The effect of heterogeneity in measles vaccination on population immunity

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SUMMARY

High overall vaccination levels sometimes hide pockets of poor coverage. We adopted a meta-population framework to model local aggregation of populations, and used this to investigate the effects of vaccination heterogeneity. A recent survey of antibody levels in a community with low vaccination levels in The Netherlands enabled us to assess the relative importance of local and long-range infective contacts, and thus identify feasible levels of aggregation in the meta-population model. In the aggregated model, we found that heterogeneity in vaccination coverage can lead to a much increased rate of infection among unvaccinated individuals, with a simultaneous drop in the average age at infection.

INTRODUCTION

When protecting populations from disease, immunization policies aim for high national levels of coverage [1]. Often, a high overall vaccination level can mask a low coverage in certain regions [2–4]. Communities with low vaccination levels can then experience dramatic outbreaks [5] in contrast to that witnessed in well-vaccinated communities. Although it has been shown that carefully targeted heterogeneous vaccination policies can be advantageous [1, 6], the effect of intrinsic heterogeneity in vaccine coverage has been less studied. In the context of the current WHO initiative to eradicate measles in Europe by 2007 [7], an understanding of the impact of aggregation of susceptibles on levels of infection is highly important.

A series of continuous-time models based on the SIR (Susceptible–Infective–Recovered) framework have successfully captured both the recurrent pre-vaccination dynamics of measles epidemics and the impact of vaccination [1, 8, 9]. Recently, there has been increasing focus on the population implications of waning of immunity [10–12]. In particular, we have developed an antibody model to describe both waning and boosting of immunity, and applied it to investigate the decrease in virus circulation that accompanies the onset of mass vaccination [13]. In a spatial context, the changes following the onset of vaccination are further complicated by spatial heterogeneity in vaccine uptake. We address that issue in this paper.

In order to model variability in local measles vaccination coverage, we adopted meta-population model. The meta-population framework is a well-established concept in population ecology [14, 15] that is increasingly being applied in epidemiology [16–18]. It allowed us to split a large population into a collection of local communities or patches. We inserted a disease transmission model into this framework, and could then specify the fraction of each individual’s infectious contacts that must occur within the local community. Throughout this paper, we refer to the local communities as ‘patches’, and the fraction of infectious contacts that occur within the patch as the...
‘aggregation parameter’. We refer to populations with a large number of local contacts as being ‘highly aggregated’.

Meta-populations have been used to model measles transmission at a number of different scales. One obvious application of the meta-population model is to split a country into its many cities. At this scale, the size of a city is extremely important for determining persistence of disease [16, 19], demonstrating the importance of mixing within cities. Conversely, analysis of spread of infection indicates that mixing between cities occurs rapidly [20]. An examination of the epidemic correlations between regions in England and Wales shows a complex urban–rural pattern in the pre-vaccination era [21], and a drop in the correlation of epidemics between major cities after the introduction of vaccination [22]. The strong seasonal forcing of epidemics associated with schooling is also a complicating factor in the interpretation of correlations [20, 23]. At a much smaller scale, mathematical analysis of meta-populations of households has shown that both the epidemic threshold [24] and the critical immunization coverage [25] differ considerably from that of a homogeneously mixing population. In this paper, we consider mixing rates at an intermediate scale, similar to the resolution adopted by Bartlett [26]. Here, our meta-population represents a large city or municipality, and each patch represents a school and its local community.

One approach to modelling spatial heterogeneity of measles is the lattice-based model [26–29], where mixing rates are determined by relative positions in the lattice. Here, we do not impose any explicit spatial structure on the meta-population, but rather assume that local mixing leads to a greater risk of transmission within the local patch. In this way, the level of aggregation in the meta-population can be varied using a single ‘aggregation parameter’. The remaining difficulty lies in estimating the value of this parameter, as it incorporates demographic information on rates of mixing and movement that are extremely difficult to measure.

In modelling measles dynamics post-vaccination, it is important to consider both loss of vaccine-induced immunity, and boosting of immunity on contact with infection. We incorporated a previously developed measles antibody model [13] into the meta-population framework, which models the immune dynamics of the population. By applying this model, we were able to measure levels of immunity in different patches of the meta-population, and compare these model predictions with data. A recent sample of antibody levels in The Netherlands found significant differences between groups with high- and low-vaccine coverage within the same municipality [4]. Comparison of model simulations with data allowed us to obtain bounds on the aggregation parameter, and then use these values in turn to simulate the effect of vaccine heterogeneity of disease incidence.

