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ABSTRACT

Madagascar reports few measles cases annually and high vaccination campaign coverage. However, the underlying age profile of immunity and risk of a measles outbreak is unknown. We conducted a nested serological survey, testing 1005 serum collected between November 2013 and December 2015 via Madagascar's febrile rash surveillance system, for measles immunoglobulin G antibody titers. We directly estimated the age profile of immunity and compared these estimates to indirect estimates based on a birth cohort model of vaccination coverage and natural infection. Combining these estimates of the age profile of immunity in the population with an age-structured model of transmission, we further predicted the risk of a measles outbreak, and the impact of mitigation strategies designed around supplementary immunization activities. The direct and indirect estimates of age-specific seroprevalence show that current measles susceptibility is over 10%, and modeling suggests that Madagascar may be at risk of a major measles epidemic.

Keywords: Measles, Serological Survey, Madagascar, Surveillance, Rubella

List of Abbreviations: World Health Organization (WHO), Supplementary Immunization Activities (SIA), Immunoglobulin G (IgG)

Measles is a highly infectious disease that is preventable with a safe, effective, and inexpensive vaccine (1). The World Health Organization (WHO) African Region aims to eliminate measles by 2020 (2, 3). Many of these countries currently achieve high vaccination coverage rates via routine and supplementary immunization activities (SIAs, i.e., multi-annual, vaccination campaigns for targeted age ranges) (2). Nonetheless, measles transmission continues and the WHO African Region has the highest reported incidence with 27.9 per 1 million incident cases in 2016 (2).

Routine measles immunization began in Madagascar in 1985. Although vaccination coverage remained low through the 80's and 90's (4), progress in reducing measles incidence has occurred since 2004, in part as a result of regularly implemented SIAs occurring at 3-5 year intervals (5). Measles cases reported to the WHO show a sharp drop since 2004, from tens of thousands of cases annually to fewer than 10 cases per year (6). Madagascar is 1 of 19 WHO African Region countries where minimal surveillance targets have been met; including investigating ≥2 cases of non-measles febrile-rash illness per 100,000 population annually, and obtaining a blood specimen from ≥1 suspected measles case in ≥80% of districts annually (2).

Although measles incidence in Madagascar is reportedly low, SIA coverage is reportedly high, and surveillance targets are being met, uncertainty as to the success of the measles program remains. Settings with low transmission and low routine coverage (< 95%), such as Madagascar, may experience a 'honeymoon period' where individuals who were missed by vaccination programs escape

infection as a result of reduced transmission, and thus susceptible individuals can accumulate (7). If additional vaccination campaigns are not routinely implemented, this accumulation of susceptible individuals may exceed a critical threshold, that can result in disease outbreaks (7, 8). Identifying a country's risk for a measles outbreak following a period of low transmission requires knowledge of the underlying age profile of susceptibility which shapes outbreak potential.

Readily available epidemiological data, including vaccination coverage and case surveillance data, can be used to indirectly infer population immunity. However, inaccurate or incomplete data sources can result in biased estimates of susceptibility (9-11). 'Post-honeymoon period' outbreaks have occurred in several WHO African Region countries despite low estimates of susceptibility based on high reported vaccination coverage (12-15). To mitigate issues associated with indirect estimates of population susceptibility, serological surveys (the detection of antigen specific antibodies in a population) can provide a direct measurement of immunity (16, 17) and may refine estimates of measles age-specific seroprevalence.

The age profile of immunity can be used to characterize a country's risk of a measles outbreak, but achieving this also requires accounting for potentially complex transmission dynamics and their variability across age. Mathematical models are a powerful tool for exploring outbreak risk and optimal design for vaccination mitigation strategies (18-20), by allowing us to track individual movement through

age or epidemiological stages while accounting for non-linearities in transmission dynamics that may be counterintuitive (21).

