Exploiting real-time genomic surveillance data to assess 4CMenB meningococcal vaccine performance in Scotland 2015-2022

Charlene Rodrigues[1,2,3], Laura MacDonald[4], Roisin Ure[5], Martin Maiden[1,] Andrew Smith[5,6], Claire Cameron[4]

1. Department of Zoology, University of Oxford, Oxford, United Kingdom. 2. Department of Infection Biology, London School of Hygiene and Tropical Medicine, London, United Kingdom. 3. Department of Paediatrics, Imperial College Healthcare NHS Trust, London, United Kingdom. 4. Public Health Scotland, Glasgow/Edinburgh, United Kingdom. 5. Bacterial Respiratory Infection Service, Scottish Microbiology Reference Laboratory, Glasgow Royal Infirmary, Glasgow, United Kingdom. 6. College of Medical, Veterinary & Life Sciences, Glasgow Dental Hospital & School, University of Glasgow, Glasgow, United Kingdom.

Introduction

- The UK implemented the first national infant immunisation schedule for meningococcal vaccine **4CMenB ('Bexsero®') in September 2015**, targeting serogroup B invasive meningococcal disease (IMD).
- Bexsero® contains four variable subcapsular proteins and post-implementation IMD surveillance was necessary as non-homologous protein variants can evade Bexsero®-elicited protection.
- **Genomic surveillance applications including MenDeVAR Index** were developed to perform post-implementation surveillance on PubMLST.org.

Aim

To identify **vaccine breakthrough cases** after Bexsero® implementation in Scotland, using genomic surveillance and routine epidemiology.

Methods

IMD cases reported in Scotland in children <5 years, from 01/09/2015 to 30/06/2022 were identified. Patient demographics and vaccination status were combined with genomic data from the causative meningococci, which was used to assess vaccine coverage with the Meningococcal Deduced Vaccine Reactivity (MenDeVAR) Index.

