The Pennsylvania State University

The Graduate School

Eberly College of Science

# MODELLING MANAGEMENT FOR THE MAINTENANCE OF MEASLES ELIMINATION

A Dissertation in

Biology

by

Amalie McKee



Submitted in Partial Fulfillment
of the Requirements
for the Degree of

Doctor of Philosophy

December 2016

The dissertation of Amalie McKee was reviewed and approved* by the following:

Katriona Shea
Alumni Professor of Biology
Dissertation Advisor

Andrew F. Read
Evan Pugh Professor of Biology and Entomology, Eberly Professor of Biotechnology
Chair of Committee

Matthew J. Ferrari
Associate Professor of Biology

Ottar Bjørnstad
Distinguished Professor of Biology and Entomology

Rachel A. Smith
Associate Professor of Communication Arts and Sciences

Tracy Langkilde
Professor of Biology
Head of the Department of Biology

*Signatures are on file in the Graduate School.

# Abstract

Despite decades of extensive control, measles remains a major contributor to vaccine-preventable childhood death. As such, measles is an important target for global eradication. Global eradication comprises two parts; achieving local elimination, and maintaining local elimination while elimination is achieved elsewhere. This dissertation focuses on the post measles elimination context, which requires high levels of population immunity to be maintained via a carefully considered vaccine policy. Vaccine policies for measles typically contain combinations of two basic vaccine strategies; routine immunization and supplemental immunization activities (SIAs). Routine immunization consists of one or more doses administered to children at specified target ages. SIAs are campaigns that typically take place over a wide geographic area, where all children within a specified target age range are vaccinated within a relatively short time. In my work I examine the interaction of human demographic structure, maternal immunity, and three health system factors (coverage, age targets, and correlation between populations receiving each dose) on the effectiveness of a vaccine strategy for the maintenance of measles elimination.

I find that, regardless of health system aspects, maternal immunity and age structure can interact so that measles elimination is impossible to maintain with a single dose routine immunization strategy. When a second dose is added, the maximum level of population immunity maintainable in a population still depends on demographic structure, but age target selection can ensure that measles elimination is sustained. The optimal age target for each of two doses of routine immunization depends on the coverage of the other dose as well as on demographic structure. Low correlation between the populations receiving each dose increases the proportion

of the population that receives at least one dose, thereby increasing population immunity, at the cost of increasing the rate of primary vaccine failure. The effect of correlation may outweigh the effects of age structure and changing coverage in a variety of real contexts. The dependence of population immunity on the correlation between doses also arises when SIAs are administered in conjunction with the second routine dose. Whether or not the second dose contributes more to population immunity than SIAs depends, not just on the coverage of all doses, but also on their correlation. While population immunity is important for maintaining elimination, optimal age target selection depends on a carefully specified objective; the optimal age targets to minimize the incidence or mortality of a reintroduction outbreak are different.

I conclude with a synthesis of my research in the context of previous measles work. Overall, I show that, while coverage is essential, human demography, maternal immunity, and other aspects of the health system (coverage, age targets and correlation) also have significant effects on population immunity, and hence the maintenance of measles elimination.

# Table of Contents

List of Figures……vii

List of Tables…… xv

Acknowledgements……...xvii

**Chapter 1: Introduction**…….. 1

References……..4

**Chapter 2: The effects of maternal immunity and age structure on population immunity to measles**…… 7

Abstract……..7

Introduction……7

Methods…… 12

Results……15

Discussion……..17

Acknowledgements……23

References……..23

**Chapter 3: Optimal vaccine schedules to maintain measles elimination with a two-dose routine policy**……... 37

Abstract……..37

Introduction……37

Methods…… 41

Results……45

Discussion……..47

Acknowledgements……52

References……..53

**Chapter 4: Correlation between measles vaccine doses: Implications for the maintenance of elimination**…….61

Abstract……..61

Introduction……62

Methods…… 65

Results……69

Discussion……..72

Acknowledgements……76

References……..76

**Chapter 5: Objectives matter: Optimal age targets to minimize incidence of a measles reintroduction outbreak are not the same as those to minimize mortality**……...87

Abstract……..87

Introduction……88

Methods…… 91

Results……93

Discussion……..97

Acknowledgements……99

References……..99

**Chapter 6: When is routine immunization better than supplemental immunization activities for maintaining elimination?**..... 111

Abstract……..111

Introduction……112

Methods…… 114

Results……122

Discussion……..126

Acknowledgements……129

References……..129

**Chapter 7: Synthesis**……142

References……..152

Appendix A……159

Appendix B…… 166

# List of Figures

**Figure 2.1:** Two sample age distributions of immunity within a population. The dark grey region is the portion still maternally immune, the pale grey region is the vaccinated proportion and the hatched region is the proportion that remains susceptible. The x-axis is shown on a log scale, so the total hatched regions in a) and b) are of similar area. In a), the vaccine is administered too late, and too many infants remain susceptible. In b), the vaccine is administered too early, so too few doses are effective. Both of these figures use a developing population age structure assuming 6 month maternal immunity……28

**Figure 2.2: a)** and **b)** Maintainable population immunity for maternal immunity waning at 6 and 3 months, respectively, in a region with a developing age structure. **c)** and **d)** Maintainable population immunity for maternal immunity waning at 6 months and 3 months, respectively, in a region with developed age structure. Strategies that meet the 95% threshold are shown in black, those that meet the 90% threshold are shown in grey……...30

**Figure 2.3: a)** The difference in population immunity due to differences in maternal immunity (i.e. the difference between **4 c** and **4 d). b)** Difference in population immunity for maternal immunity waning at 3 months between regions with a developed and developing age structure (i.e. the difference between **4 b** and **4 d).** Note that the target ages of vaccination which minimize the difference due to a difference in maternal immunity are where the difference due to a difference in age structure starts to increase…….. 31

**Figure 2.4:** The maintainable population immunity for a range of age structures. When α is 0, the age structure is the idealized developed one. When α is 1, the age structure is the idealized developing one. **a)** As the age structure shifts from developed to developing, the maximum maintainable proportion immune continuously declines. Notably, the proportion immune for long maternal immunity is lower than that for short maternal immunity, despite both being the specific maxima for that maternal immunity function. That is, the optimal vaccine policy for long maternal immunity is always less successful than the optimal for short maternal immunity. **b)** The achievable proportion immune when vaccinating at 12 months. With a developed age structure and short maternal immunity, this is a successful vaccine policy. However, as the age structure shifts towards the purely developing one, the success of the vaccine policy continually declines. With long maternal immunity, maintainable immunity is similarly low everywhere, but still worse on a developing age structure…… 33

**Figure 2.5:** These panels show the immunity gap – that is, the difference between vaccine coverage and population immunity – for a variety of target ages and coverages. Here we are comparing these vaccine schedules in a developing population with 3 month maternal immunity. **a)** At high coverage, all of these vaccine schedules could achieve herd immunity. However, as maternal immunity

is less significant at older ages, it has a different effect on the immunity gap between the different ages. Notably, the immunity gap line when vaccinating at the youngest age with high coverage is significantly curved. **b)** Focusing on the immunity gap at coverages that might be maintained in regions with measles elimination, it is clear that 12 months is the best age to vaccinate at all of these coverages in a region with this age structure and maternal immunity decay. However, whether it would be better to miss the target age by vaccinating a little too young (10 months) or a little too old (14 months) depends on coverage, with vaccinating younger ages still being worse at high coverages…….. 35

**Figure 3.1:** The optimal ages in months (shown by the contours), and maintained proportional susceptibility (shown by the color scale) for a range of first and second dose coverages, varying independently, in a population with idealized developing age structure. **A)** The optimal age for the first dose. Notably, the optimal age of the first dose depends heavily on the coverage of the second dose. **B)** The optimal age for the second dose. Notably, the optimal age of the second dose depends heavily on the coverage of the first dose……57

**Figure 3.2:** The real target ages (the blue line), the optimal target ages with 100% coverage of two doses (the red line), the optimal target ages with 90% coverage of two doses (the orange line), and the optimal target ages with 80% coverage of two doses (the yellow line). The endpoints of each line represent the first and second age target, respectively, for each country and policy. The optimal target ages for a single dose vaccine schedule with each of these coverages are shown by the diamond on each line. In all cases, the difference in age target between the first and second dose is smaller with lower coverages. In all cases, the optimal first age of vaccination is younger than the current recommendation, and in most, the optimal second age is also younger than the current recommendation. The optimal single dose ages correspond well with the current recommendation for the first dose. The countries have been ordered by proportion of the population made up by children under 5, with Bolivia having the most children under 5 and Canada having the fewest……... 58

**Figure 3.3:** The population immunity by partial adherence to schedule for countries in the Americas with two recommended age targets of vaccination. Red indicates a population immunity below 95%, the commonly accepted threshold for maintaining elimination, and blue indicates a population immunity above 95%. In the case where only one dose is optimal, the other dose is administered at the currently recommended age target……60

**Figure 4.1:** Vaccination and immunity class breakdown when first dose coverage is 85% and second dose coverage is 80%. Also shown is the rate of vaccine failure and the resulting proportion of the population that is susceptible. **a)** The vaccination classes when doses are administered dependently. The proportion of the population left susceptible here is 18.9%. **b)** The immune classes when doses are

administered dependently. The rate of primary vaccine failure here is 0.6%. **c)** The vaccine classes when doses are administered independently. The proportion of the population left susceptible here is 10%, which is less than when doses are administered dependently. **d)** The immune classes when doses are administered independently. The rate of primary vaccine failure here is 1.8%, which is greater than when doses are administered dependently……79

**Figure 4.2:** The susceptible proportion remaining for a range of first and second dose coverages, correlations, and age structure parameters. The contours indicate various threshold levels of immunity, where <5% susceptible within the population is generally considered sufficient to maintain elimination and is colored in blue. The white dashed line indicates where the coverage of each dose is equal……... 81

**Figure 4.3:** The average reported MCV1 (x-axis) and MCV2 (y-axis) coverages for each of 6 WHO health regions between 2005 and 2014. The unpointed end of the arrow represents the average coverage from 2005-2009. The pointed end represents the average coverage from 2010-2014. Missing reports were assumed to be 0. AFR is the African Region, AMR is the American Region, EMR is the Eastern Mediterranean Region, EUR is the European Region, WPR is the Western Pacific Region, and SEAR is the Southeast Asian Region……83

**Figure 4.4:** The improvement in population immunity for each WHO health region from 2005-2014, in each of four different contexts, using coverages shown in Fig. 3. AFR is the African Region, AMR is the American Region, EMR is the Eastern Mediterranean Region, EUR is the European Region, WPR is the Western Pacific Region, and SEAR is the Southeast Asian Region. The unpointed end is the population immunity maintained by the average first and second dose coverages from 2005 to 2009, and the pointed end is the population immunity maintained by the average first and second dose coverages from 2010 to 2014. The four contexts are the four crosses of developing and developed age structures ("dvg" and "dvd", respectively) with dependent and independent administration of doses ("dep" and "ind", respectively). Each of these contexts represents a corner of Fig. 4.2…….. 85

**Figure 5.1:** Each panel shows the payoff under one pre-invasion objective (proportion of the total population of children under five immune) when vaccinating with 90% first and second dose coverage at a range of first and second dose age targets (specified in months), for all combinations of two age structures and two means of implementing the second dose with respect to correlation. The optimal combination of age targets (that is, the combination that maximizes the payoff under the given objective) in each panel is highlighted by a white diamond, and given in text in the lower right. **A**-**D** The total proportion of the total population that is immune after vaccination. **E**-**H** The proportion of children under five that are immune after vaccination……104

**Figure 5.2:** Each panel shows the payoff under one post-invasion objective (to minimize incidence or to minimize mortality) when vaccinating with 90% first and second dose coverage at a range of first and second dose age targets (specified in months), for all combinations of two age structures and two means (dependent or independent) of implementing the second dose with respect to correlation. The optimal combination of age targets (that is, the combination that maximizes the payoff under the given objective) in each panel is highlighted by a white diamond, and given in text in the lower right. **A-D** The average incidence of a reintroduction outbreak. **E-H** The average mortality of a reintroduction outbreak. ..... 106

**Figure 5.3:** The difference between the optimal age targets under each objective, in months, for a range of coverages and all combinations of two age structures and the two means of administering the second dose (correlated or not with the first dose). In the pre-invasion context (A-D), this is the optimal age targets to maximize population immunity minus the optimal age targets to maximize the proportion of children under five who are immune. In the post-invasion context (E-H), this is the optimal age targets to minimize incidence minus the optimal age targets to minimize mortality risk. **A-D** The difference in age targets for the two pre-invasion objectives (maximizing population immunity and maximizing the proportion of children under 5 who are immune). **E-H** The difference in age targets for the two post-invasion objectives (minimizing incidence and minimizing mortality)..... 108

**Figure 5.4:** The cost, in performance under one objective, of choosing age targets that maximize performance under the other, for a range of coverages (assuming first and second dose coverage are the same) and all combinations of two age structures and two means of administering the second dose. **A-D** The difference in the pre-invasion objectives (maximizing population immunity and maximizing the proportion of children under 5 who are immune). **E-H** The difference in the post-invasion objectives (minimizing mortality and minimizing incidence). ..... 110

**Figure 6.1:** The proportion of the population that is immune for four combinations of vaccine strategies; one routine dose ("first") only, one routine dose and SIAs ("first SIAs"), two routine doses and SIAs ("first second SIAs"), and two routine doses ("first second"). Here, we assume that the first dose is administered at 9 months with 80% coverage, the second dose is administered at 18 months with 75% coverage, and SIAs are conducted every four years for children up to 5 with 75% coverage. We here assume that SIAs are administered independently of whether an individual had the first dose, while the second dose is administered only to children who had the first dose. The total height of the bar represents the average population immunity, with the colored blocks representing the vaccine classes that contribute to population immunity. Not all vaccine classes are visible

here, as only those that make a contribution to population immunity for these specific combinations of coverage and correlations are shown. The upper line of each bar is the average population immunity maintained by that combination of strategies, while the dots represent specific levels of population immunity arising from when a specific birth cohort falls relative to the timing of SIAs. ..... 134

**Figure 6.2:** The population immunity achieved by four combinations of strategies (single dose, two routine doses, one routine dose and SIAs, and two routine doses and SIAs), for a range of second dose coverages. The level of second dose coverage where a second routine dose surpasses SIAs in population immunity achieved is emphasized with a vertical grey line. We assume here that the first dose is administered at 9 months with 80% coverage, the second dose is administered at 18 months, and SIAs are administered every four years to children under 5 with 75% coverage. The second dose is administered only to children who had the first dose, except when second dose coverage exceeds first dose coverage, in which case the first dose is administered only to children who will eventually get the second dose. SIAs are administered independently of whether an individual had the first dose..... 136

**Figure 6.3:** The level of second dose coverage required for a second routine dose to outperform SIAs with respect to population immunity. We here assume that the first dose is administered at 9 months, the second dose at 18 months, and SIAs every 4 years in children under 5. We also assume that the routine second dose is administered dependently to children who received the first dose, while supplemental immunization activities are conducted independently of whether an individual has received a first dose. The inflection points in the contours occur where the population that was vaccinated by the first dose but did not seroconvert exceeds the population that would be vaccinated for the first time by an SIA; that is, the threshold where immunizing the population who did not seroconvert due to the first dose outweighs the importance of catching individuals who missed the first dose.....137

**Figure 6.4:** The level of second dose coverage required for a second routine dose to outperform SIAs with respect to population immunity for a range of correlations between the first dose and either a second dose or SIAs. We assume that the first dose is administered at 9 months with 80% coverage, the second dose is administered at 18 months, and SIAs are administered in children up to 5 every 4 years with 75% coverage. The lower right corner of this picture is the point at (0.8, 0.75) in Fig. 3..... 139

**Figure 6.5:** Population immunity maintained by various combinations of vaccine strategies for a range of correlations. We assume here that the first dose target is 9 months, first dose coverage is 80%, the second dose target is 18 months, second dose coverage is 75%, and SIAs are conducted every four years in children up to

five years of age with 75% coverage. a) The population immunity maintained by a two dose routine immunization strategy. As correlation between the first and second dose increases, the level of population immunity maintained decreases. As SIAs are not administered, the correlation between SIAs and the first routine dose does not affect population immunity. b) The population immunity maintained by a single routine dose and SIAs. As correlation between the routine dose and SIAs increases, population immunity decreases. As a second routine dose is not administered, the correlation between the first and second dose does not have an effect on population immunity. c) The population immunity maintained by two routine doses and SIAs. As correlation between either the second dose or SIAs increases, population immunity decreases. At each combination of correlations, the average population immunity maintained is higher when two routine doses and SIAs are administered……... 140

**Figure 7.1:** The cumulative probability of immunity by age. The blue line represents maternal immunity, which here wanes exponentially such that there is a 5% probability of retaining maternal immunity at 9 months. Each red line represents the sum of the maternal immunity distribution with the cumulative probability of having been infected by that age for a range of probabilities of infection at a given age (we do not consider an age-specific force of infection for the purposes of this illustration). The stars represent the optimal age at vaccination for the probability of infection of the correspondingly colored line, as in McLean and Anderson 1988a……..157

**Figure 7.2:** The population immunity maintained within the population by vaccination with 100% at a range of age targets. Lighter colors of blue correspond to a lower proportion of infants within the population – for the darkest line, 20% of the population is made up by children under five, for the intermediate line, 10% of the population is made up by children under five, and for the lightest line, 4% of the population is made up by children under five. The optimal ages of vaccination for each age structure are shown by stars of the corresponding color….158

**Figure A.1:** The two age structures explored **in Chapter 2**. In black is an idealized developed age structure, and speckled is the idealized developing age structure. Between the two is a sample age structure representing one of the range considered in Figure 7. The symbol α represents the relative weight of the developed age structure when we consider a weighted average of the two base age structures…… 159

**Figure A.2:** Maternal immunity functions used **in Chapter 2**. The grey represents the probability of remaining maternally immune if you were born maternally immune and maternal immunity wanes exponentially on average at 3 months. Similarly, the black represents the probability of remaining maternally immune if you were born maternally immune and maternal immunity wanes exponentially on average at 6 months……161

**Figure A.3:** Age distribution of susceptibility for a developing age structure with 3 month maternal immunity when vaccinating at 12 months over a range of vaccine coverages. The left vertical line is where the 90% threshold is satisfied for overall population immunity (but only when vaccine coverage exceeds this level), the right is where the 95% threshold is satisfied for the population; this latter only occurs for vaccine coverage of 99% or above, however…….. 162

**Figure A.4:** Four possible immunity gaps between coverage and population immunity, when vaccinating at 12 months. The most severe immunity gap is with long maternal immunity and developing age structure; the least severe immunity gap is with short maternal immunity and developed age structure. Notably, with low coverage, age structure matters more than maternal immunity – it is only above around 30% coverage that the immunity gap in a developed age structure with long maternal immunity exceeds that in a developing age structure with short maternal immunity……164

**Figure B.1:** Optimal age targets for first and second dose under different assumptions about the waning of maternal immunity. The middle panel is Figure 3.2. The endpoints of the blue line represent the current age targets for the first and second dose. The endpoints of the red line represent the optimal age targets for 100% coverage, with the red diamond representing the optimal single dose strategy. The endpoints of the orange line represent the optimal age targets for 90% coverage, with the orange diamond representing the optimal single dose strategy. Finally, the endpoints of the yellow line represent the optimal age targets for 80% coverage, with the yellow diamond representing the optimal single dose strategy. The middle graph is made assuming maternal immunity wanes exponentially with a mean at 3 months. As in the paper, the countries are arranged in descending order of the ratio of children under 5.
The top and bottom panels are that figure redrawn for a different maternal immunity waning rate. On the bottom, maternal immunity wanes at 120% of the rate we use in the paper, so individuals are susceptible at younger ages and the optimal age targets are younger. On the top, maternal immunity wanes at 80% of the rate in the paper, so individuals do not lose maternal immunity until they are older, and the optimal age targets are therefore older. When maternal immunity wanes more slowly, the window between the optimal first and second ages of vaccination is wider. In all cases, the effect of coverage is the same – a lower coverage means a shorter window between doses, and the optimal single dose strategy falls between the optimal strategy for the first and second dose. In all cases where the second dose is recommended at 2+ years, it is still beneficial to reduce the age target of the second dose……167

**Figure B.2:** Optimal age targets for first and second dose under different assumptions about the waning of maternal immunity. All panels are similar to Figure 3.2, but with a different function for maternal immunity. The endpoints of the blue line

represent the current age targets for the first and second dose. The endpoints of the red line represent the optimal age targets for 100% coverage, with the red diamond representing the optimal single dose strategy. The endpoints of the orange line represent the optimal age targets for 90% coverage, with the orange diamond representing the optimal single dose strategy. Finally, the endpoints of the yellow line represent the optimal age targets for 80% coverage, with the yellow diamond representing the optimal single dose strategy. As in the paper, the countries are arranged in descending order of the ratio of children under 5.
In these panels, maternal immunity still wanes exponentially, but with a waning rate that results in 15%, 10%, or 5% (respectively) of children still immune at 9 months. When the maternal immunity wanes faster, as on the bottom, the vaccine is more effective at 9 months and the age targets of vaccination are earlier in life than when maternal immunity wanes more slowly, as on the top. In all cases, the effect of coverage is the same – lower coverage means a shorter window between the first and second dose, and the single dose optimum falls between the two. In all countries that recommend the second dose at 3+ years, it is beneficial to reduce the age target of the second dose, regardless of the specific maternal immunity function…….. 169

# List of Tables

**Table B.1:** Optimal age targets for the first and second dose assuming maternal immunity wanes exponentially with a mean at 3 months. This table contains the data plotted in Figure 3.2, with cells colored to correspond to the line containing the data in the cells. The blue cells represent current policy, or the endpoints of the blue line in Figure 3.2. The yellow cells represent the model optima for 80% coverage, or the endpoints of the yellow line in Figure 3.2 and the yellow diamond. The orange cells represent the model optima for 90% coverage, or the endpoints of the orange line in Figure 3.2 and the orange diamond. The red cells represent the model optima for 100% coverage, or the endpoints of the red line in Figure 3.2 and the red diamond. As in Figure 3.2, the countries are arranged in descending order of the ratio of children under 5. All optima assume that maternal immunity wanes exponentially with mean at 3 months. These age targets should not be taken as operational suggestions, as the selection of age targets is sensitive to maternal immunity, as illustrated in Figures B1 and B2……. 171

**Table B.2:** The real measles-containing vaccine coverages for 2005-2014 as reported to the WHO. Coverages falling between 80 and 100% are coloured yellow to green, with greener squares being higher coverage squares. Coverages falling below 80% are highlighted in red. The average coverage over the 10 year period is also shown, with average coverages above 90% in blue, average coverages between 80 and 90% in yellow and average coverages below 80% in orange. Countries are arranged in descending order of the ratio of children under 5 ……173

**Table B.3:** Population immunity maintained by optimal and real age targets assuming real coverage. In places where MCV2 coverage is not available, we assume both doses have the same coverage. Assuming that coverage in each country is the same as the average coverage for these countries (shown in the second column from the left) and that maternal immunity wanes exponentially with a mean at 3 months, we find the population immunity maintained by the optimal age targets calculated in the paper, as well as the real age targets. Countries are arranged in descending order of the ratio of children under 5. In the third column from the left, we use the real age targets. In third column from the right, we use the optimal age targets for each country assuming 80% coverage, shown as the endpoints of the yellow line corresponding to each country in Figure 3.2. In the second column from the right, we use the optimal age targets for each country assuming 90% coverage, shown as the endpoints of the orange line corresponding to each country in Figure 3.2. Finally, in the rightmost column we use the optimal age targets for each country assuming 100% coverage, shown by the endpoints of the red line corresponding to each country in Figure 3.2. Each cell in the right four columns is coloured according to the population immunity maintained, with white cells having a relatively low population immunity and darker green cells having a higher level of population immunity. For all countries, at least one of the model

optima improved population immunity over the real age targets. Adjusting age targets with the current coverage levels can improve population immunity in all countries to above 95%.....174

# Acknowledgements

I would not be where I am today without the support of my advisors and coauthors, Katriona Shea and Matthew Ferrari. Both have provided me with endless support of all forms over the course of my degree. I also thank my committee members (Ottar Bjørnstad, Andrew Read and Rachel Smith) for their enthusiastic comments and assistance.

The contributions of my academic family, through both labs, are also not to be ignored. In no particularly order, Joe Keller, Laura Russo, Brittany Teller (amazingly also my real family), Will Probert, Shouli Li, Adam Miller, Chris Baker and countless armies of undergrads provided constant companionship through the Shea lab. Discussion with Spencer Carran, Yun Tao, Sammit Bhattacharya, Suma Ghosh, and Sheng Li, all through the Ferrari lab, helped me structure and develop my thinking.

Ottar Bjørnstad, and his lab, have also contributed significantly, both to the development of my thesis, and my development as a person. His former students, Lindsay Beck-Johnson and Megan Greischar were there as role models and endless fountains of advice when I first started out.

I also feel that it is important to acknowledge my CIDD community, although they are too numerous to list. Lauren Quevillon, the Hughes lab, and the Read lab, especially, have helped to make CIDD feel like it is truly my academic home.

Finally, I would like to acknowledge funding from a Penn State University Graduate Fellowship, a Braddock award, and the National Institutes of Health and National Science Foundation (EEID award 1 R01 GM105247-01 and NSF Ebola RAPID DMS-1514704). These grants have supported the majority of my work.

# Chapter 1

## Introduction

Measles is a highly lethal childhood infection caused by a morbillivirus, and remains a major contributor to global childhood mortality (Simons et al. 2012) despite decades of control efforts (Henao-Restrepo et al. 2005). As such, it remains a major target for global eradication (Keegan et al. 2011, Perry et al. 2014) - that is, the reduction in the global prevalence of measles to zero. Global eradication comprises two parts: the elimination of measles in places where it persists and the maintenance of elimination in places where it does not (Andrews and Langmuir 1963). Maintenance of elimination is necessary to prevent re-invasion of measles into populations where local elimination has been attained. Only when local elimination has been attained everywhere will the ultimate objective of measles eradication be achieved (Dowdle 1998).

In order to maintain measles elimination, it is vital that we maximize the proportion of individuals in a population that is immune, so that we can maintain herd immunity. Herd immunity is maintained when a sufficient proportion of individuals are immune such that endemic transmission cannot be sustained. The herd immunity threshold for measles is conservatively estimated to be 95%, as it is $1 - 1/R_0$ (McLean and Anderson 1988), where $R_0$ is the number of secondary infections from a single infectious case, typically considered to be 14-18 for measles (Anderson and May 1982), with estimates ranging up to 20 (Anderson and May 1991). In order to maintain this high level of immunity, measles containing vaccine must be administered at very high coverage. This high threshold is even more difficult to achieve as the measles vaccine is not 100% effective; vaccines may fail due to interference from maternal antibodies (Saha et al. 1985, McLean and Anderson 1988), or through other causes, such as cold chain failure (Moss and Griffin 2006). Individuals born to immune mothers are born with an titer of trans-placentally acquired IgG antibodies that wanes over time. This titer may be lower or wane faster in infants born to mothers who were vaccinated (Zhao et al. 2010, Leuridan et al. 2010), as opposed to infants born to naturally immune mothers, but it is still present. Infants who retain a sufficient antibody titer at the time of vaccination cannot be successfully immunized – the vaccine will not be effective (Cutts et al. 1995, Gans et al. 2001).

To achieve high population immunity in the face of these issues, two doses of measles containing vaccine are administered in almost all countries, through varying combinations of two basic types of vaccination programs (Hall and Jolley 2011, Fields et al. 2013). The first is routine immunization, where individuals are vaccinated at specific age targets (WHO 2013). The second is supplemental immunization activities (SIAs), where all individuals within a specified age range over a wide geographical area are sought out and vaccinated within a relatively short period of time (WHO 2013). The purpose of the second dose, regardless of whether it is administered through routine immunizations or SIAs, is twofold; 1) to catch children for whom the first dose was not effective, and 2) to catch children who missed the first dose. SIAs are commonly considered superior to routine immunizations at achieving the second purpose, although they are logistically more difficult to conduct (WHO 2013).

In this dissertation, I consider the effects of population age structure, maternal immunity to measles, and three aspects of the health system on the performance of different combinations of these measles vaccination strategies in different contexts and under various objectives. The first aspect is coverage: the proportion of the target population that receives a dose of measles containing vaccine. The second aspect is age targets: at what age(s) children are recommended to receive doses of vaccine. The third is correlation: the overlap between subpopulations receiving each dose. All code used in this dissertation has been uploaded at Penn State's institutional repository, ScholarSphere: https://scholarsphere.psu.edu/collections/sn009x90d.

In my second chapter (McKee et al. 2015), I consider the effect of age structure, maternal immunity, and the first two aspects of the health system, coverage and age targets, on the sustainability of measles elimination by a single dose routine immunization strategy. Here, I suggest that, in the disease-free setting, there is an upper limit on the age target for immunization that can maintain elimination, even at very high coverage. This upper limit is imposed by the age structure of the population. Furthermore, I show that, regardless of the age target chosen, the population immunity maintained by a single dose strategy is lower in populations with a "developing-country" age structure. In populations where children under five years of age make up a relatively large proportion of the population, a relatively large proportion of the population is susceptible before the age of vaccination. If vaccines are administered earlier to adjust for this proportion, then a smaller proportion of the vaccines will be effective due to maternal immunity.

As the vaccine is not 100% effective, coverage always exceeds population immunity; we call the difference "the immunity gap".

In my third chapter (Chapter 3), I expand the single dose analysis to consider the effect of the same two aspects of the health system (coverage and age targets) on the level of population immunity maintained by a two dose routine immunization strategy in a variety of real contexts. Here, I show that the coverage of each dose affects the optimal age target for the second, and that lower coverage results in the optimal age for the second dose falling much closer to the optimal age of the first dose than it does with higher coverage. I show the relative population immunity for modeled optimal age targets compared to currently enacted age targets for a variety of American countries, using the reported age structures of these countries. I further show that the level of immunity maintained, even by optimal age target selection, is always less when a country has a greater proportion of children under the age of five years.

In my fourth chapter, I analyze the effects of age structure and the first and third aspects of the health system, specifically coverage and correlation, on the level of immunity maintained in a population using a two dose routine immunization strategy. The second dose of measles containing vaccine is administered with two purposes; to provide children who received the first dose but did not seroconvert a second chance to become immune, and to provide children who missed the first dose a second chance to receive at least one dose (WHO 2012). When correlation is high, the first purpose is met but not the second, while when correlation is low, both purposes are achieved. I find that, at a given coverage, high correlation between the populations receiving the first and second dose reduces the proportion of the population that receives at least one dose, thereby eroding herd immunity. Low correlation increases the proportion of the population that receives at least one dose, at the cost of decreasing the proportion of the population that receives both doses, thereby increasing population immunity at the cost of primary vaccine failure. The effect of correlation on the level of population immunity maintainable within a population given a specified coverage is similar in magnitude to the effect of age structure. I also find that high correlation reduces the impact of increasing coverage of the dose with lower coverage, which is the second dose in all of the World Health Organization's 6 health regions.

In my fifth chapter, I analyze the effect of age structure and all three aspects of the health system on the performance of a two dose routine immunization strategy under a variety of objectives. Measles control objectives are usually stated as both an incidence reduction objective and a mortality reduction objective (Dowdle 1998, Perry et al. 2014). I consider these two objectives in two contexts; a disease free setting, where elimination is maintained, and a reintroduction outbreak setting, where the disease has reinvaded following temporary elimination. I first compare the two objectives in the disease free setting, by comparing age targets that maximize population immunity or maximize the proportion of children under five years of age that are immune. I then simulate disease introduction and the ensuing outbreak, and compare age targets that minimize either incidence or mortality. In this chapter, I find that the age targets to minimize incidence are not always the same as the age targets to minimize mortality, and their similarity depends on both age structure and correlation. Clearly specified disease management objectives are essential.

In my sixth chapter, I analyze the effect of the first and third aspects, coverage and correlation, on the relative performance of routine immunizations and SIAs in maintaining high levels of population immunity. If the second dose is administered dependently to children who had the first dose, while SIAs are administered independently, a routine second dose must have much higher coverage than SIAs to outperform SIAs. This is true regardless of first dose coverage, although how much higher coverage of the second dose must be depends on first dose coverage. When assumptions about the correlation, both between the first and second dose and the first dose and SIAs, are relaxed, the level of coverage required for the routine second dose to outperform SIAs decreases. However, the routine second dose must be administered with lower correlation than SIAs in order for the routine second dose to outperform SIAs at lower coverage.

Finally, in my seventh chapter, I synthesize my results in the broader context of measles management, and suggest some directions for future research.

**References**

1. Anderson RM, May RM. Directly transmitted infectious diseases: control by vaccination. Science 1982; 215: 1053–60.

2. Anderson RM, May RM (1991) Infectious Diseases of Humans: Dynamics and Control. Oxford University Press, Oxford.
3. Andrews JM, Langmuir AD. The philosophy of disease eradication. Am J Public Health 1963; 53: 1–6.
4. Cutts FT, Grabowsky M, Markowitz LE. The effect of dose and strain of live attenuated measles vaccines on serological responses in young infants. Biologicals 1995; 23: 95–106.
5. Dowdle WR. The principles of disease elimination and eradication. Bull World Health Organ 1998; 76: 22–5.
6. Fields R, Dabbagh A, Jain M, Sagar KS. Moving forward with strengthening routine immunization delivery as part of measles and rubella elimination activities. Vaccine 2013; 31: B115–21.
7. Gans H, Yasukawa L, Rinki M, et al. Immune responses to measles and mumps vaccination of infants at 6, 9, and 12 months. J Infect Dis 2001; 184: 817–26.
8. Hall R, Jolley D. International measles incidence and immunization coverage. J Infect Dis 2011; 204 Suppl: S158–63.
9. Henao-Restrepo A-M, Strebel P, Hoekstra EJ, Birmingham M, Bilous J. Experience in Global Measles Control,1990 – 2001. J Infect Dis 2005; 187: S15–21.
10. Keegan R, Dabbagh A, Strebel PM, Cochi SL. Comparing measles with previous eradication programs: enabling and constraining factors. J Infect Dis 2011; 204 Suppl: S54–61.
11. Leuridan E, Hens N, Hutse V, Ieven M, Aerts M, Van Damme P. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. Bmj 2010; 340: c1626–c1626.
12. McKee A, Ferrari MJ, Shea K. The effects of maternal immunity and age structure on population immunity to measles. Theor Ecol 2015; 8: 261–71.
13. McKee A, Shea K, Ferrari MJ. Chapter 3. Optimal age targets to maintain measles elimination.

14. McLean AR, Anderson RM. Measles in developing countries. Part II. The predicted impact of mass vaccination. Epidemiol Infect 1988; 100: 419–42.

15. McLean AR, Anderson RM. Measles in developing countries. Part I. Epidemiological parameters and patterns. Epidemiol Infect 1988; 100: 111–33.

16. Moss WJ, Griffin DE. Global measles elimination. Nat Rev Microbiol 2006; 4: 900–8.

17. Perry RT, Gacic-Dobo M, Dabbagh A, et al. Global Control and Regional Elimination of Measles, 2000–2011. MMWR Morb Mortal Wkly Rep 2014; 63: 103–7.

18. Saha SM, Aggarwal RK, Sood DK, Saxena SN. Seroconversion in different age groups after measles vaccination. Indian J Pediatr 1985; 52: 303–5.

19. Simons E, Ferrari M, Fricks J, et al. Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. Lancet 2012; 379: 2173–8.

20. WHO. A Guide to Introducing a Second Dose of Measles Vaccine into Routine Immunization Schedules. 2013.

21. Zhao H, Lu P-S, Hu Y, Wu Q, Yao W, Zhou Y-H. Low titers of measles antibody in mothers whose infants suffered from measles before eligible age for measles vaccination. Virol J 2010; 7: 87.

# Chapter 2

## The effects of maternal immunity and age structure on population immunity to measles

Amalie McKee, Matthew Ferrari, Katriona Shea

Published in Theoretical Ecology 2015; 8(2): 261-271

**Abstract**

Measles was successfully eradicated in the Pan-American Health Region in 2002. However, maintenance of elimination in parts of Africa, Europe, the USA and other regions is proving difficult, despite apparently high vaccine coverage. This may be due to the different age structure in developed and developing populations, as well as to differences in the duration of maternal immunity. We explore the interaction between maternal immunity and age structure and quantify the resulting immunity gap between vaccine coverage and population immunity; we use this immunity gap as a novel metric of vaccine program success as it highlights the difference between actual and estimated immunity. We find that for some combinations of maternal immunity and age structure, the accepted herd immunity threshold is not maintainable with a single dose vaccine strategy for any combination of target age and coverage. In all cases, the herd immunity threshold is more difficult to maintain in a population with developing age structure. True population immunity is always improved if the target age at vaccination is chosen for the specific combination of maternal immunity and age structure.

### Introduction

Great progress has been made towards worldwide measles eradication, yet it still remains an elusive objective, as endemic disease persists in some places, and is reintroduced to others where it was long absent. One aspect of the measles problem is maintenance of elimination; the disease

has begun to reemerge in places where it was thought to be eliminated. Measles was officially eliminated from the United States in 2000, and the Pan-American Health region (PAHO region) in 2002 (Castillo-Solorzano et al. 2011; CDC 2012), and, despite recent outbreaks, endemic transmission has not re-emerged. However, other countries have not been as successful at maintaining elimination. Europe has seen recent increases in transmission, despite promising improvements in the early 2000s (CDC 2011), including places like Germany (Roggendorf et al. 2010; van Treeck 2006) and France (Parent du Châtelet et al. 2010). Recent outbreaks have occurred in parts of southern Africa where measles was previously reduced near the point of elimination (Shibeshi et al. 2014). Additionally, despite the disease officially remaining eliminated in the United States, there have been recent outbreaks that cast doubt on the actual population immunity to measles in the US (Parker et al. 2006; Sugerman et al. 2010).

With measles, as with any other directly transmissible, immunizing infection, there is some threshold level of immunity in the population, called the herd immunity threshold, beyond which the disease cannot invade (Anderson et al. 1991). The goal of measles vaccination programs is to achieve and maintain a sufficiently large immunized population that this threshold will be met, and measles will be locally eradicated and unable to reinvade. The conventional wisdom for measles is that this threshold level of immunity is 90-95% (Hall and Jolley. 2011; Moss and Griffin 2006).

Measles vaccination programs since the 2002 PAHO elimination are typically composed of multiple strategies for vaccine distribution (Danet and Fermon 2013, Koehlmoos et al. 2011). Here we consider routine immunizations (RIs), in which children of specific ages are vaccinated during clinic visits (Bauch et al. 2009). RIs, in combination with other types of vaccination

campaigns, were used to effectively eradicate measles in the Americas by 2002 (Castillo-Solorzano et al. 2011). RIs are targeted at a specific age; the World Health Organization recommends measles vaccination between 9 and 12 months of age (WHO 2012).

Trans-placentally acquired maternal immunity temporarily protects infants born to immune mothers, but interferes with vaccine efficacy (Cutts et al. 1995; Gans et al. 2001). Vaccines administered before this maternal immunity wanes will be ineffective, but otherwise there is minimal disadvantage to vaccinating children as early as possible. Therefore, there is a window of susceptibility between the waning of maternal immunity and the average age of infection during which vaccination is likely to be effective and prophylactic in most children (McLean and Anderson 1988a; McLean and Anderson 1988b). The optimal age of vaccination will fall within this age window, where the lower end is determined by acquired maternal immunity (Moss and Griffin 2006; McLean and Anderson 1988a), and the upper end is classically considered to be determined by local disease incidence (McLean and Anderson 1988a).

There is uncertainty in the literature about when, on average, maternal immunity wanes in any specific population. Some evidence suggests that vaccine-derived maternal immunity wanes earlier than naturally-derived maternal immunity (that is, maternal immunity from women who have been infected with measles) (Leuridan et al. 2010), but the magnitude of this difference and the effect it may have on the optimal age at which to vaccinate is unclear. Additionally, the mother's health (Scott et al. 2005) as well as local nutrition and breast feeding practices have been shown to affect the rate of waning of maternal immunity and are difficult to know precisely (Cáceres et al. 2000). What limited evidence we have available suggests that the rate at which maternal immunity wanes varies from country to country (McLean and Anderson 1988b).

In places where measles is endemic, children may become infected and therefore become naturally resistant before the age at first vaccination. Thus, vaccines administered too late fail to prevent disease and may be considered as "wasted" doses – doses administered to a person already immune. It is classically understood that, as disease incidence declines, average age of infection increases (Roggendorf et al. 2010), thus increasing the upper age limit on the window of infant susceptibility. In these settings, a common policy is to increase the target age of routine immunizations so that a greater proportion of infants will have lost maternal immunity, and each dose is more likely to be more effective (Christie and Gay. 2011).

However, we have seen unexpected outbreaks in countries with what was thought to be good measles control, such as the 2009 epidemic in Burkina Faso (Kidd et al. 2012) and the 2010 epidemic in Malawi (Minetti et al. 2013). These countries had otherwise low disease incidence and high routine coverage. However, these unexpected epidemics indicate that despite the low measles incidence there was a substantial susceptible pool. The interaction between vaccine effectiveness, maternal immunity, and the chosen age target for routine immunization may have contributed to the rapid build-up of this susceptible pool and the underestimation of outbreak risk.

Differences in age structure could also contribute to observed differences in population immunity resulting from similarly targeted RIs. Notably, the proportion of the population in the Americas that is less than one year old is much smaller than the proportion of the African population that is less than one year old. As such, the number of children in the susceptible window in Africa will make up a relatively large proportion of the population and may suggest the need for a different target age for routine immunization. Consequently, the upper end of the infant susceptibility

window may also be determined by the age structure of the region, rather than solely by disease incidence. Importantly, if the target age of vaccination is not tailored to average local immunity and age structure, the proportion of infants no longer maternally immune but not yet vaccinated might be too large for herd immunity to be achievable (Fig. 2.1a). In essence, if more than 5% of the population is in the susceptible window between waning of maternal immunity and vaccination, a 95% population immunity level will be unachievable.

