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Immune responses to a recombinant, four-component, meningococcal serogroup B vaccine (4CMenB) in adolescents: A phase III, randomized, multicentre, lot-to-lot consistency study

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Short title: MenB vaccine kinetics in adolescents

Abbreviations: MenB- serogroup B meningococcal, fHbp - factor H binding protein, NadA - Neisserial adhesin A, NHBA - Neisseria heparin binding antigen, PorA - porin A, hSBA- serum bactericidal assay using human complement, GMC- geometric mean concentration, GMT- geometric mean titre

Keywords: *Neisseria meningitidis*, serogroup B meningococcal vaccine, immunity, immunization, adolescence

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Potential conflict of interest:

Dr Perrett has received honoraria from Pfizer for educational lectures. Dr Perrett, A/Professor McVernon and Professor Nolan's institution (MCRI) has received research grants from GSK, Novartis, CSL, Pfizer and Sanofi Pasteur.

A/Professor Richmond has received institutional funding for investigator-initiated research from GlaxoSmithKline Biologicals, Novartis, Pfizer and Merck, received travel support from Pfizer and Baxter to present study data at international meetings.

A/Professor McVernon has been an investigator on vaccine and epidemiological studies sponsored by a range of vaccine manufacturers, and in this role has received support for conference attendance, presentation of data and membership of vaccine advisory boards. A/Professor McVernon is a member of ATAGI.

A/Professor Marshall has been a member of vaccine advisory boards for GlaxoSmithKline and Novartis. A/Professor Marshall's institution (Women's and Children's Hospital) has received research grants from GlaxoSmithkline, Novartis, Pfizer and Sanofi Pasteur. A/Professor Helen Marshall has received travel support from Pfizer and Novartis for conference attendance and presentation of independent scientific data.

A/Professor Nissen directs the Queensland Paediatric Infectious Diseases laboratory that has performed the Meningococcal Antigen Testing System assay on Australian isolates causing invasive meningococcal disease on the behalf of Novartis. He has received travel support from GSK and Pfizer for conference attendance and presentation of data of independent research at international meetings, honoraria from bioCSL, Novartis and Pfizer for educational lectures, institutional funding for investigator-initiated research from Abbott Australasia, as well as been an principal investigator on vaccine and epidemiological studies sponsored by a range of vaccine manufacturers, and in this role has received support for conference attendance, presentation of data and membership of vaccine advisory boards. A/Professor Nissen is the current Chair of the Australian National Verification Committee for Measles Eradication and a past member of ATAGI.

Professor Nolan chaired (until June 2014) the Australian Government's Technical Advisory Group on Immunization (ATAGI) and is a member of the World Health Organization Strategic Advisory Group of Experts (SAGE) on Immunization.

Dr Allison August is a former employee of the study sponsor. Dr Daniela Toneatto is an employee of Novartis Vaccines. Dr Sandra Percell is an independent consultant working for Novartis Vaccines.

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Abstract:

Background: For decades, a broadly effective vaccine against serogroup B *Neisseria meningitidis* (MenB) has remained elusive. Recently, a four-component recombinant vaccine (4CMenB) has been developed and is now approved in Europe, Canada, Australia and some Latin American countries. This phase III, randomized study evaluated the lot consistency, early immune responses and the safety profile of 4CMenB in 11 to 17-year-old adolescents in Australia and Canada (NCT01423084).

Methods: In total, 344 adolescents received two doses of one of 2 lots of 4CMenB, 1-month apart. Immunogenicity was assessed before, 2-weeks and 1-month following the second vaccination. Serum bactericidal activity using human complement (hSBA) was measured against three reference strains specific for the vaccine antigens Neisseria adhesin A (NadA), factor H binding protein (fHbp) and porin A (PorA) containing outer membrane vesicle (OMV). Responses to the Neisseria heparin binding antigen (NHBA) were assessed with an enzyme linked immunosorbent assay (ELISA). Local and systemic reactions were recorded for 7 days after each vaccination; unsolicited adverse events were monitored throughout the study. .

