Target immunity levels for achieving and maintaining measles elimination

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Abstract

Vaccination has reduced the global incidence of measles to the lowest rates in history. Local interruption of measles transmission, however, requires sustained high levels of population immunity that can be challenging to achieve and maintain. The herd immunity threshold for measles is typically stipulated at 90-95%. This figure, however, does not easily translate into required immunity levels across all age groups that would be sufficient to interrupt transmission. Previous estimates of such levels were based on speculative contact patterns based on historical data from high-income countries. The aim of this study is to determine age-specific immunity levels that would ensure elimination of measles using observed contact patterns from a broad range of settings. We combined recent observations on age-specific mixing patterns with scenarios for the distribution of immunity to estimate transmission potential. We validated these models by deriving predictions based on serological studies and comparing them to observed case data. We found that 95% immunity needs to be achieved at the time of school entry to guarantee elimination. The level of immunity found in

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the 5-to-9 year old age group in serological studies was the strongest predictor of future case load. Higher levels of immunity in 5-to-9 year olds are required than the previously derived target of 90% to interrupt transmission. While such high levels can be difficult to achieve, school entry provides a clear opportunity to ensure sufficient levels of immunity.

Introduction

Measles, a highly contagious immunising infection, could be a future target for eradication.[1,2] Since the introduction of vaccination in the late 1960s, mortality and morbidity from measles has reduced drastically.[3] Nevertheless, outbreaks continue to occur, and achieving regional elimination, or interruption of transmission, has been challenging.[4]

Typically, immunity targets are set for the level of vaccination coverage at birth required in infancy to achieve "herd immunity", or the level of population immunity necessary to prevent outbreaks occurring.[5] For measles, this level is usually in the range of 90-95%.[6] Strictly speaking, however, any target based on vaccination coverage only applies to current and future birth cohorts going forward. To assess the ability of a country or region to achieve and maintain elimination at any point in time, one needs to look at immunity levels across age groups. These levels are affected by historical routine vaccination coverage, but also by vaccination campaigns and historical outbreaks and corresponding levels of natural immunity.

For this reason, in the late 1990s, the World Health Organization (WHO) European Region derived age-specific target immunity profiles, or the levels of immunity necessary in different age groups to achieve elimination.[7] These profiles are widely applied within and occasionally outside Europe.

Based on a basic reproduction number (or number of secondary cases produced by a typical infective in a totally susceptible population) of 11 and assumed age-specific contact patterns based on pre-vaccination data from England and Wales, it was recommended to ensure that at least 85% of 1–4 year olds,

90% of 5–9 year olds and 95% of 10 year olds and older possess immunity against measles.[8] These immunity targets are different from recommendations on vaccination coverage levels. Gaps in immunity can exist despite high routine coverage if coverage targets were not met in the past, or because of population migration. Immunity targets include the effect of immunity, or lack thereof, in older age groups and highlights the potential need for campaigns to close any gaps in immunity.

Much work over the past decade has gone into better quantifying the amount of transmission-relevant contact occurring between different age groups. Diary-based studies have been conducted across Europe[9,10], as well as in Viet Nam[11] and China[12], and elsewhere. While other methods for measuring social contact patterns exist[13,14,15], contact data from diary studies have become the de facto standard in studying age-specific infectious disease dynamics. Mathematical models of transmission based on these observed patterns have consistently outperformed those based on homogeneous mixing.[16,17,18]

Here, we aimed to evaluate current guidelines on target immunity levels for measles using contact patterns observed in diary studies. To this end, we combined the observed age-specific social mixing patterns with the recommended immunity levels to calculate reproduction numbers in these scenarios to evaluate the potential for sustained transmission if target immunity levels were achieved. We further compared these to alternative scenarios of greater or lower immunity than currently recommended in specific age groups. We then used the results from this analysis to compare the expected epidemiology from serological studies conducted around in the late 1990s / early 2000s with the observed case loads in the subsequent 10 years.

Results

Age-specific immunity scenarios

We first investigated reproduction numbers under previously recommended target immunity levels (85% in under-5 year olds, 90% in 5–9 year olds and 95%

in all older age groups).[7] At these levels, the estimated reproduction numbers derived taking into account age-specific mixing differed substantially from ones obtained under the assumption of homogeneous mixing (Fig. 1). With homogeneous mixing, all countries except Uganda were found to interrupt transmission at the recommended immunity levels, with median reproduction numbers R less than 1. For Uganda, the median estimate of the reproduction number at these immunity levels would be 1.2, and the probability of having a reproduction number greater than 1 in this case would be 85%.