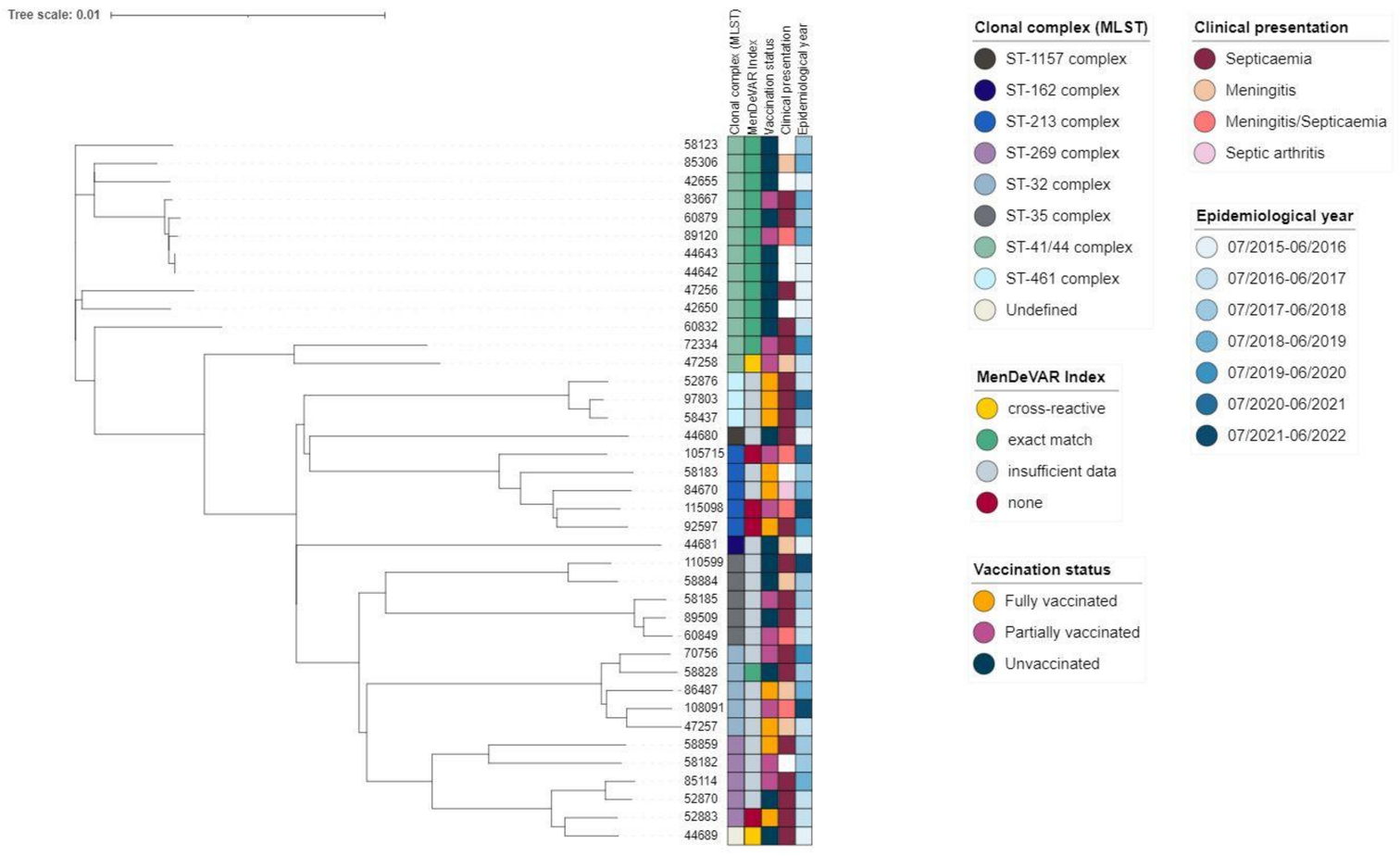

Figure 2: Phylogenetic relationships of IMD causing meningococci in children <5 years old isolated from culture-confirmed disease. Unrooted phylogeny generated using allele-based cgMLST with PubMLST ID at the end of the branches. Relevant genotypic and phenotypic data shown in coloured bars including the clonal complex; MenDeVAR Index; vaccination status; clinical presentation; and epidemiological year. Colours shown in the legends for respective columns. Fully and partially vaccinated according to the UK immunisation schedule.

