Measles immunity gaps and the progress towards elimination: a multi-country modelling analysis

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Summary

Background The persistent circulation of measles in both low-income and high-income countries requires a better characterisation of present epidemiological trends and existing immunity gaps across different sociodemographic settings. Serological surveys, which provide direct measures of population protection against the infection, are underexploited and often supply fragmentary estimates of population immunity. This study aims to investigate how measles immunity has changed over time across different socioeconomic settings, as a result of demographic changes and past immunisation policies.

Methods For this multi-country modelling analysis, we developed a transmission model to simulate measles circulation during the past 65 years in nine countries with distinct demographic and vaccination histories. The model was calibrated on historical serological data and used to estimate the reduction of disease burden as a result of vaccination and present age-specific residual susceptibility.

Findings Our model shows that estimated residual susceptibility to measles ranges from 3% in the UK to more than 10% in Kenya and Ethiopia. In high-income countries, such as Italy, Singapore, and South Korea, where routine first-dose administration produced more than 90% of immunised individuals, only about 20% of susceptible individuals are younger than 5 years. We also observed that the reduction in fertility that has occurred during the past decades in high-income countries has contributed to almost half of the reduction in measles incidence. In low-income countries, where fertility is high, the population is younger and routine vaccination has been suboptimum. Susceptible individuals are concentrated in early childhood, with about 60% of susceptible individuals in Ethiopia younger than 10 years. In these countries, Supplementary Immunization Activities (SIAs) were responsible for more than 25% of immunised individuals (up to 45% in Ethiopia), mitigating the consequences of suboptimum routine vaccination coverage.

Interpretation Future vaccination strategies in high-fertility countries should focus on increasing childhood immunisation rates, either by raising first-dose coverage or by making erratic SIAs more frequent and regular. Immunisation campaigns targeting adolescents and adults are required in low-fertility countries, where the susceptibility in these age groups will otherwise sustain measles circulation.

Funding European Research Council.

Lancet Infect Dis 2017

Published Online
August 11, 2017
http://dx.doi.org/10.1016/S1473-3099(17)30421-8

See Online/Comment
http://dx.doi.org/10.1016/S1473-3099(17)30451-6

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Introduction

Despite more than 50 years of immunisation efforts, measles is still one of the major causes of death due to a vaccine-preventable disease in children younger than 5 years.[1] The WHO Expanded Program on Immunization and Supplementary Immunization Activities, and the Measles & Rubella Initiative have contributed to the reduction in the burden of disease in terms of incidence and mortality.[2] However, regular measles epidemics are reported in several African countries, where infant mortality due to measles infection is high,[3] and episodic outbreaks continue to occur in countries in the European Union and European Economic Area[4] as well as in the Americas,[5] where local elimination was declared in September, 2016.[6] The maintenance of high vaccine uptake is questioned, even in most high-income countries, as a consequence of antivaccination movements arising from a now completely discredited claim of a link between the measles, mumps, and rubella (MMR) vaccine and autism.[7] The persistent circulation of measles in low-to-middle-income countries[8] and the partly unexpected re-emergence of measles epidemics in most industrialised regions[4,5,9,10] highlight the need for an improved understanding of present epidemiological trends across different sociodemographic settings.

Serological surveys represent ideal studies to directly estimate the levels of population protection against a particular infection, providing crucial information to design optimum vaccination strategies.[11] However, serological surveys are extremely underexploited, being resource intensive to perform and embedded with complexities and logistical challenges.[11] Their limited use makes estimates of the population immunity often fragmentary and, in some circumstances, representative of outdated epidemiological conditions. Insights on the changes of the population serological profile over time are even more infrequent and are generally provided only shortly after massive vaccination campaigns. In fact, routine epidemiological surveillance mainly reports on clinically apparent cases of infection, whereas levels of

Research in context

Evidence before this study

We searched PubMed for manuscripts published in English between database inception and April 7, 2017, containing the following terms: "birth", "demographic transition", "demographic changes", "measles", "vaccination", "immunization", and "model". We identified several studies that analysed transitions in the dynamics of many childhood diseases (including measles) caused by seasonal fluctuations in the transmission rate and changes in birth and vaccination rates. Most articles show that complex epidemiological patterns can emerge as a consequence of spatiotemporal variations in the population size and fertility, which can drive the onset of multistable and chaotic dynamics and result in transitions between regular cycles and highly episodic epidemics. We found only one study where a non-stationary, age-structured transmission model is proposed to investigate long-term measles epidemiological transitions over time. This study shows that the reduction in fertility that occurred during the prevaccination era in Italy has resulted in a remarkable decreasing trend of measles incidence. The role played by demographic changes is also confirmed by a statistical analysis showing that an increase in livebirths possibly caused the resurgence of measles in the USA in the 1990s. Finally, a catalytic model calibrated on measles incidence in six provinces in China was published in April, 2017, showing that improved vaccination and decreasing birth rates have shifted the age distribution of measles susceptibility and that regional differences are present in the impact of vaccination and the progress towards measles elimination. Country-specific demographics, developmental status, and historical vaccine coverage rates were all suggested as determinants of the heterogeneity in measles circulation across different geographical areas. However, no attempts have been made to characterise measles susceptibility and immunity profiles across different socioeconomic settings or to assess whether present vaccination strategies are suitable to fill immunity gaps that characterise countries with distinct epidemiological and demographic conditions.