The existence of this window of susceptibility (Fig. 2.1) means that population immunity will always be less than or equal to routine immunization coverage in disease-free settings. That is, some doses are administered to infants who still retain their maternal antibodies, and some susceptible infants are not yet eligible for the vaccination. Thus, for any combination of age target, age distribution, and waning rate, we can characterize the immunity gap between coverage and population immunity; this immunity gap tells us the amount by which population immunity falls short of coverage.

In this paper we develop a discrete-time age structured population model for the distribution of immunity in a disease free population, and analyze the equilibrial states of this model. We analyze the size and distribution of the cross hatched regions in Figure 2.1, which show the proportion of the population not covered by either maternal immunity or vaccination. We use this analysis to assess the relative size and age-distribution of the susceptible population resulting from a variety of vaccine plans, specified by target age and coverage, and the effect of these plans on population immunity. We also calculate the immunity gap between population immunity and coverage for each of these vaccine plans. We then evaluate these vaccine plans (specific combinations of target vaccination age and planned coverage) for a range of age

distributions to quantify the impact of age structure on vaccine program success. We then suggest some methods for selecting among a range of vaccine plans where herd immunity is equally achievable or unachievable.

**Methods**

We developed an age-structured model for a human population, using 131 age classes. Age classes are monthly, up to 5 years old, and then are yearly until 75 years old, when we assume individuals are removed from the population. The relative size of these age classes is determined by a specified age structure. We explored two base age structures – a concave one, representing an idealized developed population, as in the United States, and a convex one, representing an idealized developing population, as in Sub-Saharan Africa (see Fig. A.1 in Appendix A). Throughout this paper, we use "developing" and "developed" to refer solely to the age structure of the region, not their economic development. We also consider the effect of a range of intermediate age structures, based on a weighted ($\alpha$) average of these two base age structures.

Each of these age classes are then divided into one of three immune classes – maternally immune, susceptible, or vaccinated. In this study, we omit the naturally immune classes, as we conduct a steady state analysis under the assumption of long-term disease absence, as might be the case in most of the United States. We then quantify the relative size and age distribution of these classes, paying special attention to the susceptible class, as that is the class of interest for population immunity; the susceptible class can make up no more than 5% of the population if we are to maintain herd immunity.

To divide these age classes into the immune classes, we first calculate the proportion of individuals who are born with maternal immunity (Eqn. 1). Then, accounting for maternal

immunity waning at a specified rate, we calculate the proportion of individuals in each older age class. Once we know what proportion of individuals in each age class is maternally immune, we can calculate effective vaccine cover from a specified target age and coverage, given that maternally immune individuals cannot be successfully immunized. From there, we assume that the proportion of vaccinated individuals in each subsequent age class remains the same. We assume that the remainder of the population (that is, those not maternally immune or vaccinated) is susceptible.

Vaccines are administered at a given age, $t$, with a given coverage, $C$; this combination of specifications is termed the vaccine plan. The proportion that are successfully immunized is a proportion equal to the coverage, $C$, of the proportion of individuals that are not maternally immune in the target age class, $t$. We assume that these two proportions are independent, as a proportion of the vaccinated population is still maternally immune and so is vaccinated but does not achieve vaccine-derived immunity – that is, is not considered successfully vaccinated. Each subsequent age class has the same proportion of successfully vaccinated individuals as the first vaccinated age class, $t$, but loses some immune individuals as maternal immunity continues to wane.

The probability that any individual is born with maternal immunity depends on the equilibrium state of a generational model. The probability that an individual is born maternally immune in generation $T$, $p_{MT}$, is equal to the probability that his/her mother was successfully vaccinated in the previous generation, $V_{T-1}$. This, in turn, is dependent on the vaccine coverage, $C$, and the probability that the mother was no longer maternally immune when the vaccine was administered at age $t$, so that:

$$p_{MT} = V_{T-1} = C(1 - (\frac{\omega-1}{\omega})^t p_{M(T-1)}) \quad (1)$$

Here, $\omega$ is the average age where maternal immunity wanes. Assuming that there has been no change in vaccine policy or maternal immunity between generations, the steady state proportion of infants born with maternal immunity, $p_{M^*}$ (where $p_{M^*} = p_{MT} = p_{M(T-1)}$), is found by solving the resulting equation:

$$p_{M^*} = C(1 - (\frac{\omega-1}{\omega})^t p_{M^*}) \quad (2)$$

We find the steady state proportion of infants born with maternal immunity is $\frac{C}{1+C(\frac{\omega-1}{\omega})^t}$.

Notably, this proportion goes up with coverage, but saturates at some level dependent on the average age of maternal immunity waning and the age at vaccination.

For each successive age class, we then find the proportion of individuals that remain maternally immune, based on one of two exponential decay functions with an average age of waning of either three or six months. We chose these average ages because most estimates in the literature fall within that range (Cáceres et al. 2000, Waaijenborg et al. 2013). That is, each successive age class has $\frac{\omega-1}{\omega}$ times as many maternally immune individuals as the previous class, where $\omega$ is either 3 or 6 (see Fig. A2 in Appendix A). Maternal immunity continues to wane in this way until the 5 year age class, when we assume that no individuals are maternally immune any longer.

The proportion of each age class left susceptible is simply the proportion neither maternally immune nor immunized. From this model, we have an age distribution of susceptibility, with different numbers of susceptible individuals in each age class. We first calculate the total

proportion immune achieved by any specific vaccine plan given by a target age and coverage. We then examine the resulting age distribution of susceptibility, and how that varies with coverage. We also examine the immunity gap between programmatic vaccine coverage and achieved population immunity, with the idea that this immunity gap might provide a means of discriminating between apparently equivalent vaccine plans. Finally, we assess the dependence of this vaccine program success on age structure, both in how age structure can affect the recommended vaccine plan, and how the success of a specific vaccine plan depends significantly on age structure alone.

**Results**

We first develop contours for the maintainable population immunity for a given age structure and maternal immunity duration, under a specific vaccine plan comprising of a specified target age (in months) and coverage (Fig. 2.2). For a developing age structure with maternal immunity waning at 6 months, the commonly quoted herd immunity threshold of 95% is unachievable, no matter when children are vaccinated and what coverage is achieved (Fig. 2.2a). However, if vaccination is targeted at the older age classes (12 + months) and achieves high coverage, then over 90% of the population will be immune. When maternal immunity in a developing age structure is assumed to wane at 3 months, the herd immunity threshold is achievable, but only for extraordinarily high coverage and over a limited age range for vaccination (Fig. 2.2b). Taking the difference between these two surfaces (Fig. 2.3a) shows that the average age at which maternal immunity wanes makes the largest difference in population immunity when vaccination happens at a young age and with high coverage. The general shape of this difference in response to waning maternal immunity is the same regardless of the underlying age structure.

In comparison, it is relatively easy to achieve the herd immunity threshold with a developed age structure. With maternal immunity waning at 6 months, the herd immunity threshold is achievable if vaccination occurs at an older age and with high coverage (Fig. 2.2c). Notably, this successful age range is strictly older than the age range successful in a developing region with maternal immunity waning at 3 months (Fig. 2.2b). If maternal immunity wanes at 3 months on average, then the herd immunity threshold is achievable with high coverage at a wide range of ages (Fig. 2.2d). Comparing the results from the developed and the developing age structures shows that the shape of the differences due to underlying population age structure (Fig. 2.3b) is similar no matter the rate at which maternal immunity wanes, although the maximum magnitude of the difference varies (the shape of the immunity gap between coverage and population immunity is not the same, as shown in Fig. A4 in Appendix A).

We quantify the impact of age structure on vaccine program success by considering a range of age structures, which are linear composites of the developing and developed age structures according to some weight, $\alpha$. We use $\alpha$ to represent the proportional weight of the developed age structure – for example, when $\alpha$ is 0.25, this means that we took a weighted average of the two age structures, with a 25% weight on the developing age structure and a 75% weight on the developed age structure. When $\alpha$ is zero, the age structure is precisely the developed age structure, and when $\alpha$ is one, the age structure is precisely the developing age structure. We find that, even when vaccinating to achieve maximum population immunity given a specific age structure (Fig. 2.4a), the achieved population immunity continually decreases as the age structure becomes more and more similar to the purely developing one. With maternal immunity waning at 6 months, the 95% threshold is entirely unachievable once more than 60% of the age structure is of the developing form. The situation is even worse if the same vaccine plan (i.e. same

coverage and target age) is applied across all age structures, especially if the one that works best for the developing age structure is chosen (Fig. 2.4b).

Population immunity is always less than vaccine coverage (to see how they relate, see Fig. A3 in Appendix A), but the difference depends on the specific vaccine policy and population structure. We show the immunity gap for several target ages which are sufficient for herd immunity in a developing region, where the target age that minimizes the immunity gap changes depending on vaccine coverage (Fig. 2.5). Notably, the shape of these different curves changes depending on the target age of vaccination, as the source of the immunity gap (age structure or maternal immunity) changes depending on target age. This change in shape means that the target age that minimizes the immunity gap changes with respect to coverage. In Figure 2.5a, for coverages below around 67% (indicated by the lighter vertical line), it is best (in terms of minimizing the immunity gap) to vaccinate at 10 months of age, as low coverage will mean low levels of maternal immunity. For higher coverages, it is best to vaccinate at 12 months. At around 92% coverage – indicated by the darker vertical line in Figure 2.5a and the only vertical line in Figure 2.5b – the formerly optimal target age becomes dramatically worse due to the nonlinear interaction with maternal immunity, with the immunity gap exceeding that of all but the very oldest target ages.

**Discussion**

Our work shows that herd immunity may not be maintainable with a single dose routine vaccine plan, even administered optimally, depending on the specific age structure and maternal immunity of the region. Fortunately, strategies for the maintenance of measles elimination commonly include a second dose. However, even in the context of a second dose vaccine plan, it

does not make sense to administer the first dose of a two-dose vaccine strategy ineffectively, with the hope that the second dose will make up for failings in the first, especially if the result is a large susceptible population that is too young to be caught by a second dose vaccine strategy at all. Optimizing the first dose is beneficial in all cases. Our results suggest ways that we can maximize the impact of the first dose to improve population immunity by specifically targeting a vaccine program to the local context, specifically the demography and maternal immunity levels of the target population.

In principle, herd immunity is maintainable in all cases except when vaccinating in a population with a developing age structure and long maternal immunity (Fig. 2.2a). However, herd immunity is maintainable for a wider range of coverage and ages when vaccinating given a developed age structure (Fig. 2.2c,d). Notably, the range of target ages where herd immunity is maintainable in a developed region is much older than the age range where herd immunity is maintainable in a developing region, if it is achievable at all in a developing region.

With a developing age structure, where the average age is fairly young, more children fall below the age of first vaccination, and herd immunity is more difficult to maintain. It is especially difficult if the choice of vaccine plan is based on the recommended strategy for a developed age structure, where the average age is much older (Fig. 2.4b). This demonstrates the importance of context-dependent vaccination planning. Population immunity improves when a vaccine plan optimized to the local age structure and maternal immunity function is chosen (Fig. 2.4a), so that the difficulty imposed by the age structure is effectively minimized. Interestingly, the age at vaccination that maximizes population immunity in a developing region is often younger than that which maximizes immunity in a developed region. That is, the luxury to vaccinate older

individuals to minimize doses rendered ineffective by maternal immunity is affordable when vaccinating in a developed region, but age structure forces the vaccination of younger individuals when vaccinating in a developing region. Notably, reducing the age of first vaccination is a strategy not generally considered when making and implementing current vaccine policy.

Context-dependent vaccination planning may also be useful at a finer spatial scale. Vaccine program success in Africa is relatively patchy, with some countries having only sporadic outbreaks that suggest they are near eradication, while others still have regular seasonal outbreaks (Minetti et al. 2013; Ferrari et al. 2008). These regional differences in vaccine program success may be due to differences in logistic effectiveness, but are likely also impacted by the interaction of maternal immunity and age structure. Just as regions with developing age structures, such as Africa, are different from regions with developed age structures, such as the Americas, different regions within Africa are different from each other with regard to age structure and also, potentially, the duration of maternal immunity. A context-dependent management strategy that takes into account local patterns in immunity and age structure and evaluates their relative significance is necessary in this case.

We introduce a new measure of program success called the immunity gap, and examine the effect of changing target age or changing population age structure and maternal immunity on the relationship between coverage and the immunity gap. In some ways, the immunity gap represents "wasted" doses – that is, the difference between population vaccine coverage and population immunity achieved. Regardless of vaccine plan or population, the immunity gap always increases as coverage increases. This is, in some ways, a numerical representation of the "last mile" problem (Klepac et al. 2013) – as measles control improves, the cost per case

prevented increases. However, the way this the immunity gap scales with coverage varies depending on the source of the immunity gap.

If vaccines are administered too early (Fig. 2.5), the immunity gap varies non-linearly (almost exponentially) with coverage. This is a signature of the maternal immunity function on population immunity. If the vaccine is administered later, or to a population with shorter maternal immunity, the immunity gap scales more linearly with coverage. By looking at these together, general recommendations can be made. If the source of this immunity gap is interference with maternal immunity, vaccines should be administered at older ages. If the source is the interaction with age structure, vaccines should be administered at younger ages. The immunity gap could provide a novel way to select between apparently equal vaccine plans. Choosing a vaccine plan to minimize the immunity gap given information about local age structure, maternal immunity levels and achievable coverage, would also maximize the proportional immunity conferred per dose administered.

The immunity gap is not the only means of selecting between vaccine plans. In cases where increasing the age of vaccination reduces the immunity gap, this change in age targets may increase the potential mortality associated with an epidemic by increasing the proportion of susceptibles who are very young. Targeting younger children for vaccination may increase the immunity gap non-linearly, but could minimize loss of life, as a larger proportion of susceptibles would fall in the less at-risk age classes. When coverage is low, the immunity gap is small and the majority of susceptibles are in the oldest age classes. As coverage increases, the immunity gap increases and the proportion of susceptibles below the age of vaccination increases, although the absolute number may not. The magnitude of this shift depends on the target age of

vaccination and the age distribution and maternal immunity function of the population. Again, these younger children are the individuals that are most likely to die during an epidemic (Wolfson et al. 2009).

An additional utility of the immunity gap measure (Fig. 2.5) is that using vaccine coverage as a proxy for population immunity may lead to a severe underestimation of disease risk, and the size of this underestimate is context-dependent. This may explain some of the patterns in measles re-emergence that we see in places with what was thought to be good vaccine coverage, such as Malawi and Germany. Malawi had reasonably good measles control, having seen a period of local elimination of disease. However, in 2010, there was a devastating outbreak, with the age distribution of cases being much older than expected (Minetti et al. 2013). At the time, Malawi was officially administering a first dose of the measles vaccine to infants between the ages of 9 and 11 months, with a second dose comprising of a supplemental immunization campaign targeting individuals less than 5 years old. On the other hand, Germany has struggled to maintain herd immunity to measles for a while, with frequent outbreaks. The age distribution of some of these outbreaks (Siedler et al. 2011) is older than typically seen in a measles outbreak. In Germany, the first dose was classically administered at 12 months, with the second dose coming between 4 and 6 years of age. In 2001, Germany changed its guidelines, expanding the window for first dose administration and lowering the age of the second dose. In both cases, coverage was thought to be good, but outbreaks occurred. Thus, while administrative coverage may have been at, or above, the programmatic target, the combination of age distribution and waning of immunity may have resulted in sub-critical immunity.

Our work does not include population heterogeneity, age-specific contact patterns or age-specific force of infection. Such processes are certainly relevant for more complex dynamical analyses of measles incidence. We omit them, in part, because our work is an intentionally simple analysis to highlight the importance of an under-considered tradeoff between age structure and maternal immunity. Additionally, single dose vaccine plans are not commonly implemented intentionally (Hall and Jolley 2011). There is evidence for the existence of remote locales with low disease incidence and low second-dose coverage (Minetti et al. 2013), but most countries officially give a second dose of the measles vaccine, even though the second dose may not be administered at the recommended ages or at the ages with the largest remaining susceptible populations (Clark and Sanderson 2009). This research could provide a means to optimize vaccine policy for such locales, as well as other locales where second-dose coverage is patchy or otherwise uncertain, though future work incorporating a second dose would also be informative.

This work presents an equilibrial analysis of this disease system, meant to supplement existing dynamical work in an intuitive way. Future work could include additional aspects of vaccine program complexity, including target age ranges and a second dose vaccine strategy, as well as disease dynamics. Nonetheless, this work has some interesting implications. As a larger proportion of any population is below the age of vaccination, herd immunity becomes increasingly difficult to maintain – that is, if a population has a relatively large infant population, herd immunity to measles will be difficult, if not impossible, to maintain with a single dose vaccine plan. Population structure also interacts with the waning of maternal immunity in ways that can mislead us into thinking that population immunity is better than it really is. However, our work suggests the possibility of improving local disease control, despite obvious difficulties, by taking specific context-dependent factors into account (Hall and Jolley 2011). Our model

could be adapted to fit any specified age structure and maternally-derived immunity waning function and then used to make a recommendation that minimizes the immunity gap given an estimated coverage. These results are only complicated if maternal immunity lasts too long to effectively vaccinate any earlier. However, given a heavily youth-weighted age structure, vaccinating earlier may be beneficial, as a second dose vaccine strategy will be better at catching those for whom the vaccine was not effective.

**Acknowledgements**

We thank Ottar Bjørnstad, whose comments contributed to this manuscript. We acknowledge funding from EEID award 1 R01 GM105247-01 jointly funded through National Institutes of Health and National Science Foundation and from the Vaccine Modeling Initiative funded by the Bill and Melinda Gates Foundation.

**References**

1. Anderson RM, May RM. Infectious Diseases of Humans: Dynamics and Control. Oxford University Press, Oxford; 1991.
2. Bauch CT, Szusz E, Garrison LP. Scheduling of measles vaccination in low-income countries: projections of a dynamic model. Vaccine 2009; 27: 4090–8.
3. Cáceres VM, Strebel PM, Sutter RW. Factors determining prevalence of maternal antibody to measles virus throughout infancy: a review. Clin Infect Dis 2000; 31:110–9. doi: 10.1086/313926
4. Castillo-Solórzano C, Marsigli C, Danovaro-Holliday MC, et al. Measles and rubella elimination initiatives in the Americas: lessons learned and best practices. J Infect Dis 2011; 204 Suppl:S279–83. doi: 10.1093/infdis/jir216

5. Castillo-Solórzano C, Reef SE, Morice A, et al. Guidelines for the documentation and verification of measles, rubella, and congenital rubella syndrome elimination in the region of the Americas. J Infect Dis 2011; 204 Suppl 2:S683–9. doi: 10.1093/infdis/jir471

6. Christie AS, Gay A. The Measles Initiative: moving toward measles eradication. J Infect Dis 2011; 204:S14–7. doi: 10.1093/infdis/jir075

7. Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. Lancet 2009; 373:1543–9. doi: 10.1016/S0140-6736(09)60317-2

8. Cutts FT, Grabowsky M, Markowitz LE. The effect of dose and strain of live attenuated measles vaccines on serological responses in young infants. Biologicals 1995; 23:95–106

9. Danet C, Fermon F. Management of a measles epidemic: Practical guide for doctors, nurses, labratory technicians, medical auxiliaries and logisticians. Médecins Sans Frontières, Paris; 2013.

10. Ferrari MJ, Grais RF, Bharti N, et al. The dynamics of measles in sub-Saharan Africa. Nature 2008; 451:679–84. doi: 10.1038/nature06509

11. Gans H, Yasukawa L, Rinki M, et al. Immune responses to measles and mumps vaccination of infants at 6, 9, and 12 months. J Infect Dis 2001; 184:817–26. doi: 10.1086/323346

12. Hall R, Jolley D. International measles incidence and immunization coverage. J Infect Dis 2011; 204 Suppl :S158–63. doi: 10.1093/infdis/jir124

13. Kidd S, Ouedraogo B, Kambire C, et al. Measles outbreak in Burkina Faso, 2009: a case-control study to determine risk factors and estimate vaccine effectiveness. Vaccine 2012; 30:5000–8. doi: 10.1016/j.vaccine.2012.05.024

14. Klepac P, Metcalf CJE, McLean AR, Hampson K. Towards the endgame and beyond: complexities and challenges for the elimination of infectious diseases. Philos Trans R Soc B Biol Sci 2013; 368(1623). doi: 10.1098/rstb.2012.0137

15. Koehlmoos TP, Uddin J, Sarma H. Impact of measles eradication activities on routine immunization services and health systems in Bangladesh. J Infect Dis 2011; 204 Suppl:S90–7. doi: 10.1093/infdis/jir086

16. Leuridan E, Hens N, Hutse V, et al. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. Br Med J 2010; 340:c1626–c1626. doi: 10.1136/bmj.c1626

17. Morbidity and Mortality Weekly Report. Increased transmission and outbreaks of measles, European Region, 2011. Wkly Epidemiol Rec 2011; 86:559–64

18. McLean AR, Anderson RM. Measles in developing countries. Part I. Epidemiological parameters and patterns. Epidemiol Infect 1988; 100:111–133

19. McLean AR, Anderson RM. Measles in developing countries. Part II. The predicted impact of mass vaccination. Epidemiol Infect 1988; 100:419–42

20. Minetti A, Bopp C, Fermon F, et al. Measles outbreak response immunization is context-specific: insight from the recent experience of médecins sans frontières. PLoS Med 2013; 10:e1001544. doi: 10.1371/journal.pmed.1001544

21. Minetti A, Kagoli M, Katsulukuta A, et al. Lessons and challenges for measles control from unexpected large outbreak, Malawi. Emerg Infect Dis 2013; 19:202–9. doi: 10.3201/eid1902.120301

22. Moss WJ, Griffin DE. Global measles elimination. Nat Rev Microbiol 2006; 4:900–8. doi: 10.1038/nrmicro1550

23. Parent du Châtelet I, Antona D, Freymuth F, et al. Spotlight on measles 2010: update on the ongoing measles outbreak in France, 2008-2010. Euro Surveill 2010; 15:2008–2010

24. Parker A, Staggs W. Implications of a 2005 measles outbreak in Indiana for sustained elimination of measles in the United States. N Engl J Med 2006; 355:447–455.

25. Roggendorf H, Mankertz a, Kundt R, Roggendorf M. Spotlight on measles 2010: measles outbreak in a mainly unvaccinated community in Essen, Germany, March-June 2010. Euro Surveill 2010; 15:9–11

26. Rota P a, Brown K, Mankertz A, et al. Global distribution of measles genotypes and measles molecular epidemiology. J Infect Dis 2011; 204 Suppl 1:S514–23. doi: 10.1093/infdis/jir118

27. Scott S, Cumberland P, Shulman CE, et al. Neonatal measles immunity in rural Kenya: the influence of HIV and placental malaria infections on placental transfer of antibodies and levels of antibody in maternal and cord serum samples. J Infect Dis 2005; 191:1854–60. doi: 10.1086/429963

28. Shibeshi ME, Masresha BG, Smit SB, et al. Measles resurgence in southern Africa: challenges to measles elimination. Vaccine 2014; 32:1798-807. doi: 10.1016/j.vaccine.2014.01.089

29. Siedler A, Mankertz A, Feil F, et al. Closer to the goal: efforts in measles elimination in Germany 2010. J Infect Dis 2011; 204 Suppl:S373–80. doi: 10.1093/infdis/jir068

30. Simons E, Ferrari M, Fricks J, et al. Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. Lancet 2012; 379:2173–8. doi: 10.1016/S0140-6736(12)60522-4

31. Sugerman DE, Barskey AE, Delea MG, et al. Measles outbreak in a highly vaccinated population, San Diego, 2008: role of the intentionally undervaccinated. Pediatrics 2010; 125:747–55. doi: 10.1542/peds.2009-1653

32. van Treeck U. Measles outbreak in Germany: over 1000 cases now reported in Nordrhein Westfalen. Euro Surveill 2006; 11:11–13

33. Waaijenborg S, Hahné SJM, Mollema L, Smits GP, Berbers GAM, van der Klis FRM, de Melker HE, Wallinga J. Waning of maternal antibodies against measles, mumps, rubella, and varicella in communities with contrasting vaccination coverage. J Infect Dis 2013; 208:10–6. doi:10.1093/infdis/jit143

34. WHO. GLOBAL MEASLES AND RUBELLA. 2012.

35. Wolfson LJ, Grais RF, Luquero FJ, et al. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. Int J Epidemiol 2009; 38:192 10.3201/eid1902.120301ples.

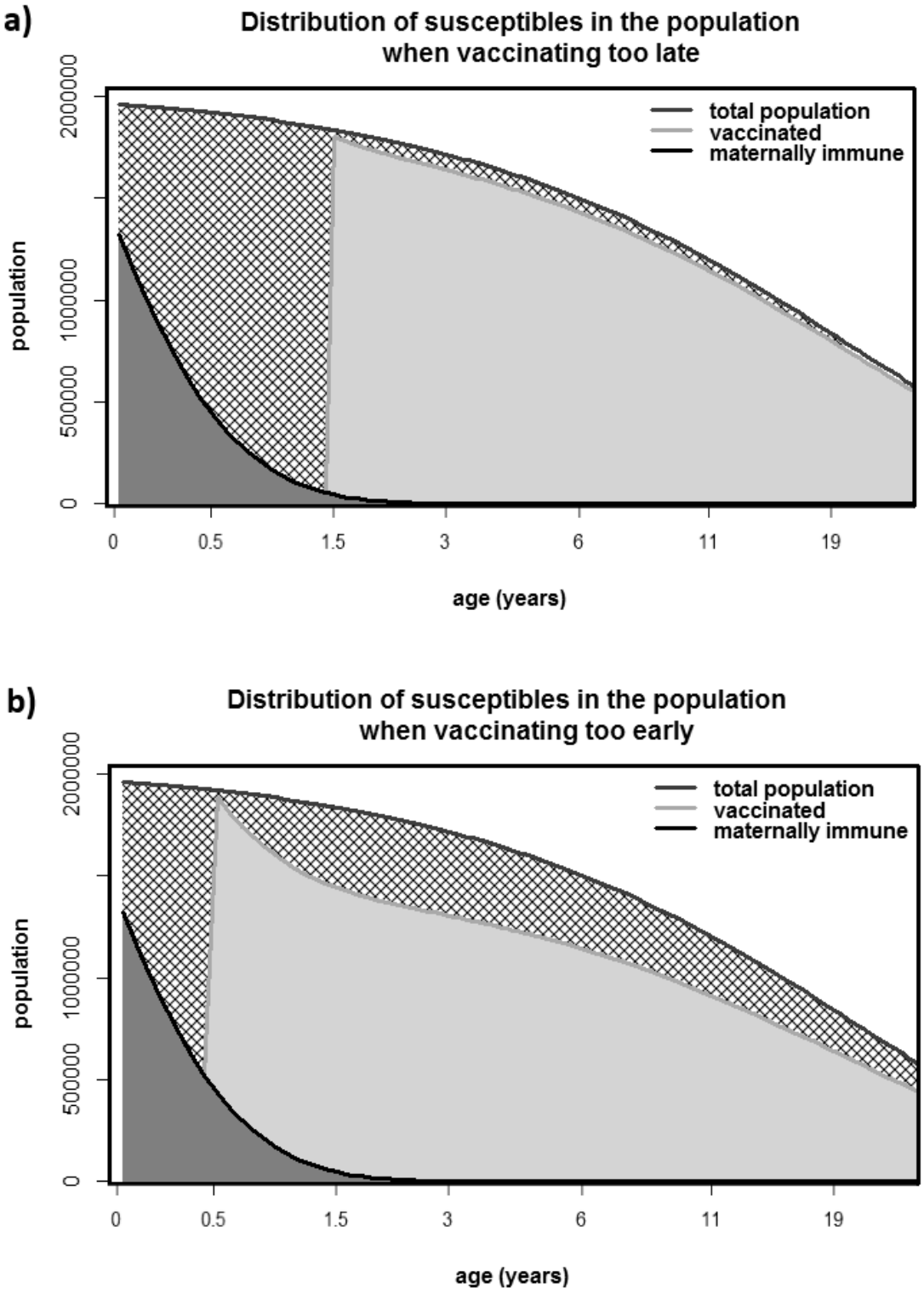



**Figure 2.1**: Two sample age distributions of immunity within a population. The dark grey

region is the portion still maternally immune, the pale grey region is the vaccinated proportion and the hatched region is the proportion that remains susceptible. The x-axis is shown on a log scale, so the total hatched regions in **a)** and **b)** are of similar area. In **a)**, the vaccine is administered too late, and too many infants remain susceptible. In **b)**, the vaccine is administered too early, so too few doses are effective. Both of these figures use a developing population age structure assuming 6 month maternal immunity.

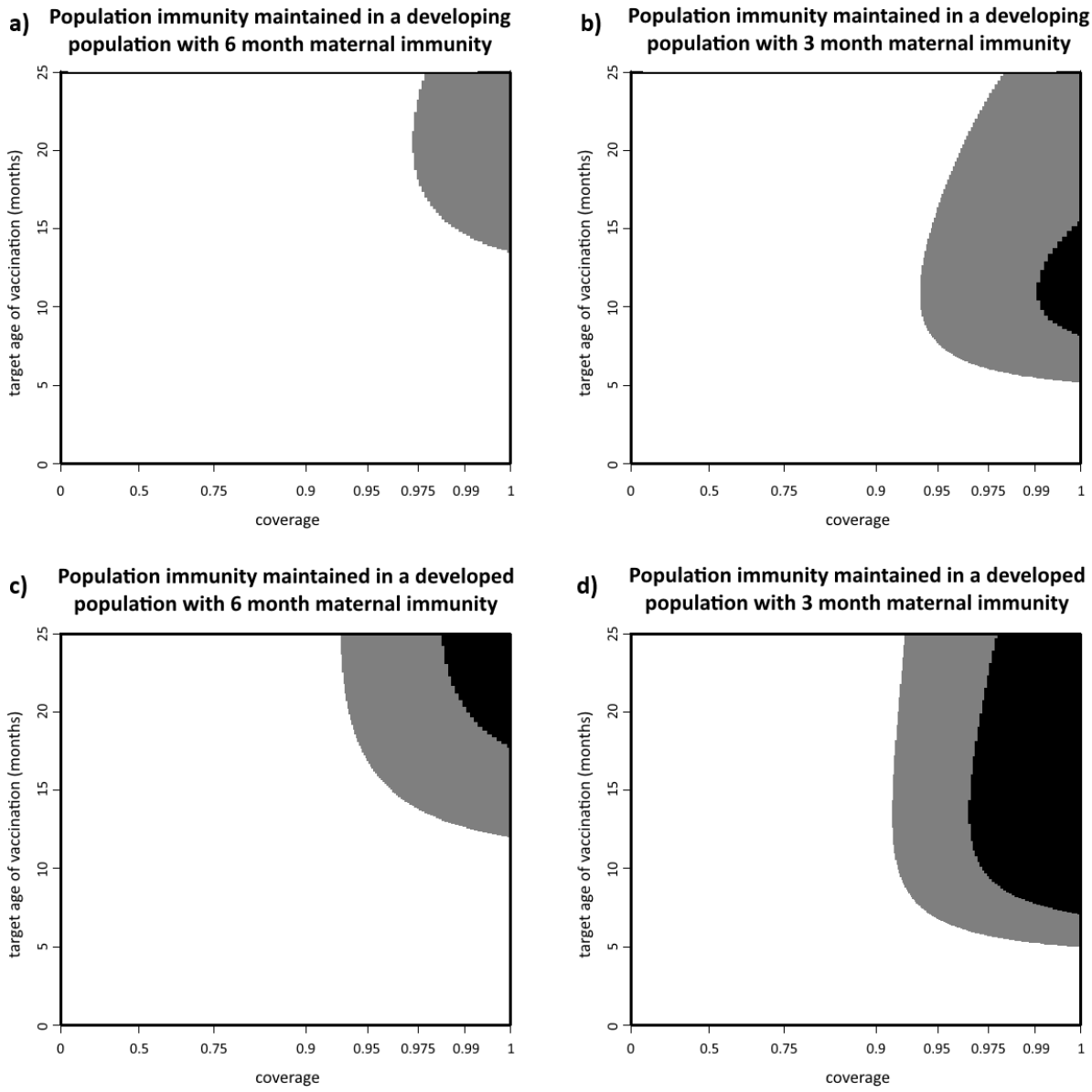
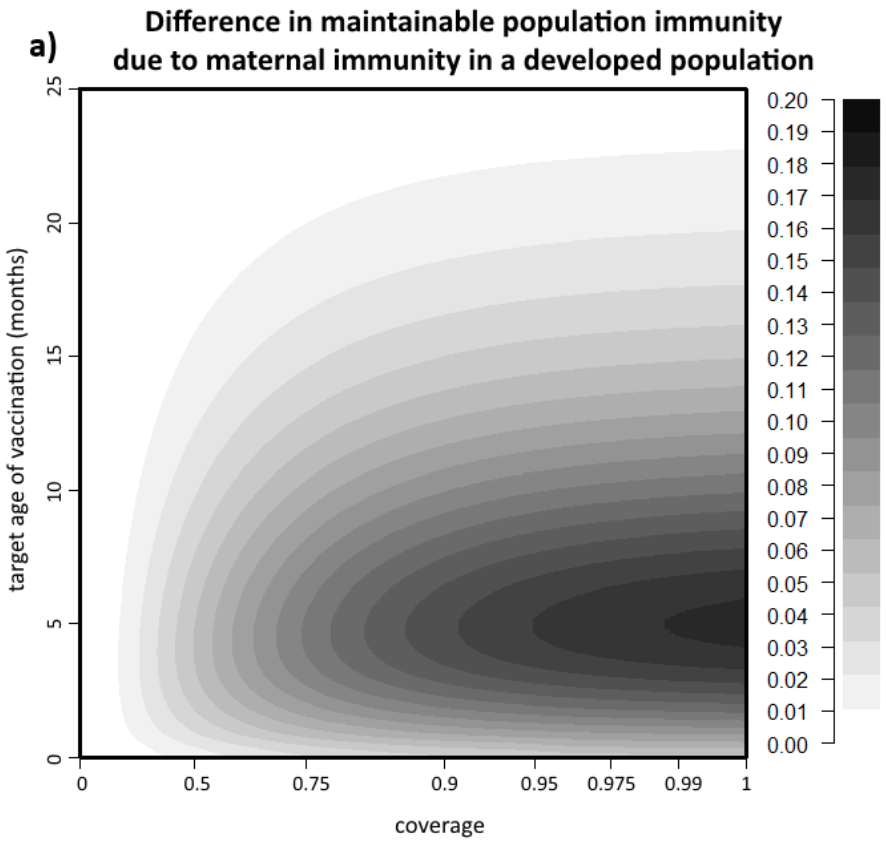



**Figure 2.2: a)** and **b)** Maintainable population immunity for maternal immunity waning at 6 and 3 months, respectively, in a region with a developing age structure. **c )** and **d)** Maintainable population immunity for maternal immunity waning at 6 months and 3 months, respectively, in a region with developed age structure. Strategies that meet the 95% threshold are shown in black, those that meet the 90% threshold are shown in grey**.**


a)
Difference in maintainable population immunity
due to maternal immunity in a developed population
target age of vaccination (months)
0
5
10
15
20
25
coverage
0
0.5
0.75
0.9
0.95
0.975
0.99
1
0.20
0.19
0.18
0.17
0.16
0.15
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00

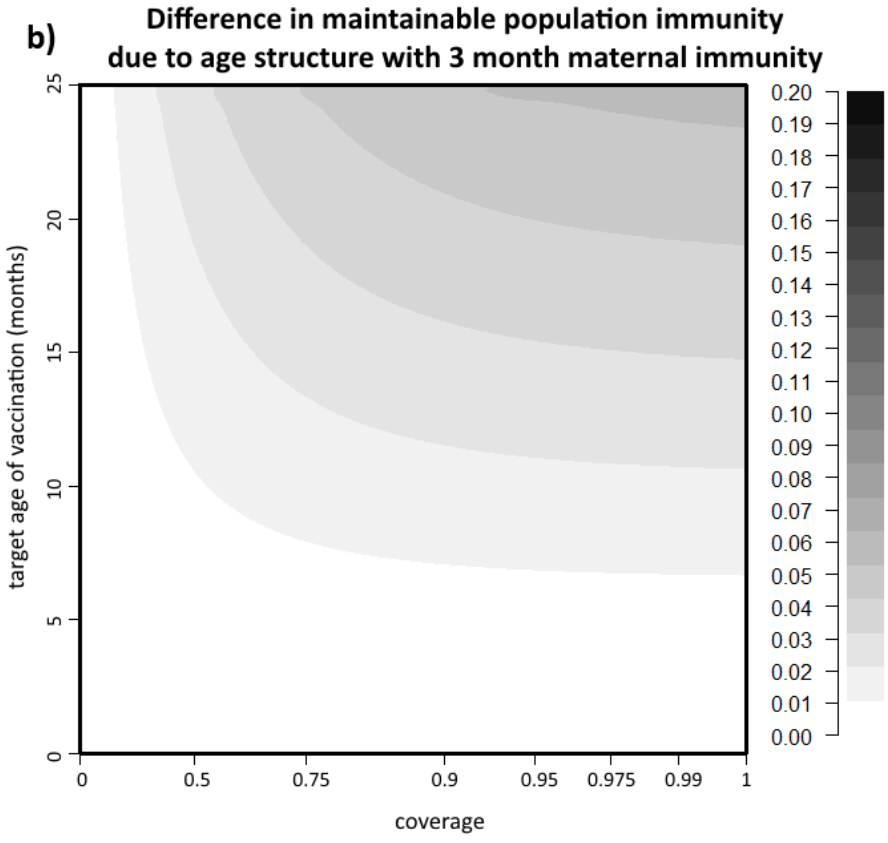
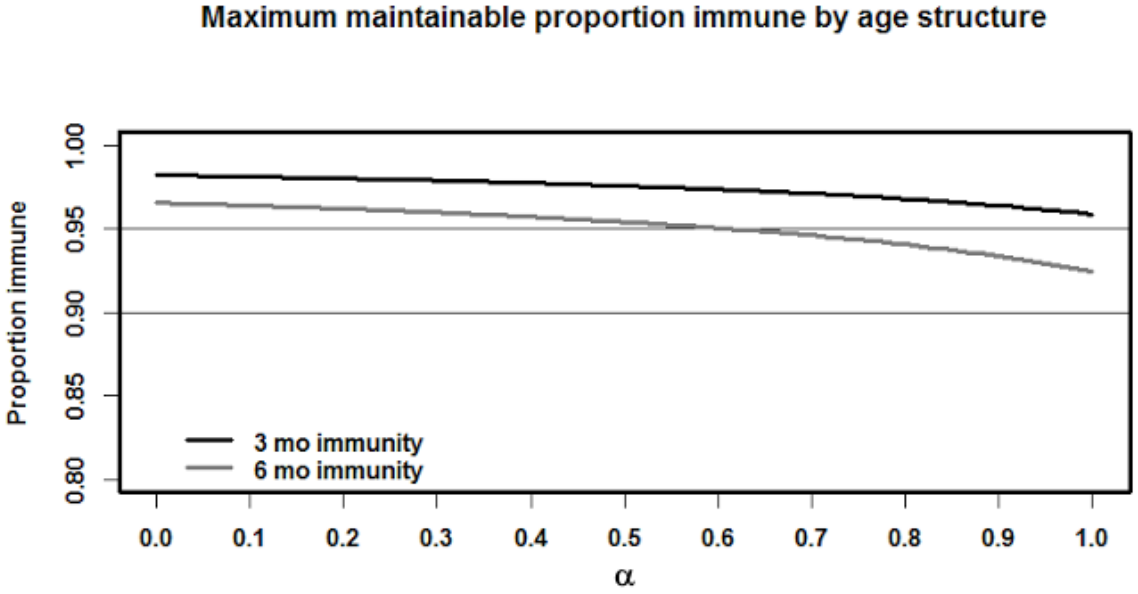

b)
Difference in maintainable population immunity
due to age structure with 3 month maternal immunity
target age of vaccination (months)
0
5
10
15
20
25
coverage
0
0.5
0.75
0.9
0.95
0.975
0.99
1
0.20
0.19
0.18
0.17
0.16
0.15
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00

**Figure 2.3: a)** The difference in population immunity due to differences in maternal immunity (i.e. the difference between **4 c** and **4 d). b)** Difference in population immunity for maternal immunity waning at 3 months between regions with a developed and developing age structure (i.e. the difference between **4 b** and **4 d).** Note that the target ages of vaccination which minimize the difference due to a difference in maternal immunity are where the difference due to a difference in age structure starts to increase.

a)


Maximum maintainable proportion immune by age structure
Proportion immune
1.00
0.95
0.90
0.85
0.80
3 mo immunity
6 mo immunity
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
α

b)

