

**Institution: University of Sussex**

**Unit of Assessment: UoA10**

**Title of case study:** The mathematical modelling of meningococcal meningitis and implications for the control of meningitis in sub-Saharan Africa

### 1. Summary of the impact

Meningococcal meningitis affects up to 100,000 people and causes around 10,000 deaths annually in the African 'meningitis belt', a region of sub-Saharan Africa stretching from Senegal in the west to Ethiopia in the east. Dr Blyuss has developed a mathematical model that is able to explain the observed patterns of dynamics of this disease in terms of immunity and seasonality. This model is currently used by the Meningitis Vaccine Project to design optimal strategies for the control of meningococcal meningitis in the endemic areas, to inform specific public-health decisions regarding the deployment of the MenAfriVac™ vaccine, and to assess its effectiveness. Other epidemiologists, including those at the World Health Organization (WHO), are also using the model to improve public-health policies aimed at combating meningitis.

### 2. Underpinning research

In collaboration with colleagues from the University of Bristol, Blyuss has developed a mathematical model of transmission of meningococcal meningitis, which is able to qualitatively reproduce different types of observed disease patterns.

Twenty-six countries in sub-Saharan Africa suffer from a higher incidence of meningococcal meningitis every dry season and experience major outbreaks of the disease every 6–14 years, causing tens of thousands of deaths, with a case-fatality rate of 5–15%. Substantial epidemiological and clinical data on meningococcal meningitis are available from different areas inside the meningitis belt – primarily from Niger, Mali and Burkina Faso – and several models have been put forward to explain these data. A number of environmental factors are believed to be important in explaining the observed seasonality in meningitis incidence, and several alternative hypotheses have been proposed to explain how these factors affect disease transmission. Despite some successes with the existing models, the precise causes of observed irregularities in the dynamics of meningococcal meningitis and the relative roles played by different factors have remained poorly understood. One of the biggest challenges for current understanding of the meningococcal meningitis specifically in the 'meningitis belt' is that the available data for this region are in contradiction with the classic Goldschneider paradigm that asserts an inverse relationship between the age-specific disease risk and immunity.

The model developed by Blyuss and his colleagues explicitly includes temporary immunity, as well as two possible types of seasonality: variation in disease transmission and changes in the rate of progression from carriage to invasive disease [see Section 3, R1]. Having fixed other demographic parameters at certain biologically realistic values, numerical simulations have been performed for various values of the disease transmission rate and the duration of temporary immunity to identify different dynamical regimes, as well as to explore the effects of these parameters on the inter-epidemic period. The main academic significance of this work lies in the highlighting of a fundamental role of temporary immunity and its interactions with seasonality in the dynamics of meningococcal meningitis. It also adds weight to an alternative explanation of why observed data contradict the classical view of the relation between disease risk and immunity.

Konstantin Blyuss began his work in this area looking at models of antigenic variation in malaria and the dynamics of dengue fever (R3, R4). On moving to Sussex in 2010 he began the work on meningococcal meningitis, that underpins this case study. Blyuss worked with PhD student Tom

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Irving (University of Bristol), Caroline Colijn (University of Bristol) and Caroline Trotter (University of Bristol). Blyuss's previous experience in mathematical modelling of infectious diseases [R2–R4] meant that he was responsible for development and analysis of the model for the dynamics of meningococcal meningitis. This included performing analytical calculations and numerical simulations, and interpreting the results.

**3. References to the research**

The mathematical model described in Section 2, that underpins the impact of this case study, has been published in:

- R1** Irving, T.J., Blyuss, K.B., Colijn, C. and Trotter, C.L. (2012) 'Modelling meningococcal meningitis in the African meningitis belt', *Epidemiology and Infection*, 140(5): 897–905.

This paper proposes a model of the dynamics of meningococcal meningitis, which provides a comprehensive explanation of observed patterns of the disease in terms of duration of the immunity period, as well as seasonal variation in the transmissibility of infection or the rate of disease progression. It utilises the dynamical systems methodology as used previously by K.B. Blyuss in the studies of other infectious diseases.

Blyuss' previous expertise in this area:

- R2** Blyuss, K.B. and Kyrychko, Y.N. (2010) 'Stability and bifurcations in an epidemic model with varying immunity period', *Bulletin of Mathematical Biology*, 72(2): 490–505.
- R3** Blyuss, K.B. and Gupta, S. (2009) 'Stability and bifurcations in a model of antigenic variation in malaria', *Journal of Mathematical Biology*, 58(6): 923–937.
- R4** Recker, M., Blyuss, K.B. and Simmons, C.P. *et al.* (2009) 'Immunological serotype interactions and their effect on the epidemiological pattern of dengue', *Proceedings of the Royal Society B*, 276(1667): 2541–2548.

Outputs R1, R2, R4 best indicate the quality of the underpinning research.

Outputs can be supplied by the University on request.

**4. Details of the impact**

To combat the devastating effect of meningococcal meningitis on communities in the African 'meningitis belt', the international Meningitis Vaccine Project, funded by the Gates Foundation and the WHO, has been working since 2001 on developing an effective and cheap vaccine to be deployed in affected countries. The resulting MenAfriVac™ vaccine has completed its trials; in 2010 it was rolled out in Burkina Faso, Mali and Niger and, in October–December 2012, it was introduced in 7 more countries. The goal is to cover all 26 countries by 2016.