Results: Immunological equivalence of the two lots of 4CMenB was established at 1-month after second vaccination. At baseline, ≤7% of participants had hSBA titres ≥5 to all the three reference strains. Two weeks following the second dose of 4CMenB, all participants had hSBA titres ≥5 against fHbp and NadA compared with 84–96% against the PorA antigens. At 1-month, corresponding proportions were 99%, 100% and 70–79%, respectively. Both lots were generally well tolerated and had similar adverse event profiles.

Conclusions: Two doses of 4CMenB had an acceptable safety profile and induced a robust immune response in adolescents with peak antibody responses observed at 14 days after vaccination. While a substantial non-uniform antigen-dependent early decline in antibody titers was seen thereafter, a significant percentage of participants continued to maintain protective hSBA titers at 1-month.

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Introduction

Over the last two decades, substantial progress has been made in reducing the burden of disease caused by *Neisseria meningitidis* through vaccination. Successful mono- and multivalent vaccines against serogroups A, C, W and Y have been developed based on serogroup-specific capsular polysaccharides and enhanced with polysaccharide-protein conjugate technology. However, this vaccine strategy cannot be employed for serogroup B, the last of the five major pathogenic meningococcal groups, due to the capsule's structural homology to human fetal neural tissues, resulting in poor immunogenicity [1, 2]. Serogroup B *Neisseria meningitidis* (MenB) is now the leading cause of meningococcal disease in infants and young children, accounting for over 80% of cases in Australia and some Latin American countries, over 70% in Europe, 66% in the UK, 50-80% in Canada and one-third in the USA [3-7].

Previously, tailor-made MenB vaccines have been developed from strain-specific outer membrane vesicles (OMV) and successfully used to combat homologous strains in clonal outbreaks [8-11]. However, due to limited or no effectiveness against heterologous strains they are not suitable for use as a general serogroup B vaccine [12]. Recently however, important advances have been made in the quest for a universal MenB vaccine with the identification of conserved sub-capsular meningococcal proteins [13, 14].

One four-component recombinant vaccine, 4CMenB, contains three recombinant proteins: factor H binding protein (fHbp), Neisserial adhesin A (NadA) protein and Neisseria heparin binding antigen (NHBA), along with porin A (PorA) containing

OMV derived from meningococcal NZ98/254 strain (previously used to control a MenB clonal outbreak in New Zealand (NZ), the main PorA antigen is P1.4) [15]. Since development, the 4CMenB vaccine has been administered in phase I, and pivotal phase IIb and III studies to over 8000 adults, adolescents and infants and has been shown to be immunogenic, as measured by serum bactericidal assay using human complement (hSBA), to a majority of reference strains within hypervirulent clusters responsible for MenB disease [16-18].

This study measured baseline immunity, and the consistency and kinetics of immune response following a two-dose schedule of two lots of 4CMenB (manufactured at different sites) in healthy Australian and Canadian adolescents. Safety and tolerability were also assessed.

Methods

Study design and participants

The study (NCT01423084) was a phase III, multicentre, observer-blind, randomized trial which involved healthy 11 to 17-year-old adolescents across five centres in Australia and seven in Canada between August and December 2011. Potential participants were identified via advertising fliers in school newsletters or on community noticeboards and from participant databases at the research centres. Exclusion criteria were: previous receipt of MenB vaccine; previous meningococcal disease (or household or intimate contact with an individual with *N. meningitidis*); recent significant acute or chronic infection or fever ≥38.0°C; recent antibiotic use; known immunodeficiency or use of immunosuppressive doses of corticosteroids; recent receipt of any blood products including immunoglobulin, planned receipt of other vaccines within 30 days (within 14 and 60 days for influenza and live viral vaccines respectively) or allergy to vaccine components. Participants were also excluded if they were pregnant, breast feeding or unwilling to use acceptable birth control measures within 30 days prior and 60 days following enrolment. A negative pregnancy test was required for all females prior to receipt of each dose of 4CMenB vaccine. Written assent was obtained from each adolescent and written informed consent was obtained from participant's parents or legal guardians. Approvals were obtained from ethics committees at each participating research centre.

Both lots of the investigational vaccine 4CMenB had identical composition but were formulated with OMV manufactured by Novartis Vaccines at two different sites in Italy: Rosia (Lot 1) and Siena (Lot 2).

