Author’s response to reviews

Title: Combining serological and contact data to derive target immunity levels for achieving and maintaining measles elimination

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Author’s response to reviews:

We thank the Editor and both Reviewers for their suggestions to improve this manuscript.

Reviewer 1

Major comments

Point raised: "1. Is there any supporting evidence to the claim that the age-specific immunity thresholds developed in the late 1990s for Europe are "widely applied within and occasionally outside Europe" (page 2, line 22)? I wonder if the authors have set up a false "straw man" and that these immunity thresholds are not as widely used as claimed. They are not
included in the WHO position paper on measles vaccines. Are there countries that explicitly aim to have only at least 85% immunity to measles virus among children 1-4 years of age?"

Reply: We now cite 9 studies (from Croatia, Romania, Spain, Belgium, Germany, Belgium, The Netherlands, UK and Czech Republic) which explicitly reference the previous immunity targets and assess progress towards elimination against them. Moreover, the original ESEN2 measles paper (17 European countries and Australia) compares the serological profiles to these targets. The referenced studies include authors from national institutes of health, indicating that the targets are part of the toolkit for assessing progress towards elimination.

Point raised: "2. It is unclear to me why the authors thought it reasonable to predict the probability measles outbreaks for a 10-year period based on seroprevalence data without accounting for changes in age-specific population immunity following changes in vaccination coverage, conduct of vaccination campaigns, or wild-type measles virus transmission over that period? This is obliquely addressed in the discussion section for countries where the model predictions were inconsistent with the data but could be explicitly addressed earlier in the manuscript."

Reply: We initially decided not to adjust immunity levels for vaccination for simplicity as this requires a model for how vaccination rates and reported cases translate into population-level immunity (including vaccine efficacy, maternal immunity, how likely different doses of vaccine are given to those already immune, proportion of cases reported etc.) as well as accurate vaccination uptake figures. However, in response to the comment, we conducted some initial analysis attempting to account for vaccination coverage (assuming that wild-type measles only causes a small portion of immunity) and found that this leads to better predictions of elimination status than using seroprevalence data alone. The additional results are reflected in the Methods and Results sections, and Tables 1 and 2. The new text reads:

(Methods: Vaccination model: projected vs. ignored)

Seroprevalence studies only provide a single, cross-sectional snapshot of immunity in a population. Following such a study, vaccination uptake, natural immunity and ageing combine to change the age-specific immunity levels. We compared a model where vaccination was ignored and the measured seroprevalence taken as fixed over the 10-year time period to one where we used an average of projected immunity levels, which were updated using information on vaccination uptake in the years following the seroprevalence study.

In principle, updating immunity levels with measured vaccination coverage and wild-type measles circulation should improve estimates of population-level immunity. In practice, this relies on accurate measurements of both vaccination coverage and case numbers as well as modelling decisions on assumed vaccine efficacy, maternal immunity and distribution of
multiple doses (e.g., randomly vs. preferentially to children that have already received a dose), which could mask any gains made from having up-to-date immunity estimates.

Here, we focused on added immunity due to vaccination and assumed that the added immunity due to wild-type measles circulation was negligible. Serological samples from under-1 year olds were only available from 7 of the 17 countries in the ESEN2 study, and the number of samples from each country too small to produce good estimates (676 samples in total), we combined all these samples to produce an overall estimate of maternal immunity of approximately 40% amongst under-1-year olds. We assumed that immunity in the age group that contained the scheduled age of the first dose of measles was given by a country-specific scaling factor multiplied with the reported coverage in that year. This factor would reflect the proportion of children in that age group immunised at any point in time, as a fraction of the ones immunised by the time of departure from the age group. The factor was estimated by comparing the observed seroprevalence with the level of overage reported in that year. For any subsequent doses, we assumed that the vaccine was preferentially given to those that had received a previous dose or doses of the vaccine, as could be estimated from the reported coverage at the time children in that cohort would have been eligible for the previous dose(s). We assumed a vaccine efficacy per dose of 95%. [32]

(Results: Contact-adjusted immunity levels from serological studies)

Comparing the immunity levels with the mean number of annual measles cases in the 10-year period yielded the expected negative correlation with most models (Table 2). Contact-adjusted immunity levels estimated based on the serological profiles were better correlated with the case load than plain immunity levels. Further, interpreting equivocal samples as positive yielded the best correlation, but scaling R0 according to measured contacts did not improve correlations compared to using a fixed R0.

Projecting national vaccination uptake in the years following the serological surveys onto the observed immunity levels yielded better correlations than just using the snapshots of seroprevalence. For the remaining analyses, we therefore used a fixed $R_0$, interpreted equivocal samples as positive and corrected immunity levels with vaccination uptake.

Point raised: "3. I think the authors should more clearly differentiate population immunity and vaccination coverage for the general reader. For example, the second paragraph of the background (page 2, lines 8-14) moves between descriptions of population immunity and references to vaccine coverage, without explicitly stating the levels of vaccine coverage that would be necessary to achieve these levels of population immunity."
Control of measles is achieved through vaccination in early childhood, and the vaccine is part of routine immunisation schedules worldwide. In principle, a functioning health system would aim to vaccinate every child. In practice 100% coverage with all recommended doses is never achieved. Moreover, not every administration of a vaccine confers immunity, and protection from a vaccine can wane over time. However, even if not everyone in a population is immune, the indirect protection provided by the presence of immune individuals can be sufficient to prevent outbreaks. [5] For measles, it has been shown that in a randomly mixing population the level of immunity required to achieve this so-called \"herd immunity\" is in the order of 90-95%. [6]

Knowledge of the level of immunity required in a population to achieve herd immunity can be used to set national vaccination targets. However, even if current levels of vaccination are high enough to achieve the level of immunisation required for herd immunity, outbreaks can occur if there are immunity gaps in older age groups.) 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 in order to achieve elimination. [7] These profiles are widely applied within and occasionally outside Europe to assess progress towards elimination. [8, 9, 10, 11, 12, 13, 14, 15, 16] 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. [17] Unlike vaccination coverage targets, immunity targets reflect the effect of susceptibility in all age groups and highlight the potential need for campaigns to close any gaps in immunity.

