, with a frequency comparable in MenB-fHBP recipients to MenB-fHBP+HPV4 recipients[25]. Most of these local reactions were mild to moderate in severity, with the frequency not increasing with subsequent doses of vaccine[25].

In all of the later Phase 2 and 3 studies assessing the safety and tolerability of MenB-fHBP in adolescents, headache and fatigue were the most common systemic reactions in MenB-fHBP

recipients, with the majority being mild to moderate in severity[9, 15, 24-27]. The systemic reactions were also of short duration with observed ranges of 1–2 days[9], 1.0–3.8 days[25] to within 7 days[27]. There was also a tendency for systemic reactions to be more common after the first dose, with no increase in frequency with subsequent dose of vaccine[9, 24-26]. The frequency of systemic reactions in MenB-fHBP recipients compared to controls has varied by study. For example, systemic reaction were reported more commonly in children receiving MenB-fHBP compared to control (MCV4+Tdap) in healthy children 10–12 years of age (66.6–87.0% vs 44.4–74.8%)[24] and local and systemic reactions were more common in healthy adolescents and young adults (10–25 years of age) receiving MenB-fHBP than in controls (HAV recipients) (27.9% vs. 11.7%, respectively; $p<0.001$)[27]. In contrast, the frequency of systemic reactions was comparable in MenB-fHBP recipient compared to controls (MenB-fHBP+HPV4) in adolescents 11–17 years of age[25].

The incidence of fever in MenB-fHBP recipients was relatively rare and of short duration. For example, the Phase 2 study investigating various two- and three-dose schedules for MenB-fHBP found a frequency of fever in MenB-fHBP and saline recipients of 1.7–4.3% vs. 1.5–2.1%, respectively, with a median duration of one day[15]. The same study found <1% of participants in any group reporting a fever >39 °C. The Phase 2 study investigating the concomitant administration of DTap/IPV and MenB-fHBP found MenB-fHBP recipients had a slightly higher incidence of fever than DTap/IPV+saline recipients, with the mean duration of fever in MenB-fHBP and DTap/IPV+saline recipients ranged from 1.2–1.6 days and 1.1–3.3 days, respectively; no study participants had a fever ≥40 °C[26]. There were also no vaccine recipients who experienced a fever >40 °C in the Phase 2 RCT assessing the concomitant administration of MenB-fHBP with HPV4 in healthy adolescents[25]. In contrast, there was one child with a reported fever >40 °C for one day in the study by Muse et al.[24]. In addition, there was one adolescent in the control group (HAV recipient) who had a fever >40 °C after the second dose of HAV and one young adult who had a fever >40 °C after the third dose of MenB-fHBP in the Phase 3 RCT examining the safety and tolerability of MenB-fHBP in adolescents and young adults[9]. Both fevers resolved in one day.

IV.8.1.2 Adults

The findings of local and systemic reactions in adults are similar to the results found in studies of children and adolescents.

In two early studies investigating different dose levels of MenB-fHBP in young adults 18–25 years of age (MenB-fHBP at doses of 20 µg, 60 µg, 200 µg)[17] and adults 18–40 years of age (MenB-fHBP at doses of 60 µg, 120 µg, 200 µg)[18], injection site pain was the most commonly reported local reaction. The Richmond et al.[17] study found injection site pain reported in 80.0–100% of MenB-fHPB recipients and 48.5–60.6% of placebo recipients, the majority of which were mild to moderate in severity and of short duration (2–3 days). There was no significant difference in frequency or severity of injection site pain with the different vaccine dose levels (20 µg, 60 µg, 200 µg) or by the number of vaccine doses received. Similarly, in the Sheldon et al.[18] study, injection site pain was reported in 60.0–87.5% of MenB-fHBP recipients compared to 58.3% of control (Tdap) recipients, with the majority of reactions mild to moderate in severity and of short duration (1–3 days). The Sheldon et al.[18] study also found the frequency of systemic events was generally greater in MenB-fHBP recipients than in the control group (Tdap), with most reactions mild to moderate in severity and resolved in 1–3 days. The Richmond et al.[17] study reported systemic reactions being more common at the higher dose levels of MenB-fHPB (60 µg, 200 µg) compared to the 20 µg dose level, with muscle pain,

headache and fatigue being the most commonly reported. There were no vaccine recipients who experienced severe fever (>40 °C) in either study. The differences in vaccine dose levels used in these studies makes it difficult to directly compare findings to those of other studies which used the final, authorized dose formulation (120 µg) of MenB-fHBP.

In the Phase 3 RCT that examined the safety and tolerability of MenB-fHBP in adolescents and young adults, injection site pain was the most common local reaction reported in 89.6% of young adult recipients of MenB-fHBP, with the majority of reactions assessed as being mild to moderate and resolving in a median of 1–3 days[9]. Three adults (two MenB-fHBP recipients, one HAV recipient) withdrew from the study due to local reactions. In the Phase 2 open-label study by Marshall et al.[16], pain at injection site was also the most common local reaction (91.2–92.7% of participants) in adults 18–40 years of age, with no location reactions lasting >10 days in duration. And finally, in a small Phase 2 open-label trial in adult laboratory workers (n=13 participants), injection site pain was the most common local reaction experienced by 100% of study participants followed by erythema, which was experienced by 37.5–42.9% of participants[20].

As in adolescents, headache and fatigue were the most common systemic reactions reported in adults. In the Marshall et al.[16] study, the systemic reactions of headache was reported by 47.4–61.7% of MenB-fHBP recipients and fatigue was reported by 41.8–60.0%, with a median duration of 1–2 days. Headache and fatigue were reported in 59.1% and 64.6% of MenB-fHBP and control (HAV) recipients, with a median duration of 1–2 days in a Phase 3 RCT assessing the safety and tolerability of MenB-fHBP in adults 18–25 years of age[9]. The local and systemic reactions were generally mild to moderate in severity, and did not increase with additional doses[9, 16, 20]. Four adults (three MenB-fHBP recipients with fever, mild arthralgia, moderate myalgia; one HAV recipient with mild chills) withdrew from the Ostergaard et al.[9] study due to systemic events. There were also four MenB-fHBP recipients who experienced severe systemic reactions: (1) fatigue, headache, nausea and vomiting for 5 days after dose 3 (full recovery); (2) fatigue, headache, joint pain, muscle pain for 25 days and nausea for 23 days with diagnosis of upper respiratory tract infections (URTI); (3) headache for 25 days with diagnosis of sinusitis felt potentially to be vaccine related; and (4) headache, fatigue, chills, joint pain, muscle pain associated with URTI that started 7 days after dose 2 and lasted for 23 days.

No vaccine recipients in the Marshall et al.[16] study experienced a fever ≥39 °C, while one young adult in the Ostergaard et al.[9] study had a fever >40 °C after the third dose of MenB-fHBP, which resolved in one day.

An observational study conducted in adults 18–26 years of age during a serogroup B meningococcal disease outbreak in a US college attempted to retrospectively assess adverse events experienced by MenB-fHBP recipients via survey after each dose of vaccine[28]. The study found self-reported local and systemic reactions were mild to moderate in severity, transient (<7 days in duration), and generally lower in frequency than rates reported in the literature. However, the study was subject to non-response bias, as only persons presenting for successive doses had the opportunity to complete surveys. In addition, low proportions of vaccine recipients (29–40%) completed the voluntary surveys and the responses were subject to recall bias as surveys were completed 2–4 months after each vaccine dose.

IV.8.2 Unsolicited adverse events

IV.8.2.1 Children and adolescents

In general, there appeared to be a comparable frequency of unsolicited adverse events (AE) reported by MenB-fHBP recipients and controls in healthy children and adolescents in most studies[9, 11, 14, 24-26]. For example, the overall frequency of unsolicited AEs in adolescents receiving MenB-fHBP or control (HAV) vaccines during the vaccination phase, within 30 days after any immunization and within 30 minutes after any immunization was similar (40.7% vs. 43.7%; 25.3% vs. 26.8%; 0.4% vs. 0.3%, respectively), with the majority of these AEs being of mild to moderate in severity[9]. However, the safety and tolerability study by Ostergaard et al.[27] documented a greater proportion of MenB-fHBP recipients who reported AEs within 30 days of immunization than control (HAV) recipients (15.0–31.5% vs. 10.8–19.0%, respectively), even when the analysis was restricted to AEs determined to be related to the study vaccine (28.9% vs. 12.4%, respectively) or when reactogenicity events were excluded (7.3% vs. 3.0%, respectively). The same study found similar proportions of MenB-fHBP and HAV recipients reported missing days of school or work due to an AE (16.8% vs. 15.9%, respectively), with participants in each group missing a median of three days[27]. The most common AEs in MenB-fHBP recipients noted in studies were upper respiratory tract infections[14, 25, 26], injection site pain [25, 27], headache[25, 27] and nasopharyngitis[15, 26].

Severe adverse reactions were relatively rare. In the study by Richmond et al.[11], there were two MenB-fHBP recipients who reported severe adverse reactions considered vaccine related (photophobia and anaphylaxis). There was one MenB-fHBP recipient who experienced syncope after the third dose of vaccine that was considered to be possibly vaccine related in the study by Senders et al.[25]. The study by Vesikari et al.[15] documented 11 vaccine recipients who reported severe adverse events (SAE) considered to be related to receipt of MenB-fHBP (headache, injection site pain, pyrexia, vomiting, injection site swelling). There were also 19 participants (1.1%) who withdrew from the study due to an adverse event, nine of which were considered vaccine related (injection site pain, n=4; headache, n=2; migraine, fatigue, vertigo, n=1 each). In the study by Nissen et al.[14] in young children and adolescents 8–14 years of age, there were a total of nine unsolicited severe adverse reactions (erythema, pain and swelling at injection site, anorexia, otitis media, nausea (x2), headache and earache) reported by six MenB-fHBP recipients (60 µg: 4, 200 µg: 2). There was no apparent trend between severe adverse reactions and the dose or number of MenB-fHPB doses received.

There were also a number of studies that examined additional outcomes, such as the proportions of participants experiencing medically attended adverse events (MAE) and newly diagnosed chronic medical condition (NDCMC) within 30 days after each vaccine dose. The study by Ostergaard et al.[27] in healthy adolescents found no significant difference between MenB-fHPB and HAV recipients in the proportion of participants experiencing MAE within 30 days of each immunization (dose 1: 7.0% vs. 6.1%, p=0.218; dose 2: 5.5% vs. 6.1%, p=0.383; dose 3: 5.3% vs. 5.5%, p=0.843). The two groups were also not significantly different in the proportions of participants experiencing MAE during the immunization phase (24.6% vs. 24.5%, p=0.974), the follow-up phase after the last dose (11.2% vs. 11.4%, p=0.852) or overall during the study (29.0% vs. 29.0%, p>0.999). The most MAEs considered to be related to MenB-fHPB were pyrexia (n=10, 0.2%), injection site pain (n=8, 0.2%), headache (n=8, 0.2%) and injection site swelling (n=6, 0.2%). The study found no significant difference in the proportions of MenB-fHBP and HAV recipients who reported NDCMCs after each immunization (0.1–0.2% vs. 0.1–0.3%, respectively), after any immunization (0.5% vs. 0.5%, respectively), during the

immunization phase (1.0% vs. 1.1%, respectively), during the follow-up phase (0.4% vs. 0.5%, respectively) and throughout the study (1.4% vs. 1.5%, respectively). There were also no notable differences in the type of NDCMCs reported in the two vaccine groups. The NDCMCs considered to be related to immunization with either vaccine were rare: alopecia areata (n=1 participant) in MenB-fHBP recipients and multiple sclerosis (n=1) in the HAV recipient group. The study by Marshall et al.[21] in healthy adolescents 11–18 years of age, identified three participants with newly diagnosed chronic medical conditions (MenB-fHBP: 2; control: 1), but they were not felt to be vaccine-related.

IV.8.2.2 Adults

As with adolescents, the study by Ostergaard et al.[9] found the overall frequency of unsolicited AEs in MenB-fHBP and control (HAV) recipients during the vaccination phase, within 30 days after any immunization and within 30 minutes after any immunization was similar (31.2% vs. 31.1%; 21.2% vs. 18.9%; 0.4% vs. 0.9%). Most of the unsolicited AEs in the studies including adults were of mild to moderate in severity[9, 18, 20] and included AEs such as upper respiratory tract infections, headache and gastroenteritis[16]. In contrast, in the study by Sheldon et al.[18],the most commonly reported AEs were mild laboratory abnormalities reported in all vaccine groups, but there were also five vaccine recipients who reported a total of six AEs that were considered vaccine related (injection site pruritus, MenB-fHPB 60 µg (n=1) and 200 µg (n=1), injection site rash (MenB-fHBP 120 µg (n=1), induration (MenB-fHBP 120 µg (n=1) and 200 µg (n=1) and throat irritation (MenB-fHBP 200 µg (n=1)). There were also seven SAE reported, all of which were laboratory abnormalities, but none were considered to be vaccine related[18].

There were also similar proportions of MenB-fHBP and control (HAV) recipients whose reported MAEs were determined to be vaccine related in young adults (0.7% vs. 0.6%)[9]. The same study found no NDCMCs determined to be vaccine related in either vaccine group. There were no reports of neuroinflammatory or autoimmune conditions in vaccine recipients in the study by Reiner et al.[20].

IV.8.3 Unsolicited serious adverse events

IV.8.3.1 Children and adolescents

In a Phase 2 RCT that assessed the safety and tolerability of escalating doses of MenB-fHBP (60 µg, 120 µg, 200 µg) versus placebo in healthy adolescents 11–18 years of age, there were 24 serious adverse events (SAE) reported by 19 study participants. However, only one of the events, a potential case of anaphylaxis in a 13-year old adolescent, was considered related to MenB-fHBP[11]. The differences in vaccine dose levels used in this study makes it difficult to directly compare findings to those of other studies which used the final, authorized dose formulation (120 µg) of MenB-fHBP.

In the study by Nissen et al.[14] in young children and adolescents 8–14 years of age, one person had a serious adverse event (SAE) two days after the first dose of MenB-fHBP (200 µg) that was felt to be vaccine-related (severe injection site pain, moderate erythema and swelling, fever, nausea, vomiting, muscle and joint pain). The adolescent was diagnosed with a “large local reaction” upon hospitalization, but remained in the study; the person had no AEs following the second dose, but had severe pain and erythema after the third dose. In a comparison of two- and three-dose MenB-fHBP immunization schedules in adolescents 11–18 years of age, there were no differences in the frequency of SAEs between MenB-fHBP and saline recipients

or between participants who received the two- vs. three-dose vaccine schedules[15]. There was also no increase in SAEs with subsequent doses of the vaccine. However, there were two participants who reported SAEs considered to be related to receipt of MenB-fHBP: one subject experienced vertigo, chills and headache after the third dose of the vaccine and the other subject experienced pyrexia and vomiting after the first dose[15]. There were comparable numbers of SAEs reported in all three vaccine groups in a study of the concomitant administration of MCV4 and Tdap in children 10–12 years of age (MCV4+Tdap+MenB-fHBP: 18, MCV4+Tdap: 13, MenB-fHBP: 12), but none were considered to be vaccine-related[24]. Similarly, in a study of healthy adolescents 11–18 years of age, there were 6 SAEs reported in MenB-fHBP recipients and 1 in the control group, but none were considered to be vaccine related[21]. There were also no vaccine-related SAEs reported in several of the other studies in adolescents identified in the literature review[9, 25, 26].

In a Phase 3 study including both healthy adolescents and young adults (10–25 years of age), there was a significantly greater proportion of controls (HAV recipients) than MenB-fHBP recipients (n=48, 2.5% vs. n=59, 1.6%, p=0.013) who reported SAE during the study period and during the immunization phase (1.8% vs. 1.2%, p=0.042). However, the proportions of vaccine recipients reporting SAE were not significantly different in the HAV and MenB-fHBP groups within 30 days of each immunization (dose 1: 0.4% vs. 0.2%, p=0.108; dose 2: 0.4% vs. 0.2%, p=0.087; dose 3: 0.1% vs 0.3%, p=0.241) or during the follow-up phase after the last dose (0.9% vs. 0.4%, p=0.079). Four SAEs (n=2 in each group) were considered vaccine-related: neutropenia and anaphylaxis in MenB-fHBP recipients and demyelination and spontaneous abortion in recipients of HAV[27].