Participants were randomized in a 1:1 ratio to receive two doses of either Lot 1 or Lot 2 of 4CMenB vaccine, one month apart. Blood samples (maximum 20 mL) were taken on day 1 before the first vaccination and 30 days after the second vaccination. At pre-selected sites, an extra blood sample was taken two weeks following the second dose in all participants to investigate the kinetics of the early immune response after vaccination (Table 2). Participants were observed for at least 30 minutes after each study vaccination. Local and systemic reactions and adverse events (AE) were collected on a diary card for seven days following each vaccination. Serious adverse events (SAE), medically attended AEs and AEs that resulted in a participant's withdrawal from the study were collected throughout the study period.

Serological responses

Assays were performed at the Clinical Laboratory Science, Novartis Vaccines Marburg, Germany. Sera were tested for bactericidal activity using a human complement source (hSBA), against each of the three *N. meningitidis* serogroup B reference strains: 44/76-SL (fHbp), 5/99 (NadA) and NZ98/254 (PorA) using the method described previously ( ). These strains were chosen as each is mismatched for all but one of the vaccine antigens, therefore each strain assesses the response to a single vaccine component (44/76-SL - fHbp, 5/99- NadA and NZ98/254-PorA). The IgG antibody concentration to the NHBA antigen were assessed using an enzyme-linked immunosorbent assay (ELISA). At the time of the study, no suitable strain for NHBA responses had been identified therefore an NHBA-specific ELISA was used against vaccine antigen 287-953 ( ).

Statistical analysis

The primary objective was to demonstrate equivalence of Lot 1 to Lot 2 of 4CMenB, as measured by hSBA geometric mean titre (GMT) against 3 reference strains (44/76-SL, 5/99 and NZ98/254) and ELISA geometric mean concentration (GMC) IgG against the NHBA, 30 days after a primary course of 2 doses administered one month apart. Equivalence was defined as the two-sided 95% confidence interval (CI) of the ratio of the hSBA GMTs and GMCs being contained within the interval (0.5, 2.0). The primary safety objective was to evaluate the safety and tolerability of two doses of two lots of 4CMenB given one month apart in healthy adolescents.

The secondary immunogenicity objectives were to: assess the increase in hSBA GMT and ELISA GMC (post- to pre-vaccination); and to calculate the percentage of participants in each lot with hSBA $\geq$ 1:5 one month following the second vaccination for each of the three reference strains (44/76-SL, 5/99 and NZ98/254). Further, in a subset of approximately 160 participants (80 per lot), the same outcome measures were assessed two weeks following the second vaccination.

For each lot and each reference strain and for the NHBA antigen, the GMT (or GMC) and two-sided 95% CI was calculated. These were obtained from a two-way analysis of variance (ANOVA) with factors for vaccine lot and study centre. For the percentage of subjects with hSBA $\geq$ 1:5, the associated 95% Clopper-Pearson confidence interval (CI) was measured. No between-group comparisons were performed for any immune measure besides the primary endpoint, because the analysis was underpowered to demonstrate equivalence. Titres and concentrations below the limit of detection (2 for hSBA and 40 for ELISA) were set to half that limit (i.e: 1 for hSBA and 20 for ELISA) for the purpose of analysis.

The planned sample size of 135 evaluable participants (160 minus 15% attrition) per arm, was calculated to provide 94% overall power to demonstrate consistency of the immune response to the two lots of 4CMenB assuming a two-sided $\alpha = 0.05$, an underlying ratio of the vaccine group GMTs or GMCs of 1.0 for each of the reference strains, and an equivalence interval of (0.5, 2.0). For an underlying ratio of the vaccine group GMTs (or GMCs) of 1.1 for each strain, the overall power to demonstrate consistency was calculated as approximately 90%.

