Target immunity levels for achieving and maintaining measles elimination

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Abstract

Background

Vaccination has reduced the global incidence of measles to the lowest rates in history. However, local interruption of measles transmission 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 does not easily translate into age-specific immunity levels required 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 was to determine age-specific immunity levels that would ensure elimination of measles when taking into account empirically observed contact patterns.

Methods

We combined estimated immunity levels from serological data in 17 countries with recent measurements of age-specific mixing patterns to derive contact-adjusted immunity levels, and used these to establish a contact-adjusted immunity threshold for elimination. We then combined a range of hypothetical immunity profiles with contact data from a wide range of socioeconomic and demographic settings to determine age-specific immunity levels that would guarantee contact-adjusted immunity levels above that threshold.

Results

We found that contact-adjusted immunity levels were better than plain immunity levels at predicting whether countries would experience outbreaks in the decade following the serological studies, with an appropriate threshold level found to be at 93% contact-adjusted immunity. Combined with observed contact patterns, the serological studies correctly predicted whether a country was to experience large outbreaks or not

in approximately two-thirds of cases. Using these results to assess the validity of previous guidelines on target immunity levels, we found that in several settings these would not be sufficient to guarantee elimination. Instead of the previously recommended 90% of population-level immunity in 5–9 year olds, we found that 95% immunity would have to be achieved by the age of five and maintained across older age groups to guarantee elimination.

Conclusions

The importance of achieving high immunity levels in 5–9 year olds presents both a challenge and an opportunity. While such high levels can be difficult to achieve, school entry itself provides an opportunity to ensure sufficient vaccination coverage. Combined with observations of contact patterns, further national and sub-national serological studies could serve to highlight key gaps in immunity that need to be filled in order to achieve national and regional elimination and, ultimately, global eradication of measles. Vaccination has reduced the global incidence of measles to the lowest rates in history.

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 declined drastically. [3] Nevertheless, outbreaks continue to occur, and achieving regional elimination, or interruption of transmission, has been challenging. [4]

Control of measles is achieved through vaccination in early childhood, and the vaccine is part of routine immunisation schedules worldwide. Typically, vaccination targets are established for the level of coverage required to achieve "herd immunity", or the level of population immunity necessary to prevent outbreaks occurring. [5] For measles, this level has been found to be in the range of 90-95%. [6] Strictly speaking, however, any target based on vaccination coverage only affects the current and future birth cohorts. With sufficient susceptibility in older age groups, outbreaks can occur even at high levels of vaccination coverage. To assess the ability of a country or region to achieve and maintain elimination, that is the sustained absence of endemic transmission, immunity levels must therefore be considered across all age groups. These levels are affected by historical and current routine vaccination coverage, but also by vaccination campaigns and past outbreaks that conferred natural immunity.

For this reason, in the late 1990s, the World Health Organization (WHO) European Region (EURO) 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, 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 distinct 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 reflect the effect of susceptibility in all age groups and highlight the potential need for campaigns to close any gaps in immunity.

The aforementioned target immunity levels derived in the late 1990s were based on assumed age-specific contact patterns based on pre-vaccination measles epidemiology in England and Wales. Since then, much work 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 Vietnam [11] China [12], Uganda [13], Zimbabwe [14] and elsewhere. While other methods for measuring social contact patterns exist [15–17], contact data from diary studies have become the de facto standard for studying age-specific infectious disease dynamics. Mathematical models of transmission based on these observed patterns have consistently outperformed those based on homogeneous mixing. [18–20]

Here, we aimed to evaluate current guidelines on target immunity levels for measles taking into account contact patterns observed in diary studies. To this end, we combined the observed age-specific social mixing patterns with observed or hypothesised immunity levels to calculate a *contact-adjusted* immunity, akin to the mean level of immunity across the population but taking into account that some age groups have more contact with each other than others. We validated this method by testing the extent to which contact-adjusted immunity levels based on serological studies conducted around in the late 1990s / early 2000s could have been used to predict the case load in the following decade. We then calculated hypothetical contact-adjusted immunity levels if previously recommended immunity levels were achieved in a range of settings where contact studies have been undertaken, and assessed whether these levels would have been sufficient for achieving and maintaining elimination. Lastly, we compared these results to alternative scenarios of greater or lower immunity than the recommendation to test whether an alternative recommendation would be more justified once mixing patterns were taken into account.