Here we conducted a nested Immunoglobulin G (IgG) serological survey by testing existing serum samples from the febrile-rash surveillance system in Madagascar to directly measure the age distribution of immunity (16, 17). Given the potential for external validity bias since the serum sample were passively collected, we assessed sampling variability by age and space, and compared our direct estimates of the age-specific profile of immunity from serological data to indirect estimates based on a birth cohort projection method that takes into account natural and vaccine-derived immunity (22). Building on these direct estimates of the age profile of immunity, we used an age-structured mathematical model to explore the impact of different SIA strategies, including the most recent SIA administered to contain the risk of a measles outbreak in Madagascar.

METHODS

Data collection and testing protocol

Serum samples were obtained from the Madagascar national surveillance system for measles and rubella. Standard protocol requires that when a patient presents for care with symptoms meeting the clinical criteria for measles (fever and rash and either cough, corzya, or conjunctivitis), the patients' serum is collected and sent to the WHO national reference laboratory located at the Institut Pasteur de Madagascar. At Institut Pasteur de Madagascar, the serum is tested for measles-

specific and rubella-specific immunoglobulin M antibodies to detect a recent infection. Any remaining serum is stored at Institut Pasteur de Madagascar.

In 2016, we tested serum collected between November 2004 and November 2015 for measles-specific IgG antibodies with an indirect ELISA test (Enzygnost® Anti-Measles Virus/IgG, Siemens, Erlangen, Germany). IgG antibodies are a marker of past exposure to either measles natural infection or vaccination, and represent immunity. Quantitative results, in mIU/mL, were obtained from IgG testing, based on a sensitivity of 90% and specificity of 100% (23). Measles seropositivity was defined as IgG antibody concentration greater than 200 mIU/mL per assay manufacturer's instructions. Due to potential non-random misclassification bias related to serum testing error and waning humoral immunity (i.e., cell mediated immunity may still play a role even if an individual tests seronegative (24)), seroprevalence does not perfectly map on to measles immunity. However, to simplify the analysis we assumed that these two were equal.

Data sample size

We excluded the febrile-rash serum samples collected prior to and during the October 2013 SIA (November 2004-October 2013) in order to estimate the most recent age-specific seroprofile and avoid biasing our estimates of age-specific seroprevalence due to sharp shifts in seroprevalence among the 2013 SIA targeted age groups. A total of 1123 samples were collected from November 2013 to December 2015. By grouping the recent 26 months, we assume monotonic increases

in immunity (natural and vaccinal) over age during this time; this assumption likely holds for natural immunity given low transmission (2); as well as for vaccinal immunity, as vaccination coverage is unlikely to have declined substantially in this time-frame, so our analysis should be robust to this assumption.

Of the 1123 samples collected between November 2013 and December 2015, 20 samples did not contain enough serum to test for measles IgG antibodies, and were removed from the analysis. Samples were removed if the patients' age in years was unknown (3 samples). We removed 17 samples that tested measles immunoglobulin M positive to reduce oversampling of measles seropositive individuals via natural infection that resulted from sampling via febrile-rash surveillance. Samples considered IgG antibody equivocal (antibody concentration between 100 and 200 mIU/mL) were retested; those that remained equivocal (78 samples) were removed from the analysis; although, we also conducted a sensitivity analysis assuming equivocal tests were seronegative. As a result, 1005 samples were used to estimate current age-specific seroprevalence.

Characterization of the data

Identifying sampling biases by age and location is key to understanding the external validity of the data to characterize age-specific seroprevalence. We compared the proportion of samples by age to the expected proportion of samples by age per United Nations Population Division estimates (25). We also investigated the degree to which the 1005 febrile-rash samples were generalizable across space, and

assessed the potential of heterogenous spatial sampling to bias our estimates of measles seroprevalence by comparing spatial variation in sampling to spatial variation in inferred vaccinal immunity. We did not assess potential spatial variation in naturally acquired immunity because i) evidence suggests that recent transmission is low, ii) we removed immunoglobulin M measles positive cases to reduce this bias, and iii) the immunoglobulin M incidence data is insufficient in sample size to assess spatial differences.

Estimates of proportion seropositive by age

We directly estimated seroprevalence by age from the IgG serological data using a non-parametric model with local polynomial estimators, given its flexibility in allowing non-monotonicity ('locfit' library in R (26)) (16) (see Web Appendix 1, Web Figure 1 for details). The estimated total population proportion seropositive was age-adjusted using Madagascar's 2015 population age structure (25).

