

## Conclusions of the SAGE Working Group on Measles and Rubella

21-22 June 2017, Geneva

### WHO Policy Recommendation on Target Immunity Levels for Elimination: Considerations for Defining Age-specific Target Levels

#### FOR DECISION

In light of the following considerations, SAGE is asked to provide recommendations on what level of population immunity is needed to achieve herd immunity in defined age groups.

#### Definitions

“Age-specific immunity levels” are the proportion of people in specified age groups that are immune to a particular pathogen (whether due to vaccination or natural infection).

“Target immunity levels” are age-specific immunity levels, usually defined to interrupt transmission by driving  $R$  below 1.

“Reproduction number” is the mean number of secondary cases generated by each infectious case. If this is less than 1, transmission is eventually stopped and elimination can be achieved.

#### Note

Results included in this document are based on yet unpublished results. Please do not share.

#### Background

The current target of the World Health Organization (WHO), as provided in the *Global Measles and Rubella Strategic Plan 2012-2020*, is to

*“achieve at least 95% coverage with both the first and second routine doses of measles vaccine (or measles-rubella-containing vaccine as appropriate) in each district and nationally.”*

The plan further states that

*“high coverage with two doses of MCV serves as the foundation required to ensure high population immunity against measles”*

and that

*“measles and rubella elimination require achieving and maintaining high levels of*

*population immunity. For measles, vaccination coverage will need to reach and remain at or exceed 95% with each of the two doses of MCV (for countries yet to introduce RCV), MR or MMR vaccines at the district and national levels.”*

Where this cannot be achieved the plan recommends Supplementary Immunization Activities (SIAs):

*“Countries not able to achieve high and homogenous vaccination coverage with the first and second dose of MCV through their routine immunization systems will need to use SIAs). These can be summarized as a one-time “catch-up” SIA targeting a broad age group (often 9 months to 14 years of age) to immunize the most susceptible children, followed by periodic “follow-up” SIAs targeting children born since the previous one regardless of vaccination status, with special efforts made to reach children who have never been vaccinated against measles.”*

Strictly speaking, any target based on child vaccination coverage only applies to current and future birth cohorts and their immunity going forward. To assess the ability of a country or region to achieve and maintain elimination, it is necessary to look at immunity levels across age groups. These levels are determined by historical routine vaccination coverage, but also by vaccination campaigns and outbreaks leading to corresponding levels of natural immunity. For this reason, in the late 1990s, the WHO European Region derived age-specific target immunity profiles, or the levels of immunity necessary in different age groups to achieve elimination.<sup>1</sup> 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 mixing patterns based on pre-vaccination data from England and Wales, it was recommended 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. These immunity levels should be distinguished from recommendations on vaccination coverage levels. Coverage targets generally need to be higher than immunity targets because vaccine effectiveness is not 100%, and they generally apply to young children. Gaps in immunity can exist despite high routine coverage if coverage targets were not met in the past, or because of population migration.

The recommendations for the WHO European Region were derived from models that used estimated contact patterns that were consistent with the age distribution of cases in high-income countries. As such, it was not clear whether the recommendations are relevant beyond the specific context of the European Region, or whether different target levels were to be recommended elsewhere. We here report results from a re-

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<sup>1</sup> Ramsay M. *A strategic framework for the elimination of measles in the European region*. 1997.

assessment of age-specific target immunity levels that take into account recent observations of age-specific contact patterns in different settings around the world.