Methods

Data

We considered the annual number of measles cases reported by each country to WHO. We used serological studies conducted in 17 countries of the WHO EURO as part of the ESEN2 project to determine immunity levels at the times of the studies [25]. Equivocal samples were interpreted as positive as in the original study, but we also tested scenarios where they were removed from the sample or interpreted as negative. We took into account uncertainty by drawing from the individual samples using a bootstrap ($n = 100$), and using the re-sampled immunity levels with re-sampled contact matrices to estimate contact-adjusted immunity. Since contact studies were not available for all countries in ESEN2, contact studies from representative countries were used where necessary (for mediterranean countries: Italy; for Eastern European countries: Poland; for Sweden: Finland; for Ireland: Great Britain).

We used diary studies available on the Zenodo Social Contact Data Repository (`https://zenodo.org/communities/social_contact_data`), to determine contact matrices for 17 countries and the Hong Kong Special Administrative Region of China [26–30], and a further study conducted in five countries of South East Asia.

Contact-adjusted immunity

To calculate the effective reproduction number R, we used an age-structured SIR-type model [21, 22]. In this model, the force of infection λ_i experienced by age group i is the sum of the forces of infection exerted on those in age group i by those in the same and all other age groups:

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

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 individuals in age group i contact individuals out of a total number N_j in age group j and become infected if these are infectious, and I_j is the number of infectious people in age group j. This formulation of the force of infection assumes that the rate of infection between two random individuals depends on their ages only, and that the probability of a given contacted member of age group j to be with someone infectious depends on population-level prevalence of infection only.

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

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

where p_{Inf} is the probability that a contact between an susceptible and infectious person leads to infection, here assumed age-independent, and ϕ_{ij} is the number of contacts an individual of age group j makes with those of age group i per unit time.

The basic reproduction number R_0 is defined as the spectral radius (or largest eigenvalue) of the next-generation matrix (NGM) $\mathbf{K}$ [23]

$$R_0 = \rho(\mathbf{K}) \tag{3}$$

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

$$k_{ij} = q\phi_{ij}\frac{N_i}{N_j} \tag{4}$$

where q is a scale factor that, in the simplest case, is the probability of infection upon contact p_{Inf} multiplied with the duration of infectiousness D_{Inf}. If a proportion r_i of age group i is immune, this changes the initially susceptible population from N_i to $N_i(1-r_i)$. The reproduction number for an invading infection in such a population is

$$R = \rho(\mathbf{K}') \tag{5}$$

where, again, ρ denotes the spectral radius and $\mathbf{K}'$ is a matrix with elements

$$k'_{ij} = q\phi_{ij}\frac{N_i(1-r_i)}{N_j}. \tag{6}$$

In classical mathematical epidemiology in a well-mixed population, the relationship between the basic reproduction number R_0 and the effective reproduction number R is

$$R = (1-r)R_0 \tag{7}$$

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

$$r' = (1 - R/R_0) = \left(1 - \frac{\rho(\mathbf{K}')}{\rho(\mathbf{K})}\right) \tag{8}$$

as contact-adjusted immunity, that is the equivalent of population immunity once age-specific contact patterns are taken into account.