IV.8.3.2 Adults

In an early Phase 1 RCT exploring escalating doses of MenB-fHBP (20 µg, 60 µg, 200 µg) in healthy adults (18–25 years of age), there were three persons who experienced SAEs reported (head injury; cellulitis and subcutaneous abscess; post-tooth extraction hemorrhage), but none were considered vaccine related[17]. In another small Phase 1 RCT comparing safety and tolerability of escalating doses of MenB-fHBP (60 µg, 120 µg, 200 µg) compared to control (Tdap) in healthy adults (18–40 years of age), there were no vaccine-related SAEs or deaths reported during the study[18].

Among young adults (18–25 years of age) in a Phase 3 RCT, 1.3% of both MenB-fHBP and HAV recipients reported SAEs, but only in MenB-fHBP recipients (0.1% of total) were three SAEs determined to be vaccine related[9]. There was also one SAE (upper respiratory tract infection reported seven days after the second dose of MenB-fHBP) considered to be vaccine-related in a small Phase 2 open-label trial of healthy adults (18–40 years of age)[16]. And finally, no SAEs or deaths were recorded during a small (n=13 participants) Phase 2 open-label trial of MenB-fHBP recipients at a single health care facility in the US[20].

IV.9 Contraindications and Precautions

Contraindications to administration of the vaccine include hypersensitivity to the vaccine or any of its components. A severe allergic reaction to any previous dose of the vaccine or to any its components is also a contraindication to MenB-fHBP administration[6].

There are no data available on the use of MenB-fHBP in immunocompromised individuals or in pregnant women. It is also not known whether MenB-fHBP is excreted in human breast milk. In

addition, there are no data on potential effects of the vaccine on human fertility, although animal studies have not indicated impairment of fertility in females[6].

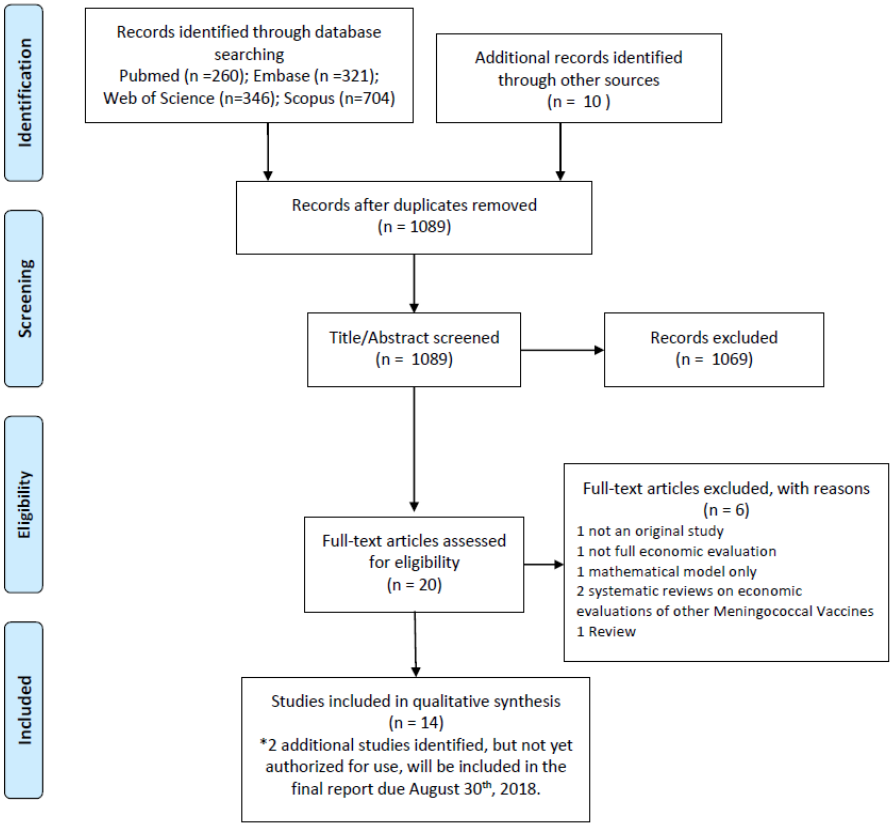
The safety and efficacy of the vaccine have not been established in children less than 10 years of age, with only a single study identified that included a small number of children as young as 8 years of age[14]. The vaccine has also not been studied in older adults (>65 years)[6].

V. ECONOMICS

The following is a shorter narrative summary of the full results of the studies identified in the literature review of economic evaluations of protein-based meningococcal vaccines against serogroup B. The full report of the literature review will be published separately. A full description of methods can be found in section II.3.

The literature search identified 1,631 records in journal-indexing databases and 10 records through manual search of key stakeholders' websites. After removing duplicates, 1,089 titles and abstract were screened, but only 14 out of 20 studies examined during full-text review were finally included for qualitative synthesis (Figure 5).

Figure 5: Flow diagram, screening process for literature review of economic evaluations of protein-based meningococcal serogroup B vaccines



The 14 articles identified in the literature review were published between 2013 and 2017.[29-42] These articles comprise 10 peer-reviewed studies and four study reports published by agencies, one of which was peer-reviewed despite it has not been translated into a journal publication. Studies were performed for six European countries (n=10 studies): Belgium (n=1), England (n=3), France (n=1), Germany (n=1), Italy (n=3) and the Netherlands (n=1), as well as Canada (n=3) and Israel (n=1). All studies were economic evaluations of 4CMenB; no published economic evaluations of MenB-fHBP were identified. In communication with the manufacturer of the MenB-fHBP vaccine, the authors were made aware of an unpublished cost-effectiveness study that has been conducted but remains confidential and is therefore not included here. Authorization for accessing and using this assessment for the purpose of this review has been requested. Most studies were financed by a public health agency or research institute (n=9), one study was financed by the Pharmaceutical Industry (Novartis-Canada), and in some studies authors received no funding (n=2), or no information regarding sponsorship was provided (n=2).

Eight studies used static models; three used dynamic transmission models (compartmental transmission dynamic models using a Susceptible-Infected-Susceptible structure), while the remaining three used both static and dynamic models (included herd effect in the sensitivity analysis). Eight studies provide results under a societal or a societal and healthcare system's payer perspective; while the remaining six only used a healthcare system's or payer perspective. Most studies applied uniform discount rates for both costs and benefits, with eight studies using a 3% or 3.5% discount rate that remained constant for the entire time horizon selected, while two studies used a 3.5% or a 4% discount rate for the first 30 years and

progressively decreased the rate after that. The remaining studies (n=3) used differential discounting with lower rates for health effects (i.e. 3%–4% for costs and 1.5% for benefits). One study used a constant discount rate of 5% for both costs and benefits. All studies included in this review used quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs) as a measure of health outcomes in cost-utility analysis (CUA). A number of studies also provided cost per life-years (LYs) gained without quality adjustment in cost-effectiveness analysis (CEA). The resulting incremental cost-effectiveness ratios (ICERs) varied considerably across studies conducted for different countries, as well as for the same country.

All studies predicted the introduction of 4CMenB would reduce the number of IMD cases. In high-income countries with low serogroup B IMD incidence, analyses using the manufacturer's list price for the vaccine ($61.00–$140.90) found that the costs per quality adjusted life years were higher than commonly accepted thresholds for adoption of the vaccine. This applies to routine infant, routine adolescent, routine infant and adolescent, as well as infant/toddler catch-up immunization programs. The cost-effectiveness thresholds used in the studies to assess cost-effectiveness ranged from as low as CAN$33,694 to as high as CAN$137,044 and reflects a variety of country specific and World Health Organization recommended thresholds.

Contrary to the differences between countries, there is less variation within Canada in terms of vaccine prices and health services costs. However, there can be substantial differences in disease incidence and vaccine administration costs, depending on whether vaccination is offered predominantly by the public health infrastructure or through individual healthcare providers. Three studies were conducted in the Canadian setting: one for Ontario only, one for Quebec only, and one for Canada, Ontario and Quebec (Novartis-Canada). According to the Ontario study, a 2, 4, 6 +12 months schedule would cost approx. $5,096,195/QALY gained from the healthcare system's perspective. For the incremental cost-effectiveness ratio to be below $50,000/QALY gained, the disease incidence would have to be ten times higher or the vaccine price to be unrealistically zero. The study conducted by the manufacturer that examined the introduction of the same infant schedule or an infant + adolescents schedule showed incremental cost-effectiveness ratios ranging from $333,233/QALY gained (2, 4, 6, +12 months and adolescents schedule; societal perspective) to $782,186/QALY gained (2, 4, 6 +12 months schedule; healthcare payer perspective). In 2014, Quebec conducted an assessment to determine the cost-effectiveness of a public health intervention aiming to control the increased incidence of IMD serogroup B in three eastern Quebec regions: Quebec City, Chaudiere-Appalaches and Saguenay-Lac-Saint-Jean. Incremental cost-effectiveness ratios varied considerably but were more favourable when including herd immunity effects in regions with the highest incidence rate and under competitive vaccine prices. For example, assuming low herd immunity and vaccine prices between $32–63.70 per dose, incremental cost-effectiveness ratios obtained ranged from $16,774 to $77,333/QALY gained from the societal perspective. These results would only apply under higher incidence rates (3.7 cases per 100,000) than those observed in most provinces (0.19, 1.7 cases per 100,000), relatively low vaccine costs, herd immunity effects and from a societal perspective.

The applicability of the studies identified in the literature review to MenB-fHBP is challenging, because the studies were conducted for 4CMenB. No economic assessment of MenB-fHBP has been published to date.

The economic literature review found that 4CMenB , which was authorized for use in Canada in individuals 2 months through 17 years of age, is not cost-effective at commonly used thresholds because of the low incidence of invasive serogroup B meningococcal disease (0.19 – 3.17

cases per 100,000) and the relatively high vaccine cost. A total of 149 cases of IMD were reported among individuals 10 to 25 years of age old, with 63.8% (n=95) associated with serogroup B. The annual incidence rates ranged from 0.3 to 0.9 cases per 100,000 populations within this age group. The MenB-fHBP vaccine is immunogenic, although its effectiveness, impact on carriage and herd immunity, and its duration of protection remain unknown. Based on the economic evidence for 4CMenB and the age distribution of the burden of invasive serogroup B meningococcal disease (highest in children < 10 years of age), it is unlikely that MenB-fHBP would be cost-effective. However, economic evidence on MenB-fHBP in the Canadian setting would be helpful to fully understand its value.

VI. RECOMMENDATIONS

Following the review of available evidence on the burden of illness from IMD, as well as the immunogenicity and the safety of MenB-fHBP, NACI makes the following recommendations for public health level and individual level decision-making.

Due to the lack of evidence and some uncertainty related to various aspects of the vaccine, such as the effectiveness of the vaccine at the population level, the effect of immunization on carriage and herd immunity, the need for booster doses, the potential coverage of circulating meningococcal serogroup B strains in Canada, as well as the use of the vaccine in high-risk populations[a], NACI will continue to monitor the scientific developments related to MenB-fHBP and will update recommendations as evidence becomes available. The scope of this statement does not include comparative recommendations on the use of MenB-fHBP and 4CMenB.

Please note:

- A *strong recommendation* applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.
- A *discretionary recommendation* may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

Please see Table 4 for a more detailed explanation of strength of NACI recommendations and grade of the body of evidence.

VI.1 General Recommendations and Guidance

The two serogroup B meningococcal vaccines currently authorized for use in Canada (MenB-fHBP and 4CMenB) are not interchangeable; the two vaccine products contain different antigens and there are no published studies on the immunogenicity resulting from a vaccination series combining the two products. Therefore, the same vaccine product should be used for all doses in a vaccination series. If, in a person with an incomplete vaccination series, it is unknown what vaccine product they initially received,

[a] Definition of high risk is provided in the Canadian Immunization Guide (https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-13-meningococcal-vaccine.html#p4c12a5)

the initial dose(s) should be discounted and the vaccination series repeated using the same vaccine product for all doses in the new, repeated series.

VI.2 Recommendations for Public Health Program Level Decision-making (i.e., provinces/territories making decisions for publicly funded immunization programs)

In considering these recommendations and for the purposes of publicly funded immunization program implementation, provinces and territories may take into account multiple factors, such as the local epidemiology of IMD, cost-benefit evaluation and other local programmatic and operational factors (e.g., current immunization programs, resources).

Recommendation 1: **NACI recommends that the MenB-fHBP vaccine should not be offered in routine universal immunization programs in Canada at this time. (Strong NACI Recommendation)**

- **NACI concludes there is insufficient evidence to recommend routine universal immunization (Grade I Evidence)**

Summary of Evidence and Rationale:

- Serogroup B is currently the most common cause of IMD in Canada. Between 2012 and 2016, 60.5% (n=353) of IMD cases were due to serogroup B, with the highest incidence in children <1 year of age (n=10 cases annually; 2.7 cases per 100,000) followed by children 1–9 years (14 cases annually; 0.9 cases per 100,000) and adolescents 15–19 years (11 cases annually; 0.5 cases per 100,000). In the same time period, 63.8% (n=95) of cases of IMD in individuals 10–25 years were due to serogroup B, representing an incidence of 0.3–0.9 cases per 100,000 population in this age group.
- There are no population-level data on the effectiveness of MenB-fHBP or its effect on meningococcal carriage or herd immunity.
- There is limited evidence from two MenB-fHBP studies on persistence of the immune response up to 48 months post-vaccination in adolescents and 9–11 months in a small study in adults (24–66 years) and no data on the need for booster doses after the primary immunization series.
- The MenB-fHBP vaccine has been found to be immunogenic against both primary and secondary MenB test strains containing a range of fHBP variants that were representative of circulating strains causing IMD at the time in Europe and the US.
- There are no published data on the cost-effectiveness of MenB-fHBP. However, based on the economic evidence for the 4CMenB vaccine and the age distribution of the burden of invasive serogroup B meningococcal disease (highest in children < 10 years of age), it is unlikely that the MenB-fHBP vaccine would be cost-effective.

The greatest incidence of serogroup B IMD is in children of an age for which the vaccine is not authorized for use. There is also only limited data on the persistence of the vaccine immune response and no data on the need for booster doses after the primary immunization series. In addition, some caution may be required in extrapolating findings on the immune response generated by the vaccine against the breadth of strains covered in clinical trials to the Canadian context; in the limited analysis performed to date on the common fHBP variants present in Europe and the US at the time of the study compared to Canada, it appeared the fHBP variant

B44 was more common in Canada. The studies identified in the current NACI literature review have found the immune response elicited by MenB-fHBP against fHBP B44 is in general lower than for the other fHBP variants present in the primary MenB test strains assessed in the studies. And finally, economic evidence for the MenB-fHBP vaccine in the Canadian setting would be helpful to better understand its value. Therefore, NACI concluded that, on a population level, there is currently insufficient evidence to support the use of the MenB-fHBP vaccine in routine universal immunization programs in Canada

Recommendation 2a: **NACI recommends that a serogroup B meningococcal vaccine (MenB-fHBP or 4CMenB) should be offered in jurisdictions experiencing serogroup B meningococcal disease outbreaks or with the emergence of hyperendemic *N. meningitidis* strains that are predicted to be susceptible to the vaccine. (Strong NACI Recommendation)**

- **NACI concludes there is fair evidence to recommend vaccine use during outbreaks (Grade B Evidence).**

Recommendation 2b: **NACI recommends that the MenB-fHBP vaccine may be considered as an option for use in individuals 10 years of age and older in such circumstances. (Discretionary NACI Recommendation)**

- **NACI concludes there is insufficient evidence of the MenB-fHBP vaccine use in such circumstances (Grade I Evidence); therefore, this recommendation is based on expert opinion.**

Summary of Evidence and Rationale:

- The MenB-fHBP vaccine is safe with no associated SAEs reported in immunocompetent individuals 10-25 years of age. Most systemic and local AEs are mild to moderate in intensity and transient in duration (lasting 1–3 days).
- The MenB-fHBP vaccine is immunogenic in both adolescents (primarily 11–18 years) and young adults (primarily 18–25 years).
- There are currently limited data on the immunogenicity of MenB-fHBP in young children (<10 years), adults >25 years and no data in older adults (>65 years). However, in an outbreak setting and when the strain is predicted to be susceptible, based on expert opinion, its use is considered appropriate for individuals greater than 25 years of age when the potential benefits outweigh the risks.
- In cases where an alternate product is available, there is currently insufficient evidence to recommend the use of MenB-fHBP in an outbreak setting for individuals less than 10 years; a multicomponent meningococcal serogroup B–specific vaccine (4CMenB) is authorized for use in Canada in persons from 2 months to 25 years of age. However, in cases where an alternate product is not available and when the strain is predicted to be susceptible, based on expert opinion, MenB-fHBP use may be considered for individuals less than 10 years of age when the potential benefits outweigh the risks.
- While the MenB-fHBP vaccine has been found to be immunogenic against both primary and secondary MenB test strains containing a range of fHBP variants that were representative of circulating strains causing IMD at the time in Europe and the US, there is insufficient evidence of its use in outbreak settings.