Results

Of the 344 participants enrolled into the study, 170 were included in Lot 1 (Rosia) and 174 in Lot 2 (Siena) of whom 99% and 98% of participants completed the study, respectively. The per-protocol immunogenicity population (299 participants) included adolescents with no major protocol violations who provided sera for testing (147 and 152 participants from Lot 1 and 2, respectively) (Figure 1). The safety population comprised 342 participants (169 participants from Lot 1 and 173 from Lot 2). The demographic and baseline characteristics were well matched except for gender. The mean age at enrolment was 13.7 years [± 1.9] (Table 1). The per protocol population for the extra blood taken two weeks following the second vaccination (visit 2) consisted of 76 and 71 participants in Lot 1 and 2, respectively.

At baseline, of 299 participants, 6 (2%) had hSBA titres ≥ 5 to the reference strains for fHbp (44/76-SL), 20 (7%) for NadA (5/99) and 5 (2%) for PorA (NZ98/254).

Primary objective

One month following the second vaccination, the ratios of hSBA GMTs in Lot 1 to Lot 2 were 1.0, 0.92 and 0.81 for each of the 3 reference strains 44/76-SL, 5/99 and NZ98/254 respectively, with corresponding CI of (0.82, 1.23), (0.77, 1.1) and (0.6, 1.09) (Table 2). The Lot 1 to Lot 2 ratio of the ELISA GMCs against the NHBA, one month following the second vaccination, was 0.83 (95% CI: 0.67, 1.02) (Table 2). Statistical equivalence of the two vaccine lots was met, as each ratio and CI were contained within the interval 0.5 and 2.0.

Secondary objectives

Immune response one month following the second vaccination:

The proportion of participants with hSBA ≥1:5, one month following the second dose of 4CMenB vaccine, were generally similar for reference strains 44/76-SL and 5/99 in both vaccine lots (99% each and 100% each, respectively). For the NZ98/254 strain, a higher proportion of participants in Lot 2 (79%, CI 72-86) presented with hSBA ≥1:5 compared to Lot 1, 70% (62-77) In addition (although statistically equivalent), the ELISA GMR to baseline against NHBA antigen was slightly higher in Lot 2 (153 (CI 131-179) compared to Lot 1 (122 (103-143). Reverse cumulative distribution (RCD) functions of hSBA titres were similar for the two groups (Lot 1 and 2) for each of the 3 reference strains 44/76-SL, 5/99 and NZ98/254 and for ELISA concentrations for NHBA antigen, both at baseline and at one month following the second vaccination.

Immune response at two weeks following the second vaccination:

In the subset population, two weeks and one month following 4CMenB, 100% of participants in both Lot 1 and Lot 2 groups attained hSBA ≥ 1:5 against reference strains 44/76-SL and 5/99. However against strain NZ98/254, only 84% and 96% of adolescents achieved an hSBA titre ≥ 5 at 2 weeks, and these proportions fell to 64% and 80% by 1 month following the second vaccination, for Lot 1 and Lot 2, respectively (Figure 2).

In general, for both Lot 1 and Lot 2 vaccines, there was a substantial but non-uniform decline in hSBA GMT levels for the 3 reference strains and ELISA GMCs against the NHBA antigen, from two weeks to one month following the second vaccination (Table 2). RCD curves of the hSBA titres and ELISA concentrations at two weeks

and at one month after second vaccination are shown in Figure 1. For both lots, and for hSBA titres against each reference strain and ELISA concentrations against NHBA antigen, separation (shift to the left) is noted between the RCD at two weeks and one month following the second vaccination, indicating a decline in immune response between these 2 time-points.

No meaningful differences were observed in the pattern of the immune responses at any time point, when analyzed by center and country

Safety and Tolerability

Overall, both lots of 4CMenB had similar safety profiles and were generally well tolerated. Almost all adolescents (98% in Lot 1 and 99% in Lot 2) reported at least one local, systemic or other reaction during the 7 days after either vaccination. The proportion of participants with local reactions was similar between groups (96% Lot 1 and 98% Lot 2). Most local and systemic reactions were mild to moderate in nature (Tables 3 and 4). The most frequently reported local reaction after any vaccination was pain (96% and 98%), reported as severe in 14% and 17% of Lot 1 and 2 participants, respectively. The most frequently reported solicited systemic reaction was myalgia (59% and 68%), followed by headache (44% and 51%) and fatigue (44% and 49%) in Lot 1 and 2 participants, respectively. Fever $\geq$ 38°C was infrequently reported (5% and 3% in Lot 1 and 2 participants respectively). One participant in Lot 2 withdrew from the study on day 34 due to an adverse event (infectious mononucleosis) that started in day 14, with moderate severity and was judged as unrelated to the study vaccine by the investigator. No death, serious adverse event or pregnancy occurred.