We compared our direct empirical estimates of age-specific seroprevalence to indirect estimates of the age profile of immunity. The indirect method, developed by (22), estimates the proportion of each birth cohort that is immune based on routine immunization, SIAs, and natural infection. We estimated the proportion of each birth cohort vaccinated from each vaccination opportunity, routine vaccination or SIA, per WHO coverage estimates (4), and estimated the fraction of natural infection over time from estimated measles incidence extracted from (27) (see Web Appendix 2, Web Tables 1-2, Web Figure 2 for details).

Exploring the effect of measles SIA scenarios

We assessed the impact of 16 different SIA scenarios by "administering" each SIA (taking into account vaccination effectiveness) to Madagascar's population, assuming age-specific susceptibility reflects the direct estimates based on the serological data. SIA scenarios differed by the targeted upper age and the assumed vaccination coverage. We included the age group targeted by the 2016 SIA conducted post data collection (9 months through 4 years old) (5), a typically targeted age group (9 months through 14 years old), and two non-classically targeted age groups (9 months through 9 years old, through 19 years old). For each scenario, we analyzed an upper and lower bound of potential vaccination campaign coverage (70% and 95%; based on Madagascar's reported range from the WHO (5), but setting the maximum to 95%, despite reports exceeding 100% due to known over-reporting issues using administrative data (10)). Simulated SIAs assumed independence between SIA vaccination and prior immunity, i.e., all individuals in the target age range had an equal probability of being vaccination by the SIA regardless of immunity status. We assumed SIA vaccine effectiveness by age followed a logistic function modeled on data from (28) saturating at 97%, and no correlation between prior immunity and SIA vaccination.

We used four approaches to evaluate the impact of each SIA scenario. First, we compared estimated population susceptibility levels post SIA to the theoretical susceptibility threshold for elimination. In an unstructured population, the critical

immunity threshold (p_c) required to achieve herd immunity is defined as $p_c = 1 - (1/R_0)$ (29), where R_0 is the basic reproductive number evaluated at 10, 15, and 20 (30); the susceptibility threshold is its complement ($1 - p_c$). The critical immunity threshold does not account for the pattern of transmission and immunity over age. Therefore, we additionally estimated the effective reproductive number, R_{eff}, post SIA (assuming assortative age contacts following (31)) and compared this to the elimination threshold of 1 (30). R_{eff} is the average number of secondary cases per typical infected individual, here estimated using next generation techniques to account for age-specific patterns (32).

The third SIA evaluation approach compared the estimated number of measles cases post SIA to the estimated number of cases if no SIA was implemented. We used a discrete-time deterministic age-structured mathematical model to simulate Madagascar's measles transmission dynamics with and without a SIA following the introduction of an infected individual. Finally, we estimated the number of vaccine doses needed to vaccinate one susceptible individual, accounting for vaccine effectiveness per (28), and accounting for the fact that SIAs target all individuals within an age target regardless of their immunity status. See Web Appendix 3 and 4 for details on scenario evaluation and the age-structured model, respectively.

RESULTS

Data characterization

Of the 1005 samples, we found that individuals less than 15 years old were oversampled (Figure 1a), likely because age is significantly associated with measles seroprevalence (33). Estimated total population immunity was accordingly adjusted for age.

Figure 1b shows evidence of spatial sampling bias: some regions (tinted red) were oversampled, and other regions (tinted purple) under-sampled. However, we find variation in vaccination coverage is unlikely to be an important driver of variation in the number of samples per region because the sampling ratio by region (Figure 1b) and the vaccination ratio by region (Figure 1c) are not correlated (see Web Appendix 5, Web Figure 3).