There are no data on the effectiveness of the MenB-fHBP vaccine or its effect on meningococcal carriage or herd immunity. Previous experience with the use of conjugate serogroup C and serogroup B outer membrane vesicle vaccines against emerging hyperendemic and/or hypervirulent strains expressing homologous antigens to those present in a vaccine has been demonstrated to be an effective public health strategy for managing clonal IMD outbreaks.

This recommendation is consistent with the public health management approach taken for other meningococcal serogroups in Canada and internationally, and is recommended on the basis of expert opinion. However, consultation with public health officials and/or expert in communicable disease is required for optimal management of meningococcal disease outbreaks.

Recommendation 3a: **NACI recommends that a serogroup B meningococcal vaccine (MenB-fHBP or 4CMenB) should be offered, in addition to chemoprophylaxis, for protection of individuals who are close contacts with a case of invasive meningococcal disease caused by serogroup B *Neisseria meningitidis*. (Strong NACI Recommendation)**

- **NACI concludes there is insufficient evidence of vaccine effectiveness in close contacts of cases of IMD (Grade I Evidence); therefore, this recommendation is based on expert opinion.**

Recommendation 3b: **NACI recommends that the MenB-fHBP vaccine may be considered as an option for use in individuals 10 years of age and older who are close contacts with a case of IMD caused by serogroup B *Neisseria meningitidis*. (Discretionary NACI Recommendation)**

- **NACI concludes there is insufficient evidence of the MenB-fHBP vaccine use in close contacts (Grade I Evidence); therefore, this recommendation is based on expert opinion.**

Summary of Evidence and Rationale:

- The MenB-fHBP vaccine is safe with no associated SAEs reported in immunocompetent individuals 10-25 years of age. Most systemic and local AEs are mild to moderate in intensity and transient in duration (lasting 1–3 days).
- The MenB-fHBP vaccine is immunogenic in both adolescents (primarily 11–18 years of age) and young adults (primarily 18–25 years of age). The immune response is greater with a three-dose vaccine schedule than with a two-dose schedule.
- There are currently limited data on the immunogenicity of MenB-fHBP in young children (<10 years of age), adults >25 years of age and no data in older adults (>65 years of age). However, based on expert opinion, when the potential benefits outweigh the risks, its use is considered appropriate in individuals greater than 25 years who are close contacts with a case of IMD caused by serogroup B *Neisseria meningitidis*.
- In cases where an alternate product is available, there is currently insufficient evidence to recommend the use of MenB-fHBP for individuals less than 10 years; a multicomponent meningococcal serogroup B–specific vaccine (4CMenB) is authorized for use in Canada in persons from 2 months to 25 years of age. However, in cases where an alternate product is not available, based on expert opinion, its use may be considered for individuals less than 10 years of age where the potential benefits outweigh the risks.

- The vaccine has been found to be immunogenic against both primary and secondary MenB test strains containing a range of fHBP variants that are representative of strains causing IMD in Europe and the US.

There are no data on the population-level effectiveness of the MenB-fHBP vaccine or its effectiveness in close contacts of a case of IMD caused by serogroup B *N. meningitidis*. Close contacts of individuals with meningococcal infections have an increased risk of developing IMD and should receive immunoprophylaxis in addition to chemoprophylaxis. The risk is greatest for household contacts and may persist for up to one year after disease in the index case. Vaccination of close contacts should be carried out independent of tests of strain susceptibility to the vaccine to ensure there are no delays in contact management. NACI considered that for the individual, there is currently sufficient evidence that MenB-fHBP, when given according to the schedules used in clinical trials, is safe, immunogenic and may offer protection against a range of fHBP variants present in MenB strains causing IMD. There is a lack of data on the population-level effectiveness of the vaccine or its effectiveness in preventing IMD in close contacts of a case of IMD caused by serogroup B *N. meningitidis*. However, this recommendation is consistent with NACI recommendations for other meningococcal vaccines and is based on expert opinion.

Recommendation 4a: **NACI recommends that a serogroup B meningococcal vaccine (MenB-fHBP or 4CMenB) should be offered for the active immunization of individuals with underlying medical conditions that would put them at higher risk of meningococcal disease than the general population to reduce the risk of invasive serogroup B meningococcal disease. (Strong NACI Recommendation)**

- **NACI concludes there is insufficient evidence of vaccine use in high-risk populations (Grade I Evidence); therefore, this recommendation is based on expert opinion.**

Recommendation 4b: **NACI recommends that the MenB-fHBP vaccine may be considered as an option for use in high-risk individuals 10 years of age and older, in a 3-dose schedule (0, 1–2, 6 months), to reduce the risk of invasive serogroup B meningococcal disease. (Discretionary NACI Recommendation)**

- **NACI concludes there is insufficient evidence of the MenB-fHBP vaccine use in high-risk populations (Grade I Evidence); therefore, this recommendation is based on expert opinion.**

Summary of Evidence and Rationale:

- The MenB-fHBP vaccine is safe with no associated SAEs reported in immunocompetent individuals 10-25 years of age. Most systemic and local AEs are mild to moderate in intensity and transient in duration (lasting 1–3 days).
- Clinical trials with the MenB-fHBP vaccine did not include persons with underlying medical conditions that would put them at high risk for IMD. Two small studies involved adult laboratory workers who would be at increased risk of exposure to serogroup B meningococcal isolates.
- The MenB-fHBP vaccine is immunogenic in both adolescents (primarily 11–18 years) and young adults (primarily 18–25 years). The immune response is greater with a three-dose vaccine schedule than with a two-dose schedule.

- The shorter interval between the first and second dose of the three-dose the MenB-fHBP immunization schedule would be expected to provide earlier protection and maximize short-term immunogenicity for those at higher risk of exposure.
- There are currently limited data on the immunogenicity of MenB-fHBP in young children (<10 years), adults >25 years and no data in older adults (>65 years). However, based on expert opinion, when the potential benefits outweigh the risks, its use is considered appropriate in individuals greater than 25 years of age.
- In cases where an alternate product is available, there is currently insufficient evidence to recommend the use of MenB-fHBP for individuals less than 10 years; a multicomponent meningococcal serogroup B–specific vaccine (4CMenB) is authorized for use in Canada in persons from 2 months to 25 years of age. However, in cases where an alternate product is not available, based on expert opinion, its use may be considered for individuals less than 10 years of age when the potential benefits outweigh the risks.
- The MenB-fHBP vaccine has been found to be immunogenic against both primary and secondary MenB test strains containing a range of fHBP variants that were representative of circulating strains causing IMD at the time of study in Europe and the US.

NACI considered that for the individual, there is currently sufficient evidence that the MenB-fHBP vaccine, when given according to the schedules used in clinical trials, is safe, immunogenic and may offer protection against a range of fHBP variants present in MenB strains causing IMD. However, the clinical trials identified in the literature recruited healthy adolescents and adults (or a small number of adults with chronic medical conditions not felt likely to affect immune responses). There was insufficient evidence identified regarding the safety and immunogenicity of the vaccine in any individuals with underlying medical conditions that would result in a higher risk of IMD. However, this recommendation is consistent with NACI recommendations for other meningococcal vaccines and is based on expert opinion.

VI.3 Recommendations for Individual Level Decision-making (i.e., individuals wishing to prevent serogroup B IMD or clinicians wishing to advise individual patients about preventing this outcome with vaccines that may not be currently included in publicly funded immunization programs; and organizations or decision makers responsible for programs offering vaccine services to various groups including individuals at risk of acquiring this outcome)

When advising on immunization with the serogroup B meningococcal vaccine, individual preferences and regional serogroup B IMD epidemiology should be considered. In circumstances in which the potential benefits outweigh the risks of adverse events following immunization, the use of the vaccine may be considered.

Recommendation 5a: **NACI recommends that a serogroup B meningococcal vaccine (MenB-fHBP or 4CMenB) should be offered for the active immunization of individuals at higher risk of exposure to serogroup B meningococcal isolates than the general population to reduce the risk of invasive serogroup B meningococcal disease. (Strong NACI Recommendation)**

- **NACI concludes there is insufficient evidence of vaccine use in high-risk populations (Grade I Evidence); therefore, this recommendation is based on expert opinion.**

Recommendation 5b: **NACI recommends that the MenB-fHBP vaccine may be considered as an option for use in such high-risk individuals 10 years of age and older, in a 2-dose schedule (0, 6 months), to reduce the risk of invasive serogroup B meningococcal disease. (Discretionary NACI Recommendation)**

- **NACI concludes there is insufficient evidence of the MenB-fHBP vaccine use in high-risk populations (Grade I Evidence); therefore, this recommendation is based on expert opinion.**

Summary of Evidence and Rationale:

- The MenB-fHBP vaccine is safe with no associated SAEs reported in immunocompetent individuals 10-25 years of age. Most systemic and local AEs are mild to moderate in intensity and transient in duration (lasting 1–3 days).
- The MenB-fHBP vaccine is immunogenic in both adolescents (primarily 11–18 years) and young adults (primarily 18–25 years). The immune response is greater with a three-dose vaccine schedule than with a two-dose schedule.
- There are currently limited data on the immunogenicity of MenB-fHBP in young children (<10 years), adults >25 years and no data in older adults (>65 years). However, based on expert opinion, when the potential benefits outweigh the risks, its use is considered appropriate in individuals greater than 25 years of age. In cases where an alternate product is available, there is currently insufficient evidence to recommend the use of MenB-fHBP for individuals less than 10 years; a multicomponent meningococcal serogroup B–specific vaccine (4CMenB) is authorized for use in Canada in persons from 2 months to 25 years of age. However, in cases where an alternate product is not available, based on expert opinion, its use may be considered for individuals less than 10 years of age when the potential benefits outweigh the risks.
- Two small studies involved adult laboratory workers immunized with MenB-fHBP who would be at increased risk of exposure to serogroup B meningococcal isolates.
- The MenB-fHBP vaccine has been found to be immunogenic against both primary and secondary MenB test strains containing a range of fHBP variants that were representative of circulating strains causing IMD at the time of study in Europe and the US.

NACI considered that for the individual, there is currently sufficient evidence that MenB-fHBP, when given according to the schedules used in clinical trials, is safe, immunogenic and may offer protection against a range of fHBP variants present in MenB strains causing IMD. However, only two, small studies of laboratory workers at increased risk of exposure to serogroup B meningococcal isolates were identified in the literature. This recommendation is consistent with NACI recommendations for other meningococcal vaccines and is based on expert opinion.

Recommendation 6: **NACI recommends that the MenB-fHBP vaccine may be considered as an option for individuals 10-25 years of age who are not at higher risk of meningococcal disease than the general population, in a 2-dose schedule (0 and 6 months), to reduce**

the risk of invasive serogroup B meningococcal disease. (Discretionary NACI Recommendation)

- **NACI concludes there is fair evidence of vaccine immunogenicity to recommend the MenB-fHBP vaccine when given according to the schedule used during clinical trials (Grade B Evidence).**

Summary of Evidence and Rationale:

- The MenB-fHBP vaccine is safe with no associated SAEs reported in immunocompetent individuals 10-25 years of age. Most systemic and local AEs are mild to moderate in intensity and transient in duration (lasting 1–3 days).
- The MenB-fHBP vaccine is immunogenic in both adolescents (primarily 11–18 years) and young adults (primarily 18–25 years). The immune response is greater with a three-dose vaccine schedule than with a two-dose schedule.
- There are currently limited data on the immunogenicity of MenB-fHBP in young children (<10 years), adults >25 years and no data in older adults (>65 years). However, based on expert opinion, when the potential benefits outweigh the risks, its use is considered appropriate in individuals greater than 25 years of age.
- In cases where an alternate product is available, there is currently insufficient evidence to recommend the use of MenB-fHBP for individuals less than 10 years; a multicomponent meningococcal serogroup B–specific vaccine (4CMenB) is authorized for use in Canada in persons from 2 months to 25 years of age. However, in cases where an alternate product is not available, based on expert opinion, its use may be considered for individuals less than 10 years of age when the potential benefits outweigh the risks.
- There is also limited evidence from two MenB-fHBP studies on persistence of the immune response up to 48 months post-vaccination in adolescents and 9–11 months in a small study in adults (24–66 years).
- The MenB-fHBP vaccine has been found to be immunogenic against both primary and secondary MenB test strains containing a range of fHBP variants that were representative of circulating strains causing IMD at the time of study in Europe and the US.

NACI considered that for the individual, there is currently sufficient evidence that MenB-fHBP, when given according to the schedules used in clinical trials, is safe, immunogenic and may offer protection against a range of fHBP variants present in MenB strains causing IMD. However, there are limited data available on the persistence of immunogenicity elicited by the vaccine, and available data show protection declines rapidly 12 months after vaccination.

When advising on immunization with the vaccine, individual preferences should be considered. In circumstances in which the potential benefits outweigh the risks of AEs following immunization, the use of the vaccine may be considered.

VII. RESEARCH PRIORITIES

There are a number of evidence gaps regarding the MenB-fHBP vaccine that also apply to meningococcal serogroup B vaccines in general and which were identified in the NACI Advisory Committee Statement: Advice for the use of the multicomponent meningococcal serogroup B

(4CMenB) vaccine. These evidence gaps include the potential of serogroup B vaccines to protect against meningococcal serogroup B strains circulating in Canada and against other meningococcal serogroups; the effectiveness of these vaccines (individually and relative to each other); the duration of protection offered by the vaccines; the need for a booster dose(s); and the vaccines' effects on carriage and herd immunity; and the safety, immunogenicity and effectiveness of these vaccines in specific subpopulations (e.g., pregnant women, immunocompromised). In addition, research could explore the perceptions and acceptability of serogroup B meningococcal vaccines to the general public, healthcare workers and public health authorities.