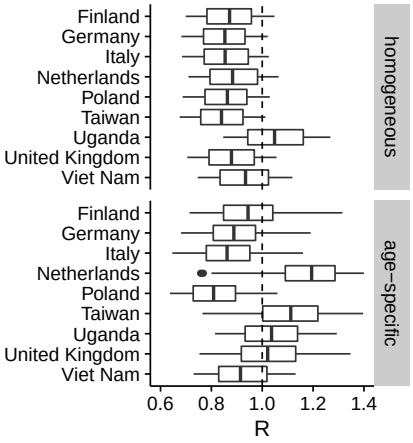

Figure 1: Estimates of what the reproduction numbers of measles would be in a scenario of immunity at current target levels, under assumptions of homogeneous (top) versus age-specific (bottom) mixing. Selected countries are shown for clarity; a larger version of this graph with more countries can be found in the Supplementary Material (Fig. S1).

When considering measured age-specific mixing patterns instead of assuming homogeneous mixing, the ranges of reproduction numbers broadened, and the reproduction numbers increased in almost all scenarios. The Netherlands, Uganda, the United Kingdom and Taiwan all would have estimated reproduction number greater than 1 at previously recommended target levels when mixing patterns were taken into account, indicating that continued outbreaks would be possible. Germany, Italy, Finland and Viet Nam all would have more than 10%

probability of $R > 1$ at these levels.

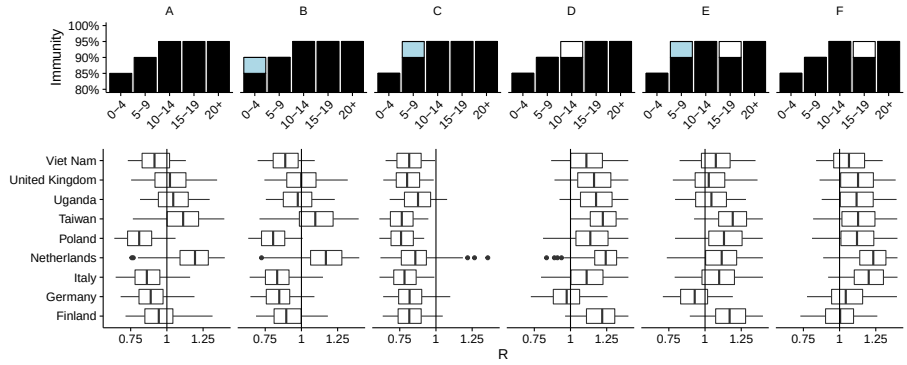

Figure 2: Estimates of what the reproduction numbers of measles would be in different scenarios, with age-specific mixing as measured in diary studies. Top: Scenarios of immunity levels. Bottom: Estimated reproduction numbers. Left to right: A) Current target levels. B) 5% higher immunity in under 5 year olds. C) 5% higher immunity in 5–9 year olds. D) 5% lower immunity in 10–14 year olds. E) 5% higher immunity in 5–9 year olds and 5% lower immunity in 15–19 year olds. F) 5% lower immunity in 15–19 year olds. Selected countries are shown for clarity; a larger version of this graph with more countries can be found in the Supplementary Material (Fig. S2).

With alternative scenarios, the reproduction numbers changed (Fig. 2). Raising immunity in under-5-year olds by 5% to 90% would reduce the estimated reproduction numbers slightly. In this scenario, all countries that would have reproduction numbers greater than 1 under the previously recommended target immunity levels would still have had reproduction numbers equal to or greater than 1. Only in Germany and Italy would the estimated probabilities of having $R > 1$ drop to below 5%. On the other hand, raising immunity in 5-to-9-year olds by 5% to 95% would sharply reduce reproduction numbers. In this scenario, all countries would have a median estimated reproduction number well below 1, and only the Netherlands (10%) and Uganda (13%) would be estimated to have a probability greater than 5% of having $R > 1$.

Scenarios in which a gap in immunity is introduced in older generations resulted in significantly higher reproduction numbers. Reducing immunity levels

in 10-to-14-year olds by 5% to 90% compared to the previously recommended target immunity levels would increase the median reproduction numbers in all scenarios except Germany to above 1. Even if immunity in 5-to-9-year olds was increased to 95% at the same time, all countries would retain a high probability of having $R > 1$ (Germany 30%, all other above 50%). Reducing immunity in 14-to-19 year olds by 5% to 90% from the previously recommended target immunity levels would increase the probabilities of $R > 1$ to greater than 50% in all countries. Reducing immunity in all over-19 year olds by 5% to 90% from the previously recommended target immunity levels would increase the probabilities of $R > 1$ to greater than 90% in all countries.

