Assessing 4CMenB strain coverage of invasive meningococcal strains in an English and Welsh vaccine-eligible cohort using non-culture draft genome sequences.

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INTRODUCTION

The meningococcal serogroup B vaccine 4CMenB (Bexsero, GlaxoSmithKline) was added to the UK routine infant immunisation programme in 2015 as a reduced dosage regimen. 4CMenB is composed of several meningococcal outer membrane proteins and, as a result, predicting the strain coverage of this vaccine against circulating meningococcal strains is a complex task (1).

The Meningococcal Antigen Typing System (MATS) is used to estimate 4CMenB strain coverage among meningococcal isolates *in vitro* and has proven to be a conservative predictor. Unfortunately, a meningococcal isolate is required for the assessment and only approximately one half of laboratory-confirmed meningococcal disease cases in England and Wales yield a viable organism. The remaining 'non-culture' cases are confirmed through meningococcal real-time PCR alone and only residual DNA with clinical specimens is preserved.

In order to allow prediction of strain coverage in the absence of a viable organism, the Genetic MATS (gMATS) scheme was published in 2019 (2). gMATS uses historical MATS data from isolates to statistically predict the coverage of specific antigenic variants. This scheme can be used to estimate coverage for cases without isolates as only genotyping of the relevant antigens is required.

To provide these genotypic data for non-culture cases, whole genome sequencing of meningococcal DNA directly from clinical specimens using the Agilent SureSelect system was demonstrated in 2018 (3). Here we describe the use of this technology to sequence meningococcal genomes from a large number of clinical samples from non-culture cases occurring among vaccine-eligible children in England and Wales. We used these data to assess gMATS coverage and compare to coverage among corresponding culture cases.

METHODS

Non-culture cases

Between Sept 2015 and Aug 2018 there were 327 group B cases among vaccine eligible children (0-5 years) that were confirmed by PCR alone. Of these, 100 (30.6%) featured samples with sufficient meningococcal DNA for successful whole genome sequencing (Fig. 1). Illumina sequencing was performed following RNA-bait enrichment using the Agilent SureSelect system and sequences were screened for human reads before assembly (3). Draft genomes were indexed and annotated within PubMLST.org/Neisseria.

Culture cases

Between Sept 2015 and Aug 2018 there were 276 group B cases among vaccine eligible children (0-5 years) that were confirmed by culture. The isolate-derived antigenic data for corresponding vaccine-eligible culture cases were extracted from the Meningococcal Genome Library (MGL) on PubMLST.org/Neisseria.

gMATS analysis

4CMenB coverage for the non-culture and culture cases was predicted using the published gMATS scheme according to Muzzi et al. (2019) (2). A small proportion of non-culture genomes yielded incomplete antigen profiles. These were considered 'unpredictable' in the absence of a covered antigenic variant.

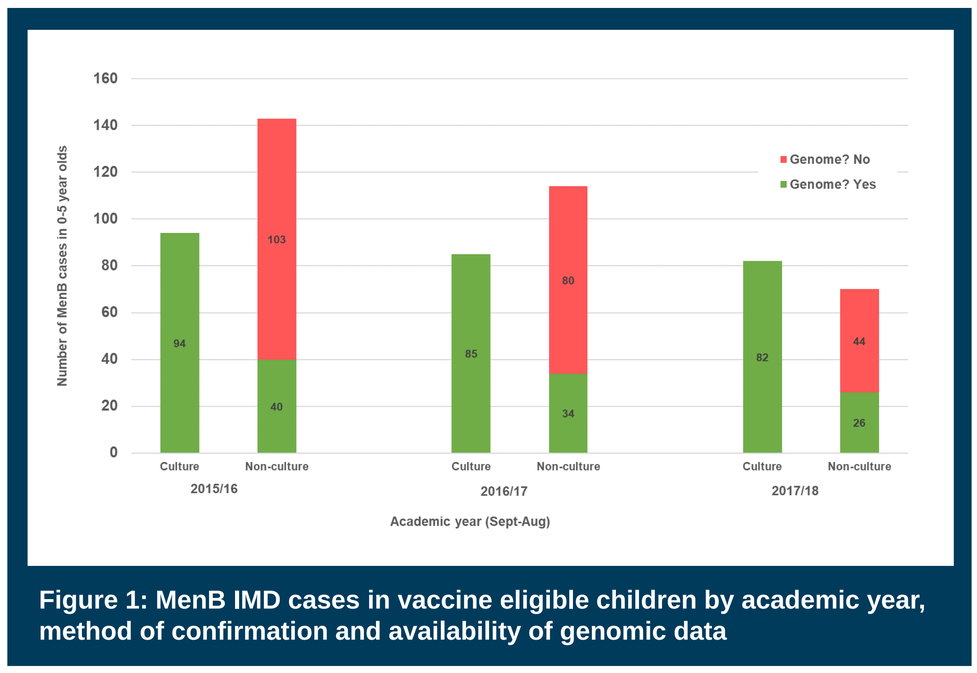

Figure 1: MenB IMD cases in vaccine eligible children by academic year, method of confirmation and availability of genomic data

RESULTS

Factor H-Binding Protein (fHbp)

The proportion of culture and non-culture strains harbouring fHbp variants considered covered in the gMATS scheme were similar (Fig 2., 42.8% and 43%, respectively). A greater proportion of non-culture strains were unpredictable for fHbp (33% vs 22.5% for culture).