VIII. SURVEILLANCE ISSUES

Ongoing and systematic data collection, analysis, interpretation and timely dissemination are fundamental to planning, implementation, evaluation, and evidence-based decision-making. Due to the number of uncertainties about meningococcal serogroup B vaccines, high-quality post-marketing surveillance is important to evaluate the impact of these vaccines. To support such efforts, NACI encourages surveillance improvements in the following areas:

1. Epidemiology

    - Collection of variables (e.g., vaccination status, confirmed case status) to facilitate calculation of vaccine effectiveness and the potential indirect effects of immunization (herd immunity)

2. Laboratory

    - Capacity of reference laboratories to microbiologically characterize (e.g., surface proteins, such as PorA, NHBA, NadA, fHBP) and classify meningococcal serogroup B isolates in order to generate profile of serogroup B meningococcal strains causing IMD in Canada
    - Systematic use of polymerase chain reaction (PCR) testing for suspected IMD cases
    - Assessment of the potential of serogroup B meningococcal vaccines to protect against predominant circulating serogroup B meningococcal strains in Canada using immunological surrogates of protection (e.g., bactericidal activity or assays testing antigenic expression) and classical epidemiological studies in populations in which these vaccines have been used

3. Vaccine

    - Enhancement of post-marketing surveillance to collect additional data on AEs following immunization

TABLES

Table 2: Ranking Individual Studies: Levels of Evidence Based on Research Design

Level	Description
I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table 3: Ranking Individual Studies: Quality (internal validity) Rating of Evidence

Quality Rating	Description
Good	A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

* General design specific criteria are outlined in Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001; 20: 21–35.

Table 4: NACI Recommendations: Strength of Recommendation and Grade of Evidence

STRENGTH OF NACI RECOMMENDATION	GRADE OF EVIDENCE
Based on factors not isolated to strength of evidence (e.g., public health need)	***Based on assessment of the body of evidence***
Strong "*should/should not be* offered" ➢ Known/Anticipated advantages outweigh known/anticipated disadvantages ("should"), OR Known/Anticipated disadvantages outweigh known/anticipated advantages ("should not") ➢ Implication: A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present	A - *good evidence* to recommend
	B – *fair evidence* to recommend
	C – *conflicting evidence*, however other factors may influence decision-making
	D – *fair evidence* to recommend against
	E – *good evidence* to recommend against
	I – *insufficient evidence* (in quality or quantity), however other factors may influence decision-making
Discretionary "*may be* considered" ➢ Known/Anticipated advantages closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists ➢ Implication: A discretionary recommendation may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.	A - *good evidence* to recommend
	B – *fair evidence* to recommend
	C – *conflicting evidence*, however other factors may influence decision-making
	D – *fair evidence* to recommend against
	E – *good evidence* to recommend against
	I – *insufficient evidence* (in quality or quantity), however other factors may influence decision-making

LIST OF ABBREVIATIONS

4CMenB	Multicomponent meningococcal serogroup B vaccine (Bexsero®)
AE	Adverse event
CUA	Cost-utility analysis
DTap/IPV	Diphtheria, tetanus, acellular pertussis, inactivated polio virus vaccine
fHBP	Factor-H binding protein
GMT	Geometric mean titre
HPV4	Quadrivalent human papillomavirus vaccine
hSBA	Human serum bactericidal assay
ICER	Incremental cost-effectiveness ratio
IgG	Immunoglobulin class G antibodies
IMD	Invasive meningococcal disease
MAE	Medically attended adverse event
MCV4	Meningococcal conjugate ACWY vaccine
MenB	Meningococcal serogroup B
MenB-fHBP	Bivalent factor-H binding protein vaccine (Trumenba®)
NACI	National Advisory Committee on Immunization
NDCMC	Newly diagnosed chronic medical condition
NOC	Notice of Compliance
rLP2086	Recombinant lipoprotein 2086
PHAC	Public Health Agency of Canada
QALY	Quality-adjusted life years
RCT	Randomized controlled trial
SAE	Serious adverse event
Tdap	Tetanus, diphtheria, acellular pertussis vaccine
URTI	Upper respiratory tract infection
US	United States

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APPENDIX A: SUMMARY OF IMMUNOGENICITY FINDINGS

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Immunogenicity						
Anderson et al. (2013)	Bivalent rLP2086 Study 1: Bivalent rLP2086 (120µg) in 3-dose schedule (0,2,6 months) Study 2: Bivalent rLP2086 (120µg) in 3-dose schedule (0,1,6 months)	Sub-analysis of data presented in previous studies MenB test strains containing fHBP* antigenic variants (A04, A05, A22, A56, B02, B03, B16, B24, B44) obtained from reference laboratories in United States and Europe (represent fHBP variants found in ~70% of invasive MenB isolates from 2000–2006) Common MenB fHBP antigenic variants in carriage isolates determined from study of high school students in United States and college students in United Kingdom *fHBP: factor H binding protein	Sera from subjects from two previously published clinical trials†: Study 1: Multicentre, randomized single-blind, placebo controlled trial in Australia, Poland, Spain (n=25 sites) Adolescents 11–18 years of age (n=198) Study 2: Randomized, phase1/2, open-label trial in Australia Healthy adults 18–25 years of age (n=19–26) †Richmond et al. (2012a) and Marshall et al. (2013), respectively. Marshall et al. is subsequent publication of study referred to in conference poster referenced in current study. See later in table for summary of both studies	Seroprotection** • 75–100% of immunized adolescents and adults had seroprotective hSBA titres against each of the fHBP variants common in IMD isolates from the US and Europe. Study not designed to assess whether immunization with bivalent rLP2086 could reduce MenB carriage, transmission or disease incidence in unimmunized individuals via herd protection. Comparison of fHBP antigenic variants between invasive and carriage MnB strains • 17 common fHBP antigenic variants in common between IMD (representing 83% of invasive disease isolates) and carriage isolates (representing >90% of isolates analyzed) in these adolescents and young adults. • 16 (89%) fHBP variants prevalent in adolescents and young adult carriage isolates also prevalent (78%) in isolates from invasive MenB disease in infants **Seroprotection: hSBA titre ≥1:4 using hSBA from baseline to 1 month after dose 3 against invasive MnB strains expressing fHBP antigenic variants: A05, B02, A22, B44, B24, A04, A56, B03, B16	II-2	Fair
Harris et al. (2017)	Bivalent rLP2086 (120 µg) in a 3-dose schedule	Analysis of immunogenicity of sera	Adolescents (11–18 years of age) and adults (18–25 years of age)	Seroprotection** Dose | Proportion of respondents (%)	II-2	Fair

<table>
<tr><th colspan="4">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Vaccine</th><th>Study Design</th><th>Participants</th><th>Summary of Key Findings</th><th>Level of Evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td>collected from three previous clinical trials*

Participants' sera selected in "unbiased fashion" without regard to previous hSBA data

"Unbiased algorithm" used to select MenB test strains prevalent in US and Europe and from 2 US college outbreaks, representing 14 different fHBP† variants

All fHBP variants heterologous to vaccine variants (with exception of A05)

*Publications by Marshall et al. (2013) and Richmond et al. (2012a) – see below; as well as, conference presentation by Vesikari et al. (2014), possibly later published as Vesikari et al. (2015) – see below

†fHBP: Factor H binding protein</td><td>enrolled in 3 previous clinical trials</td><td>
<table>
<tr><th>fHBP variant</th><th></th><th>Adolescents</th><th>Adults</th></tr>
<tr><td rowspan="2">A04</td><td>2</td><td>100</td><td>75</td></tr>
<tr><td>3</td><td>100</td><td>93.3</td></tr>
<tr><td rowspan="2">A05</td><td>2</td><td>89</td><td>88–95.8</td></tr>
<tr><td>3</td><td>97.4</td><td>95.8–100</td></tr>
<tr><td>A07</td><td>3</td><td>71.4</td><td>-</td></tr>
<tr><td>A12</td><td>3</td><td>61.7</td><td>-</td></tr>
<tr><td rowspan="2">A19</td><td>2</td><td>66.7</td><td>-</td></tr>
<tr><td>3</td><td>95.8</td><td>-</td></tr>
<tr><td rowspan="2">A22</td><td>2</td><td>88.7</td><td>60–75</td></tr>
<tr><td>3</td><td>88–95</td><td>88.2–94.7</td></tr>
<tr><td rowspan="2">A56</td><td>2</td><td>94.9</td><td>87.5</td></tr>
<tr><td>3</td><td>87.5</td><td>100</td></tr>
<tr><td rowspan="2">B02</td><td>2</td><td>77.9</td><td>92</td></tr>
<tr><td>3</td><td>84.6</td><td>95.8</td></tr>
<tr><td rowspan="2">B03</td><td>2</td><td>33.3</td><td>46.2</td></tr>
<tr><td>3</td><td>75.6</td><td>85</td></tr>
<tr><td rowspan="2">B09</td><td>2</td><td>-</td><td>31.8–56.5</td></tr>
<tr><td>3</td><td>-</td><td>55.6–75.0</td></tr>
<tr><td rowspan="2">B16</td><td>2</td><td>-</td><td>54.5–61.9</td></tr>
<tr><td>3</td><td>-</td><td>68.4–75.0</td></tr>
<tr><td rowspan="2">B24</td><td>2</td><td>55.6–77.8</td><td>68.0</td></tr>
<tr><td>3</td><td>88.9–100</td><td>81.0</td></tr>
<tr><td rowspan="2">B44</td><td>2</td><td>68.7</td><td>63.6–78.3</td></tr>
<tr><td>3</td><td>88.7</td><td>83.3–94.7</td></tr>
<tr><td rowspan="2">B153</td><td>2</td><td>44.4–66.7</td><td>-</td></tr>
<tr><td>3</td><td>77.8–100</td><td>-</td></tr>
</table>
** Seroprotection: The proportion of subjects achieving serum bactericidal assay using human complement (hSBA) titres ≥1:8 against MnB test strains, measured at 1 month after dose 2 and 1 month after dose 3, which is more stringent than the accepted correlate of protection (hSBA titre ≥1:4</td><td></td><td></td></tr>
<tr><td>Lujan et al. (2017)</td><td>Bivalent rLP2086 (120µg) in a three</td><td>Post-licensure immunogenicity study</td><td>Microbiologists or health care workers</td><td>Primary outcome: Seroconversion†
(1) After dose 2 (n=17)</td><td>II-2</td><td>Fair /Poor</td></tr>
</table>

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
	dose schedule (0,2,6 months)	MenB test strains (n=15) comprising 8 different fHBP variants (A19 (x3), A23, A25, A76, B01 (x4), B15 (x3), B276, B510) obtained from recent US university outbreaks (n=6), jurisdictions in Canada and Norway with hyperendemic MenB disease (n=3), states in the United States with endemic MenB disease (n=5), and a mutant strain with lower fHBP expression (n=1) Immunogenicity against MnB test strains assessed using hSBA at one month post dose 2 and one month post dose 3 Reciprocal geometric mean titres (GMTs) also assessed at various time points after vaccination: 1 month post doses 2 (n=17), 1 month post dose 3 (n=15), 4–6 months post dose 2 (n=10) [Subjects with pre-vaccination titres >1:8 excluded]	UCSF-Benioff Children's Hospital Oakland (n=13)* University of Massachusetts School of Medicine (n=5)* Median age: 40 years of age (range: 24–66 years) *Number of participants who contributed to final immunogenicity testing at each time point and for each MnB test strain varied	• ≥70% of subjects for 3/6 fHBP subfamily A variants (one of three A19 isolates, A23, A76) • ≥70% of subjects for 2/9 subfamily B variants (one of four B01 isolates, B510) (2) After dose 3 (n=15) • >70% of subjects for all fHBP subfamily A variants (A19, A23, A25, A76) • >70% of subjects for 7/9 fHBP subfamily B variants (three of four B01 isolates, two of three B15 isolates, B276, B510) Secondary outcomes (3) Reciprocal geometric mean titres (rGMTs) • Rapid decline in titres between 1 and 4–6 months post dose 2 • High booster response seen 1 month post dose 3 • After dose 2 ▪ rGMT: approx. 15–70 (A19, A23, A25, A76) ▪ rGMT: approx. 8–25 (B01, B15, B276, B510) After dose 3 ▪ rGMT: 33 to >151 (A19, A23, A25, A76) ▪ rGMT: 22–76 (B01, B15, B276, B510) (4) Seroprotection** • 94–100% of subjects against all MenB test strain fHBP variants 1 month after dose 3 • At 9–11 months post dose 3: ▪ 27–80% of subjects against a subset of 3 fHBP subfamily A variants (A19(x2), A25) ▪ 33–85% of subjects against a subset of 6 fHBP subfamily B variants (B01(x3), B15(x3), B276) †Seroconversion: Proportion of subjects with ≥4-fold rise in hSBA titre 1 month after dose 2 or dose 3 compared to pre-immunization titre. If baseline hSBA titer <1:4, a protective response was defined as an hSBA titer ≥1:16		

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		hSBA persistence was assessed using samples collected 9–11 months post dose 3 (n=10–13)		**Seroprotection: Proportion of subjects achieving serum bactericidal assay using human complement (hSBA) titres of ≥1:4 against MenB test strains		
Marshall et al. (2013)	Bivalent rLP2086 (120µg) 3 dose schedule (0,1,6 months)	Phase 2, open-label trial Australia Multisite (n=3) Selected MenB test strains represent >90% of invasive disease-causing isolates fHBP variants (A05, B02, A22, B44, B24) from US and Europe Sera from all participants used to assess hSBA against vaccine homologous (A05) or near homologous (B02) fHBP variants Sera from subset of participants 18–25 years used to assess hSBA against remaining MenB test strain fHBP variants (A22, B24, B44)	Healthy adults (18–40 years of age) (n=60) Mean age 28.6±6.7 years 73.3% female	(1) Seroconversion† Subjects achieving seroconversion tended to increase with increasing doses After dose 2: 58.3–65.5% After dose 3: 70.7–94.7% (2) Seroprotection* After dose 2 • Approx. 70–85% (A05, B02, A22, B44) • Approx. 75% (B24) After dose 3 • >94% (A05, B02, A22, B44) • 81.0% (B24) (3) Geometric mean titres (GMTs) After dose 2 hSBA GMTs: Not calculated** (A05, B02, B24); approx. 100 (A22); approx. 50–60 (B44) After dose 3 • hSBA GMTs: 37.8–109.6 (A05, A22, B02, B24, B44) †Seroconversion defined as a ≥4-fold rise in hSBA titre from pre-immunization levels *Seroprotection defined as hSBA titre ≥1:4 using hSBA against MenB strains which express vaccine-homologous (A05), near-homologous (B02) and additional (A22, B44, B24) fHBP variants. **Not calculated if >25% of data was below the lower level of quantitation (hSBA titre of 1:4)	II-2	Fair /Poor