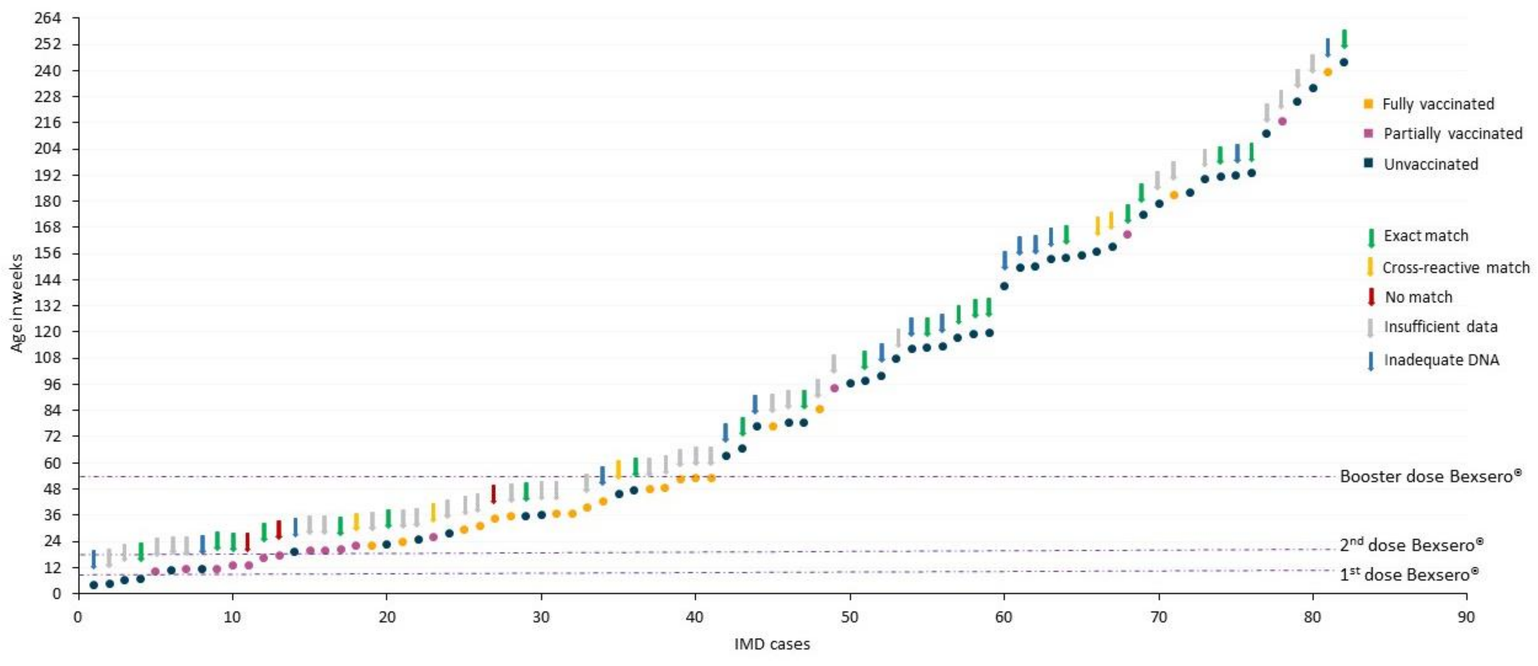

Figure 1: Distribution of all IMD cases in children <5 years old in Scotland from September 2015 to June 2022. Cases are shown in dots by increasing age at onset of IMD, measured in weeks. The dots are coloured by vaccination status (fully vaccinated yellow, partially vaccinated purple, unvaccinated navy blue). For each case, the MenDeVAR Index for their invasive meningococcal isolate is shown by the arrow above the dot, coloured green for exact match to vaccine variants, amber for cross-reactive match to vaccine variants, red for no match to vaccine variants, grey for Insufficient data to interpret reactivity, and blue for inadequate DNA to determine antigenic profile for PCR confirmed cases. The timing of the 2+1 Bexsero vaccine dosing schedule is shown with the yellow dotted line with the 1st dose at 8 weeks, second dose at 16 weeks and the booster dose at 12 months. Fully and partially vaccinated according to the UK immunisation schedule.