METHODS

The meta-population model

We adopted a simple meta-population model consisting of N patches of size M as shown in Figure 1. As measles infection largely occurs in children, we identified patches with the local community surrounding
a school, so that the meta-population as a whole forms a large city or municipality. Each individual in the meta-population has a fraction

- $\varepsilon_1$ of contacts with individuals outside the meta-population;
- $\varepsilon_2$ of contacts with randomly chosen individuals within the meta-population;
- $\varepsilon_3$ of contacts with individuals within the patch;

where $\varepsilon_1$, $\varepsilon_2$, and $\varepsilon_3$ sum to 1. We assumed that there is a reservoir of infection outside the meta-population that can enter via parameter $\varepsilon_1$. This immigration term has little effect on the dynamics of large meta-populations, but is important for ensuring persistence when the population size is at or below the critical community size of 250 000–300 000 individuals [19].

A recent analysis [30] of mixing between populations is particularly relevant to this parameter, which is concerned with movement between cities. Within the meta-population, we assumed a slightly different mixing mechanism – rather than moving between school communities, we assumed that all individuals spend some fraction of their time in a general region (perhaps the town centre, local cinema or sports ground), where they can encounter any individual in the meta-population.

To simplify the number of parameters in the model, we assumed a fixed value for $\varepsilon_1$ of 0.005, and a fixed patch size of 1000. The degree of aggregation is then completely determined by the aggregation parameter, $\varepsilon_3$. If $\varepsilon_3 = 0$, the meta-population becomes one homogeneously mixed population, and if $\varepsilon_3 = 1 - \varepsilon_1 = 0.995$, the patches become entirely disconnected from one another. The seasonality in contact rate induced by the school term is modelled by assuming that the transmission parameter varies annually as $b(t)$. The form of forcing function chosen (sinusoidal [31, 32] or term-time [8]) has little effect on the results; we adopted the former.

The antibody model

A valuable opportunity for measuring the effects of population aggregation is provided by antibody data collected in areas with low vaccine coverage in The Netherlands [33]. Although national vaccination coverage is high (94%), there are a number of regions in which vaccination levels are low (62–84%) [4]. These low-vaccine communities (LVCs) contain geographically aggregated groups who refuse vaccination for religious reasons [33], and whose antibody levels differ significantly from the national levels. A further distinction is made within the LVC by classifying individuals as either orthodox (who refuse vaccination) or non-orthodox.

In order to compare this antibody data with model simulations, we incorporated into the meta-population a modified version of a SIR model that includes immunity of individuals. The model is described in Figure 2, and further details may be found in [13]. Each individual in the model has an antibody level that is determined by that individual's prior infectious contacts. In the absence of infection, the antibody level decays exponentially to a limit value. On contact with infection, a vaccinated or recovered individual will become subclinically infected if their antibody level is below a threshold level, and this subclinical infection induces a boost to their antibody level. Susceptible individuals have an antibody level of zero, which is then raised to a maximum value by (clinical) infection. To ensure population heterogeneity, antibody levels are log-normally distributed about the mean values described by the antibody decay equations.

As discussed in [13] this model, with parameters assigned as in Figure 2, reproduces the national antibody-age profile seen in [4] very well. Figure 3a presents the national data, reproduced from [4], and Figure 3b the corresponding profile for a sample of 100 000 individuals from a simulation of 4 million. At the time that the antibody data were collected, vaccination had been in place for approximately 20 years. To reproduce the changes in immunity induced by the introduction of vaccination, the model is simulated for 100 years without vaccination, followed by 20 years with 90% vaccination. In Figure 3c, the comparison of data from the national and LVCs is reproduced from [4]. Individuals in the LVCs are identified as being either orthodox (light grey) or non-orthodox (dark grey). Observe that antibodies in the orthodox community are significantly lower than in both the national and non-orthodox samples for the 1–4 years age group, and significantly higher for age groups 10–14, 15–19 and 20–24 years. Significant differences between national and non-orthodox antibody levels can also be seen in the 1–9 years and 15–24 years age groups.

In our later simulations, we assumed a population size of 1 million. This is likely to be greater than the LVC municipalities surveyed in [4]. Although our simulations demonstrate the same broad results for smaller population sizes, the stochastic nature of the
model leads to a fair degree of variability between replicates. We have chosen to present results from the model with a relatively large population, because this provides a more representative (and reproducible) picture of the typical behaviour of the model.