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Marshall et al. (2017)	Bivalent rLP2086 (120 µg) in 3 dose schedule (0,2,6 months)	Phase 2 randomized, single-blind, placebo-controlled trial (February 2009–March 2014) Australia, Poland, Spain Multisite (n=25) Stage 2 of study to assess immune response up to 48 months after dose 3 Blood samples collected at 6, 12, 24 and 48 months after dose 3 hSBA titres assessed against four MenB serogroup test strains with fHBP variants heterologous (A22, B24, A56, B44) to vaccine strain Test strains reflect diversity of serogroups and represent >90% of circulating IMD isolates in US and Europe	Healthy adolescents 11–18 years of age (n=170)** **Number of participants who contributed to immunogenicity testing at each time point and for each MenB test strain varied	Seroprotection† (1) Persistence of hSBA titre (6–48 months post dose 3) • After initial decrease 6 months post dose 3 for all 4 MenB test strains (A22, A56, B24, B44), generally stable to month 48 A22, A56 and B24 >50% of recipients demonstrated seroprotection at each post dose 3 timepoint: • 6 months: 57–89% • 12 months: 54–69% • 24 months: 53–54% • 48 months: 51–59% B44 Proportion of recipients demonstrating seroprotection at each post dose 3 timepoint: • 6 months: 37% • 12 months: 29% • 24 months: 22% • 48 months: 20% (2) 19% (8/42) of participants achieved composite response (seroprotection for all 4 test strains) at 48 months post dose 3 Geometric Mean Titre (GMT) hSBA GMTs for all MnB test strains remained stable from month 12 to month 48 and above correlate of protection from month 6 to month 48: • A22: 19.3–21.6 • A56: 16.2–49.8 • B24: 11.3–12.6 • B44: 6.6–8.5 †Proportion of participants achieving an hSBA titre ≥lower limit quantification of the assay of 1:8 (A56, B24, B44 test strains) or	I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				1:16 (A22), which is a more conservative assessment of response than using the limit of detection (hSBA titre of 1:4), which is the accepted correlate of protection		
Muse et al. (2016)	Bivalent rLP2086 (120 µg) in a 3-dose schedule (0,2,6 months) Quadrivalent meningococcal conjugate vaccine (MCV4) Tetanus, diphtheria, acellular pertussis vaccine (Tdap)	Phase 2, randomized controlled clinical trial United States Multicentre (n=80 sites) Selected MenB test strains expressing two most prevalent fHBP variants in US that are heterologous to vaccine variants (A22, B24).	Healthy children (10–12 years of age) Children randomly assigned (1:1:1) to one of 3 groups: (1) MCV4 + Tdap + rLP2086 (n=888) (2) MCV4 + Tdap (n=878) (3) rLP2086 alone (n=882)	Non-inferiority of immune response (1) MCV4+Tdap+rLP2086 compared to MCV4+Tdap alone • Non-inferiority criteria* met for 6 Tdap, 4 MCV4 antigens • GMT ratios varied from 0.88–1.02 (2) MCV4+Tdap+bivalent rLP2086 compared to bivalent rLP2086 alone • Non-inferiority criteria* met for both bivalent rLP2086 antigens ▪ A22: 0.92 (95% CI: 0.84–1.02) ▪ B24: 0.90 (95% CI: 0.82–1.00) Protective bactericidal antibody response in MCV4+Tdap+bivalent rLP2086 (similar responses for bivalent rLP2086 alone) (3) Seroprotection† After dose 2 • A22: 68.0% (95% CI: 65.4–70.5) • B24: 64.2% (95% CI: 61.5–66.8) After dose 3 • A22: 89.4% (95% CI: 87.7–91.0) • B24: 91.3% (95% CI: 89.7–92.8) (4) Seroconversion** After dose 2 • A22: 64.3% (95% CI: 60.5–67.9) • B24: 56.3% (95% CI: 52.4–60.2) After dose 3 • A22: 84.0% (95% CI: 81.0–86.6) • B24: 85.7% (95% CI: 82.8–88.3) (5) Composite response (proportion of subjects achieving seroconversion to all MCV4 and Tdap antigens):	I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				• MCV4+Tdap+bivalent rLP2086: 68.1–98.6% • MCV4+Tdap alone: 72.7–98.3% * the 1.5-fold non-inferiority criterion: the lower limit of the two-sided 95% confidence interval for the geometric mean ratios were >0.67 for all Tdap and MCV4 antigens and for the two MnB test strains †Seroprotection: The proportion of subjects achieving serum bactericidal assay using human complement (hSBA) titres ≥lower limit of quantitation (LLOQ) (≥1:8 for B24 and ≥1:16 for A22) at each blood sampling time point. **Seroconversion: The proportion of subjects achieving ≥4-fold rise in hSBA titres (if baseline hSBA titer <1:4, a protective response was defined as an hSBA titer ≥1:16; for subjects with a baseline hSBA titer ≥1:4, a substantial response was a ≥4-fold rise in hSBA titer (≥4 times the LLOQ or ≥4 times the baseline titer, whichever is greater))		
Nissen et al. (2013)	Bivalent rLP2086 in a 3-dose schedule (0,1,6 months) Hepatitis A and B vaccine (Twinrix)	Phase 1/2 randomized, controlled trial (November 2006–January 2008) Australia Multiple hospital centres (n=6) Immunogenicity assessed from serum drawn immediately before first vaccination (baseline) and 1 month after bivalent rLP2086 doses 2 and 3 hSBA titres assessed against 5 MenB	Healthy children and adolescents (8–14 years of age) (n=127) Children randomized to one of four groups: (1) rLP2086, 20µg (n=16) (2) rLP2086, 60µg (n=45) (3) rLP2086, 200µg (n=45) (4) Twinrix (n=21)	Seroprotection* After dose 2 • A05, B02: approx. 25–85% • A22, B09, B24: approx. <30% (with exception of 60µg and 200 µg rLP2086 dose against A22, which was >40%) After dose 3 • A05, B02: 68.8–97.7% • A22, B09, B24: <60% (with exception of 60µg rLP2086 dose against B24, which was >60%) Seroconversion† After dose 2 • A05, B02: approx. 20–82% • A22, B09, B24: approx. 5–50% (but only at higher 60µg and 200µg rLP2086 dose levels) After dose 3 • A05, B02: 68.8–95.3%	I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		serogroup test strains homologous (A05), near homologous (B02) and heterologous (A22, B09, B24) to the vaccine antigens and representing 4 of the 6 bivalent rLP2086 subgroups		• A22, B09, B24: 39.5–66.7% (but only at higher 60µg and 200µg rLP2086 dose levels) Geometric mean titres (GMTs) rLP2086-specific IgG binding GMT (A05, A22, B02, B09, B24), *not hSBA GMTs* • Dose 2: approx. 500–1000 • Dose 3: approx. >1000 *Seroprotection: Proportion of participants achieving hSBA titres of >1:4 † Seroconversion: ≥4-fold rise in hSBA titres from baseline to 1 month after dose 3		
Ostergaard et al. (2017)	Bivalent rLP2086 (120 µg) in a three dose schedule (0,2,6 months) Hepatitis A vaccine (HAV)	Phase 3 randomized, controlled, observer-blinded, multicentre trials 10 countries (Canada, Czech Republic, Denmark, Finland, Germany, Italy, Poland, Spain, UK, US) Adolescents randomized 5:2:2:3 to receive one of 3 manufacturing lots of rLP2086 or HAV Young adults randomized 3:1 to receive rLP2086 or saline	Healthy adolescents (10–18 years of age) and adults (18–25 years of age) Adolescents (n=3596) recruited April 2013–June 2015 Adults (n=3304) recruited May 2013–July 2015	(1) Seroconversion* 4 MenB test strains (A22, A56, B24, B44) Adolescents: • Dose 2: 56.0–85.3% • Dose 3: 78.8–90.2% Adults: • Dose 2: 54.6–85.6% • Dose 3: 78.9–89.7% (2) Seroprotection† (a) 4 MenB test strains (A22, A56, B24, B44) Adults: • Dose 2: 67.3–97.4% • Dose 3: 87.1–99.3% (b) Composite outcome against all 4 MenB test strains (A22, A56, B24, B44) Adolescents: • Dose 2: 53.7% (95% CI: 50.9–56.5%) • Dose 3: 82.7% (95% CI: 80.4–84.7%) Adults: • Dose 2: 63.3% (95% CI: 61.1–65.6%) • Dose 3: 84.5% (95% CI: 82.7–86.1%)	I	Good

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		Four primary (A22, A56, B24, B44) and 10 supplementary (A06, A07, A12, A15, A19, A29, B03, B09, B15, B16) MenB test strains selected in unbiased fashion and representative of fHBP expression and diversity among disease causing isolates circulating strains in Europe and US, as well as variants heterologous to vaccine variants. Immunogenicity assessed one month after rLP2086 dose 2 and 3 (4 primary Men B test strains) or after dose 3 (10 additional MenB test strains) Post-hoc analysis of positive predictive value to determine whether responses to primary strains predicted immune response to supplementary test strains expressing fHBP in same subfamily		(c) 10 supplementary MenB test strains (A06, A07, A12, A15, A19, A29, B03, B09, B15, B16) Adolescents: • Dose 2: 58.8–99.0% • Dose 3: 75.3–98.7% Adults: • Dose 2: 51.5–98.0% • Dose 3: 71.5–99.3% (3) hSBA Geometric mean titre (GMTs) (a) 4 MenB test strains (A22, A56, B24, B44) Adolescents: • Dose 2: 14.3–130.0 • Dose 3: 23.7–218.4 Adults: • Dose 2: 21.7–113.3 • Dose 3: 46.3–175.3 (b) 10 supplementary MenB test strains (A06, A07, A12, A15, A19, A29, B03, B09, B15, B16) Adolescents: • Dose 2: 13.1–68.1 • Dose 3: 21.4–93.6 Adults: • Dose 2: 11.8–87.4 • Dose 3: 20.7–97.0 (4) Positive predictive value (PPV) Adolescents: Subfamily A • Dose 2: 64.4–100% • Dose 3: 75.6–99.6% Subfamily B • Dose 2: 78.9–100% • Dose 3: 86.4–99.6% Adults: • Dose 2: 61.6–100%		

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				• Dose 3: 72.2–100% Subfamily B • Dose 2: 70.0–100% • Dose 3: 80.5–98.8% *Seroconversion: A 4-fold response was defined as follows: for subjects with a baseline hSBA titer below the limit of detection (LOD) or an hSBA titer <1:4, a 4-fold response was an hSBA titre ≥1:16 or the lower limit of quantitation (LLOQ), whichever was higher; for subjects with a baseline hSBA titre ≥LOD (i.e., hSBA titre ≥1:4) and <LLOQ, a 4-fold response was an hSBA titre ≥4 times the LLOQ; and for subjects with a baseline hSBA titre ≥LLOQ, a 4-fold response was an hSBA titre ≥4 times the baseline titre. The LLOQ is the lowest titre that can be determined with suitable precision and is within the linear assay range, as determined during assay qualification or validation. †Seroprotection: An hSBA titre that reached or exceeded the LLOQ one month after dose 3. The LLOQ was either 1:8 (A07, A15, A29, A56, B03, B09, B15, B16, B24, B44) or 1:16 (A06, A12, A19, A22).		
Reiner et al. (2016)	Bivalent rLP2086 (120µg) in a 3-dose schedule (0,2,6 months)	Phase 2, single-arm, open-label trial (February 2013–February 2014) United States Single centre Immunogenicity assessed using hSBA against four MenB test strains (A22, A56, B24, B44) heterologous to vaccine fHBP variants and from 4 of 6 major phylogenetic subgroups representing >90% of	Laboratory workers working directly with pathogenic *N. meningitidis* serogroup B in the bivalent rLP2086 development program (n=13)* 24–62 years of age (mean age: 44 years) 69% female *Number of participants who contributed to immunogenicity testing at each time point and for each MenB test strain varied	Seroprotection† Only n=6 subjects had evaluable immunogenicity results After Dose 2 • A22: 60% (3/5) • A56, B24: 100% (6/6) • B44: 50% (3/6) After Dose 3 • A22, A56, B24: 100% (6/6) • B44: 50% (3/6) Composite response After dose 2: 60% (3/5) (A22, A56, B24, B44) After dose 3: 60% (3/5) (A22, A56, B24, B44) Seroconversion** After dose 3 • A22: 83% (5/6)	II-2	Fair/Poor

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		disease isolates in the United States and Europe		• A56: 100% (5/5) • B24: 67% (4/6) • B44: 50% (3/6) †Immunogenicity assessed one month after bivalent rLP2086 doses 2 and 3. Protective hSBA response assessed as the proportion of subjects achieving serum bactericidal assay using human complement (hSBA) titres ≥lower limit of quantitation (LLOQ) (≥1:8 for A56, B24, B44 and ≥1:16 for A22). These LLOQs are more stringent than the recognized correlate of protection, an hSBA titre of ≥1:4 **Seroconversion: ≥4-fold rise in hSBA titres from baseline to 1 month after dose 3		
Richmond et al. (2012a)	Bivalent rLP2086 in 3-dose schedule (0,2,6–9¥ months) ¥Protocol amended to expand time window for third vaccination due to protocol-defined study pause to investigate a serious adverse event (episode of anaphylaxis)	Phase 2 randomized, single-blind, placebo-controlled trial (February 2009–May 2010) Australia, Poland, Spain Multisite (n=25) Three dosing formulations of vaccine used (60µg, 120µg and 200µg) Blood samples collected at 1 month after 2nd and 3rd doses of bivalent rLP2086 hSBA titres assessed against 8 MenB serogroup test strains (A04, A05, B02, B03,	Healthy adolescents (11–18 years of age) (n=536)* Placebo: n=121 Bivalent rLP2086 (60µg): n=22 Bivalent rLP2086 (120µg): n=198 Bivalent rLP2086 (200µg): n=195 *Number of participants who contributed to immunogenicity testing at each time point and for each MenB test strain varied	Seroprotection† (n=349) After dose 2 A04, A05, A56, B02, B03, B44: approx. 35–100% of participants receiving either 120µg or 200µg of rLP2086 After dose 3 A04, A05, A56, B02, B03, B44: 67.9–100% of participants receiving either 120µg or 200µg of rLP2086 • Immune response did not significantly increase in proportion to increasing rLP2086 dose (120µg versus 200µg) Seroconversion** (n=40)†† After dose 3 A22: 88.0% (95% CI: 68.8–97.5) B24: 83.9% (95% CI: 66.3–94.5) †Seroprotection: Participants achieving an hSBA titre ≥lower limit of quantification of the assay (ranging from 1:7 to 1:18 depending on hSBA assay and strain), which is a more conservative assessment of response than using the limit of detection (hSBA titre of 1:4), which is the accepted correlate of protection **Seroconversion: a four-times or more increase in hSBA titre	I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		A56, B44, A22, B24) reflecting diversity of serogroups circulating between 2000 and 2006 in the United States and Europe and causing IMD		††Subset of n=40 participants who received dose of 120µg, selected with a random number generator, analyzed for seroconversion to MnB serogroup test strains A22 and B24		
Richmond et al. (2012b)	Bivalent rLP2086 in a 3-dose schedule (0,1,6 months)	Phase 1, double-blind, randomized controlled trial (March 2006–May 2007) First study of bivalent rLP2086 in humans Australia Multicentre (n=3) Immunogenicity testing against six MenB test strains (A05, A17, A22, B02, B09, B24) from fHBP subfamily A and B proteins	Healthy adults (18–25 years of age) (n=103)* Mean age: 22 years; 72% female Participants randomized (2:1) to receive either one of three doses of vaccine or placebo Placebo: n=35 Bivalent rLP2086 (20µg): n=21 Bivalent rLP2086 (60µg): n=23 Bivalent rLP2086 (200µg): n=24 *Number of participants who contributed to immunogenicity testing at each time point and for each MnB test strain varied	Geometric mean titres (GMTs) rLP2086 specific IgG A05, B01 • 19–168-fold increase in IgG GMT after dose 2 across all dose levels • GMT higher post dose 3 but only for 60µg and 200 µg dose levels • In general, increased GMTs with escalating dose levels, but 95% confidence intervals overlapping • Highest titres observed with 200µg dose at all assessment time points hSBA GMTs A05, A17, A22, B02, B09, B24 • GMTs increased with ascending dose levels • 60 µg and 200 µg generally more immunogenic than 20 µg dose • At 200 µg dose level, post dose 2 ▪ Approx. >15 (A05, A17, A22, B02, B09, B24) ▪ >100 (A05, A17, B09) • At 200 µg dose level, post dose 3 ▪ >60 (A05, A17, A22, B02, B09, B24) ▪ >100 (A05, A17, A22, B02) Seroprotection** A05, A17, A22, B02, B09, B24 After dose 2 ▪ Placebo: approx. 15–40% ▪ 20 µg: approx. 40–80% ▪ 60 µg: approx. 35–95%	I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				▪ 200 µg: approx. 65–100% After dose 3 ▪ Placebo: 16–52% ▪ 20 µg: 47–90% ▪ 60 µg: 75–100% ▪ 200 µg: 88–100% Seroconversion† A05, A17, A22, B02, B09, B24 After dose 2 ▪ Placebo: 0–11.8% ▪ 20µg: 15.8–73.7% ▪ 60µg: 27.3–81.8% ▪ 200µg: 42.9–90.0% After dose 3 ▪ Placebo: 0–22.6% ▪ 20µg: 22.2–83.3% ▪ 60µg: 55.0–95.0% ▪ 200µg: 50.0–100.0% **seroprotection: proportion of participants achieving an hSBA titre of ≥1:4 against each of the six MnB test strains †hSBA seroconversion: proportion of participants achieving a ≥4-fold increase in hSBA titre from baseline. If baseline titres below lower level of quantitation (LLOQ) of 1:4, a titre of 1:8 post-vaccination required to be considered seroconversion		
Senders et al. (2016)	Bivalent rLP2086 (120µg) in 3-dose schedule (0,2,6 months) HPV-4 vaccine (quadrivalent human papilloma virus)	Phase 2, randomized controlled trial United States Multisite (n=63) Samples for immunogenicity testing collected before dose 1	Healthy adolescents (11–17 years of age) (n=2483) Mean age: 13.6 years 66.5% male	Non-inferiority of immune response induced by induced by rLP2086+HPV4 compared to bivalent rLP2086 alone • Non-inferiority criteria* met for GMT ratios against MenB test strains ▪ A22: 0.92 (95% CI: 0.85–1.00) ▪ B24: 0.92 (95% CI: 0.84–1.01) Non-inferiority of immune response induced by bivalent rLP2086+HPV4 compared to HPV4 alone	I	Good