Age-specific measles susceptibility profiles

Direct and indirect estimates of immunity differed over age (Figure 2; see Web Appendix 6 and Web Figure 4 for sensitivity analysis assuming equivocal tests were seronegative). The blue line and shaded light blue area represents the mean and 95% confidence interval of direct estimates of the age profile of immunity fit to serological data. Over 40 years old, everyone sampled tested seropositive for measles. Prior to this age, there was a general increase in the proportion of individuals seropositive over age with an exception around 13-years, where there was a drop in immunity. The indirect method, represented by the green dashed line, estimated 95% immunity among ages 8 to 26 years as a result of routine measles vaccination and frequent SIAs, and a large pocket of susceptible individuals aged 27

to 32 years. This encompasses individuals who were not eligible for any SIAs, who were exposed to low estimated routine coverage during childhood, and for those individuals missed by the routine vaccine, were potentially also exposed to low measles transmission throughout their childhood and adolescence via indirect protection (see Web Appendix 2 for details on how past transmission was discounted during vaccination years).

Despite differences in direct and indirect estimates of immunity by age, both suggest overall high population susceptibility in Madagascar as of 2015. Using the direct method, we estimated that 83.2% of Madagascar's current population was immune to measles (95% confidence interval: 74.7%, 87.7%). The indirect estimate of the proportion immune (88.9%) fell just outside the 95% confidence interval. Both imply that population immunity in Madagascar is below the simple unstructured estimate of the critical threshold for herd immunity (90-95%) (3). Additionally, direct estimates of R_{eff} surpass the elimination threshold of 1 (ranging 1.7-6.0; Figure 3A, 3B, 3C, black squares). These results suggest that Madagascar may be at risk of a significant measles outbreak (34, 35).

The effect of measles SIA scenarios

The SIA conducted in late 2016 among children through 4 years old may have been insufficient to reduce the risk of a measles outbreak in Madagascar given that our estimates of R_{eff} remains above 1 post-SIA (Figure 3A, 3B, 3C, purple lines). The model indicates that, were a measles outbreak to start, measles cases will be

reduced by at most 29.2% with the designed SIA, compared to if no SIA was administered. Overall, extending the vaccination campaign to include more ages would result in a larger reduction in the proportion of susceptible individuals and a lower R_{eff} (Figure 3A, 3B, 3C). Our analysis suggests that a SIA campaign targeting children 9 months old through 14 years old best balances cases prevented per vaccine dose administered and total case numbers; it would successfully vaccinate a susceptible person per every 3 to 5 doses delivered and would reduce the number of measles cases in a measles outbreak between 66% and 100%, depending on R_0 and the true starting age immunity profile (Figure 3D, 3E, 3F). This finding is the result of the unusual gap in measles immunity directly estimated between ages 10 and 15 years (Figure 2). These results were qualitatively robust to assuming age-contact matrix reflecting the six countries assessed in the European POLYMOD diary study (31).

Assuming R_0 was 20, resulted in general agreement between the two elimination thresholds (proportion susceptible < $(1 - p_c)$ and $R_{eff} < 1$) in their evaluation of the impact of SIA scenarios (Figure 3C). However, for lower values of R_0 (10 and 15), we find scenarios in which the estimated R_{eff} was greater than 1 post-SIA, even though the population proportion susceptible was less than $(1 - p_c)$ post-SIA (Figure 3A, 3B).

DISCUSSION

Over the past decade, Madagascar has reported low numbers of measles cases and high SIA vaccination coverage; but how this translates into population immunity and its pattern over age has not previously been described. Serological data can be used to directly estimate the age-specific seroprevalence and discern whether susceptibility remains below the theoretical critical threshold to sustain elimination or whether the population is at risk of a measles outbreak (16, 36, 37). Here, we leveraged existing serum samples by conducting a nested serosurvey within Madagascar's febrile-rash surveillance system, avoiding the financially and logistically challenging features of a nationally representative serosurvey (38). Age-structured mathematical models, in combination with age-specific seroprevalence estimates, are then used to explore the impact of different SIA designs to contain the risk of a measles outbreak (39, 40).

While neither our direct or indirect estimates can be validated as true, as the former is affected by the fact that a sample based on passive febrile-rash surveillance is potentially non-representative, and the latter is affected by uncertainty and known biases in vaccination coverage data (10) and incidence data (27), both the indirect and direct estimates suggest that Madagascar may be at risk of a measles outbreak (29, 34, 35, 41).