RESULTS

When modelling post-vaccination measles dynamics, it is important to include the effects of waning immunity and subclinical infection. By introducing the antibody model (see Fig. 2) into the meta-population model, we were able to compare levels of immunity in different patches of the meta-population. Surveys of vaccination coverage in LVCs in The Netherlands estimated coverage within the orthodox community of 44% and within the non-orthodox community of 96%, while overall vaccination levels ranged from 62 to 84% [4]. We used our model to simulate a LVC with an overall average of 62% vaccination, split into 650 ‘orthodox’ patches with low vaccination (44%) and 350 ‘non-orthodox’ patches with high vaccination (96%). We expected that the significant

![Diagram, rates and parameters for the antibody model.](image-url)

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unvaccinated birth</td>
<td>(m(1-p)N)</td>
</tr>
<tr>
<td>Vaccinated birth</td>
<td>(mpN)</td>
</tr>
<tr>
<td>Infection of susceptible</td>
<td>(bS(IN) + bS(C/N))</td>
</tr>
<tr>
<td>Subclinical infection of vaccinated individual</td>
<td>(V f(A_I)(b(IN) + b(C/N)))</td>
</tr>
<tr>
<td>Subclinical infection of recovered individual</td>
<td>(R f(A_R)(b(IN) + b(C/N)))</td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>(g_I)</td>
</tr>
<tr>
<td>Subclinical recovery</td>
<td>(g_C)</td>
</tr>
</tbody>
</table>

\(f(A_J)\) = fraction of individuals in immune class \(J\) with antibody below \(a_T\)

Antibody decay equations

- Clinical infection: \((x_I - l_I)e^{-c_I t} + l_R\)
- Vaccination: \((x_V - l_V)e^{-c_V t} + l_V\)
- Subclinical infection: \((x_C - l_C)e^{-c_C t} + l_R\)

<table>
<thead>
<tr>
<th>Clinically infected individuals</th>
<th>Maximum antibody level</th>
<th>Minimum antibody level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission rate</td>
<td>(b) 477.31</td>
<td>(x_I) 1.0</td>
</tr>
<tr>
<td>Recovery rate</td>
<td>(g) 28.07</td>
<td>(l_R) 0.4</td>
</tr>
<tr>
<td>Antibody decay rate</td>
<td>(c_I) 0.7</td>
<td></td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Subclinically infected individuals</th>
<th>Maximum antibody level</th>
<th>Minimum antibody level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission rate</td>
<td>(\hat{b}) 95.46</td>
<td>(x_C) 0.5</td>
</tr>
<tr>
<td>Recovery rate</td>
<td>(\hat{g}) 52.16</td>
<td>(l_R) 0.4</td>
</tr>
<tr>
<td>Infection threshold</td>
<td>(a_t) 0.2</td>
<td>(c_I) 0.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccinated individuals</th>
<th>Maximum antibody level</th>
<th>Minimum antibody level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody decay rate</td>
<td>(c_V) 0.7</td>
<td>(x_V) 0.9</td>
</tr>
<tr>
<td>Minimum antibody level</td>
<td>(l_V) 0.2</td>
<td></td>
</tr>
</tbody>
</table>

Other parameters

- Birth rate \(m\) 0.02
- Fraction vaccinated \(p\)
differences between the two communities to be in individuals below the age of 25 years, as the older individuals would be expected to have had measles before the onset of vaccination. When we compared the output of the model with the data collected in The Netherlands, we found that the age group most sensitive to changes in aggregation is the 10–14 years group. Figure 4 compares the data with the model simulations for increasing values of the aggregation parameter ($\epsilon_3$). We see that without aggregation, the orthodox community has significantly lower antibody levels than that of the non-orthodox community – entirely the reverse of the data.

As the aggregation increases, unvaccinated orthodox individuals become more likely to be infected, and their overall geometric mean titre increases. Meanwhile, non-orthodox individuals become better protected from both clinical and subclinical infection, and their titres decrease. For $\epsilon_3 \geq 0.5$, the model reproduces the pattern of the data, and all significant differences between the various communities identified in the other age groups.