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		and approximately 1 month after doses 2 and 3 Immunogenicity testing after dose 3 against four MenB test strains (A22, A56, B24, B44) from fHBP subfamily A and B proteins representing >90% of disease isolates in the United States and Europe	Participants randomly assigned (2:2:1) to one of 3 groups: Group 1: rLP2086 + HPV4 (n=992) Group 2: rLP2086 + saline (n=990) Group 3: saline + HPV4 (n=501)	• Non-inferiority criteria* met for GMT ratios against 3 of 4 HPV4 antigens ▪ HPV6: 0.82 (0.72–0.94) ▪ HPV11: 0.82 (0.74–0.91) ▪ HPV16: 0.78 (0.68–0.88) ▪ HPV18: 0.71 (0.62–0.81) Seroprotection† (a) Bivalent rLP2086+HPV4 Proportion of participants with seroprotective hSBA titres against four MenB test strains A22 • Dose 2: 83.0% (95% CI: 80.2–85.5) • Dose 3: 94.0% (95% CI: 92.2–95.6) A56 • Dose 2: 97.5% (95% CI: 96.1–98.4) • Dose 3: 98.9% (95% CI: 97.9–99.5) B24 • Dose 2: 70.6% (95% CI: 67.3–73.8) • Dose 3: 90.5% (95% CI: 88.2–92.4) B44 • Dose 2: 54.5% (95% CI: 51.0–58.1) • Dose 3: 82.7% (95% CI: 79.9–85.3) (b) Bivalent rLP2086 alone A22 • Dose 2: 85.8% (95% CI: 83.2–88.1) • Dose 3: 96.3% (95% CI: 94.7–97.5) A56 • Dose 2: 98.5% (95% CI: 97.4–99.2) • Dose 3: 99.4% (95% CI: 98.6–99.8) B24 • Dose 2: 74.2% (95% CI: 70.9–77.2) • Dose 3: 92.6% (95% CI: 90.5–94.3) B44 • Dose 2: 57.1% (95% CI: 53.5–60.6) • Dose 3: 85.7% (95% CI: 83.0–88.0)		

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				Composite response†† achieved by: • Dose 2: 49.9% (bivalent rLP2086+HPV4) and 51.9% (bivalent rLP2086 alone) • Dose 3: 81.0% (bivalent rLP2086+HPV4) and 83.9% (bivalent rLP2086 alone) Seroconversion** of hSBA titres against four MenB test strains in both groups receiving bivalent rLP2086 vaccine A56 • Dose 2: 92% • Dose 3: 95% A22, B24, B44 • Dose 2: 46–74% • Dose 3: 77–86% * the 1.5-fold non-inferiority criterion: the lower limit of the two-sided 95% confidence interval for the geometric mean ratios at one month after dose 3 were >0.67 for each of the HPV4 antigens and for each of the two MnB test strains †Seroprotection: the proportion of subjects achieving serum bactericidal assay using human complement (hSBA) titres ≥lower limit of quantitation (LLOQ) (≥1:8 for A56, B24, B44 and ≥1:16 for A22) at each blood sampling time point ††Composite response: Seroprotection achieved for all 4 MenB test strain fHBP antigens **Seroconversion: the proportion of subjects achieving ≥4-fold rise in hSBA titres from baseline		
Sheldon et al. (2012)	Bivalent rLP2086 given in 3-dose schedule (0,2,6–9 months)* Tetanus, diphtheria, acellular pertussis vaccine (Tdap)	Phase 1, randomized, open-label, active and placebo-controlled trial (April 2009–March 2010) United States Single site	Healthy adults (18-40 years of age) (n=48)† Mean age: 28.8 years 60.4% female Placebo (n=12)	Geometric mean titres (GMTs) • Significant increase in bivalent rLP2086-specific IgG titres against vaccine homologous antigens • GMTs tended to increase with additional dose, but difference not significant • After dose 2 ▪ A05: >1,000 ▪ B02: Approx. 1,000 • After dose 3	I	Poor

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
	with saline given for dose 2 and dose 3 *Protocol amended to expand time window for third vaccination due to protocol-defined study pause to allow investigation of a serious adverse event (episode of anaphylaxis) in a separate study	Subjects randomly selected (1:1:1:1 ratio) to receive bivalent rLP2086 (either 60µg, 120µg, 200µg) or Tdap IgG titres (GMT) against vaccine homologous rLP2086-specific antigens (A05, B02) assessed from blood samples collected 1 month after dose 2 and dose 3	Bivalent rLP2086 60µg (n=12) 120µg (n=12) 200µg (n=12) †A total of n=14 subjects withdrew after randomization: 5 from Tdap group and 9 from the various rLP2086 groups (60ug: 4, 120ug: 2; 200ug: 3). Therefore, the number of participants who contributed to immunogenicity testing varied by group for dose 2 (n=9–12) and dose 3 (n=7–10)	▪ A05: >1,000 ▪ B02: >1,000		
Taha et al. (2017)	Bivalent rLP2086 (120µg) in a three dose schedule (0,2,6 months)	Sub-analysis of sera obtained from subjects in previously conducted Phase 2, randomized, placebo-controlled, single blind clinical trial of rLP2086* MenB test strains (one strain per outbreak) obtained from IMD patients during 6 MenB outbreaks in France (2011–2015) Immunogenicity assessed against MenB test strains (A22, B03, B24(2), B44,	Healthy adolescents (11–18 years of age)† (n=15) 11–13 years: (n=8, 53%) 14–18 years: (n=7, 47%) †convenience sample from subjects with sufficient sera remaining to assess hSBA titres	Seroprotection** After dose 2 A22: 47% B24: 40–60% B44: 93% B03: 67% B228: 60% After dose 3 A22: 73% B24: 73–87% B44: 100% B03: 100% B228: 100% Seroconversion†† After dose 2 A22: 40% B24: 33–47% B44: 80%	II-2	Fair/Poor

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		B228) heterologous to vaccine strains and among most common variants in France (with exception of B228), as well as being found in United States and other European countries *Vesikari et al. (2015), see below		B03: 67% B228: 53% After dose 3 A22: 73% B24: 60–73% B44: 100% B03: 100% B228: 87% ** Seroprotection rate: The proportion of subjects with an hSBA titre ≥1:4 ††Seroconversion: the proportion of subjects achieving ≥4-fold rise in hSBA titres from baseline		
Vesikari et al. (2015)	Bivalent rLP2086 (120µg)	Phase 2, multicentre, randomized, single-blind trial (March 2011–August 2013) Czech Republic, Denmark, Finland, Germany, Poland, Spain, Sweden Subjects randomized (3:3:3:2:1) into 5 groups based on bivalent rLP2086 dosing schedule Immunogenicity assessed against 4 MnB test strains (A22, A56, B24, B44) heterologous to the vaccine strains and	Healthy adolescents (11–18 years of age) (n=1713) Group 1 (0,1,6 months) n=427 Group 2 (0,2,6 months) n=430 Group 3 (0,6 months) n=427 Group 4 (0,2 months) n=286 Group 5 (0,4 months) n=143 Mean age: 14.4 years 49–52% female	Seroprotection** after 3 doses 0,1,6 month dosing group • A22: 91.7% • A56: 99.4% • B24: 89.0% • B44: 88.5% 0,2,6 month dosing group • A22: 95% • A56: 98.9% • B24: 88.4% • B44: 86.1% Seroprotection**after 2 doses 0,6 month dosing group only • A22: >90% • A56: >98% • B24: >69% • B44: >70% Geometric mean titres (GMTs) • Increased with each bivalent rLP2086 dose • Highest among subjects receiving 3 doses	I	Good

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		representing 4 of the 6 major factor-H binding protein (fHBP) variant subgroups accounting for >90% of IMD isolates circulating in the United States and Europe	Age at first injection: 36–37% (11–13 years of age); 63–64% (14–18 years of age) n=1450, evaluable for immunogenicity* *Number of participants who contributed to immunogenicity testing at each time point and for each MnB test strain varied	• Higher in those with longer interval between doses (6>4>2>1 months) 0,1,6 month dosing group • A22: 55.1, A56: 152.9, B24: 29.1, B44: 40.3 0,2,6 month dosing group • A22: 56.3, A56: 155.6, B24: 25.6, B44: 35.0 After 2 doses (all groups) • A22: 37.1–48.4 • A56: 104.9–125.6 • B24: 14.7–20.6 • B44: 17.8–22.5 **Seroprotection: the proportion of subjects who achieved serum bactericidal assay using human complement (hSBA) titres ≥1:8 for the four MnB test strains (A22, A56, B24, B44) one month after doses 2 or 3. An hSBA titres ≥1:8 is a more conservative indicator of seroprotection than a titre of ≥1:4, which is the recognized correlate of protection against meningococcal disease		

Vesikari et al. (2016)	Bivalent rLP2086 (120 µg) in a three dose schedule (0,2,6 months)
	
	Diphtheria, tetanus, acellular pertussis, inactivated polio vaccine (DTaP/IPV)
		Phase 2, randomized, placebo-controlled, single-blind trial
		
		Finland, Germany, Poland
		
		Multisite (n=34)
		
		Participants randomly assigned (1:1):
		• Group 1 (bivalent rLP2086 + DTaP/IPV)
		• Group 2 (saline + DTaP/IPV)
			Healthy adolescents (11–18 years of age) (n=749)*
			
			Mean age: 13.9 years
			
			Group 1: bivalent rLP2086 + DTaP/IPV (n=373)
			
			Group 2: saline + DTaP/IPV (n=376)
			
			*Number of participants who contributed to immunogenicity testing at
				Non-inferiority** of immune response induced by DTaP/IPV + bivalent rLP2086 compared to DTaP/IPV alone
				• Non-inferiority criteria* met for percentage difference in proportion of persons achieving prespecified antibody levels against all 9 DTaP/IPV antigens
				  • Diphtheria: 0.0% (-1.6 to 1.5)
				  • Tetanus: 0.0% (-1.1 to 1.1)
				  • Pertussis (x4): -1.3 to 0.0% (-4.7 to 1.9)
				  • Polio (x3): 0.0% (-1.1 to 1.1) all three
				
				Geometric mean titre (GMT)
				GMT ratio of immune response induced by DTaP/IPV + rLP2086 compared to DTaP/IPV alone
				• Similar between the two groups for each DTaP/IPV antigen
					I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		Samples for immunogenicity testing collected before dose 1 and approximately 1 month after doses 1, 2 and 3 Sera from ~50% of subjects in each group tested against MnB test strains A22, B24 and ~50% from each group tested against test strains A56 and B44 MnB test strains represent >90% of invasive MnB disease-causing isolates in United States and Europe Electronic diaries used to capture self-reported local and systemic reactions for 7 days after each vaccination	each time point and for each MnB test strain varied	**Concomitant Vaccine Antigen** / **Bivalent rLP2086 + dTaP/IPV (N[a]=337)** GM[b] (95% CI)[c] / **Saline + dTaP/IPV (N[a]=348)** GM[b] (95% CI)[c] / **Difference Ratio (95% CI)[d]** Diphtheria: 1.4 (1.28, 1.55) / 1.5 (1.34, 1.63) / 0.95 (0.83, 1.09) Tetanus: 12.3 (11.50, 13.11) / 12.4 (11.52, 13.25) / 0.99 (0.90, 1.09) Pertussis toxoid: 27.1 (24.45, 30.07) / 26.5 (23.95, 29.38) / 1.02 (0.88, 1.18) Pertussis FHA: 119.4 (111.15, 128.17) / 122.9 (115.14, 131.13) / 0.97 (0.88, 1.07) Pertussis PRN: 317.0 (285.64, 351.80) / 336.1 (305.82, 369.30) / 0.94 (0.82, 1.09) Pertussis FIM types 2 + 3: 339.1 (296.35, 387.94) / 364.5 (320.62, 414.42) / 0.93 (0.77, 1.12) Poliovirus type 1: 662.1 (567.36, 772.67) / 672.6 (581.87, 777.55) / 0.98 (0.80, 1.22) Poliovirus type 2: 840.5 (725.11, 974.29) / 995.8 (860.54, 1152.41) / 0.84 (0.69, 1.04) Poliovirus type 3: 2237.4 (1945.81, 2572.65) / 2450.1 (2152.60, 2788.70) / 0.91 (0.76, 1.10)		

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				dTaP/IPV=diphtheria tetanus and pertussis-inactivated poliovirus vaccine; rLP2086=bivalent rLP2086; FHA, filamentous hemagglutinin; FIM, fimbrial agglutinogens, GM, geometric mean; PRN, pertactin [a]N = number of subjects with valid and determinate assay results for the given antigen. [b]Geometric mean (GMs) were calculated using all subjects with valid and determinate assay results. [c]Confidence intervals (CIs) are back transformations of confidence levels based on the Student t distribution for the mean logarithm of assay results. [d]Confidence Intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student *t* distribution for the mean difference of the logarithms of the measures (rLP2086+dTaP/IPV group – saline+dTaP/IPV group. hSBA GMTs against four MnB test strains (rLP2086 + TDaP/IPV vs. saline + TDaP/IPV) After dose 2 • A22: 35.5 (95% CI: 30.3–41.6) vs 11.2 (95% CI: 10.0–12.5) • A56: 91.1 (78.0–106.5) vs 8.3 (6.8–10.3) • B24: 15.9 (13.6–18.6) vs 4.8 (4.4–5.2) • B44: 14.6 (11.6–18.4) vs 4.7 (4.2–5.1) After dose 3 • A22: 63.4 (95% CI: 55.3–72.8) vs 11.0 (95% CI: 9.9–12.3) • A56: 151.5 (131.5–174.6) vs 8.5 (6.9–10.5) • B24: 28.3 (24.5–32.7) vs 4.8 (4.4–5.2) • B44: 36.5 (28.9–46.2) vs 4.7 (4.3–5.2) Seroprotection[†] Against four MnB test strains A22 • Dose 2: 81.8% • Dose 3: 95.6% A56 • Dose 2: 97.3% • Dose 3: 100%		

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				B24 • Dose 2: 81.0% • Dose 3: 96.8% B44 • Dose 2: 55.5% • Dose 3: 81.5% **Non-inferiority criterion: The lower limit of the two-sided 95% confidence interval for the difference in proportion of participants (rLP2086+DTap/IPV group – saline+DTaP/IPV group) achieving the pre-specified antibody level criteria is greater than -10% at one month after vaccination dose 1 for all 9 DTaP/IPV antigens †Seroprotection: the proportion of subjects achieving serum bactericidal assay using human complement (hSBA) titres ≥lower limit of quantitation (LLOQ) (≥1:8 for A56, B24, B44 and ≥1:16 for A22) at each blood sampling time point		