Added value of this study

Routine epidemiological surveillance mainly reports on clinically apparent cases of infection, and the population's susceptibility and immunity represent hidden variables of the dynamics of infection. Serological surveys, providing the most direct estimate of the population protection against the infection, are extremely resource intensive to perform, making estimates of the population immunity often fragmentary and reflecting—in some circumstances—outdated epidemiological conditions. The novelty of this study lies in the ability to identify necessary requirements to achieve measles elimination across different socioeconomic settings by estimating the present age-specific immunity profiles in nine countries with distinct demographic and vaccination history, and by disentangling the contributions of different immunisation programmes and long-term demographic processes in shaping the age segments more at risk for future epidemics.

Implications of all the available evidence

The performed analysis suggests that a change of present measles control strategies is required. Particularly, our results show that first-dose programmes should be optimised in low-income countries, characterised by a fast generational replacement. In more developed areas, where fertility rates are lower, catch-up campaigns targeting adolescents are instead essential to achieve measles elimination.

population susceptibility and immunity remain unknown variables of the underlying process of infection.

The serological profile of a population reflects the results of past vaccination campaigns and the immunity acquired by individuals of different ages through natural infection. Recent studies[3,12–15] have also highlighted the contribution of demographic processes in shaping the circulation of childhood infections. The aim of this study is to use a model-based approach to better characterise the residual measles susceptibility across different sociodemographic settings and to investigate how measles immunity has changed over time. Our analysis allows the contribution of different immunisation programmes, disease transmissibility, and long-term demographic processes in shaping the serological profile of a population to be disentangled, and the identification of the age segments more at risk for future measles epidemics.

Measles epidemiology varies widely across countries, and so do vaccination programmes currently in place.[16] The proposed study includes nine countries that are representative of regions at different stages of the demographic transition and characterised by remarkably different vaccination histories against measles:[2,16–18] Australia, Ethiopia, Kenya, Ireland, Italy, South Korea, Singapore, the UK, and the USA. The adopted multi-country perspective gives substantial insights into the adequacy of present vaccination programmes in filling the existing immunity gaps on the basis of local demographic and epidemiological patterns.

Methods

Model structure

For this multi-country modelling analysis, we obtained simulations of the demographic dynamics characterising each country by initialising the model with a population reflecting the age structure and population size recorded in each country during 1950 and by running the model for 65 consecutive years. We simulated changes in local demographic conditions at the country level using longitudinal data on variations of fertility, mortality, and migration rates as reported by the UN World Population

Prospects.[19] We validated demographic trends estimated across countries against the age distributions of the population recorded at different years and the reported variations in the overall number of individuals.

We simulated measles transmission dynamics using a compartmental deterministic model structured in 85 1-year age classes. We assumed that maternal antibodies protect newborn individuals against measles infection for 6 months on average,[8] after which they become susceptible and can get infected upon contact with infectious individuals under the assumption of homogeneous mixing. Measles generation time was set to 14 days on average.[12] Once an individual has recovered from natural infection, they gain permanent immunity against measles reinfection. Country-specific routine first and second dose programmes and nationwide Supplementary Immunization Activities (SIAs) were simulated by mimicking schedule and coverage data as reported by international organizations,[20] complemented with national administrative records and published studies.[21,22] Immunisation activities done at a country level are summarised in the table. We assumed that only a fraction of vaccinated individuals develop immunity against measles virus infection and that for these individuals the vaccine-derived protection is lifelong. Vaccine efficacy is assumed to be 85% when the vaccine is administered to individuals younger than 14 months, and 95% otherwise.[23] Only individuals who have been previously vaccinated with a first dose are deemed eligible for a second dose, whereas all individuals can be vaccinated during an SIA (appendix pp 2–3).

	Age at first dose	Age at second dose	Years of Supplementary Immunization Activities
Australia	12 months	4 years	1998
Ethiopia	9 months	..	2005, 2006, 2008, 2010
Ireland	12 months	4 years	1995, 2009, 2013
Italy	18 months	5 years	2005
Kenya	9 months	..	2003, 2006, 2009, 2012
South Korea	12 months	4 years	2001
Singapore	12 months	18 months*	..
UK	12 months	5 years	1994, 2013
USA	15 months	5 years	..

*Second dose was initially administered at 11 years of age, and progressively moved at 6 years of age in 2007 and at 18 months in 2011.

***Table*: Immunisation activities performed at a country level**

Model calibration and validation

The transmission model was calibrated separately for each country, using available age-specific serological profiles. Free model parameters are represented by a country-specific measles transmission rate and a parameter used to adjust for the uncertainty on coverage levels associated with different SIAs when present[18,24] and their effectiveness in reducing the population susceptibility. A formal model evaluation based on the deviance information criterion shows that the inclusion of this latter parameter improves the model's capability of reproducing the observed serological profiles (appendix p 16). The demographic and transmission model was initialised according to the population age structure in 1950. The initial number of susceptible, infected, and immune individuals reflected the corresponding fraction associated with the equilibrium solution obtained with a specific transmission rate in the absence of vaccination. We calculated the equilibrium solution by running the transmission model with constant fertility and with mortality rates fixed to those recorded in 1950, and by initialising the system with ten infected individuals in a fully susceptible population. We obtained simulations of measles dynamics from 1950 to 2015 by running the model with time varying crude birth, net migration, and age-specific mortality rates, and by mimicking vaccination programmes implemented during the considered period.

