Mathematical Modelling of the Dynamics of Meningococcal Meningitis in Africa

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Abstract Every year a significant area in sub-Saharan Africa is affected by an infection with meningococcal meningitis. Large outbreaks of this disease occur every 6–14 years killing tens of thousands of people. Due to being a major public health problem, meningococcal meningitis has attracted significant attention from the perspective of disease control and prevention. At the same time, it has raised a number of fundamental questions about the disease dynamics that have to be properly understood and addressed before an efficient disease control programme can be developed and implemented. In this work, we have used mathematical models to identify crucial factors that determine the meningitis dynamics. Our results have suggested that temporary population immunity plays a very important role and has to be taken into account during disease monitoring and when measuring the efficiency of vaccines being deployed.

Introduction

Meningococcal meningitis is an infectious disease caused by a bacterium *Neisseria meningitidis*, it affects 1.2 million people worldwide and results in around 135,000 deaths annually. A particularly substantial burden of this disease is experienced by the 26 countries in the so-called *African meningitis belt*, which spans sub-Saharan Africa from Senegal to Ethiopia, as shown in Fig. 1. Patterns of meningococcal meningitis dynamics in this region are distinct and quite unique: cases of disease appear every dry season and stop with the start of the rainy season, and every 6–14 years there is a major epidemic outbreak resulting in a large number of deaths throughout the region. Due to a significant problem this poses to public health, major efforts have been made in the last few years to develop and introduce an effective vaccine that would reduce the disease burden and save lives. A successful introduction of such vaccine to a large extent depends on good understanding of the fundamental properties of epidemiology and immunology of meningogococcal meningitis.

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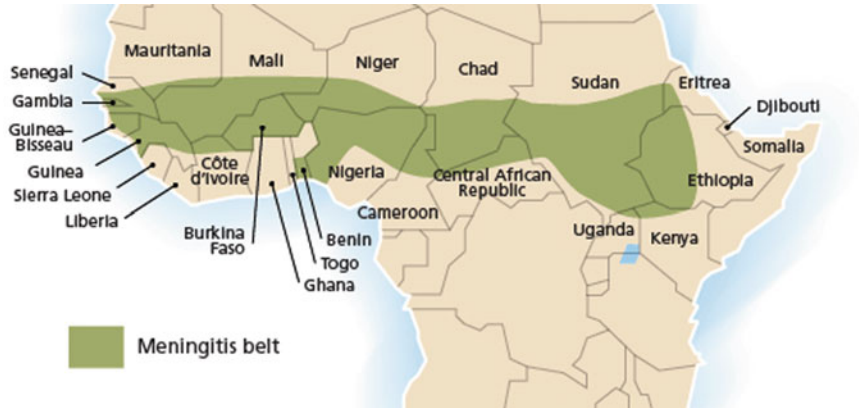

Fig. 1 The African meningitis belt (World Health Organisation, 1998, WHO/EMC/BAC/98.3)

Substantial data is available on the spread of meningococcal meningitis in the African meningitis belt, and several alternative hypotheses have been put forward to explain observed epidemiological patterns [1]. However, the precise causes of irregularities of epidemic outbreaks and the impact of individual factors on disease dynamics have remained poorly understood. Several mathematical models [2–4] have attempted to reproduce certain individual features of dynamics of meningococcal meningitis, but despite their successes, so far they have failed to explain observed levels of variation in disease carriage rates. One particular aspect that has not been properly explained by those earlier models is the relation between disease patterns and immunity. Hence, a new mathematical model was needed that would include temporary immunity from disease and relate it to different dynamical scenarios.

Mathematical Model

To understand the dynamics of meningogococcal meningitis, we have proposed a new model [5], in which the overall population is divided into susceptible S, carriers C, infected I and recovered R individuals, so that the total population is $N = S + C + I + R$. The model has the form

$$\begin{aligned}
\frac{dS}{dt} &= b + \phi R - \beta \frac{S(C+I)}{N} - \mu S, \\
\frac{dC}{dt} &= \beta \frac{S(C+I)}{N} - (a + \alpha + \mu)C, \\
\frac{dI}{dt} &= aC - (\rho + \gamma + \mu)I, \\
\frac{dR}{dt} &= \rho I + \alpha C - (\phi + \mu)R,
\end{aligned} \tag{1}$$

where β is the transmission rate, carriers develop an invasive disease at a rate a and recover at a rate α, and individuals with invasive disease recover at a rate ρ. Once recovered, individuals lose their immunity at a rate ϕ and become susceptible again, which effectively means that the average duration of immunity is $1/\phi$. The model takes into account both the natural μ and disease-induced mortality γ. Individuals are assumed to be born at a rate $b = \mu N + \gamma I$, so that the total population N is constant. Rescaling all variables with N, and using the fact that after the rescaling we have $S + C + I + R = 1$, the above system can be reduced to the following

$$\begin{aligned} \dot{C} &= \beta(1 - C - I - R)(C + I) - (a + \alpha + \mu)C, \\ \dot{I} &= aC - (\rho + \gamma + \mu)I, \\ \dot{R} &= \rho I + \alpha C - (\phi + \mu)R. \end{aligned} \tag{2}$$

