# Durability of immunogenicity and strain coverage of MenBvac, a meningococcal vaccine based on outer membrane vesicles: Lessons of the Normandy campaign.

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Running title: Response of OMV-containing meningococcal vaccines

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**Abstract**

**Objectives:** MenBvac® is an outer membrane vesicle (OMV)-based meningococcal vaccine. From 2006 to 2012, it was used to control a clonal B outbreak in Normandy (France). We aimed to analyse the durability of the response against the epidemic strain and coverage beyond the vaccine strain. These data should help to optimize the use of OMV-containing vaccines, such as the new 4CMenB/Bexsero® recombinant vaccine.

**Methods:** Serum bactericidal activity (SBA) was measured in two cohorts of children who received their first dose of MenBvac® at 1-5 years of age and accepted to provide a blood sample either one or four years after a 2+1+1 schedule. All sera were tested against the outbreak strain. Sera from responder subjects were also tested against 12 additional B or C strains which were chosen to entirely, partially, or not at all match the two variable regions (VR1 and VR2) of the PorA vaccine strain.

**Results:** Only 47.9% and 31.3% of subjects showed an SBA titre consistent with protection one and four years, respectively, after the last boost. Protective SBA titres were observed in all sera against B or C strains that entirely matched P1.7,16, and was high (75-100%) for all but one strain that partially matched VR1 or VR2. Extrapolating our data to the OMV component of 4CMenB/Bexsero® suggests that 14.5% of the current B strains would be covered based on PorA matching to the OMV component of 4CMenB/Bexsero® (regardless of the coverage of the three other vaccine components).

**Conclusions:** Our data confirm that OMV-based vaccines elicit short-lasting SBA titres and may require repeated booster injections. However, strain coverage may be greater than expected.

**Keywords**: *Neisseria meningitidis* serogroup B; serum bactericidal activity; outbreak; persistence of vaccine response; invasive meningococcal disease; PorA; vaccination

The Authors declare no conflict of interest.

## Highlights

- Meningococcal outbreaks can be controlled by OMV-based vaccines, such as MenBvac
- Serum bactericidal activity of sera from vaccinated subjects was evaluated
- Serum bactericidal activity rapidly declined
- Meningococcal strains expressing partially matching PorA were covered
- OMV-containing vaccines may offer broader protection than originally expected.

## Introduction

Capsular polysaccharide vaccines have been successfully developed against *Neisseria meningitidis* of serogroup A, C, W, and Y. Such an approach is not possible for serogroup B strains due to the homology between the group B capsule and the human neural cellular adhesion molecule, leading to poor immunogenicity and a potential risk of autoimmunity. This is particularly problematical because most invasive meningococcal disease in developed countries is caused by serogroup B strains. Since the 1980s, tailor-made meningococcal B vaccines, based on outer membrane vesicles (OMV), have been developed in response to outbreaks, with campaigns in South Africa, Cuba, Norway, Brazil, Chile, and New Zealand [1]. OMV vaccines elicit an immune response that is mainly directed against the protein porin A (PorA) of the outer membrane which includes two variable regions, VR1 and VR2, with a large diversity for both of them. The response is generally "strain specific" and is not cross-reactive with divergent PorA variants. The last application of an OMV alone-based meningococcal B vaccine was reported in Normandy, France, from 2006 to 2012, where a clonal meningococcal outbreak, due to a strain of serotype 14, sero-subtype P1.7,16 and clonal complex 32 (B:14:P1.7,16/cc32), was controlled using MenBvac®, a Norwegian vaccine designed in the 1980s against a strain expressing the same PorA variant (B:15:P1.7,16/cc32) [2].

Since then, multi-component protein-based vaccines that offer broad coverage against group B *N. meningitidis* have been developed. Such new vaccines do not necessarily make former OMV meningococcal vaccines obsolete [3]. The new multi-component protein-based vaccines do not cover all circulating serogroup B isolates. Indeed, 4CMenB/Bexsero®, the only meningococcal B vaccine available in Europe, has been first evaluated to cover 73–87% of the B strains circulating in different European countries [4]. More recent data have predicted a 66% coverage in the UK [5]. These data imply that a tailor-made OMV vaccine

might be requested in the future to control an outbreak due to an uncovered strain. Moreover, OMV have adjuvant properties [6]. They have therefore been included in 4CMenB/Bexsero® (using the preparation developed for MenZB, the OMV vaccine used in New Zealand) to increase both the immunogenicity and persistence of the immune response against the other vaccine components. Also, OMV vaccines may provide cross protection against strains that do not express perfectly matching PorA proteins [7-9]. Importantly, antibodies generated by OMV are independent of those targeting the capsule; thus OMV should work against meningococcal strains from different serogroups, providing that they partially or entirely share the PorA of the vaccine strain. Finally, animal experimentation, as well as several clinical studies, suggest that the Norwegian OMV-based vaccine reduces meningococcal carriage and may hence confer herd protection [10, 11].

