POTENTIAL COVERAGE OF ENGLISH AND WELSH CAPSULAR GROUP B ISOLATES BY AN INVESTIGATIONAL MENINGOCOCCAL GROUP B VACCINE (4CMenB)

J. Findlow[1], S Gilchrist[1], D Thompson[1], M Stella[2], G Frosi[2], R. Borrow[1].

[1]Vaccine Evaluation Unit, Health Protection Agency, Manchester, U.K.

[2]Novartis Vaccines, Siena, Italy.

Background

➢Due to the unavailability of a broadly cross-reactive vaccine, *Neisseria meningitidis* group B (MenB) remains a globally important cause of meningitis and septicaemia associated with significant mortality and long-term morbidity [1].

➢An investigational multi-component meningococcal group B vaccine (4CMenB) has been developed and has proven safe and immunogenic in phase I-III clinical trials.

➢The vaccine contains three recombinant proteins; (i) factor H Binding Protein (fHBP).
(ii) Neisserial Heparin Binding Antigen (NHBA).
(iii) Neisserial adhesin A (NadA).

➢The recombinant proteins are formulated with Outer Membrane Vesicles prepared from the New Zealand outbreak strain NZ 98/254 (B:4:P1.7-2, 4: ST42: cc41/44) of which the PorA protein is immunodominant.

➢Determining the coverage afforded by 4CMenB is crucial for informing potential implementation decisions and understanding likely impact of the vaccine.

➢Calculating coverage is complicated as protection afforded by 4CMenB will depend upon antigen expression and cross-reactivity of induced antibody to antigen variants.

➢To address this issue, a meningococcal antigen typing system (MATS) has been developed to predict whether 4CMenB covers individual isolates [2].

Aims

➢ As MenB currently accounts for approximately 85% of meningococcal disease in England and Wales, we investigated the potential coverage of 4CMenB in England and Wales using MATS.

Methods

Isolates

➢All MenB case isolates (n= 535) received at the Health Protection Agency Meningococcal Reference Unit between July 2007 and June 2008 (epidemiological year) were utilised.

➢ Genotypic characterisation revealed that 70% harboured cross-reactive fHBP variant 1 proteins (6% have vaccine homologous variant 1.1), 5.4% harboured cross-reactive NadA variant 1 or 2 proteins and 100% harboured NHBA proteins (25% had vaccine homologous variant P0002).

MATS

➢ For each of the recombinant antigens (fHBP, NHBA and NadA) MATS was used individually to determine a relative potency (RP) value.

➢The RP value is dependent upon the amount of antigen expression by the isolate and the cross-reactivity of the assay detection antibody to the protein variant expressed by the isolate (detection antibody is raised against vaccine antigen).

➢A positive bactericidal threshold (PBT) has been published for each of the recombinant antigens [2]. Isolates with a RP value > PBT are highly likely to be killed in the serum bactericidal antibody assay by post vaccination sera and are therefore considered "covered" by the vaccine.

PorA

➢PorA was characterised genetically.

Coverage calculation

➢ The proportions of isolates with either 0, 1, 2 or 3 recombinant antigens with a RP > PBT or harbouring a homologous variable region 2 PorA (P1.4) were calculated.

Results

Of the 535 MenB isolates,;
528 gave a valid RP in MATS for all recombinant antigens.
534 were genetically characterised for PorA.

Figure 1. Predicted coverage of 4CMenB against English and Welsh MenB isolates, per individual antigen*

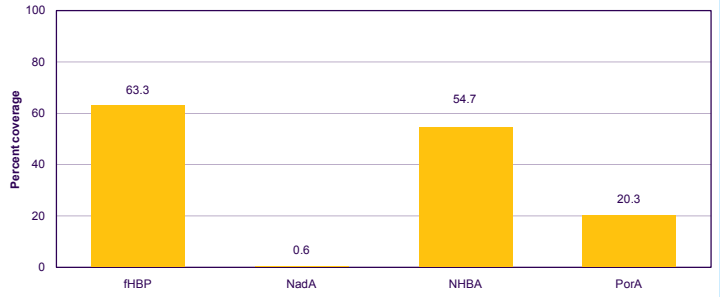
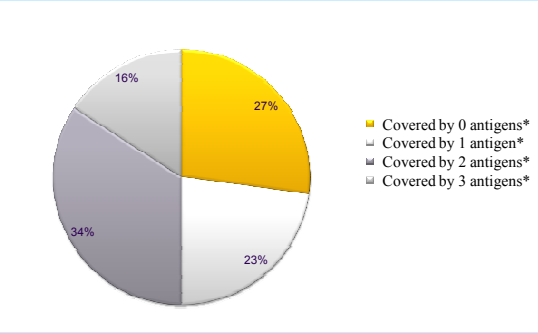
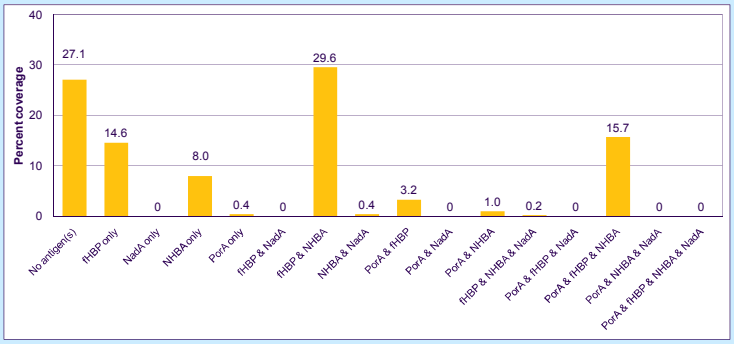