Evaluating age-specific immunity levels from serological studies

Reproduction numbers estimated based on immunity profiles measured in the late 1990s / early 2000s were weakly correlated with the number of cases in the 10 subsequent years as per WHO figures (Spearman rank coefficient between estimated R and cases per capita; homogeneous mixing model: 0.35, observed mixing model: 0.49; Fig. 3A). Out of 17 countries in which serological studies were conducted as part of the ESEN2 study, eight reported more than 5 measles cases per million per year in the following 10 years. Of these, Spain (3419 cases over the course of 10 years) had a median estimated reproduction numbers of 0.19 (homogeneous mixing) and 0.54 (observed mixing), respectively, and probability 0 of a reproduction number greater than 1 with both models. Israel (1792 cases) had a median estimated reproduction number of > 0.9 in both models, and a probability greater than 20% of $R > 1$ with both models. The United Kingdom (6601 cases) had a median reproduction number of 0.53 (homogeneous mixing) and 1.1 (observed mixing), respectively, with corresponding probabilities of 0% (homogeneous mixing) and 62% (observed mixing) of $R > 1$. The other five countries (Belgium: 1066 cases, Bulgaria: 24,416 cases, Cyprus: 111 cases, Ireland: 1687 cases, Romania: 20,570 cases) all had median estimated reproduction numbers greater than 1 with both models and, correspondingly, high probabilities of $R > 1$.

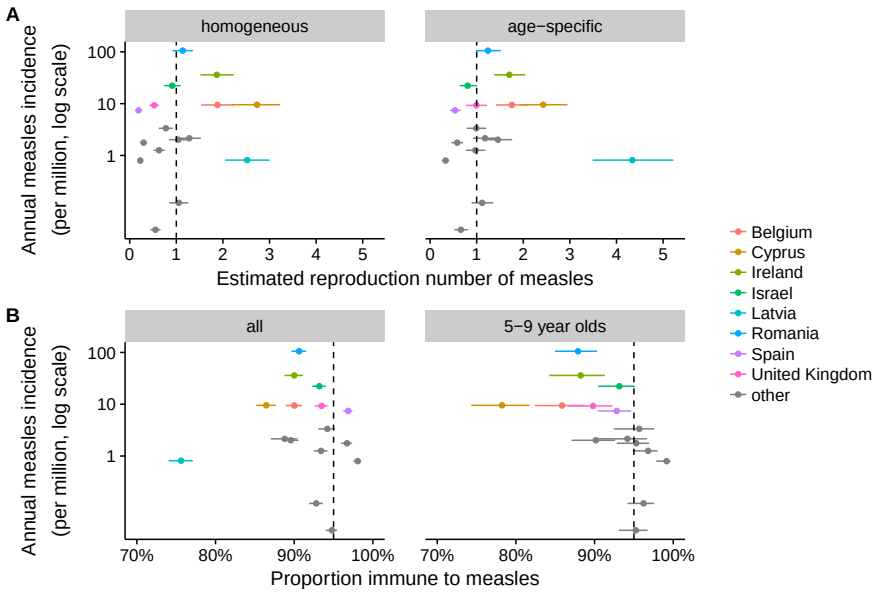

Figure 3: Estimates derived from serological studies conducted around 2000 compared to reported rate of cases across the following 10 years. Top (A): Estimated reproduction numbers for measles under assumptions of homogeneous (left) and observed (right) mixing. Bottom (B): Proportion estimated immune to measles from serological studies in the whole population (left) and 5-to-9 year olds (right). Countries with estimated mean reproduction numbers greater than 2 and/or more than 5 cases per million per year in the 10 years following the serological study are highlighted in colour. Not shown in bottom right panel: Latvia (proportion of 5–9 year olds estimated immune: 62% (95% confidence interval, 57%–67%), 0.8 cases per million per year).

Five further countries (Hungary, Latvia, Lithuania, Malta and Sweden) had median estimated reproduction numbers greater than one with observed mixing, but did not report many cases the following 10 years (maximum: 131 in Sweden). Of these, Cyprus and Latvia were estimated to have reproduction numbers well above 1, while the others were closer to one, with probability of the reproduction number being less than 1 greater than 15% in all cases except Lithuania (median reproduction number: 1.4, 16 cases).