During the Normandy outbreak, we performed two immunogenicity studies [11, 12] to evaluate different schedules of MenBvac®. Several volunteers accepted to provide blood five years after the first dose to evaluate the durability of the response and the spectrum of coverage by measuring serum bactericidal titres (SBA), not only against the epidemic strain, but also against other B and non-B strains which are currently endemic in the country.

## Methods

### *Serum bactericidal activity*

SBA assays were performed using human serum, devoid of meningococcal lysis activity, as a complement source (hSBA) for serogroup B isolates. Baby rabbit complement (rSBA) was used for serogroup C isolates as previously described [2, 12]. The serum bactericidal activity titres corresponded to the inverse of the final serum dilution causing 50% killing of the inoculum after 1 h of incubation. A protective immune response was defined by an hSBA titre $\geq 4$ or a rSBA titre $\geq 8$, as these titres have been suggested as a surrogate for protection [13, 14].

Titres were compared using the percentage of subjects achieving the threshold for protection and by calculating the geometric means of titres (GMT). Data were analyzed using the Chi-squared test, Student's *t*-test, and analysis of variance (ANOVA). A $P$ value of $< 0.05$ was considered to be statistically significant. The Bonferroni correction was applied when the Chi-squared test involved several comparisons.

### *Durability of immunogenicity against the targeted epidemic strain*

The SBA titres against the epidemic clone were analyzed for the two previously assembled cohorts, the first in 2006 from subjects living in the Dieppe area and the second in 2009 from subjects living in the Neufchâtel-en-Bray area [2, 12]. Briefly, children were aged 1-5 years at the time of the first MenBvac® dose. They were selected by random sampling from all subjects of the same age-range of the area eligible to receive MenBvac®. Both cohorts had received a 2+1+1 schedule. The time of administration of the second boost (i.e., the last dose) differed slightly between the two cohorts due to a production shortage of the vaccine that required several adaptations of the initially planned scheme [2]. Thus, subjects received MenBvac® at D0, W6, M8, and M23 in the Dieppe area, and at D0, W6, M8, and M36 in the

Neufchâtel-en-Bray area. Previously enrolled subjects were asked to provide a blood sample four years after the last boost (i.e., at M71) for the Dieppe area [2] and one year after the last boost (i.e., at M50) for the Neufchâtel-en-Bray area [12]. The extension of the former study was approved for both cohorts by the regional ethics committee (Comité de Protection des Personnes Nord-Ouest-1) and written informed consent was obtained from parents or legal guardians of every participant.

***Strain coverage***

We evaluated the range of strain coverage by MenBvac® by testing a subset of frozen serum samples (collected six weeks after the second boost) of 12 subjects from the Neufchâtel-en-Bray area cohort. The sera came from subjects who responded against strain LNP21362 (B:14:P1.7,16/cc32), which was previously used as a reference strain for SBA assays for the Normandy outbreak [2]. These subjects did not show protective SBA titres before vaccination (D0). Sera were tested against the reference strain (LNP21362), as well as 13 other strains of serogroup B or C harbouring different PorA variable regions (14 SBA tests being the maximal possible due to the low volume of residual serum available for each of these sera). The other 13 strains were selected from B- and C-subgroup strains analysed in 2015 by the National Reference Centre (NRC) for meningococci. In France, almost all cases of invasive meningococcal disease are biologically confirmed by culture and/or PCR at the NRC. The NRC performs complete genotyping of all strains by multi-sequence locus typing (clonal complex) of PorA and FetA [15]. The 13 strains were selected to represent the different combinations of variable regions, VR1 and VR2, partially matching PorA P1.7,16, that are currently circulating in the country. When the same PorA profile was shared by several strains belonging to different clonal complexes, one strain per clonal complex was selected. Human complement was used for the SBA assay of serogroup B isolates. Baby rabbit complement

was used for serogroup C isolates due to the intrinsic meningococcal lysis against these serogroup C strains in all human sera that were used as complement sources.