### Diary-based studies on contact patterns

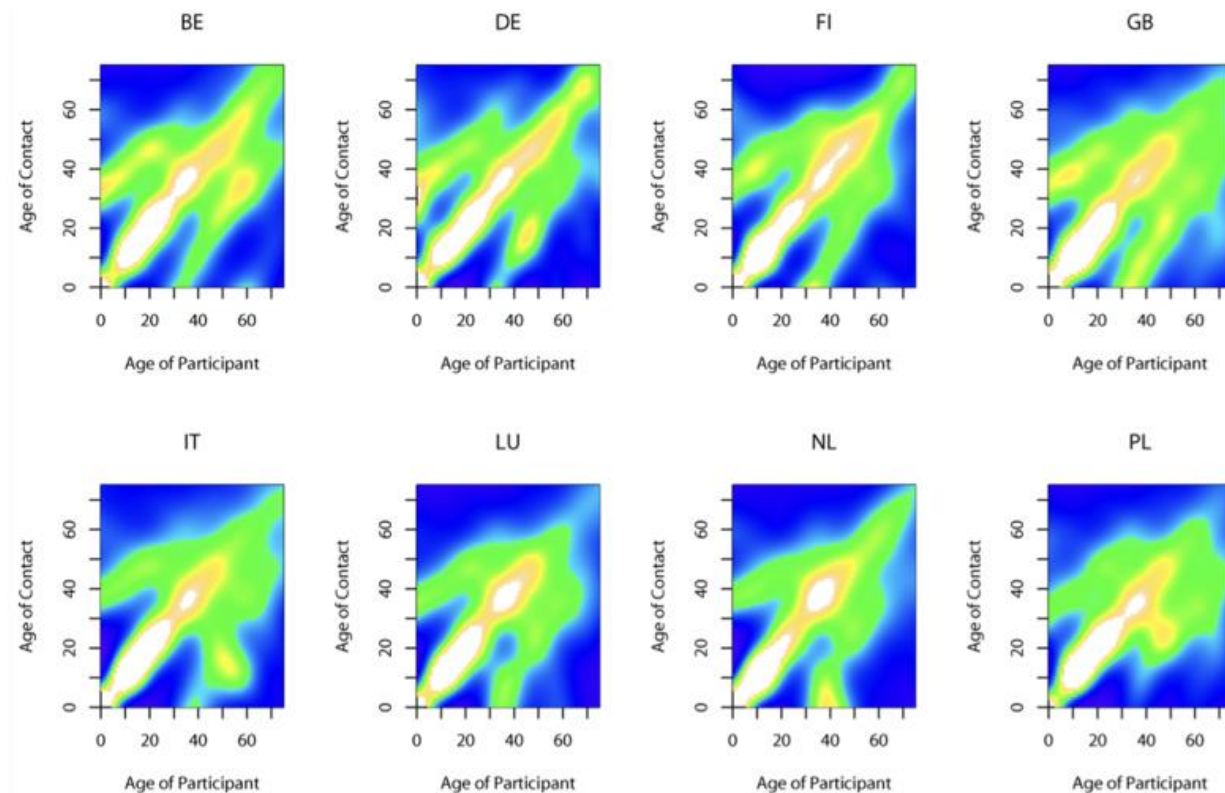


Figure 1. Age-specific contact patterns in 8 different European countries, shown as heat maps (brighter colours: more contact). Shown is the reported age of participants (bottom axis) and the reported age of their contacts (left axis). Countries: Belgium, Germany, Finland, Great Britain, Italy, Luxembourg, Netherlands, Poland. Reproduced from Mossong et al.<sup>2</sup>

Much work over the past decade has gone into better quantifying the amount of transmission-relevant contact occurring between different age groups (Figure 1). Diary-based studies have been conducted across Europe, as well as in Viet Nam, China, Uganda and elsewhere.<sup>2</sup> While other methods for measuring social contact patterns exist, contact data from diary studies have become the de facto standard in studying age-specific infectious disease dynamics. Mathematical models of transmission based on

<sup>2</sup> Mossong J, Hens N, Jit M, Beutels P, Auranen K, Mikolajczyk R, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med 2008;5(3):e74. URL: <http://dx.doi.org/10.1371/journal.pmed.0050074>. doi:10.1371/journal.pmed.0050074.

these observed patterns have consistently outperformed those based on homogeneous mixing.<sup>3</sup>

### Age-specific immunity scenarios

We first investigated reproduction numbers in 8 countries (Finland, Germany, Italy, Netherlands, Poland, Taiwan, Uganda, United Kingdom and Viet Nam) 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). If homogeneous mixing is assumed, all countries except Uganda would interrupt transmission with immunity at these levels, their median reproduction numbers  $R$  being less than 1 (Fig. 2). Only Uganda, which has a large proportion of children in the population (35% of the population less than 10 years of age) was found to have a reproduction number significantly greater than 1 (median: 1.05) if immunity was at the previously recommended target immunity levels.