Homogeneous mixing approximation

An assumption of homogeneous mixing is equivalent to assuming that $\phi_{ij} = \delta n_j$, that is the rate of contact of group i being with group j depends only on an overall level of contact δ and the proportion $n_j = N_j/N$ of the population that are in group j, $N = \sum N_j$ being the overall population size. This, in turn, means that the infection rate is $\beta_{ij} = \delta p_{\mathrm{inf}} n_j$ and the force of infection (Eq. 1) is independent of age group:

$$\lambda_i = \delta p_{\mathrm{inf}}\frac{I}{N} \tag{9}$$

This is equal to the force of infection in a standard 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 that case the NGM of Eq. (4) reduces to

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

with $q = p_{\text{Inf}} D_{\text{Inf}}$. This matrix has rank 1 (as all rows are equal) and its only non-zero eigenvalue is given by the trace:

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

If the proportion immune of those in age group i is r_i, the elements of $\mathbf{K}'$ are

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

and

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

where r is the proportion of the population that is immune, recovering the expression used above to define contact-adjusted immunity.

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 $c_{ij} n_i = c_{ji} n_j$ by rescaling

$$c_{ij} = \frac{1}{2} \frac{1}{n_i} \left(d_{ij} n_i + d_{ji} n_j \right) \tag{14}$$

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).

Differences in contact patterns (due to factors such as cultural difference, schooling, population density or demography) could be expected to underlie differences in the value of the basic reproduction number R_0 between countries [24]. It is unclear, though, whether such differences could be measurable in diary studies, or whether it is masked by differences in study design and data collection. Because of this, we tested two models of contact: one where the basic reproduction number R_0 is independent of the measured contact matrix, and one where it scales with the mean number of contacts (weighted by the population in each age group), such that contact-adjusted immunity becomes

$$r'_{\text{c}} = 1 - (1 - r')c \tag{15}$$

where c is a contact scale factor, calculated as the spectral radius of a given contact matrix divided by the mean of the spectral radii across countries.

Predicting outbreaks from seroprevalence data

We established population-level immunity levels from seroprevalence data and estimated contact-adjusted immunity by combining them with observed contact patterns. We used a threshold for the derived contact-adjusted immunity levels to classify countries as

being at risk of outbreaks or not. We calculated the misclassification error (MCE) as the proportion of countries that were incorrectly classified based on the given immunity threshold level and a threshold of the number of cases experienced in the 10 years following the seroprevalence study. We also calculated the Brier score, a so-called proper forecasting score, to determine the predictive ability of the seroprevalence studies when using the probability of being above the established threshold as a probability for experiencing outbreaks. The Brier score is defined as

$$\frac{1}{N}\sum_{t=1}^{N}(f_t - o_t)^2$$

where N is the number of observations (here: $N = 17$, the number of countries in which seroprevalence was established in the ESEN2 study), f_t is the probability of country t being above the contact-adjusted immunity threshold, and o_t is 1 when the number of cases in country t exceeded the threshold for outbreaks and 0 when it did not. Lower values of the Brier score indicate better predictive ability.

Computation

All computations were done with the *R* statistical computing language using the *socialmixr* and *epimixr* packages [32–34].