We estimated the posterior distributions of the free model parameters using a Markov chain Monte Carlo approach with random walk Metropolis-Hastings sampling[12] applied to the binomial likelihood of the observed country-specific measles serological profiles (appendix pp 11–16).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

See Online for appendix

Results

Observed historical trends confirm that the analysed countries reflect different stages of the demographic transition[17] (ie, changes in the population age structure due to the reduction of fertility and death rates, which characterise regions developing from a preindustrial to an industrialised economic system). In particular, countries such as Italy, South Korea, and Singapore had a marked progressive ageing of the population during the past 65 years. By contrast, countries like Kenya and Ethiopia exhibit a persisting young population, although a decrease in the percentage of preschool children during the past 20 years is detectable.

The model was capable of reproducing the observed serological patterns for all countries (figure 1). The estimated measles incidence over time was found to be significantly correlated with WHO records of measles cases between 1974 and 2015 across the nine analysed countries (appendix pp 17–18).[20] The goodness of fit is discussed in the appendix (p 16).

Mean estimates of the transmission rate, ranging from 0·39 per day in Kenya to 2·01 per day in the UK, show substantial differences in disease transmissibility across countries, possibly reflecting heterogeneities of

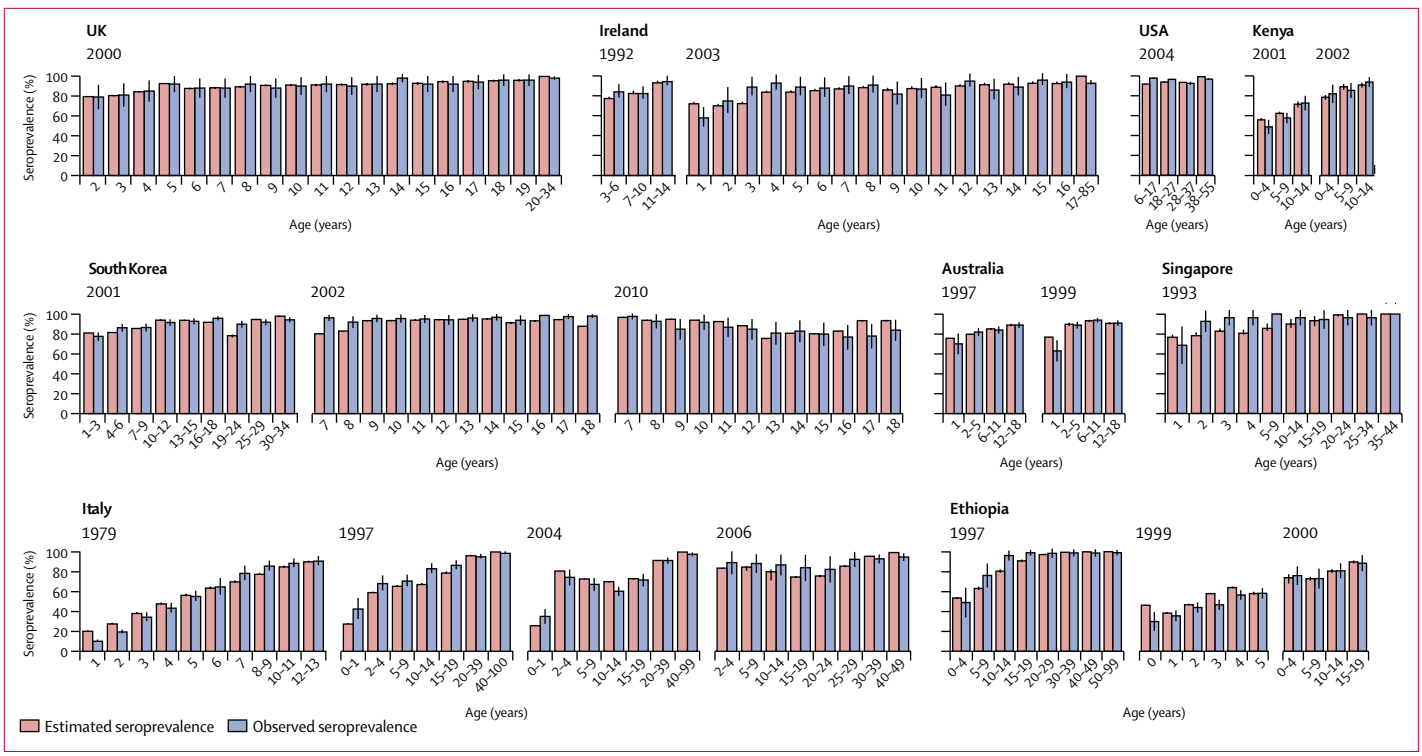

Figure 1: **Model calibration**
Observed age-specific serological profiles and model estimates in different countries. Vertical lines represent 95% credible intervals associated with data records and model estimates.

