Genomic-based coverage prediction for MenB vaccines on Portuguese invasive *Neisseria meningitidis* strains

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INTRODUCTION & OBJECTIVES

Neisseria meningitidis is a commensal bacteria of the human nasopharynx that occasionally cause serious invasive infections including fatal sepsis and meningitis. Meningococci are classified into 12 serogroups based on structural differences in capsular polysaccharide, but only six serogroups (A, B, C, W, Y, and more recently X) are the most frequent causes of invasive meningococcal disease (IMD) worldwide [1].

Portugal registered 1359 of IMD confirmed cases between 2003 and 2019, with MenB harboring 71% of all confirmed cases, followed by serogroup C with only 9.7%. Cases due to serogroup Y (MenY) accounted for 5.1%, while serogroup W showed a marked increase in cases over the last four years, ranging from 1.4% in 2012 to 15.5 % in 2019 [2].

To prevent IMD caused by MenB two vaccines are available: the 4CMenB included in the Portuguese routine immunization programme in October 2020, being recommended for children above two months of age, and the bivalent rLP2086 licensed in 2017 for individuals older than 10 years old [3-4]. Moreover, these vaccines have been shown to have potential in several meningococcal serogroups other than serogroup B.

The multicomponent vaccine 4CMenB includes two fusion proteins, namely the Neisserial Heparin Binding Antigen-GNA1030 (NHBA, peptide 2) and the factor H binding protein-GNA2091 (fHbp, peptide 1, subfamily B), and the single antigen Neisserial adhesin A (NadA, peptide 8), combined with the outer membrane vesicles (OMV) the PorA peptide 4 of the variable region 2 (P1.4) [5]. Regarding the bivalent rLP2086 vaccine, it contains two subfamilies of the fHbp namely the subfamily A (peptide 45) and subfamily B (peptide 55) that are classified based on their genetic variation [6].

The aim of this study was to predict the coverage of the 4CMenB and rLP2086 vaccines against Portuguese *Neisseria meningitidis* isolates collected between 2012 and 2019 and, provide an analysis on the diversity of the vaccine antigens based on genomic analysis.

METHODS

Whole-genome sequence (WGS) data from invasive strains (n=324) isolated in Portugal between 2012 and 2019 were analysed both for genotype characterization and for vaccine antigen reactivity. To predict strain coverage by 4CMenB and rLP2086 vaccines, vaccine antigen reactivity was assessed using the MenDeVar index available on the PubMLST Neisseria website (https://pubmlst.org/organisms/neisseria-spp).

The antigen reactiveness was considered as exact match (isolate containing the exact vaccine peptide), cross-reactive (isolate containing cross-reactive vaccine peptide), or none (isolate containing no peptide that are either exact matches or cross-reactive) [7]. Isolates were predicted to be covered by the vaccines whenever at least one antigen has been considered as exact match or cross-reactive. The proportion of isolates predicted to be covered was evaluated using the total number of isolates with available information as a denominator.

RESULTS

In the eight-year period 2012-2019, the National Reference laboratory of invasive meningococcal disease in Portugal studied 235 invasive MenB isolates and 89 isolates from other serogroups, including 68 invasives isolates and 21 isolates from carriers.

1. Distribution of the most representative meningococcal vaccine peptide variants among Portuguese invasive MenB isolates

The rLP2086 vaccine

- Out of 235 invasive MenB isolates studied, 125 (53.2%) were found to belong to subfamily A, 109 to subfamily B (46.4%) and one isolate (fHbp peptide 207) was an A/B hybrid peptide (Fig. 1A).
- Peptide 45 (exact match) **subfamily A** was present in 6.4% (n=15) of MenB isolates. Peptide 19 **subfamily A** was the most common fHbp predicted to be cross-reactive, being present in 10.6% (n=25) of MenB isolates mostly assigned to clonal complex (cc) ST 41/44.
- fHbp 13 **subfamily B** was present in 7.9% (n=18) and fhbp14 was present in 7.2% (n=17) of MenB isolates, being both cross reactive and mostly associated to cc ST 41/44.