Results

Contact-adjusted immunity levels from serological studies

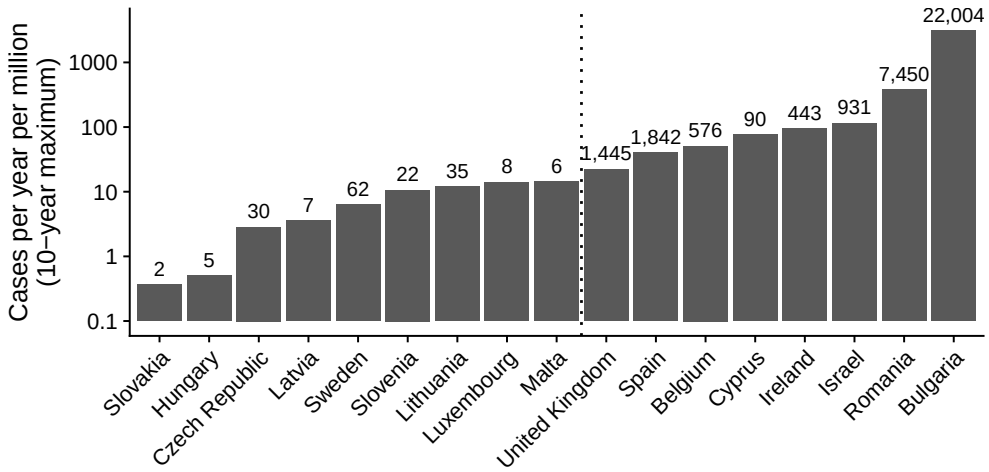

Fig 1. Maximum number of cases in a year out of the 10 years following the ESEN2 study, in cases per million inhabitants, on a logarithmic scale. Numbers at the top of the bars are the total number of cases reported in the year with most cases. The dotted vertical line indicates the threshold delineation between countries that did (right) or did not (left) experience large outbreaks when testing the ability of population-level immunity metrics to predict either.

Overall, the 17 countries that took part in the ESEN2 study reported 59,494 measles cases to WHO in the 10 years following the serological studies. The number of cases experienced by individual countries varied widely (Fig. 1 and Table 1). Slovakia, where measles was declared eliminated in 1999, only reported a total of 2 cases (both in 2004) in these 10 years. Bulgaria, on the other hand, reported over 20,000 cases, largely as part of a large outbreak in 2009/10.

Table 1. Measles cases in the 10 years following the ESEN2 serological study, and estimated population immunity (contact-adjusted or not) based on the study.

	Cases				Immunity	
Country	Total (10 years)	Maximum annual	Mean annual (per million)	Maximum annual (per million)	Contact-adjusted	Plain
Slovakia	2	2	0.037	0.37	0.95	0.96
Hungary	12	5	0.12	0.51	0.94	0.96
Czech Republic	84	30	0.8	2.8	0.97	0.98
Latvia	16	7	0.81	3.6	0.67	0.85
Sweden	210	62	2.1	6.3	0.94	0.95
Slovenia	26	22	1.3	11	0.94	0.96
Lithuania	58	35	2	12	0.86	0.94
Luxembourg	10	8	1.8	14	0.95	0.98
Malta	14	6	3.3	14	0.90	0.95
United Kingdom	6001	1445	9.3	22	0.92	0.97
Spain	3419	1842	7.4	40	0.95	0.99
Belgium	1066	576	9.4	51	0.89	0.95
Cyprus	111	90	9.5	77	0.84	0.94
Ireland	1687	443	36	94	0.88	0.92
Israel	1792	931	22	115	0.94	0.95
Romania	20570	7450	105	382	0.91	0.96
Bulgaria	24416	22004	341	3078	0.77	0.89

Contact-adjusted immunity levels estimated based on the serological profiles (taking equivocal samples to be positive) were better correlated with the case load than plain immunity levels (i.e., population-averaged immunity not taking into account age-specific contact patterns). Comparing the immunity levels with the maximum number of cases per million in the 10-year period yielded negative correlation of 0.42 (Spearman's rank correlation, 90% credible interval (CI) 0.27–0.53, $p = 0.12$) for contact-adjusted immunity and 0.23 (90% CI 0.17–0.29, $p = 0.37$) for plain immunity. Notable outliers in the correlation between immunity levels and case load were Latvia (contact-adjusted immunity 67%, plain 85%, 16 cases over 10 years), Lithuania (contact-adjusted immunity 86%, plain 94%, 58 cases) in one direction, and Spain (contact-adjusted immunity 95%, plain 99%, > 3000 cases) and Israel (contact-adjusted immunity 94%, plain 95%, > 1500 cases) in the other. Excluding equivocal samples gave similar correlation levels (contact-adjusted: 0.39, 90% CI 0.34–0.44; plain: 0.22, 90% CI 0.20–0.24) while interpreting them as negative reduced them (contact-adjusted: 0.18, 90% CI 0.12–0.24; plain: 0.09, 90% CI 0.07–0.11). For the remaining analyses, we chose to contact-adjusted immunity and interpreted equivocal samples as positive.