Neisserial Heparin Binding Antigen (NHBA)

For NHBA, a higher percentage of cultured isolates harboured a covered variant than non-culture strains (41.7% vs 37.0%, respectively). With similar proportions of unpredictable variants among the two data sets, NHBA coverage was lower among the non-culture strains.

PorA variable region (VR) 2

Strains harbouring the P1.4 subtype considered covered by gMATS represented only 14.86% of the cultures isolates and 17.0% of non-culture strains.

Overall gMATS coverage

Looking at coverage of isolates based on all three antigens above, a similar proportion of strains in the culture and non-culture data sets harboured at least one antigen considered covered in the gMATS scheme (56.9% vs 54.0%, respectively).

Of the remaining strains, a greater proportion of the non-culture strains harboured at least one unpredictable variant than the cultured isolates. The lack of complete antigen data in a small minority of non-culture genomes (and therefore antigen is considered unpredictable) is likely to have contributed to this.

In the gMATS scheme, one half of the unpredictable are considered covered and the other half not covered in order to reach an overall coverage estimate. Overall gMATS coverage estimates for culture and non-culture data sets were 70.7% and 70.0%, respectively.

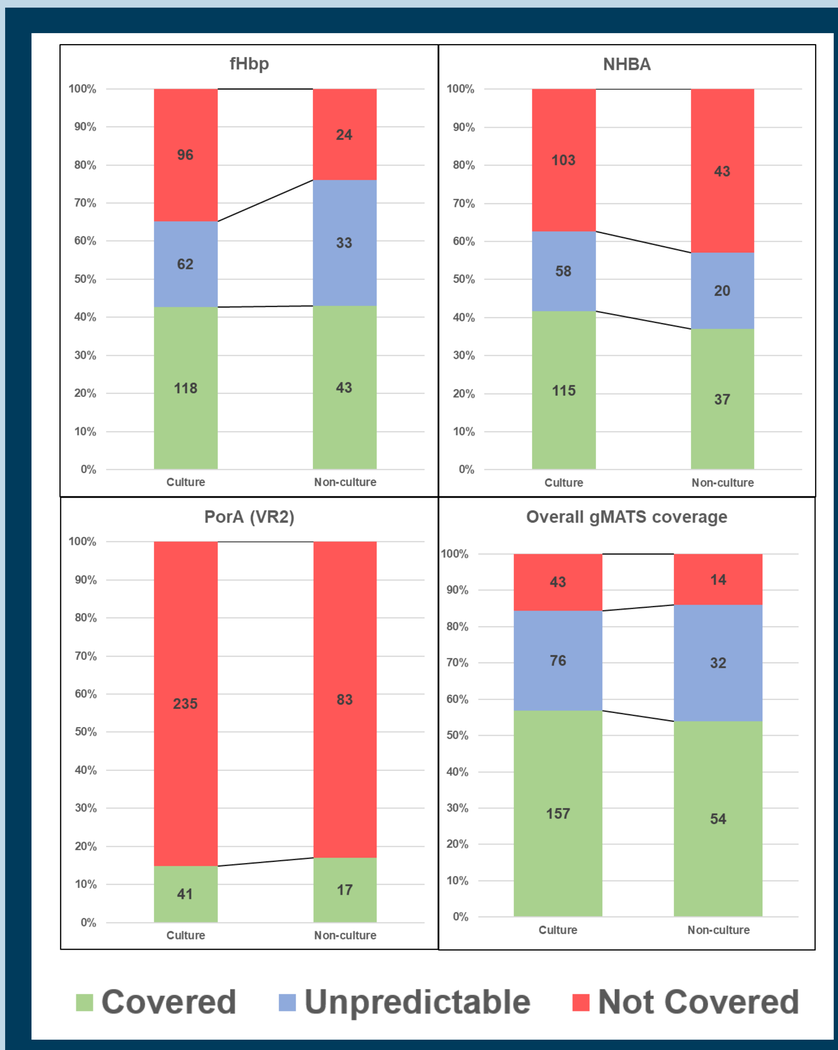

Figure 2. gMATS coverage of culture and non-culture MenB cases. Results are shown for each individual antigen and overall gMATS coverage for all antigens combined (bottom right).

DISCUSSION & CONCLUSIONS

The results indicate no major differences between E&W culture and non-culture strains in terms of 4CMenB strain coverage. This suggests that MenB isolates are sufficiently representative of all circulating MenB strains to be used for 4CMenB strain coverage predictions.

One limitation of the study is that it only included a minority of non-culture cases in the age group studied, however, the results are consistent with previous studies describing antigen distribution among MenB culture and non-culture strains more broadly (4).

Whole genomes sequencing of non-culture meningococcal strains is possible but remains restricted to the samples with higher bacterial loads (3). More advanced techniques/technology needed to improve % of non-culture strains that can be sequenced.

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