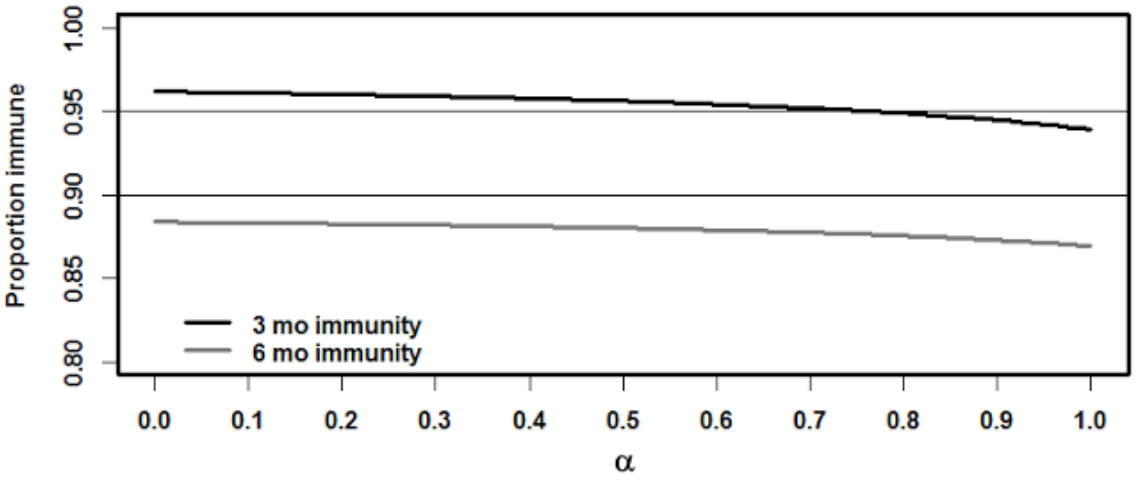
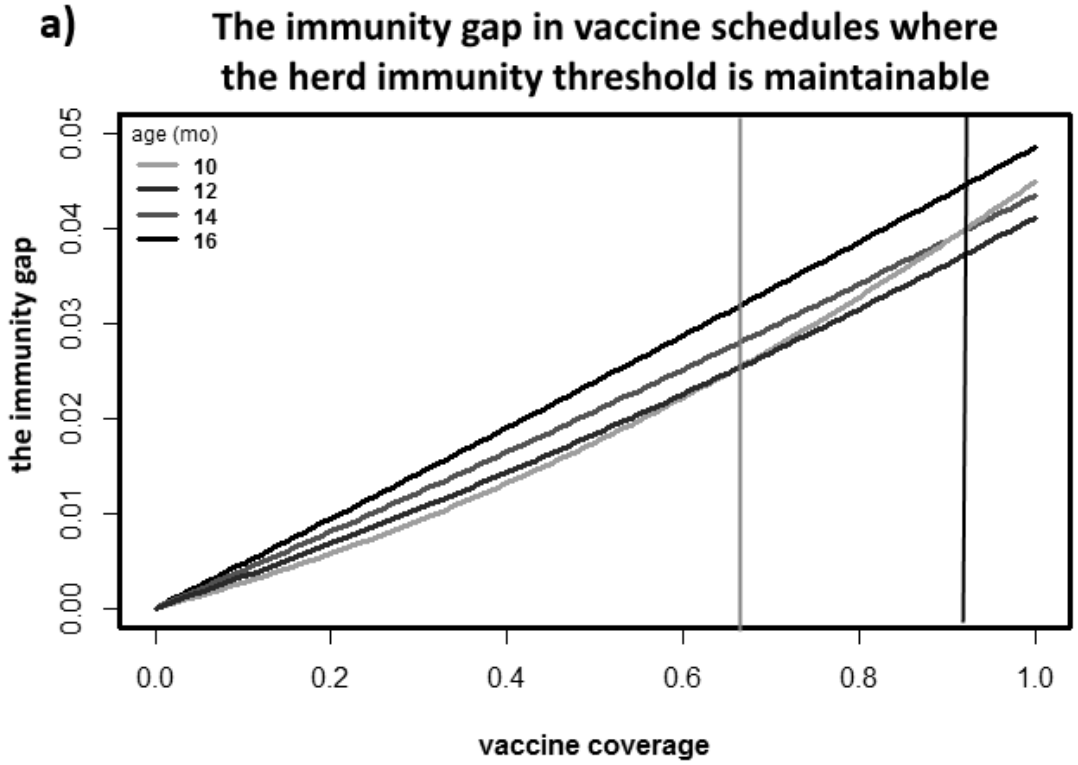

Proportion immune by age structure
when vaccinating at 12 months with 98% coverage
Proportion immune
1.00
0.95
0.90
0.85
0.80
3 mo immunity
6 mo immunity
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
α

**Figure 2.4:** The maintainable population immunity for a range of age structures. When α is 0, the age structure is the idealized developed one. When α is 1, the age structure is the idealized developing one. **a)** As the age structure shifts from developed to developing, the maximum maintainable proportion immune continuously declines. Notably, the proportion immune for long maternal immunity is lower than that for short maternal immunity, despite both being the specific maxima for that maternal immunity function. That is, the optimal vaccine policy for long maternal immunity is always less successful than the optimal for short maternal immunity. **b)** The achievable proportion immune when vaccinating at 12 months. With a developed age structure and short maternal immunity, this is a successful vaccine policy. However, as the age structure shifts towards the purely developing one, the success of the vaccine policy continually declines. With long maternal immunity, maintainable immunity is similarly low everywhere, but still worse on a developing age structure.

a)


The immunity gap in vaccine schedules where
the herd immunity threshold is maintainable
age (mo)
10
12
14
16
the immunity gap
0.00
0.01
0.02
0.03
0.04
0.05
0.0
0.2
0.4
0.6
0.8
1.0
vaccine coverage

b)

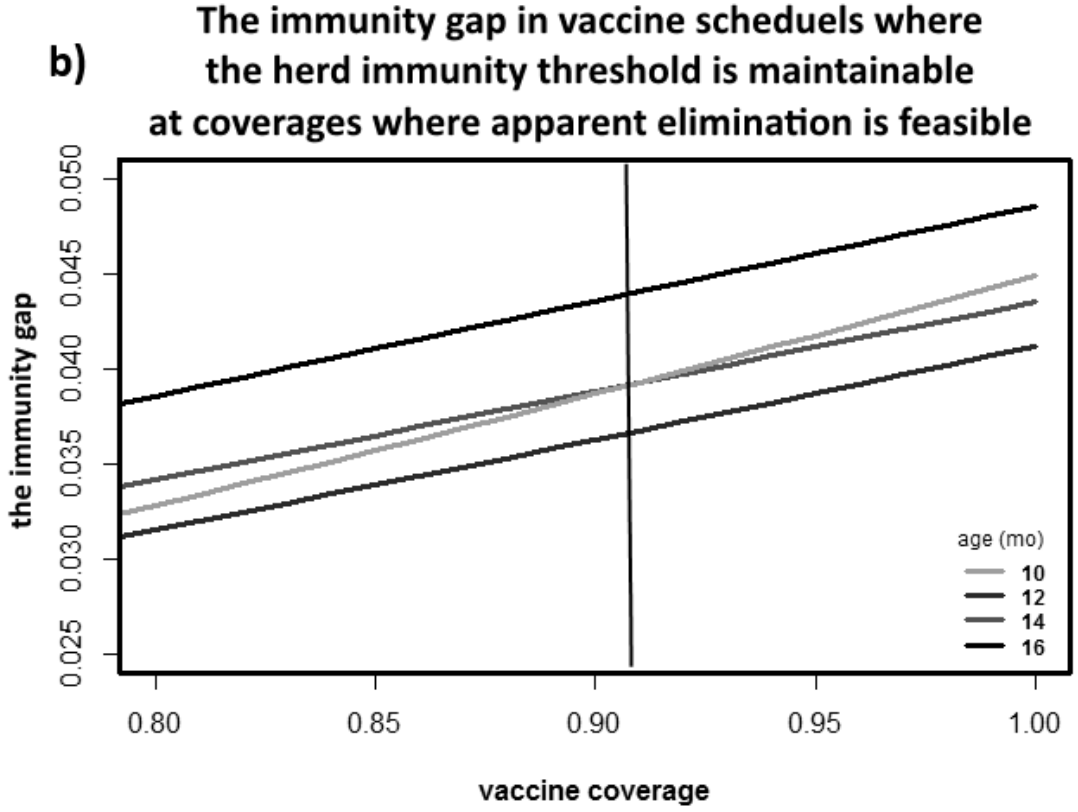

The immunity gap in vaccine scheduels where
the herd immunity threshold is maintainable
at coverages where apparent elimination is feasible
the immunity gap
0.025
0.030
0.035
0.040
0.045
0.050
0.80
0.85
0.90
0.95
1.00
vaccine coverage
age (mo)
10
12
14
16

**Figure 2.5:** These panels show the immunity gap – that is, the difference between vaccine coverage and population immunity – for a variety of target ages and coverages. Here we are comparing these vaccine schedules in a developing population with 3 month maternal immunity. **a)** At high coverage, all of these vaccine schedules could achieve herd immunity. However, as maternal immunity is less significant at older ages, it has a different effect on the immunity gap between the different ages. Notably, the immunity gap line when vaccinating at the youngest age with high coverage is significantly curved. **b)** Focusing on the immunity gap at coverages that might be maintained in regions with measles elimination, it is clear that 12 months is the best age to vaccinate at all of these coverages in a region with this age structure and maternal immunity decay. However, whether it would be better to miss the target age by vaccinating a little too young (10 months) or a little too old (14 months) depends on coverage, with vaccinating younger ages still being worse at high coverages.

# Chapter 3

## Optimal vaccine schedules to maintain measles elimination with a two-dose routine policy

Amalie McKee, Katriona Shea, and Matthew Ferrari

Accepted at Epidemiology and Infection

**Abstract**

Measles was eliminated in the Americas in 2002 by a combination of routine immunizations and supplementary immunization activities. Recent outbreaks underscore the importance of reconsidering vaccine policy in order to maintain elimination. We constructed an age-structured dynamical model for the distribution of immunity in a population with routine immunization and without disease, and analyzed the steady state for an idealized age structure and for real age structures of countries in the Americas. We compared the level of immunity maintained by current policy in these countries to the level maintainable by an optimal policy. The optimal age target for the first routine dose of measles vaccine depends on the timing and coverage of both doses. Similarly, the optimal age target for the second dose of measles vaccine depends on the timing and coverage of the first dose. The age targets for the first and second dose of measles vaccine should be adjusted for the post-elimination era, by specifically accounting for current context, including realized coverage of both doses, and altered maternal immunity. Doing so can greatly improve the proportion immune within a population, and therefore the chances of maintaining measles elimination, without changing coverage.

### Introduction

Measles, a viral illness, infects millions of children every year and currently results in more than 100 thousand deaths per year in children under five (Wolfson et al. 2009, Liu et al. 2014). As

such, it is an important target for global eradication (van de Ent et al. 2011). This eradication process includes two key components – achieving local elimination where the disease is present and maintaining elimination where the disease is absent. Different combinations of routine immunization strategies and supplemental immunization campaigns are used to achieve and maintain a high level of immunity (Lessler et al. 2011). Regional success was achieved when measles was eliminated from the Americas in 2002 using a combination of a two-dose routine immunization strategy with periodic supplemental immunization campaigns (Castillo-Solorzano et al. 2011a). While endemic disease has not reemerged, recent outbreaks, such as the outbreak in and around Disneyland, California from December 2014 to February 2015 (Zipprich et al. 2015), have cast doubt on the continued ability to maintain elimination. Optimizing the design of these vaccine strategies to maintain elimination in the Americas and achieve it worldwide is critical for continued success, for the eventual global eradication of measles, and for the end of childhood mortality attributable to measles.

Since elimination was achieved in 2002, maintenance of elimination in the Americas has involved two routine doses of vaccine administered to children who come to a clinic at specific target ages. These age targets for routine immunization have changed very little since measles was endemic in the Americas (Castillo-Solorzano et al. 2011b). Conventionally, the timing of these doses is considered to be dependent on two underlying factors (McLean and Anderson 1988a, McLean and Anderson 1988b). The first is maternal immunity; infants born to immune mothers are born with measles IgG antibodies, which are passively transferred through the placenta before birth (Niewiesk 2014). Infants are born with these antibodies regardless of whether their mother was vaccinated or naturally infected, although the initial titer is generally lower in children of vaccinated mothers (Brugha et al. 1996, Niewiesk 2014). While these

maternal antibodies provide infants some protection from the disease, they interfere with the efficacy of the vaccine and infants vaccinated before antibody titer has dropped below a threshold level will not be effectively immunized (Cutts et al. 1995, Gans et al. 2001). The second factor is the force of infection in the local population. Infants must be vaccinated before they become infected with, and potentially die from, measles (McLean and Anderson 1988a). Where measles incidence is high, children are likely to be exposed to infection earlier in life; thus it is more important to vaccinate children at younger ages. This second factor is absent in a disease free setting, as is the case when measles elimination is being maintained.

Recent work suggests that the selection of these target ages may also depend on an additional context-dependent factor: demography (McKee et al. 2015). If too many children fall below the age of first vaccination, there will be a large population of infant susceptibles contributing to the proportion of the overall population that is susceptible, thus decreasing the chances of maintaining measles elimination. Thus, even in the disease-free setting, this provides an upper bound on the age target for vaccination in order to maintain population level immunity above the herd immunity threshold.

Here, we show that the optimal age target may also depend on the coverage of the first and second dose. If coverage of the first dose is poor, the timing of the second dose should be adjusted to compensate, to account for the relatively large proportion of susceptible children between the first and second target ages of vaccination. If the coverage of the second dose is poor, the timing of the first dose should be adjusted to maximize efficacy, relative to the waning of maternal immunity, to compensate for the low probability of a second dose opportunity.

Each of these context-dependent factors can create immunity gaps between apparent vaccine coverage and actual population immunity (McKee et al. 2015). Unfortunate combinations of these factors can result in larger gaps than might otherwise be expected. For example, long duration of maternal immunity leads to low efficacy of the first dose at any given age, and if the timing of the second dose is not adjusted accordingly, a large population of individuals will remain susceptible between the first and second dose.

As a result of these immunity gaps, reported administrative coverage can greatly overestimate the true level of immunity within the population. In the absence of serological surveys, it is hard to know these true immunity levels in any population. When coverage is apparently high (not accounting for these context-dependent factors) and disease incidence appears low, it can be easy to assume that the population threshold for elimination is being maintained. However, the absence of disease is not the absence of risk. Many places have seen large unexpected outbreaks after years of apparently good coverage and low incidence, such as Brazil in 1997 (Prevots et al. 2003), Burkina Faso in 2009 (Kidd et al. 2012), Malawi in 2010 (Minetti et al. 2013), Wales in 2012 (Moore et al. 2015), and Brazil in 2013 (Leite et al. 2015), among others. Such unexpected outbreaks are indicative of an unrecognized gap between coverage and population immunity.

At the country level, specific selection of age targets can account for these factors to reduce local susceptibility and therefore improve the chances that elimination will be effectively maintained. By explicitly accounting for age structure, country-specific variations in maternal immunity, and the expected coverage of each dose, age targets can be chosen that minimize the total proportion of individuals left susceptible. In this paper, we use a discrete-time age structured population model for the distribution of immunity in a disease free population with two routine doses, and

analyses the equilibrial states of this model. We use this model to find the combination of age targets that minimizes the susceptible population given a specified combination of age structure, maternal immunity and coverages. We also use the model to explore the immunity gap between apparent coverage and actual population immunity, and how the size of this gap changes based on age structure, coverage of each dose and age targeting, although we generally ignore operational constraints. We use the results to suggest the source of some discrepancies between apparent coverage and disease risk. Further, we suggest that changing age targets may address these discrepancies, and thus help to maintain elimination in currently measles-free settings, such as the Americas.

**Methods**

We developed an age structured model for immunity within a human population, using 131 age classes. Age classes are divided monthly up to 5 years of age, and then yearly up to 75 years. Individuals within these age classes are then further divided into one of three immune classes: maternally immune, susceptible, or successfully immunized. As we are concerned with maintaining measles elimination, we omit the disease process (there are no classes for individuals who are infectious or immune as a result of infection).

In this model, we track the immune status of individuals via these classes through life. Vaccines administered at any age have some rate of primary vaccine failure, as individuals may fail to seroconvert when receiving vaccination. One major cause of primary vaccine failure is maternal immunity. Individuals born to susceptible mothers are born to the first susceptible class, while individuals born to immune mothers are born to the maternally immune class, since they are born with antibodies that confer protection while their immune system develops (Niewiesk 2014), but

also interfere with the efficacy of the vaccine. The maternal antibody titer wanes over time (Brugha et al. 1996), so a smaller proportion of individuals in any older age class will retain this maternal immunity, and therefore these individuals will have a lower rate of primary vaccine failure. Vaccines are administered at some initial target age, usually before all individuals are susceptible, so only a proportion of the vaccines are effective (which we assume is equal to the proportion of that age class that was never or is no longer maternally immune). A second dose of vaccine is administered at a second target age, to individuals independently of whether they had the first dose. While the rate at which maternal immunity wanes is likely dependent on country, as it depends on the immune status of the average mother (Brugha et al. 1996, Zhao et al. 2010), we assume that maternal immunity wanes exponentially with a mean at 3 months for the purpose of our model, and use this function as a proxy for the age-specific rate of primary vaccine failure. This function leads to vanishingly small rates of failure in older age classes (see Appendix B for a sensitivity analysis of the rate at which maternal immunity wanes). We also assume a constant rate of primary vaccine failure of 5% across all age classes (which may arise from issues such as cold chain disruption), although we ignore all other operational constraints.

By tracking these immunizing processes throughout an individual's life, we can calculate the proportion of adults that have been successfully immunized, which will give us the proportion of infants in the next generation that will be born with maternal immunity. By solving for the steady state, we can find the stable proportion of infants born with maternal immunity in a disease-free setting.

The proportion of individuals who have been successfully immunized is the simply the sum of the proportion of individuals for whom the first dose was immunizing and the proportion of

remaining susceptible individuals for whom the second dose was immunizing. That is, the proportion successfully vaccinated in generation T, $V_T$, is:

$V_T$ = (proportion of people for whom the first dose was immunizing)

+ (proportion of people for whom the second dose was immunizing)

= ((first dose coverage)*(first dose efficacy))

+ ((second dose coverage)*(second dose efficacy)*(proportion of people for whom the first dose was not effective))

$$= \left(v_1 * \left(1 - \omega_{t_1} p_{MT}\right)\right) + \left(v_2 * \left(1 - \omega_{t_2} p_{MT}\right) * \left(1 - v_1 * \left(1 - \omega_{t_1} p_{MT}\right)\right)\right).$$

Here, first dose coverage is $v_1$, second dose coverage is $v_2$. $\omega_{t1}$ and $\omega_{t2}$ are the proportion of individuals retaining maternal antibodies at the first and second age targets, respectively – we assume here that maternal immunity wanes exponentially with a mean at 3 months (Leuridan et al. 2010). The proportion of individuals born with maternal immunity in generation T is $p_{MT}$. Since vaccination is the only source of immunity, the proportion of individuals born with maternal immunity in generation T+1 is simply $V_T$. We can then solve for the equilibrium and get:

$$0 = \left(-v_1 v_2 \omega_{t_1} \omega_{t_2}\right) p_M^2 + \left(v_1 v_2 \left(\omega_{t_1} + \omega_{t_2}\right) - v_1 \omega_{t_1} - v_2 \omega_{t_2} - 1\right) p_M + (v_1 + v_2 - v_1 v_2),$$

which we can then solve to find $p_M$.

$$p_M$$

$$= \frac{\left(1 + v_1\omega_{t_1} + v_2\omega_{t_2} - v_1v_2\left(\omega_{t_1} + \omega_{t_2}\right)\right)}{2 * (v_1v_2\omega_{t_1}\omega_{t_2})}$$

$$- \frac{\sqrt{\left(v_1v_2\left(\omega_{t_1} + \omega_{t_2}\right) - v_1\omega_{t_1} - v_2\omega_{t_2} - 1\right)^2 + 4 * \left(v_1v_2\omega_{t_1}\omega_{t_2}\right) * (v_1 + v_2 - v_1 * v_2)}}{2 * (v_1v_2\omega_{t_1}\omega_{t_2})}$$

Once we know the equilibrial proportion of individuals born with maternal immunity, we can find the distribution of immunity throughout the age-structured population. We calculate the difference between this value and the expected coverage of the vaccine ($v_1 + v_2 - v_1 * v_2$), to find the immunity gap caused by maternal immunity, local population age structure, and vaccine age targets. We can then choose optimal age targets for specific coverages by minimizing this immunity gap.

In this work, we first examine the effects of coverage of each dose on the optimal targets for an idealized developing country age structure, i.e. a concave age structure where a constant proportion of individuals die each year. We then perform the same optimization for a range of coverages on real age structures (UN Population Division 2015) representing countries in the Americas (specifically for all countries in North and South America for which age targets for two routine doses and age structure were readily available), chosen because these countries are in the process of maintaining measles elimination. We also compare the population immunity achieved by our optimization to that achieved by the real age targets on these real age structures (UN Population Division 2015, WHO 2016a).

**Results**

The coverage of each dose has a significant effect on the optimal target ages for the first and second dose and the resulting proportion of the population that remains susceptible with a generic developing country age structure (Fig. 3.1). Susceptibility varies straightforwardly with coverage; as coverage of either dose increases, the remaining proportion susceptible decreases. In the lower left of both panels, the coverage of both doses is low, and population immunity is similarly low. In the upper right of both panels, the coverage of both doses is high, and population immunity is high. In the lower right, where first dose coverage is high and second dose coverage is low, and the upper left, where first dose coverage is low and second dose coverage is high, population immunity is similarly high. The optimal target ages, shown by the contours, also vary with coverage of both doses. The optimal target age for the second dose varies more with first dose coverage (Fig. 3.1b) than second dose coverage; that is, the contours in Fig. 3.1b run nearly parallel to the second dose coverage axis but indicate a steep change in optimal second dose timing for a relatively small change in first dose coverage. The optimal target age for the first dose is strongly dependent on first dose coverage when second dose coverage is low, but depends more strongly on second dose coverage when second dose coverage is high (Fig. 3.1a).

We test these ideas with real age structures, using age structures from countries in the Americas. For every country, we find the optimal age for the first and second dose for a range of coverages (80%, 90% and 100%) for both doses, assuming each dose has equal coverage (Fig. 3.2, Table B1). For all countries, the higher the coverage, the longer the recommended time between doses. The model-recommended age for the first dose was at a younger age than current policy in all countries, and the model-recommended age of the second dose was also at a younger age than

the current policy in most countries; Brazil, Canada and Peru are exceptions that recommend second dose administration before two years of age. We also find the optimal single dose age target – that is, the one-dose strategy that minimizes the proportion susceptible – for this range of coverages in all these countries (Fig. 3.2). Interestingly, this is usually close to current policy recommendations for the first dose – around 12 months. In the Appendix B we present a comparison of these idealized coverage levels with current age targets and coverage of MCV1 and 2.

We also calculate the differences that changing age targets make in population immunity (Fig. 3.3). All countries are expected to see a reduction in the proportion susceptible using our model-specified optimal age targets for both the first and second dose in place of current age targets. However, implementing our optimal age target for only one dose, but not the other, can be detrimental in some cases. For example, in Costa Rica, our model predicts that the current policy of vaccinating at 15 months and 7 years would maintain population immunity at 90.6%, given 90% coverage. If only the first dose age target in Costa Rica were changed to our model-recommended optimum of 9 months, the level of population immunity maintained would be reduced to 88.9%. If the second dose age target in Costa Rica were reduced to our model-recommended optimum of 19 months, with the first dose age target held at the current recommendation, population immunity would be improved over that maintained by current policy to 96.3%. Finally, if the age targets of both doses in Costa Rica were changed to our model-recommended optima, population immunity could be maintained at 96.7%. While this is an illustrative example where changing the age target of the second dose can dramatically improve population immunity, note that these policy recommendations should not be

implemented without further country-specific analysis, as our model ignores several operational constraints.

In general, if the second dose is recommended relatively late in life, say at 6 years of age as it is in Argentina, lowering the recommended age for the first dose from 12 months to 8 months would reduce first dose efficacy and expand the duration of susceptibility between doses, thereby reducing population immunity. Conversely, if both doses are already administered relatively close together, as they are in Peru where they are recommended at 12 and 18 months, lowering the second dose age target to 16 or 17 months without adjusting the first dose age target can reduce second dose efficacy without substantially reducing the duration of the susceptibility window between doses. However, in most countries, reducing the age target of the second dose alone will result in an increase in the proportion of the population that is immune. Changing age targets may be enough to make measles elimination maintainable in places where it was not, without changing coverage, most notably in Argentina, Chile, Costa Rica, Ecuador and Mexico, although the maximum maintainable population immunity is still dependent on age structure.

**Discussion**

Measles is a highly lethal disease, killing hundreds of children worldwide each day. With more than a thousand cases in the Americas in the first half of 2015 (WHO 2016b) and hundreds of cases spanning five outbreaks in the United States alone (CDC 2016), re-emergence is a serious threat. It is important that we focus our attention on optimizing current policy in order to prevent continued reemergence, and maintain elimination. By reconsidering vaccination policy in the context of the continued absence of both disease and supplemental immunization activities

(SIAs), we can increase the proportion immune within the population and better maintain elimination.

Here we show that the optimal target age for each dose depends on the coverage of the other; thus optimal scheduling should not consider the doses independently. Optimal selection of both age targets together may have a large impact on the resulting population immunity. Optimal coverage for both doses is 100%, and vaccination efforts should, and do, aim to maximize coverage. However, realized coverage is often lower than administrative goals. If first dose coverage is discovered, by coverage surveys or other mechanisms, to be low due to poor compliance with, or effectiveness of, vaccination programs, the age target of the second dose should be adjusted accordingly, and *vice versa*. These adjustments to the timing of doses may dramatically improve population immunity without changing coverage at all. Consequently, the target ages of vaccination should be adjusted according to estimated levels of program efficacy, vaccine abstention and noncompliance with vaccine policy, in order to maximize the population immunity achieved with current coverage.

When applied to real age structures from the Americas, our model optimization gives recommendations that differ from current strategies in most countries. In nearly all cases, our model recommends lowering the age target for both doses. The optima for a two dose strategy look very different from current policy, although they match the single dose optimum, which happens to be similar to the current recommended first dose age target, when coverage for the second dose is set to zero. However, the similarity between these targets is coincidental as current first dose targeting was chosen to balance maternal immunity and force of infection in the context of endemic disease and SIAs (McLean and Anderson 1988a), while our model

optima were chosen to balance maternal immunity and age structure. Adjusting current policy to account for the current epidemiological and management context, even partially, may have a significant impact on the feasibility of maintaining measles elimination in these countries.

In most countries, simply decreasing the age target of the second dose may dramatically improve population immunity by minimizing the susceptible population between doses. The exception to this is if current policy already recommends the second dose relatively early, as it does in Bolivia, Belize and Peru. In these countries, significant reductions in the remaining susceptible proportion of the population can be had by reducing the age target of the first dose, but reducing the second dose age target without adjusting the first dose age target reduces the efficacy of the second dose with little benefit. The minimum susceptible proportion under any management strategy in these countries still depends on the proportion of children under 5. Note that Canada does not face the same issue as Boliva, Belize and Peru, despite also having a relatively early second dose recommendation, because of its age structure. When a large fraction of the population falls below and between the age targets for vaccination, a low level of susceptibility can be hard to maintain, but this can be mitigated by selecting locally optimal, country-specific age targets.

Interactions between age structure, maternal immunity and age targets for vaccination can cause gaps between apparent coverage and the resulting population immunity (McKee et al. 2015). These gaps may provide alternate explanations for cases where measles control has failed in the Americas, such as in Saõ Paolo during the 1997 outbreak (Prevots et al. 2003). Rather than simply looking for failures in vaccine coverage, such as issues with vaccine scheduling and current vaccine delivery mechanisms, it may be important to reconsider the target ages for

vaccination as well. Improvements in population immunity are possible by adjusting scheduling to account for partial compliance, especially in countries where compliance with vaccine policy has been fairly consistent over time and is unlikely to change as a result of changes in scheduling.

There are a number of operational caveats not explicitly considered in our model. Our results are sensitive to, and conditional on, a given function for maternal immunity. The real rate at which maternal immunity wanes in a specific country, and therefore the age-specific rate of primary vaccine failure, should be determined and explicitly considered as part of a reevaluation of current policy. The optimal age target should be estimated based on the anticipated age-specific response to vaccination, as well as population level measures, such as coverage and age structure. This age-specific response will vary from country to country, as time since elimination (and therefore the ratio of vaccinated to naturally immune mothers) varies from country to country. It can be difficult to determine the age-specific waning of maternal immunity, as it would require high resolution longitudinal serosurveys in children not exposed to disease or vaccination. Similarly, directly measuring the age-specific response to vaccination would require detailed cohort studies. If maternal immunity wanes slowly, so that older children have a relatively high rate of primary vaccine failure, age targets should be kept the same or increased. However, if maternal immunity wanes more quickly, as it is likely to do due to the relatively high proportion of mothers who are vaccinated rather than naturally immune, then the age targets should be shifted earlier (Fig. 3.2).

The results we have presented here reflect a mathematical optimum and do not explicitly account for the logistical constraints of vaccine program implementation. In our model, we assumed

coverage was independent of age target selection, but in reality, changing age targets will likely change coverage, for a variety of reasons (Ciofi Degli Atti et al. 2004). For example, if a change in age target requires an additional clinic visit from parents, then many parents may fail to comply. Similarly, multivalent vaccines (the measles vaccine is typically packaged with mumps and rubella vaccines) may impose constraints; that is, changing the age target for the measles vaccine could require either decoupling it from the mumps and rubella vaccines or changing the ages at which those partner vaccines are administered. This might impose a large disruption on vaccine schedules, and could require children to receive an additional shot, with attendant additional complications in supply chains. Nevertheless, our work presents a theoretical optimum and a framework to evaluate an optimal age target given known maternal immunity and operational constraints on possible age targets.

We also ignore Supplemental Immunization Activities (SIAs) in this model. SIAs are periodic campaigns where everyone within a target age range is vaccinated. Some countries in the Americas still perform these campaigns (Thompson et al. 2015). Data on the details and post-campaign assessments of coverage among the unvaccinated population are sparse, and performing our optimization to account for infrequent campaigns of variable coverage would provide less generalizable results. SIAs provide an additional source of immunity and thus could also affect optimal age targets, which should be considered before implementing any change in policy if SIAs are anticipated to happen frequently or at regular intervals. Additionally, we note that SIAs could help to smooth transient disruptions in immunity caused by changing age targets.

These results are the product of an equilibrial analysis in the absence of disease. Disease absence is important to consider when planning for the maintenance of elimination, as outbreaks provide

an additional immunizing factor and can help maintain high levels of population immunity – considering the situation in the absence of disease provides us with a conservative analysis of the levels of immunity within a population. A more realistic model could include disease and demographic dynamics, including seasonality of the disease, which our model excludes, in order to capture the historical dynamic changes in population immunity following measles elimination, but would likely provide more optimistic results than our model. We would strongly recommend a more detailed analysis on a country by country basis, using locally appropriate assumptions about demographic structure, historical coverage levels and waning of maternal immunity, before policy is changed. Nevertheless, our results support the potential benefit of such a reanalysis, especially given the absence of endemic disease and supplemental immunization activities, and provide a conservative estimate of the levels of immunity maintainable in a population. After more than a decade of absence, and using data on actual vaccine uptake, future policy should consider anticipated coverage of both doses in order to avoid reestablishment of measles and to prevent future mortality.

**Acknowledgements**

We thank Ottar Bjørnstad, whose comments contributed to this manuscript. We acknowledge funding from the National Institutes of Health and National Science Foundation (EEID award 1 R01 GM105247-01 and NSF Ebola RAPID DMS-1514704). Matt Ferrari is also separately funded by the Bill and Melinda Gates foundation.

## References


1. Brugha R, Ramsay M, Forsey T, Brown D. A study of maternally derived measles antibody in infants born to naturally infected and vaccinated women. Epidemiol Infect 1996; 117: 519–24.
2. Castillo-Solorzano C, Marsigli C, Danovaro-Holliday MC, Ruiz-Matus C, Tambini G, Andrus JK. Measles and rubella elimination initiatives in the Americas: lessons learned and best practices. J Infect Dis 2011; 204 Suppl : S279–83.
3. Castillo-Solorzano C, Matus CR, Flannery B, Marsigli C, Tambini G, Andrus JK. The Americas: paving the road toward global measles eradication. J Infect Dis 2011; 204 Suppl : S270–8.
4. CDC. Centers for Disease Control and Prevention: Measles cases and outbreaks. 2016; http://www.cdc.gov/measles/cases-outbreaks.html
5. Ciofi Degli Atti ML, Rota MC, Bella A, Salmaso S. Do changes in policy affect vaccine coverage levels? Results of a national study to evaluate childhood vaccination coverage and reasons for missed vaccination in Italy. Vaccine 2004; 22: 4351–7.
6. Cutts FT, Grabowsky M, Markowitz LE. The effect of dose and strain of live attenuated measles vaccines on serological responses in young infants. Biologicals 1995; 23: 95–106.
7. Gans H, Yasukawa L, Rinki M, et al. Immune responses to measles and mumps vaccination of infants at 6, 9, and 12 months. J Infect Dis 2001; 184: 817–26.

8. Kidd S, Ouedraogo B, Kambire C, et al. Measles outbreak in Burkina Faso, 2009: a case-control study to determine risk factors and estimate vaccine effectiveness. Vaccine 2012; 30: 5000–8.
9. Leite RD, Barreto JLTMS, Sousa AQ. Measles Reemergence in Ceará, Northeast Brazil, 15 Years after Elimination. Emerg Infect Dis 2015; 21: 1681–3.
10. Lessler J, Metcalf CJE, Grais RF, Luquero FJ, Cummings DAT, Grenfell BT. Measuring the performance of vaccination programs using cross-sectional surveys: a likelihood framework and retrospective analysis. PLoS Med 2011; 8: e1001110.
11. Leuridan E, Hens N, Hutse V, Ieven M, Aerts M, Van Damme P. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. Bmj 2010; 340: c1626–c1626.
12. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 2014; 385: 430–40.
13. McKee A, Ferrari MJ, Shea K. The effects of maternal immunity and age structure on population immunity to measles. Theor Ecol 2015; 8: 261–71.
14. McLean AR, Anderson RM. Measles in developing countries. Part I. Epidemiological parameters and patterns. Epidemiol Infect 1988; 100: 111–33.
15. McLean AR, Anderson RM. Measles in developing countries. Part II. The predicted impact of mass vaccination. Epidemiol Infect 1988; 100: 419–42.
16. Minetti A, Kagoli M, Katsulukuta A, et al. Lessons and challenges for measles control from unexpected large outbreak, Malawi. Emerg Infect Dis 2013; 19: 202–9.

17. Moore C, Cottrell S, Hoffmann J, et al. Self-collected buccal swabs and rapid, real-time PCR during a large measles outbreak in Wales: Evidence for the protective effect of prior MMR immunisation. J Clin Virol 2015; 67: 1–7.
18. Niewiesk S. Maternal antibodies: Clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. Front Immunol 2014; 5: 1–15.
19. Prevots D, Parise M, Segatto T, et al. Interruption of measles transmission in Brazil, 2000–2001. J Infect Dis 2003; 187: S111–20.
20. Thompson KM, Odahowski CL, Goodson JL, Reef SE, Perry RT. Synthesis of Evidence to Characterize National Measles and Rubella Exposure and Immunization Histories. Risk Anal 2015.
21. UN Population Division. Annual population by age groups. 2015; http://esa.un.org/unpd/wpp/DVD/
22. van den Ent MMVX, Brown DW, Hoekstra EJ, Christie A, Cochi SL. Measles mortality reduction contributes substantially to reduction of all cause mortality among children less than five years of age, 1990-2008. J Infect Dis 2011; 204 Suppl : S18–23.
23. WHO. WHO vaccine-preventable diseases: monitoring system. 2016 global summary. 2016; http://apps.who.int/immunization_monitoring/globalsummary/schedules
24. WHO. Global Alert and Response: Measles – the Americas. 2016; http://www.who.int/csr/don/13-february-2015-measles/en/
25. Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. Int J Epidemiol 2009; 38: 192–205.

26. Zhao H, Lu P-S, Hu Y, Wu Q, Yao W, Zhou Y-H. Low titers of measles antibody in mothers whose infants suffered from measles before eligible age for measles vaccination. Virol J 2010; 7: 87.
27. Zipprich J, Winter K, Hacker J, Xia D, Watt J, Harriman K. Measles Outbreak – California, December 2014-February 2015. MMWR Morb Mortal Wkly Rep 2015; 64: 153–4.

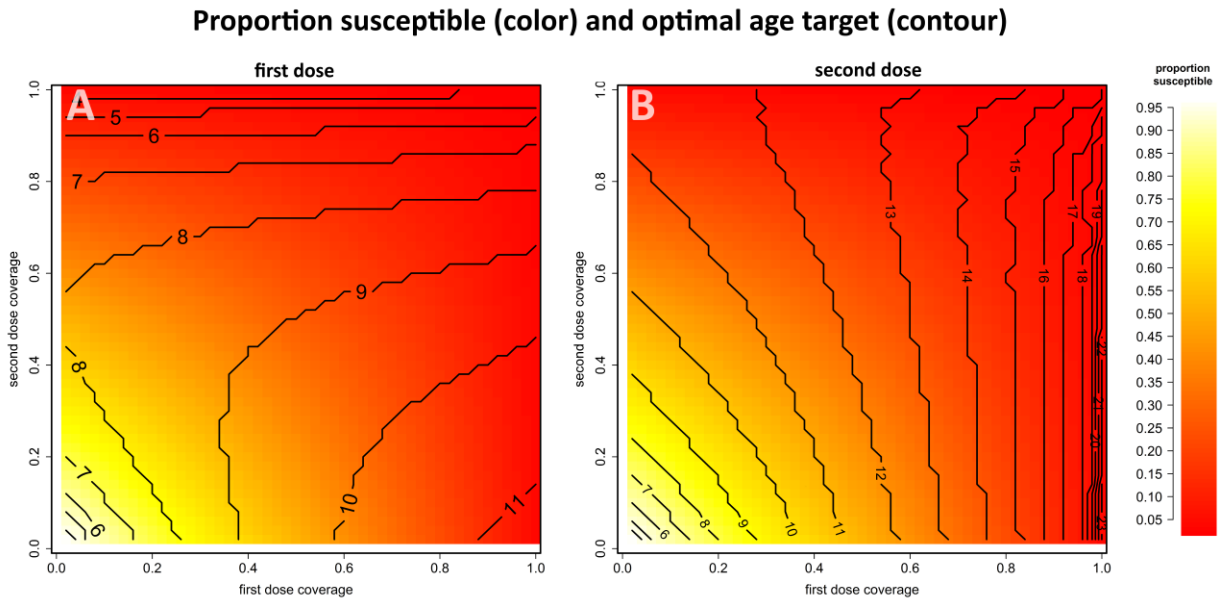



**Figure 3.1:** The optimal ages in months (shown by the contours), and maintained proportional susceptibility (shown by the color scale) for a range of first and second dose coverages, varying independently, in a population with idealized developing age structure. **A)** The optimal age for the first dose. Notably, the optimal age of the first dose depends heavily on the coverage of the second dose. **B)** The optimal age for the second dose. Notably, the optimal age of the second dose depends heavily on the coverage of the first dose.

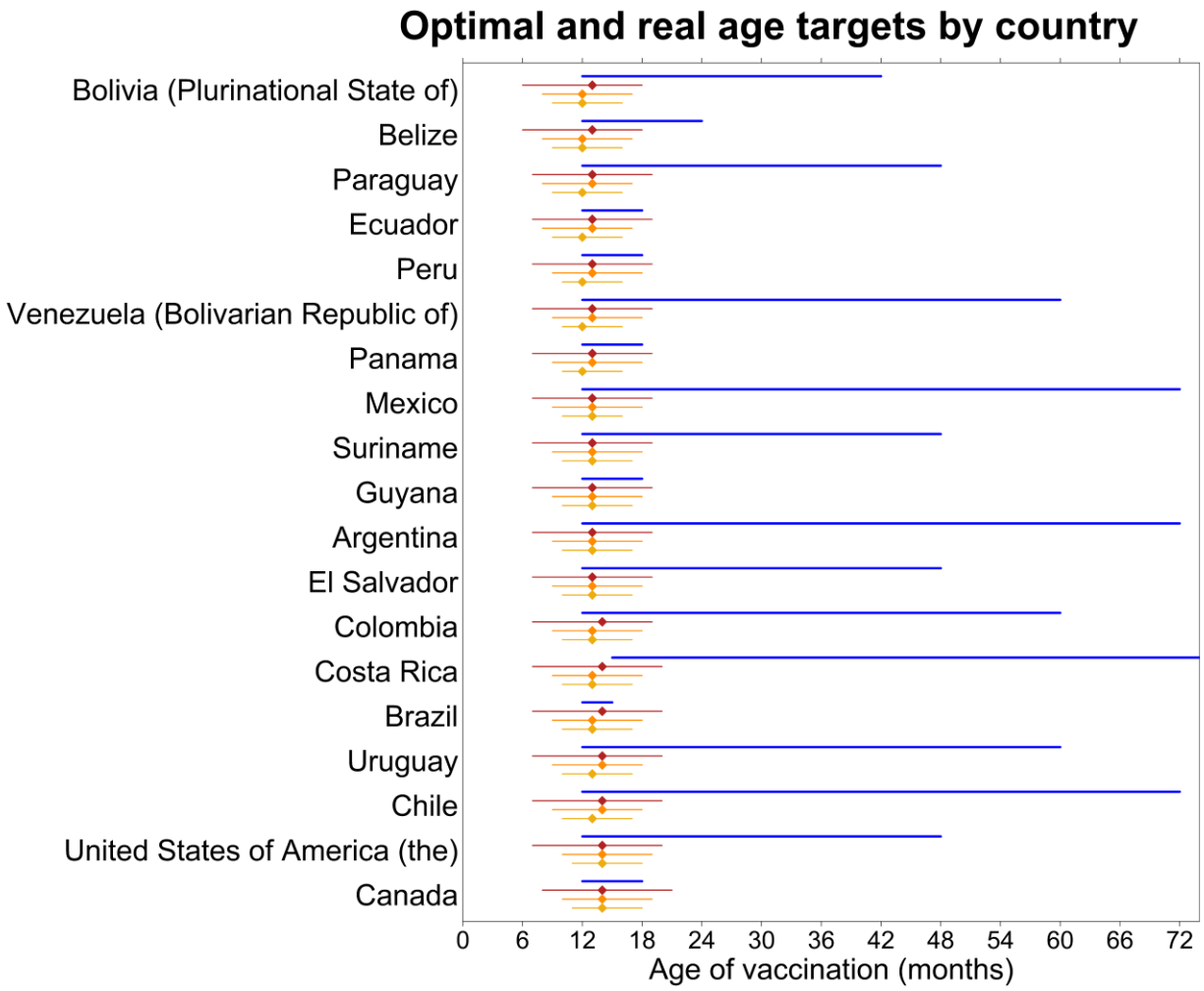



**Figure 3.2:** The real target ages (the blue line), the optimal target ages with 100% coverage of two doses (the red line), the optimal target ages with 90% coverage of two doses (the orange line), and the optimal target ages with 80% coverage of two doses (the yellow line). The endpoints of each line represent the first and second age target, respectively, for each country and policy. The optimal target ages for a single dose vaccine schedule with each of these coverages are shown by the diamond on each line. In all cases, the difference in age target between the first and second dose is smaller with lower coverages. In all cases, the optimal first age of vaccination is younger than the current recommendation, and in most, the optimal second age is also younger than the current recommendation. The optimal single dose ages correspond

well with the current recommendation for the first dose. The countries have been ordered by proportion of the population made up by children under 5, with Bolivia having the most children under 5 and Canada having the fewest.