To test the predictive ability of estimated seroprevalence levels in combination with age-specific mixing we split the countries into those that experienced large outbreaks in the 10 years following the serological studies and those that did not. We set the threshold at a maximum annual cases of 20 per million or, equivalently, an average of 5

per million (see dashed line in Fig. 1). We then tested different threshold immunity levels (ranging from 80% to 99%, in increments of 1%) and classified countries as being at risk of outbreaks or not based on whether their estimated immunity levels fell below the threshold or not.

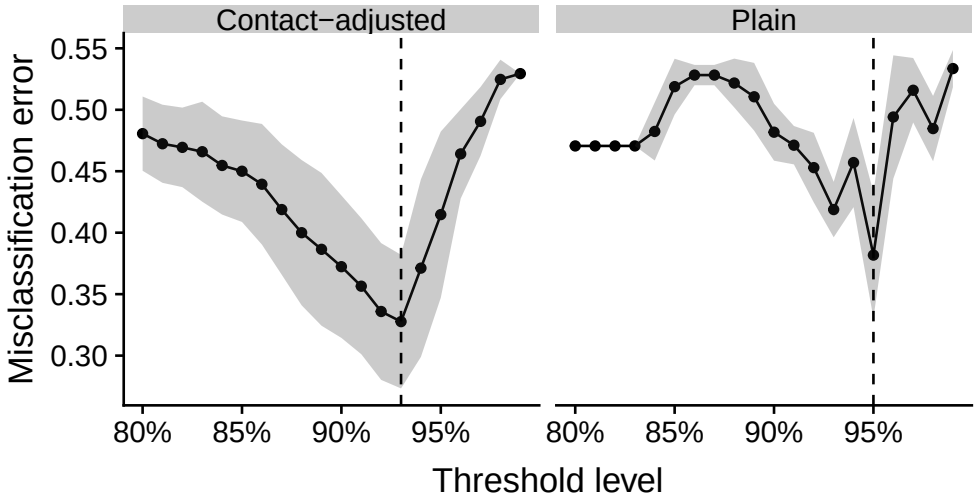

Fig 2. Misclassification error (MCE) as a function of the threshold level of for contact-adjusted or plain immunity. Dots give the mean MCE at the tested threshold levels, connected by a line to guide the eye. The grey shades indicate a standard deviation around the mean (uncertainty coming from both the serological sample and from the contact sample). Dashed vertical lines indicate the location of minimal MCE.

The threshold of contact-adjusted immunity yielding best predictions was 93%, in which case about two-thirds of countries were correctly classified (Fig. 2). With plain immunity this level is at 95%, the corresponding MCE is greater than with contact-adjusted immunity. More generally, the behaviour of the MCE as a function of threshold level was more erratic when considering plain instead of contact-adjusted immunity. The Brier score as another measure of predictive ability was also optimised at a threshold of 93% for contact-adjusted immunity (Brier score: 0.28) and 95% for plain immunity (Brier score: 0.34).

Scenarios

We investigated contact-adjusted immunity 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) in the settings for which we had access to contact studies (17 countries and Hong Kong, Fig. 3A). Again, we assumed no scaling of R_0 with the overall level of contact. We used the identified threshold level of 93% as an indicator of being at risk of outbreaks. In this scenario, 5 out of 18 settings had greater than 10% probability of adjusted immunity levels lower than the 93% level found to best identify countries at risk of outbreaks: Taiwan (probability 95%), The Netherlands (90%), Peru (68%), Uganda (63%) and the United Kingdom (40%).

With alternative scenarios, the reproduction numbers changed (Fig. 3B–E). Raising immunity in under-5-year olds by 5% to 90% would increase adjusted immunity levels only slightly, with 4 out of the 5 countries (exception: Uganda) at risk under current target immunity levels still at greater than 20% risk. On the other hand, raising