APPENDIX B: SUMMARY OF SAFETY FINDINGS

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Safety						
Fiorito et al. (2017) (online publication ahead of print)	Bivalent rLP2086 in a three dose schedule (0,2,6 months)	Cohort study (February 2015–May 2016) United States College experiencing invasive meningococcal B disease outbreak Vaccination of eligible persons during outbreak and as part of new policy for incoming freshmen Paper-based and electronic (after 3rd dose only) surveys of vaccine recipients for self-reported AEs following *previous* vaccination (e.g., survey regarding AEs following dose 1 administered at time of receipt of dose 2) Systematic literature review of clinical trials of Trumenba® safety to establish expected type and frequency of AEs	Adults (18–26 years of age)* Eligible persons at time of outbreak (n=3745) Eligible incoming freshmen (n=1050) Exclusion criteria: Otherwise eligible persons who had a recent illness diagnosed by a physician that could account for symptoms compatible with an adverse event following immunization *all undergraduate students, graduate students residing in dormitories, persons who were in intimate relationship with someone residing on campus, graduate assistants and faculty, persons with medical conditions that put them at increased risk for meningococcal disease meeting this age criterion	Vaccination coverage of eligible persons • Dose 1: 92% (4418/4795) • Dose 2: 74% (3531/4795) • Dose 3: 44% (2124/4795) Survey response rates Dose 1 • 39% (1736/4418) of persons who received dose 1 • 49% (1736/3531) of persons who had an opportunity to complete the survey (i.e., received dose 2) Dose 2 • 40% (1395/3531) of persons who received dose 2 • 66% (1395/2124) of persons who had an opportunity to complete the survey (i.e., received dose 3) Dose 3 • 29% (609/2124) of persons receiving dose 3 • 36% (609/1712) of persons who had an opportunity to complete the survey (i.e., provided a legible email address to receive electronic survey) • 23% (1081/4795) of eligible persons completed one or more surveys • 14% (477/3531) of persons who received dose 2 completed surveys about doses 1 and 2 • 10% (220/2124) of persons who received dose 3 completed all three surveys Local and systemic** AEs • 64–78% self-reported injection site pain • Myalgia (47%) and fatigue (35%) most frequently self-reported systemic reactions	II-2	Poor

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				• Proportions of subjects self-reporting local and/or systemic adverse events after each dose comparable to proportions reported in clinical trials SAEs • 0.3–4.8% of survey respondents reported a serious adverse event (e.g., report of any allergic reaction; hospitalization; difficulty breathing; hives, welts, or severe rash; swelling of face, mouth, throat) • Majority of hospitalizations felt to be unrelated to vaccine administration or allergic reaction to vaccine **Systemic adverse events: fatigue, headache, chills, confirmed fever, myalgia		
Marshall et al. (2013)	Bivalent rLP2086 (120 µg) 3 dose schedule (0,1,6 months)	Phase 2, open-label trial Australia Multisite (n=3) Selected MenB test strains represent >90% of invasive disease-causing isolates fHBP variants (A05, B02, A22, B44, B24) Sera from all participants used to assess hSBA against vaccine homologous (A05) or near homologous (B02) fHBP variants Sera from subset of participants 18–25	Healthy adults (18–40 years of age) (n=60) Mean age 28.6±6.7 years 73.3% female	(1) Local reactions (most common) • Pain at injection site: 91.2–92.7% of subjects after each vaccination • Induration: 21.1–27.3% of subjects after each vaccination; 3 severe reactions after 3rd dose • Erythema: 10.0–14.5% of subjects after each vaccination; 4 severe reactions (1 after 2nd dose, 3 after 3rd dose) No local reactions lasted >10 days (2) Systemic reactions* (most common) • Headache: 47.4–61.7% of subjects • Fatigue: 41.8–60.0% of subjects Median duration of symptoms 1–2 days after vaccination Frequency generally decreased with subsequent vaccinations No severe systemic events after doses 1 and 2. One participant experienced severe fatigue, headache, nausea, and vomiting 5 days after dose 3; no source of concurrent illness identified. Had full recovery	II-2	Good

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		years used to assess hSBA against remaining MenB test strain fHBP variants (A22, B24, B44)		No recipients had fever ≥39 °C Four vaccine recipients reported constellations of symptoms (e.g., fatigue, headache, joint pain, muscle pain) associated with upper respiratory tract infection (2), sinusitis (1) and no identified cause (1), with durations from 5–25 days after various vaccine doses (3) Unsolicited AEs • 46 (76.7%) of subjects reported 108 AEs: URTI (31.7%), headache (10.0%), gastroenteritis (6.7%) (4) Unsolicited SAEs • 1 event considered vaccine related: URTI reported 7 days after 2nd dose *systemic reactions: fatigue, headache, diarrhea, nausea, vomiting, chills, muscle pain, joint pain, and fever		
Marshall et al. (2017)	Bivalent rLP2086 (120 µg) in 3 dose schedule (0,2,6 months)	Phase 2 randomized, single-blind, placebo-controlled trial (February 2009–March 2014) Australia, Poland, Spain Multisite (n=25) Stage 2 of study to assess immune response up to 48 months after dose 3 Safety assessment limited to reporting of SAEs, newly diagnosed chronic	Healthy adolescents 11–18 years of age (n=170)	Any AEs • Bivalent rLP2086 recipients: 8 (5%) • Controls: 2 (3%) SAEs • Bivalent rLP2086 recipients: 4 (2%) • Controls: 1 (1%) • None of the events felt to be vaccine-related (e.g., alcohol poisoning, depression) Newly diagnosed chronic medical disorders • Bivalent rLP2086 recipients: 2 (1%) • Controls: 1 (1%) • None deemed to be vaccine related (e.g., rheumatoid arthritis, CNS germinoma, factor V Leiden mutation)	I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		medical disorders, neuroinflammatory and autoimmune disorders				
Muse et al. (2016)	Bivalent rLP2086 (120 µg) in a 3-dose schedule (0,2,6 months) Quadrivalent meningococcal conjugate vaccine (MCV4) Tetanus, diphtheria, acellular pertussis vaccine (Tdap)	Phase 2, randomized controlled clinical trial United States Multicentre (n=80 sites)	Healthy children (10–12 years of age) Children randomly assigned (1:1:1) to one of 3 groups: (1) MCV4 + Tdap + bivalent rLP2086 (n=888) (2) MCV4 + Tdap (n=878) (3) Bivalent rLP2086 alone (n=882)	(1) Local reactions* Generally most common after dose 1 and did not increase with subsequent doses MCV4+Tdap+bivalent rLP2086 • Dose 1: 95.6% (95% CI: 94.0–96.8) • Dose 3: 88.6% (95% CI: 86.1–90.8) MCV4+Tdap • Dose 1: 46.5% (95% CI: 43.2–49.9) • Dose 3: 20.1% (95% CI: 17.3–23.1) Bivalent rLP2086 • Dose 1: 91.4% (95% CI: 89.3–93.2) • Dose 3: 86.5% (95% CI: 83.8–88.9) Pain at injection site was most common local reaction Most reactions mild or moderate and transient. (2) Systemic reactions** More common in all groups after dose 1 and did not increase with subsequent dosing MCV4+Tdap+bivalent rLP2086 • Dose 1: 87.0% (95% CI: 84.6–89.2) • Dose 3: 70.3% (95% CI: 66.9–73.6) MCV4+Tdap • Dose 1: 74.8% (95% CI: 71.8–77.7) • Dose 3: 44.4% (95% CI: 40.8–48.1) Bivalent rLP2086 • Dose 1: 81.7% (95% CI: 79.0–84.3) • Dose 3: 66.6% (95% CI: 63.0–70.0)	I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				Headache and fatigue most common systemic reactions Systemic reactions generally mild to moderate severity SAEs were relatively infrequent. One participant had fever >40 °C for one day. (3) Unsolicited AEs No clinically relevant unsolicited AEs were reported by subjects receiving bivalent rLP2086 (4) SAEs Comparable number of SAEs reported between groups: • MCV4+Tdap+bivalent rLP2086: 18 • MCV4+Tdap: 13 • Bivalent rLP2086: 12 None considered vaccine related (e.g., infections, infestations, psychiatric disorders) *Local reactions: redness, pain or swelling **systemic reactions: fever, vomiting, diarrhea, headache, fatigue, chills, muscle or joint pain		
Nissen et al. (2013)	Bivalent rLP2086 in a 3-dose schedule (0,1,6 months) Hepatitis A and B (Twinrix)	Phase 1/2 randomized, controlled trial (November 2006–January 2008) Australia Multiple hospital centres (n=6) Local and systemic reactions following immunization self-recorded by	Healthy children and adolescents (8–14 years of age) (n=127) Children randomized to one of four groups: (1) Bivalent rLP2086, 20 µg (n=16) (2) Bivalent rLP2086, 60 µg (n=45) (3) Bivalent rLP2086, 200 µg (n=45)	(1) Local reactions* Frequency higher with bivalent rLP2086 than with Twinrix, but most mild–moderate in severity • Reports more common with 200µg dose recipients (2) Systemic reactions** Frequency comparable between bivalent rLP2086 and control recipients Among bivalent rLP2086 recipients, systemic reactions more frequent with 200 µg dose (3) Unsolicited AEs	I	Good

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		participants using an electronic diary on day of vaccination and for further 13 days. Unsolicited AEs could be reported up to last study visit (43 days after final vaccination)	(4) Twinrix (n=21)	Most common adverse events reported in similar frequency between control and bivalent rLP2086 recipients • Upper respiratory tract infection (52.4% vs. 31.3–55.6%) • Headache (57.1% vs. 25.0–51.1%) 6 bivalent rLP2086 recipients (60 µg: 4, 200 µg: 2) reported 9 severe reactions (erythema, pain and swelling at injection site, anorexia, otitis media, nausea (n=2), headache and earache) • No apparent trend between severe adverse event and dose or dose number (4) SAEs • One person had a serious adverse event felt to be vaccine-related (severe injection site pain, moderate erythema and swelling, fever, nausea, vomiting, muscle and joint pain) • No deaths *Local reactions: Pain, induration, erythema **Systemic reactions: Fever, fatigue, headache, rash, nausea, vomiting, chills, muscle pain, joint pain		
Ostergaard et al. (2016)	Bivalent rLP2086 (120 µg) in a three dose schedule (0,2,6 months)* Hepatitis A virus vaccine (HAV) *HAV recipients, vaccine given in 2 doses (0,6 months)	Phase 3, randomized controlled trial (November 2012–September 2014) Multicountry (Australia, Chile, Czech Republic, Denmark, Estonia, Finland, Germany, Lithuania, Poland, Spain, Sweden, United States) Multisite (n=78)	Healthy adolescents and adults (10–25 years of age) (n=5712) Median age: 18 years (range: 10, 25 years) 10–18 years of age (57.9%) 19–26 years of age (42.1%)	(1) Solicited SAE Overall • Greater proportion of HAV than bivalent rLP2086 recipients reported ≥1 SAE ▪ during the study period (n=48, 2.5% vs. n=59, 1.6%, p=0.013) ▪ during immunization phase (1.8% vs. 1.2%, p=0.042) • Proportions of HAV and bivalent rLP2086 recipients reporting ≥1 SAE not significantly different ▪ within 30 days of each immunization (dose 1: 0.4% vs. 0.2%, p=0.108; dose 2: 0.4% vs. 0.2%, p=0.087; dose 3: 0.1% vs 0.3%, p=0.241)	I	Good

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		Subjects randomized (2:1) to receive either rLP2086 or HAV Data on safety collected at monthly visits/contacts during months 0–7 (vaccination phase) and approximately 6 months after last vaccination (follow-up phase) No immunogenicity data collected	Bivalent rLP2086 recipients (n=3804) HAV recipients (n=1908)	▪ during the follow-up phase after the last dose (0.9% vs. 0.4%, p=0.079). • Only four (n=2 in each group) of these SAEs were considered vaccine-related: neutropenia, anaphylaxis (MenB-fHBP) and demyelination and spontaneous abortion (HAV). (2) Medically-attended adverse events (MAE) Percentage of subjects with ≥1 MAE† (bivalent rLP2086 vs. HAV) • Most MAEs were mild–moderate in severity • Similar proportions within 30 days after each vaccination • Vaccination 1: 7.0% vs. 6.1%, p=0.218 • Vaccination 2: 5.5% vs. 6.1%, p=0.383 • Vaccination 3: 5.3% vs. 5.5%, p=0.843 • Similar proportions during vaccination stage (24.6% vs. 24.5%, p=0.974) and follow-up phase (11.2% vs. 11.4%, p=0.852) • No notable differences between groups in types of MAEs (e.g., upper respiratory tract infection, headache, bronchitis) • Most common MAEs related to vaccination in bivalent rLP2086 group were: ▪ pyrexia (n=10, 0.2%) ▪ injection site pain (n=8, 0.2%) ▪ headache (n=8, 0.2%) ▪ injection site swelling (n=6, 0.2%) (3) Newly-diagnosed chronic medical conditions (NDCMC) Percentages of subjects with NDCMC† (bivalent rLP2086 vs. HAV) • Similar proportions within 30 days after each vaccination: 0.1–0.2% vs. 0.1–0.3% • Similar proportions during vaccination stage (1.0% vs. 1.1%) and follow-up phase (0.4% vs. 0.5%)		

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***

				• No notable differences between groups for types of NDCMCs during any analysis interval
				• Most commonly reported NDCMCs
				  ▪ Bivalent rLP2086: myopia (n=4, 0.1%), ADHD (n=3, 0.8%)
				  ▪ HAV: type 1 diabetes mellitus, anxiety, dysthymic disorder, major depression (n=2, 0.1% for each condition)
				• NDCMCs considered related to vaccination rare
				  ▪ Bivalent rLP2086: alopecia areata (n=1)
				  ▪ HAV: multiple sclerosis (n=1)
				
				(4) Solicited adverse events (AE) (rLP2086 vs. HAV)
				• Greater proportion of bivalent rLP2086 recipients reported AEs
				• Within 30 days after each vaccination: 15.0–31.5% vs. 10.8–19.0%
				• During vaccination stage (51.1% vs. 42.5%)
				• Greater proportion of bivalent rLP2086 recipients reported local injection site AEs
				• Most commonly reported AEs during vaccination phase
				  ▪ Bivalent rLP2086: injection site pain (n=722, 19.0%), headache (n=234, 6.2%), pyrexia (n=231, 6.1%)
				  ▪ HAV: injection site pain (n=149, 7.8%), headache (n=92, 4.8%), nasopharyngitis (n=83, 4.4%)
				• Excluding reactogenicity events, bivalent rLP2086 had higher proportion of subjects reporting AEs related to study vaccine (7.3% vs. 3.0%)
				
				(5) Reactogenicity events† (bivalent rLP2086 vs. HAV)
				• More common in bivalent rLP2086 recipients during vaccination phase: 27.9% vs. 11.7%
				• Most reactions mild–moderate
				• Most severe events resolved in <7 days
				• Similar proportions of subjects reported days missed from school or work because of an AE: 16.8% vs. 15.9%		

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				†MAE, medically attended adverse event: non-serious adverse events requiring evaluation at a healthcare facility; NDCMC, newly diagnosed chronic medical condition: a disease or medical condition, not previously identified, that was expected to be persistent or otherwise long-lasting in its effects; Reactogenicity events: any event with an onset within 7 days after vaccination and matching a predefined list of reactogenicity terms		
Ostergaard et al. (2017)	Bivalent rLP2086 (120 µg) in a three dose schedule (0,2,6 months) Hepatitis A vaccine (HAV)	Phase 3 randomized, controlled, observer-blinded, multicentre trials 10 countries (Canada, Czech Republic, Denmark, Finland, Germany, Italy, Poland, Spain, UK, US) Adolescents randomized 5:2:2:3 to receive one of 3 manufacturing lots of bivalent rLP2086 or HAV Young adults randomized 3:1 to receive rLP2086 or saline Safety assessed in bivalent rLP2086 recipients and controls in participants who had received at least one dose of vaccine	Healthy adolescents (10–18 years of age) and adults (18–25 years of age) Adolescents (n=3596) recruited April 2013–June 2015 Adults (n=3304) recruited May 2013–July 2015	Local reactions (redness, swelling, pain) • Pain most common reaction in both adolescents and young adults (92.6% and 89.6%, respectively) • Frequency of reactions generally highest after dose 1 • 6 adolescents (rLP2086 recipients) and 3 adults (2 bivalent rLP2086 recipients, 1 control) withdrew due to local reactions • Median onset of local reactions in bivalent rLP2086 recipients 1–2 days, median duration 1–3 days • Majority of local reactions mild to moderate in severity Systemic events** • Headache and fatigue were most common events in both adolescents (67.1% and 65.5%, respectively) and adults (59.1% and 64.6%, respectively) • Frequency of events most common after dose 1 in all groups • 1 adolescent (bivalent rLP2086 recipient with chills) and 4 adults (3 rLP2086 recipients with fever, mild arthralgia, moderate myalgia; 1 saline recipient with mild chills) withdrew due to systemic events • Median onset of local reactions in bivalent rLP2086 recipients 1–5 days, median duration 1–2 days • One adolescent (HAV group) had fever >40 °C after 2nd dose of HAV; one young adult had fever >40 °C after 3rd dose of bivalent rLP2086, resolve in 1 day Adverse events (AE)†† • Overall frequency of AE similar in bivalent rLP2086 and control recipients during vaccination phase, within 30	I	Good