Finally, the results were extrapolated to the 2015 NRC data to determine the percentage of invasive meningococcal strains currently endemic in the country that completely or partially match the OMV component of MenBvac® (P1.7,16) or 4CMenB/Bexsero® (P1.7-2, 4).

## Results

### *Durability of immunogenicity against the targeted epidemic strain*

Table 1 shows the long-term SBA titres for the two cohorts (last line) and compares them to the results previously reported for each scheme [2, 11].

For the Dieppe area cohort, 115 children among the 243 initially included (47%) agreed to participate in the final phase of the study four years after the second boost, amongst which only 31.3% (95% CI 22.8 to 39.8) had an hSBA titre consistent with protection, whereas the geometric mean hSBA was only 3.3 (95% CI 2.8-3.9). These data are in accordance with the marked decline of hSBA titres previously observed 15 months after the first boost, for which only 56% of subjects showed protective titres.

For the Neufchâtel-en-Bray area cohort, 96 children among the 213 initially included (45%) agreed to participate in the final phase of the study one year after the second boost, amongst which only 47.9% (95% CI 37.9 to 57.9) showed protective hSBA titres. This percentage, as well as the geometric mean hSBA value (4.4; 95% CI 3.5-5.5), were not significantly different from those previously achieved one year after the first boost (i.e., at M20).

### *Strain coverage*

The characteristics of the 14 strains studied and the hSBA or rSBA titres achieved against each of them in the sera from 12 (10 for serogroup C due to a limited amount of sera) high responders to MenBvac are presented Table 2.

Among the 14 strains, two (one of serogroup B used as a control and one of serogroup C) completely matched the PorA of MenBvac (P1.7,16) and both belonged to cc32. Nine strains (seven of serogroup B and two of serogroup C) shared either VR1 or VR2 with the vaccine strain or were variants of the P1.7 (VR1) or P1.16 (VR2) family. The last three serogroup B

strains had PorA which completely differed from that of the strain vaccine (P1.22, 9, P1.19-2, 13-1 and P1.19-1, 15-11). Ten of the 14 strains (71%) belonged to major hyperinvasive clonal complexes (cc11, cc32, cc41/44, cc269).

As expected, hSBA titres against the serogroup B isolate (LNP21362) that matched the vaccine strain (P1.7,16) were significantly higher than the threshold of 4 for all 12 sera tested, with a lower limit of the 95% CI > 4.

In contrast, the lower limit of the 95% CI of the GMT was lower than the threshold of 4 for the SBA titres against the three isolates (LNP27143, LNP27050 and LNP27000) that did not at all match PorA. One of these strains (LNP27000) did not show coverage in any tested serum. However, 25% and 42% of the volunteers had hSBA titres of 4 and 8 against the other two strains LNP27143 and LNP27050, respectively. Additionally, strain LNP27200, a non-cc32 strain with a partial PorA match (P.21,16-36), also showed a low GMT, with 25% of tested sera displaying hSBA titres of 4.

The GMT and the lower limits of the 95% CI were above 4 for the remaining six B strains. The SBA titres were high in all 12 tested sera for three of the six strains (LNP27338, LNP27087 and LNP27386 all belonged to the cc32) and were not significantly different from those achieved against the reference strain (LNP21362). The hSBA titres differed greatly (depending on the strain) for the three remaining strains (LNP27372, LNP27010 and LNP27114). However, the lower limit of the 95% CI remained higher than 4, although the GMT were significantly lower than those obtained against the reference strain LNP21362.

We also studied three strains of serogroup C, amongst which one entirely matched PorA of MenBvac (LNP25514) and two partially matched (LNP25553 and LNP26251). The rSBA threshold of 8 was achieved against the three C strains in all tested sera. A hierarchy of

responses was however observed, with the rSBA titres being significantly higher against the strain which entirely matched the vaccine PorA than the other two serogroup C strains.

The percentages of invasive meningococcal strains predicted to be covered by either MenBvac® or 4CMenB/Bexsero® based on their PorA variable regions, and regardless their serogroups, are shown in Table 3. For MenBvac®, only 2.6% of the current French strains totally matched PorA. This putative coverage increased to 16.9% when considering both complete and partially matching (i.e. strains with family 7 VR1 and/or strains with family 16 VR2 ). For 4CMenB/Bexsero®, the respective percentages were 8.1% and 14.5%.

