Modelling long-term vaccination strategies with MenAfriVac® in the African meningitis belt

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Introduction

The introduction of MenAfriVac® in mass campaigns targeting 1-29 year olds across countries of the African meningitis belt has successfully reduced meningitis incidence and carriage due to *Neisseria meningitidis* group A (NmA) [1-3]. Policy makers now need to consider which subsequent vaccination strategies to recommend in order to sustain population protection in the long term. The overall aim of this project is to develop and apply mathematical models of NmA transmission and disease to investigate the optimal future use of MenAfriVac® to inform these decisions.

Models have become an important tool for immunisation policy makers. They allow a wide range of immunisation strategies to be explored and the uncertainties underlying both model structure and model parameters can be examined. Transmission dynamic models allow the direct and indirect (herd immunity/protection) effects of vaccination programmes to be measured. Only two transmission dynamic models of NmA in the African meningitis belt have been published to date [4 5]. Here, we build on our previous work[4, 6] and utilise recently available evidence from Africa to investigate appropriate policy options for the sustained use of MenAfriVac®.

Methods

Epidemiology of NmA

A model should be able to capture the key features of the epidemiology of NmA in the African meningitis belt. There are periodic but irregular epidemics of meningococcal meningitis in the meningitis belt which vary in magnitude[7]. Meningitis incidence is highly seasonal; epidemics occur in the dry season and die out with the onset of the rains[7]. Meningococci are spread through respiratory droplets and usually infection results in a period of asymptomatic carriage with disease being a relatively rare event; thus any model attempting to capture the transmission dynamics of meningococci must essentially include the carrier state. Our previous work[4] showed that the complex and irregular timing of epidemics could be explained by the interaction of temporary immunity conferred by carriage of the bacteria together with seasonal changes in the transmissibility of infection. The inclusion of 'natural' immunity following carriage is further supported by studies showing high seroprevalence to NmA[8] before MenAfriVac® introduction. The risk of NmA disease varies by age, affecting mainly children and being uncommon in older adults[9]; carriage prevalence also varies by age so an appropriate model must include age-structuring.

Model structure and parameters

We developed a compartmental model that divides the population into the following states;
(1) susceptible, (2) carrier of NmA, (3) disease due to NmA, (4) immune, and in vaccinated populations a mirror of these four states: (5) vaccinated susceptible, (6) vaccinated carrier, *etc*. The population is further structured into 19 age groups; 0 to <3 months, 3 to <9 months, 9 to <12 months, 1 to 4 years, 5 to 9 years for those aged < 10 years, with 5 year age groups to age 80 years subsequently and continuous ageing between groups. We included seasonal forcing of the transmission and invasion rates using a sinusoidal function with annual stochastic variation to reflect climactic[10] or other external variability.

We considered a range of vaccination strategies, starting five or ten years after initial vaccine introduction, including routine Expanded Programme on Immunization (EPI) immunisation, periodic mass campaigns and EPI plus catch-up immunisation of children born since the initial mass campaigns. Vaccination was implemented in different ways according to the strategy used. For mass vaccination, we assumed that

* Report prepared by Andromachi Karachaliou & Caroline Trotter (clt56@cam.ac.uk), University of Cambridge, UK.

vaccination occurred as a discrete event at one point in time. Routine immunisation was implemented as a continuous event, with individuals being vaccinated at 3, 9 or 12 months of age according to the schedule considered. Vaccinated individuals have some protection against both carriage and disease, so that vaccination resulted in both direct and indirect protection.

Model parameters were based on the available literature wherever possible. It was necessary to estimate several parameters, using available data and model fitting techniques to inform these estimates.

The model was coded and run using R-3.1.0, using package deSolve to perform the numerical integration of differential equations. The time step was 1 day. The model was run for 40 years after the initial mass vaccination campaign. For each vaccination strategy the average of 300 simulations was taken and the distribution of the results explored. The model was reviewed by the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) in September 2014 (cf. Reports from other Advisory Committees on Immunization: IVIR-AC, session 3 for information, SAGE October 2014). Full details of the model structure are available on request.