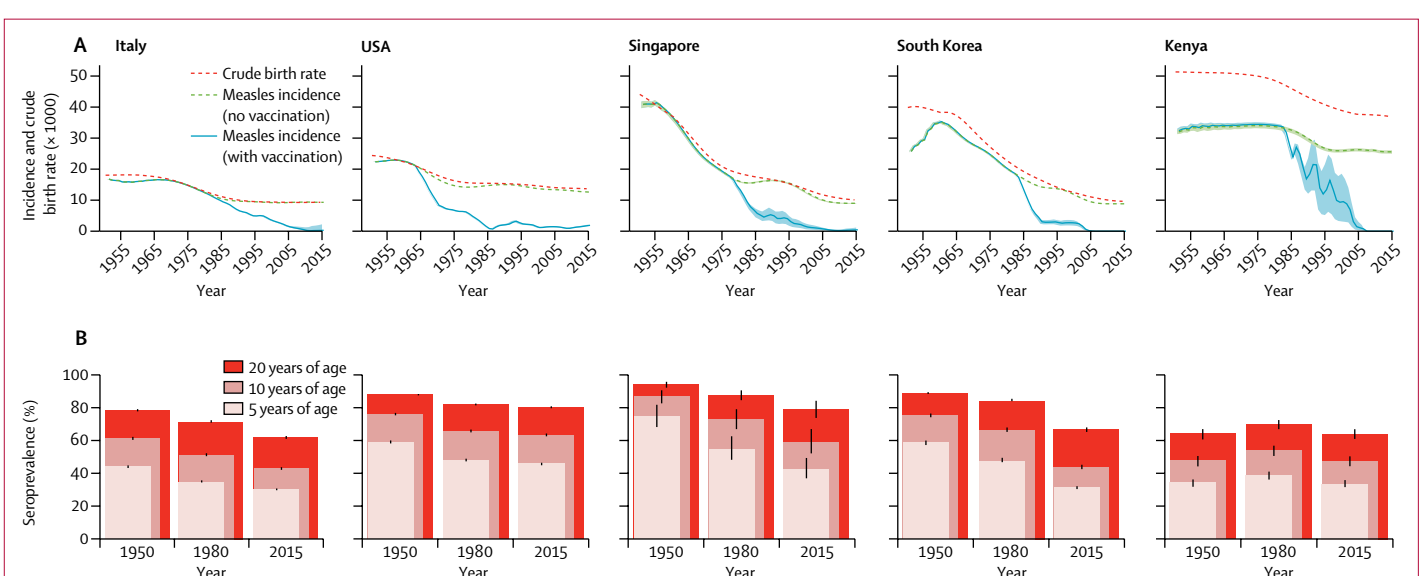

Figure 2: **Temporal trends in measles circulation**
(A) Model estimates of yearly measles incidence per 1000 individuals over time, averaged over a moving window of 7 years, as obtained with and without vaccination, shown along with the reported crude birth rate. Shaded areas represent 95% credible intervals associated with model estimates. (B) The effect of demographic processes on measles epidemiology. Barplots show the simulated average measles seroprevalence in the absence of vaccination among individuals at 5, 10, and 20 years of age for 1950, 1980, and 2015. Vertical bars show 95% credible intervals.

social mixing patterns in the different regions. This hypothesis is supported by the significant positive Pearson correlations between the average estimates of country-specific transmission rates and the percentage of children attending primary school, the percentage of urbanised area, and gross domestic product. We did correlation tests separately for each sociodemographic indicator (appendix p 21). The coverage adjusting factor was found, on average, to be lower than 20% in the UK and Ireland, and between 75% and 90% in other countries. Uncertainty surrounding parameter estimates is discussed in the appendix (pp 14–16).

The progressive intensification of immunisation efforts performed by different public health systems has substantially reduced measles incidences with respect to prevaccination levels (figure 2): by roughly 90% in Italy, the USA, the UK, Ireland, and Singapore, and by more than 95% in the remaining countries. However, the reduction in fertility that has occurred between 1950 and 2015 in high-income countries has contributed to almost half of the reduction in measles incidence recorded after the introduction of vaccination. This result was obtained by simulating an illustrative scenario wherein, in the absence of vaccination, the epidemiological transitions were only determined by demographic changes. We found that an increase in fertility rates produces a rise in the fraction of susceptible individuals in the host population, increasing measles circulation and decreasing the median age at infection. This conclusion is supported by the high correlation between the crude birth rate and the estimated measles incidence without vaccination over time (figure 2). The changes in measles epidemiology are more pronounced in regions characterised by a faster demographic transition, such as Singapore and South Korea, and less evident in those populations with a more stable age-structure, as is the case for Kenya (figure 2). Using long-term Italian incidence data, we validated empirically the estimated contribution of demographic trends in shaping measles circulation (appendix pp 23–24). A significant positive correlation was found between measles incidence and crude birth rate from 1926 and 2010 in Italy (appendix pp 23–24).