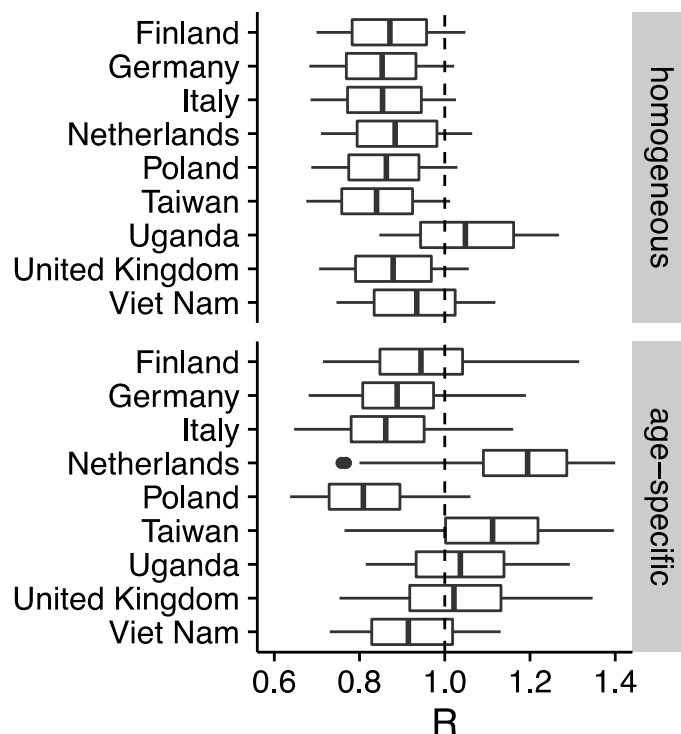


Figure 2. Estimates of what the reproduction numbers of measles would be in a scenario of immunity at current target levels, under assumptions of homogeneous (top) versus age-specific (bottom) mixing.

<sup>3</sup> Wallinga J, Teunis P, Kretzschmar M. Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents. *Am J Epidemiol* 2006;164(10):936–44. URL: <http://dx.doi.org/10.1093/aje/kwj317>. doi:10.1093/aje/kwj317.

Using the same immunity levels but with age-specific mixing as observed in diary studies, the Netherlands, Uganda, the United Kingdom and Taiwan would have estimated reproduction number greater than 1 (Figs. 2 and 3A), indicating that continued outbreaks would be possible. Germany, Italy, Finland and Viet Nam would have more than 10% probability of reproduction numbers greater than 1 at these levels.