There is a negative correlation between population-level immunity levels as

determined from serology and outbreaks (Spearman rank coefficient between estimated population-level immunity and cases per capita: -0.38; Fig. 3B, left), with several outbreaks in countries reporting high levels of immunity (Israel, Spain and the United Kingdom). The correlation is stronger when considering only immunity in 5-to-9 year olds (Spearman rank coefficient between estimated immunity in 5-to-9 year olds and cases per capita: -0.62; Fig. 3B, right). Of the 6 countries (Czech Republic, Hungary, Luxembourg, Malta, Slovakia, Slovenia and Sweden) that found a proportion greater than 94% of 5-to-9 year olds immune in the serological studies, none experienced a significant outbreak in the subsequent 10 years. Immunity in all other age groups were also negatively correlated with cases per capita over the next 10 years, but at lower levels of correlation (0-to-4: -0.42; 10-to-14: -0.50; 15-19: -0.42, 20+: -0.06).

Discussion

Current guidelines on target immunity levels are based on estimates derived almost 20 years ago, and were based on assumed mixing patterns matched to pre-vaccination data from England and Wales. We have used transmission models in combination with recently observed age-specific contact patterns from a variety of European and some non-European countries to assess whether these guidelines are sufficient for achieving measles elimination.

We have investigated a range of countries with different demographic profiles and cultural contexts: from high-income settings characterised by low birth rates and an ageing population (e.g., Germany or the United Kingdom) to having more (Viet Nam) or less (Taiwan) recently undergone the demographic transition to low birth rates, and Uganda as a low-income country characterised by a high birth rate and young population. Investigating these scenarios with a model assuming homogeneous mixing, the estimated reproduction number with given immunity levels depended solely on the demographic composition of the population. In that case, only Uganda, which has a large proportion of children in the population (35% of the population less then 10 years of age and therefore

with immunity only at 90% in this scenario) would be expected to have a reproduction number significantly greater than one under previously recommended target immunity levels. With observed mixing patterns, more countries were found to be at risk of outbreaks even if they achieved previously recommended target immunity levels, including ones with very different demographic profiles. This suggests that observed mixing patterns and, consequently, reproduction numbers are driven less by demography than by cultural and social contexts such as schooling patterns, or differences in survey design and execution.

Of the countries investigated, Finland and the Netherlands have been verified to have eliminated measles.[19] Finland eliminated indigenous measles in the early 1990s, and has achieved vaccination coverage of greater than 95% since. The Netherlands have high immunity levels of more than 95% in 5-to-9 year olds, although immunity gaps at the sub-national level continue to cause outbreaks.[20,21]

We estimated that achieving 95% immunity in 5-to-9 year olds would reduce transmission sufficiently to achieve elimination in all except the most extreme scenarios. Verifying this finding with serological studies, we found that of the countries estimated to have immunity levels greater than 94% in this age groups none experienced a significant outbreak in the following 10 years. On the other hand, only two of the 10 countries with mean immunity levels of less than 94% in 5-to-9 year olds did not experience more than 5 cases per million per year in the following 10 years: Latvia and Lithuania. These two are among the smallest in our group of countries for which we had serological data available and may be at lower risk of imported cases. Still, they would have been expected to have seen more cases given the results of the serological studies in 2003 and 2004, respectively. Latvia in particular reported immunity levels as low as 76% among all age groups and 62% in 5-to-9 year olds in 2003, but only reported 16 cases of measles in the 10 years 2004–13. To our knowledge, there were no supplementary immunisation activities that could explain the absence of outbreaks. It would be of value to determine whether these countries are now at high risk of large outbreaks in spite of having previously interrupted transmission, or whether

there were issues with the serological tests conducted.

The importance of immunity levels in 5-to-9 year olds presents both a challenge and an opportunity: Levels as high as 95% in this age group can only be maintained through high levels of two-dose immunisation prior to school entry. At the same time, school entry itself involves a level of organisation which provides the opportunity to both check the immunisation status of children and offer additional vaccinations if necessary. The experience of the Pan-American Health Organization in eliminating measles supports these findings. A key component to interrupting measles transmission were periodic 'follow-up' vaccination campaigns of pre-school children, timed at 4 year intervals to ensure high immunisation by the time of school entry.[22,23] Studies in the United States, where measles was eliminated in 2000, suggest that different minimum vaccine coverage levels are required to prevent measles transmission among different age groups.[24] School-aged populations accounted for the majority of measles cases between 1976 and 1988, and compulsory vaccination as part of school attendance laws played an important role in reducing measles incidence on the path to elimination.[25] Where there were less stringent vaccination requirements at school entry, more case of measles were observed.[26] Analyses of pre-elimination measles outbreaks in the US indicated that transmission occurred among highly vaccinated school-aged populations, indicating that higher population immunity levels are needed among school-aged children compared to preschool-aged children.[27] It has been suggested that minimum coverage levels as low as 80% at the second birthday of children may be sufficient to prevent transmission among preschool-aged children in the United States if population immunity is at least 93% among over-5 year olds.[28]