The reduction of the measles burden of disease as a result of vaccination was quantified by combining longitudinal estimates of measles incidence (with and without vaccination) with longitudinal rates of measles age-specific disability-adjusted life-years (DALYs), as estimated for different economic settings (appendix p 30).[25] DALYs represent a measure of the overall disease burden, expressed as the number of years lost caused by illness, disability, or early death. We found that, up to 2015, the cumulative DALYs averted in the analysed countries range from 120 000 years to more than ten million years in Kenya and Ethiopia (figure 3). DALYs averted per dose of vaccine were more than six times higher in the African countries analysed, where measles

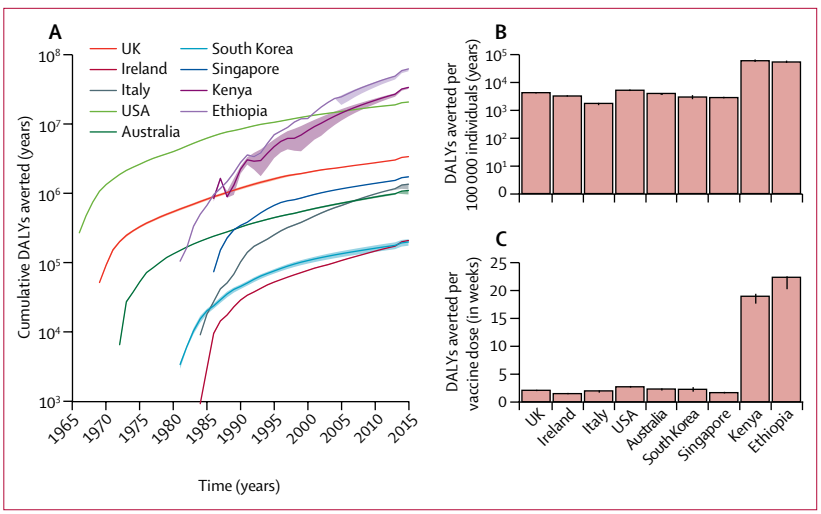

Figure 3: **Estimated DALYs averted through vaccination**
(A) Model estimates of the cumulative number of DALYs, expressed in years, averted through vaccination across different countries over time. Shaded areas represent 95% credible intervals. (B) Cumulative DALYs averted (in years) since the introduction of vaccination to 2015, normalised for each country by the overall population size in 2015. (C) Cumulative DALYs averted (in weeks) per vaccine dose since the introduction of vaccination to 2015. DALYs=disability-adjusted life-years.

mortality has been highest, than in the other analysed countries.

We disentangled the relative contribution of different activities in reducing measles susceptibility for the nine analysed countries (figure 4).

According to our results, routine universal administration of a first dose of measles vaccine accounts for more than 90% of the overall number of immunised individuals in most countries. However, in Ethiopia and Kenya, catch-up and follow-up campaigns contributed substantially to mitigate the effect of suboptimum routine vaccine coverage, generating about 45% of the immunised fraction of the population in Ethiopia and about 25% in Kenya. The contribution of a second booster dose to the total amount of immunised individuals is less than 7% for all countries analysed. However, in Singapore, changes in the age at second dose administration (from 11 years to 6 years of age in 2007, and from 6 years to 18 months in 2011), aimed at reducing measles infection in early childhood, have generated two persisting immunisation gaps in individuals currently aged 5–9 years and 13–18 years, respectively.

Substantial differences characterise the estimated residual susceptibility across countries, ranging from less than 3·0% of the overall population in the UK to around 12·6% in Ethiopia (appendix pp 28–29). More than 70% of susceptible individuals in Italy, the USA, Australia, Singapore, and South Korea were estimated to be older than 5 years of age, and more than 60% older than 10 years. By contrast, in Ethiopia, more than 60% of susceptible individuals are estimated to be younger than 10 years, and in Kenya children younger than 5 years represent about 40% of individuals exposed to the risk of