## Discussion

This study was performed in an area of Normandy recently affected by a clonal meningococcal B outbreak that was controlled using MenBvac, an OMV vaccine [2]. The two major results of this study were: (i) the short durability of protection against the targeted strain, despite a four dose vaccination scheme and (ii) an extension of the strain coverage to other B and non-B strains that at least partially shared the PorA of the vaccine strain.

The short persistence of protection was observed even after a second booster dose, although the absence of samples from six weeks after the second booster dose in the Dieppe cohort limits the extrapolation of this conclusion. Several previous studies on OMV vaccines have also reported the rapid decline of SBA titres elicited against the targeted strain [16]. This is not necessarily a major drawback, as such "tailor-made" vaccines are aimed to control an outbreak rather than to offer persistent protection against sporadic events. For the control of a clonal outbreak, two doses of a targeted OMV vaccine given at a 4-6 week interval can be sufficient to "put the fire out" as reported during the first application of MenBvac® in Norway [17]. However, because clonal B outbreaks might naturally persist for up to two decades, obtaining immunity for several years in an affected area is probably pertinent. The four-dose MenBvac® regimen applied during a two-year period in Normandy resulted in limited persistence of the SBA titres against the outbreak strain (B:14:P1.7,16/cc32) which was observed in less than one third of vaccinated 1-5 year-old children 5 years after the first dose. Such poor results do not necessarily exclude a better response in adolescents and young adults, as shown for other OMV vaccines [18]. The short observed persistence of bactericidal antibodies against B:14:P1.7,16/cc32 (even in the Dieppe area, epicentre of the outbreak) may be due to the rapid decline of the response to the vaccine and the lack of natural immunity favoured by a very low rate of pharyngeal carriage of the epidemic strain in the population, as reported by a carriage study performed at the height of the outbreak [10].

The broader strain coverage of MenBvac® is relevant in meningococcal vaccinology as the 4CMenB/Bexsero® vaccine includes an OMV component. OMV-based vaccines elicit an immune response that is mainly directed against the PorA outer membrane protein. Due to the high variability of PorA among isolates, this type of vaccine is classically considered strain-specific [19]. However, several previous studies with MenBvac® [8, 9, 18, 20] and other OMV vaccines [7, 9, 18, 20] have reported protection beyond the vaccine strain. Rosenqvist *et al.* have shown that MenBvac® induced in adult volunteers significant SBA response against variants of the vaccine strain lacking some outer membrane proteins [8]. The Norwegian Institute of Public Health team had performed a study in adult volunteers comparing the immunogenicity of MenBvac® (P1.7,16 strain) and MeNZB® (P1.7-2,4 strain) showing that SBA titres were better against the homologous strain than with the heterologous strain [9, 20]. Tappero *et al* have reported that both MenBvac (P1.7,16 strain) and the Finlay Institute OMV vaccine (P1.15 strain) did not induce significant response in infants while children and adults showed SBA titres against a heterologous strain but to a lesser extent than to the vaccine homologous strain[18]. Boutriau *et al* have analyzed a bivalent OMV vaccine designed to cover a large proportion of B strains circulating in Europe that induced increased SBA titres against the two vaccine strains as well as against three heterologous strains but this vaccine did not reach the market [7]. Our study provides additional data, suggesting that strain coverage can be larger than initially expected. Completely or partially matching one of the two variable regions of PorA (VR1 and VR2) may lead to coverage by the MenBvac® irrespective of the serogroup. However, SBA titres were significantly higher when both VR1 and VR2 matched the vaccine, suggesting synergism of serum bactericidal activity against these variable regions. Further studies may be needed to explore how the alterations of VR regions affect serum bactericidal activity. Moreover, other minor proteins in the OMV can confer protection, as suggested by the SBA

titres against the strain LNP27050 that did not match variable regions of PorA P1.7,16. This part of the study had however three limitations. (i) Due to low volumes of residual serum available, it was impossible for a given strain to test all subvariants in terms of VRs; all sub-variants of P1.7,16 may not be covered and testing several other strains may be required. (ii) It was also impossible to evaluate the protection at baseline against the tested strains. However, we have previously reported low level of protective SBA titres against the stain with P1.7,16 before the first dose of MenBvac®) [12].