The differences in the age profiles of immunity between methods highlight gaps in our understanding of vaccination programs. In particular, direct estimates obtained from the serological data suggests that the 2004 SIA was heterogeneously applied

across ages, an important and yet rarely described feature of this type of intervention. Peak vaccination coverage of the 2004 SIA appears to have been achieved for children whose age was around the middle of the target age range, and dropped for children at the bottom and top of the target age ranges. The direct estimates also showed no increased probability of being immune in children targeted by the 2007 SIA, potentially suggesting overestimated SIA coverage. Madagascar experienced a political crisis in 2009 that may have negatively impacted routine measles vaccination, potentially explaining the beginning of decline in immunity after 5 years old as of 2015.

Our analysis also provides an important window into evaluating recent measles immunization policy. Madagascar conducted a measles SIA in October 2016 among children aged 9 months through 59 months, with reported 96% coverage (5). While our model assumed spatial homogeneity in R_0, and that individuals were will mixed across Madagascar (since necessary data to estimate this was not available), so that measles outbreak size will be over-estimated, differences relative to the absence of a campaign are likely to be broadly informative of SIA impact. Our results suggest that the 2016 SIA was insufficient to reduce the risk of a measles outbreak given high estimated susceptibility among ages outside the target age range. Rather a SIA targeting children through 14 years old would further decrease potential outbreak size while successfully vaccinating the most susceptible individuals per dose delivered. Fortunately, there is an opportunity to conduct an SIA of this magnitude in the near future. Madagascar is considering introduction of the rubella-containing

vaccine which, if eligible for financial support from Gavi the vaccine alliance, would include a measles-rubella vaccination campaign targeting children 9 months through 14 years old (42).

In order to explore the relevance of heterogenous age immunity and transmission on the effect of SIAs, we compared two different elimination thresholds (proportion susceptible < $(1 - p_c)$ and $R_{eff} < 1$) and found that age-specific transmission increasingly affected outbreak potential as measles transmission (R_0) decreased. In Madagascar, evidence suggests that the R_0 for measles may in fact be low (10-15), given high estimated measles susceptibly, and inferred low transmission. Therefore, age-specific transmission may play a significant role in understanding and maintaining measles elimination in Madagascar. This result may also more broadly applicable in settings where successful vaccination programs have reduced measles transmission, such that finer scale age contact data and analysis may be required to achieve appropriate targeting as countries move closer to elimination.

There are a number of limitations and assumptions in this analysis. The non-probability sample via the febrile-rash passive surveillance system may misrepresent measles seroprevalence at the country level. For example, following vaccination, up to 5% of individuals may experience transient fever or rash (43), such that febrile-rash surveillance may oversample measles vaccinated individuals, biasing seroprevalence estimates upwards. Non-generalizability of serological samples collected and sent for testing may also play a role in biasing estimates of

measles immunity. A problematic systematic bias might emerge if healthcare workers used knowledge of a patients' past vaccination record (via recall or vaccination card) to inform their diagnosis and decision to collect and send serological samples, rather than abiding by the febrile-rash surveillance guidelines. This would result in fewer samples from vaccinated individuals and a potential over-estimation of measles susceptibility in Madagascar.

In this analysis, we corrected for age sampling bias by age-adjusting estimates of population susceptibility. However, we are unable to correct for age bias if under-sampling of older individuals resulted in insufficient power to correctly estimate measles immunity for these ages. We additionally assessed the potential for spatial sampling bias on estimates of the age profile of vaccinal immunity. We found that the febrile-rash surveillance system sampled vaccination coverage and connected areas representatively across regions on average, suggesting this may not be an important source of bias. This paper is the first to demonstrate the use of a nested IgG serosurvey within febrile-rash surveillance systems to assess population immunity. However, much work remains to assess the external validity of this data source.

Measles IgG serological surveys provide a direct measure of an age immunity profile to identify susceptible ages and inform the need for SIAs. Despite age-specific differences in seroprevalence, both our direct and indirect estimates of total proportion immune suggested high measles susceptibility as of 2015. Building on

these direct estimates by modeling measles transmission dynamics and their variability across age, our simulated results suggest Madagascar is at risk of a measles outbreak. Madagascar's measles control program must remain vigilant to reduce the number of susceptible individuals via vaccination and reduce the risk of outbreaks.