The 4CMenB vaccine

- fHbp peptide 1 (exact match) **subfamily B** was found in 3.0% (n=7), while fHbp peptide 14 was the most common peptide predicted to be covered (cross-reactive) present in 7.2% (n=17) of MenB isolates associated to cc ST 41/44.
- Analysis on NHBA showed that peptides with no data available on vaccine reactivity correspond to 60% of the study MenB genomes (Fig. 1B). The NHBA peptide 2 was the most common peptide predicted to be covered (exact match), present in 14.2% (n=33) of MenB isolates exclusively associated with cc ST 41/44.
- NadA peptides showed a high number of isolates (92.8%) with no data available on vaccine peptide reactivity. NadA 1 and NadA 100 are non-covered peptides and are present in 6.8% (n=16) of MenB isolates. Only one isolate was cross-reactive for the NadA 3 peptide (Fig. 1C).
- PorA variable region 2 (VR2) revealed a high antigenic diversity (38 different peptides) with variant subtype P1.4 present in 16.2% (n=38) of isolates (Fig. 1D).

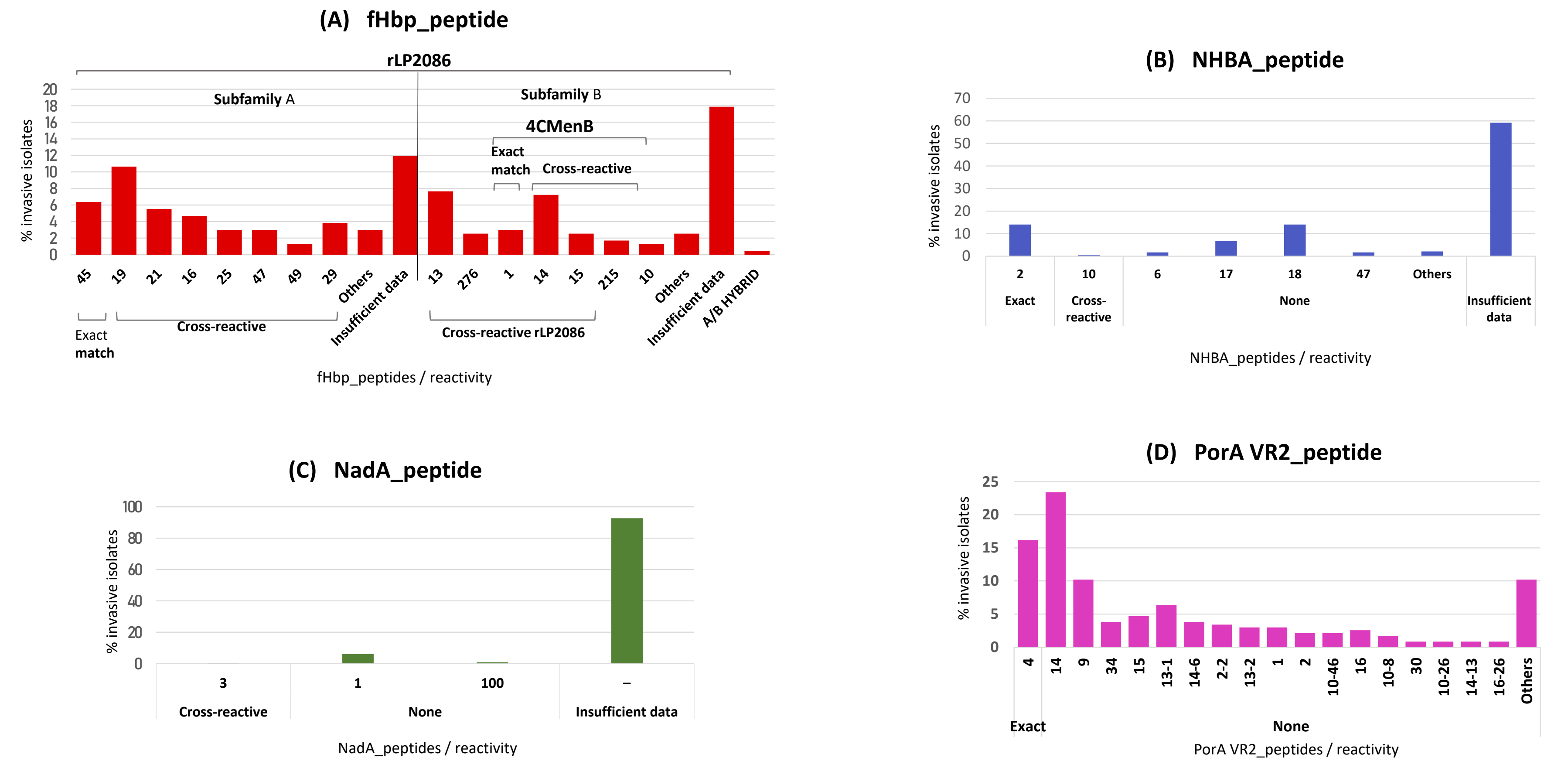

Figure 1 - Distribution of the most representative vaccine peptide variants among Portuguese invasive MenB isolates (n=235) collected between 2012 and 2019. Others included peptides present in only one isolate. Insufficient data have included isolates that have not been tested experimentally. Exact, cross-reactive, none, and insufficient classification according to the MenDeVAR index was used to provide information on 4CMenB and rLP2086 reactivity against antigenic variants [7].

3. Predicted coverage of non-serogroup B isolates by MenB vaccines

- 24 (27%) out of the 89 non-serogroup B study isolates had available data on 4CMenB vaccine reactivity and 51 isolates (57.3%) had data on rLP2086 reactivity(Table 4).
- Analysis of 4CMenB coverage showed that 19 isolates were covered by 4CMenB vaccine due to cross-reactive and four isolates had specific reactivity.
- 100% (12/12) of MenW cc ST 11 were predicted to be covered by the 4CMenB vaccine. In contrast, MenW isolates cc ST 11 were not covered by rLP2086.
- The remaining non-serogroup B isolates (n=51) were covered by rLP2086 vaccine due to cross-reactivity.

2. Predicted coverage of Men B isolates by MenB vaccines