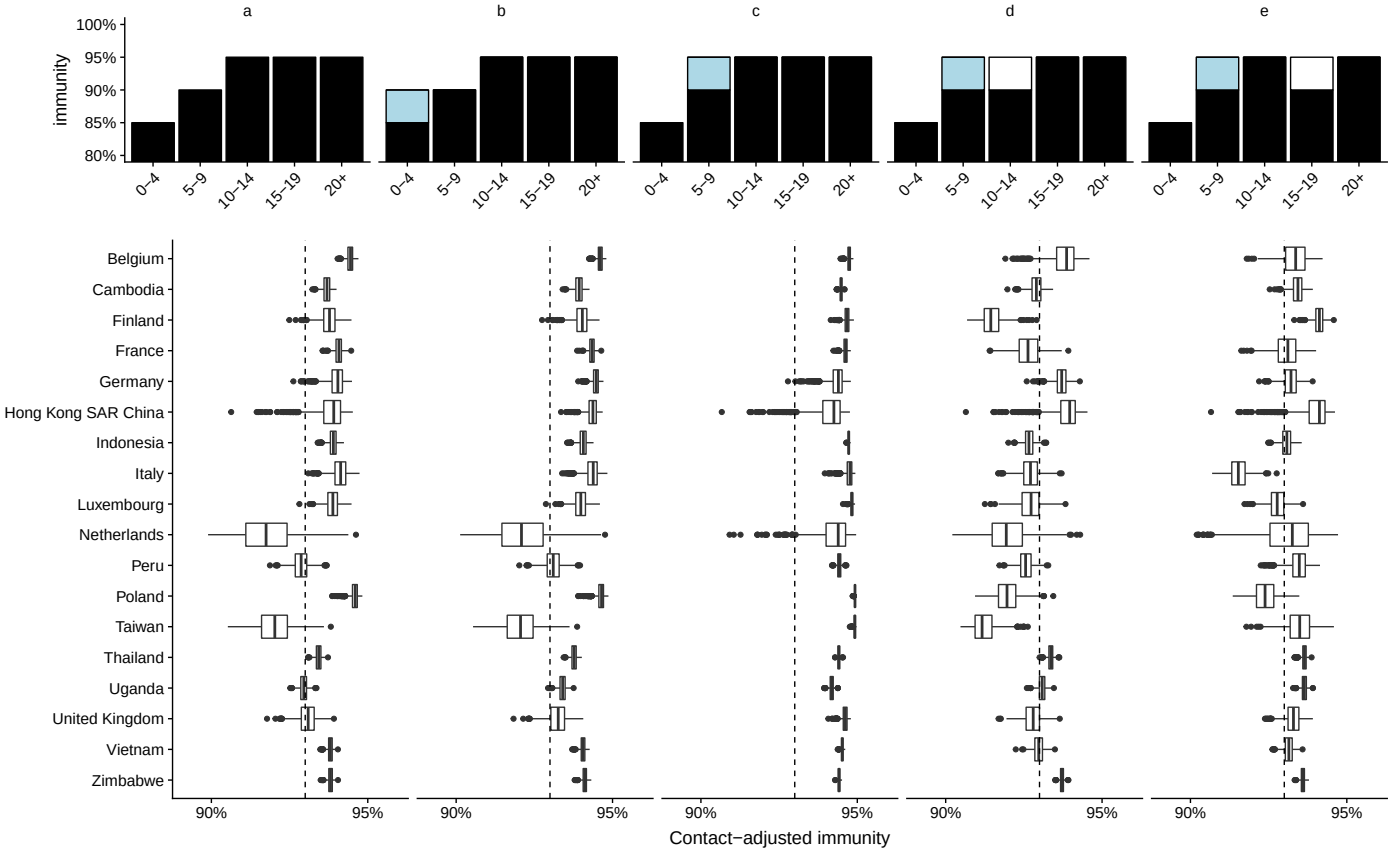

Fig 3. Contact-adjusted immunity in different theoretical scenarios, with age-specific mixing as measured in diary studies. Each column represents one of the scenarios of age-specific immunity (top), with differences between the settings given by their different mixing patterns. Scenarios from left to 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.

immunity in 5-to-9-year olds by 5% to 95% would sharply increase contact-adjusted immunity. In this scenario, all countries would have 5% or less probability of being at risk of outbreaks, with 16 out of 18 at less than 1% risk (exceptions: Hong Kong 5%, Netherlands 3%).