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REFERENCES

1. Plotkin S, Orenstein W, Offit P eds. Vaccines, 6th Edition. Philadelphia, PA: Elsvier, 2013.
2. CDC. Progress Toward Measles Elimination - African Region, 2013-2016. *Morbidity and Mortality Weekly Report* 2017;66(17):436-443.
3. World Health Organization. Measles vaccines: WHO position paper. *Wkly Epidemiol Rec* 2009;84(35):349-360.
4. World Health Organization, UNICEF. Estimates of National Immunization Coverage (WUENIC), estimates for 1980 to 2016. Geneva; 2017. (http://www.who.int/immunization/monitoring_surveillance/data/en/). (Accessed May 21 2018).
5. World Health Organization. Retrospective Measles Data on Supplementary Immunization Activities, 2000-2015. Geneva: WHO/IVB Database; 2016. (http://www.who.int/immunization/monitoring_surveillance/data/en/). (Accessed May 21 2018).
6. World Health Organization. WHO vaccine-preventable diseases: monitoring system. 2017 global summary - Incidence time series for Madagascar (MDG). 2017. (http://apps.who.int/immunization_monitoring/globalsummary/incidences?c=MDG). (Accessed September 1 2017).
7. McLean AR. After the honeymoon in measles control. *Lancet* 1995;345(8945):272.
8. Verguet S, Johri M, Morris SK, et al. Controlling measles using supplemental immunization activities: a mathematical model to inform optimal policy. *Vaccine* 2015;33(10):1291-1296.
9. Cutts FT, Hanson M. Seroepidemiology: an underused tool for designing and monitoring vaccination programmes in low- and middle-income countries. *Trop Med Int Health* 2016;21(9):1086-1098.
10. Cutts FT, Izurieta HS, Rhoda DA. Measuring coverage in MNCH: Design, implementation, and interpretation challenges associated with tracking vaccination coverage using household surveys. *PLoS Med* 2013;10(5).
11. 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(10).
12. CDC. Measles Outbreaks and Progress Toward Measles Pre-elimination --- African Region, 2009--2010. *Morbidity and Mortality Weekly Report* 2011;60(12):374-378.
13. Minetti A, Kagoli M, Katsulukuta A, et al. Lessons and challenges for measles control from unexpected large outbreak, Malawi. *Emerg Infect Dis* 2013;19(2):202-209.
14. 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(33):5000-5008.

15. Luquero FJ, Pham-Orsetti H, Cummings DAT, et al. A Long-Lasting Measles Epidemic in Maroua, Cameroon 2008-2009: Mass Vaccination as Response to the Epidemic. *J Infect Dis* 2011;204:S243-S251.
16. Hens N, Shkedy Z, Aerts M, et al. *Modeling infectious disease parameters based on serological and social contact data : a modern statistical perspective*. New York, NY: Springer; 2012.
17. Metcalf CJE, Farrar J, Cutts FT, et al. Use of serological surveys to generate key insights into the changing global landscape of infectious disease. *The Lancet* 2016;388(10045):728-730.
18. Trentini F, Poletti P, Merler S, et al. Measles immunity gaps and the progress towards elimination: a multi-country modelling analysis. *Lancet Infect Dis* 2017;17(10):1089-1097.
19. Massad E, Burattini MN, de Azevedo Neto RS, et al. A model-based design of a vaccination strategy against rubella in a non-immunized community of Sao Paulo State, Brazil. *Epidemiol Infect* 1994;112(3):579-594.
20. Prada JM, Metcalf CJ, Takahashi S, et al. Demographics, epidemiology and the impact of vaccination campaigns in a measles-free world - Can elimination be maintained? *Vaccine* 2017;35(11):1488-1493.
21. Heesterbeek H, Anderson RM, Andreasen V, et al. Modeling infectious disease dynamics in the complex landscape of global health. *Science* 2015;347(6227):aaa4339.
22. Takahashi S, Metcalf CJ, Ferrari MJ, et al. Reduced vaccination and the risk of measles and other childhood infections post-Ebola. *Science* 2015;347(6227):1240-1242.
23. Cohen BJ, Parry RP, Doblas D, et al. Measles immunity testing: comparison of two measles IgG ELISAs with plaque reduction neutralisation assay. *J Virol Methods* 2006;131(2):209-212.
24. Ruckdeschel JC, Graziano KD, Mardiney MR, Jr. Additional evidence that the cell-associated immune system is the primary host defense against measles (rubeola). *Cell Immunol* 1975;17(0008-8749 (Print)):11-18.
25. United Nations. World Population Prospects: The 2015 Revision, DVD Edition. 2015. (https://esa.un.org/unpd/wpp/Download/Standard/Population/). (Accessed May 21 2018).
26. Loader C. *Local Regression and Likelihood*. New York: Springer; 1999.
27. 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(9832):2173-2178.
28. Boulianne N, De Serres G, Ratnam S, et al. Measles, mumps, and rubella antibodies in children 5-6 years after immunization: effect of vaccine type and age at vaccination. *Vaccine* 1995;13(16):1611-1616.
29. Fine PE. Herd immunity: history, theory, practice. *Epidemiol Rev* 1993;15(2):265-302.
30. Anderson RM, May RM. *Infectious Diseases of Humans: Dynamics and Control*. New York, NY: Oxford University Press; 1991.

31. Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS Med* 2008;5(3):381-391.
32. Klepac P, Caswell H. The stage-structured epidemic: linking disease and demography with a multi-state matrix approach model. *Theor Ecol* 2011;4(3):301-319.
33. Grenfell BT, Anderson RM. The Estimation of Age-Related Rates of Infection from Case Notifications and Serological Data. *J Hyg (Lond)* 1985;95(2):419-436.
34. Anderson RM, May RM. Age-Related-Changes in the Rate of Disease Transmissions - Implications for the Design of Vaccination Programs. *J Hyg (Lond)* 1985;94(3):365-436.
35. Moss WJ, Griffin DE. Global measles elimination. *Nat Rev Microbiol* 2006;4(12):900-908.
36. Gay NJ, Hesketh LM, Morgancapner P, et al. Interpretation of serological surveillance data for measles using mathematical-models - Implications for vaccine strategy. *Epidemiol Infect* 1995;115(1):139-156.
37. Vyse AJ, Gay NJ, Hesketh LM, et al. Interpreting serological surveys using mixture models: the seroepidemiology of measles, mumps and rubella in England and Wales at the beginning of the 21st century. *Epidemiol Infect* 2006;134(6):1303-1312.
38. WHO Regional Office for Europe. Guidance on conducting serosurveys in support of measles and rubella elimination in the WHO European Region. 2013. (http://www.euro.who.int/__data/assets/pdf_file/0011/236648/Guidance-on-conducting-serosurveys-in-support-of-measles-and-rubella-elimination-in-the-WHO-European-Region.pdf?ua=1). (Accessed April 26, 2018).
39. Gay N, Ramsay M, Cohen B, et al. The epidemiology of measles in England and Wales since the 1994 vaccination campaign. *Commun Dis Rep CDR Rev* 1997;7(2):R17-21.
40. Nigatu W, Samuel D, Cohen B, et al. Evaluation of a measles vaccine campaign in Ethiopia using oral-fluid antibody surveys. *Vaccine* 2008;26(37):4769-4774.
41. Kermack WO, McKendrick AG. Contribution to the mathematical theory of epidemics. *Proceedings of the Royal Society of London Series a-Containing Papers of a Mathematical and Physical Character* 1927;115(772):700-721.
42. GAVI Alliance. Measles-rubella vaccine support. 2014. (http://www.gavialliance.org/support/nvs/rubella/). (Accessed August 1 2014).
43. Duclos P, Ward BJ. Measles vaccines: a review of adverse events. *Drug Saf* 1998;19(6):435-454.
44. Tatem AJ, Garcia AJ, Snow RW, et al. Millennium development health metrics: where do Africa's children and women of childbearing age live? *Population Health Metrics* 2013;11.
45. WorldPop. (www.worldpop.org). (Accessed May 1 2018).
46. Institut National de la Statistique Madagascar, ICF Macro. Enquête Démographique et de Santé Madagascar 2008-2009. Antananarivo,

Madagascar 2010. (https://dhsprogram.com/pubs/pdf/FR236/FR236.pdf). (Accessed April 26 2018).