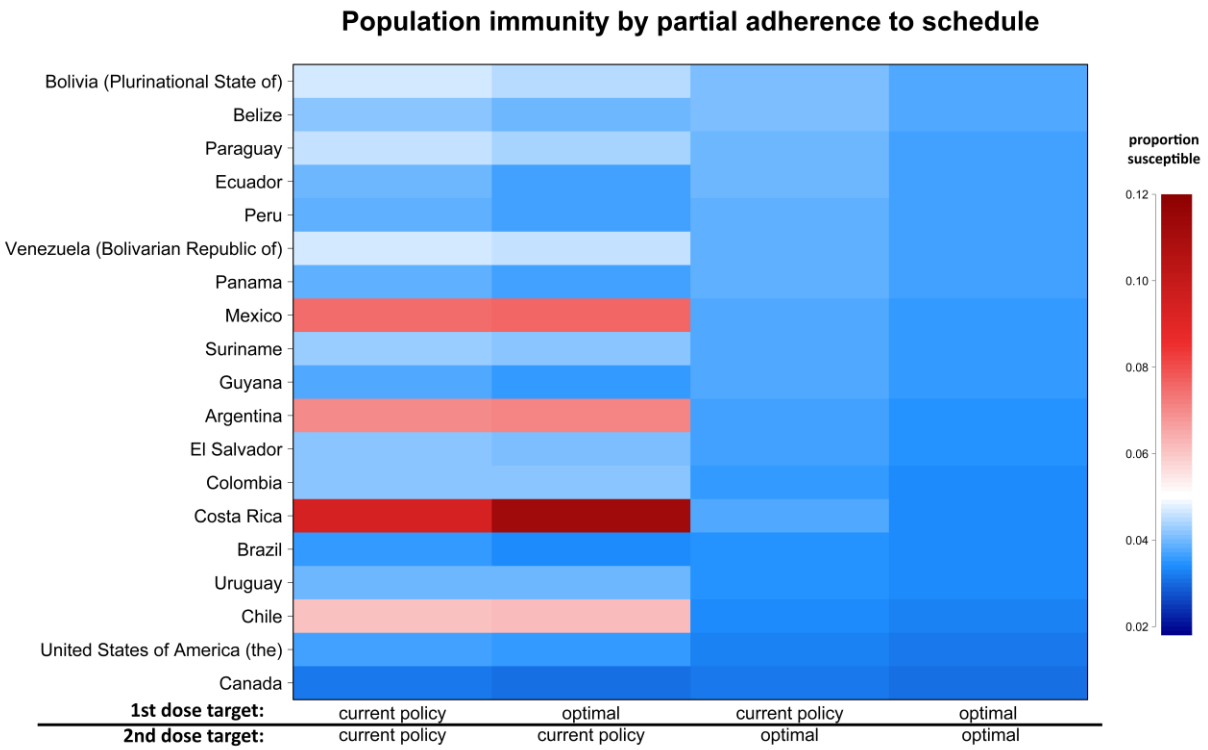



**Figure 3.3:** The population immunity by partial adherence to schedule for countries in the Americas with two recommended age targets of vaccination. Red indicates a population immunity below 95%, the commonly accepted threshold for maintaining elimination, and blue indicates a population immunity above 95%. In the case where only one dose is optimal, the other dose is administered at the currently recommended age target.

# Chapter 4

## Correlation between measles vaccine doses: Implications for the maintenance of elimination

Amalie McKee, Matthew Ferrari, Katriona Shea

**Abstract**

Measles eradication efforts have been successful at achieving elimination in many countries worldwide. Such countries actively work to maintain this elimination by continuing to improve coverage of two routine doses of measles vaccine following measles elimination. While improving coverage is always beneficial, we show, using a steady state analysis of a dynamical model, that the correlation between populations receiving the first and second routine dose also has a significant impact on the population immunity achieved by a specified combination of first and second dose coverage. If the second dose is administered to people independently of whether they had the first dose, high second dose coverage improves the proportion of the population receiving at least one dose, and will have a large effect on population immunity. If the second dose is administered only to people who have had the first dose, high second dose coverage reduces the rate of primary vaccine failure, but does not reach people who missed the first dose; this will therefore have a relatively small effect on population immunity. When doses are administered dependently, and assuming the first dose has higher coverage, increasing the coverage of the first dose has a larger impact on population immunity than does increasing the coverage of the second. In all six WHO health regions, correlation has a significant impact on the level of population immunity maintained by current vaccination coverage, potentially outweighing the effects of age structure and, in some cases, recent improvements in vaccine

coverage. It is therefore important to understand vaccine correlation, as correlation may have a large impact on the effectiveness of measles vaccination strategies.

**Introduction**

As of 2014 measles was officially eliminated from 7 countries in the Western Pacific, 22 countries in Europe, and all countries in the Americas aside from Brazil (Perry et al. 2015). As measles is a leading cause of vaccine-preventable childhood death (Liu et al. 2015), it is important that we continue to maintain elimination. Due to increased globalization (Gushulak and MacPherson 2004) and the highly transmissible nature of the disease, measles is at constant risk of reemergence in the countries where it is eliminated. Several reintroduction outbreaks have occurred; for example, the 2013 outbreak in Brazil, which lasted more than a year and changed Brazil's elimination status (Leite et al. 2015, Perry et al. 2015) and the 2015 outbreak in Mongolia (WHO 2016), which occurred less than a year after Mongolia was certified measles free (WHO 2014). A reevaluation of management strategies for measles in order to better maintain elimination would be valuable (Chapter 3).

It is important that we maintain high levels of immunity within the population in order to maintain elimination. When immunity is high, outbreaks caused by reintroduction events have lower incidence and shorter duration (Ferrari et al. 2013). In particular, as measles is a highly transmissible disease, the herd immunity threshold (that is, the proportion of the population that needs to be immune in order to prevent a reintroduction event sparking prolonged reemergence of the disease) is commonly considered to be around 95% (Anderson and May 1985). The true threshold depends on population structure (Ellner et al. 1998), and so varies from place to place and is difficult to measure, but maximizing the proportion of the population that is immune is the

best way to ensure that that proportion is above the true threshold. In order to maintain high levels of immunity, extensive vaccination efforts are continued in countries that have achieved elimination. In most countries, these vaccination efforts involve administering two doses of measles containing vaccine (WHO 2016). The second dose may come through one of two primary means; a second routine immunization or supplemental immunization activities (SIAs). We focus on the former, as it is the most common method in countries where elimination has been achieved.

Typically, agencies are concerned with maximizing the coverage of each dose (de Quadros et al. 1998, Irons and Dobbins 2011, Elam-Evans et al. 2014); that is, the proportion of the population that gets vaccinated at each specified target age. However, coverage alone does not tell the full story. While the maintainability of measles elimination depends on the proportion of the population that is immune to measles (Anderson and May 1985), that proportion differs from, but directly depends on, the proportion of the population that gets at least one dose of measles containing vaccine. The reason for this difference is twofold: first, maternal immunity interferes with the efficacy of the vaccine (Niewiesk 2014), and second, age structure creates immunity gaps as some individuals simply have not yet received a vaccine (McKee et al. 2015). There are three subparts of the susceptible population maintained by a two dose strategy (Fig. 4.1, the red part in panels b and d): individuals who are no longer maternally immune but are too young to receive the first dose (the portion of the red part left of the left black line), individuals who missed the first dose or for whom the first dose was ineffective but are too young to receive the second dose (the red part between the two black lines), and individuals who either missed both doses or who failed to seroconvert after receiving one or both doses (the portion of the red part to

the right of the right black line). These subparts sum to the total proportion of the population that is susceptible, and can contribute to transmission in case of a reintroduction event.

The first dose of measles containing vaccine (MCV1) should be administered early enough to minimize the number of susceptible individuals who are too young to have yet received a vaccine, but late enough that maternal-acquired antibodies, which interfere with the efficacy of the measles vaccine, have sufficiently waned, so that relatively few individuals are susceptible between doses. The second dose (MCV2) is administered later in life, with two purposes: one, to catch children for whom the first dose was not effective, and two, to provide a second opportunity for children who did not have the first dose to receive at least one dose. In most countries, this means that the first dose of the measles vaccine is administered when the child is nine to twelve months old, and the second dose is administered sometime later in life, often immediately before school entry (WHO 2016). The efficacy of this strategy, and the proportion of the population that receives at least one dose, directly depends on the coverage of each dose. However, it also depends on the overlap in the populations receiving each dose.

If the overlap in populations receiving each dose is high, then the second dose of measles containing vaccine acts as a true second dose – that is, it is the second dose an individual receives in their life. However, if the overlap is relatively low, and all children are equally likely to receive the second dose (ie. at the second age target) regardless of whether they had the first dose, then the second dose acts more as a second opportunity – that is, the second chance an individual has to be caught by the healthcare system and provided with at least one dose of measles containing vaccine. We call this overlap the correlation; when the populations receiving each dose have a high overlap and the second dose acts as a true second dose, we say that they

are totally dependent, and when the populations have a relatively low overlap and the second dose acts only as a second opportunity, we say that they are independent.

Understanding the effects of correlation on population immunity resulting from a two dose strategy can provide two key insights. It can provide a more accurate estimate of the range of population immunity maintainable by a two dose strategy with specific coverages. This therefore motivates the benefit to designing a surveillance system to monitor correlation, perhaps through a combination of administrative data and health surveys. It can also suggest ways to adapt management strategies to account for the observed correlation between the populations receiving each dose. We model the effects of correlation on the maintainability of measles elimination using a steady state analysis of a dynamical model for the distribution of immunity within a population in the absence of disease. We use this model to find the proportion of susceptible individuals remaining in the population when vaccinating with specified first and second dose age targets, as well as specified coverage of each dose and correlation between the populations receiving each dose. We also find the proportion of individuals who have received at least one dose, but have not seroconverted and therefore are not immune to measles as adults. Finally, we consider the interaction between coverage and correlation for a range of age structures.

**Methods**

We calculate the proportion of individuals left susceptible by a specified vaccine schedule, with specified coverages and correlation using an age structured model. From a specified coverage and age target for each dose, as well as specified correlation, we divide each age class into one of four vaccine classes (Fig. 4.1 a and c); unvaccinated (shown in grey), a recipient of the first dose

only (shown in green), a recipient of the second dose only (shown in dark blue), and a recipient of both doses (shown in light blue). Using a specified age-specific efficacy function (based on an age-specific probability of retaining maternal immunity), we then divide each vaccine class into one of three immunity classes; susceptible, maternally immune, and effectively immunized. We then calculate the age distribution and proportion of susceptible individuals left in the population by multiplying the age-specific probability of being susceptible with the age structure, which we do for multiple age structures. We also find the rate of primary vaccine failure – that is, the proportion of individuals who receive at least one dose of measles containing vaccine but fail to seroconvert. We assume the system is at equilibrium, so that the proportion of children born with maternal immunity is equal to the proportion of adults that have been effectively immunized by vaccination. Notably, we omit any disease-derived immunity as we are concerned with the maintenance of elimination in the disease-free setting.

We define correlation to be the proportion of the dose with lower coverage administered non-independently to people who had the other dose. In cases where second dose coverage is lower than first dose coverage, this is the proportion of the second dose administered non-independently to people who had the first dose. In this case, when correlation is one, the second dose is administered solely to children who had the first dose, achieving only the aim of providing those individuals a second chance to become immune in case of primary vaccine failure. When first dose coverage is lower than second dose coverage, correlation is the proportion of the first dose administered non-independently to people who will later receive the second dose. When correlation is one in this case, everyone who receives a first dose later receives a second dose. In both cases, when correlation is zero, the second dose is administered independently of whether the child had the first dose – notably, in this case, the "second dose"

means only a dose administered at the second target age, not necessarily the second dose a specific individual receives. When doses are independent, all individuals have a second chance to receive a vaccine and hopefully become immune, regardless of whether they have been vaccinated already.

Age classes are divided monthly up to 5 years, and yearly afterwards, until 75 years of age. To divide age classes into vaccination classes, we assume a proportion of individuals, equal to the coverage of the first dose, $v_1$, is vaccinated with the first dose at the first age target, $t_1$, and therefore moves from the unvaccinated class into the first dose only vaccine class. This proportion remains constant up to the age target for the second dose, $t_2$, when a proportion of individuals are vaccinated with the second dose. For the purposes of this paper, we assume the first dose age target is 12 months and the second dose age target is 48 months, although the qualitative results are the same regardless of age targets chosen.

If $v_1 > v_2$, then $p(MCV2|MCV1) = v_2(1 - corr) + \frac{v_2}{v_1} corr$ and $p(MCV2 \mid \neg MCV1) = v_2(1 - corr)$, where $v_2$ is the coverage of the second dose and $corr$ is the correlation between the two doses. Here, $\mid$ means "given" and $\neg$ means "not", so $p(MCV2 \mid \neg MCV1)$ is the proportion that get MCV2 given that they did not receive MCV1. Therefore, $v_1 - v_1 * v_2(1 - corr) - v_2 * corr$ adults receive only the first dose, $v_1 * v_2 (1 - corr) + v_2 corr$ adults receive both doses, and $(1 - v_1)v_2(1 - corr)$ adults receive only the second dose. The remainder are unvaccinated.

If $v_1 \leq v_2$, then $p(MCV2|MCV1) = v_2(1 - corr) + corr$ and $p(MCV2 \mid \neg MCV1) = v_2(1 - corr) + corr(v_2 - v_1)$. Therefore, $v_1 - v_1 * v_2(1 - corr) - v_1 corr$ adults receive

only the first dose, $v_1 * v_2\ (1 - corr) + v_1\ corr$ adults receive both doses, and $(1 - v_1)v_2(1 - corr)$ adults receive both doses. Again, the remainder are unvaccinated.

However, not all vaccines successfully confer immunity in the recipient. The primary reason for this failure to seroconvert is interference of maternally derived antibodies, although we also include the chance that the vaccine was rendered ineffective by other means, such as cold-chain failure. To divide vaccine classes into immune classes, we developed a function for age-specific efficacy based on maternal immunity. The proportion of individuals born with maternal immunity, $p_m$, is the proportion of individuals successfully immunized in the previous generation. Assuming the system is at equilibrium, this is just

$$p_m = \left(1 - p_m\, w_{t_1}\right) * \left(1 - p_f\right) * (first\ dose\ only\ adults) + \left(1 - p_m\, w_{t_2}\right) * \left(1 - p_f\right) * (second\ dose\ only\ adults) + \left(\left(1 - p_m w_{t_1}\right) * \left(1 - p_f\right) + \left(1 - \left(1 - p_m w_{t_1}\right) * \left(1 - p_f\right)\right) * \left(1 - p_m w_{t_2}\right) * \left(1 - p_f\right)\right) * (both\ dose\ adults).$$

We can then solve for $p_m$ using the quadratic formula. Here, $w_t$ is the waning function for maternal immunity, so $w_{t_1}$ is the proportion of individuals born with maternal immunity that retain it at the first target age, and $w_{t_2}$ is the proportion of individuals born with maternal immunity that retain it at the second target age. We assume this waning function is exponential with a mean at 3 months. We assume $p_f$, which is the probability that the vaccine fails for some other reason such as cold chain failure, is constant across age classes – specifically, we assume a constant 5% failure rate for reasons not relating to the immune status of the recipient (Uzicanin and Zimmerman 2011).

To find the rate of primary vaccine failure, we simply take the difference in the proportion of adults who have had at least one dose and the proportion of adults who are immune. This rate depends on both the waning of maternal immunity and the correlation between doses.

**Results**

For a constant level of first and second dose coverage, reducing the correlation between doses increases the proportion of the population that receives at least one dose, but decreases the proportion of the population that receives both doses (Fig. 4.1). As a result, the proportion of the population that is susceptible to measles is reduced. Because decreasing correlation decreases the proportion of individuals that receive both doses, it increases the proportion of adults that have been vaccinated but not immunized. Individuals who received a dose at the first age target but did not seroconvert are less likely to receive a dose at the second age target when correlation is low, and so are less likely to be given a second chance to seroconvert, increasing the rate of primary vaccine failure (Fig. 4.1 b and d). Improving coverage of either dose will always reduce the proportion of individuals that are susceptible, and thereby improve the chances of maintaining measles elimination. However, improving coverage is not the only way to reduce the susceptible proportion – reducing correlation between each dose does so as well (Fig. 4.2). This holds true regardless of the underlying age structure.

When doses are administered independently, a relatively large proportion of the population gets both doses (Fig. 4.1), and increasing the coverage of either dose has a large effect on population immunity (Fig. 4.2), although increasing the coverage of the dose with higher coverage has a larger impact. For example, if the second dose has lower coverage than the first dose, and the doses are administered independently, then the second dose is administered with equal

proportional coverage to the population of individuals who missed the first dose as it is to the population of individuals who received the first dose. Improving second dose coverage by 10% would provide an additional 10% coverage to the population of individuals who missed the first dose. In comparison, improving first dose coverage by 10% would provide an additional 10% coverage to the population of individuals who will later miss the second dose, which is a larger population as second dose coverage is lower. Regardless, improving coverage of either dose increases the proportion of the population that receives at least one dose and reduces primary vaccine failure.

In contrast, high correlation reduces the benefit incurred by increasing the coverage of a given dose. When doses are administered in a totally dependent fashion, increasing the coverage of the dose with lower coverage has very little benefit. For example, if the second dose has lower coverage than the first dose, and the doses are totally dependent, then the second dose is administered only to individuals who have already had the first dose. Therefore, increasing the coverage of the second dose will be minimally beneficial, as it will not increase the proportion of the population receiving at least one dose, but simply increase the proportion of the population receiving both doses and therefore reduce primary vaccine failure. By comparison, increasing the coverage of the first dose in this case will increase the proportion of the population receiving at least one dose and thus have a much larger effect on the resulting population immunity, despite increasing the proportion of people who get just one dose, and therefore increasing primary vaccine failure.

When estimating population immunity from coverage, it is therefore important that we know the correlation. Second dose coverage has improved from 2005 to 2015 in all six WHO Health

regions, and first dose coverage has improved in five of them (all regions except the Americas (AMR)) (Fig. 4.3). We estimated population immunity from those coverages for four contexts; i) developing age structure with doses administered dependently, ii) developing age structure with doses administered independently, iii) developed age structure with doses administered dependently and iv) developed age structure with doses administered independently (Fig. 4.4). The two age structures differed in the proportion of children under five. Each region is made up of many countries, all with different age structures, so we compared the population immunity for the two extremes of the range of age structures, rather than estimating the true average age structure of a region. For each health region, the level of population immunity maintained by vaccination was much greater when doses were administered independently. In four health regions (the American Region (AMR), the Eastern Mediterranean Region (EMR), the European Region (EUR), and the Western Pacific Region (WPR)), the improvement in population immunity achieved by the improvement in coverage was dwarfed by the improvement in population immunity that could be achieved by decorrelating doses. The Southeast Asian Region (SEAR) had a much larger increase in coverage than the others (Fig. 4.3), so coverage improved population immunity slightly more than decorrelating doses would (Fig. 4.4). In the African Region (AFR), first dose coverage improved a lot relative to second dose coverage (Fig. 4.3), so the improvement in coverage significantly improved population immunity (Fig. 4.4). In all regions, decorrelating first and second doses had a larger effect on population immunity than differences in age structure did. In regions close to elimination, correlation between the doses could be the difference between achieving or maintaining elimination or not, although this will depend on the specific local age structure, as it did in Chapter 3.

**Discussion**

In most countries, a two dose routine immunization strategy is used to maintain high levels of population immunity to measles and, in places where the disease is eliminated, prevent prolonged reemergence of this deadly disease (WHO 2016). The second dose of a two dose strategy to maintain measles elimination is administered with two main goals (Gupta et al. 2011). One is to reduce primary vaccine failure by providing a second chance for individuals for whom the first dose was ineffective to become immune. The second is to provide a chance for individuals who missed the first dose to be vaccinated at all. Correlation between the populations receiving each dose affects how well each of these aims are met, with high correlation improving performance under the first objective and low correlation improving performance under the second objective. When coverage of each dose is 100%, then everyone receives both the first and second dose, so the proportion of the population receiving at least one dose is unchanged regardless of correlation. However, when coverage falls short of 100%, correlation has a significant impact on the proportion of the population receiving at least one dose, and therefore on the proportion of the population that is immune.

When doses are administered in a totally dependent fashion and coverage of each dose is relatively similar, almost every individual who receives at least one dose receives both doses, as the dose with smaller coverage is administered solely to individuals who had the other dose. In this case, only the first aim of the second dose is met – the second dose solely catches individuals for whom the first dose was ineffective. When doses are administered independently with the same coverage, more individuals receive at least one dose, and the second aim is met, at the partial expense of the first aim, as fewer individuals receive two doses, and therefore fewer receive two chances to seroconvert. However, this still invariably results in a smaller proportion

of susceptible individuals remaining in the population and therefore a greater chance of maintaining measles elimination overall.

While not reported, correlation is unlikely to be independent of age structure and coverage. In developed countries, there is a relatively small proportion of children under five, and healthcare access is relatively high, so coverage is also likely high. Unvaccinated individuals likely cannot or will not receive a dose of measles containing vaccine, regardless of whether they are able to access healthcare at the appropriate age. In these countries, correlation between two routine doses of measles containing vaccine is likely relatively high. In comparison, developing countries have a relatively large proportion of children under five, but also often have poor health access, and therefore lower coverage with routine immunization. Individuals in these countries who miss one dose may be willing and able to receive vaccine, they were just unable to access healthcare at the appropriate age to receive a dose. In this case, doses are likely to be administered more or less independently, as children receive what doses they have access to receive. However, it is also possible that health access is highly heterogeneous, with some individuals able to access healthcare routinely and other individuals never able to access healthcare – in this case, correlation between each dose would be high, even in the developing context.

It is important to understand correlation when making management recommendations. In a scenario when one dose has much higher coverage than the second dose, it may seem intuitive to focus on improving coverage of the dose that has relatively low coverage. However, if correlation between the populations receiving each dose is high, this will in fact be much less beneficial than working to improve coverage of the dose that already has higher coverage.

Average MCV2 coverage was lower than average MCV1 coverage in every WHO health region (Fig. 4.3 – all arrows fall below the 1:1 line). If doses in the component countries were administered dependently, focusing on increasing first dose coverage would have the biggest impact, however, MCV2 coverage increased far more than MCV1 coverage did in all regions except Africa – in fact, in the American health region, MCV1 coverage actually declined while MCV2 coverage increased. While high MCV2 coverage is important to effectively maintain elimination, its relative importance to high MCV1 coverage depends on correlation.

The effects of correlation are likely to pertain to supplemental immunization activities (SIAs) as well as routine immunization (Chapter 6). SIAs are typically thought to be able to reach populations that are not reached by the routine health system (WHO Measles and Rubella Initiative 2013), but that may not always be the case (Lessler et al. 2011). If SIAs are administered independently of whether children received a routine dose of measles containing vaccine, then SIAs will substantially improve the proportion of the population receiving at least one dose. However, SIAs are logistically difficult to perform, and may reach the populations with the best access to the health system first (Metcalf et al. 2015), meaning that they may be administered primarily to children who also receive routine immunization. If the populations reached by SIAs are highly correlated with the populations receiving routine immunizations, the true impact of SIAs could be greatly overestimated, leading to misconceptions about the true state of immunity in the population unless we measure that correlation.

A high correlation may result from routinely missed populations, such as the Roma populations in Europe (Nedeljković et al. 2016). While increasing the coverage of either dose always decreases the proportion left susceptible in the population, exploring novel vaccination strategies

may provide opportunities to reduce the susceptible population by decorrelating doses, without necessarily improving coverage of either dose. For example, mobile vaccination strategies could provide opportunities for groups with poor healthcare access to receive at least one dose. Modelling these strategies in a spatially explicit way, but also accounting for correlation, could provide estimates of how much population immunity would be improved, depending on how well these strategies reach people who are not otherwise reached by the routine health system.

Decorrelating doses does come at the cost of vaccine efficacy – as fewer individuals receive two doses, fewer individuals receive both opportunities to seroconvert. This may cause misleading indicators, as the observed rate of primary vaccine failure will increase, perhaps indicating a failure of vaccination in a place where the susceptible proportion is actually decreasing. While our model is relatively simple, a more complex model could explore this tradeoff in full.

The simplicity of our modeling approach comes with one significant advantage, however, in that it could be applied to many diseases with a multiple dose vaccine schedule. The tradeoff between primary vaccine failure and the proportion of the population receiving at least one dose that comes with correlation pertains to many other vaccine schedules. However, if individuals require multiple doses to successfully seroconvert, population immunity may depend more on the proportion of the population that receives at least two doses than on the proportion of the population that receives at least one. In this case, high correlation would outperform low correlation with respect to population immunity. Thus, the relative benefits of low or high correlation could be reversed for other diseases, depending on the probability that an individual fully seroconverts following just one dose. In short, our work shows that careful consideration of both coverage and correlation of doses of measles containing vaccine may allow

improvements in population immunity that would be more difficult to achieve by addressing coverage alone.

**Acknowledgements**

We acknowledge funding from the National Institutes of Health and National Science Foundation (EEID award 1 R01 GM105247-01 and NSF Ebola RAPID DMS-1514704). Matt Ferrari is also separately funded by the Bill and Melinda Gates foundation.

**References**

1. Anderson RM, May RM. Vaccination and herd immunity to infectious diseases. Nature 1985; 318: 323–9.
2. de Quadros CA, Hersh BS, Nogueira AC, Carrasco PA, da Silveira CM. Measles eradication: experience in the Americas. Bull World Health Organ 1998; 76 Suppl 2: 47–52.
3. Elam-Evans LD, Yankey D, Singleton JA, Kolasa M. National, state, and selected local area vaccination coverage among children aged 19-35 months - United States, 2013. MMWR Morb Mortal Wkly Rep 2014; 63: 741–8.
4. Ellner SP, Bailey BA, Bobashev GV, Gallant AR, Grenfell BT, Nychka DW. Noise and Nonlinearity in Measles Epidemics: Combining Mechanistic and Statistical Approaches to Population Modeling. Am Nat 1998; 151: 425–40.
5. Ferrari MJ, Grenfell BT, Strebel PM. Think globally, act locally: the role of local demographics and. Philos Trans R Soc B Biol Sci 2013; 368.
6. Gupta SK, Sosler S, Haldar P, Hombergh H van den, Bose AS. Introduction Strategy of a Second Dose Measles Containing Vaccine in India. Indian Pediatr 2011; 48: 379–82.

7. Gushulak BD, MacPherson DW. Globalization of infectious diseases: the impact of migration. Clin Infect Dis 2004; 38: 1742–8.
8. Irons B, Dobbins JG. The Caribbean experience in maintaining high measles vaccine coverage. J Infect Dis 2011; 204 Suppl: S284-8.
9. Leite RD, Barreto JLTMS, Sousa AQ. Measles Reemergence in Ceará, Northeast Brazil, 15 Years after Elimination. Emerg Infect Dis 2015; 21: 1681–3.
10. Lessler J, Metcalf CJE, Grais RF, Luquero FJ, Cummings DAT, Grenfell BT. Measuring the performance of vaccination programs using cross-sectional surveys: a likelihood framework and retrospective analysis. PLoS Med 2011; 8: e1001110.
11. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 2014; 385: 430–40.
12. McKee A, Shea K, Ferrari MJ. Chapter 3. Optimal age targets to maintain measles elimination with a two-dose routine policy.
13. McKee A, Ferrari MJ, Shea K. The effects of maternal immunity and age structure on population immunity to measles. Theor Ecol 2015; 8: 261–71.
14. Metcalf CJE, Tatem A, Bjornstad ON, et al. Transport networks and inequities in vaccination: remoteness shapes measles vaccine coverage and prospects for elimination across Africa. Epidemiol Infect 2015; 143: 1457–66.
15. Nedeljković J, Rakić Adrović S, Tasić G, et al. Resurgence of measles in Serbia 2010-2011 highlights the need for supplementary immunization activities. Epidemiol Infect 2016; 144: 1121–8.

16. Niewiesk S. Maternal antibodies: Clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. Front Immunol 2014; 5: 1–15.
17. Perry RT, Murray JS, Gacic-Dobo M, et al. Weekly epidemiological record: Progress towards regional measles elimination, worldwide, 2000–2014. World Heal Organ 2015; 46:623–631.
18. Uzicanin A, Zimmerman L. Field effectiveness of live attenuated measles-containing vaccines: a review of published literature. J Infect Dis 2011; 204 Suppl: S133-48.
19. WHO Representative Office: Mongolia (2016) Measles outbreak in Mongolia – FAQs. http://www.wpro.who.int/mongolia/mediacentre/releases/20160505-measles-outbreak-faqs/en/
20. WHO Measles and Rubella Initiative (2013) A Guide to Introducing a Second Dose of Measles Vaccine into Routine Immunization Schedules.
21. World Health Organization: Western Pacific Region (2014) Mongolia certified measles free. http://www.wpro.who.int/mediacentre/releases/2014/20140708/en/
22. World Health Organization (2016) Vaccine-preventable diseases: monitoring system 2016 global summary. http://apps.who.int/immunization_monitoring/globalsummary/schedules

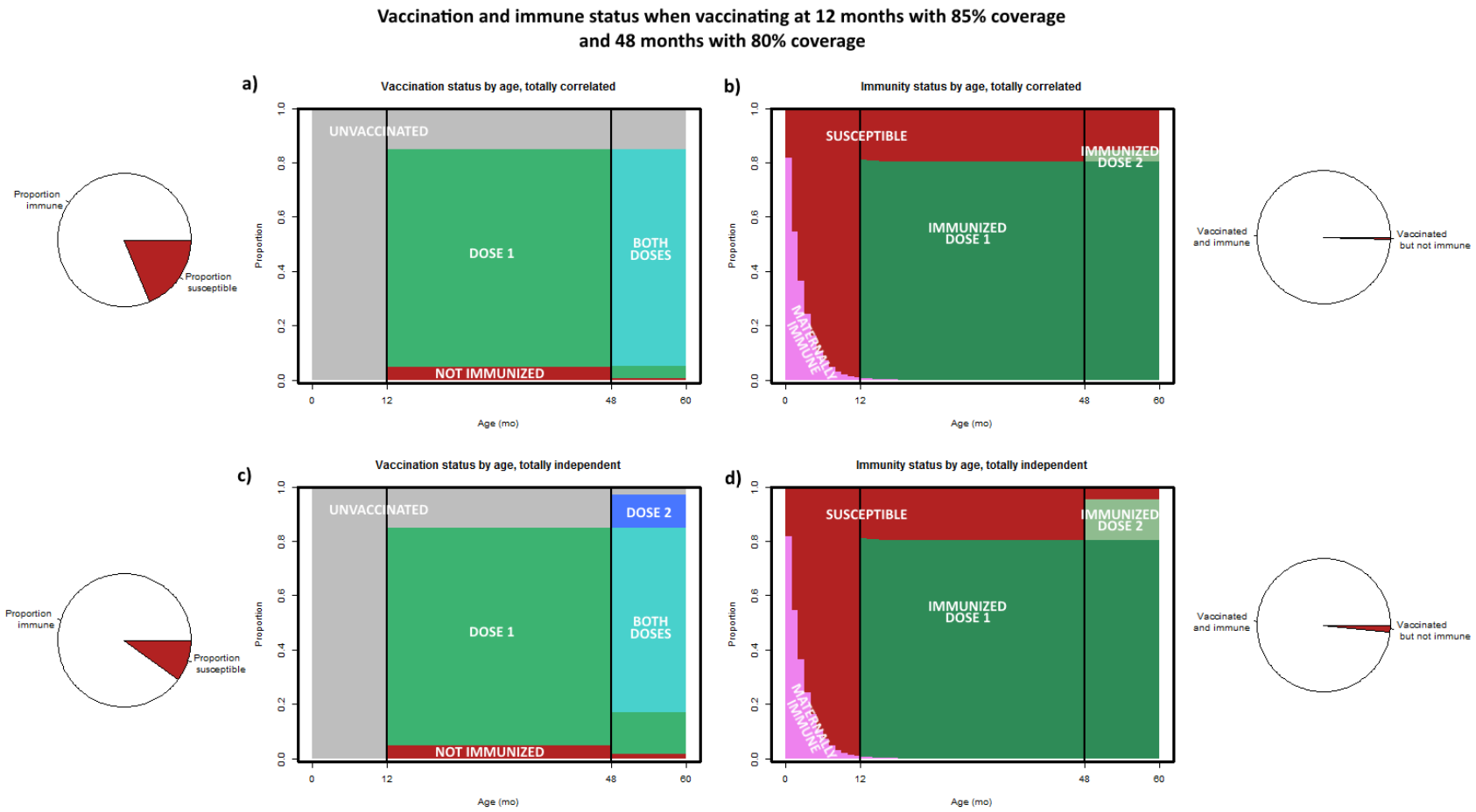



Figure 4.1: Vaccination and immunity class breakdown when first dose coverage is 85% and second dose coverage is 80%. Also shown is the rate of vaccine failure and the resulting proportion of the population that is susceptible. **a)** The vaccination classes when doses are administered dependently. The proportion of the population left susceptible here is 18.9%. **b)** The immune classes when

doses are administered dependently. The rate of primary vaccine failure here is 0.6%. **c)** The vaccine classes when doses are administered independently. The proportion of the population left susceptible here is 10%, which is less than when doses are administered dependently. **d)** The immune classes when doses are administered independently. The rate of primary vaccine failure here is 1.8%, which is greater than when doses are administered dependently.

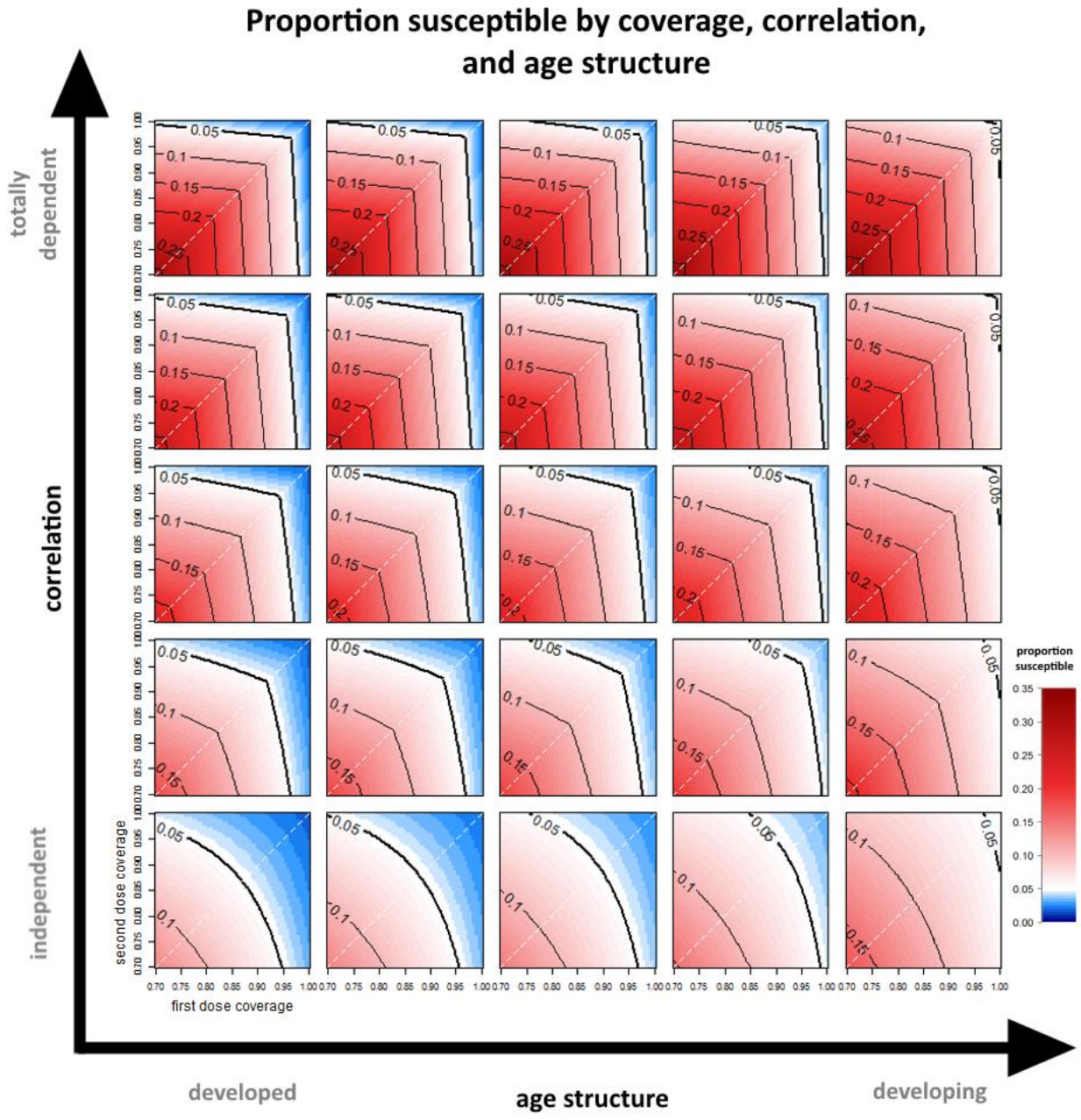



**Figure 4.2:** The susceptible proportion remaining for a range of first and second dose coverages, correlations, and age structure parameters. The contours indicate various threshold levels of immunity, where <5% susceptible within the population is generally considered sufficient to

maintain elimination and is colored in blue. The white dashed line indicates where the coverage of each dose is equal.

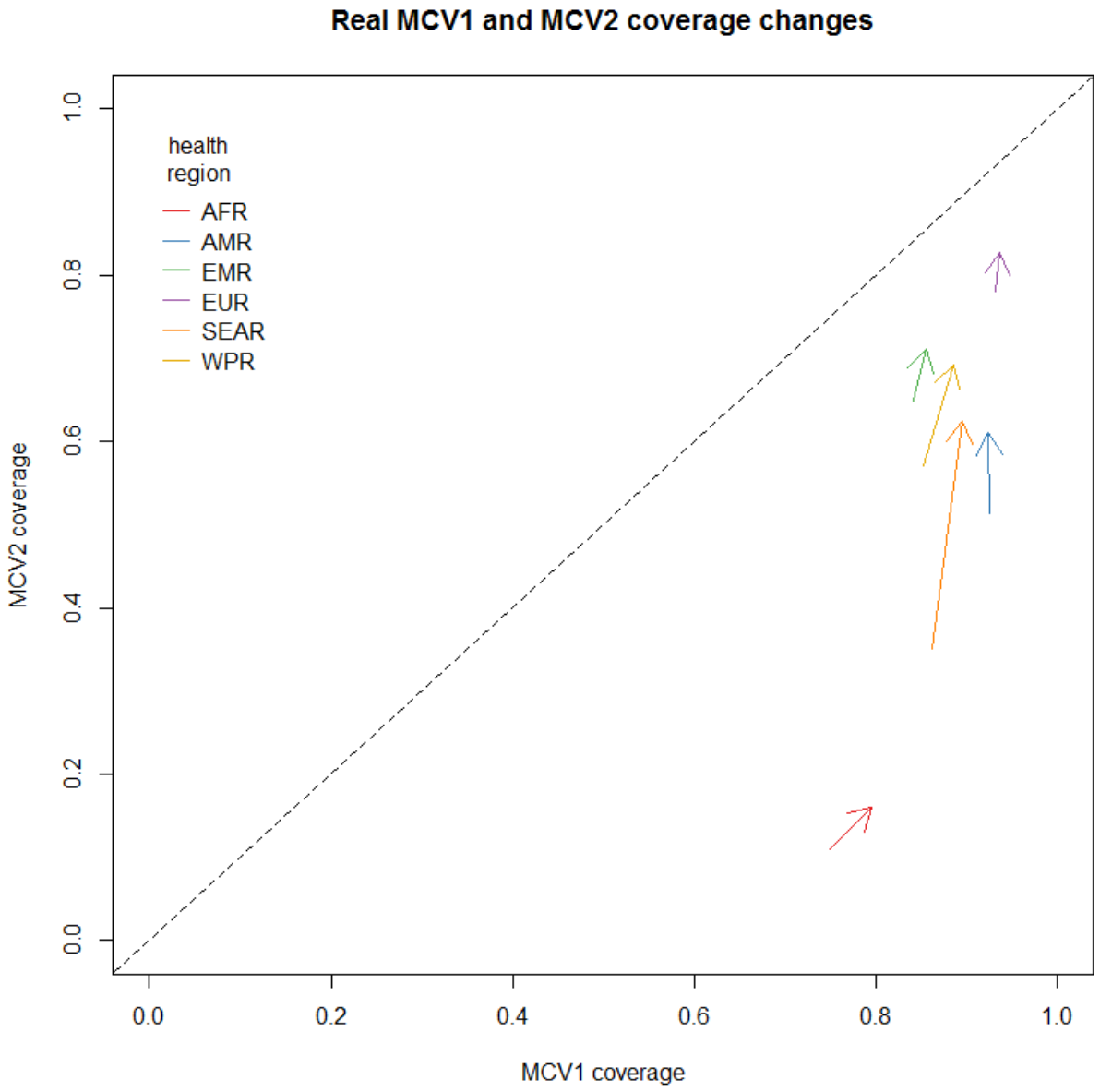



**Figure 4.3:** The average reported MCV1 (x-axis) and MCV2 (y-axis) coverages for each of 6 WHO health regions between 2005 and 2014. The unpointed end of the arrow represents the average coverage from 2005-2009. The pointed end represents the average coverage from 2010-2014. Missing reports were assumed to be 0. AFR is the African Region, AMR is the American

Region, EMR is the Eastern Mediterranean Region, EUR is the European Region, WPR is the Western Pacific Region, and SEAR is the Southeast Asian Region.