(iii) The broader of coverage has been studied only for MenBvac®; it is not excluded that results may differ for other OMV based vaccines.

The strain coverage by 4CMenB/Bexsero® has been extensively studied for the three proteins NadA, fHbp, and NHBA, but much less for its fourth component, corresponding to PorA P1.7-2, 4 from MeNZB® [21]. Previous reports have suggested that the VR1 region (7-2) of PorA was poorly recognised by a monoclonal antibody against subtype P1.7 due to an internal deletion, leading to masking of this region [22]. However, our study shows that polyclonal anti-PorA antibodies, obtained after vaccination in several subjects, achieved SBA titres against the two strains (LNP27010 and LNP27114) that only had VR1 7-2. The potential protection against non-B strains, as suggested by our data, is of interest, as this is expected to enlarge strain converge. Such protection was suggested in reports on the use of 4CmenB® against serogroups W and X [23, 24]. The subjects of our study were not vaccinated against serogroup C meningococci when MenBvac® vaccination started. Indeed, the recommendation for vaccination against MenC only started in France in 2010. The uptake of the vaccine remains very low in France and vaccine coverage in 1-4 year olds was only 50% by the end of 2013 [25].

Based on the 2015 database from the NRC, 14.5% of the current serogroup B strains are predicted to be covered by the OMV component of 4CMenB/Bexsero® (regardless of the

coverage by the three other components of the vaccine). The Meningococcal Antigen Typing system (MATS) predicted 85% overage of the serogroup B isolates in France. Importantly, among the 15% (n = 30) of uncovered strains, 13% (n = 4) could be covered on the basis of partial matching with PorA [4]. Thus, strain coverage could be higher than that predicted solely by MATS.

In conclusion, the results of the current study show that OMV-containing vaccines induce immunity, although of short duration, far below that of the vaccine strain. This argues for adapting the OMV component from new meningococcal vaccines to improve the coverage of local strains, particularly in the event of outbreaks that may not be covered by the other components of the vaccines.

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**Tables**

**Table 1**

Immunogenicity of MenBvac® vaccine and persistence of the response against B:14:P1.7,16 (strain LNP21362) in two cohorts of children of 1-5 years of age at first dose and previously analyzed at short term.

| Dieppe cohort MenBvac at D0-W6-M8-M23 | | | | Neufchâtel-en-Bray cohort MenBvac at D0-W6-M8-M36 | | | |
|---|---|---|---|---|---|---|---|
| Time of sampling | Number | % of subjects with hSBA ≥ 4 [95% CI] | GMT of hSBA titres [95% CI] | Time of sampling | Number | % of subjects with hSBA ≥ 4 [95% CI] | GMT of hSBA titers [95% CI] |
| - | - | - | - | D0* | 213 | 10.8 (6.6-15) | 2.3 (2.1-2.5) |
| - | - | - | - | M3 | 172 | 41.3 (33.9-48.7) | 3.3 (2.9-3.7) |
| M8* | 243 | 37.0 (30.9-39.8) | 2.8 (2.6-2.9) | M8* | 159 | 25.5 (19-32.6) | 2.8 (2.5-3.1) |
| M9.5 | 235 | 87.7 (83.5-91.9) | 11.3 (9.5-13.4) | M9.5 | 126 | 84.1 (77.7-90.5) | 10.9 (8.7-13.6) |
| - | - | - | - | M20 | 126 | 39.7 (31.2-48.2) | 4.1 (3.4-5) |
| M23* | 193 | 56.3 (49.2-63.3) | 3.9 (3.5-4.5) | - | - | - | - |
| - | - | - | - | M36* | 117 | 21.4 (14-21.4) | 2.7 (2.4-3.1) |
| - | - | - | - | M37.5 | 99 | 86.9 (80.3-93.5) | 17.5 (13.2-23.2) |
| - | - | - | - | M50 | 96 | 47.9 (37.9-57.9) | 4.4 (3.5-5.5) |
| M71 | 115 | 31.3 (22.8-39.8) | 3.28 (2.8-3.9) | - | - | - | - |

*Sample collected before dose.
D=day. W=week. M=month.