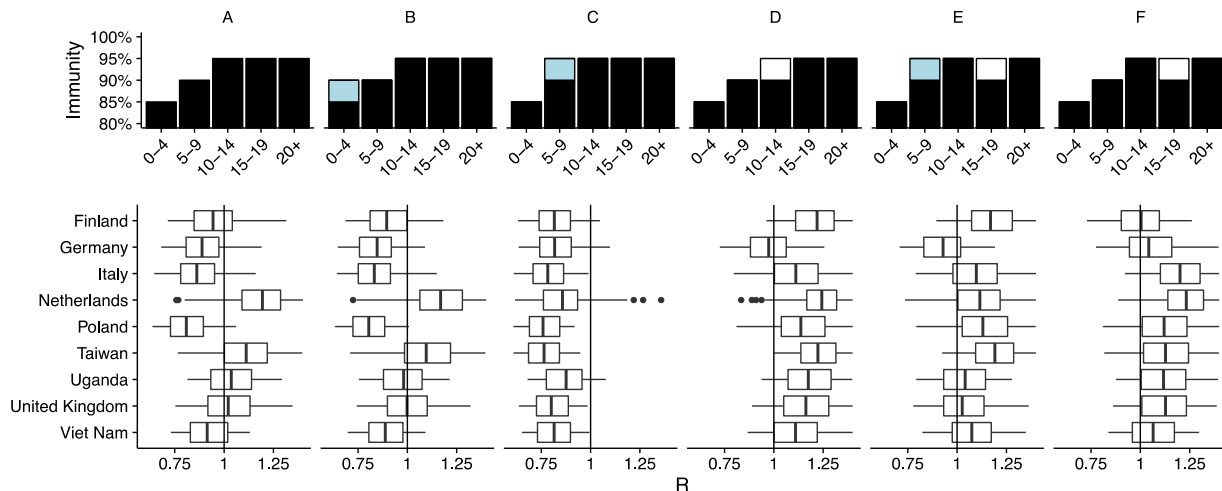


Figure 3. Estimates of what the reproduction numbers of measles would be in different scenarios, with age-specific mixing as measured in diary studies. Top: Scenarios of immunity levels. Bottom: Estimated reproduction numbers. Left to right: A) Current target levels. B) 5% higher immunity in under 5 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.

With alternative scenarios, the reproduction numbers changed (Fig. 3, scenarios B to F). Raising immunity in under-5-year olds (scenario B) 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 a reproduction number greater than 1 drop to below 5%. On the other hand, raising immunity in 5-to-9-year olds by 5% to 95% (scenario C) 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 a reproduction number greater than 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 (scenario D) 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 a reproduction

number greater than 1 (Germany 30%, all other above 50%). Reducing immunity in 15-to-19 year olds by 5% to 90% from the previously recommended target immunity levels (scenario E) would increase the probabilities of a reproduction number greater than 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 (scenario F) would increase the probabilities of a reproduction number greater than 1 to greater than 90% in all countries.

### **Evaluating age-specific immunity levels from serological studies**

To validate our approach, we derived predictions from serological studies conducted in the late 1990s and early 2000s with observed case data in the following period. Reproduction numbers estimated using age-specific mixing based on these serological data 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: 0.49). Out of 17 countries in which serological studies were conducted as part of the ESEN2 study in the early 2000s<sup>4</sup>, 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 number of 0.54 and probability 0 of a reproduction number greater than 1. Israel (1792 cases) had a median estimated reproduction number of > 0.9, and a probability greater than 20% of a reproduction number greater than 1. The United Kingdom (6601 cases) had a median reproduction number of 1.1, with a probability of 62% of a reproduction number greater than 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 and, correspondingly, high probabilities of a reproduction number greater than 1.

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<sup>4</sup> Andrews N, Tischer A, Siedler A, Pebody RG, Barbara C, Cotter S, et al. Towards elimination: measles susceptibility in Australia and 17 European countries. Bulletin of the World Health Organization 2008;86:197–204. URL: <http://www.who.int/bulletin/volumes/86/3/07-041129/en/>.