Discussion

We evaluated the consistency and kinetics of the immune response following vaccination with one of two lots of 4CMenB administered as two doses, one month apart in healthy 11-17 year old adolescents. We found immunological equivalence between two lots of 4CMenB at one month after second vaccination in terms of hSBA GMTs against each of the three MenB reference strains for fHbp, NadA and PorA antigens and ELISA IgG GMCs against the NHBA antigen. A variable but a substantial decline in GMTs/GMCs was observed from two weeks to one month following the second vaccination. However it should be noted that protective titers (hSBA ≥5) were maintained in 100% of subjects for strains 44/76-SL and 5/99 and in 75% subjects for strain NZ98/254, even at one month. Low levels of pre-existing immunogenicity to the meningococcal vaccine antigens, suggest the possibility of little environmental exposure to these meningococcal reference strains in the Australian and Canadian adolescent population.

This is the first study to measure the early immune response following 4CMenB vaccination. It was postulated that immune responses may remain static or decline slightly from 2 to 4 weeks following 4CMenB vaccination in adolescents. However, a substantial decline over the two weeks was not expected. The finding of the peak antibody response at 14 days following immunization is similar to that reported following meningococcal serogroup C conjugate vaccine, *Haemophilus influenzae* type b (Hib) polysaccharide and Hib conjugate vaccines (peak at 10-14 days), which subsequently wane [19-21]. Recently, measurement of the longer term kinetics of immune responses following the second dose of 4CMenB vaccine in university

students has shown ongoing waning of hSBA titers from 1-month to 11-months following vaccination [22].

Also of note, we found a difference in the rate of decline of hSBA titres between the strains from two weeks to one month following the second 4CMenB vaccination. The largest declines (a fall in hSBA GMT of 48%) were observed for reference strains 5/99 and NZ98/254 against the NadA and PorA vaccine antigens respectively. The PorA antigen also generated the lowest peak immune response of the four vaccine components (as determined by fold-rise from baseline to two weeks following the second vaccination and proportion of adolescents generating titres considered protective, hSBA ≥5). Lower seroresponses to this same PorA antigen (NZ98/254) have previously been reported. Following three doses of the monovalent MenB OMV vaccine (MeNZB) used to help control a clonal outbreak in New Zealand: only 74% of 6-8 month-old [23], 75% of 16-24 month-old [24] and 74-79% of 8-12 year-old children [25] developed a seroresponse, as assessed at 4 weeks after dose 3 (four-fold rise in hSBA titre compared to baseline). Age-dependent antibody decline against this PorA vaccine antigen was also described; 7 months following the third dose of MeNZB in 6-8 month-old infants only 28% had persistent hSBA ≥4; compared to 36%, 14 months following the third dose in 8-12 year-old children; and 50%, 10 months following the third dose in adults [26]. Accordingly, as the rate of decline of hSBA titres (or waning of antibody) is differential according to age and strain, it is possible that susceptibility to meningococcal infection and duration of vaccine protection might be differential according to age and geographical region (depending on the expression of proteins in the circulating disease-causing strains). Importantly, vaccine efficacy has been shown to mirror a rapid decline in circulating bactericidal

antibodies following vaccination with monovalent MenB OMV vaccines in Norway and New Zealand [27, 28] and with MenC conjugate vaccines in the UK [29].