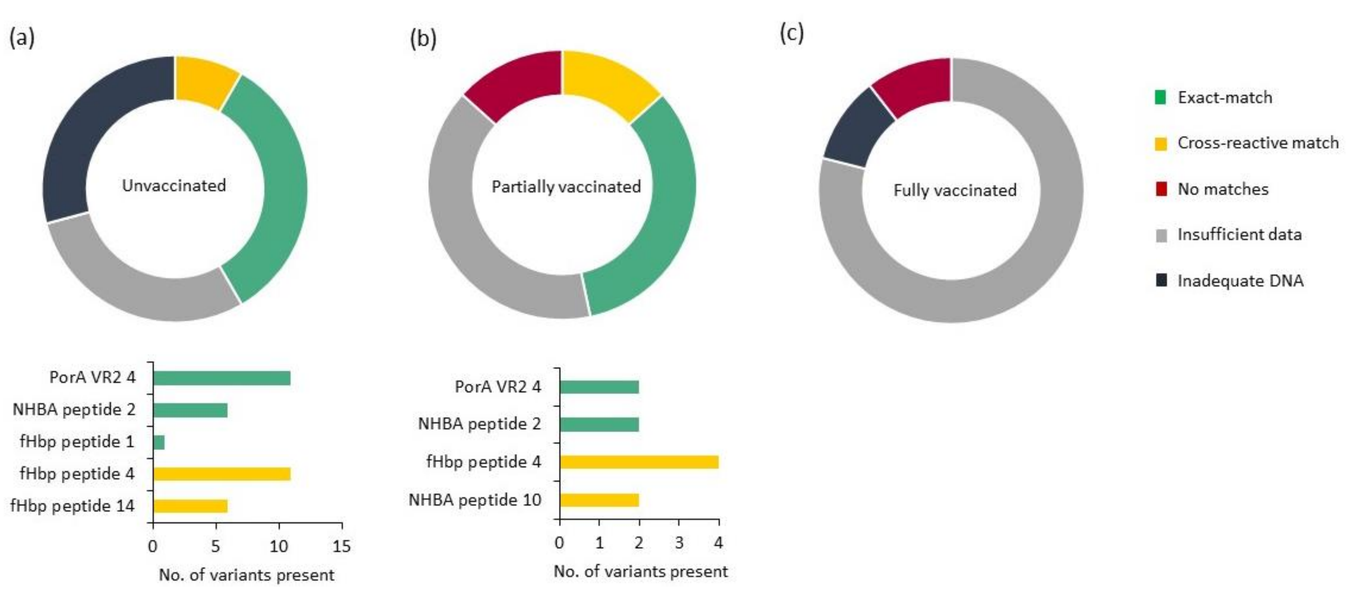

Figure 3: MenDeVAR Index output for IMD cases for each group of children considering vaccination status. Segments of the pie chart are coloured according to exact, cross-reactive, no matches to vaccine variants. Bar charts below demonstrate the frequency of peptide variants present in the isolates that were deemed to be vaccine-preventable. The number of variants is greater than the number of isolates as some isolates possess multiple vaccine-reactive antigens; 4/7 meningococci isolated from unvaccinated individuals and 14/20 meningococci isolated from partially vaccinated individuals had ≥1 potentially cross-reactive/exact antigen.

Results

Eighty-two serogroup B IMD cases occurred in children >5 years, 48 (58.5%) of which were in unvaccinated children and 34 (41%) were in children who had received ≥1 Bexsero® dose; 15/34 vaccinated children had received one dose, 17/34 had received two doses and 2/34 had received three doses (Fig 1). For 39 cases, meningococcal sequence data were available enabling MenDeVAR Index deductions of vaccine preventable (M-VP) and nonvaccine preventable (M-NVP) meningococci (Fig 2).

Unvaccinated - 40/48 were ineligible for vaccination and 20/48 had IMD caused by M-VP meningococci, with deductions not possible for 14 meningococci (Fig 3a).

Partially vaccinated - Amongst the 15 children partially vaccinated to schedule (1 dose), 7 were infected by M-VP meningococci and 2 with M-NVP meningococci, with 6 for which deductions were not possible (Fig 3b).

Fully vaccinated - none of the 19 children immunised ≥2 times had IMD caused by M-VP meningococci, 2 cases had NVP meningococci, and no deduction was possible for 17 (Fig 3c).

Discussion

These data are consistent with **2 and 3 doses** of Bexsero®, delivered according to schedule, **providing good protection** against invasive disease caused by M-VP. **Single doses provide poorer protection** to infants.

Impact on healthcare practice:

- These data can provide public health reassurance when vaccinated individuals develop IMD with non-vaccine preventable variants.
- Confirmation that incomplete or absent doses in infancy lead to reduced protection, supports public health and general practitioners in promoting timely vaccination according to schedule.
- Additional testing is needed on variants for which no immunological data exist to improve estimates of protection, although these data suggest the uncharacterised variants are unlikely to be covered by Bexsero®.

This study demonstrates the value of post-implementation genomic surveillance of vaccine preventable pathogens in providing information on real-world vaccine performance.

wellcome
Thrasher Research Fund
Medical research grants to improve the lives of children

mBio publication

MenDeVAR Index