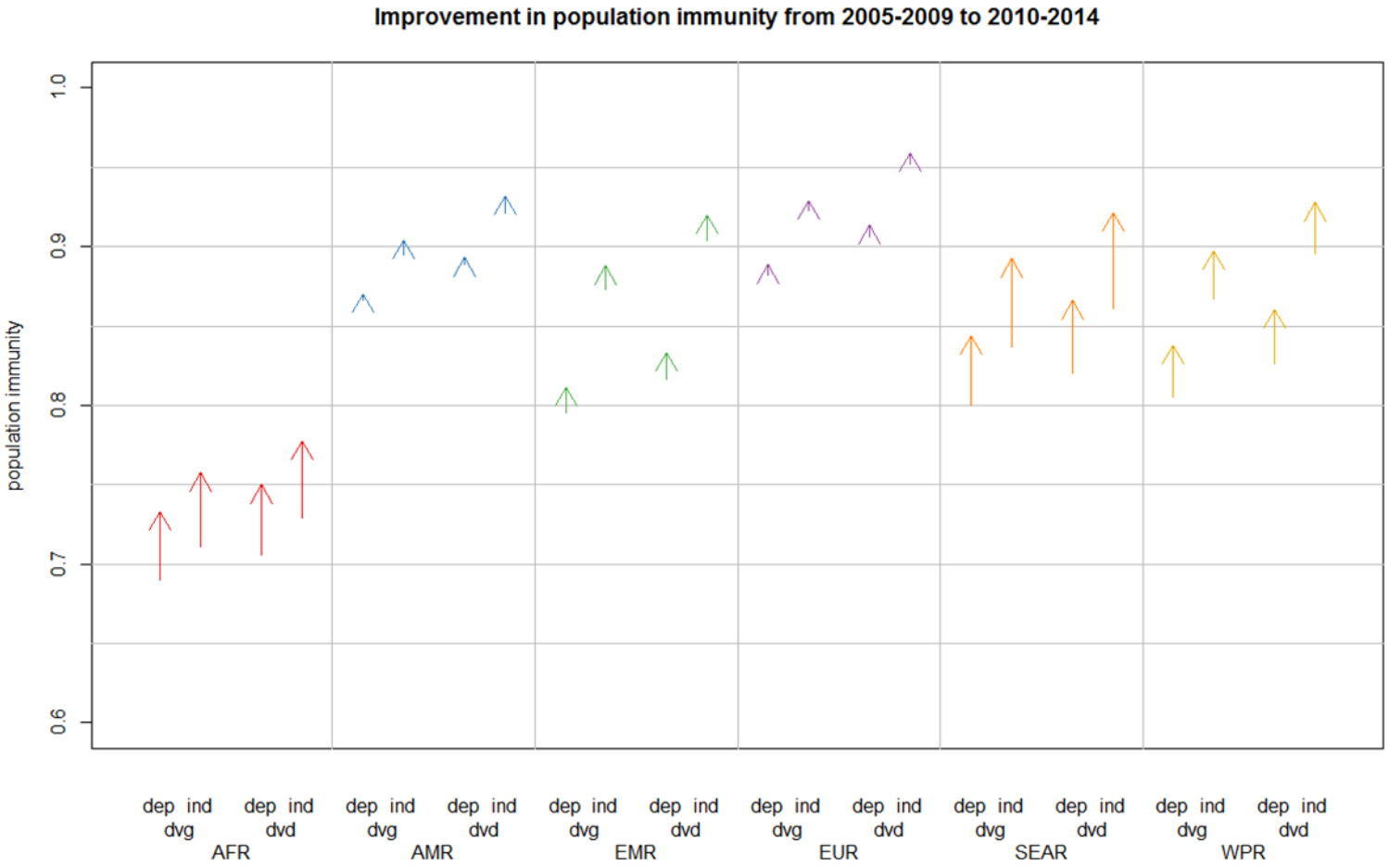



**Figure 4.4**: The improvement in population immunity for each WHO health region from 2005-2014, in each of four different contexts, using coverages shown in Fig. 3. AFR is the African Region, AMR is the American Region, EMR is the Eastern Mediterranean Region, EUR is the European Region, WPR is the Western Pacific Region, and SEAR is the Southeast Asian Region. The unpointed

end is the population immunity maintained by the average first and second dose coverages from 2005 to 2009, and the pointed end is the population immunity maintained by the average first and second dose coverages from 2010 to 2014. The four contexts are the four crosses of developing and developed age structures ("dvg" and "dvd", respectively) with dependent and independent administration of doses ("dep" and "ind", respectively). Each of these contexts represents a corner of Fig. 4.2.

# Chapter 5

## Objectives matter: Optimal age targets to minimize incidence of a measles reintroduction outbreak are not the same as those to minimize mortality

Amalie McKee, Matthew Ferrari, Katriona Shea

**Abstract**

Clearly specified objectives are crucial to inform management actions. However, measles management objectives are usually stated as non-specific "control" objectives, or as a dual objective to reduce incidence and reduce mortality. Using the combination of a steady-state analysis of the distribution of immunity in a disease-free state and an outbreak simulation, we show that the optimal age targets of a two dose routine immunization strategy are not the same under different objectives. When measles is absent, the age targets that maximize population immunity and those maximize the proportion of children under five years of age that is immune are different. When an outbreak happens, the age targets that minimize incidence and those that minimize mortality are often different. How similar or different they are depends on the coverage of each dose, the correlation between the populations receiving each dose, and the age structure of the population. For the situations examined here, outcomes for pre-invasion objectives differed by up to nearly 10%, while outcomes for post-invasion objectives differed by up to 2%. Choosing age targets to optimize under one objective may come with a significant sacrifice in performance under the other objective; a clear *a priori* statement of objective is essential before management actions can be satisfactorily evaluated.

## Introduction

Formal decision analysis, often encapsulated in structured decision making, can be used objectively to compare management alternatives in pursuit of a specific objective (Intriligator 1971, Clemen and Reilly 2001, Dorazio and Johnson 2003, Martin et al. 2009). Decision analysis has been used to evaluate management in a variety of ecological systems (Williams and Johnson 1995, Conroy et al. 2008), and recent work has begun to apply this approach to epidemiological systems as well (Shea et al. 2014). Decision theory requires managers to explicitly state the objective, as no optimization can proceed without a formal measure against which to evaluate the performance of different management strategies (Possingham et al. 2001, Runge 2011). However, objectives are often non-specific; for example, the aim to 'control' an epidemic may in fact be interpreted variously as 'to reduce spread', 'to reduce incidence', or 'to reduce mortality'. The importance of a formally specified objective has been shown, not just in ecological systems (e.g. Shea et al. 2010, Game et al. 2013), but also for epidemiological systems (Probert et al. 2016).

Measles, a leading cause of vaccine-preventable childhood death (Cutts et al. 2013), is an important target for global eradication (Christie and Gay 2011). This global eradication comprises two parts; achieving elimination in places where the disease is present, and maintaining elimination in places where the disease is absent. Many countries, including every country in the Americas, seven in the Western Pacific Region, and 22 in Europe, have achieved elimination (Perry et al. 2015), but must still continuously work to maintain it. As increased globalization means countries face constant potential reintroduction events (Gushulak and MacPherson 2004), successfully maintaining elimination requires mitigating the outbreaks sparked by these reintroduction events – for example, Brazil is no longer considered measles

free, as an outbreak that started in 2013 sustained transmission for more than one year (Perry et al. 2015). It is important for countries to carefully choose an immunization strategy to minimize the impact of such reintroduction events. The need for continued measles control is recognized globally, and the 4th UN Millennium Development Goal, under which measles is managed, has a stated objective to reduce child mortality (WHO 2011). Measles vaccination coverage is used as an indicator of performance under this goal (WHO 2011). However, measles control objectives are often stated as a combination of incidence and mortality reduction targets (Dowdle 1998, Perry et al. 2014).

Most countries that have achieved elimination use a two dose strategy to maintain it (Christie and Gay 2011). This two dose strategy consists of either one routine dose and a second dose administered through supplemental immunization activities or multiple routine doses of measles containing vaccine administered at two specified age targets (Hall and Jolley 2011) – we focus here on the latter. The vaccine has an age-specific efficacy, as maternal-acquired antibodies prevent children from seroconverting if they are vaccinated before their antibody titer has sufficiently waned (de Quadros et al. 1998). Age targets for vaccination are chosen to balance this age-specific efficacy with the effectiveness of the program (McLean and Anderson 1988, et al. 2015). In places where the disease is endemic, this means vaccinating infants after their maternal antibodies have waned but before they are exposed to the disease (McLean and Anderson 1988). In places where the disease has been eliminated, the upper bound on effective age targets for vaccination is not explicit, but vaccination must still occur at a young enough age that a sufficient proportion of the population is sufficiently immune to maintain elimination (McKee et al. 2015).

A two dose vaccination strategy results in a susceptible population with three subpopulations; individuals younger than the first dose age target, individuals between the two age targets, and individuals older than the second dose age target. The second dose may either serve as a second opportunity (that is, simply a second time individuals can come to a clinic and receive at least one dose), or a true second dose (which is only administered to children who had the first dose). Whether the second dose is a true second dose or a second opportunity depends on the health system. This, along with coverage of each dose, has a strong effect on the proportion of the population that falls into each of the three susceptible subpopulations.

In order to minimize incidence, it is important to minimize the total proportion of the population susceptible to measles (Steffens et al. 2010). However, measles has an age-specific mortality risk; children under five are much more likely to die if infected than are older children and adults (Wolfson et al. 2009). How much more likely depends on location, vaccine status, and nutritional status. Wolfson et al. analyze case fatality ratios reported by 102 studies in 29 countries. For each study that reported a different case fatality ratio for yearly age classes up to 5+ years old, case fatality ratio was lowest in children who were 5+ years old, but the overall worldwide trend in case fatality ratio with age was less clear (Wolfson et al. 2009). Therefore, the first two susceptible subpopulations resulting from a two dose vaccine policy (children too young to receive the first dose and children between the first and second dose) may disproportionately contribute to mortality. Due to this disproportionate contribution, the optimal age targets to minimize incidence may not be the optimal age targets to minimize mortality.

Thus, "controlling an outbreak" or "minimizing the impact of an outbreak" may refer to either minimizing mortality or minimizing incidence, but the two are different objectives and the optimal age targets for the two may differ. Only in the situation of complete elimination will the

two objectives necessarily coincide; zero cases lead to zero fatalities. We find the optimal age targets to minimize incidence and to minimize mortality, first by using a steady state analysis of a deterministic dynamical model in the disease free setting, and then after disease invasion by using the outcomes of a stochastic epidemic model. We compare the optimal age targets for each of the two objectives for two correlations (low and high) between the first and second dose, and two population structures, to find under what conditions the two objectives are or are not congruent.

**Methods**

We use two basic models in this paper, to model two different settings. The first model is a steady-state model for the age distribution of susceptibility maintained by two routine doses of vaccine in a disease-free setting (based on the models in Chapters 3 and 4). This model represents the post-elimination state, before disease reinvasion, where the only sources of immunity in the population are maternal immunity and vaccine-derived immunity. The second model is a stochastic model of the disease dynamics following disease invasion (Metcalf et al. 2011). This model represents the consequences of a reintroduction event, and we can use it to find the incidence and mortality risk of an outbreak.

We first find the optimal age targets for the disease-free setting using a steady state analysis of an age-structured dynamical model. We divide the population into 77 age classes; monthly up to age 5, then yearly up to age 20, then 20-50, and 50+. We use two basic age structures; one where children under 5 make up 10% of the population (which we call a "developed" age structure), and one where children under 5 make up 15% of the population (which we call a "developing" age structure) (McKee et al. 2015, Chapter 2). Each age class is then divided into

one of four vaccine classes; unvaccinated, vaccinated with the first dose only, vaccinated with the second dose only, and vaccinated with both doses.

Each vaccine class is then divided into one of three immune classes; maternally immune, susceptible, and immunized. We assume that maternal immunity wanes exponentially, with 10% of individuals who were born with maternal immunity retaining maternal immunity at 9 months. In previous chapters, we assumed that maternal immunity waned exponentially with a mean at 3 months, meaning around 5% of children would have retained maternal antibodies at 9 months, but we now use a different distribution for added realism. The qualitative results of previous chapters are the same regardless of the actual function used for maternal immunity. We assume that the proportion of individuals born with maternal immunity is equal to the proportion of individuals who were successfully vaccinated in the previous generation, and find the equilibrial proportion using a generational model. We also assume that each dose is only 95% effective when administered to a susceptible individual, in order to account for other means of vaccine failure, such as cold chain disruption (Lessler et al. 2011). In total, this means that only 85% of doses administered at 9 months to children born with maternal immunity are effective (Simons et al. 2011).

From this age-specific distribution of immune classes, we can find the age distribution of susceptibility within the population and the total proportion susceptible. As children under five years of age are more likely to die due to infection (Wolfson et al. 2009), we also find the total proportion of children under five who are susceptible from a given combination of vaccine age targets and coverages. We find the population immunity and proportion of children under 5 for each combination of age targets for a range of specified coverages, and then find which age targets maximize population immunity or the proportion of children under 5 who are immune.

We then simulate disease dynamics for two years after disease invasion using a stochastic SIR model adapted from Metcalf et al. (2011). We use a two week time step, so that individuals are only infectious for one time step, as is consistent with measles epidemiology. We assume homogenous mixing, but use an age structured transmission parameter, so that the force of infection is peaked at 3 years of age (Ferrari et al. 2010) and scale it so that $R_0$, the basic reproductive ratio of the disease, is 20 (Moss and Griffin 2006). We seed the epidemic by randomly selecting 1% of the susceptible population to be infected. We include population demography in our model, but scale birth and death rates so that the population size and age structure are both constant. For each combination of coverage, age targets, age structure, and means of administering the second dose, we find the age-specific incidence and total mortality risk. As true case fatality rates vary from place to place (Wolfson et al. 2009), we do not find the absolute mortality due to an outbreak, but rather assume that mortality risk is some function of age-specific incidence for simplicity. Here, we assume children under five are twice as likely to die due to infection as older children and adults (Metcalf et al. 2011). While the true case fatality rate in children under five is not always double the case fatality rate in older children and adults, it is always greater, and the relative value varies country to country (Wolfson et al. 2009). We then compare incidence and mortality risk for outbreaks across a selection of age targets, in order to find the optimal age targets to minimize mortality or incidence conditional on coverage, age structure, and means of implementing the second dose.

**Results**

We divide our results into eight basic categories; all possible combinations of three pairs of basic scenario alternatives. The first pair of alternatives is the disease context; pre-invasion (Fig. 5.1, Fig. 5.3 a-d, Fig. 5.4 a-d) and post-invasion (Fig. 5.2, Fig. 5.3 e-h, Fig. 5.4 e-h). The second pair

is the means of administering the second dose; dependently (Fig. 5.1-5.4 a-b and e-f), where the second dose is administered only to children who have had the first dose, or independently (Fig. 5.1-5.4 c-d and g-h), where the second dose is administered independently of whether children had the first dose. The third pair is the age structure; developed, with a relatively small proportion of children under five, (Fig. 5.1-5.4 a, c, e, g) and developing, with a relatively large proportion of children under five (Fig. 5.1-5.4 b, d, f, g). In each category, we compare two basic objectives. In the pre-invasion state, we compare minimizing the total proportion susceptible (Fig. 5.1 a-d) with minimizing the total proportion of children under five who are susceptible (Fig. 5.1 e-h). In the post invasion state, we compare minimizing incidence (Fig. 5.2 a-d) with minimizing mortality (Fig. 5.2 e-h).

In the pre-invasion scenario, when the second dose is administered dependently, the optimal first dose target to maximize population immunity (given 90% first and second dose coverage) occurs earlier in life than if the second dose was administered independently (Fig. 5.1 a-b vs. c-d), regardless of age structure. This is because every individual who has the first dose gets the second dose and all individuals who fail to seroconvert the first time will have a second chance to become immune, so the efficacy of the first dose is less important for population immunity. However, while the optimal age target for the first dose occurs later in life when the doses are administered independently, much higher levels of population immunity are achieved.

In the pre-invasion scenario, the optimal age targets to maximize the proportion of children under 5 who are immune (given 90% first and second dose coverage) occur much earlier in life than the optimal age targets to maximize population immunity (Fig. 5.1 e-h vs. a-d), regardless of age structure or correlation of the second dose. This reduces the proportion of susceptible individuals too young to receive the first dose and the proportion of susceptible individuals

between doses, at the cost of increasing the total proportion of susceptible individuals. Therefore, the two pre-invasion objectives are not congruent in any scenario when first and second dose coverage are 90%.

In the post-invasion scenario, when doses are administered dependently, the optimal first dose age target to minimize both incidence and mortality (given 90% first and second dose coverage) falls very early in life, regardless of age structure – at 2 months of age (Fig. 5.2 a-b, e-f). While this means that the first dose has a very low efficacy, every individual who gets the first dose will later get the second dose, so each individual will have a second chance at becoming immune. As the force of infection peaks in very young children, and very young children are most likely to die due to infection, protecting very young children is especially important, thereby driving the optimal age target for the first dose down.

When doses are administered independently in the post-invasion scenario, the optimal first and second dose age targets to minimize both incidence and mortality (given 90% first and second dose coverage) are both later in life than the optimal age targets when they are dependent (Fig. 5.2 c-d vs. a-b and g-h vs. e-f), regardless of age structure. However, incidence is much lower for a much wider range of age targets, as a much greater proportion of the population has received at least one dose.

The differences, in months, between the optimal age targets to optimize performance under the two pre-invasion objectives (maximize population immunity and maximize the proportion of children under five that are immune), is greatest for high first dose coverage and low second dose coverage when doses are administered dependently (Fig. 5.3 a-b), and for any first dose coverage with low second dose coverage when doses are administered independently (Fig. 5.3 c-d). The optimal age targets to maximize population immunity are always later in life than the

optimal age targets to maximize the proportion of children under five who are immune. This is true for both age structures, although the overall difference is larger on a developed age structure (Fig. 5.3 a and c vs. Fig. 5.3 b and d), as the high proportion of children under 5 means that the optimal age targets to maximize population immunity fall earlier in life on a developed age structure.

The differences, in months, between the optimal age targets to optimize performance under the two post-invasion objectives (minimize incidence and minimize mortality) have a much less clear pattern. The optimal age targets to minimize incidence are always later in life, or at equal ages, to the optimal age targets to minimize incidence. When doses are administered dependently, there is no clear relationship between first and second dose coverage and the difference in the optimal age targets (Fig. 5.3 e-f), regardless of age structure. However, when doses are administered independently, the difference is greatest for low first dose coverage, regardless of age structure (Fig. 5.3 g-h). Note that the very young ages of the optimal age targets, as well as the resolution of this figure, may contribute to the difficulty distinguishing a pattern.

The population immunity achieved when vaccinating using age targets chosen to maximize the proportion of children under five that is immune can differ by as much as 4% from the population immunity achieved when using age targets chosen to maximize population immunity (Fig. 5.4 a-d). The proportion of children under five that is immune when vaccinating using age targets chosen to maximize total population immunity can differ by as much as 9.5% from the proportion of children under five that is immune when using age targets chosen to maximize that proportion (Fig. 5.4 a-d). In this situation, using age targets chosen to optimize performance under one pre-invasion objective comes with a sacrifice in performance under the other pre-

invasion objective. This sacrifice is present regardless of age structure and means of administering the second dose, although it is largest when doses are administered independently to a population with a developed age structure. As coverage increases, the difference in payoffs when using age targets chosen to maximize the other objective decreases (Fig. 5.4 a-d).

Incidence can increase by up to 2% when using age targets chosen to minimize mortality risk and mortality risk can increase by up to 1.5% when using age targets chosen to minimize incidence (Fig. 5.4 e-h). There is often, but not always, a difference in performance under one post-invasion objective when using age targets chosen to optimize performance under the other. This loss is especially large when doses are administered dependently, although the pattern with respect to coverage is much less clear for the difference in performance under one post-invasion objective when using age targets chosen to minimize the outcome under the other objective, and the effect is usually smaller than for the pre-invasion scenario (less than 2%).

**Discussion**

In order to maintain measles elimination, it is important that we control outbreaks sparked by reintroduction events. However, "controlling" these outbreaks could mean either minimizing the incidence of or minimizing the mortality due to these outbreaks (Dowdle 1998, Perry et al. 2014). While the two objectives seem similar at first glance, they may not always be the same when it comes to making management recommendations, as not all children are equally likely to die due to measles infection. Ultimately, the two objectives will be the same in the context of eradication, as no cases means no disease-induced mortality, but in the interim, explicitly stating a management objective in terms of one specific measure could change management recommendations.

The incidence of an outbreak depends on the age-specific force of infection and age-distribution of susceptibility prior to an outbreak (Ferrari et al. 2010). In a disease-free setting, knowing the former may be difficult, so choosing age targets to maximize the proportion of the population that is immune to measles may be the most intuitive way to minimize the incidence of an outbreak, as it minimizes the number of susceptible individuals who may be infected. Without knowing the dynamics of an outbreak, which are dependent on population contact structure (Burr and Chowell 2009), knowing the true age-specific risk can be difficult. However, we do know that children under five are more likely to die due to infection (Wolfson et al. 2009), so maximizing the proportion of children under five who are immune may be the most effective way to minimize the mortality of an outbreak without knowing the age-specific force of infection or contact structure. The age targets to maximize the proportion of children under five who are immune are not the same as the age targets that maximize population immunity, however, and generally fall much earlier in life, at the cost of efficacy of each dose (Fig. 5.1 a-d vs. e-h).

After an outbreak, the age-specific risk of infection can be inferred from the age-specific incidence (Ferrari et al. 2010). If the force of infection in highest in very young children, the optimal age targets to minimize incidence and to minimize mortality fall much earlier in life than the optimal age targets to maximize population immunity. How much earlier depends on the way the second dose is administered (as in Chapter 3); if the second dose is the true second dose, then the first dose should be administered almost at birth, as each individual will have a second chance to become immune, whereas if the second dose is the second opportunity to receive vaccine at all, then the first dose should be administered slightly later in life. Here we assume children under five are twice as likely to die as older children and adults, but true case fatality ratios are more variable (Wolfson et al. 2009). A more severe difference in case fatality ratios

might result in even younger optimal age targets. Furthermore, specific case fatality ratios may depend on a variety of factors; both constant factors, such as location, and factors that may vary over the course of an outbreak, such as healthcare availability or the number of concurrent cases. This could change age target selection for the different objectives.

The difference in optimal age targets under each objective, and the difference in payoff for choosing age targets that are optimal for a different objective, depends on coverage and age structure as well as on the way in which the second dose is administered. It is possible that win-win scenarios exist, where performance under each objectives are optimal or at least within some target range (Perry et al. 2015), but this will not always pertain. Coverage is generally relatively consistent year-to-year in places where the disease has been eliminated, so we recommend that countries reevaluate the age targets at which they administer vaccines in the context of their specific coverage levels, correlation and age structure, and being explicit about what objective they are trying to achieve.

**Acknowledgements**

We acknowledge funding from the National Institutes of Health and National Science Foundation (EEID award 1 R01 GM105247-01 and NSF Ebola RAPID DMS-1514704).

**References**

1. Burr T, Chowell G. The reproduction number Rt in structured and nonstructured populations. Math Biosci Eng 2009; 6: 239–59.
2. Christie AS, Gay A. The Measles Initiative: moving toward measles eradication. J Infect Dis 2011; 204: S14–7.
3. Clemen RT, Reilly T. Making hard decisions with decision tools. Duxbury Press, California, 2001.

4. Conroy MJ, Barker RJ, Dillingham PW, Fletcher D, Gormley AM, Westbrooke IM. Application of decision theory to conservation management: Recovery of Hector's dolphin. Wildl Res 2008; 35: 93–102.
5. Cutts FT, Lessler J, Metcalf CJE. Measles elimination: progress, challenges and implications for rubella control. Expert Rev Vaccines 2013; 12: 917–32.
6. de Quadros CA, Hersh BS, Nogueira AC, Carrasco PA, da Silveira CM. Measles eradication: experience in the Americas. Bull World Health Organ 1998; 76 Suppl 2: 47–52.
7. Dorazio RM, Johnson FA. Bayesian Inference and Decision Theory -- A Framework for Decision Making in Natural Resource Management. Ecol Appl 2003; 13: 556–63.
8. Dowdle WR. The principles of disease elimination and eradication. Bull World Health Organ 1998; 76: 22–5.
9. Ferrari MJ, Djibo a, Grais RF, Grenfell BT, Bjørnstad ON. Episodic outbreaks bias estimates of age-specific force of infection: a corrected method using measles as an example. Epidemiol Infect 2010; 138: 108–16.
10. Game ET, Kareiva P, Possingham HP. Six Common Mistakes in Conservation Priority Setting. Conserv Biol 2013; 27: 480–5.
11. Gushulak BD, MacPherson DW. Globalization of Infectious Diseases: The Impact of Migration. Clinical Infectious Disease 2004; 38:1742–1748. doi: 10.1086/421268
12. Hall R, Jolley D. International measles incidence and immunization coverage. J Infect Dis 2011; 204 Suppl : S158–63.
13. Intriligator, MD. Mathematical optimization and economic theory. Prentice-Hall, New Jersey, 1971.

14. Lessler J, Metcalf CJE, Grais RF, Luquero FJ, Cummings D a T, Grenfell BT. Measuring the performance of vaccination programs using cross-sectional surveys: a likelihood framework and retrospective analysis. PLoS Med 2011; 8: e1001110.
15. Martin J, Runge MC, Nichols JD, Lubow BC, Kendall WL. Structured decision making as a conceptual framework to identify thresholds for conservation and management. Ecol Appl 2009; 19: 1079–1090. doi:10.1890/08-0255.1
16. McKee A, Ferrari MJ, Shea K. The effects of maternal immunity and age structure on population immunity to measles. Theor Ecol 2015; 8: 261–71.
17. McLean AR, Anderson RM. Measles in developing countries. Part I. Epidemiological parameters and patterns. Epidemiol Infect 1988; 100: 111–33.
18. Metcalf CJE, Klepac P, Ferrari M, Grais RF, Djibo a, Grenfell BT. Modelling the first dose of measles vaccination: the role of maternal immunity, demographic factors, and delivery systems. Epidemiol Infect 2011; 139: 265–74.
19. Moss WJ, Griffin DE. Global measles elimination. Nat Rev Microbiol 2006; 4: 900–8.
20. Perry RT, Gacic-Dobo M, Dabbagh A, et al. Global Control and Regional Elimination of Measles, 2000–2011. MMWR Morb Mortal Wkly Rep 2014; 63: 103–7.
21. Perry RT, Murray JS, Gacic-Dobo M, et al. Weekly epidemiological record: Progress towards regional measles elimination, worldwide, 2000–2014. World Health Organization 2015; 46:623–631.
22. Possingham HP, Andelman SJ, Noon BR, Trombulak S, Pulliam HR. Making smart conservation decisions. In: Conservation biology: research priorities for the next decade. 2001: 225–44.

23. Probert WJM, Shea K, Fonnesbeck CJ, et al. Decision-making for foot-and-mouth disease control: Objectives matter. Epidemics 2016; 15: 10–9.
24. Runge MC. An Introduction to Adaptive Management for Threatened and Endangered Species. J Fish Wildl Manag 2011; 2: 220–33.
25. Shea K, Jongejans E, Skarpaas O, Kelly D, Sheppard A. Optimal management strategies to control local population growth or population spread may not be the same. Ecol Appl 2010; 20(4): 1148-1161
26. Shea K, Tildesley MJ, Runge MC, Fonnesbeck CJ, Ferrari MJ. Adaptive Management and the Value of Information: Learning Via Intervention in Epidemiology. PLoS Biol 2014; 12: 9–12.
27. Simons E, Mort M, Dabbagh A, Strebel P, Wolfson L. Strategic planning for measles control: using data to inform optimal vaccination strategies. J Infect Dis 2011; 204 Suppl: S28–34.
28. Steffens I, Martin R, Lopalco P. Spotlight on measles 2010: measles elimination in Europe—a new commitment to meet the goal by 2015. Euro Surveill 2010; 15: 1–26.
29. WHO. Millennium Development Goals: Child and maternal goals: MDGs 4 and 5. 2011. http://www.who.int/pmnch/media/press_materials/fs/about_mdgs/en/#
30. Williams BK, Johnson FA. Adaptive Management and the Regulation of Waterfowl Harvests. Wildl Soc Bull 1995; 23: 430–6.
31. Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. Int J Epidemiol 2009; 38: 192–205.

32. World Health Organization (2016) Vaccine-preventable diseases: monitoring system 2016 global summary. http://apps.who.int/immunization_monitoring/globalsummary/schedules

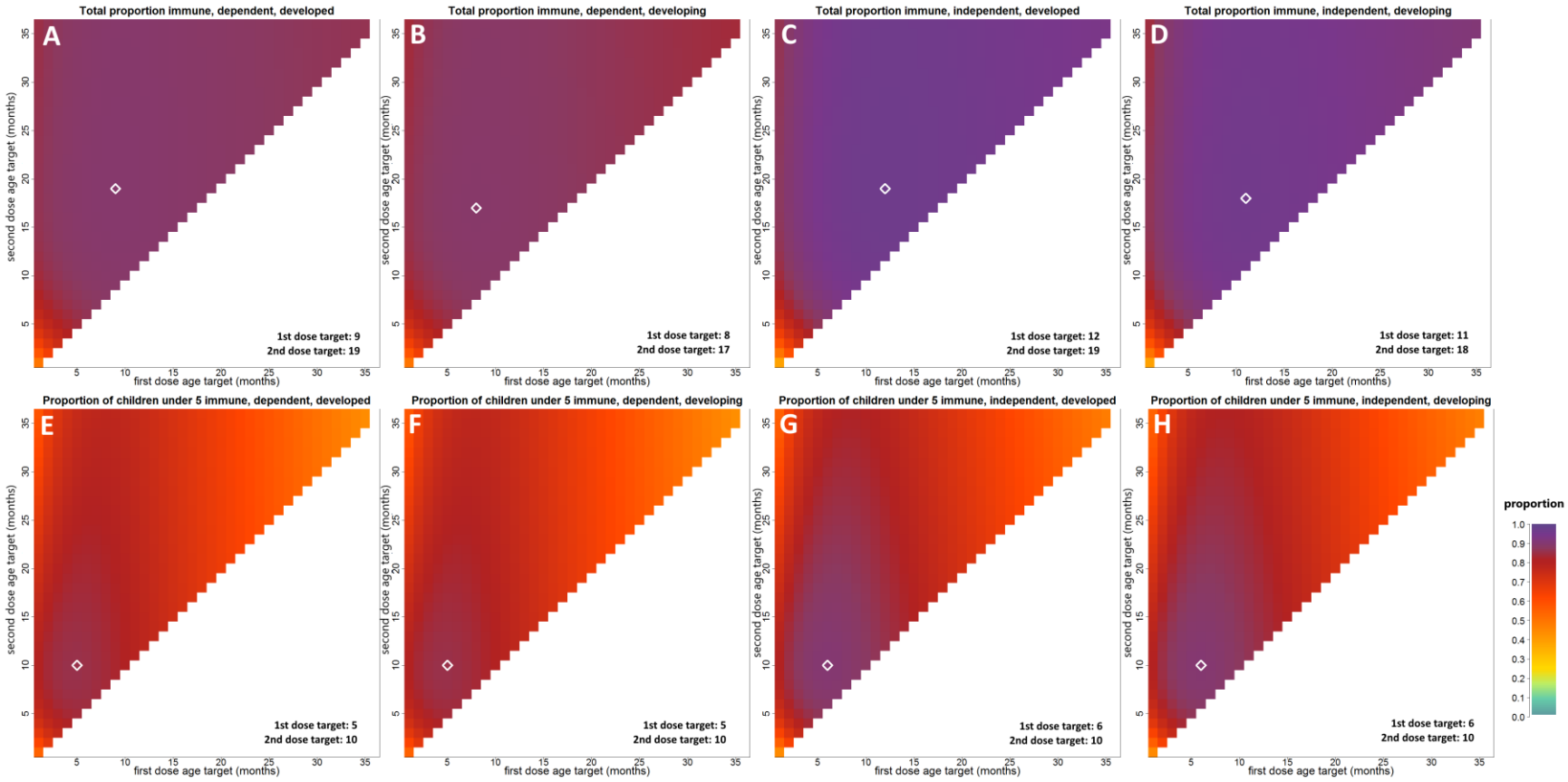



**Figure 5.1:** Each panel shows the payoff under one pre-invasion objective (proportion of the total population of children under five immune) when vaccinating with 90% first and second dose coverage at a range of first and second dose age targets (specified in months), for all combinations of two age structures and two means of implementing the second dose with respect to correlation. The optimal combination of age targets (that is, the combination that maximizes the payoff under the given objective) in each panel is

highlighted by a white diamond, and given in text in the lower right. **A-D** The total proportion of the total population that is immune after vaccination. **E-H** The proportion of children under five that are immune after vaccination.

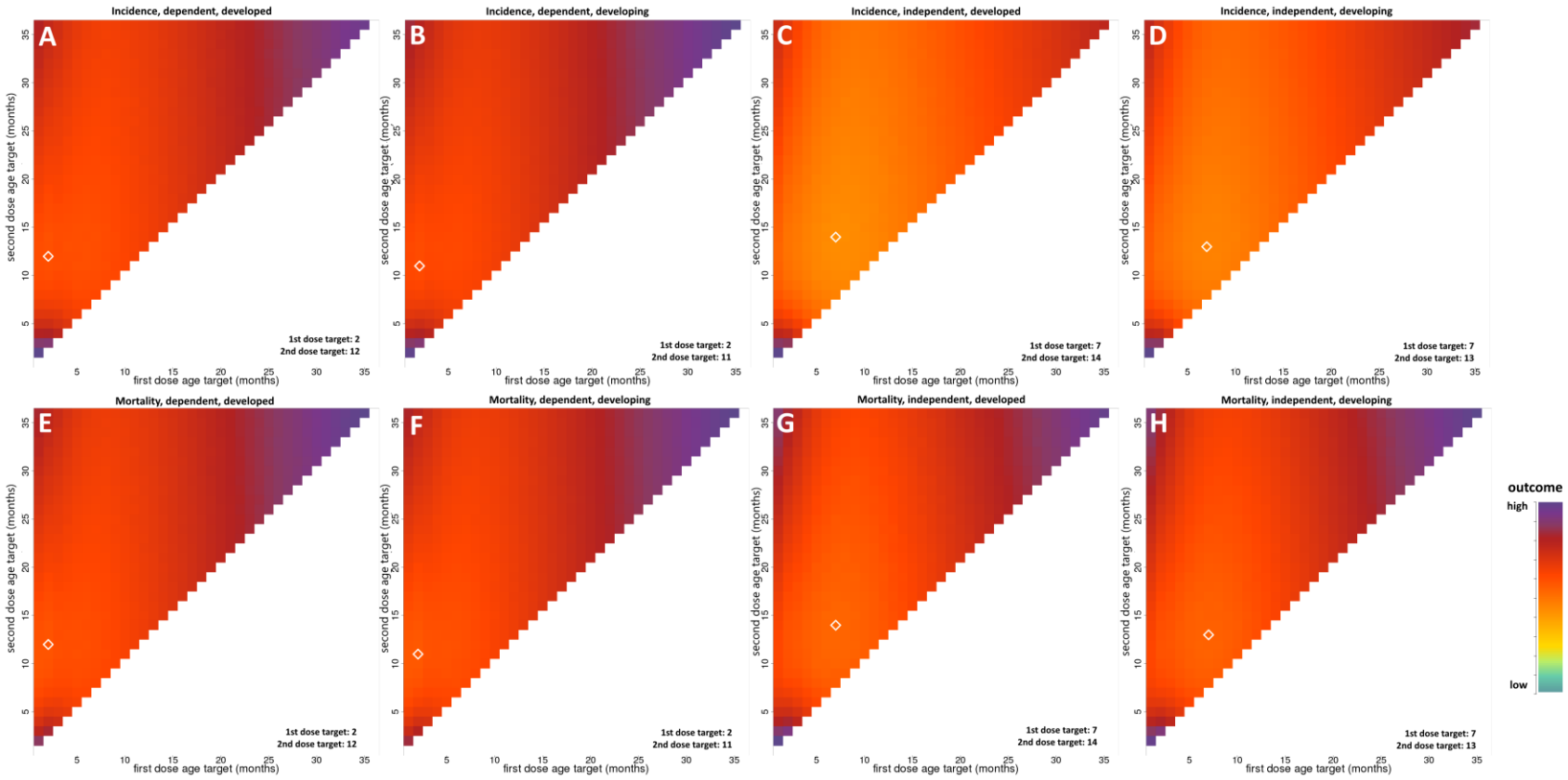



**Figure 5.2:** Each panel shows the payoff under one post-invasion objective (to minimize incidence or to minimize mortality) when vaccinating with 90% first and second dose coverage at a range of first and second dose age targets (specified in months), for all combinations of two age structures and two means (dependent or independent) of implementing the second dose with respect to correlation. The optimal combination of age targets (that is, the combination that maximizes the payoff under the given objective) in

each panel is highlighted by a white diamond, and given in text in the lower right. **A-D** The average incidence of a reintroduction outbreak. **E-H** The average mortality of a reintroduction outbreak.

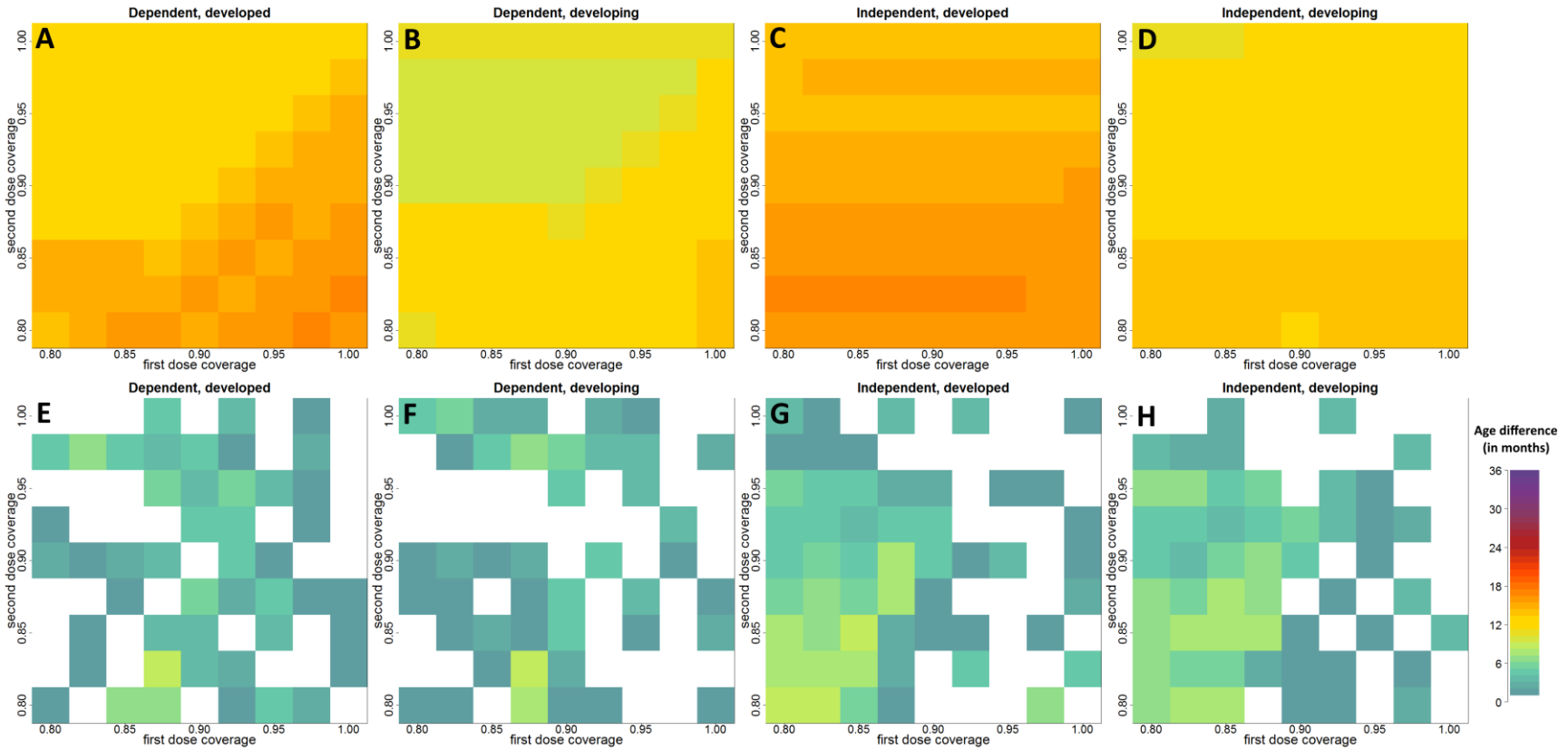



**Figure 5.3:** The difference between the optimal age targets under each objective, in months, for a range of coverages and all combinations of two age structures and the two means of administering the second dose (correlated or not with the first dose). In the pre-invasion context (A-D), this is the optimal age targets to maximize population immunity minus the optimal age targets to maximize the proportion of children under five who are immune. In the post-invasion context (E-H), this is the optimal age targets to minimize incidence minus the optimal age targets to minimize mortality risk. **A-D** The difference in age targets for the two pre-

invasion objectives (maximizing population immunity and maximizing the proportion of children under 5 who are immune). **E-H** The difference in age targets for the two post-invasion objectives (minimizing incidence and minimizing mortality).