Point raised: "4. Another complicating factor, not included in these models, is the impact of spatial clustering on the critical vaccination threshold."

Reply: We have amended the section in the discussion referencing spatial clustering to emphasise the effect on the critical vaccination threshold: Moreover, if those lacking immunity are preferentially in contact with each other because they cluster socially or geographically, outbreaks could occur in these groups, 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. [52] More generally, herd immunity thresholds have been shown to increase if non-vaccination is clustered. [53].

Minor comments

Point raised: "1. I suggest the authors use "measles virus" rather than "measles" when referring to what is transmitted, e.g. line 16 in the abstract."
Reply: Done.

Point raised: "2. I suggest the results section of the abstract include reference to the findings in 5-9 year old children. This is mentioned in the abstract conclusions but not in the results."
Reply: We amended the Results section in the abstract as follows:
Testing different scenarios of immunity with this threshold level using contact studies from around the world, we found that 95% immunity would have to be achieved by the age of five and maintained across older age groups to guarantee elimination. This reflects a greater level of immunity required in 5-9 year olds than established previously.

Point raised: "3. Page 2, line 3: measles vaccine was introduced in the early 1960s, e.g. in 1963 in the United States."
Reply: Corrected.

Point raised: "4. Page 3, line 3: suggest deleting "around" and changing to "countries in the late 1990s and early 2000s"
Reply: Done.

Point raised: "5. Page 3, line 35: I think it would be helpful to the general reader, who is familiar with the common definition of the basic reproduction number, to briefly explain the
The basic reproduction number $R_0$ is defined as the mean number of new cases generated by a single infectious individual in a completely susceptible population. In a system with multiple host types (here: age groups), it can be calculated as the spectral radius (or largest eigenvalue) of the next-generation matrix (NGM) $K$ [30].

Reviewer 2

Point raised: "Page 2, lines 11-13 "Strictly speaking...": I may agree with your sentence although I'm not entirely sure that I understand where it comes from. Please, explain and justify this assertion."

Reply: We have removed this sentence and rewritten the paragraph, which now reads:

Knowledge of the level of immunity required in a population to achieve herd immunity can be used to set national vaccination targets. However, even if current levels of vaccination are high
enough to achieve the level of immunisation required for herd immunity, outbreaks can occur if there are immunity gaps in older age groups. 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.

Point raised: "Page 2, line 29 "because of population migration": I agree, but I suggest that you discuss the importance of migration as a potential limitation to the methodology and/or an explication for the discrepancies. That may participate to the fact that highly vaccinated countries still have outbreaks."

Reply: We added a sentence to the discussion as suggested, but refrained from speculating on migration as an underlying factor for outbreaks in Israel and Spain, as we did not find any evidence that migration played a significant role in these outbreaks. This now reads:

For example, immunity may be high just after a major outbreak but such outbreaks could occur again if coverage is sub-optimal. In addition, population migration can change immunity levels in a way that is not captured by vaccination coverage figures. 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.

Point raised: "One of the disputable aspect is the relationship between immunity levels and case load. In absence of better approach in the literature and/or standard one, it has the merit of existing and of efficiency. However, a discussion about the numerous co-factors that could have influenced the relationship between immunity levels and case load -thus the difficulty to explore it- would be useful."

Reply: We have added the following text to the discussion:

Lastly, we assumed that immunity levels and contact patterns alone are sufficient to predict the expected case load. In reality, numerous co-factors such as sub-national heterogeneity or contact patterns that are not captured in age-specific contact matrices (e.g., household and schooling structures) could have influenced this relationship.

Point raised: "Page 3, line 31: an susceptible or a susceptible?"

Point raised: "Page 6, line 16: n=100 for a bootstrap seems a small number. Has the exploration of the validity of the chosen number of bootstrap shown consistency across countries?"

Reply: We have increased this to n=1000.

Point raised: "Page 6, line 45: "with most models 2." What is "2.""

Reply: Removed.

Point raised: "Page 7, line 7: "...had correlation of was": A bit heavy formulation"

Reply: Corrected.

Point raised: "Page 7, line 24: Two thirds of correctly classified countries is low, which requires discussion on the validity of the methods."

Reply: This is now 70%, taking into account vaccination uptake. We have amended the Discussion to reflect that classification is not perfect:

We therefore argue that while the achieved 70% of accuracy in predicting outbreaks is far from perfect, 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.

Point raised: "Page 10, lines 30 and further. I suggest to emphasize how taking into account heterogeneity is crucial. Open question: What about, in order to take into account heterogeneity, to apply a similar method, but at a lower level such as municipalities or counties? Data are available."

Reply: We have added the following to the final paragraph in the Discussion:

"These examples highlight that taking into account heterogeneity is crucial. Our method can be applied to lower levels than countries, such as municipalities or counties.

Point raised: "In order to facilitate the generalization of the method, I suggest to make both the data and the R code available."

Reply: This is now available at https://github.com/sbfnk/immunity.thresholds