Under assumption of all parameters being constant, the reduced model (2) has a disease-free steady state $E_0 = (0, 0, 0)$, which is stable for $\mathscr{R}_0 < 1$, and unstable for $\mathscr{R}_0 > 1$, where the basic reproduction number can be found as

$$\mathscr{R}_0 = \frac{\beta(\gamma + \rho + \mu + a)}{(\gamma + \rho + \mu)(a + \alpha + \mu)}.$$

As $\mathscr{R}_0$ crosses the value of $\mathscr{R}_0 = 1$, the system (2) acquires another biologically realistic endemic steady state $E^* = (C^*, I^*, R^*)$ given by

$$C^* = K(\phi + \mu)(\rho + \gamma + \mu), \qquad I^* = Ka(\phi + \mu), \qquad R^* = K[\alpha(\rho + \gamma + \mu) + \rho a],$$

where

$$K = \frac{(\rho + \gamma + \mu)(a + \alpha + \mu)}{\beta(\rho + \gamma + \mu + a)[(\rho + \gamma + \mu)(\phi + \mu + \alpha) + a(\phi + \mu + \rho)]}(\mathscr{R}_0 - 1).$$

The steady state E^* is stable for $\mathscr{R}_0 > 1$, i.e. whenever it exists. An important feature of the model (2) is the fact that it explicitly includes temporary immunity both from carriage and invasive disease. We have analysed other scenarios, where there is no immunity, or there is an immunity from the disease only, but such models do not produce biologically realistic results [5].

The Role of Seasonality and Temporary Immunity

Before delving into investigation of the role of temporary immunity, it is instructive to make the model more realistic by explicitly accounting for seasonal changes in the rates of transmissibility and disease progression. Seasonality is a very prominent

feature of the meningococcal meningitis, and it has been attributed to a number of external factors, of which most important is considered to be the Harmattan, a dry wind affecting the region during the dry season. To incorporate this into the model, we introduce seasonally varying rates of transmission and disease progression as follows,

$$a(t) = a_0(1 + \varepsilon_a \cos 2\pi t), \qquad \beta(t) = \beta_0(1 + \varepsilon_\beta \cos 2\pi t).$$

Extensive numerical simulations suggest that dynamics of the model when both a and β are periodically forced is qualitatively similar to that when only the transmission rate β is varying seasonally, hence it is sufficient to consider the seasonality in β only.

Figure 2 shows how the model can exhibit a variety of dynamical behaviours with oscillations of different periods and possible chaotic dynamics depending on the duration of temporary immunity period (given by $1/\phi$) and the transmission rate. There are several important observations that can be made from this Figure. The first one concerns the fact that a longer period of temporary immunity, i.e. small value of ϕ, is associated with a longer inter-epidemic period, as should be expected due to the fact that longer immunity means that the number of people who can acquire an infection stays small for longer. The model demonstrates a large range of possible inter-epidemic periods, with those in the range of 2–10 years being most common. Realistically long inter-epidemic periods of 6–14 years correspond to the values of temporary immunity period that is larger than two years. It is also noteworthy that gradual changes in the duration of temporary immunity or the transmission rate lead to sudden transitions between regular multi-annual cycles of different periods and irregular behaviour.

In Fig. 3 we illustrate time series associated with epidemic outbreaks of different periods. Simulations suggest that the model (2) is able to produce both regular annual epidemics, as well as epidemics with longer quiescent periods between successive outbreaks, epidemics with non-equal amplitudes, and chaotic series with out-