While our results stress the role of 5-to-9 year olds, they also highlight the importance of having no gaps in immunity in older age groups. This is particularly important close to elimination as a lower force of infection pushes cases into older age groups.[29] Given the higher rate of complications of measles when experienced at older age, ensuring immunity among adults will be important not only for interrupting transmission, but also to prevent serious episodes of

disease.[30]

Our study has several limitations. We relied on broad estimates of the basic reproduction number, derived from pre-vaccination era dynamics.[31] While these numbers are well-established values in mathematical epidemiology, recent studies have produced both lower and higher estimates, depending on the method used and the type of setting investigated.[32,33,34]

Moreover, the reproduction numbers we estimated from serological studies did not always correctly predict where outbreaks could be expected. In particular, Israel, Spain and the United Kingdom experienced large numbers of cases in the following 10 years in spite of reproduction number estimates which would indicate interruption of transmission. Three potential causes for this discrepancy suggest themselves: First, drops in vaccination coverage as well as vaccination campaigns may have changed the risk of outbreaks during the 10 years following the serological studies. Second, samples used for the serological studies were a combination of residual and population-based samples and may not be representative of population-level antibody levels. In Spain, a disproportionate number of cases occurred in young adults[35], but there was nothing in the serological data to suggest that this might be expected. Moreover, if those lacking immunity are preferentially in contact with each other because they cluster socially or geographically, outbreaks could occur in these groups, and population-level serology might not provide a good estimate of realised immunity levels in outbreak settings. In Israel, outbreaks occurred in orthodox religious communities with very low vaccination coverage.[36] Third, mixing levels between 5-to-9 year olds might be even stronger than suggested by the diary-based studies underlying the contact matrices used here. This would be in line with findings from the pre-vaccination era in England and Wales showing a sharp increase in age-specific incidence at the age, coincident with the age of first exposure to a school setting.[37] Israel, Spain and the United Kingdom were all found to have levels of immunity in 5-to-9 year olds of 90–95% in serological studies, and yet experienced significant outbreaks in the following 10 years. It is conceivable that even these levels might be too low to guarantee interruption

of transmission of measles, especially in the presence of sub-national variation in immunity.

Lastly, we repeat that population immunity represents past levels of vaccine coverage or natural infection which may not be reflective of the future. For example, immunity may be high just after a major outbreak but such outbreaks could occur again if coverage is sub-optimal. An important caveat is therefore that seeing immunity sufficient to interrupt transmission does not guarantee that elimination is maintained if current of coverage are insufficient.

In summary, we have tested different immunity thresholds for measles using observed mixing patterns between age groups. We found that previously stated guidelines might be insufficient for interrupting transmission, and that very high levels of immunity among 5-to-9 year olds while maintaining similarly high levels in older age groups are paramount to achieving elimination. Further sub-national serological and epidemiological studies, particularly in low-income countries at high risk of measles outbreaks, could generate key insights on the relationship between immunity levels, heterogeneity of susceptibility and outbreak risk.[38,39] At the same time, further studies of contact patterns across settings, combined with models of such patterns where no data have been collected, will make it possible to expand our results to other countries and regions.[40] Combined with observations of contact patterns, these would serve to highlight key gaps in immunity that need to be filled in order to achieve regional elimination and, ultimately, global eradication of measles.

Methods

Age-specific forces of infection

We are considering an age-structured SIR-type model with A age groups.[41,42] The force of infection λ_i experienced by age group i can be written as the sum of the forces of infection exerted on those in age group i by those in the same and all other age groups:

$$\lambda_i = \sum_j \lambda_{ij} = \frac{1}{N_i} \sum_j \beta_{ij} I_j \tag{1}$$

where λ_{ij} is the force of infection exerted by age group j on age group i, β_{ij} is the infection rate, or the rate at which infected individuals in age group j contact and infect (if susceptible) individuals out of a total number N_i in age group i, and I_j is the number of infectious people in age group j. This assumes that the rate of infection between two random individuals depends on their ages only, and that the probability of a given member of age group i to be susceptible depends on population-level susceptibility only.