This study highlights the complexity in assessing immunogenicity and determining generalizability of the four-component MenB vaccine for different geographical regions. At baseline, pre-existing immunity to the meningococcal vaccine antigens in our Australian and Canadian adolescent population was low (2%–7%) of adolescents had hSBA titres ≥5 to strains for fHbp, NadA and PorA antigens, respectively, compared to 34%–44% with hSBA titres ≥4 in a prior 4CMenB adolescent study conducted in Santiago and Valparaiso, Chile [17]. In the current study, while 99-100% of adolescents achieved protective titres (hSBA ≥5) to reference strains 44/76-SL and 5/99, one month following the second 4CMenB vaccination, only 75% did so for the NZ98/254 strain. In comparison, in the Chilean study, 99-100% of adolescents achieved hSBA titres ≥ 4 (albeit a slightly less conservative measure) to each of these 3 reference strains [17]. The difference in baseline immunogenicity between the two similar 11-17 year-old adolescent vaccine-naïve populations could partially relate to assays conducted in to different laboratories, but may more likely be due to different levels of acquisition of natural immunity though nasopharyngeal carriage in each population. Higher baseline immunogenicity levels may suggest higher levels of environmental exposure to the meningococcal vaccine strains in Chilean than in the Canadian and Australian populations. Indeed, even accounting for different laboratories, the RCD function curves of hSBA responses for the reference strain NZ98/254 (PorA) in Chilean adolescents, who received the accelerated two-dose schedule (one month apart), were noticeably shifted to the right (higher hSBA titres) compared to the current study. However hSBA titres were similar against reference

strains 44/76-SL and 5/99 in both studies [17]. Further, Chilean adolescents with higher baseline levels (hSBA titres ≥4) generated higher post vaccination antibody titres than vaccine antigen naïve adolescents (hSBA titres <4 at baseline) and these differences persisted up to 6 months [17]. Recently, assays done in a subset of University students in a UK meningococcal carriage study found high baseline immunity to the 4CMenB vaccine antigens, similar to the Chilean study (these assays were also performed at Public Health England laboratory, UK) [22] together with high rates of carriage (33%) [30]. In comparison, meningococcal carriage rates are low in Canada. No carriage data are available for Australia. Accordingly, in populations with low baseline immunity to MenB, persistence of antibody may be reduced. The possibility of an additional vaccine impact on carriage may further amplify these differences in population-specific effects.

The hSBA GMTs and ELISA GMCs at one month after second vaccination in the two vaccine groups were statistically equivalent for each of the three MenB reference strains for vaccine antigens fHbp, NadA PorA and NHBA antigen, respectively. This finding was not unexpected. Both vaccine lots were identical in composition, but formulated with OMV manufactured at two different facilities.

There was a slightly higher frequency of systemic reactions reported by adolescents who received Lot 2 vaccine (compared to Lot 1). Overall, the rate of reported systemic reactions was slightly higher in our study than previously reported, although rates of fever ≥ 38°C were similar [17]. Of note, in both studies the vast majority of reported systemic reactions were of mild or moderate severity, a similar number were

reported as severe and no evidence of increasing rates of reactions with subsequent dosing was identified [17].

The 4CMenB (Bexsero®) vaccine was licensed for use in the European Union in January 2013, and subsequently in Australia, Canada and some Latin American countries, for individuals from 2 months-of age [31]. In March 2014, the UK became the first country to recommend its use in a National Immunization Program (at 2, 4 and 12 months of age) [32] where coverage of 4CMenB is estimated at 88% of invasive MenB strains [33] (subject to vaccine pricing and cost-effectiveness requirements by the UK Government). In addition, a second MenB vaccine, a bivalent vaccine containing recombinant factor H binding protein variants (also called rLP2086), manufactured by Pfizer, has undergone Phase II clinical trials [34-36] and was licensed in the US in October 2014 for use in adolescents and young adults. Both 4CMenB and rLP2086 had received Breakthrough Therapy designation from the US FDA. In January 2015, 4CMenB was also approved in United States (US) as a 2-dose series in adolescents 11- 25 years ( ) .

In conclusion, this study demonstrated the lot to lot consistency of 4CMenB vaccine manufactured at different sites. Two doses of 4CMenB, given one month apart, had an acceptable safety profile and induced robust immune responses in adolescents, though waning of titers was observed from 2 weeks to 1 month after vaccination. Further**,** this study's finding of differential baseline antibody titres to 4CMenB vaccine antigens compared with age-matched but geographically distinct populations, affecting immunogenicity, is important. Population-based post-implementation

460 disease surveillance to assess the potential differential vaccine impact (on herd
461 immunity and duration of protection) in each region will be imperative.
462

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