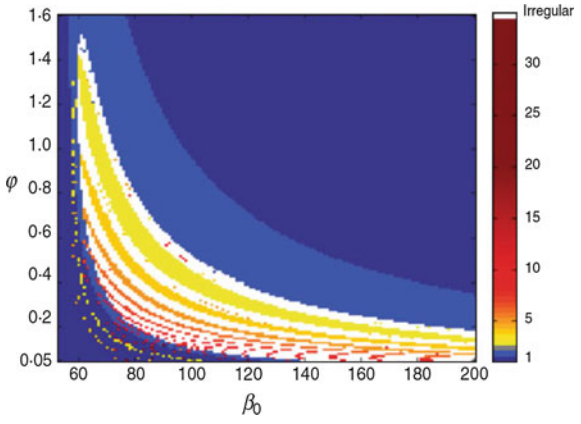

Fig. 2 The inter-epidemic period (years) depending on parameters ϕ and β. Parameter regions in which epidemics occur at irregular intervals are marked in *white*. Parameter values: $a = 0.8$, $\varepsilon_a = 0$, $\varepsilon_\beta = 0.4$, $\alpha = 52$. Figure taken from Irving et al. (2012) [5], reprinted with permission

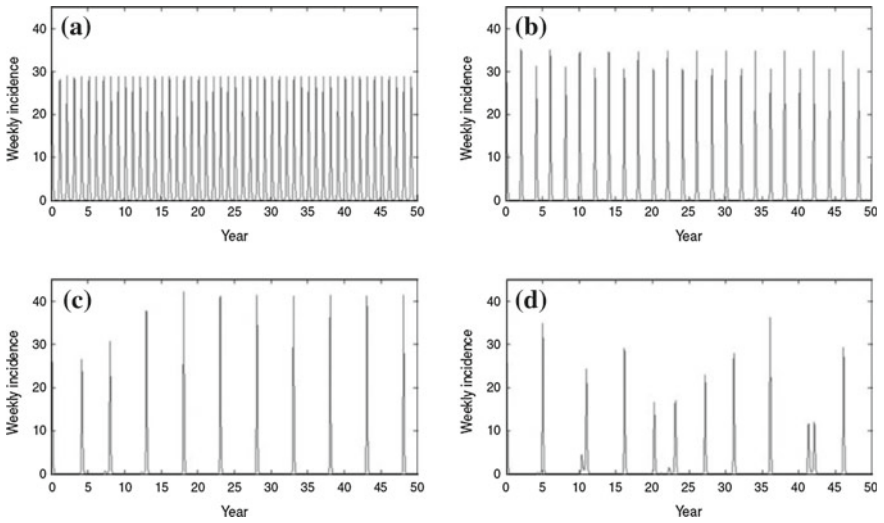

Fig. 3 Weekly incidence of meningitis per 100 000 population for different lengths of immunity. **a** Annual epidemics. **b** Biennial epidemics. **c** Epidemics every 5 years. **d** Epidemics of unpredictable magnitudes and occurring in unpredictable years. Parameter values: $a_0 = 0.2$, $\alpha = 26$, $\varepsilon_a = 0$, $\beta_0 = 90$, $\varepsilon_\beta = 0.5$. **a** $\phi = 0.5$; **b** $\phi = 0.25$; **c** $\phi = 0.1$; **d** $\phi = 0.085$. Figure taken from Irving et al. (2012) [5], reprinted with permission

breaks taking place at irregular times and having significantly different amplitudes. An inclusion of temporary immunity in both carriage and invasive disease leads to epidemics of realistic sizes. Moreover, in the chaotic regime the time series often have epidemics in successive years, as observed in the meningitis belt, where the incidence is negligible during rainy seasons but picks up in consecutive dry seasons.

Impact of the Model and Future Outlook

The main impact of the model is in highlighting the fundamental role played by temporary immunity in determining the kind of dynamics observed in epidemiological patterns of meningococcal meningitis. This has changed the view of epidemiologists and clinical scientists on epidemiology of meningococcal meningitis, thus helping them to improve public-health policies aimed at combating the disease.

Besides purely academic interest, the model we developed also has a very practical impact. The first aspect of it concerns efforts of the MERIT (Meningitis Environment Risk Information Technologies) project coordinated by the World Health Organization and aimed at disease surveillance. More specifically, it has helped epidemiologists better understand the prevalence, incidence and relative impact of different risk factors in the endemic areas. Another impact of the model is in helping health professionals design optimal and targeted vaccination strategies, as well as to assess the

population-wide efficiency of the vaccine once it is deployed. With a vaccine being currently rolled out throughout the African meningitis belt, optimising vaccination campaigns leads to a significant reduction of economic costs for the affected countries. Understanding the role of the temporary immunity in the disease dynamics is helping to correctly quantify the effectiveness of the vaccine.

There are several directions in which the model can be further improved in terms of biological realism and practical applications. From the modelling perspective, the model can include age-structure of the population, as well as spatial effects associated with the movement of people and various environmental factors. Through integration of model predictions with real-time satellite and meteorological data, it should be possible to design a system of advanced disease warning, and to optimise efforts at disease containment.

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