In scenarios immunity in 5-to-9 year olds was raised but a gap in immunity was introduced in older generations contact-adjusted immunity dropped below the threshold level of 93% in some settings. A scenario of reduced immunity in 10-to-14-year olds by 5% to 90% while retaining higher immunity in younger age groups resulted in elevated risks of outbreaks in 13 out of 18 countries. A scenario of reduced immunity in 14-to-19 year olds by 5% to 90% while retaining higher immunity in younger age groups resulted in elevated risks of outbreaks in 11 out of 18 countries.

Discussion

Taking into account age-specific mixing patterns and applying these to immunity levels observed across Europe, we were better able to predict outbreaks than by considering

immunity alone. This improvement was not large enough to be considered certain or statistically significant given the relatively small sample size. Yet, combined with previous evidence that observed age-specific mixing improve the accuracy of mathematical models, we believe that there is a strong case for taking these into account when interpreting the results of serological studies [18–20].

A threshold of 93% contact-adjusted immunity was found to be the best predictor of outbreaks in the subsequent decade, with approximately two-thirds of countries correctly assessed to either be facing large outbreaks or not. In the absence of any more detailed information on setting-specific basic reproduction numbers, however, such a threshold will only ever be an approximation. On the other hand, setting-specific parameters are difficult to establish, are subject to method-specific biases and can span a wide range of values [24, 35].

In principle, country-specific reproduction numbers would, to some degree, depend on the frequency and types of contact within the population and should therefore be amenable to measurement in contact studies such as the ones used here. However, scaling estimated susceptibility levels with the relative number of contacts reported in each study gave results almost identical to the simpler version not using such scaling. These results indicate that differences in survey methodology mask any such difference in contacts that would be reflected in the value of R_0. We argue that aiming to achieve 93% or greater contact-adjusted immunity in a population is a pragmatic choice that can be informed by measurable quantities, that is age-specific immunity levels and mixing patterns.

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 settings to assess whether these guidelines are sufficient for achieving measles elimination. We investigated a range of settings 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 (Vietnam) or less (Taiwan) recently undergone the demographic transition to low birth rates, or characterised by a high birth rate and young population (Uganda).

With observed mixing patterns, several settings were found to be at risk of outbreaks even if they achieved previously recommended target immunity levels, including ones with very different demographic profiles. Achieving 95% immunity in 5-to-9 year olds, on the other hand, would reduce transmission sufficiently to achieve elimination in all except the most extreme scenarios.

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. [36, 37] 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. [38] 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. [39] Where there were less stringent vaccination requirements at school entry, more case of

measles were observed. [40] Analyses of pre-elimination measles outbreaks in the US indicated that transmission occurred among highly vaccinated school-aged populations, suggesting that higher population immunity levels are needed among school-aged children compared to preschool-aged children. [41] It has been proposed 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. [42]

While our results stress the role of 5-to-9 year olds, they also highlight the importance of not having 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. [43] 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. [44]

Our study has several limitations. The delineation of countries into having experienced outbreaks or not is somewhat arbitrary, if in agreement with a milestone towards measles eradication established by the World Health Assembly [45]. Depending on the local situation with respect to measles elimination, a country may decide to apply less or more stringent immunity thresholds. Moreover, 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 levels of coverage are insufficient.

Lastly, the contact-adjusted immunity levels we estimated from serological studies did not always correctly predict where outbreaks could be expected. On the one hand, Latvia and Lithuania did not experience large numbers of cases in spite of low levels of contact-adjusted immunity. 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.

Israel and Spain, on the other hand, experienced large numbers in spite of high levels of contact-adjusted immunity. Two 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, serology based on residual and population-based samples may not always be representative of relevant immunity levels. In Spain, a disproportionate number of cases occurred in young adults [46], 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. [47]

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. [49, 50] 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. [51] Combined with observations of contact patterns, these would serve to highlight key gaps in immunity that need to be filled in order to achieve national and regional elimination and, ultimately, global eradication of measles.

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