Individual-based approaches to infectious disease modelling; the example of measles

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In March, I attended the SACEMA course *Individual-Based Modelling in Epidemiology: A Practical Introduction*. As I sat in class, my recent training and experience in the more traditional ordinary differential equation (ODE) models was still very fresh in my mind. However, as part of my own learning process, I had dabbled in formulating simple individual-based models (IBMs) alongside ODE models, and was keen to find out more about when and how they are used to model the transmission of infectious diseases.

In contrast to population-level ODE models, IBMs are a bottom-up approach to modelling, where computer-generated unique and discrete individuals interact through a set of rules to form a system. In the last decade, IBMs have been frequently used across a range of disciplines, from economics to ecology, as computing power has increased. As highlighted in a systematic review published this year, the use of IBMs in epidemiology has similarly been on the rise (1).

This systematic review reported that almost half of IBM publications in 2016 were focused on the assessment of interventions against disease – increasing from <10 in 2006 to >50 in 2016. Particularly in previous years, an equal number of papers have focused on methodology – the purpose being to describe the structure and set-up of an IBM rather than to address specific questions (1). This perhaps highlights that because IBMs often cannot be easily summarised succinctly by a set of mathematical equations, their verbal description with generic outputs has sometimes been published alone, prior to being used to analyse the specific dynamics of a disease in a given setting, or the effects of an intervention.

The simplest of ODE models, for directly-transmitted pathogens, frequently assume that there is no variation between infected individuals in the rate at which they stop being infectious and acquire immunity, that the probability of transmission given contact between an infected and susceptible individual is the same for everybody and that the rate at which individuals make contacts with any other individual in the population is the same across the population. However, ODEs can and have frequently been extended to account for heterogeneities in the above processes. The choice between using a set of ODEs, or an IBM is therefore perhaps not clear cut, and is likely influenced by the skills of the individual and the question of interest. Here, I summarise two papers that have used IBMs to assess intervention strategies for measles, which give a flavour of the types of scenarios and questions for which IBMs have been used.

Measles outbreak response vaccinations

Despite the presence of global vaccination programmes, measles remains an important cause of childhood mortality, particularly in sub-Saharan Africa (2). During an outbreak of measles, a response vaccination strategy is an option for reducing morbidity and mortality (3). Grais *et al.* (4) used an IBM to estimate what the likely impact of an outbreak response vaccination had been during a measles outbreak in Niamey, Niger in 2003-2004. They also used the model to ask what would have happened had the intervention occurred earlier and what difference it would have made if the target age range had been expanded.

The first complexity that the model accounted for was that the city of Niamey is divided into three communes. During the outbreak, cases were first reported in commune 1, spreading to commune 2 after several weeks and were not being reported in commune 3 until later in the epidemic. The authors therefore subdivided the simulated population into the three communes and within each commune into health centres and quartiers using census data.

The authors also noted from their previous work that local transmission within quartiers within a commune was more rapid than transmission between communes. They therefore had separate transmission rates between children within the same quartier, within the same health centre catchment area, within the same commune, and city-wide between communes.

Although individuals were modelled as discrete entities, the duration of latent and infectious periods was assumed to be the same for all infected individuals. In addition, only children were

modelled that belonged to either a 6-59 month, or a 5-15 year age group. The number of individuals in each age group was determined based on an age pyramid for Niger. Variation in vaccination history was included, assuming 30% of children under 15 were susceptible and of these, 75% were between 6 and 59 months, again based on the age pyramid. In reality, the intervention began 23 weeks after the beginning of the outbreak, and over 10 days, 57% of children aged 6-59 months were vaccinated, regardless of previous vaccination or disease status. This intervention was simulated in the model by assuming that vaccines were randomly distributed across the risk group.

The IBM was fitted to reported measles cases from each commune and obtained a good fit to the data. For model fitting, and for exploring interventions using the fitted model, 1000 simulations were carried out. Multiple simulations were required because the model was stochastic and model results were expressed as medians of the distribution of estimated outcomes (e.g. averted cases). They compared the simulated epidemic with and without the implemented intervention and determined that a median of 7.6% of cases, calculated from 1000 model simulations, had been averted as a consequence of the intervention. The IBM was then used to assess what would have happened, for a range of hypothetical modifications to the intervention. In conclusion, the model showed that timely outbreak response vaccinations can be effective at averting measles cases, but that the proportion of averted cases was depending on the vaccination coverage and the number of birth cohorts targeted for vaccination.

Clustering of measles immunity and vaccination coverage

In a second, more recent paper published in 2015, Liu *et al*. (5) adapt the previously published Framework for Reconstructing Epidemiological Dynamics (FRED) (6) IBM to examine the effects of vaccination coverage, individual behaviours and public health response, on measles outbreaks in California. Despite the elimination of endemic measles transmission in the US, cases continue to occur from importation and subsequent outbreaks can result from groups of intentionally unvaccinated individuals. When this occurs, health authorities carry out contact tracing to identify susceptible individuals who have come into contact with the infected person. Their model intended to determine under which circumstances contact

tracing activities and the associated interventions help to control measles epidemics.

Their simulated population of individuals was generated from a Synthetic Population Database by RTI International. The population represented every individual in the geographic location of interest and were given attributes consistent with census data from the Californian government. Each individual had an age and sex attribute, and locations for social activity including household, neighbourhood, school or workplace and child day care centres. Depending on the assigned locations of social activity, each individual visited his or her household and neighbourhood each day. If the individual was associated with other locations, they could also have visited those. Individuals could then interact with other individuals who shared the same locations on the same day. The numbers of contacts an individual made per day varied by location, according to available data. The immune status of individuals was also tracked and the degree of immune clustering could be varied. Transmission of measles was then simulated on this population.

Contact investigation was simulated in the model. It was assumed that the contacts of an infectious case residing in their neighbourhood could not be identified by the public health department. However, it was assumed that each of the contacts of an identified infectious case from the household, school, day care and workplace settings could be traced and identified, with probability between 0.7 and 1.

The model was used to explore the effects of varying several parameters, including those associated with contact tracing and immune clustering, on the control of measles. In conclusion, their model showed that clustering of immunity and vaccination coverage are important characteristics that influence the ability to control a measles epidemic.

Individual-based models may be associated with complexity, but that does not have to be the case. The model by Grais *et al*. (4) was relatively simple in that it did not consider detailed spatial dynamics, used constant contact rates in only two age groups of children and assumed that the proportion of susceptibles was the same in all quartiers. They highlight that more complex models will be explored. Importantly, starting with a simpler model should allow a better understanding of what

the effects of adding in extra complexities has on model predictions of the effects of simulated interventions.

The model by Liu *et al.* (5) was perhaps more complex, assigning individuals age, sex and specific location attributes, variable contact rates depending on location, in addition to varying the level of vaccination coverage and clustering of individuals with immunity. It was acknowledged that there was not a lot of empirical evidence for the behaviour-related parameters in the model, but to account for this they incorporated a broad range of parameter values to explore the effects of changing these parameters on model outputs. The emphasis of this model was to explore the effects of these complexities on an outbreak, thus detailed sensitivity analyses were sufficient to account for uncertainty in parameter values.

Together, these two papers highlight that IBMs can have varying levels of complexity, should, where possible, be fitted to data, must be subject to thorough sensitivity analyses in the case of missing data, and can be very useful for the assessment of intervention strategies in specific times and places.

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