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Towards better targeting: lessons from a posthoneymoon measles outbreak in Madagascar, 2018–2019

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Summary box

- After many years of very low measles incidence, a measles outbreak began in the central region of Madagascar in September 2018.
- The outbreak reached all 22 regions of the island, causing nearly 1000 deaths, with more than 100 000 cases reported.
- The magnitude of the outbreak, the age profile of cases and the history of incidence and vaccination in Madagascar align with a core expectation from epidemiological theory, the concept of a 'posthoneymoon period' outbreak where large outbreaks can occur following years of (apparently) successful control.
- An emergent important public health challenge is how to characterise the risk of post-honeymoon outbreaks for measles and other vaccine preventable infections, and how to learn from this outbreak to build preparedness for future outbreak prevention and response strategies.
- Madagascar's experience indicates that investment in relevant data streams (from case surveillance, to vaccination deployment and serology) alongside efforts to develop national capacity for integrative analysis of such diverse data could help enable deployment of timely targeted vaccination campaigns to prevent such outcomes in the future.

MEASLES AND OUTBREAK RISK

Measles vaccination is often referred to as a 'best buy' in public health, because of the high case fatality rate associated with infection, alongside the existence of a safe and inexpensive vaccine. The current WHO recommendation is that all children have access to two doses of the measles vaccine.[1] In 2011, countries in the WHO African region adopted a measles elimination goal to be reached by 2020. In the last decades, substantial gains have been made in numbers of cases and deaths averted. Yet, an important feature of measles epidemiology is that large outbreaks can occur following years of (apparently) successful control. This phenomenon is known as a 'posthoneymoon period' outbreak.[2] The 'honeymoon' consists of the period following vaccine introduction where cases drop substantially. This 'honeymoon' is at risk of ending in an outbreak if vaccination coverage is subsequently suboptimal. Every year, children born into the population that are left unvaccinated are also unlikely to experience immunisation by natural infection, because measles incidence is low. These children, thus, remain susceptible to measles, and over the years, as children are born and left unvaccinated, susceptible individuals accumulate in the population, across the range of ages reflecting cohorts born during the low incidence years. Once the size of the susceptible pool exceeds the threshold for herd immunity (defined as the proportion susceptible in the population exceeding $1/R_0$ where R_0 is the number of new infections per susceptible individual in a completely susceptible population, which may be as high as 20 for measles[3]), a new outbreak can take hold, and it will grow at a speed defined by the effective reproductive number $R_E=R_0S$ where S is the proportion of the population that is susceptible.

THE CONTEXT OF THE OUTBREAK

Since 2004, the number of measles cases reported in Madagascar had plummeted from tens of thousands of annual cases to fewer than 20 confirmed cases per year.[4] This drop in cases followed a successful expansion of the immunisation programme (figure 1A) in which consistent (although low) routine

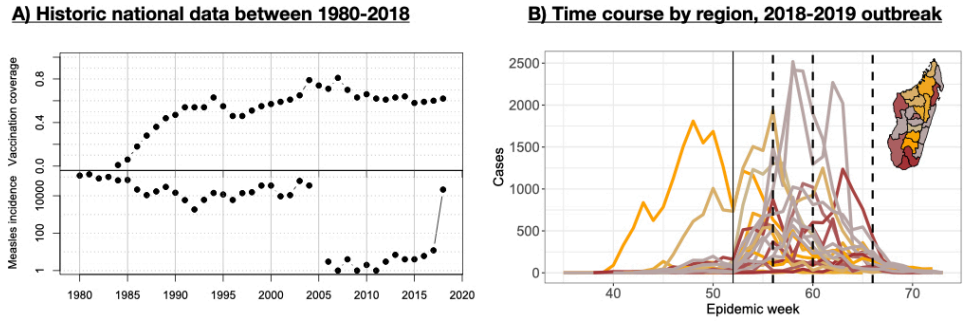

Figure 1 Historical context of measles in Madagascar and the recent outbreak (A) measles first dose vaccination coverage estimates from UNICEF (y-axis, top) and measles incidence from who (y-axis, log scale, bottom) from 1980 to 2018 (x-axis), showing a sharp decline in cases in 2005 with 10 or less cases in each years following 2005 until the start of the focal outbreak in 2018 when more than 21 000 cases reported; (B) time series of suspected cases (y-axis) against time (indicated epidemic week starting in 2018, thin vertical line shows the separation between 2018 and 2019) from the 2018 to 2019 line-list data in each of the 22 regions, coloured by the timing of the peaks (orange is earliest, grey intermediate, and brown latest); dashed vertical lines indicate the approximate timing of the three waves of vaccination (different districts were targeted in each wave, see text); inset shows the regions of Madagascar coloured as for the time series (orange is the earliest peaks, grey intermediate and brown the latest).