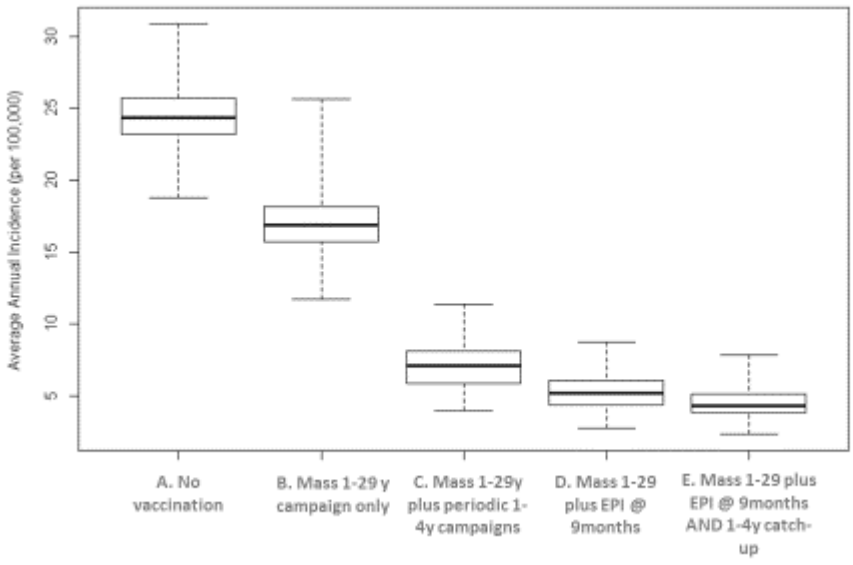
Results

This model was able to capture the typical annual incidence of meningitis in the pre-vaccine era, with irregular epidemics of varying size.

Following initial mass vaccination of 1-29 year olds at high uptake, disease control was excellent in the short term. With no subsequent immunisation, the model predicted a strong resurgence in disease incidence approximately 15 years after vaccine introduction, assuming an average of 10 years of protection by vaccination. With a shorter duration of protection, disease incidence increased more quickly (e.g. after around 10 years assuming 5 years vaccine protection).

Several long-term immunisation strategies were considered and all were effective in maintaining control of disease (figure, options C, D, E). There was considerable overlap in the distribution of results, but routine EPI immunisation at 9 months of age (D) resulted in lower average annual incidence than regular mass campaigns of 1-4 year olds (C), provided EPI coverage was above ~60%. The strategy with the lowest overall average annual incidence and longest time to resurgence was introduction into EPI at 9 months, 5 years after the initial mass campaigns, with a catch-up targeting unvaccinated 1-4 year olds (E).

Figure: Box plot to show the median, inter-quartile range and full range of the predicted annual incidence per 100,000 for different immunisation strategies in the 40 years following vaccine introduction from 300 model simulations



Discussion

We developed a model of NmA transmission and disease that was able to adequately describe the epidemiology observed in the African meningitis belt. We simulated the initial mass vaccination campaigns and predicted a period of very low incidence for at least ten years following these mass campaigns, even when assuming a short duration of protection of around 5 years. The indirect effects of the vaccine were clearly important in maintaining this low incidence post-introduction; we assumed a high degree of protection against carriage, consistent with the observed data[1, 3]. Of the long-term immunisation strategies, we predicted that a 'combination' strategy of routine EPI vaccination after 5 years together with a catch-up campaign targeting children aged 1-4 years born after the initial campaigns was the most effective.

Our conclusions are different to another model of MenAfriVac® vaccination, which suggested that periodic mass campaigns were superior to routine EPI. Although there are potentially important differences in model structures and implementation, this is probably largely because the duration of protection they assumed was much greater (essentially lifelong) for children immunised in campaigns than through EPI, whereas we assumed that protection in 1-4 year olds would be similar to those immunised at the age of 9 months, based on data from MVP (Meningitis Vaccine Project) MenAfriVac® trials (http://www.meningvax.org/research-development.php).

Our model structure was based upon extensive previous work that used a range of deterministic models, to explore the importance of seasonality and immunity following colonisation[4]. As such, we feel we have good understanding of the underlying system dynamics. We extended our previous model to incorporate vaccination, age structuring and stochastic variation in seasonal forcing (to capture unknown external forces including for example dust or humidity conditions[11]).

Some model parameters were known, others could be inferred or estimated from existing data and in some cases where parameters were unknown a plausible range was defined. More information on a range of parameters would be desirable, including the duration of temporary immunity following carriage, contact patterns and age-specific duration of vaccine protection; the latter being a particularly influential in determining the relative impact of different immunisation strategies. Our work would also benefit from greater exploration of structural and parameter uncertainty; this is planned for the future.

Acknowledging the strengths and weaknesses of our approach, these results can be used to inform policy recommendations for long term vaccination strategies with MenAfriVac®.

References

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