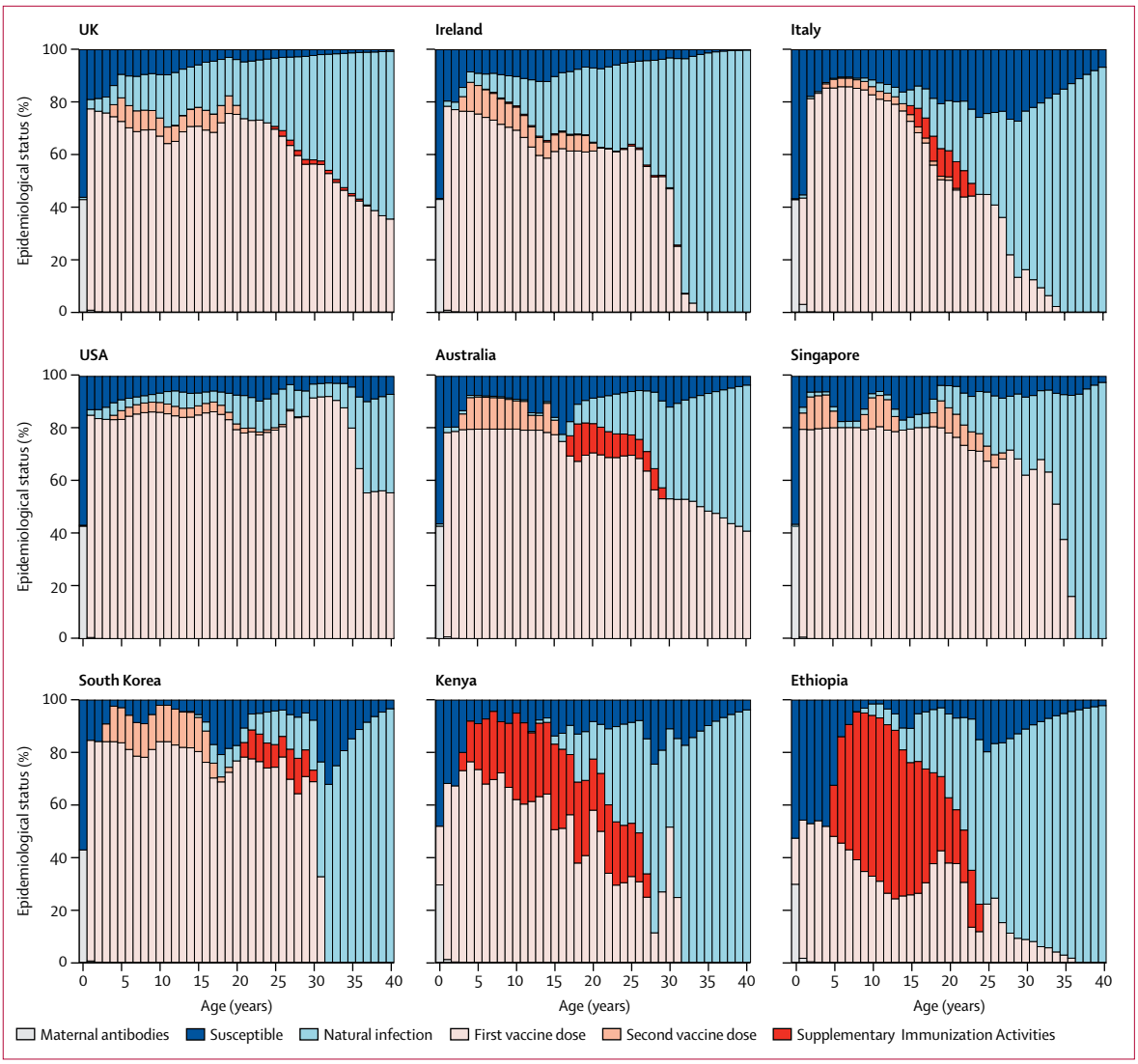

Figure 4: **Estimated immunity profiles**
Model estimates of the epidemiological status at different ages and in different countries for 2015. Shown for each age stratum is the percentage of individuals susceptible to infection or protected against infection by immunity provided by maternal antibodies and by immunity acquired through natural infection, routine first-dose vaccination, second booster administration, or Supplementary Immunization Activities.

infection. Model estimates of the age distribution of residual measles incidence comply with the age distribution of reported measles cases across different countries between 2000 and 2014 (appendix pp 18–19).

Present measles circulation among different ages is partly mirrored by the median age at infection, which is estimated for 2015 to be ages 5–10 years in the UK, Ireland, and Ethiopia; ages 10–15 years in the USA, Australia, Singapore, and Kenya; and older than 20 years in Italy and South Korea (appendix p 27). Temporal variations in measles transmissibility are mirrored by the dynamics of the effective reproduction number, defined as the expected number of secondary cases generated by one infected individual in a population partly immunised, either by vaccination or by natural infection.[12] Estimates of this quantity obtained through the proposed analysis suggest that measles incidence might increase in Italy, Australia, and Singapore, and that the rapid increase in the number of susceptible individuals that is currently ongoing in Ethiopia puts this country at high risk of future outbreaks (appendix p 23).

The calibrated model was used to simulate how the proportion of susceptible individuals in the population and the age-distribution of measles susceptibility have changed between 1950 and 2015, and how, in the absence of measles circulation, these variables are expected to continue to change until 2030. Specifically, we estimated future temporal variations of population susceptibility by projecting 15 years ahead of the estimated immunity profile in 2015, assuming that birth rates and mortality