measles vaccination coverage (between 55% and 85%) was combined with vaccination campaigns targeting ages from 9 months to 14 years (in 2004) or 9 months to 4 years (in 2007, 2010, 2013, 2016).[5] The combination of low incidence and the potential for incomplete vaccination coverage over a number of years suggested that Madagascar might have a large susceptible population distributed across a wide age range, yielding potential for a wide age range, fast-growing outbreak.

THE SCALE, AGE RANGE AND EARLY GROWTH OF THE OUTBREAK

In September 2018, a cluster of laboratory-confirmed measles cases was detected via Madagascar's national febrile/rash surveillance system for measles and rubella, whereby local health centres send samples taken from suspected cases in to the national reference lab in Antananarivo.[6–8] At that time, the positivity rate of measles suspected cases reached 2.12% every year compared with an average of 0.54% during the last previous 5 years (ranged from 0.22% to 0.95%). By October 2018, increasing numbers of measles cases were detected by the health system (figure 1B). Subsequently, over 100 000 suspected cases were reported, with 37% of the 2930 tested individuals being confirmed measles cases.[8] The outbreak began on the highlands in the region of Analamanga (province of Antananarivo) and spread to every region in the country (online supplemental figure S1).

Typically, in the absence of vaccination, the average age of measles infection ranges from 2 to 5 years. In the 2018–2019 Madagascar outbreak, the average age of infection in suspected cases was 9 years (and rates of laboratory confirmation did not vary over age, see online supplemental text). Regionally, there was a significant positive correlation between the average age of infection and vaccination coverage in 2009 (figure 2A, $\rho = 0.61, n = 22, p < 0.005$). Regions with higher vaccination coverage should have smaller numbers of infected individuals, and, as a result, encounters between susceptible individuals and infected individuals in the years preceding the outbreak will also have been rare. Unvaccinated (and unimmunised) individuals could thus remain susceptible for longer in regions with historically high vaccination rates, leading to pools of older susceptible individuals and a higher average age of infection (figure 2A). Following the logic of a 'honeymoon' described above, the balance between immunisation achieved by vaccination, and reduced immunisation resulting from declines in natural infection over the years preceding the outbreak, might even be tilted such that regions with higher vaccination coverage might also have larger pools of susceptible individuals. This could allow faster epidemic growth in these regions. Comparing the early growth of the epidemic estimated using R_E (or the number of new infections per infectious individual[6]) indicates that, indeed, the outbreak grew faster in some regions with historically high levels of vaccine coverage (figure 2B).

THE OUTBREAK RESPONSE

In October 2018, rapidly growing case numbers in the Analamanga region (where the capital city of Antananarivo is located) prompted deployment of a vaccination campaign across a limited spatial extent (four health districts of the urban community of Antananarivo) targeting children up to 5 years of age. The history of incidence (figure 1A) and the age profile of cases in the first weeks further suggested that the age range at risk might extend up to 15 years. However, the resources necessary to deploy an outbreak response of the scale indicated (national vaccination, reaching up to 15 years old) were lacking. Coordinating funds from across the donor community (including the Measles and Rubella Initiative, the African Development Bank Group, the Central Emergency Response Fund, etc) took time, even as the outbreak was progressing. Given these delays, the decision was made to initially target for vaccination