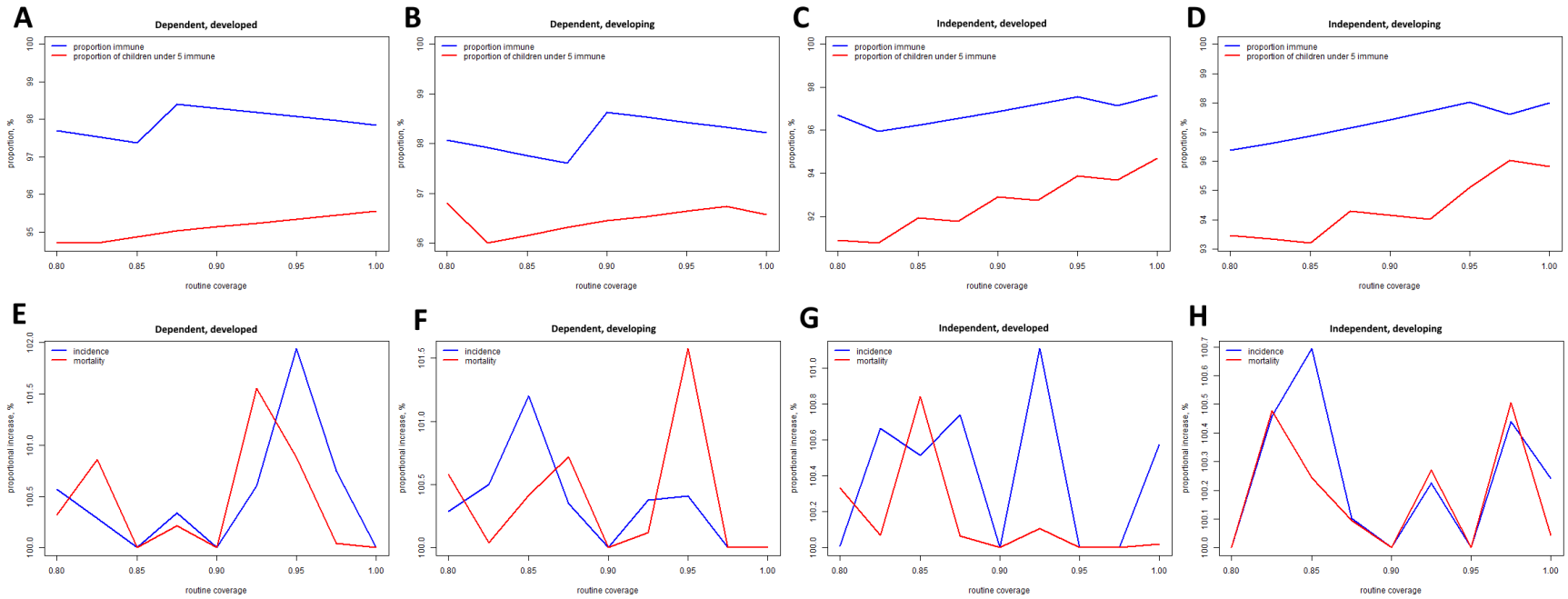



**Figure 5.4:** The cost, in performance under one objective, of choosing age targets that maximize performance under the other, for a range of coverages (assuming first and second dose coverage are the same) and all combinations of two age structures and two means of administering the second dose. **A**-**D** The difference in the pre-invasion objectives (maximizing population immunity and maximizing the proportion of children under 5 who are immune). **E**-**H** The difference in the post-invasion objectives (minimizing mortality and minimizing incidence).

# Chapter 6

## When is routine immunization better than supplemental immunization activities for maintaining elimination?

Amalie McKee, Katriona Shea, Matthew Ferrari

**Abstract**

In regions where measles has been eliminated, sustaining high population immunity levels is critical to avoid reinvasion of the disease. Control efforts typically consist of two doses of measles containing vaccine, with the first dose administered through routine immunization at a specific target age. The second dose may be administered either as a second routine dose at a later target age, or through supplemental immunization activities (SIAs), which vaccinate all children within a specified age range over a short period of time. We evaluate the relative performance of each means of administering the second dose, alone and combined, on maintaining high levels of population immunity using a steady state analysis of a dynamical model for immunity within a disease-free population. We find that, in order to outperform SIAs, a second routine dose must usually have much higher coverage than SIAs, though the magnitude required depends on first dose coverage. The exception is if the overlap between the populations receiving the first and second dose is much lower than expected (low correlation between the first and second routine doses) and the overlap between the populations receiving the first dose and SIAs is much higher than expected (high correlation between the first dose and SIA). When both routine doses and SIAs are administered, population immunity is always improved, but the magnitude of improvement is uncertain without knowing correlation. Careful selection of long-term maintenance of elimination strategies, including whether to phase out SIAs under current programmatic conditions, should take correlation into consideration as well as coverage.

## Introduction

After decades of control efforts (Henao-Restrepo et al. 2005), measles remains an important contributor to global childhood mortality (Simons et al. 2012). As such, it is a primary target for global eradication (WHO 2011, Moss and Strebel 2011). Eradication comprises two steps; achieving local elimination, and then maintaining local elimination (Andrews and Langmuir 1963). In order to achieve either part, the proportion of the population immune to measles must be extremely high, and therefore measles containing vaccine coverage must also be high (Orenstein et al. 2000). High coverage is achieved worldwide through two doses of measles containing vaccine (Hall and Jolley 2011). The first dose is typically a routine dose, where children come to a clinic to be vaccinated at a specified target age, usually early in life (Metcalf et al. 2011). A second dose is usually administered, either through a second routine dose at another target age or through supplemental immunization activities (SIAs), where children within a target age range are vaccinated at a specific time (Christie and Gay 2011). However, routine immunizations and supplemental immunization activities may perform substantially differently, both with respect to coverage and the resulting population immunity (Lessler et al. 2011).

Routine immunizations for measles are administered as part of an extensive childhood vaccine schedule (WHO 2016a). In places where healthcare access is good, coverage of these immunizations is typically high (WHO 2016b, WHO 2016c). However, in places where healthcare access is poor, coverage of these immunizations may be low, and children who cannot access a clinic to receive the first dose may also be unable to receive the second dose (Favin et al. 2010, WHO 2016b, WHO 2016c). As such, when the second dose is administered through routine immunization, correlation between populations receiving the first and second dose is

likely high (WHO 2013), and the second dose is unlikely to reach children who missed the first dose (Chapter 4).

SIAs are campaigns conducted over an extensive area, with millions of doses administered within a very short time period (Vijayaraghavan 2007). Doses are typically administered to children within a specified age range (Wagner 2016). SIAs may overlap, in that an individual may be eligible for vaccination in multiple sequential SIAs (WHO 2015). SIAs are difficult to run, more expensive than routine immunization (WHO 2013, Gandhi and Lydon 2014), and often funded by external sources (Hoekstra et al. 2011, MSF 2013). There is great uncertainty about the impact of these campaigns, with reported coverage often exceeding 100% (WHO 2015), although true coverage is usually estimated, through combinations of health surveys and administrative data, to be much lower (Lessler et al. 2011). One benefit of these campaigns has typically been thought to be that they reach children who are not reached by the routine health system (WHO 2013, Vijayaraghavan 2007). However, this may not be entirely true, as children who are accessible to the routine health system are likely also the most accessible to these SIAs (Metcalf et al. 2015). Thus, while the correlation between the populations receiving the first dose and SIAs is likely low, it may be much higher than anticipated.

Typically, as a country proceeds towards elimination, policy makers start by recommending a combination of a single routine dose and SIAs (WHO 2012). Once coverage of the first routine dose is sufficiently high, typically around 80% (WHO 2013), introduction of a second routine dose is recommended. Once elimination has been achieved, or routine coverage of both doses is sufficiently high, SIAs are phased out (WHO 2012). This approach has been very successful in many countries, including most countries in the Americas (Castillo-Solorzano et al. 2011). However, the relative importance of SIAs and routine immunization likely depends on the health

system, and what populations are reached by each method of administering a second dose of measles containing vaccine (WHO 2013).

In this paper, we consider the impact of different combinations of vaccine strategies on the maintenance of elimination. Specifically, we consider the population immunity maintained by four combinations of vaccine strategies; one routine dose, one routine dose and SIAs, two routine doses, and two routine doses and SIAs. To estimate the resulting population immunity, we conduct a steady state analysis of a dynamical model for immunity within a disease-free population. We conduct this analysis for a range of coverages and correlations between doses, here for specific age targets, maternal immunity and age structure. This allows us to ask three critical questions: 1) What coverage does a second dose require, relative to SIAs and first dose coverage, to outperform SIAs with respect to population immunity maintained? 2) How does this threshold coverage change if the first dose and SIAs are not administered independently (as expected)? 3) In what situations should a routine second dose be added in place of SIAs to maintain population immunity?

**Methods**

For each of the four combinations of vaccine strategies we model the proportion immune. We first divide the proportion into vaccine classes, then divide each vaccine class into age-specific immunity classes, then sum them to find the total proportion and age distribution of immunity. To divide the population into vaccine classes, we first find the proportion of the population that receives the first and second doses (Eqn. 1 a-b), and the proportion that receives the first dose and SIAs (Eqn. 2 a-b).We divide the population into eight vaccine classes; i) individuals who receive all three doses (Eqn. 3), ii) individuals who receive only the first and second routine doses (Eqn. 4), iii) individuals who receive only the first dose and SIAs (Eqn. 5), iv) individuals

who receive only the second dose and SIAs (Eqn. 6 a-d, for each of the four combinations of ways first dose coverage can overlap with second dose coverage and SIA coverage), v) individuals who receive only the first dose (Eqn. 7), vi) individuals who receive only the second dose (Eqn. 8), vii) individuals who receive only SIAs (Eqn. 9), and viii) individuals who miss all doses (Eqn. 10).

The proportion of the population that receives the first and second doses depends on the coverage of each dose. If first dose coverage exceeds or equals second dose coverage, the proportion that receives both doses is:

$$if\,(v_1 \geq v_2)\colon p(1st, 2nd) = \; v_1\left(v_2(1 - corr_2) + corr_2\frac{v_2}{v_1}\right) \qquad (1a)$$

When the correlation between the two doses ($corr_2$) is 0, this is simply the product of the coverages of the first and second dose, as we would expect if the doses are administered independently. When the correlation is 1, this is simply the coverage of the second dose; the second dose is administered only to individuals who received the first dose.

If first dose coverage is less than second dose coverage, the proportion that receives both doses is:

$$if\,(v_1 < v_2)\colon p(1st, 2nd) = v_2\left(v_1(1 - corr_2) + corr_2\frac{v_1}{v_2}\right) \qquad (1b)$$

When the correlation between the two doses ($corr_2$) is 0, this the product of the coverages of the first and second dose. When the correlation is 1, this is simply the coverage of the first dose; the second dose is administered first to all individuals who received the first dose, and then the remaining doses are administered to other individuals. These equations (1 a-b) are the same equations we used to find the proportion of the population immunized with both doses in Chapter 4.

The proportion of the population that gets the first dose and SIAs also depends on the coverage of each dose. If first dose coverage exceeds or equals SIA coverage, this proportion is:

$$if(v_1 \geq v_{SIA}): p(1st, SIA) = v_1 \left(v_{SIA}(1 - corr_{SIA}) + corr_{SIA} \frac{v_{SIA}}{v_1}\right) \quad (2a)$$

If the correlation between the first dose and SIAs ($corr_{SIA}$) is 0, this is simply the product of first dose coverage and SIA coverage, as we would expect if the two are independent. If the correlation is 1, this is simply SIA coverage, as in this situation, SIAs would be administered only to children who already had the first dose.

If first dose coverage is less than SIA coverage, the proportion of the population that receives the first dose and SIAs is:

$$if(v_1 < v_{SIA}): p(1st, SIA) = v_{SIA} \left(v_1(1 - corr_{SIA}) + corr_{SIA} \frac{v_1}{v_{SIA}}\right) \quad (2b)$$

When the correlation between the first dose and SIAs is 0, this is again the product of the first dose coverage and SIA coverage. When the correlation is 1, this is first dose coverage, as every individual who receives the first dose will eventually receive an SIA, but SIAs are administered to some children who never received the first dose.

These proportions ($p(1st, SIA)$, $p(2nd, SIA)$), each include the proportion of the population that receives all three doses. We assume the second dose is administered independently of SIAs, so that the proportion of the population that receives all three doses is:

$$p(1st, 2nd, SIA) = \left(\frac{p(1st,2nd)}{v_1}\right)\left(\frac{p(1st,SIA)}{v_1}\right) v_1 \quad (3)$$

The proportion of the population that receives the first and second dose that also receives an SIA is simply the proportion of the population that receives the first dose that receives an SIA.

Therefore, the proportion of the population that receives the first and second dose but not an SIA is simply:

$$p(1st, 2nd, \neg SIA) = p(1st, 2nd) - p(1st, 2nd, SIA) \quad (4)$$

Here, $\neg$ means "not", so that "$p(1st, 2nd, \neg SIA)$" is the proportion that get the 1st and 2nd doses, but not SIAs. Similarly, the proportion of the population that receives the first dose and an SIA, but not the second dose is:

$$p(1st, \neg 2nd, SIA) = p(1st, SIA) - p(1st, 2nd, SIA) \quad (5)$$

The proportion of the population that receives the second dose and SIAs but not the first dose depends on coverage of all three doses. If first dose coverage exceeds or equals second dose coverage and SIA coverage, this proportion is simply:

$$if\,(v_1 \geq v_2 \,\&\, v_1 \geq v_{SIA}): p(\neg 1st, 2nd, SIA) = \big(v_2(1 - corr_2)\big)\big(v_{SIA}(1 - corr_{SIA})\big)(1 - v_1) \quad (6a)$$

This is because the second dose and SIAs have low enough coverage that they are not administered to individuals who did not receive the first dose if the doses are administered dependently.

If first dose coverage exceeds or equals second dose coverage but is less than SIA coverage, the proportion of the population that receives the second dose and SIAs but not the first dose is:

$$if\,(v_1 \geq v_2 \& v_1 < v_{SIA}): p(\neg 1st, 2nd, SIA) = \big(v_2(1 - corr_2)\big)\big(v_{SIA}(1 - corr_{SIA})\big)(1 - v_1) + \big(v_2(1 - corr_2)\big)(v_{SIA} - v_1)corr_{SIA} \quad (6b)$$

Even when SIAs are administered dependently to individuals who had the first dose, some individuals (a proportion $v_{SIA} - v_1$ of the population) who did not receive the first dose are caught by SIAs, as SIAs have larger coverage.

If first dose coverage is less than second dose coverage, but exceeds or equals SIA coverage, the proportion of the population that receives the second dose and SIAs but not the first dose is:

$$if(v_1 < v_2 \& v_1 \geq v_{SIA}): p(\neg 1st, 2nd, SIA) = \big(v_2(1 - corr_2)\big)\big(v_{SIA}(1 - corr_{SIA})\big)(1 - v_1) + (v_2 - v_1)corr_2\big(v_{SIA}(1 - corr_{SIA})\big) \quad (6c)$$

If SIAs are administered dependently to individuals who had the first dose, no one who missed the first dose gets an SIA since first dose coverage exceeds SIA coverage, however, if the second dose is administered dependently to individuals who had the first dose, a proportion of the population $(v_2 - v_1)$ who missed the first dose eventually gets the second dose.

Finally, if both second dose coverage and SIA coverage exceed first dose coverage, the proportion of the population that gets the second dose and SIAs, but not the first dose, equals:

$$if(v_1 < v_2 \& v_1 < v_{SIA}): p(\neg 1st, 2nd, SIA) = \big(v_2(1 - corr_2)\big)\big(v_{SIA}(1 - corr_{SIA})\big)(1 - v_1) + (v_2 - v_1)corr_2\big(v_{SIA}(1 - corr_{SIA})\big) + \big(v_2(1 - corr_2)\big)(v_{SIA} - v_{1st})corr_{SIA} + (v_2 - v_1)corr_2(v_{SIA} - v_1)corr_{SIA} \quad (6d)$$

Even when administered dependently to individuals who had the first dose, both the second dose and SIAs reach some people who did not have the first dose due to their relative coverage. They otherwise overlap independently.

The proportion of the population that receives the first dose, but not the second or SIAs, is simply the proportion who receive the first dose (that is, first dose coverage), without the proportion that receive the first and second, but not SIAs, the proportion that receive the first and SIAs, but not the second, and the proportion that receive all three.

$$p(1st, \neg 2nd, \neg SIA) = v_1 - p(1st, 2nd, \neg SIA) - p(1st, \neg 2nd, \neg SIA) - p(1st, 2nd, SIA) \quad (7)$$

The proportion of the population who receives the second dose, but not the second or SIAs, is the proportion who receive the second dose (second dose coverage), without the proportion that receive the first and second, but not SIAs, the proportion that receives the second and SIAs, but not the first, and the proportion that receive all three.

$$p(\neg 1st, 2nd, \neg SIA) = v_2 - p(1st, 2nd, \neg SIA) - p(\neg 1st, 2nd, SIA) - p(1st, 2nd, SIA) \quad (8)$$

The proportion of the population who receives SIAs, but not the first or second doses, is the proportion who receive SIAs (SIA coverage), without the proportion that receive the first and SIAs, but not the second, the proportion that receive the second and SIAs, but not the first, and the proportion that receive all three. Notably, there may be overlap in SIAs, where some individuals receive multiple SIAs, but the later SIA campaign is administered dependently to individuals who received the first SIA.

$$p(\neg 1st, \neg 2nd, SIA) = v_{SIA} - p(1st, \neg 2nd, SIA) - p(\neg 1st, 2nd, SIA) - p(1st, 2nd, SIA) \quad (9)$$

The proportion of the population that is unvaccinated, is simply the proportion of the population that does not receive any combination of three doses.

$$p(\neg 1st, \neg 2nd, \neg SIA) = 1 - p(1st, 2nd, SIA) - p(1st, 2nd, \neg SIA) - p(1st, \neg 2nd, SIA) - p(\neg 1st, 2nd, SIA) - p(1st, \neg 2nd, \neg SIA) - p(\neg 1st, 2nd, \neg SIA) - p(\neg 1st, \neg 2nd, SIA) \quad (10)$$

Here, $v_1$ is first dose coverage, $v_2$ is second dose coverage, $v_{SIA}$ is SIA coverage, $corr_2$ is the correlation between populations receiving the first and second doses, and $corr_{SIA}$ is the

correlation between populations receiving the first dose and SIAs. We assume that SIAs are administered independently of the second routine dose.

Once individuals have been divided into vaccine classes, we sort each vaccine class into age classes. We use 77 age classes in our model; monthly up to age 5, then yearly up to age 20, then 20-50 and 50+. We assume a stable age structure, where 10% of children are under 5 (this is the "developed" age structure we consider in Chapter 5). We then divide each age-specified vaccine class into one of three immune classes; maternally immune, susceptible, and successfully immunized. We assume that maternal immunity wanes exponentially, with 10% of the population retaining maternal immunity at 9 months (this is the same function we used for the waning of maternal immunity in Chapter 5). For simplicity, we assume that the proportion of infants born with maternal immunity is simply the proportion of the population who will eventually receive at least one dose $\left(1 - p(\neg 1st, \neg 2nd, \neg 3rd)\right)$, not the proportion of the population who will eventually receive at least one effective dose. That is, we ignore the rate of primary vaccine failure when determining the proportion of children born with maternal immunity, unlike the models in Chapters 2-5. We do this for simplicity and tractability, as three potential sources of vaccine-derived immunity mean that the proportion of children born with maternal immunity would be the solution to a cubic equation.

At specified age targets, a proportion of all non-maternally immune individuals in that age-specific vaccine class are immunized. Since age classes are divided by vaccine class, that proportion is simply the complement of some failure rate; here, we assume a constant 5% failure rate of the vaccine (Moss and Griffin 2006), to account for all methods of vaccine failure unrelated to maternal immunity. We then find the true proportion of that age-specific vaccine class immunized (out of all individuals, not just out of all susceptible individuals), and subtract

that proportion from the susceptible proportion of all subsequent age classes in that vaccine class. For example, we assume that the first dose is administered at 9 months with 80% coverage. This means that 80% of the susceptible individuals in the 9 month age class of 4 vaccine classes are vaccinated; the populations receiving all three doses, first and second routine doses only, first dose and SIAs only, and first dose only. Since only 90% of those classes are susceptible due to maternal immunity, and we assume a 5% failure rate of the vaccine, this means that only 68% of those age-specific vaccine classes are immunized. Since older individuals in those vaccine classes will have received the first dose at 9 months, we assume 68% of all subsequent age-specific vaccine classes are also immunized.

Since SIAs happen periodically, an individual could receive an SIA at a number of different specific ages, depending on the timing of SIAs relative to when they are born; individuals may receive their first SIA the month they are born, or when they are 1 month old, or when they are 2 months old, etc, up to the month before the next SIA is administered (in this analysis, their $47^{th}$ month). In order to account for all possible combinations of SIA timings, we repeat our analysis for each possible timing relative to birth (this is done a number of times equal to the SIA frequency in months; here, 4x12=48 times), with the age target at which SIAs are administered increasing each time, so that all possible timings of SIAs with respect to a specific birth cohort are captured; we then average across the results. This thus approximates an inherently dynamical process. As the time since the last SIA increases, the age of the youngest individual that was eligible for the last SIA also increases. Here, each of our analyses represents a possible time since the last SIA (in months), and we then find the average age distribution of susceptibility by taking the average over all possible times since the last SIA. SIAs may be administered multiple times to the same individual if SIAs occur twice during the time a child is

under the maximum SIA age (e.g. in our work, a child who receives her first SIA at 3 months old, will receive a second at 51 months old). In this work, we focused on SIAs administered every four years in children under five years of age, as these were the campaigns recommended in the Americas preceding widespread elimination (de Quadros et al. 1998). Our model could straightforwardly be extended to consider a wider range of SIA frequencies and age ranges; we have uploaded a version of our model where SIA coverage, timing and age range can also be manipulated at http://54.173.213.31:3838/firstSecondSIAShiny/.

Finally, we sum the susceptible proportion by age class for all vaccine classes, to find the age distribution of susceptibility. From that age distribution of susceptibility, we find the total proportion of the population that is immune for a specific combination of age targets, coverages, and correlations. We can find this both for all possible SIA age targets, and the average across all possible SIA age targets.

**Results**

When the second dose is administered dependently and SIAs are administered independently, SIAs outperform a routine second dose, even at identical coverage (Fig. 6.1). This is because the second dose is administered only to individuals who had the first dose, while SIAs are administered to individuals regardless of whether they have had the first dose, in concordance with our results from Chapter 4. As a result, SIAs immunize a relatively large proportion of the population that was missed by the first dose. In this situation, transitioning away from SIAs may come at a relatively large cost to population immunity.

However, a routine second dose can outperform SIAs in some situations (Figs. 6.2-6.4). When coverage of the second routine dose is especially high relative to the coverage of SIAs, the second dose achieves a much higher level of population immunity than SIAs (Figs. 6.2, 6.3).

When correlation is changed, either correlation between the populations receiving the first and second dose, or correlation between populations receiving the first dose and SIAs (Fig. 6.4), the level of coverage required for the second dose to outperform SIAs is dramatically decreased.

SIAs result in some variance in population immunity (Fig. 6.1). When SIAs are administered every 4 years, some children have to wait until they are four years old before receiving a second dose, whereas others are vaccinated by SIAs immediately after they receive their first routine dose. While the average immunity maintained is fairly high, the variation could provide opportunities for the disease to re-emerge unexpectedly. This variation is present whether SIAs are administered in conjunction with the second dose or not.

When SIAs are administered independently of whether an individual had the first dose and the second routine dose is administered dependently, the second routine dose needs to have very high coverage in order to outperform SIAs (Fig. 6.2). For the specific first dose and SIA coverage used in Figure 6.2, the second routine dose needs to have 17% higher coverage than SIAs in order to match them in performance. Furthermore, it needs to have 12% higher coverage than the routine first dose, which is rarely achieved in practice (WHO 2016 b-c). In this situation, transitioning away from SIAs will come at a relatively large cost to population immunity unless coverage of all doses is very close to 100%. When coverage of all doses is 100%, then correlation is irrelevant, as all individuals eventually receive all doses. However, as that is likely impossible to achieve in practice, the correlation between populations receiving doses of measles containing vaccine is especially important.

An inflection point occurs when second dose coverage matches first dose coverage (Fig. 6.2). Since the two routine doses are administered independently, when the second dose has lower coverage than the first dose, the second dose is administered only to people who already had the

first dose, so the improvement in population immunity is relatively small. However, when second dose coverage outpaces first dose coverage, then the second dose is administered to people who have not had any dose, and the improvement in population immunity is much more rapid. This is a theoretical result that illustrates the mechanics of the system; in reality, second dose coverage rarely outpaces first dose coverage (WHO 2016 b-c). This inflection point occurs whether or not the second routine dose is administered in conjunction with SIAs. This is akin to the inflection point that occurs when crossing the 1:1 line while increasing second dose coverage in Fig. 4.2 of Chapter 4.

The level of coverage required for the second dose to achieve levels of population immunity greater than the average achieved by SIAs is always greater than or equal to SIA coverage, and only equal when the coverage of both is 100% (Fig. 6.3). As SIA coverage increases, the coverage required for the routine second dose to outperform SIAs also increases. As coverage of the first dose increases, the required coverage of the second dose initially also decreases. This is because the second dose is administered to people who have already had the first dose, while SIAs are administered both to people who have had the first dose and people who have not. If most individuals are immunized by the first dose, the second dose is largely redundant compared to SIAs. However, once first dose coverage sufficiently exceeds SIA coverage, the coverage required for a routine second dose to outperform SIAs dramatically decreases. This is because the population who failed to seroconvert after vaccination by the first dose begins to exceed the population for whom an SIA would be the first dose. An inflection point occurs in the contour lines at that threshold value, with the level of SIA coverage at which the inflection point occurs increasing nonlinearly with the level first dose coverage.

The level of coverage required for the second dose to outperform SIAs is dependent on correlation, both the correlation between the second dose and the first dose and the correlation between SIAs and the first dose (Fig. 6.4). When SIAs are administered independently of whether the recipient has had the first dose, the correlation between the first and second dose must also be zero in order for the second dose to outperform SIAs without having higher coverage than SIAs. However, as the correlation between the populations receiving the first dose and SIAs increases, the threshold level of correlation between the populations receiving the first and second dose below which the second dose to outperform SIAs without having higher coverage increases correspondingly.

Population immunity is highly variable at a given coverage based on the correlation between the first dose and each method of administering a second dose (routine or SIA) (Fig. 6.5). When a routine second dose is administered in conjunction with the first dose, but not SIAs, then correlation between the two can change population immunity by 5-10% (Fig. 6.5a). When SIAs are administered in conjunction with the first dose, but not the second, then correlation between the two can also change population immunity by 5-10% (Fig. 6.5b). However, when both routine doses are administered in conjunction with SIAs, correlation, both between the two routine doses and between the first dose and SIAs, can change population immunity by more than 15% (Fig. 6.5c). If either SIAs or the second dose are administered dependently, the correlation between the other and the first dose can change population immunity by 10-15% (Fig. 6.5c). However, population immunity is on average higher when all three strategies are implemented, especially when either correlation is low.

## Discussion

As countries transition to a routine second dose of measles containing vaccine in place of supplemental immunization activites (SIAs), they should take into account not just the coverage of the first dose, second dose and SIAs, but the correlations between the populations receiving these doses. The second dose strategy outperforms SIAs in many situations, especially when the correlation between populations receiving the first dose and populations receiving SIAs is high. SIAs are typically thought to outperform routine immunization in places where healthcare access is poor as they can reach typically underserved populations (WHO 2013). In determining whether this is true, it is important to discover the true correlation between populations vaccinated with the first dose and populations vaccinated during SIAs. This correlation could likely be determined by using a combination of health surveys and administrative data in addition to current SIA evaluation methods (WHO Regional Office for Africa 2006), in a similar approach to that used to determine true vaccine coverage (Lessler et al. 2011).

Supplemental immunization activities are a crucial strategy for achieving and maintaining elimination (WHO 2012, WHO 2013). Reported coverage of these campaigns is typically quite high (WHO 2015), although the true coverage may be lower than expected (Lessler et al. 2011). However, the impact of SIAs does not just depend on coverage, but also on the correlation between the populations vaccinated by the first routine dose and during an SIA. If SIAs truly reach people who are not reached by the routine health system (Vijayaraghavan 2002), this correlation may be very low. However, it is likely true that individuals with good healthcare access are also highly accessible during SIAs (Metcalf et al. 2015), meaning that SIAs may only reach people underserved by the routine health system when coverage exceeds routine

immunization coverage. If this is the case, the correlation between SIAs and the first routine dose is likely high.

Routine immunizations are another common strategy for maintaining measles elimination. Together, two routine doses can maintain high levels of immunity in a population where disease is absent (Chapter 3). The level of immunity they maintain depends on the correlation between the two doses (Chapter 4). We may expect this correlation to be high when coverage is high, as the only people left unvaccinated are individuals who cannot or will not vaccinate. However, we might also expect this correlation to be high when coverage is low, as access to the health system may be similarly low, so the only people who vaccinate are the people who have good healthcare access. Regardless, this correlation likely varies place to place, and we reiterate that it is important to understand the true level of correlation. It can likely be measured as described above, and, if measured, should be reported to better inform measles management. Regardless of the method used to administer the second dose (routine immunization or SIAs), population immunity can be improved by deliberately targeting the second dose to people who missed the first dose to decrease correlation (as in Chapter 4) (Minetti et al. 2013).

As countries transition from endemic measles to elimination, they will likely use combinations of all three vaccine strategies (WHO 2012, WHO 2013). Our model illustrates that, in order for the second routine dose to outperform supplemental immunization activities, it requires coverage of the second routine dose to exceed SIA coverage, unless correlation between the populations receiving the first and second dose is lower than correlation between the populations receiving the first dose and SIAs. In many countries, routine second dose coverage is much lower than first dose coverage, and lower than reported SIA coverage (WHO 2016b-c, WHO 2015). In these countries, the routine health system needs to be strengthened dramatically before SIAs can

be phased out in favor of the routine second dose, which is consistent with current recommendations (WHO 2013). In the interim, more vaccination is always better, so, while it may be expensive, adding a routine second dose in addition to a routine first dose and SIAs is always beneficial, even if first dose coverage and SIA coverage are unchanged. However, just how beneficial adding an additional dose is depends on correlation; not knowing correlation makes the effectiveness of a specific combination of vaccine strategies uncertain (Fig. 6.5, Chapter 4).

Even in cases where routine immunization outperforms SIAs, it may be beneficial to conduct the occasional SIA. In places where measles has re-emerged, such as Brazil and Malawi, the age distribution of the resulting outbreak has been indicative of a slow accumulation of older susceptibles, as individuals make it to adolescence and even adulthood without being exposed to an effective dose of measles containing vaccine. An SIA targeting older individuals can reduce this susceptible population before it is large enough to sustain endemic transmission. Additionally, outbreak response SIAs can be conducted when a case is observed to deplete the susceptible population and prevent an outbreak from being too large or lasting too long.

In this work, we omit explicit consideration of vaccine schedules, other than the presence or absence of a routine second dose. As the age distribution of susceptibles is important for transmission, so are age targets for immunization (Chapter 3) and age structure (McKee et al. 2015, Chapter 3). For example, if the first dose has low coverage, the optimal age target for the second dose is earlier in life, so that it can catch children who missed the first dose and reduce the susceptible population between doses (Chapter 3). In this situation, the routine second dose may have an advantage over SIAs. If SIAs are administered instead of a routine second dose, some children would not get a second dose through an SIA until relatively late in life, depending

on SIA frequency. Adjusting the age targets and frequency of SIAs would also certainly change the relative benefit of performing one over the other. We have uploaded a version of our model where age targets and frequency are also manipulable at http://54.173.213.31:3838/firstSecondSIAShiny/. In considering whether to transition from SIAs to a routine second dose for specific contexts, a simple change in SIA frequency or age target should also be considered.

In this work, we only consider the population immunity maintained by a specified combination of vaccine strategies in a disease-free state. When the disease is present, the age distribution of susceptibles in the population is especially important, as the bulk of transmission happens in very young children (Ferrari 2010), who are most likely to die due to infection (Wolfson 2009). Furthermore, even if the average level of population immunity maintained by SIAs in addition to the first dose is equal to, or greater than, the level of population immunity maintained by two routine doses, the fluctuations in population immunity arising from SIA schedules may create opportunities for the disease to reinvade. Certainly, countries contemplating phasing out SIAs and transitioning to a routine second dose only should consider disease dynamics and the potential for re-invasion, as well as coverage and correlation.

**Acknowledgements**

We acknowledge funding from the National Institutes of Health and National Science Foundation (EEID award 1 R01 GM105247-01 and NSF Ebola RAPID DMS-1514704).

**References**

1. Andrews JM, Langmuir AD. The philosophy of disease eradication. Am J Public Health 1963; 53: 1–6.

2. Castillo-Solorzano C C, Matus CR, Flannery B, Marsigli C, Tambini G, Andrus JK. The Americas: paving the road toward global measles eradication. J Infect Dis 2011; 204 Suppl : S270–8.
3. Christie AS, Gay A. The Measles Initiative: moving toward measles eradication. J Infect Dis 2011; 204: S14–7.
4. de Quadros CA, Hersh BS, Nogueira AC, Carrasco PA, da Silveira CM. Measles eradication: experience in the Americas. Bull World Health Organ 1998; 76 Suppl 2: 47–52.
5. Favin M, Steinglass R, Fields R, Banerjee K, Sawhney M. Why children are not vaccinated: A review of the grey literature. Int Health 2012; 4: 229–38.
6. Ferrari MJ, Djibo a, Grais RF, Grenfell BT, Bjørnstad ON. Episodic outbreaks bias estimates of age-specific force of infection: a corrected method using measles as an example. Epidemiol Infect 2010; 138: 108–16.
7. Gandhi G, Lydon P. Updating the evidence base on the operational costs of supplementary immunization activities for current and future accelerated disease control, elimination and eradication efforts. BMC Public Health 2014; 14: 67.
8. Hall R, Jolley D. International measles incidence and immunization coverage. J Infect Dis 2011; 204 Suppl: S158–63.
9. Henao-Restrepo A-M, Strebel P, Hoekstra EJ, Birmingham M, Bilous J. Experience in Global Measles Control,1990 – 2001. J Infect Dis 2005; 187: S15–21.
10. Hoekstra EJ, Van Den Ent MMVX, Dao H, Khalaf H, Salovaara A. Measles supplementary immunization activities and GAVI funds as catalysts for improving injection safety in Africa. J Infect Dis 2011; 204. DOI:10.1093/infdis/jir073.

11. Lessler J, Metcalf CJE, Grais RF, Luquero FJ, Cummings DAT, Grenfell BT. Measuring the performance of vaccination programs using cross-sectional surveys: a likelihood framework and retrospective analysis. PLoS Med 2011; 8: e1001110.
12. McKee A, Ferrari MJ and Shea K. Chapter 4. Correlation between measles vaccine doses: Implications for the maintenance of elimination.
13. McKee A, Ferrari MJ and Shea K. Chapter 3. Optimal vaccine schedules to maintain measles elimination with a two-dose routine policy.
14. McKee A, Shea K and Ferrari MJ. Chapter 5. Objectives matter: Optimal age targets to minimize incidence of a measles reintroduction outbreak are not the same as those to minimize mortality.
15. Médicins Sans Frontières. 65,000 children vaccinated against measles in DRC's South Kivu. 2013; http://www.msfaccess.org/content/65000-children-vaccinated-against-measles-drcs-south-kivu
16. Metcalf CJE, Klepac P, Ferrari M, Grais RF, Djibo A, Grenfell BT. Modelling the first dose of measles vaccination: the role of maternal immunity, demographic factors, and delivery systems. Epidemiol Infect 2011; 139: 265–74.
17. Metcalf CJE, Tatem A, Bjornstad ON, et al. Transport networks and inequities in vaccination: remoteness shapes measles vaccine coverage and prospects for elimination across Africa. Epidemiol Infect 2015; 143: 1457–66.
18. Minetti A, Hurtado N, Grais RF, Ferrari M. Reaching hard-to-reach individuals: Nonselective versus targeted outbreak response vaccination for measles. Am J Epidemiol 2014; 179: 245–51.
19. Moss WJ, Griffin DE. Global measles elimination. Nat Rev Microbiol 2006; 4: 900–8.

20. Moss WJ, Strebel P. Biological Feasibility of Measles Eradication. J Infect Dis 2011; 204: S47–53.
21. Orenstein WA, Strebel PM, Papania M, Sutter RW, Bellini WJ, Cochi SL. Measles eradication: Is it in our future? Am J Public Health 2000; 90: 1521–5.
22. Simons E, Ferrari M, Fricks J, et al. Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. Lancet 2012; 379: 2173–8.
23. Vijayaraghavan M, Martin RM, Sangrujee N, et al. Measles supplemental immunization activities improve measles vaccine coverage and equity: Evidence from Kenya, 2002. Health Policy (New York) 2007; 83: 27–36.
24. Wagner AL, Zhang Y, Mukherjee B, Ding Y, Wells E V., Boulton ML. The impact of supplementary immunization activities on the epidemiology of measles in Tianjin, China. Int J Infect Dis 2016; 45: 103–8.
25. WHO. WHO vaccine-preventable diseases: monitoring system. 2016 global summary. 2016; http://apps.who.int/immunization_monitoring/globalsummary/schedules
26. WHO. WHO-UNICEF estimates of MCV1 coverage. 2016; http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragemcv1.html
27. WHO. WHO-UNICEF estimates of MCV2 coverage. 2016; http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragemcv2.html
28. WHO. A guide to introducing a second dose of measles vaccine into routine immunization schedules. 2013.

29. WHO. Retrospective measles data on supplementary immunization activities 2000-2016. 2015; http://www.who.int/immunization/monitoring_surveillance/data/en/
30. WHO. GLOBAL MEASLES AND RUBELLA: Strategic plan 2012-2020. 2012.
31. WHO Regional Office for Africa. Evaluation guidelines for measles supplemental immunization activities. 2006.
32. Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. Int J Epidemiol 2009; 38: 192–205.
33. World Health Organization. Proceedings of the Global Technical Consultation to assess the feasibility of measles eradication, 28-30 July 2010. J Infect Dis 2011; 204: S4–13.

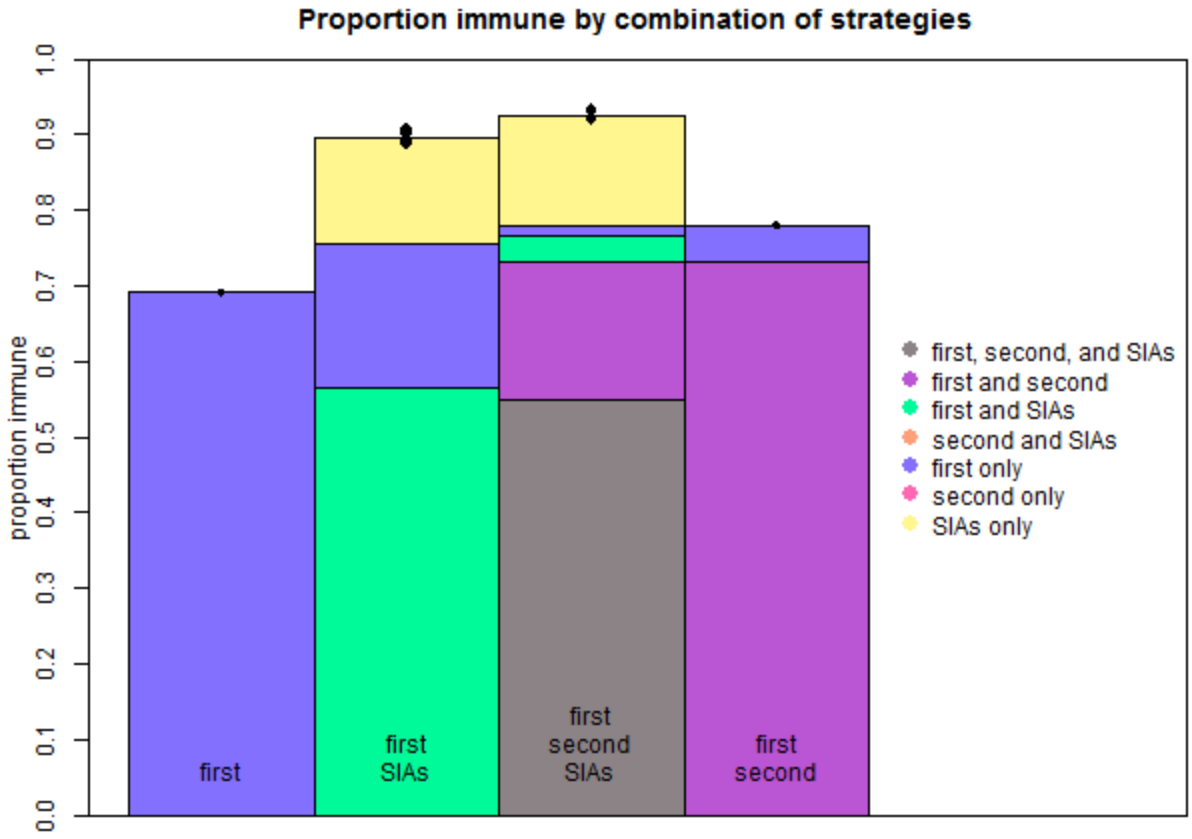



**Figure 6.1** The proportion of the population that is immune for four combinations of vaccine strategies; one routine dose ("first") only, one routine dose and SIAs ("first SIAs"), two routine doses and SIAs ("first second SIAs"), and two routine doses ("first second"). Here, we assume that the first dose is administered at 9 months with 80% coverage, the second dose is administered at 18 months with 75% coverage, and SIAs are conducted every four years for children up to 5 with 75% coverage. We here assume that SIAs are administered independently of whether an individual had the first dose, while the second dose is administered only to children who had the first dose. The total height of the bar represents the average population immunity, with the colored blocks representing the vaccine classes that contribute to population immunity. Not all vaccine classes are visible here, as only those that make a contribution to

population immunity for these specific combinations of coverage and correlations are shown. The upper line of each bar is the average population immunity maintained by that combination of strategies, while the dots represent specific levels of population immunity arising from when a specific birth cohort falls relative to the timing of SIAs.