**Table 2** Immunogenicity of MenBvac® vaccine against strains of serogroups B or C in 12 responder subjects. Results are expressed in comparison to reference strains that completely match PorA of the vaccine strain.

| Study strain number (LNP) | Genotyping | | | | | SBA | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Group | PorA VR1 | PorA VR2 | cc | FetA | Range of SBA titres (Proportions of sera with protective titres) | GMT of hSBA titres [95% CI] | GMT [95% CI] | p-value |
| Serogroup B strains; SBA using human complement (hSBA); protective response for hSBA ≥ 4 | | | | | | | | | |
| Complete match with the vaccine strain | | | | | | | | | |
| LNP21362 | B | 7 | 16 | 32 | F3-3 | 16-128 (100%) | 107.6 | 73.5-157.6 | Ref* |
| Partial match with the vaccine strain | | | | | | | | | |
| LNP27010 | B | 7-2 | 4 | 41/44 | F1-5 | 2-16 (92%) | 6.4 | 4.3-9.4 | 0.0005 |
| LNP27087 | B | 7 | 16-26 | 32 | F3-3 | 32-128 (100%) | 114 | 88.4-147.1 | >0.99 |
| LNP27114 | B | 7-2 | 4 | 162 | F5-9 | 2-128 (75%) | 15.1 | 5.9-39 | 0.002 |
| LNP27338 | B | 7-2 | 16-26 | 32 | F3-3 | 128-128 (100%) | 128 | 128-128 | >0.99 |
| LNP27372 | B | 7-1 | 1 | 32 | F3-3 | 2-128 (92%) | 24 | 9.7-59.5 | 0.00195 |
| LNP27200 | B | 21 | 16-36 | 865 | F5-8 | 2-4 (25%) | 2.4 | 1.9-2.9 | 0.0005 |
| LNP27386 | B | 21 | 16 | 41/44 | F1-7 | 128-128 (100%) | 128 | 128-128 | >0.99 |
| No match with the vaccine strain | | | | | | | | | |
| LNP27000 | B | 19-1 | 15-11 | 269 | - | 2-2 (0%) | 2 | 2-2 | 0.0005 |
| LNP27050 | B | 19-2 | 13-1 | 461 | - | 2-8(42%) | 4 | 2.1-7.5 | <0.0001 |
| LNP27143 | B | 22 | 9 | 269 | F1-5 | 2-8 (25%) | 2.7 | 1.9-3.8 | 0.0005 |
| Serogroup C strains; SBA using rabbit complement (rSBA); protective response for rSBA ≥ 8 | | | | | | | | | |
| Complete match with the vaccine strain | | | | | | | | | |
| LNP25514 | C | 7 | 16 | 32 | F3-3 | 16-512 (100%) | 64 | 26.7-153.2 | Ref** |
| Partial match with the vaccine strain | | | | | | | | | |
| LNP25553 | C | 17 | 16-3 | 11 | F1-1 | 16-32 (100%) | 18.4 | 14.9-22.7 | 0.016 |
| LNP26251 | C | 21-7 | 16 | 1157 | F5-36 | 64-512 (100%) | 161.3 | 59.7-435.8 | 0.019 |

** Significance level p < 0.005 after Bonferroni correction for 10 comparisons*
*** Significance level p < 0.025 after Bonferroni correction for 2 comparisons*

**Table 3**
Percentage of current invasive meningococcal strains in France that are expected be covered by either MenBvac® or 4CMenB/Bexsero® based on their PorA domain (for 4CMenB/Bexsero® the coverage is largely enhanced by the three other components of the vaccine).

| | 2015 French *N. meningitidis* isolates with complete typing available (n=344) | | | | | |
|---|---|---|---|---|---|---|
| | Matching with the P1.7,16 PorA antigen of MenBvac | | | Matching with the P1.7-2,4 PorA antigen of 4CMenB/Bexsero | | |
| | Complete | Incomplete | Null | Complete | Incomplete | Null |
| B strains (n=170) | 8 (4.7%) | 45 (26.5%) | 117 (68.8%) | 28 (16.5%) | 21 (12.4%) | 121 (71.1%) |
| Strains of other groups (n=174) | 1 (0.6%) | 4 (2.3%) | 169 (97.1%) | 0 (0%) | 1 (0.6%) | 173 (99.4%) |
| Total (n=344) | 9 (2.6%) | 49 (14.3%) | 286(83.1) | 28 (8.1%) | 22 (6.4%) | 294 (85.5%) |