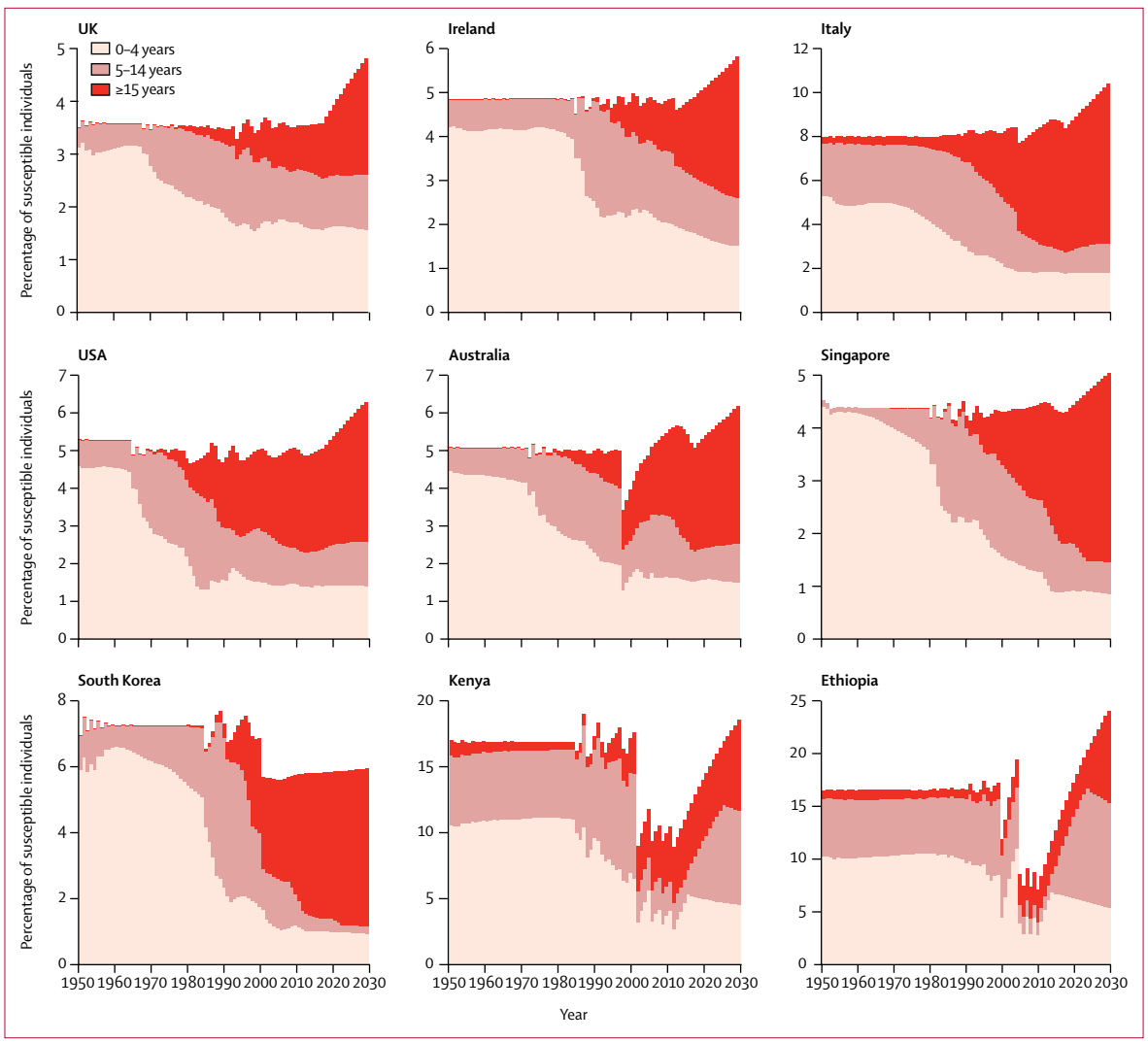

Figure 5: **Estimated temporal trends for the population susceptibility**
Model estimates and forecasts of the percentage of susceptible individuals in the population between 1950 and 2030. Different colours show the contribution of individuals of different ages to the overall fraction of susceptible individuals in the population: younger than 5 years; 5–15 years; older than 15 years.

rates will follow the population projections reported in 2015 UN World Population Prospects,[19] whereas routine coverage levels and vaccination schedules are assumed to not remarkably change in the near future and no further SIAs will be implemented. Our results suggest that the susceptible fraction of the population is expected to increase in most of the analysed countries, and that a substantial fraction of future susceptibility will be represented by individuals older than 15 years (figure 5).

Our analysis suggests that, after the introduction of vaccination, the contribution of children younger than 10 years to the effective reproductive number has progressively decreased as a consequence of the increase in the number of individuals protected by vaccination. Moreover, the decrease in measles circulation as a result of vaccination has gradually reduced infection rates in unvaccinated individuals, increasing the fraction of susceptible individuals at older ages and generating, in some countries, considerable immunity gaps in individuals aged 30–40 years (figure 4). This phenomenon is expected to be more notable in countries where the fraction of adults in the population is higher. Indeed, despite high levels of susceptibility among individuals aged 25–40 years in Kenya (figure 4), the overall contribution of young adults to the effective reproductive number seems to be marginal in this country. Estimated temporal trends in the age-specific effective reproductive number across countries are provided in the appendix (p 23).

Discussion

The multi-country perspective adopted in this study, and the explicit inclusion of time varying demographic components, allowed us to disentangle the contribution of different immunisation activities and local

demographic conditions in the progress towards measles elimination. This Article differs from previous studies[3,14,15,18] by explicitly modelling epidemiological transitions occurring over 65 years, while being informed by longitudinal data on country-specific immunisation activities, including routine programmes and catch-up and follow-up campaigns, and taking into account changes in demographic conditions between 1950 and 2015. We found that although demographic changes substantially contributed to decrease the measles incidence after the introduction of vaccination, immunisation programmes markedly reduced the potential disability and mortality caused by measles in all the analysed countries.