- Concerning MenB isolates, data on 4CMenB and RLP2086 vaccines reactivity were available in the PubMLST database for 121 and 140 Portuguese MenB genomes, respectively (51.5% and 59.6%, from the total of the studied invasive MenB isolates).
- The predicted strain coverage by the 4CMenB vaccine was 73.5% (95% CI: 64.8%-81.2%). More than half of the isolates (54.5%) were classified as exact match and 19.0% were cross-reactive (Table 1).
- The predicted coverage by the rLP2086 vaccine was 100%, mostly due to cross-reactivity (89.3%).
- In the most vulnerable age groups including children and adolescents, the average coverage by 4CMenB was estimated to be 73.8% and 81.8% (Table 2).
- Protein P1.4 of MenB isolates was the vaccine peptide that most contributed to the exact match, representing 29.2 % of coverage followed by NHBA peptide 2 with 23.6% of coverage (Table 3). On the other hand, the multiple variants of the fHbp peptide were the most contributed to the cross-reactivity (23.6%) (Table 3).
- We observed that 85.4% of MenB isolates were covered by just one antigen, namely fHbp (30.3%), P1.4 (29.2%), and NHBA (24.7%).

Table 1 - Predicted coverage of invasive MenB isolates by the vaccines 4CMenB and rLP2086 according to MenDeVar index in Portugal, 2012-2019.

Reactivity 0	4CMenB		RLP2086	
	No. of isolates	% of isolates covered	No. of isolates	% of isolates covered
Exact match	66	54.5	15	10.7
Cross-reactive	23	19.0	125	89.3
None	32	26.4	0	0.0
Predict coverage, % (95% CI)	73.5 (64.8 - 81.2)		100	

Table 2 - Predicted coverage of invasive MenB strains by 4CMenB vaccine by age group, Portugal, 2012-2019.

Age group in years	Strain coverage %
<1	73.8
1-4	74.1
5-9	80.0
10-19	81.8
20-45	72.7
>45	63.2

Table 3 - Number and percentage of MenB isolates covered by 4CMenB vaccine, by vaccine antigen/combination of antigens, in Portugal, 2012-2019.

MenDeVar Index	4CMenB vaccine antigens/combination of antigens	No. of isolates	% of isolates covered
Exact match	fHbp (peptide 1)	6	6.7
	NHBA (peptide 2)	21	23.6
	Por A (P1.4)	26	29.2
	fHbp + PorA (peptide 1 + P1.4)	1	1.1
	NHBA + P1.4 (NHBA 2 + P1.4)	12	13.5
Cross-reactive	fHbp peptides: 4(n=1), 10(n=3), 12(n=1), 14(n=5), 15(n=6), 37(n=1), 144(n=1), 215(n=3)	21	23.6
	NHBA (peptide 10)	1	1.1
	NadA (peptide 3)	1	1.1

Table 4 - Non-serogroup B isolates are predicted to be covered by 4CMenB and/or rLP2086 vaccines, by vaccine antigen/combination of antigens, serogroup, and clonal complex.