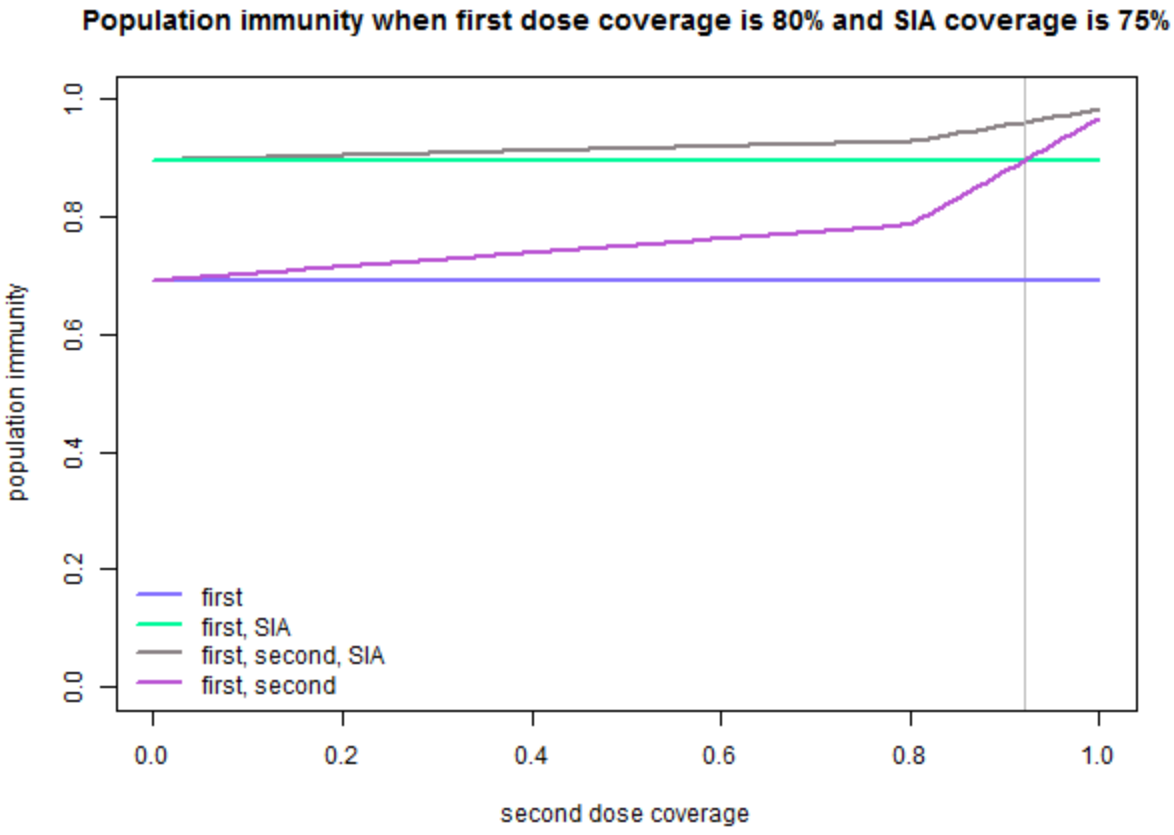



**Figure 6.2** The population immunity achieved by four combinations of strategies (single dose, two routine doses, one routine dose and SIAs, and two routine doses and SIAs), for a range of second dose coverages. The level of second dose coverage where a second routine dose surpasses SIAs in population immunity achieved is emphasized with a vertical grey line. We assume here that the first dose is administered at 9 months with 80% coverage, the second dose is administered at 18 months, and SIAs are administered every four years to children under 5 with 75% coverage. The second dose is administered only to children who had the first dose, except when second dose coverage exceeds first dose coverage, in which case the first dose is administered only to children who will eventually get the second dose. SIAs are administered independently of whether an individual had the first dose.

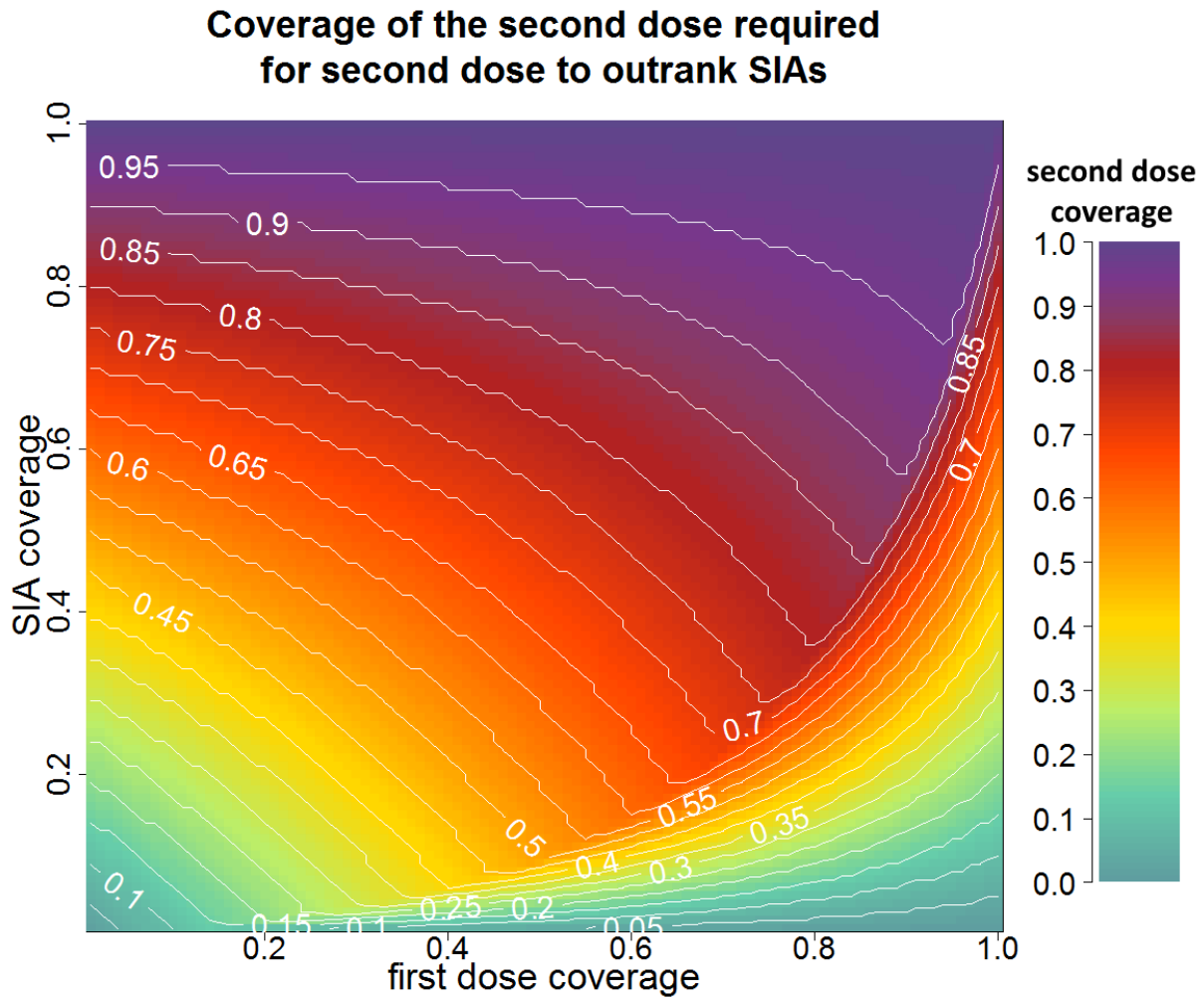



**Figure 6.3** The level of second dose coverage required for a second routine dose to outperform SIAs with respect to population immunity. We here assume that the first dose is administered at 9 months, the second dose at 18 months, and SIAs every 4 years in children under 5. We also assume that the routine second dose is administered dependently to children who received the first dose, while supplemental immunization activities are conducted independently of whether an individual has received a first dose. The inflection points in the contours occur where the population that was vaccinated by the first dose but did not seroconvert exceeds the population that would be vaccinated for the first time by an SIA; that is, the threshold where immunizing the

population who did not seroconvert due to the first dose outweighs the importance of catching individuals who missed the first dose.

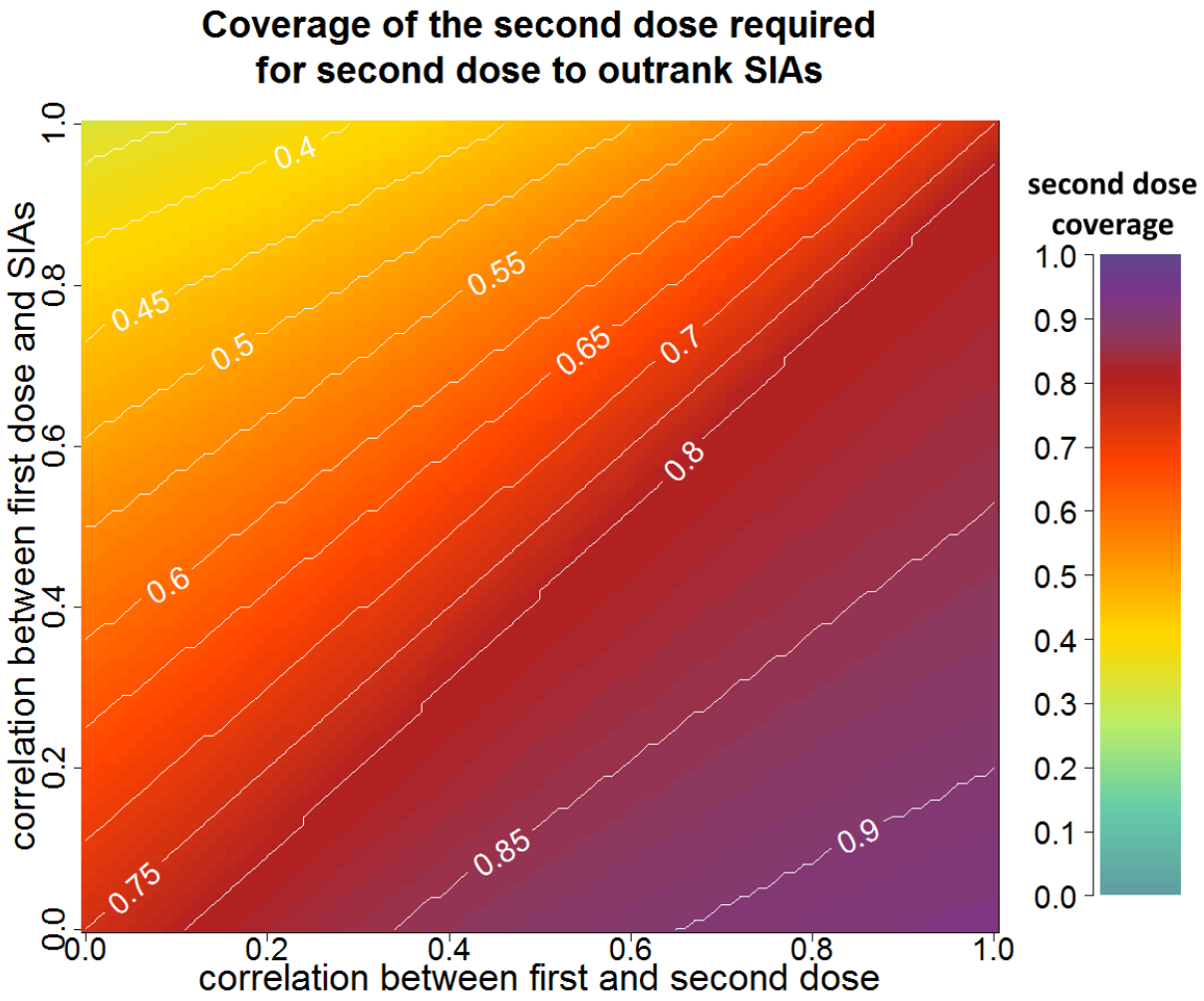



**Figure 6.4** The level of second dose coverage required for a second routine dose to outperform SIAs with respect to population immunity for a range of correlations between the first dose and either a second dose or SIAs. We assume that the first dose is administered at 9 months with 80% coverage, the second dose is administered at 18 months, and SIAs are administered in children up to 5 every 4 years with 75% coverage. The lower right corner of this picture is the point at (0.8, 0.75) in Fig. 3.

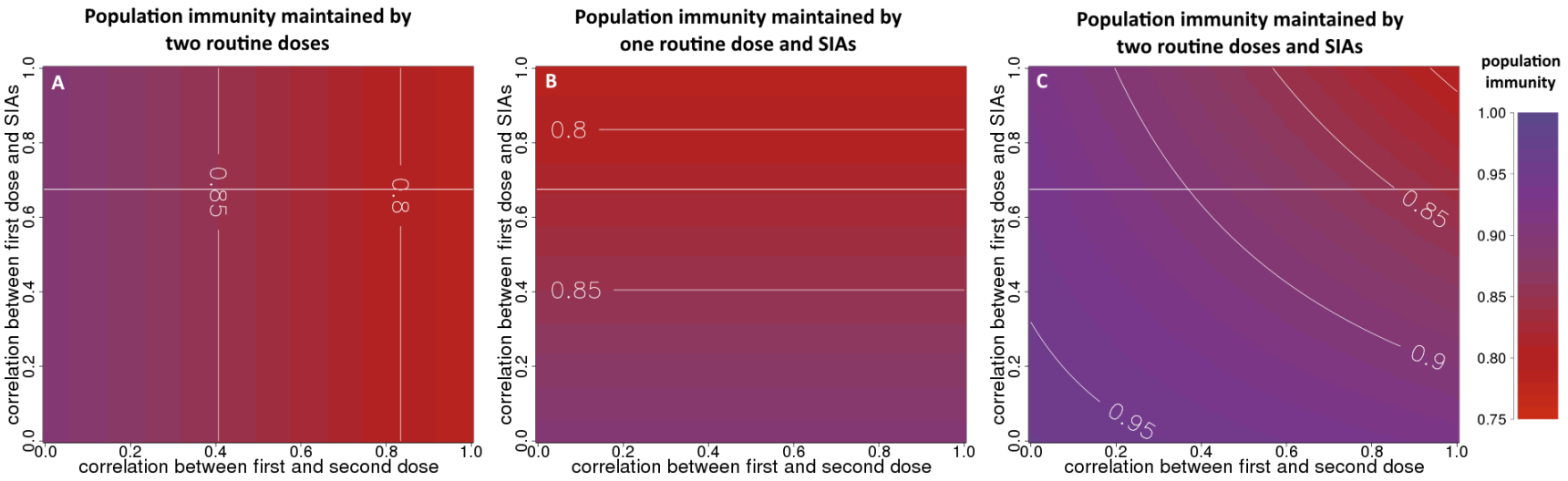



**Figure 6.5** Population immunity maintained by various combinations of vaccine strategies for a range of correlations. We assume here that the first dose target is 9 months, first dose coverage is 80%, the second dose target is 18 months, second dose coverage is 75%, and SIAs are conducted every four years in children up to five years of age with 75% coverage. **a)** The population immunity maintained by a two dose routine immunization strategy. As correlation between the first and second dose increases, the level of population immunity maintained decreases. As SIAs are not administered, the correlation between SIAs and the first routine dose does not affect population immunity. **b)** The population immunity maintained by a single routine dose and SIAs. As correlation between the routine dose and SIAs increases, population immunity decreases. As a second routine dose is not administered, the correlation between the first and second dose does not have an effect on population immunity. **c)** The population immunity maintained by two routine doses and SIAs. As correlation between either the second dose or SIAs increases, population immunity decreases. At

each combination of correlations, the average population immunity maintained is higher when two routine doses and SIAs are administered.

# Chapter 7

## Synthesis

Measles, an acute childhood infection caused by a morbillivirus (Katz 1995), is an important contributor to global childhood mortality (Simons et al. 2012). Intensive control efforts to reduce the burden of measles have spanned decades (Henao-Restrepo et al. 2005), ever since the development of a stable vaccine in the 1960s (Katz 2009). More recently, measles has been managed under the 4$^{th}$ UN Millennium Development Goal to reduce child mortality (WHO 2011). Not only is it important to control measles because of the direct contribution measles makes to global child mortality (Simons et al. 2012), but measles control has also been used as a general indicator of a health system's performance under this goal (WHO 2011).

When measles is endemic, it may demonstrate cyclic behavior in the population, where the number of cases at a given time depends on the phase of the infection process (Grenfell, Bjørnstad, and Kappey 2001). This cyclic behavior depends on seasonality within the population (Ferrari et al. 2008). For example, measles had very well described cycles in the pre-vaccine era in England and Wales (Finkenstadt and Grenfell 2000), as children had very low transmission during school holidays and then relatively high transmission at the start of the school term (Bolker and Grenfell 1993). When vaccination coverage is high and the disease is near elimination, these cycles fade to more stochastic or chaotic outbreaks, where the disease may be absent entirely for short periods, before a large outbreak is sparked by a reintroduction event (Earn et al. 2000). Post-elimination, the disease is almost entirely absent; reintroduction outbreaks may still occur, but typically are much shorter with much lower incidence (Gay 2004).

Specific measles case fatality rates vary country to country, and depend largely on individual-specific parameters, such as nutrition (Wolfson et al. 2009). It can be difficult to know true measles case fatality rates, as the definition of "case", and "measles-induced fatality" vary from place to place (Wolfson et al. 2009). Lab confirmation of measles infection is rarely done (Wolfson et al. 2009), and when it is assessed, it has a high false positive rate in places where measles is rare (Hersh et al. 2000, Hutchins et al. 2004). Measles is a severe immunosuppressive agent, so mortality following measles infection could also be the result of secondary infection by a different pathogen (Fugier-Vivier et al. 1997, Mina et al. 2015). However, regardless of the context and definitions under which measles case fatality ratios are examined, they are lowest in vaccinated children and highest in unvaccinated children under five years of age (Wolfson et al. 2009).

It is therefore important that we achieve and maintain high vaccination coverage in order to avert the bulk of measles cases and measles mortality (Hall and Jolley 2011). The measles vaccine produces acute immunity, but is ineffective if administered to an infant who still retains his/her maternal antibodies (Yeager et al. 1977), and redundant if administered to a child who has already been infected. There is therefore an optimal time to vaccinate children; after the age at which their maternal antibodies have sufficiently waned, and before they are particularly likely to be infected (Fig. 7.1) (McLean and Anderson 1988a). If vaccines are administered too early in life, most children will still have their maternal antibodies, and the vaccine will not be particularly effective. If the vaccine is administered too late in life, most children will have already been infected with measles. This optimal age of vaccination depends on the rate at which measles is circulating the population (McLean and Anderson 1988a). When measles is circulating at high levels within the population, most children are infected at very young ages,

and so, in order to be protective, vaccine must be administered at relatively young ages (Fig. 7.1). In comparison, when measles is circulating at low levels in the population, individuals live for a relatively long time on average before they become infected with measles, and the vaccine can be administered relatively late in life and still be protective (Fig. 7.1). Following local elimination of measles, natural infection ceases to be a source of immunity; however, vaccination is still necessary at this point, as the disease may be reintroduced (de Quadros et al. 1998), and therefore, the probability of infection with the disease is still non-zero. It can be tempting to consider vaccinating at a relatively old age at this point, as each individual is more likely to seroconvert if vaccinations are administered later in life (Gans et al. 2001), but children susceptible before the age of first vaccination will contribute to the susceptible population and therefore reduce population immunity (Chapter 2).Vaccination confers some indirect benefit to the population when a sufficient proportion has been vaccinated. That benefit, commonly referred to as herd immunity, prevents the disease from circulating endemically. A sufficient proportion of the population must be immune so that a single infectious person is unlikely to have disease-transmissible contact with a susceptible person before recovering from infection. This proportion, commonly referred to as the critical immunity threshold, is $1 - 1/R_0$ for a directly transmissible disease (McLean and Anderson 1988b). Measles is one of the most infectious diseases on the planet, with an $R_0$ between 14 and 18, so this proportion is between 90 and 95% in most populations (Anderson and May 1982), which is incredibly difficult to maintain using a single dose vaccine policy. Some work has been done on how using a target age window instead of a target age could increase coverage; expanding this window to younger children could provide additional protection to some of the most vulnerable individuals (Metcalf et al. 2011).

In my dissertation I contribute to measles vaccine policy research by explicitly considering vaccination policies in the context of disease elimination; that is, in the setting where natural infection does not contribute to population immunity and the primary objectives of a vaccination program are to provide individual protection and minimize the potential for infection to re-invade. All code used in this dissertation has been uploaded at Penn State's institutional repository, ScholarSphere: https://scholarsphere.psu.edu/collections/sn009x90d. The specific age target that maximizes population immunity (that is, the proportion of the population that is immune to measles), and thus minimizes the probability of measles re-invasion, in the absence of disease is still relatively early in life (13-19 months, depending on age structure), although it still falls after most children have lost their maternal immunity (Fig. 7.2, McKee et al. 2015). The upper bound is imposed by the age structure of the population; if too many children fall below the age at the first vaccination, a significant proportion of the population will be susceptible. This restriction is especially true when the population has a large proportion of children under five years of age. As the proportion of children under five goes up, the optimal age target to maximize population immunity goes down, as does the maximum level of population immunity maintainable (Fig. 7.2, Chapter 2). This tradeoff between age-specific vaccine efficacy and age structure can mean that population immunity is impossible to maintain above the critical immunity threshold for measles with a single dose vaccine policy. Where it is possible to maintain, vaccinations must be administered with very high coverage at an age target determined by the specific rate at which maternal immunity wanes in the population and the age structure (Chapter 2).

Because of the difficulty in maintaining high levels of population immunity with a single dose that is not 100% effective, the World Health Organization recommends a second dose of measles

containing vaccine be administered to children in all countries (WHO 2013). This second dose provides a second opportunity for children to become immune (Wolfson et al. 2005). In places where measles is endemic, this dose protects children who were not protected by the first dose, further decreasing incidence and mortality (Wolfson et al. 2005). In places where the disease is eliminated, the second dose bolsters population immunity by immunizing children who were not immunized by the first dose (Orenstein et al. 2000).

The second dose may be administered in one of two ways. It may be administered through routine immunization, where children visit a healthcare provider at a specified target age and receive a dose of measles containing vaccine (WHO 2013). Alternatively, it may be administered through supplemental immunization activities (SIAs), which are campaigns where all children within a specified target age range are vaccinated within a relatively short time (WHO 2013). Both strategies can provide a second dose to an individual, but the population level benefits vary.

Much work has been done on the benefits and timing of SIAs in the context of endemic disease (Bauch, Szusz and Garrison 2009, Bishai et al. 2011, Khetsuriani 2011). SIAs cause periodic fluctuations in population immunity that can provide windows of opportunity for outbreaks to occur. SIAs should be conducted frequently enough that these windows are not too wide, and that population immunity never falls so low that an especially large outbreak may occur. How frequently this is depends on the rate of accumulation of susceptible individuals within the population, which depends in turn on the birth rate and routine vaccination coverage in the population (Bauch, Szusz and Garrison 2009).

SIAs may also be conducted in response to outbreaks (Luquero et al. 2011). Outbreak response vaccination may deplete the susceptible population faster than infection alone, driving the

outbreak to extinction faster, and greatly reducing the number of cases (Goodson et al. 2011). Models support the use of these campaigns, especially if intervention occurs early enough in the outbreak (Grais et al. 2008). These campaigns have been used in the past, with varying levels of effectiveness (Cairns et al. 2011).

Guidelines set by the WHO suggest introducing a second routine dose when first dose coverage reaches 80%, which is well below levels sufficient to achieve the herd immunity threshold (Christie and Gay 2011, WHO 2013). These guidelines further recommend that the second dose be administered either at 16-18 months, as this coincides with other vaccines in the vaccine schedule, or at school entry, whichever local health officials feel would maximize coverage (WHO 2013). These guidelines, while very specific, do not mention any consideration of the effectiveness of these policies beyond high coverage. As some recent outbreaks have shown (Sugerman et al. 2008), high coverage is not necessarily sufficient to achieve or maintain elimination - population immunity must also be considered.

Population immunity depends on the proportion of the population receiving at least one dose as well as the efficacy of each dose. As multiple doses of measles containing vaccine are administered, this depends both on the coverage of each dose and on the overlap in populations receiving each dose. In settings where healthcare access is high, the only people who do not receive either dose may be people who cannot or will not vaccinate. In this case, the overlap in populations receiving each dose is likely high, as people who do not receive one dose will not receive the other dose – thus the likelihood of receiving the second dose is highly correlated with receiving the first. Increasing populatoin coverage in these cases may be especially difficult, as people are left unvaccinated for reasons other than vaccine availability. In settings where healthcare access is more sporadic, individuals may miss a dose by being unable to access

healthcare at the appropriate age. In this case, the populations receiving each dose may be independent, or uncorrelated, as individuals receive each dose if they can access it. In settings where healthcare access is especially heterogeneous, individuals who receive one dose may be the individuals with the best access to healthcare, in which case they will also be the individuals who receive a second dose, and the doses will also be highly correlated. As long as coverage is less than 100%, administering doses independently results in the largest proportion of individuals receiving at least one dose, and therefore the largest proportion of the population that is immune to measles.

When disease is not present, no one is infected. While this means that no one suffers severe consequences from infection, it also means that no one is immunized by infection. Maintaining high levels of population immunity in the absence of disease, while essential to maintain elimination, is especially challenging. Specifically, population immunity steadily declines following elimination, as individuals who were immune from natural infection begin to age out of the population, and no new individuals are infected to make up the different in population immunity. The period of high population immunity immediately following elimination has been described as the honeymoon period (McLean 1988b). This means that high vaccine coverage is especially important, as is carefully choosing vaccine policies and schedules to maximize the population immunity resulting from vaccination programs.

In places where a two dose routine immunization policy is used to maintain measles elimination, age targets should be chosen conditional on the coverage of each dose, as well as age structure, maternal immunity, and various programmatic and sociological constraints (Chapter 3). Current policy recommends the first dose be administered at 9 or 12 months, and the second dose sometime later in life, often before school entry. I find that population immunity can be

improved by administering both doses earlier in life – if coverage is high, even administering the first dose as early as six months. While this results in a lower vaccine efficacy, it improves the effectiveness of the program. The reduced efficacy of the first dose does not have a large impact on population immunity, as children are given a second chance to seroconvert. The maximum level of population immunity maintainable depends on the age structure of the population and maternal immunity, but the qualitative results do not change with maternal immunity – when coverage is low, the first and second dose should be administered relatively close together, and population immunity is almost always improved by administering the second dose to younger individuals.

Of course, changing age targets may have an effect on coverage, and potentially an effect on the correlation of vaccination opportunities. If the second dose was no longer administered right before school entry, or in conjunction with another routine doctor visit, more children may miss the second dose. If a child could not or would not vaccinate at a specific age, and both doses are administered around that age, that child would miss both doses, resulting in an increase in correlation. High correlation means that relatively fewer children receive at least one dose, so population immunity is relatively low (Chapter 4). While administering the second dose earlier would protect children earlier in life, it may not result in a higher population immunity if it comes at a significant tradeoff in coverage or correlation. The severity of the tradeoff between coverage and correlation that eliminates the benefit of changing age targets could be determined through careful population modelling.

In order to maintain elimination, it is especially important to minimize the chance that a prolonged reintroduction will occur. With this objective in mind, it is important to choose vaccine age targets to maximize population immunity. However, conditional on an outbreak

occurring, it is also important to minimize incidence and mortality. However, the policies that minimize incidence may not be the same as those that minimize mortality. Population modelling to determine vaccine policy should also take into account a carefully specified objective. When the disease is absent, both incidence and mortality are zero. However, the specific age distribution of a reintroduction outbreak is important. As children under five years of age are most likely to die due to infection (Wolfson et al. 2009), protecting children early in life may be especially important if the primary objective is to minimize mortality. This may hold as well if the bulk of transmission also happens in children under five, reinforcing the need to administer both doses earlier in life than current policy (Chapter 5). The exact level of transmission that happens in children under five depends on population-specific mixing patterns, which can be determined through careful study and modelling work. This further reinforces the need for precise population modelling in vaccine policy.

The correlation between doses does not just affect population immunity and the rate of primary vaccine failure (Chapter 4), but also the relative benefit of performing a second routine dose and SIAs (Chapter 6). One benefit of SIAs is commonly considered to be that they are performed independently of routine immunization activities, and likely reach populations that are not reached by routine immunization activities (WHO 2013). If this is true, then the coverage of a second routine dose must be much higher than SIA coverage in order for a second routine dose to outperform SIAs. However, if there is some correlation between SIAs and the first routine dose, then the relative coverage at which the second routine dose outperforms SIAs is much lower. Notably, the uncertainty in population immunity when coverage is constant, but correlation is uncertain, is highest when SIAs are administered in conjunction with two routine doses (Chapter 6). While increasing coverage can reduce the uncertainty in population immunity

due to uncertain correlation (Chapter 4), administering more doses does not (Chapter 6). As correlation has a large impact on population immunity (Chapter 4, 6), it is important that we report it where known and use it to inform management.

For any policy, the effectiveness of a vaccine strategy depends on maternal immunity and age structure (McKee et al 2015; Chapter 2). These effects may be mitigated or enhanced by the health system. In my work, I consider three manipulable aspects of the health system; coverage, age targets, and correlation. Currently, age targets for routine immunization are chosen by policy makers, taking coverage into account (WHO 2013), but not correlation. Coverage and correlation may be relatively difficult to measure and control, but their impact on population immunity is large. Coverage has a direct effect on population immunity, and higher coverage is always better. However, I show that which dose has a stronger effect on population immunity depends on correlation. Correlation alone may have a stronger effect on population immunity achieved by measles vaccination than either age structure or coverage improvements (Chapter 4). Currently, coverage of measles containing vaccine is reported to the World Health Organization based on administrative numbers, although demographic health survey data indicates that these reports are not always reliable (Lessler et al. 2011). Correlation between the populations receiving each dose is not yet reported, although it could likely be determined through a combination of administrative reports, especially in places with reliable census information, and survey data (Lessler et al. 2011). As correlation can have such a large impact on population immunity, it is important to report this number where possible, and use it when making management recommendations.

Much of the work in my thesis uses a steady-state approach to model the distribution of immunity in the post-elimination scenario. This methodology provides a simple framework to

rethink management in the absence of disease. I show how the optimal policy depends on demography, maternal immunity, coverage, correlation between doses, and the stated objective. While I consider some interactions between these factors throughout my thesis, there are additional complexities that I do not yet consider; there are many opportunities to expand this work, and to look for theoretically motivated and empirically-determined thresholds where management strategies should shift.

**S**trategies that successfully ***achieve*** elimination may not be optimal to ***maintain*** elimination. In many of my chapters, I find that vaccination at younger target ages than are currently chosen may be beneficial in spite of maternal immunity. Vaccine policy should be reconsidered following elimination, as high levels of immunity are crucial in order to prevent disease reinvasion. The focus of a new policy should be on program effectiveness, not simply the efficacy of each dose. While I suggest factors to include in this reanalysis, a more complete reanalysis would also include realistic operational constraints, including vaccine efficacy and consideration of the complete vaccine schedule (i.e., not just age targets at which measles containing vaccine is administered). However, as many of my results depend on the health system and are not specific to measles biology, these factors could apply to a range of diseases that are managed through a multi-dose vaccine policy. Any multi-dose vaccine policy's effectiveness likely depends on some combination of these and other factors, and so each policy should be chosen after careful examination, including population modelling that accounts for these factors.

**References**

1. Anderson RM, May RM. Directly transmitted infectious diseases: control by vaccination. Science 1982; 215: 1053–60.

2. Bauch CT, Szusz E, Garrison LP. Scheduling of measles vaccination in low-income countries: projections of a dynamic model. Vaccine 2009; 27: 4090–8.
3. Bishai D, Johns B, Nair D, et al. The cost-effectiveness of supplementary immunization activities for measles: a stochastic model for Uganda. J Infect Dis 2011; 204 Suppl : S107–15.
4. Bolker BM, Grenfell BT. Chaos and biological complexity in measles dynamics. Proc R Soc Biol Sci 1993; 251: 75–81.
5. Cairns KL, Perry RT, Ryman TK, Nandy RK, Grais RF. Should outbreak response immunization be recommended for measles outbreaks in middle- and low-income countries? An update. J Infect Dis 2011; 204 Suppl: S35–46.
6. Christie AS, Gay A. The Measles Initiative: moving toward measles eradication. J Infect Dis 2011; 204: S14–7.
7. de Quadros CA, Hersh BS, Nogueira AC, Carrasco PA, da Silveira CM. Measles eradication: experience in the Americas. Bull World Health Organ 1998; 76 Suppl 2: 47–52.
8. Earn DJD, Rohani P, Bolker BM, Grenfell BT. A Simple Model for Complex Dynamical Transitions in Epidemics. Science 2000; 287: 667–70.
9. Ferrari MJ, Djibo A, Grais RF, Grenfell BT, Bjørnstad ON. Episodic outbreaks bias estimates of age-specific force of infection: a corrected method using measles as an example. Epidemiol Infect 2010; 138: 108–16.
10. Ferrari MJ, Grais RF, Bharti N, et al. The dynamics of measles in sub-Saharan Africa. Nature 2008; 451: 679–84.

11. Finkenstadt BF, Grenfell BT. Time Series Modelling of Childhood Diseases : A Dynamical Systems Approach. Appl Stat 2000; 49: 187–205.
12. Fugier-Vivier I, Servet-Delprat C, Rivailler P, Rissoan MC, Liu YJ, Rabourdin-Combe C. Measles virus suppresses cell-mediated immunity by interfering with the survival and functions of dendritic and T cells. J Exp Med 1997; 186: 813–23.
13. Gans H, Yasukawa L, Rinki M, et al. Immune responses to measles and mumps vaccination of infants at 6, 9, and 12 months. J Infect Dis 2001; 184: 817–26.
14. Gay NJ. The theory of measles elimination: implications for the design of elimination strategies. J Infect Dis 2004; 189: S27–35.
15. Goodson JL, Sosler S, Pasi O, et al. Impact of a measles outbreak response immunization campaign: Maroua, Cameroon, 2009. J Infect Dis 2011; 204 Suppl : S252–9.
16. Grais RF, Conlan AJK, Ferrari MJ, et al. Time is of the essence: exploring a measles outbreak response vaccination in Niamey, Niger. J R Soc Interface 2008; 5: 67–74.
17. Grenfell BT, Bjørnstad ON, Kappey J. Travelling waves and spatial hierarchies in measles epidemics. Nature 2001; 414: 716–23.
18. Hall R, Jolley D. International measles incidence and immunization coverage. J Infect Dis 2011; 204 Suppl: S158–63.
19. Henao-Restrepo A-M, Strebel P, Hoekstra EJ, Birmingham M, Bilous J. Experience in Global Measles Control,1990 – 2001. J Infect Dis 2005; 187: S15–21.
20. Hersh BS, Tambini G, Nogueira a C, Carrasco P, de Quadros C a. Review of regional measles surveillance data in the Americas, 1996-99. Lancet 2000; 355: 1943–8.

21. Hutchins SS, Papania MJ, Amler R, et al. Evaluation of the measles clinical case definition. J Infect Dis 2004; 189 Suppl: S153–9.
22. Katz, M. Clinical spectrum of measles. In: Measles Virus. 1995: 1-12.
23. Katz SL. John F. Enders and the measles virus vaccine – a reminiscence. In: Measles: History and Basic Biology. 2009: 3-12.
24. Khetsuriani N, Deshevoi S, Goel A, Spika J, Martin R, Emiroglu N. Supplementary immunization activities to achieve measles elimination: experience of the European Region. J Infect Dis 2011; 204 Suppl: S343–52.
25. Lessler J, Metcalf CJE, Grais RF, et al. Measuring the performance of vaccination programs using cross-sectional surveys: a likelihood framework and retrospective analysis. PLoS Med 2011; 8:e1001110.
26. Luquero FJ, Pham-Orsetti H, Cummings D a T, et al. A long-lasting measles epidemic in Maroua, Cameroon 2008-2009: mass vaccination as response to the epidemic. J Infect Dis 2011; 204 Suppl: S243–51.
27. McKee A, Ferrari MJ, Shea K. The effects of maternal immunity and age structure on population immunity to measles. Theor Ecol 2015; 8: 261–71.
28. McLean AR, Anderson RM. Measles in developing countries. Part I. Epidemiological parameters and patterns. Epidemiol Infect 1988; 100: 111–33.
29. McLean AR, Anderson RM. Measles in developing countries. Part II. The predicted impact of mass vaccination. Epidemiol Infect 1988; 100: 419–42.
30. Metcalf CJE, Klepac P, Ferrari M, Grais RF, Djibo a, Grenfell BT. Modelling the first dose of measles vaccination: the role of maternal immunity, demographic factors, and delivery systems. Epidemiol Infect 2011; 139: 265–74.

31. Mina MJ, Metcalf CJE, de Swart RL, Osterhaus ADME, Grenfell BT. Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. Science 2015; 348: 694–9.
32. Orenstein WA, Strebel PM, Papania M, Sutter RW, Bellini WJ, Cochi SL. Measles eradication: Is it in our future? Am J Public Health 2000; 90: 1521–5.
33. Simons E, Ferrari M, Fricks J, et al. Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. Lancet 2012; 379: 2173–8.
34. Sugerman DE, Barskey AE, Delea MG, et al. Measles outbreak in a highly vaccinated population, San Diego, 2008: role of the intentionally undervaccinated. Pediatrics 2010; 125: 747–55.
35. WHO. Millennium Development Goals: Child and maternal goals: MDGs 4 and 5. 2011. http://www.who.int/pmnch/media/press_materials/fs/about_mdgs/en/#
36. WHO. A Guide to Introducing a Second Dose of Measles Vaccine into Routine Immunization Schedules. 2013.
37. Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. Int J Epidemiol 2009; 38: 192–205.
38. Wolfson LJ, Strebel PM, Gacic-Dobo M, Hoekstra EJ, McFarland JW, Hersh BS. Has the 2005 measles mortality reduction goal been achieved? A natural history modelling study. Lancet 2007; 369: 191–200.
39. Yeager AS, Davis JH, Ross LA, Harvey B. Measles immunization. Successes and failures. JAMA 1977; 237: 347–51.

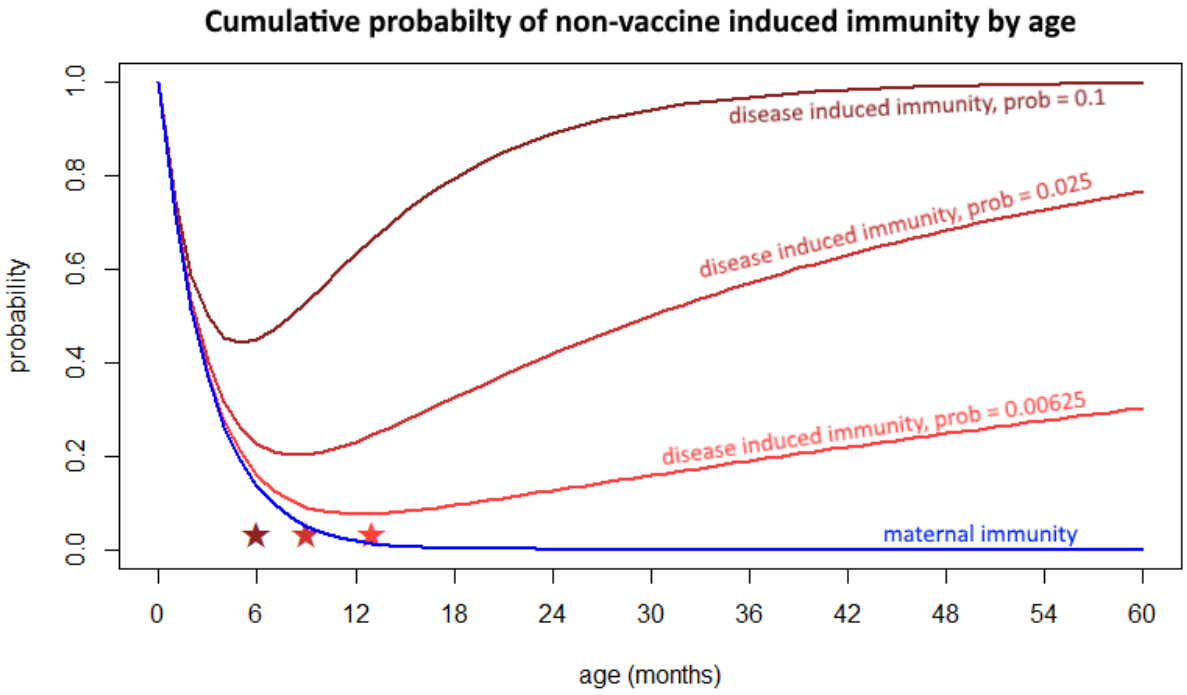



**Figure 7.1** The cumulative probability of immunity by age. The blue line represents maternal immunity, which here wanes exponentially such that there is a 5% probability of retaining maternal immunity at 9 months. Each red line represents the sum of the maternal immunity distribution with the cumulative probability of having been infected by that age for a range of probabilities of infection at a given age (we do not consider an age-specific force of infection for the purposes of this illustration). The stars represent the optimal age at vaccination for the probability of infection of the correspondingly colored line, as in McLean and Anderson 1988a.