Any advance towards measles elimination will rely on the ability of public policies to decrease the residual susceptibility inherited from the past, and to mitigate the natural replenishment of susceptible individuals in the population due to new births. Our results show that although in younger populations the residual susceptibility is mainly concentrated in early childhood, a substantial fraction of susceptible individuals is found across all ages in countries characterised by low fertility levels. Moreover, more marked variations in the immune fraction of the overall population, possibly induced by changes in routine coverage, are likely to occur in high-fertility countries.

From a policy-making perspective, these results imply that low-income countries can more rapidly achieve but also deviate from a target level of immunity than high-income countries and that even a local interruption of frequent follow-up programmes can represent a major risk for measles re-emergence. In high-fertility countries, coverage levels associated with first-dose programmes are often suboptimum and benefits of past catch-up campaigns are expected to rapidly wane over time. Consequently, future vaccination strategies in these countries should focus either on raising first-dose coverage or on making erratic SIAs more frequent and regular—possibly promoting intensification of follow-up campaigns as part of routine immunisation activities to mitigate the progressive inflow of children not adequately immunised. Interestingly, and in line with results reported by Lessler and colleagues,[18] we estimated that in countries where massive supplementary immunisation campaigns were done, such as Ethiopia and Kenya, coverage levels associated with SIAs were 20–35% lower than those reported, suggesting that the effect of catch-up and follow-up campaigns is often overestimated. The use of aerosolised vaccine as a needle-free method of immunisation against measles is also being considered to enhance the overall sustainability of regular SIAs, although it was shown to produce a lower seroconversion compared with the subcutaneous vaccine.[26]

Additional efforts might focus on increasing vaccine efficacy (eg, by delaying the age at first-dose administration to facilitate the immunological response of vaccinated children) and on improving cold chain operations and vaccine maintenance. Integrative processes that prioritise system strengthening and improve surveillance capacity and the quality and use of data would certainly be beneficial.[27]

Immunisation campaigns aimed at filling immunity gaps among adolescents and young adults are instead required in high-income countries, where the effect of past immunisation activities, either beneficial or detrimental, are expected to persist longer than in low-income countries as a consequence of a slower generational replacement. Since the beginning of 2017, more than 1900 measles cases have been reported in Italy (308 cases in the same 4 months of 2016), 56% of which occurred among people aged 15–39 years and 16% among people aged 40–64 years.[28] The observed age distribution of cases is coherent with our estimates of the Italian serological profile. Despite efforts that have been put in place to increase the proportion of children vaccinated through routine programmes, no targeted campaigns to reach these older age groups have been implemented. However, the estimated low efficacy of SIAs done in the UK and Ireland might reflect difficulties in immunising individuals who escaped both first-dose and second-dose routine vaccination and specific efforts should focus on the feasibility and acceptability of vaccination among these age segments. Reviewing the vaccination history of school leavers and offering vaccination at the time of school leaving was suggested as logistically convenient.[29]

The paucity of epidemiological data associated with different timepoints, and the assumptions of homogeneous mixing and a constant transmission rate over time are three crucial limitations of the proposed investigation.

Unfortunately, data on realistic social mixing patterns by age are not available for all analysed countries and different epochs. However, a modelling study[12] published in 2014 has shown that the inclusion of static estimates on mixing patterns by age in a model similar to the present study's does not affect yearly incidence trends over time.

The effects of the explicit inclusion of seasonal variations in measles transmission due to school terms was analysed in a sensitivity analysis (appendix pp 19–20) and shown to not affect the estimated temporal trends in yearly incidence rates or the estimated longitudinal changes in the population immunity profiles.

Available serological data for Ethiopia and Kenya might reflect only local epidemiological conditions so that obtained results for these two countries might not be representative of measles circulation at a national level. Possible within-country heterogeneities due to geographical differences in vaccine uptake were investigated by simulating measles epidemiological transition in a low-coverage area and a high-coverage area of Ethiopia using data available at a regional level.[8] The percentage of susceptible individuals younger than 5 years was found to

be highly variable within the country, ranging from 29·7% to 53·7%, possibly resulting in local episodic outbreaks, such as those reported in Ethiopia after 2010 (appendix p 17).

The proposed model is not suited to make predictions on the likelihood of future occurrence of outbreaks, and the identification of cost-effective logistic strategies to better immunise individuals is beyond the scope of our study. Moreover, in our model we did not take into account geographically localised outbreak response immunisation activities performed in some countries (eg, in the USA[30]) and possible waning effects in the immunity provided by the vaccine. However, the proposed comparison with different incidence records—although representing only a fraction of the infected cases—provides evidence supporting the epidemiological patterns identified by our analysis. Our results suggesting possible existing immunity gaps across different countries could help to define appropriate immunisation efforts on the basis of specific age priority targets, possibly improving the suitability and sustainability of future vaccination programmes across different demographic and socioeconomic settings.

Contributors

FT, PP, SM, and AM conceived and designed the experiments. FT and PP did the experiments and drafted the first version of the manuscript. All authors contributed to the interpretation of the results and edited and approved the final manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

The research leading to these results has received funding from the European Research Council (ERC) under the European Union's Seventh Framework Programme (FP7/2007–2013) and the ERC Grant agreement number 283955 (DECIDE) to FT, PP, and AM. We thank Elizabeth Miller for useful discussion and comments that helped us to better ground our findings to the challenges in the field.

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