Serogroup (n)	ST/cc	Vaccine antigens/combination of antigens	Isolates predicted to be covered by 4CMenB		Isolates predicted to be covered by rLP2086	
			No. of isolates	Reactivity	No. of isolates	Reactivity
Serogroup W (n=19)	cc11	NadA peptide 6	12	Cross reactive	-	-
	cc22	fHbp peptide 16	-	-	4	Cross reactive
Serogroup Y (n=36)	cc23	fHbp peptide 25	1	None	18	Cross reactive
	cc103	fHbp peptide 25	-	-	4	Cross reactive
	cc103	fHbp peptide 14	4	Cross reactive	4	Cross reactive
	cc167	fHbp peptide 23	-	-	2	Cross reactive
	cc22	fHbp peptide 13	-	-	1	Cross reactive
	ST-10346	fHbp peptide 16	-	-	2	Cross reactive
Serogroup C (n=17)	cc11	fHbp peptide 13	-	-	4	Cross reactive
	cc60	fHbp peptide 13	-	-	2	Cross reactive
	ST-7006	P1.4/fHbp peptide 16	1	Exact match	1	Cross reactive
Serogroup Z (n= 2)	ST-13741	NadA peptide 8/fHbp peptide 19	1	Exact match	1	Cross reactive
	cc865	fHbp peptide 19	-	-	1	Cross reactive
Serogroup X (n= 2)	cc103	P1.4	1	Exact match	-	-
	ST-14273	fHbp peptide 14	1	Cross reactive	1	Cross reactive
Serogroup E (n= 1)	cc254	fHbp peptide 13	-	-	1	Cross reactive
Non-grupable (n= 2)	cc174	NadA peptide 8/fHbp peptide 21	1	Exact match	1	Cross reactive
	cc269	fHbp peptide 15	1	Cross reactive	1	Cross reactive
Capsule null (n=10)	cc198	fHbp peptide 4	1	Cross reactive	1	Cross reactive
	cc1117	fHbp peptide 21	-	-	1	Cross reactive
	ST-14871	fHbp peptide 16	-	-	1	Cross reactive

CONCLUSIONS & DISCUSSION

Despite the genomic heterogeneity of the fHbp peptides, the fHbp peptide 19 (subfamily A) and fHbp peptide 14 (Subfamily B) were the most common with cross-reactivity and associated mostly with the cc ST 41/44. In addition, MenB isolates assigned to cc ST 41/44 were the most frequent in Portugal, with a predicted coverage by the 4CMenB vaccine of 93.8%, and all were predicted to be covered by the rLP2086 vaccine.

Regarding the peptides included in the 4CMenB vaccine, 85.4% (76/89) of isolates were covered by just one antigen, being the peptides, fHbp (30.3%), P1.4 (29.2%), and NHBA (24.7%) those that independently most contributed to the efficacy of the 4CMenB vaccine.

The results of this study showed that between 2012 and 2019, 73.6% (95% CI: 64.8%-81.2%) of the Portuguese MenB isolates were predicted to be covered by 4CMenB vaccine and 100% by rLP2086 vaccine, which is in line with data from several European countries [8-9].

Moreover, the 4CMenB vaccine showed high potential effectiveness against serogroup W cc ST 11 (100%) while the vaccine rLP2086 displayed a high potential coverage for all the remaining serogroups, except for serogroup W cc ST 11.

Noteworthy, this study had a high number of isolates without available data on vaccine peptide reactivity, which is a limitation of this study. This may be a consequence of the emergence of new alleles or a combination of alleles encoding antigenic components of the vaccine. Therefore, further studies on the correlation of phenotypic and genomic data are needed to update the MenDevar database for more accurate analysis.

The 4CMenB and rLP2086 vaccines showed potential coverage against invasive *Neisseria meningitidis* strains regardless the capsular group. These vaccines should be considered to control possible outbreaks caused by serogroups for which no specific vaccine is available. The high diversity of peptides variants reinforces continuous surveillance to detect the potential emergence of vaccine-resistant genotypes.

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