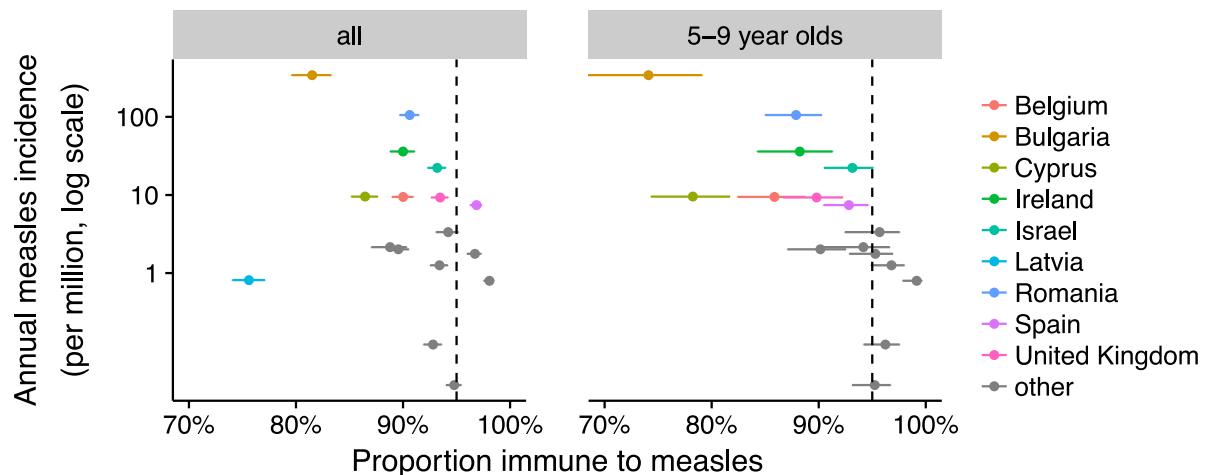


Figure 4. Estimates derived from serological studies conducted around the year 2000 compared to reported rate of cases across the following 10 years. Shown is the proportion estimated immune to measles from serological studies in the whole population (left) and 5-to-9 year olds (right). Countries with 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 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 other countries (Hungary, Latvia, Lithuania, Malta and Sweden) had median estimated reproduction numbers greater than 1, 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 was 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. 4, 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. 4, 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 was 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).

## **Limitations**

This study has several limitations. It relied on broad estimates of the basic reproduction number, derived from pre-vaccination era dynamics. 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<sup>5</sup>. For example, settings with high population density, large birth cohorts and massive in-migration from endemic areas may have higher basic reproduction number. 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 are that: First, decreases in vaccination coverage as well as the presence/absence of 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. For example in Spain, a disproportionate number of cases occurred in young adults, 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. 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 of school entry, coincident with the age of first exposure to a school setting. 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 virus, especially in the presence of sub-national variation in immunity.

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<sup>5</sup> Guerra, F. M.; Bolotin, S.; Lim, G.; Heffernan, J.; Deeks, S. L.; Li, Y. & Crowcroft, N. S. The basic reproduction number ( $R_0$ ) of measles: a systematic review. *The Lancet Infectious Diseases, Elsevier, 2017*



## **Conclusions:**

Based on the study, the authors propose that target immunity levels be recommended for elimination based on the original levels derived for WHO European Region, but with a requirement of higher immunity of 95% in 5–9 year olds.

## **Draft Recommendations**

The following recommendations are proposed by the SAGE WG on Measles and Rubella for considerations by the SAGE based on the evidence presented above.

1. Achieving homogeneous immunity of at least 95% through coverage of at least 95% with 2 doses of MCV remains the primary goal for measles elimination.
2. Countries should include immunity targets in addition to coverage targets as part of necessary strategies for achieving measles elimination
  - Neglecting immunity gaps in older age groups could make it difficult and costly to achieve elimination
  - Neglecting immunity gaps particularly in school-aged children could increase disease burden and mortality among infants younger than 1 year of age as school-aged children could be the transmitters of infection (as siblings in school or in the future as parents).
3. Recommend immunity levels of 95% in all age groups from 5 years
  - in particular when conducting follow-up campaigns, in addition to ensuring high coverage in children 1-4 years of age, the campaigns should address possible immunity gaps in the 5-9 year olds in order to prevent outbreaks”.

## **Annex 1: Estimating reproduction numbers from mixing patterns and immunity profiles**

The basic reproduction number  $R_0$  can be calculated as the spectral radius (or largest eigenvalue) of the next-generation matrix (NGM)  $K$ ,<sup>6</sup>

$$R_0 = \rho(K)$$

We can write the elements of the next-generation matrix  $K$  as

$$k_{ij} = q\delta_i p_{ij}$$

where  $q$  is a scale factor that, in the simplest case, is the probability of infection upon contact multiplied with the duration of infectiousness,  $\delta_j$  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  $i$ . Given a value of  $R_0$  and a contact matrix, we can use these two equations to calculate  $q$ , then calculate the elements of the reproduction matrix  $M$  taking into account immunity levels

$$m_{ij} = q\delta_i p_{ij}(1 - r_j)$$

where  $r_j$  is the proportion of people in age group  $j$  that is immune and the reproduction number  $R$  as the spectral radius of  $M$ ,

$$R = \rho(M) \quad (7)$$

which is the equivalent of  $R_0$  when taking into account current immunity levels in the population.

An assumption of homogeneous mixing would be 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  $j$ ).

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<sup>6</sup> Diekmann, O.; Heesterbeek, J. A. P. & Roberts, M. G.

The construction of next-generation matrices for compartmental epidemic models.

*J R Soc Interfac.*, **2010**, 7, 873-885