The infection rate β_{ij} can be further split,

$$\beta_{ij} = p_{\text{Inf}}\phi_{ij} = p_{\text{Inf}}\delta_j p_{ij} \tag{2}$$

where p_{Inf} is the probability that a contact between an susceptible and infectious person leads to infection, here assumed age-independent, ϕ_{ij} is the number of contacts an individual of age group j makes with those of age group i per unit time, δ_j is the rate at which individuals in age group j make contact with others, or the number of people they meet per unit time (assumed independent of population age structure), p_{ij} is the probability that a contact made by an individual in age group j is with someone in age group i, $\sum_i p_{ij} = 1$

Calculating the reproduction number

To estimate the reproduction number under different immunity profiles, we calculate an immunity-adjusted contact probability

$$v_{ij} = p_{ij}(1 - r_j) \tag{3}$$

where r_j is the proportion of individuals in age group j that are immune, and v_{ij} can be interpreted as the probability that a contact someone in age group i makes is with a non-immune person in age group j.

The basic reproduction number R_0 is defined as the spectral radius (or largest eigenvalue) of the next-generation matrix (NGM) $\mathbf{K}$.[43]

$$R_0 = \rho(\mathbf{K}) \tag{4}$$

In our age-structured SIR-type model, the elements of the next-generation matrix $\mathbf{K}$ are

$$k_{ij} = q\delta_j p_{ij} \tag{5}$$

where q is a scale factor that, in the simplest SIR model, is the probability of infection upon contact p_{Inf} multiplied with the duration of infectiousness D_{Inf}. Given a value of R_0 and a contact matrix, we can use Eqs. 4 and 5 to calculate q, then calculate the elements of the reproduction matrix $\mathbf{M}$, taking into account immunity levels:

$$m_{ij} = q\delta_j v_{ij} \tag{6}$$

and the reproduction number R as the spectral radius of $\mathbf{M}$,

$$R = \rho(\mathbf{M}) \tag{7}$$

Contact matrices

We established contact matrices from diary studies conducted in a range of different settings using a bootstrap, randomly sampling P individuals with replacement from the P participants of a contact survey. We then determined a weighted average d_{ij} of the number of contacts in different age groups j made by participants of each age group i, giving weekday contacts 5/2 times the weight of weekend contacts. We further obtained symmetric matrices, i.e. ones fulfilling $c_{ij}n_j = c_{ji}n_i$ by rescaling

$$c_{ij} = \frac{1}{2}\frac{1}{n_i}\left(d_{ij}n_j + d_{ji}n_i\right) \tag{8}$$

where n_i was the proportion of the underlying population that is in age group i. This gave the elements of the contact matrix $\phi_{ij} = c_{ij}/T$, scaled by the time period T over which contacts were measured (usually 24 hours).

Homogeneous mixing approximation

An assumption of homogeneous mixing is equivalent to assuming that $\delta_i = \delta$ (each individual has the same number of contacts, no matter which age group they are in) and $p_{ij} = n_j$ (the probability of a contacts of group i being with

group j is equal to the proportion of individuals that are in group j). For the contact matrix D, this means that $d_{ij} = \delta n_j$. This, in turn, means that the infection rate is $\beta_{ij} = \delta p_{\text{inf}} n_j$ and the force of infection (Eq. 1) is independent of age group:

$$\lambda_i \approx \delta p_{\text{inf}} \frac{I}{N} \tag{9}$$

This is equal to the classic SIR model with infection rate β if we set $\beta = \delta p_{\text{inf}}$, that is the infection rate is equal to the rate of contact times the probability of infection upon contact between a susceptible and infectious individual.

In this case the NGM of Eq. (5) reduces to

$$k_{ij} = q n_i \delta \tag{10}$$

with $q = p_{\text{Inf}} D_{\text{Inf}}$ and spectral radius

$$R_0 = \beta D_{\text{Inf}} \tag{11}$$

If the proportion immune of those in age group j is r_j, the reproduction matrix is

$$m_{ij} = q(1 - r_i) n_i \delta \tag{12}$$

and

$$R = \beta D_{\text{Inf}} \sum_j (1 - r_i) n_i = r R_0 \tag{13}$$

where r is the proportion of the population that is immune.

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