Our results suggest that significant levels of aggregation are required to explain the high antibody levels in areas of low vaccine coverage. Within this context, patchiness in vaccination uptake can have a noticeable effect on infection dynamics, as susceptibles become grouped together. We test the effect of increasing the discrepancy between high- and low-vaccine regions in a meta-population with a fixed overall vaccination level, and a fixed level of local contacts. Figure 5 gives the results of simulations of 1000 patches of size 1000, 20 years after introducing vaccination. For each figure, error bars give the 95% confidence interval for the mean. Note that while the units in (a) and (c) are IU/ml, the simulations use a dimensionless measure, calibrated by the parameters in Figure 2.

Fig. 3. Comparison of the antibody model (b) with data reproduced from [4] [(a) and (c)]. Panel (a) gives the geometric mean titre with age for the national sample, and panel (c) compares the national sample (black) with samples from an area with low vaccine coverage, where individuals are further split into orthodox (light grey) and non-orthodox (dark grey) communities. Panel (b) gives the antibody-age profile of 100 000 individuals from a simulation of 4000 patches of size 1000, 20 years after introducing vaccination. For each figure, error bars give the 95% confidence interval for the mean. Note that while the units in (a) and (c) are IU/ml, the simulations use a dimensionless measure, calibrated by the parameters in Figure 2.
As $h$ is increased, vaccination decreases in 100 of the patches, and increases in the remaining 900 to maintain the overall vaccination at 90%.

We see from Figure 5 that increased heterogeneity in vaccination leads to an overall increase in the risk of infection. In the model with homogeneous vaccination, on average 50% of susceptibles are infected, with individual patches ranging from 40 to 60%. As $h$ increases, individuals in patches of low vaccination coverage become increasingly likely to become infected. We do see a simultaneous drop in the probability of infection of susceptibles in high vaccination areas, but as these susceptibles represent a decreasing fraction of the total susceptible population, this does not counteract the overall trend. A consequence of the increase in infection is a decrease in the average age at infection, led by the low-vaccination patches.

The rise in frequency of fadeouts suggests that outbreaks become more sporadic and thus also more dramatic.

**DISCUSSION**

Standard models of measles transmission within urban communities assume that individuals mix homogeneously, even at population sizes in which some degree of aggregation of contacts must occur. Nevertheless, these models have been remarkably successful in reproducing measles dynamics, particularly the pre-vaccination time-series [34–36]. Our results suggest that this is because moderate levels of aggregation have only a small effect on the dynamical properties of measles in the pre-vaccination era, or when vaccination is homogeneous.
The situation changes when vaccination becomes patchy – low vaccine areas become infection hotspots, with more dramatic outbreaks and a drop in the average age at infection. Data gathered from individuals in LVCs in The Netherlands [4] provides us with an opportunity to estimate the degree of aggregation present in these communities. We find that the antibody-age profiles can only be reproduced if we assume moderate to high levels of aggregation. Our model of immunity is very simple, assuming a single transmission rate between all age groups, and ignoring the effects of maternal immunity. Nevertheless it is able to reproduce all significant differences noted in The Netherlands data.

With the levels of aggregation estimated from the data, we then experiment with varying the patchiness in vaccination coverage within a hypothetical city with 1 million inhabitants, 10% of which are poorly vaccinated. We found that increasing vaccination heterogeneity leads to an increase in the average fraction of susceptibles infected, from approximately 50 to 90% in a highly heterogeneous population. Standard models predict that vaccination of young children should significantly increase the mean age at infection of measles [1, 37, 38]. Our results indicate that strong spatial or social heterogeneity in vaccine uptake can mitigate this effect – we see a drop in the age at infection from \( y_{20} (h=0) \) to \( y_{6} (h=0.95) \).

Clearly, the very high levels of heterogeneity represent an extreme case that is rarely seen, however the mean age at infection is reduced by even moderate levels of heterogeneity. These results are consistent with empirical findings – a recent outbreak of measles at an orthodox school in The Netherlands saw an attack rate of 91% among susceptibles, with 78% of the 138 cases occurring in children between the ages of 2 and 8 years [5]. It is clear that unvaccinated children face a much greater risk of infection when their...
local community has a low vaccine coverage. Such LVCs face a constant danger of large outbreaks of infection, even when national levels of vaccination are high.

Throughout this paper, we have adopted the simplest form of meta-population model and ignored the effect of spatial structure. In future work we will look at models in which each patch mixes preferentially with its neighbours, and consider the effect that clustering of patches has on the meta-population dynamics.

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REFERENCES