Figure 1: The febrile-rash surveillance serological samples by age and region. A) The population and sample age structure by 5-year age groups, the sample age distribution is represented by the grey bars (N=1005), and the population age distribution (based on UNPD data (25)) is represented by the hollow black bars. Younger ages (<15 years old) are over represented in the sample. B) The sampling ratio of observed to expected samples (i.e., the proportion of samples from each region (N=1005) divided by the proportion of Madagascar's population that resides in each region (44, 45). The regions in red tints were oversampled. C) The vaccination ratio of observed to expected measles vaccination coverage (i.e., measles vaccination coverage by region divided by the national measles vaccination coverage, which is 0.69 (4, 46)). The central plateau and some eastern regions report the highest vaccination coverage.

Figure 2: Direct and indirect estimates of proportion measles seropositive by age. The black dots represent the observed seroprevalence per age in months based on the nested serological data (N=1005), where the size of the dots corresponds to the number of samples for each age in months. The blue solid and light blue shaded areas represent the mean and 95% confidence interval (CI) of the directly estimated proportion seropositive based on the serological data, and shows a general increase in seroprevalence with age with the exception of a dip around age 13 years old. The dashed green line represents the indirect estimates of proportion seropositive by age based on the birth cohort projection method. The four SIAs conducted prior to 2015, including a 2004 SIA that targeted children ages 9 month through 14 years old, had a large impact on indirectly inferred immunity (see Web Appendix 1 for history of SIAs). The indirect method estimates high immunity in children and adults up to age 25 and a large pocket of susceptibility for those ages just outside the 2004 SIA targeted age group.

Figure 3: The Impact of a SIA on proportion susceptible, R_{eff}, campaign efficiency, and outbreak size. Using an age-structured model informed by the direct age-specific seroprevalence estimates we evaluated the impact of each Supplemental Immunization Activity (SIA). A-C) We compared the proportion of the population susceptible (x-axis) to R_{eff} (y-axis) for assumed R_0 values of 10 (A), 15 (B), and 20 (C), one week following the implementation of measles SIA scenarios (age target lower age of 9 months old (mo) through upper ages of 4, 9, 14, and 19 years old (yo)). For reference, the black dashed lines indicate the thresholds of $R_{eff}=1$ and susceptibility threshold ($1-p_c$). Colors indicate the campaign age targets including if no SIA was conducted (the purple line specifically representing the 2016 SIA which targeted children through 4 years old). Thick lines indicate the expectation for the directly estimated mean age profile, solid and dotted thin lines correspond to the upper and lower confidence bounds of the directly estimated age profile, respectively. Lines span the range of outcomes for coverage rates of 70-95% (right to left on the lines) for each SIA. We found that for all values of R_0, broader age ranges (i.e., up to 14 or 19 years old) were necessary to achieve R_{eff} less than 1. If R_0 was 10 or 15, we found disagreement between the two evaluated elimination thresholds (proportion susceptible < ($1-p_c$) and $R_{eff} < 1$) in their evaluation of the

impact of SIA scenarios. D-F) We compared the estimated percent reduction in the number of measles cases over time (x-axis) and campaign efficiency (number of doses delivered to successfully vaccinate 1 susceptible individual; y-axis) for assumed R_0 values of 10 (D), 15 (E), and 20 (F), across measles SIA scenarios (age target lower age of 9 mo through upper ages of 4, 9, 14, and 19 yo). Colors indicate the campaign age targets (the purple line specifically representing the 2016 SIA which targeted children through 4 years old). Thick lines indicate the expectation for the directly estimated mean age profile, solid and dotted thin lines correspond to the upper and lower confidence bounds of the directly estimated age profile, respectively. Lines span the range of outcomes for coverage rates of 70-95% (left to right on the lines) for each SIA. We found that a SIA campaign that targeted children through 14 years old is the most efficient at deploying dosages to susceptible individuals while also reducing a large percentage of cases.