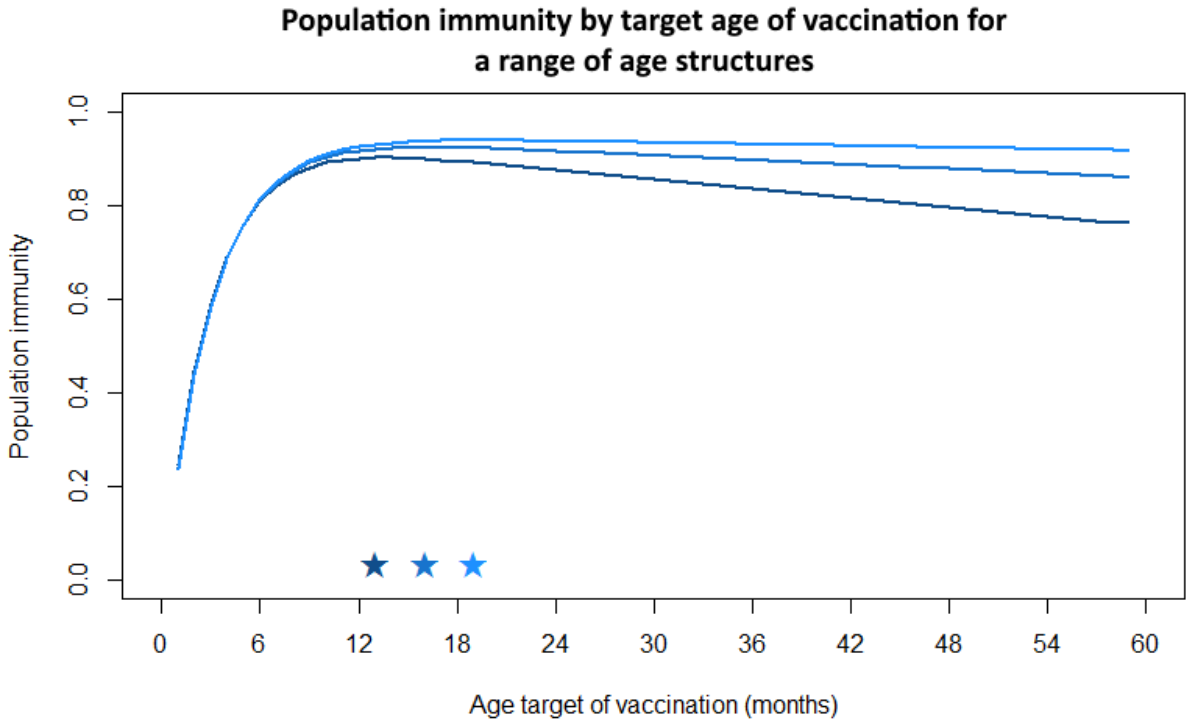



**Figure 7.2** The population immunity maintained within the population by vaccination with 100% at a range of age targets. Lighter colors of blue correspond to a lower proportion of infants within the population – for the darkest line, 20% of the population is made up by children under five, for the intermediate line, 10% of the population is made up by children under five, and for the lightest line, 4% of the population is made up by children under five. The optimal ages of vaccination for each age structure are shown by stars of the corresponding color.

# Appendix A

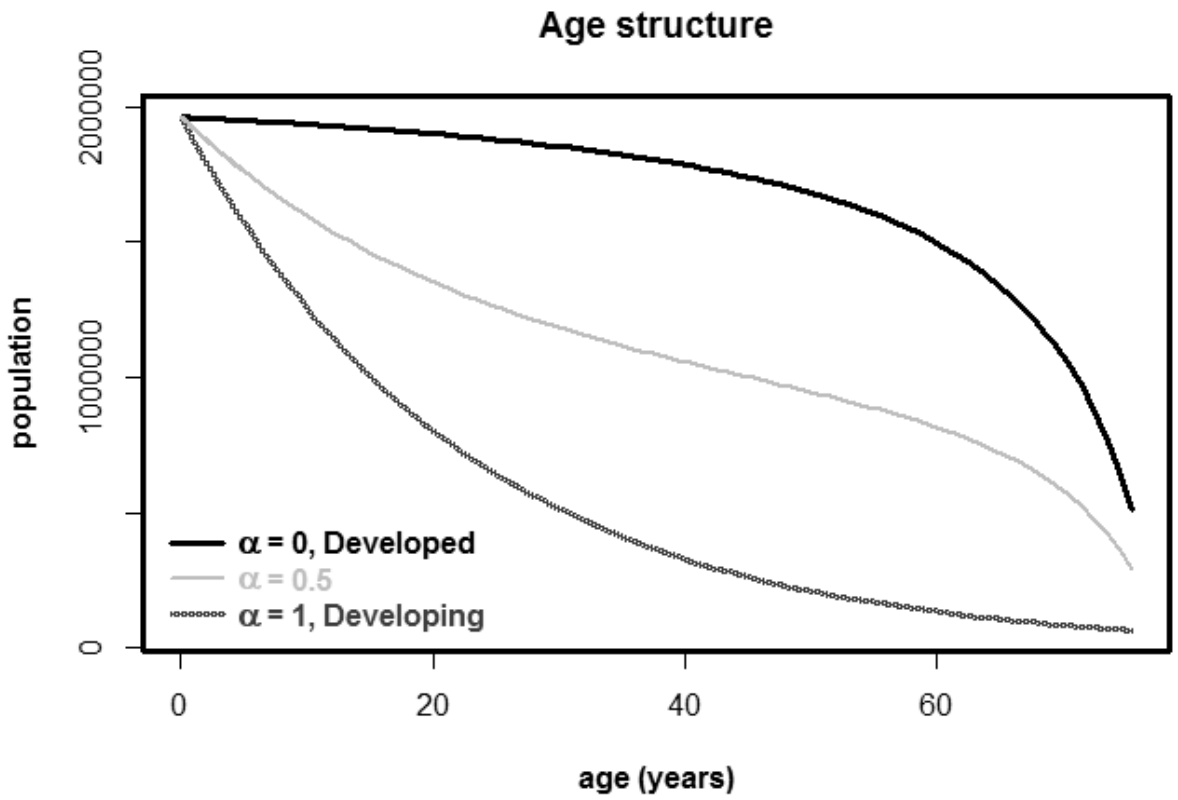



**Figure A1:** The two age structures explored in Chapter 2. In black is an idealized developed age structure, and speckled is the idealized developing age structure. Between the two is a sample age structure representing one of the range considered in Figure 7. The symbol α represents the relative weight of the developed age structure when we consider a weighted average of the two base age structures.

In our model, we explore two base age structures – a convex one, representing an idealized developed population (represented by the black curve in Figure A1), as in the United States, and a concave one, representing an idealized developing population (represented by the speckled curve in Figure A1), as in Sub-Saharan Africa. We also explore a range of age structures, which

are linear composites of these two base age structures, where α represents the proportional weight of the developed age structure.

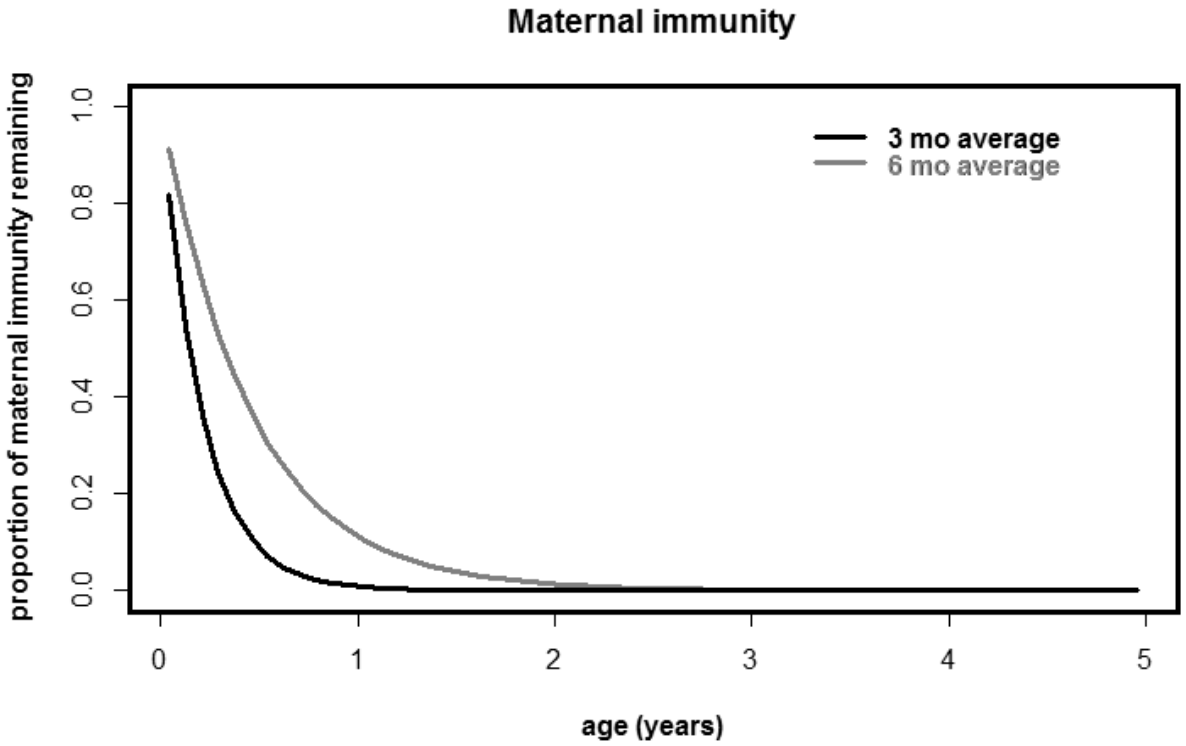



**Figure A2:** Maternal immunity functions used in Chapter 2. The grey represents the probability of remaining maternally immune if you were born maternally immune and maternal immunity wanes exponentially on average at 3 months. Similarly, the black represents the probability of remaining maternally immune if you were born maternally immune and maternal immunity wanes exponentially on average at 6 months.

We consider two basic functions for maternal immunity within the population – an exponential distribution with a mean at three months and an exponential distribution with at six months. These functions give the proportion of the population that remains maternally immune at the specified age.

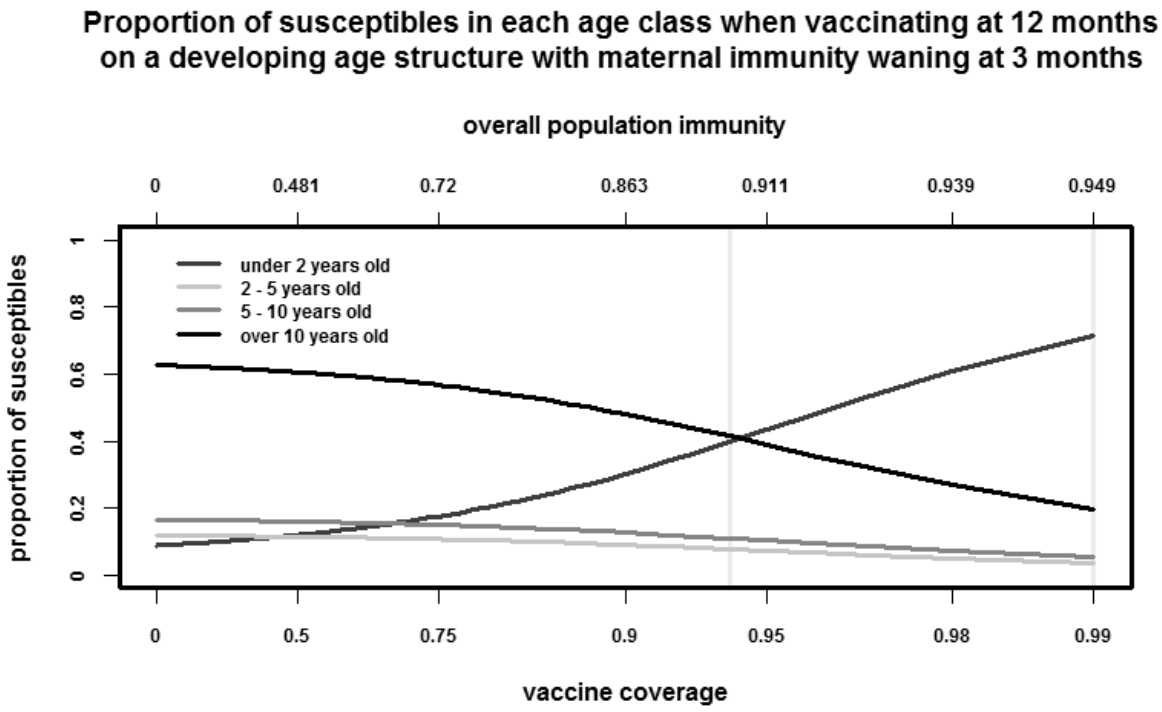



**Figure A3:** Age distribution of susceptibility for a developing age structure with 3 month maternal immunity when vaccinating at 12 months over a range of vaccine coverages. The left vertical line is where the 90% threshold is satisfied for overall population immunity (but only when vaccine coverage exceeds this level), the right is where the 95% threshold is satisfied for the population; this latter only occurs for vaccine coverage of 99% or above, however.

All positive values of vaccine coverage exceed the level of resulting population immunity. However, the immunity gap between coverage and population immunity does not vary linearly with coverage; the bottom axis indicates vaccine coverage, while the top axis indicates population immunity (Fig. A3).

Given a specific vaccine plan, the age distribution of susceptible individuals changes with coverage (Fig. A3). Notably, as coverage increases, the proportion of the remaining susceptibles who are very young – many below the age at first vaccination – increases. This does not mean

the absolute number of infant susceptibles increases, rather that they are a larger proportion of the overall susceptible population – the absolute number actually decreases. Since the case fatality rate of measles infection is inversely related to age, this would mean that the case fatality for any outbreaks that occur as coverage increases should increase, as cases would be disproportionately in the pre-vaccine age class.

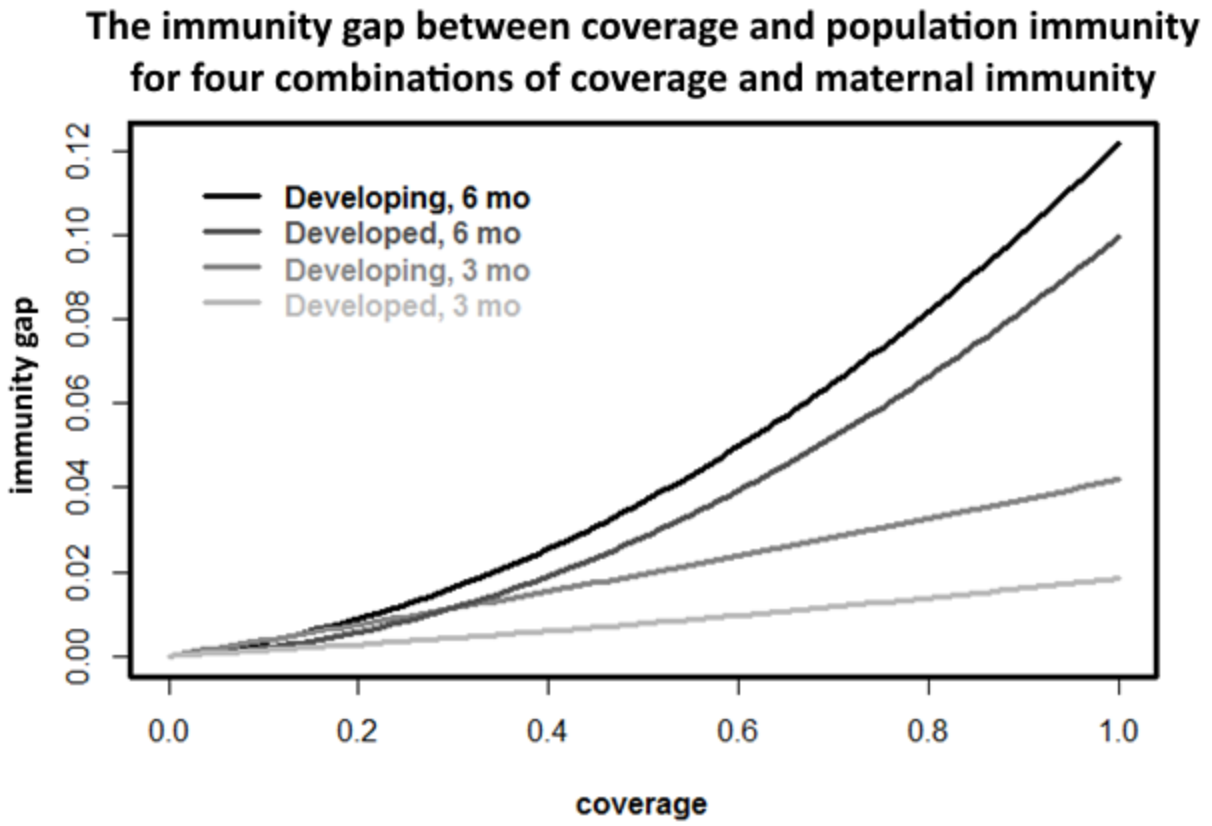



**Figure A4:** Four possible immunity gaps between coverage and population immunity, when vaccinating at 12 months. The most severe immunity gap is with long maternal immunity and developing age structure; the least severe immunity gap is with short maternal immunity and developed age structure. Notably, with low coverage, age structure matters more than maternal immunity – it is only above around 30% coverage that the immunity gap in a developed age structure with long maternal immunity exceeds that in a developing age structure with short maternal immunity.

The immunity gap between coverage and achieved immunity when vaccinating at 12 months increases with coverage for all four combinations of base age structure and maternal immunity duration (Fig. A4). The immunity gap when vaccinating a population with a developed age

structure is always smaller than when vaccinating a population with a developing age structure (although the general functional form of the relationship is the same), due to the relatively small proportion of the population eligible for vaccination in a developed age structure. When maternal immunity wanes, on average, at 6 months, the immunity gap increases rapidly with coverage with both a developing and developed age structure, as high coverage means more infants are born with maternal immunity, which means proportionally fewer doses of the vaccine will be effective. However, if maternal immunity wanes, on average, at 3 months, then the immunity gap is simply due to the proportion of the population that is below the target age of vaccination, which remains relatively constant as coverage increases.

# Appendix B

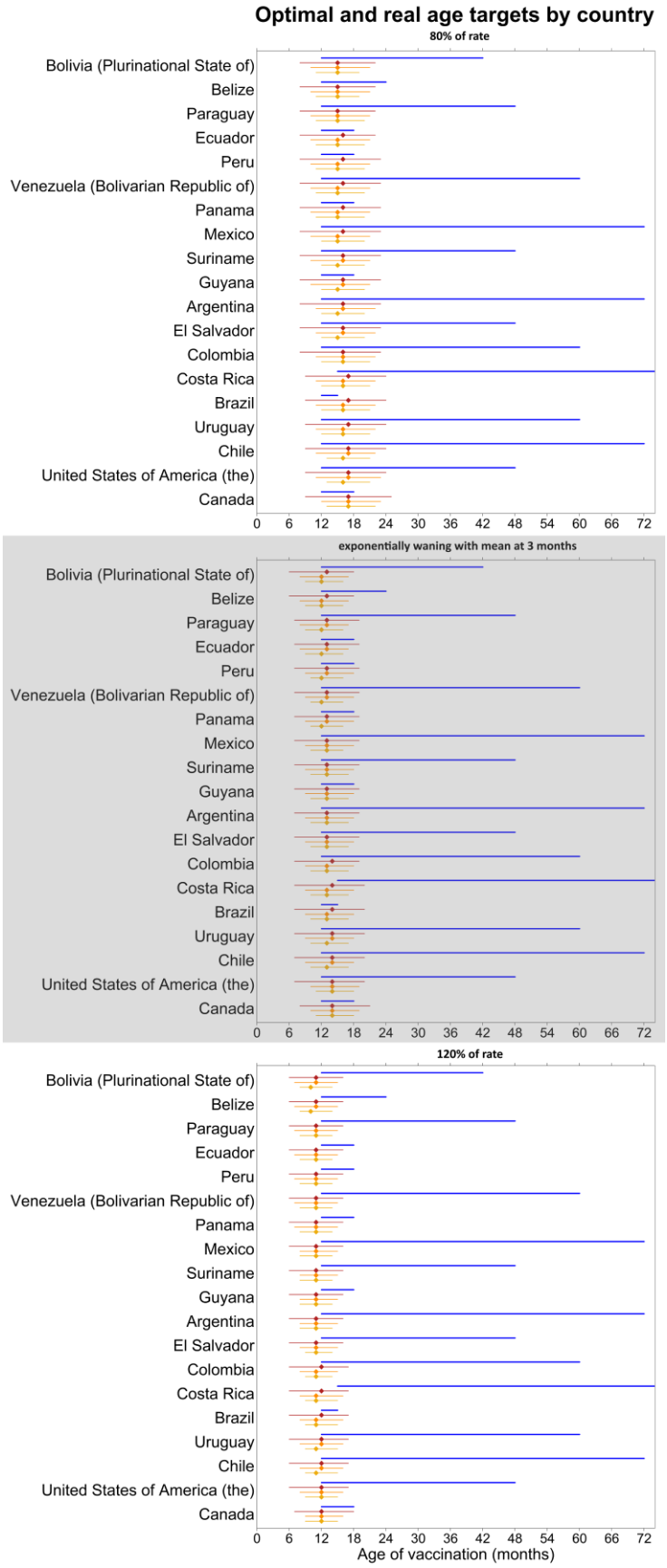

Optimal and real age targets by country
80% of rate
exponentially waning with mean at 3 months
120% of rate
Bolivia (Plurinational State of)
Belize
Paraguay
Ecuador
Peru
Venezuela (Bolivarian Republic of)
Panama
Mexico
Suriname
Guyana
Argentina
El Salvador
Colombia
Costa Rica
Brazil
Uruguay
Chile
United States of America (the)
Canada
0 6 12 18 24 30 36 42 48 54 60 66 72
Age of vaccination (months)

**Figure B1:** Optimal age targets for first and second dose under different assumptions about the waning of maternal immunity. The middle panel is Figure 3.2. The endpoints of the blue line represent the current age targets for the first and second dose. The endpoints of the red line represent the optimal age targets for 100% coverage, with the red diamond representing the optimal single dose strategy. The endpoints of the orange line represent the optimal age targets for 90% coverage, with the orange diamond representing the optimal single dose strategy. Finally, the endpoints of the yellow line represent the optimal age targets for 80% coverage, with the yellow diamond representing the optimal single dose strategy. The middle graph is made assuming maternal immunity wanes exponentially with a mean at 3 months. As in the paper, the countries are arranged in descending order of the ratio of children under 5.

The top and bottom panels are that figure redrawn for a different maternal immunity waning rate. On the bottom, maternal immunity wanes at 120% of the rate we use in the paper, so individuals are susceptible at younger ages and the optimal age targets are younger. On the top, maternal immunity wanes at 80% of the rate in the paper, so individuals do not lose maternal immunity until they are older, and the optimal age targets are therefore older. When maternal immunity wanes more slowly, the window between the optimal first and second ages of vaccination is wider. In all cases, the effect of coverage is the same – a lower coverage means a shorter window between doses, and the optimal single dose strategy falls between the optimal strategy for the first and second dose. In all cases where the second dose is recommended at 2+ years, it is still beneficial to reduce the age target of the second dose.

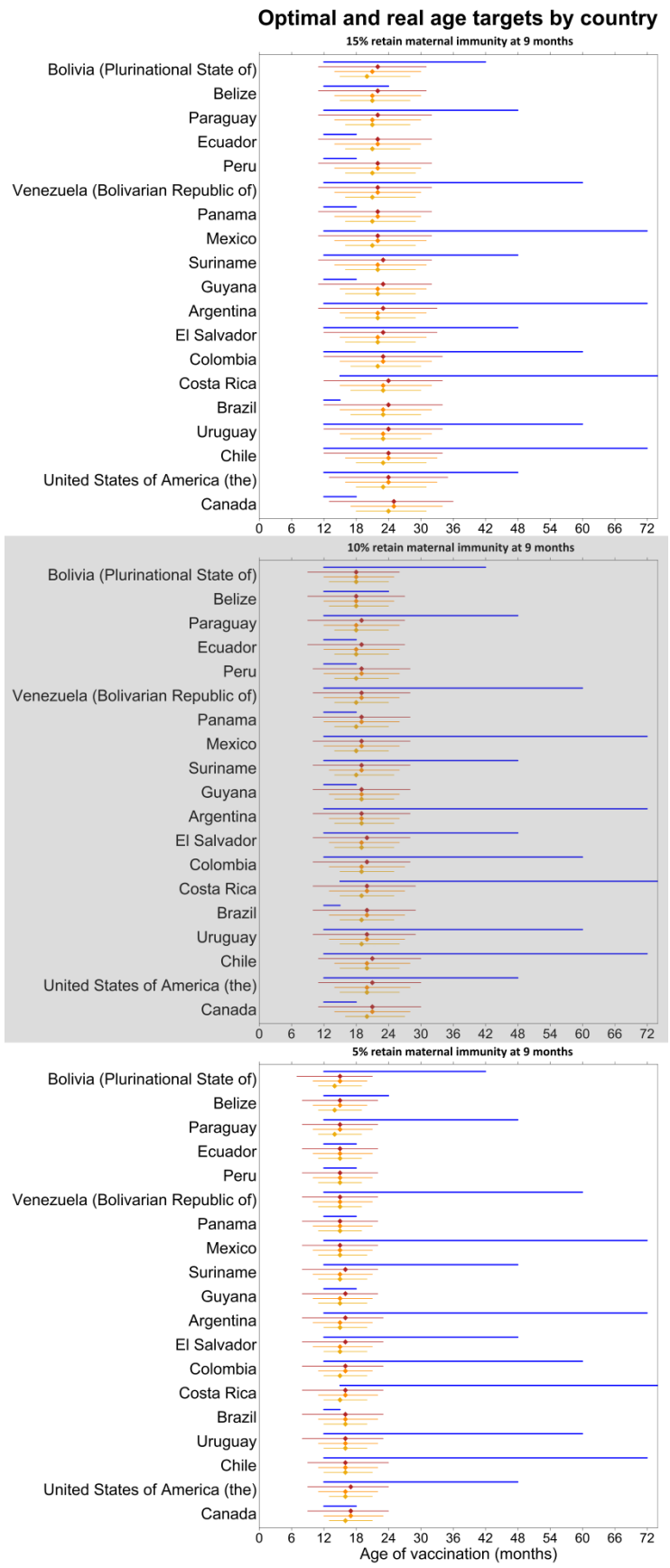

Optimal and real age targets by country
15% retain maternal immunity at 9 months
10% retain maternal immunity at 9 months
5% retain maternal immunity at 9 months
Bolivia (Plurinational State of)
Belize
Paraguay
Ecuador
Peru
Venezuela (Bolivarian Republic of)
Panama
Mexico
Suriname
Guyana
Argentina
El Salvador
Colombia
Costa Rica
Brazil
Uruguay
Chile
United States of America (the)
Canada
0 6 12 18 24 30 36 42 48 54 60 66 72
Age of vaccination (months)

**Figure B2:** Optimal age targets for first and second dose under different assumptions about the waning of maternal immunity. All panels are similar to Figure 3.2, but with a different function for maternal immunity. The endpoints of the blue line represent the current age targets for the first and second dose. The endpoints of the red line represent the optimal age targets for 100% coverage, with the red diamond representing the optimal single dose strategy. The endpoints of the orange line represent the optimal age targets for 90% coverage, with the orange diamond representing the optimal single dose strategy. Finally, the endpoints of the yellow line represent the optimal age targets for 80% coverage, with the yellow diamond representing the optimal single dose strategy. As in the paper, the countries are arranged in descending order of the ratio of children under 5.

In these panels, maternal immunity still wanes exponentially, but with a waning rate that results in 15%, 10%, or 5% (respectively) of children still immune at 9 months. When the maternal immunity wanes faster, as on the bottom, the vaccine is more effective at 9 months and the age targets of vaccination are earlier in life than when maternal immunity wanes more slowly, as on the top. In all cases, the effect of coverage is the same – lower coverage means a shorter window between the first and second dose, and the single dose optimum falls between the two. In all countries that recommend the second dose at 3+ years, it is beneficial to reduce the age target of the second dose, regardless of the specific maternal immunity function.

| Country | current policy | | 80% coverage optima | | | 90% coverage optima | | | 100% coverage optima | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | first | second | first | second | single | first | second | single | first | second | Single |
| Bolivia (Plurinational State of) | 12 | 42 | 9 | 16 | 12 | 8 | 17 | 12 | 6 | 18 | 13 |
| Belize | 12 | 24 | 9 | 16 | 12 | 8 | 17 | 12 | 6 | 18 | 13 |
| Paraguay | 12 | 48 | 9 | 16 | 12 | 8 | 17 | 13 | 7 | 19 | 13 |
| Ecuador | 12 | 18 | 9 | 16 | 12 | 8 | 17 | 13 | 7 | 19 | 13 |
| Peru | 12 | 18 | 10 | 16 | 12 | 9 | 18 | 13 | 7 | 19 | 13 |
| Venezuela (Bolivarian Republic of) | 12 | 60 | 10 | 16 | 12 | 9 | 18 | 13 | 7 | 19 | 13 |
| Panama | 12 | 18 | 10 | 16 | 12 | 9 | 18 | 13 | 7 | 19 | 13 |
| Mexico | 12 | 72 | 10 | 16 | 13 | 9 | 18 | 13 | 7 | 19 | 13 |
| Suriname | 12 | 48 | 10 | 17 | 13 | 9 | 18 | 13 | 7 | 19 | 13 |
| Guyana | 12 | 18 | 10 | 17 | 13 | 9 | 18 | 13 | 7 | 19 | 13 |
| Argentina | 12 | 72 | 10 | 17 | 13 | 9 | 18 | 13 | 7 | 19 | 13 |
| El Salvador | 12 | 48 | 10 | 17 | 13 | 9 | 18 | 13 | 7 | 19 | 13 |
| Colombia | 12 | 60 | 10 | 17 | 13 | 9 | 18 | 13 | 7 | 19 | 14 |
| Costa Rica | 15 | 84 | 10 | 17 | 13 | 9 | 18 | 13 | 7 | 20 | 14 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Brazil** | **12** | **15** | **10** | **17** | **13** | **9** | **18** | **13** | **7** | **20** | **14** |
| **Uruguay** | **12** | **60** | **10** | **17** | **13** | **9** | **18** | **14** | **7** | **20** | **14** |
| **Chile** | **12** | **72** | **10** | **17** | **13** | **9** | **18** | **14** | **7** | **20** | **14** |
| **United States of America (the)** | **12** | **48** | **11** | **18** | **14** | **10** | **19** | **14** | **7** | **20** | **14** |
| **Canada** | **12** | **18** | **11** | **18** | **14** | **10** | **19** | **14** | **8** | **21** | **14** |

**Table B1:** Optimal age targets for the first and second dose assuming maternal immunity wanes exponentially with a mean at 3 months. This table contains the data plotted in Figure 3.2, with cells colored to correspond to the line containing the data in the cells. The blue cells represent current policy, or the endpoints of the blue line in Figure 3.2. The yellow cells represent the model optima for 80% coverage, or the endpoints of the yellow line in Figure 3.2 and the yellow diamond. The orange cells represent the model optima for 90% coverage, or the endpoints of the orange line in Figure 3.2 and the orange diamond. The red cells represent the model optima for 100% coverage, or the endpoints of the red line in Figure 3.2 and the red diamond. As in Figure 3.2, the countries are arranged in descending order of the ratio of children under 5. All optima assume that maternal immunity wanes exponentially with mean at 3 months. These age targets should not be taken as operational suggestions, as the selection of age targets is sensitive to maternal immunity, as illustrated in Figures B1 and B2.

| | MCV1 Coverage | | | | | | | | | | | MCV2 Coverage | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | AVG | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | AVG |
| Bolivia | 89 | 88 | 86 | 92 | 93 | 88 | 96 | 96 | 95 | 95 | 91.8 | | | | | | | | | | | |
| Belize | 95 | 99 | 96 | 96 | 97 | 98 | 98 | 96 | 99 | 95 | 96.9 | 87 | 92 | 89 | 90 | 92 | 91 | 98 | 93 | 92 | 92 | 91.6 |
| Paraguay | 91 | 91 | 91 | 91 | 91 | 94 | 93 | 91 | 92 | 90 | 91.5 | 28 | 58 | 63 | 70 | 63 | 64 | 65 | 62 | 64 | 64 | 60.1 |
| Ecuador | 93 | 97 | 98 | 98 | 97 | 95 | 94 | 96 | 97 | 85 | 95 | | | | | 99 | 91 | 92 | 55 | 83 | 59 | 79.8 |
| Peru | 77 | 93 | 92 | 92 | 91 | 94 | 96 | 94 | 85 | 89 | 90.3 | | | 9 | 17 | 42 | 57 | 70 | 63 | 54 | 44 | 44.5 |
| Venezuela | 76 | 82 | 87 | 93 | 87 | 79 | 86 | 87 | 85 | 89 | 85.1 | | | | | 6 | 31 | 26 | 33 | 38 | 50 | 30.7 |
| Panama | 99 | 95 | 95 | 96 | 96 | 97 | 97 | 98 | 92 | 90 | 95.5 | 89 | 60 | 80 | 60 | 99 | 73 | 81 | 72 | 68 | 90 | 77.2 |
| Mexico | 96 | 96 | 96 | 96 | 96 | 95 | 98 | 99 | 89 | 97 | 95.8 | 97 | 55 | 85 | 94 | 92 | 91 | 97 | 92 | 76 | 95 | 87.4 |
| Suriname | 91 | 83 | 85 | 86 | 88 | 90 | 85 | 73 | 93 | 85 | 85.9 | 86 | | | | | | | | 18 | 18 | 40.7 |
| Guyana | 92 | 90 | 96 | 95 | 97 | 95 | 98 | 99 | 99 | 99 | 96 | 72 | 74 | 90 | 84 | 84 | 82 | 84 | 90 | 95 | 91 | 84.6 |
| Argentina | 99 | 97 | 94 | 96 | 99 | 98 | 95 | 94 | 94 | 95 | 96.1 | 99 | 91 | 91 | 86 | 96 | 98 | 91 | 90 | 82 | 96 | 92.0 |
| El Salvador | 99 | 98 | 99 | 95 | 91 | 92 | 89 | 93 | 94 | 94 | 94.4 | 99 | 89 | 86 | 79 | 82 | 78 | 81 | 95 | 85 | 85 | 85.9 |
| Colombia | 96 | 95 | 93 | 95 | 89 | 88 | 88 | 94 | 92 | 91 | 92.1 | 73 | 85 | 93 | 69 | 71 | 73 | 76 | 79 | 72 | 88 | 77.9 |
| Costa Rica | 89 | 90 | 90 | 89 | 81 | 83 | 83 | 90 | 91 | 95 | 88.1 | | | | 89 | 84 | 79 | 80 | 95 | 92 | 90 | 87.0 |
| Brazil | 99 | 99 | 99 | 99 | 99 | 99 | 99 | 97 | 97 | 97 | 98.4 | | | | 56 | 55 | 53 | 99 | 96 | 99 | 96 | 79.1 |
| Uruguay | 95 | 94 | 96 | 95 | 94 | 95 | 95 | 96 | 96 | 96 | 95.2 | | | | | | | | | 92 | 93 | 92.5 |
| Chile | 90 | 91 | 92 | 96 | 93 | 93 | 91 | 90 | 90 | 94 | 92 | 96 | 95 | 95 | 89 | 89 | 84 | 77 | 74 | 78 | 88 | 86.5 |
| United States of America | 92 | 92 | 92 | 92 | 90 | 92 | 92 | 92 | 91 | 91 | 91.6 | | | | | | | | | | | |
| Canada | 94 | 93 | 94 | 94 | 95 | 95 | 95 | 98 | 95 | 95 | 94.8 | | | | | | | | 94 | | | 94.0 |

**Table B2:** The real measles-containing vaccine coverages for 2005-2014 as reported to the WHO. Coverages falling between 80 and 100% are coloured yellow to green, with greener squares being higher coverage squares. Coverages falling below 80% are highlighted in red. The average coverage over the 10 year period is also shown, with average coverages above 90% in blue, average coverages between 80 and 90% in yellow and average coverages below 80% in orange. Countries are arranged in descending order of the ratio of children under 5.

| Country | Average coverage 2005-2014 | | immunity maintained by: | | | |
|---|---|---|---|---|---|---|
| | MCV1 | MCV2 | real targets | 80% optima | 90% optima | 100% optima |
| Bolivia (Plurinational State of) | 91.8 | | 95.39 | 96.18 | 96.20 | 95.97 |
| Belize | 96.9 | 91.6 | 95.80 | 96.18 | 96.22 | 96.04 |
| Paraguay | 91.5 | 60.1 | 95.42 | 96.29 | 96.32 | 96.26 |
| Ecuador | 95 | 79.8 | 96.07 | 96.31 | 96.33 | 96.27 |
| Peru | 90.3 | 44.5 | 96.12 | 96.30 | 96.36 | 96.32 |
| Venezuela (Bolivarian Republic of) | 85.1 | 30.7 | 95.28 | 96.31 | 96.37 | 96.35 |
| Panama | 95.5 | 77.2 | 96.17 | 96.34 | 96.39 | 96.33 |
| Mexico | 95.8 | 87.4 | 92.44 | 96.37 | 96.42 | 96.36 |
| Suriname | 85.9 | 40.7 | 95.71 | 96.41 | 96.46 | 96.42 |
| Guyana | 96 | 84.6 | 96.28 | 96.43 | 96.47 | 96.40 |
| Argentina | 96.1 | 92.0 | 92.91 | 96.46 | 96.50 | 96.42 |
| El Salvador | 94.4 | 85.9 | 95.82 | 96.47 | 96.51 | 96.43 |
| Colombia | 92.1 | 77.9 | 95.79 | 96.57 | 96.61 | 96.52 |
| Costa Rica | 88.1 | 87.0 | 90.62 | 96.64 | 96.67 | 96.58 |
| Brazil | 98.4 | 79.1 | 96.49 | 96.65 | 96.67 | 96.55 |
| Uruguay | 95.2 | 92.5 | 95.99 | 96.68 | 96.70 | 96.58 |
| Chile | 92 | 86.5 | 93.91 | 96.75 | 96.77 | 96.65 |
| United States of America (the) | 91.6 | | 96.39 | 96.79 | 96.82 | 96.64 |
| Canada | 94.8 | 94.0 | 96.86 | 96.90 | 96.92 | 96.86 |

**Table B3:** Population immunity maintained by optimal and real age targets assuming real coverage. In places where MCV2 coverage is not available, we assume both doses have the same coverage. Assuming that coverage in each country is the same as the average coverage for these countries (shown in the second column from the left) and that maternal immunity wanes exponentially with a mean

at 3 months, we find the population immunity maintained by the optimal age targets calculated in the paper, as well as the real age targets. Countries are arranged in descending order of the ratio of children under 5. In the third column from the left, we use the real age targets. In third column from the right, we use the optimal age targets for each country assuming 80% coverage, shown as the endpoints of the yellow line corresponding to each country in Figure 3.2. In the second column from the right, we use the optimal age targets for each country assuming 90% coverage, shown as the endpoints of the orange line corresponding to each country in Figure 3.2. Finally, in the rightmost column we use the optimal age targets for each country assuming 100% coverage, shown by the endpoints of the red line corresponding to each country in Figure 3.2. Each cell in the right four columns is coloured according to the population immunity maintained, with white cells having a relatively low population immunity and darker green cells having a higher level of population immunity. For all countries, at least one of the model optima improved population immunity over the real age targets. Adjusting age targets with the current coverage levels can improve population immunity in all countries to above 95%.

# Vita

**Amalie McKee**

**Education:**

The Pennsylvania State University, University Park, PA - 2011-2016
Biology PhD, December 2016
Case Western Reserve University, Cleveland, OH – 2007-2011
Applied Mathematics BS, May 2011

**Publications:**

**McKee, A.**, Ferrari, M., and K. Shea. "The effects of maternal immunity and age structure on population immunity to measles". Theoretical Ecology 2015; 8(2): 261-271.
**McKee, A.**, Shea, K., and M. Ferrari. "Optimal vaccine schedules to maintain measles elimination with a two-dose routine policy". Epidemiology and Infection 2016; *in press*.

**Presentations:**

The effects of correlation between the first and second scheduled doses of measles vaccine on the maintainability of measles elimination
Ecological Society of America 100th Anniversity Meeting, Baltimore, Maryland - August 12, 2015
Center for Infectious Disease Dynamics seminar, Pennsylvania State University – April 2, 2015

Locally tailored strategies improve maintenance of measles elimination – Center for Infectious Disease Dynamics seminar, Pennsylvania State University – October 3, 2013

**Teaching Experience:**

"Using disease models for management" - Guest lecture in a Math REU - Pennsylvania State University - June 21, 2016

Bio 419/519 – Teaching assistant for "Ecological and Environmental Problem Solving", undergraduate and graduate sections – Pennsylvania State University – Spring 2014, Spring 2015

Bio 220W – Teaching assistant for two lab sections of "Biology: Populations and Communities" – PSU – Spring 2013

**Honors and Awards:**

2016-2017 Jeanette Ritter Mohnkern Graduate Student Scholarship in Biology - Pennsylvania State University - 2016
2014-2015 "Excellence in Teaching" Award - Pennsylvania State University - 2015
University Graduate Fellowship – Pennsylvania State University – 2011-2012
Braddock Award – Pennsylvania State University – 2011