From a public-health perspective, there are two major issues with the introduction of the MenAfriVac™ vaccine. The first concerns the logistical constraints of optimising a vaccination campaign to target those individuals most at risk of infection, and the second is the need for a robust means of assessment of the population-wide efficiency of the vaccine. The model developed by Blyuss and his colleagues is helping public-health professionals on the ground to address both of these issues. Through close collaboration with the MenAfriCar Consortium, we have ensured that the results of the research do not remain academic but rather are translated into practical recommendations for the design of optimal vaccination strategies in vaccine deployment and for assessment of the efficacy of the new vaccine. Experts from the international MenAfriCar Consortium have used the model and its subsequent developments (an age-structured and meta-population version of the model) to understand the prevalence, incidence and relative impact of

different risk factors in the endemic areas. Furthermore, they have used this work to develop targeted, age-structured vaccination strategies [see Section 5, C3].

Besides MenAfriVac™ vaccine deployment, the results of the underpinning research have also been taken up by the MERIT (Meningitis Environment Risk Information Technologies) Project coordinated by the World Health Organization for the purposes of disease surveillance [C4], and epidemiologists from the GAVI (Global Alliance for Vaccines and Immunisation) are developing further detailed models for the assessment of effects of vaccine interventions based on the Blyuss model [C7].

Since its publication in March 2012, this work has received substantial interest [C5–C8] from epidemiologists and public-health professionals. As, at present, there are several alternative hypotheses for the role of different epidemiological and environmental factors in the dynamics of meningococcal meningitis, the work has provided a new level of understanding of the relative contributions of those factors. This has resulted in a radically improved understanding of the dynamics of meningococcal meningitis by epidemiologists and clinical scientists, thus helping them to design and deliver efficient public-health policies aimed at combating the disease.

## **5. Sources to corroborate the impact**

**C1** Member of the MenAfriCar Consortium, Cambridge University).

Can corroborate how the mathematical model we derived and analysed has influenced and has been the basis for development of optimal vaccination strategies aimed at controlling meningococcal meningitis in the African meningitis belt.

**C2** Programme Manager of the MenAfriCar Consortium, London School of Hygiene and Tropical Medicine).

Can confirm that the mathematical model has had a major effect on how epidemiologists on the ground in the African meningitis belt view and interpret the population-level dynamics of meningococcal meningitis, and on the development of optimal vaccination strategies in preparation for the deployment of the new meningococcal vaccine.

References shown below indicate some recent publications where the results of the analysis were interpreted in the light of our work highlighting the role of immunity in the dynamics of meningitis.

**C3** MenAfriCar Newsletter, August 2012.  
(<http://www.menafricar.org/sites/www.menafricar.org/files/Newsletter%20final.pdf>)

**C4**

- Thomson, M.C., Firth, E., Jancloes, M., Mihretie, A., Onoda, M., Nickovic, S., Bertherat, E. and Hugonnet, S. (2011) 'Climate and public health – the MERIT initiative: a climate and health partnership to inform public health decision makers'. World Climate Research Programme.
- Thomson, M.C., Firth, E., Jancloes, M., Mihretie, A., Onoda, M., Nickovic, S., Broutin, H., Sow, S., Perea, W., Bertherat, E. and Hugonnet, S. (2013) 'A climate and health partnership to inform the prevention and control of meningococcal meningitis in sub-Saharan Africa: the MERIT initiative', in Asrar, G.R. and Hurrell, J.W. (eds) *Climate Science for Serving Society: Research, Modeling and Prediction Priorities*. Springer, 459–484.

**C5** Paireau, J., Girond, F., Collard, J.-M., Mainassara, H.B. and Jusot, J.-F. (2012) 'Analysing spatio-temporal clustering of meningococcal meningitis outbreaks in Niger reveals

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opportunities for improved disease control', *PLOS Neglected Tropical Diseases*, 6: e1577.

'Recently, Irving *et al.* suggested that population immunity may be a key factor in causing the unusual epidemiology of meningitis in the Belt'.

- C6** Agier, L., Deroubaix, A., Martiny, N., Yaka, P. Djibo, A. and Broutin, H. (2013) 'Seasonality of meningitis in Africa and climate forcing: aerosols stand out', *Journal of the Royal Society Interface*, 10(79): 1742-5662.

'The current epidemiological [Irving *et al.*]...models for meningitis considered ... seasonality of the meningitis transmission dynamics. We now suggest integrating dust data into these models to make them more realistic and usable in a public health perspective'.

- C7** Papaevangelou, V. and Spyridis, N. (2012) 'MenACWY-TT vaccine for active immunization against invasive meningococcal disease', *Expert Review of Vaccines*, 11(5): 523–537.

- C8** Trotter, C.L. Yaro, S. and Njanpop-Lafourcade B.M. *et al.* (2013) 'Seroprevalence of bactericidal, specific IgG antibodies and incidence of meningitis due to group A *Neisseria meningitidis* by age in Burkina Faso', *PLoS ONE*, 8(2): e55486.

'Such hypothesis needs to be considered critically, as the regular recurrence of epidemic waves strongly suggest, according to general infectious disease dynamics and recent modelling evaluation [Irving *et al.*], a major role of acquisition and waning of natural immunity'.