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		Data regarding local and systemic reactions collected using electronic diary for first 7 days after each injection SAEs, MAEs and newly diagnosed chronic medical conditions assessed for 6 months after dose 3		days after any immunization and within 30 minutes after any immunization in both adolescents (40.7% vs. 43.7%; 25.3% vs. 26.8%; 0.4% vs. 0.3%) and adults (31.2% vs. 31.1%; 21.2% vs. 18.9%; 0.4% vs. 0.9%). • Most AE were mild to moderate in severity • No vaccine-related serious AEs reported among adolescents; among adults, vaccine-related serious AEs reported by 0.1% (n=3) participants **Systemic events included fever, headache, fatigue, muscle pain, chills, joint pain, diarrhea and vomiting ††Adverse events include both adverse events within 30 days of any vaccination and immediate adverse events within 30 minutes of any vaccination		
Reiner et al. (2016)	Bivalent rLP2086 (120 µg) in a 3-dose schedule (0,2,6 months)	Phase 2, single-arm, open-label trial (February 2013–February 2014) United States Single centre AEs data collected using electronic diaries for 7 days after each vaccination and by telephone at follow-up 6 months after last dose	Healthy (or stable pre-existing chronic disease) laboratory workers 24–62 years of age who work directly with pathogenic *N. meningitidis* serogroup B in the bivalent rLP2086 development program* (n=13) Mean age: 44 years; 69% female *Number of participants who contributed to immunogenicity testing at each time point and for	Incidence and severity of local reactions and systemic events¥ • Most common local reaction is injection site pain (100%) followed by erythema (37.5–42.9%) • Generally of mild–moderate severity and short duration • No potentiation with subsequent vaccinations • No fevers reported after any doses Adverse events (AE), serious AEs, newly diagnosed (ND) medical conditions also recorded • 5/13 (38%) subjects reported 6 AEs after dose 1 and 1 subject reported 1 AE after dose 3 • Most AEs were mild–moderate in severity • Only 1 severe AE (chills) was considered related to vaccination and resolved the same day • There were no deaths, no serious AEs, and no reports of neuroinflammatory or autoimmune conditions in the study	II-2	Poor

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
			each MnB test strain, as well as safety data varied	¥Local reactions: Pain at injection site, redness, swelling; Systemic events: headache, fatigue, chills, muscle pain, joint pain, use of antipyretic medication		

Richmond et al. (2012a)	Bivalent rLP2086 in 3-dose schedule (0,2,6–9¥ months)
	
	¥Protocol amended to expand time window for third vaccination due to protocol-defined study pause to investigate a serious adverse event (episode of anaphylaxis)
		Phase 2 randomized, single-blind, placebo-controlled trial (February 2009–May 2010)
		
		Australia, Poland, Spain
		
		Multisite (n=25)
		
		Three dosing formulations of vaccine used (60 µg, 120 µg and 200 µg)
		
		Blood samples collected at 1 month after 2nd and 3rd doses of bivalent rLP2086
		
		hSBA titres assessed against 8 MenB serogroup test strains (A04, A05, B02, B03, A56, B44, A22, B24) reflecting diversity of serogroups circulating between 2000 and 2006 in the United States and Europe and causing IMD
			Healthy adolescents (11–18 years of age) (n=536)*
			
			Placebo: n=121
			
			Bivalent rLP2086 (60 µg): n=22
			
			Bivalent rLP2086 (120 µg): n=198
			
			Bivalent rLP2086 (200 µg): n=195
			
			*Number of participants who contributed to immunogenicity testing at each time point and for each MenB test strain varied
				(1) Local** and systemic† reactions
				Local reactions
				• Induration and erythema only seen with bivalent rLP2086
				• Pain at injection site most common reaction (e.g., bivalent rLP2086 (44.5–72.7%) vs placebo (14.4–15.1%))
				• Reactions did not increase with subsequent doses and were mostly mild–moderate and of limited duration:
				  • pain: 2–3 days
				  • induration: 1–4.5 days
				  • erythema: 2–4 days
				
				Systemic reactions
				• For all doses, most common reactions among recipients were headache, fatigue, myalgia
				  • Bivalent rLP2086: 7.9–37.5%
				  • Placebo: 0.8–31.9%
				• Reactions did not increase with subsequent doses and were mostly mild–moderate with a mean duration of 1–3 days
				• 57 participants reported 65 episodes of fever (≥38.6 C); none exceeded 40 C.
				  • Placebo: 5/65 (8%)
				  • Bivalent rLP2086 (120 µg): 24 (37%)
				  • Bivalent rLP2086 (200 µg): 35 (54%)
				
				(2) Unsolicited UAEs
				Frequency similar between bivalent rLP2086 (120 µg: 38.9%; 200 µg: 47.2%) and placebo (44.6%) recipients
				
				Severe reactions
					I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				There were 29 severe reactions: • Bivalent rLP2086 (60 µg): 4 (18.2%) • Bivalent rLP2086 (120 µg): 8 (4.0%) • Bivalent rLP2086 (200 µg): 11 (5.6%) • Placebo: 6 (5.0%) 2 of these reactions were felt to be vaccine-related: • photophobia in bivalent rLP2086 recipient (120 µg dose) • anaphylaxis in bivalent rLP2086 recipient (200 µg dose) (3) Serious adverse events There were 24 serious adverse events reported by 19 participants; only one (potential anaphylaxis) considered vaccine-related **Local reactions: Pain at injection site, induration, erythema †Systemic reactions: Fatigue, headache, diarrhea, nausea, vomiting, chills, myalgia, arthralgia, fever		
Richmond et al. (2012b)	Bivalent rLP2086 in a 3-dose schedule (0,1,6 months)	Phase 1, double-blind, randomized controlled trial (March 2006–May 2007) First study of bivalent rLP2086 in humans Australia Multicentre (n=3) Participants provided with electronic diaries to record any local or systemic reactions on	Health adults (18–25 years of age) (n=103)* Mean age: 22 years; 72% female Participants randomized (2:1) to receive either one of three doses of vaccine or placebo Placebo: n=35 Bivalent rLP2086 (20 µg): n=21	Local reactions (pain, erythema, induration) • Injection site pain most commonly reported (bivalent rLP2086: 80.0–100%; placebo: 48.5–60.6%); majority mild–moderate; short duration (2–3 days); no difference in frequency or severity by dose level or by number of doses received • Induration and erythema more common with 200 µg dose, but generally mild–moderate and lasting 1–2 days Systemic reactions (fever, fatigue, headache, rash, nausea, vomiting, chills, muscle pain, joint pain) • Tended to be reported more frequently in 60 µg and 200 µg groups compared to 20 µg group • Muscle pain, headache and fatigue most commonly reported	I	Good

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		evening of day of vaccination and following 13 days. Other adverse events could be reported up to 43 days after last vaccination	Bivalent rLP2086 (60 µg): n=23 Bivalent rLP2086 (200 µg): n=24 *Number of participants who contributed to immunogenicity testing at each time point and for each MnB test strain varied	• Fever rarely reported and categorized as mild–moderate; duration did not exceed 1 day Serious adverse events • 3 serious adverse events, none of which deemed vaccine related (head injury, cellulitis/abscess not at injection site, impacted wisdom tooth/post-extraction hemorrhage)		
Senders et al. (2016)	Bivalent rLP2086 (120 µg) in 3-dose schedule (0,2,6 months) HPV-4 vaccine (quadrivalent human papilloma virus)	Phase 2, randomized controlled trial United States Multisite (n=63) Electronic diaries used to capture self-reported local and systemic reactions for 7 days after each vaccination	Healthy adolescents (n=2483) (11–17 years of age; mean: 13.6 years) 66.5% male Participants randomly assigned (2:2:1) to one of 3 groups: Group 1: bivalent rLP2086 + HPV4 (n=992) Group 2: bivalent rLP2086 + saline (n=990) Group 3: saline + HPV4 (n=501)	Local (redness, swelling, pain) reactions • Transient, mild–moderate pain at injection site most common local reaction • Incidence did not increase with subsequent doses • Incidence and severity with bivalent rLP2086 similar to that seen when co-administered with HPV4 Systemic (fever, headache, fatigue) reactions • Fatigue and headache most common systemic reactions; generally mild–moderate; mean duration 1–3.8 days • No fevers ≥40 C • Incidence did not increase with subsequent doses Serious adverse events • No vaccine-related serious AEs	I	Fair
Sheldon et al. (2012)	Bivalent rLP2086 Tetanus, diphtheria,	Phase 1, randomized, open-label, active and placebo-controlled trial	Healthy adults 18-40 years of age (n=48)[†] Mean age: 28.8 years	Local reactions (pain at injection site, induration, erythema) • Pain at injection site most commonly reported reaction • Most reactions of mild–moderate severity; most resolved in 1–3 days	I	Poor

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***

	acellular pertussis vaccine (Tdap)	(April 2009–March 2010)
		
		United States
		
		Single site
		
		Subjects randomly selected (1:1:1:1 ratio) to receive rLP2086 (either 60µg, 120µg, 200µg) or Tdap
		
		Vaccine administered in 3-dose schedule: 0, 2, 6–9 months* (for Tdap group, saline injections given for dose 2 and dose 3)
		
		Electronic diaries used to record local and systemic reactions for 7 days after each vaccination.
		Unsolicited adverse events reported throughout study
		
		*Protocol amended to expand time window for third vaccination due to protocol-defined study pause to allow investigation of a serious adverse event (episode of anaphylaxis) in a separate study
			60.4% female
			
			Placebo (n=12)
			
			Bivalent rLP2086
			60 µg (n=12)
			120 µg (n=12)
			200 µg (n=12)
			
			†A total of n=14 subjects withdrew after randomization: 5 from Tdap group and 9 from the various rLP2086 groups (60ug: 4, 120ug: 2; 200ug: 3). Therefore, the number of participants who contributed to immunogenicity testing varied by group for dose 2 (n=9–12) and dose 3 (n=7–10)
				• When reported, severe reactions more common with 120 µg (pain, n=1; induration, n=1; erythema, n=2) or 200 µg doses (pain, n=1; erythema, n=1)
				
				Systemic events**
				• Frequency generally higher in bivalent rLP2086 recipients than in controls
				• Most events were mild–moderate in severity and resolved in 1–3 days
				
				Adverse events (AEs)
				• AEs generally comparable between bivalent rLP2086 and control recipients
				• n=6 AEs reported in 5 subjects considered vaccine related:
				  • mild severity
				  • injection site pruritus (n=2), injection site rash (n=1), induration (n=2), throat irritation (n=1)
				• Severe AEs (n=7) all laboratory abnormalities (increased potassium, n=3; increased sodium, n=1; decreased neutrophils, n=1; proteinuria, n=1)
				  • Not considered vaccine related
				  • Did not worsen with additional vaccinations
				• There were no serious AEs and no deaths
				
				**Systemic events: fatigue, headache, diarrhea, nausea, vomiting, chills, muscle pain, joint pain		

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***

Vesikari et al. (2015)	Bivalent rLP2086 (120 µg)	Phase 2, multicentre, randomized, single-blind trial (March 2011–August 2013)
		
		Czech Republic, Denmark, Finland, Germany, Poland, Spain, Sweden
		
		Subjects randomized (3:3:3:2:1) into 5 groups based on bivalent rLP2086 dosing schedule
		
		Reactogenicity data (local reactions, systemic events) collected by electronic diary for 7 days after each injection. Unsolicited adverse events collected up to 1 month after last injection. Serious adverse events collected throughout study
			Healthy adolescents (11–18 years of age) (n=1713)
			
			Group 1 (0,1,6 months) n=427
			
			Group 2 (0,2,6 months) n=430
			
			Group 3 (0,6 months) n=427
			
			Group 4 (0,2 months) n=286
			
			Group 5 (0,4 months) n=143
			
			Mean age: 14.4 years
			
			49–52% female
			
			Age at first injection: 36–37% (11–13 years of age); 63–64% (14–18 years of age)
			
			n=1450, evaluable for immunogenicity*
			
			*Number of participants who contributed to immunogenicity testing at each time point and for each MnB test strain varied
				(1) Local and systemic reactions
				Local reactions
				• Pain at injection site most commonly reported; most mild–moderate in severity
				  • Severe pain: <9.9% bivalent rLP2086 vs. <0.3% saline
				  • 4 patients with pain reported duration >14 days
				• Mean duration of all local reactions 2.1–3.2 days
				
				Systemic reactions†
				• Most commonly reported were headache and fatigue; mostly mild–moderate in severity
				  • Severe headache ≤1.6% of subjects (after either rLP2086 or saline)
				  • Severe fatigue ≤3.6% (after either rLP2086 or saline)
				• Fever ≥39 C rare (<1% of subjects); median duration was 1 day
				  • Antipyretic use: 13.6–16.2% (rLP2086) vs. 7.5–9.1% (saline)
				
				(2) Unsolicited adverse events (AE)
				• 35.5–37.5% of subjects reported ≥1 AE; most mild–moderate in severity
				• Most commonly reported: nasopharyngitis (5.5–10.1%)
				• Severe AE reported by 11 subjects considered related to rLP2086:
				  • Headache, injection site pain, pyrexia, vomiting, injection site swelling, chills, vertigo
				
				(3) Serious adverse events
				No differences in serious AE between 3- and 2-dose schedules
				• No increase in SAE with subsequent dosing
				• No deaths reported
				
				†Systemic events: fever, vomiting, diarrhea, joint pain, chills, muscle pain, headache, fatigue
					I	Good

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Vesikari et al. (2016)	Bivalent rLP2086 (120 µg) in a three dose schedule (0,2,6 months) Diphtheria, tetanus, acellular pertussis, inactivated polio vaccine (DTaP/IPV)	Phase 2, randomized, placebo-controlled, single-blind trial Finland, Germany, Poland Multisite (n=34) Participants randomly assigned (1:1): • Group 1 (bivalent rLP2086 + DTaP/IPV) • Group 2 (saline + DTaP/IPV) Electronic diaries used to capture self-reported local and systemic reactions for 7 days after each vaccination	Healthy adolescents (11–18 years of age) (n=749)* Mean age: 13.9 years Group 1: Bivalent rLP2086 + DTaP/IPV (n=373) Group 2: saline + DTaP/IPV (n=376) *Number of participants who contributed to immunogenicity testing at each time point and for each MnB test strain varied	(1) Local and systemic reactions Local reactions (pain at injection site, redness, swelling) • More common with bivalent rLP2086 than with saline • Injection site pain most commonly reported after each vaccination • Most local reactions mild–moderate in severity and duration comparable between groups • Incidence did not increase with subsequent doses Systemic reactions (fever, joint pain, chills, muscle pain, headache, fatigue) • Fatigue and headache most common systemic reactions in both groups; generally mild–moderate • Somewhat higher incidence of systemic events in bivalent rLP2086 group • No fevers ≥40 C • No increase in incidence or severity with subsequent doses (2) Serious adverse events • No SAE related to vaccination	I	Fair