Figure 2. Predicted coverage of 4CMenB against English and Welsh MenB isolates, per number of antigens*



*>MATS PBT for fHBP, NadA and NHBA, or homologous genotype for PorA

Figure 3. Predicted coverage of 4CMenB ,by antigen combination against English and Welsh MenB isolates*



*>MATS PBT for fHBP, NadA and NHBA, or homologous genotype for PorA

Summary of Results

Predicted coverage per individual antigen (Figure 1)

➢fHBP and NHBA contribute the greatest to coverage with at least 54% of isolates covered.

➢All isolates with the vaccine homologous fHBP 1.1 variant had positive MATS phenotypes.

➢Only three isolates had positive MATS phenotype for NadA which were all ST-11, harbouring variant 2 NadA proteins.

➢131/133 (98%) of isolates with the vaccine homologous NHBA P0002 variant has positive MATS phenotypes.

➢ The P1.4 PorA provides a coverage of approximately 20% which were all cc41/44 isolates.

➢NadA provides <1% coverage.

Predicted coverage per number of antigens (Figure 2)

➢ 72.9 % (95% CI 59.8-89.6) of isolates were covered by at least one antigen of 4CMenB.

➢ Furthermore, 50% of isolates were covered by at least two antigens of 4CMenB.

Predicted coverage by antigen combination (Figure 3)

➢No isolates were covered by NadA alone and only two isolates were covered by the P1.4 PorA alone.

➢ The most frequent combination of antigens in coverage were fHBP and NHBA.

Discussion

Results

➢The overall coverage estimate is heavily influenced by the proportion of isolates harbouring fHBP variant 1 proteins and the low number of isolates harbouring vaccine cross-reactive NadA variants.

➢ This study utilised isolates from invasive disease, however, in the majority of disease cases, no isolate is recovered. We have therefore made the assumption that this collection of isolates is representative of the entire disease causing MenB population.

➢ The fact that 50 and 16% of isolates were covered by two and three antigens, respectively, may be advantageous as it may reduce the likelihood of vaccine escape mutants occurring.

Coverage estimates

➢The MATS PBT and hence subsequent coverage estimates presented here are based upon immunological cross-reactivity in 13-month olds following a three dose priming schedule and a booster dose at 12 months of age [2].

➢Immunogenicity data have demonstrated that cross-reactivity of induced antibody to fHBP increases with age [3].

➢Therefore, it is likely that the coverage estimate will overestimate and underestimate coverage in infants (7 months of age and younger) and adults, respectively.

➢Different antibody populations induced by the different antigens of 4CMenB may act synergistically and therefore coverage maybe higher than when predicted individually per antigen.

➢ The low coverage of NadA may be due to its phase variability and that the in vitro MATS may not be capturing the true contribution to coverage by NadA.

Ongoing and future work

➢This study provides coverage estimates based upon the epidemiology of a single year. However, similar studies have been undertaken by other European and non-European countries which will provide a more robust insight to potential coverage.

➢ Protection afforded by 4CMenB may not only be restricted to MenB isolates, therefore potential coverage against meningococci from other serogroups must be considered.

Conclusions

➢Using MenB isolates from the epidemiological year 2007/2008, we predict that 4CMenB would have a coverage of 72.9 % (95% CI 59.8-89.6) in England and Wales.

➢ Coverage of 50% of isolates would be afforded by at least two antigens in 4CMenB decreases the likleyhood of vaccine escape mutants occurring.

➢ **We conclude that 4CMenB has the potential to protect against a significant proportion of MenB disease in England and Wales.**

Acknowledgements

➢All in the HPA Meningococcal Reference Unit, in particular Steve Gray and Ed Kaczmarski.

➢ All in the MATS project team, in particular John Donnelly, Mariagrazia Pizza and Duccio Medini.

References

1. Tan LK, Carlone GM, Borrow R. Advances in the development of vaccines against *Neisseria meningitidis*. N Engl J Med. 2010 362:1511-20.

2.Donnelly J, Medini D, Boccadifuoco G *et al.*, Qualitative and quantitative assessment of meningococcal antigens to evaluate the potential strain coverage of protein based vaccines. Proc Natl Acad Sci USA. 2010 107:19490-5.

3. Brunelli B, Del Tordello E, Palumbo E *et al.*, Influence of sequence variability on bactericidal activity sera induced by Factor H binding protein variant 1.1. Vaccine 2011 29:1072-81.