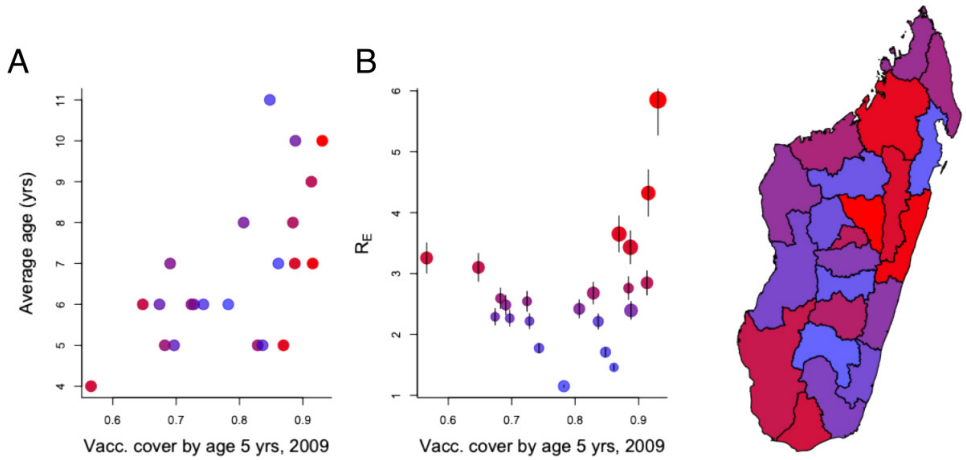

Figure 2 Outbreak characteristics. (A) Measles vaccination coverage at 5 years in each of the 22 regions estimated from Madagascar's 2009 Demographic and Health Survey (x-axis) plotted against (A) the median age distribution of cases (y-axis) and (B) the R_E of the outbreak in each region (y-axis). On both plots, regions with higher r_E are shaded from blue to red; and these are also shown in the MAP, to indicate fastest early growth of the outbreak in central/norther regions. Two regions (Androy and Atsimo Andrefana) have high r_E despite low vaccination coverage (red points to the left of B). Regional connectivity might be sufficiently low in these remote locations that even at low vaccination coverage, local extinction occurs, allowing susceptible build-up, or vaccination coverage in 2009 might provide a poor proxy for changes over the intervening decade.

individuals up to 10 years of age, and 25 of the most urban and highly connected districts (out of a total 114 districts across the country); and then to follow-up as resources could be mobilised. In all, the outbreak response included three waves of vaccination (14–18 January 2019, 18–22 February 2019 and 25 March–5 April 2019) (figure 1B, online supplemental figure S1 and table S1), eventually reaching all districts.

Three things determine the success of outbreak response vaccination campaigns: (1) the coverage achieved; (2) the timing of the campaign relative to the time course of the epidemic[9] and (3) the age range targeted.[10] The outbreak response aimed to achieve high coverage, and was deployed as fast as possible along lines shaped by the practical considerations detailed above. Nevertheless, time series of suspected cases suggest that in many regions, waves of vaccination occurred after susceptible depletion had started to reduce spread (figure 1, online supplemental figure S1). The decision was made to target children up to 10 years of age because of a lack of funds, which may have missed a fraction of the susceptible population (online supplemental figure S3, across the country 36% of cases occurred in children aged over 10 years of age).

STRENGTHENING THE RESPONSE

Many lines of evidence suggest that Madagascar experienced a 'posthoneymoon' measles outbreak. An obvious and critical public health question is whether we can identify that a country is experiencing a 'honeymoon period'. This would allow the public health sector to anticipate, and perhaps even avert the outbreak by laying the groundwork for vaccination campaigns, or outbreak response vaccination. The experience of Madagascar underscores that there are rich opportunities to leverage existing data to this end. This outbreak reflects an important missed opportunity—existing data could have been better exploited to position human, financial and health resources ahead of the response. First, data on vaccination coverage,[7] historical incidence[4] and local demography[11] can be combined with mathematical models to define outbreak risk, building increased specificity into existing approaches. Critically, such efforts should occur in tandem with approaches to strengthen the quality and spatial and temporal resolution of these sources of information. Indeed, in 2017, analysis via the WHO Measles Programmatic Risk Assessment tool (which can be explored here[12]), which integrates spatially resolved indicator scores on population immunity, surveillance quality and programme performance in the last 3 years had first suggested that the risk of an outbreak was large, a concern amplified by various lines of evidence suggesting generalised system weaknesses. However, part of this system weakness was associated with data quality issues, which complicated interpreting the results and launching a response. Second, existing convenience serological samples (eg, fever-rash surveillance for which samples are already available) could be leveraged to test for population immunity to measles. This approach had been applied to existing fever-rash surveillance in Madagascar, and did indeed suggest important outbreak risk in Madagascar prior to 2018 outbreak,[6] as a result of accumulation of susceptible individuals resulting from a combination of low circulation and incomplete vaccination coverage. However, convenience samples of this type are generally spatially variable, and thus may be non-representative. Thus, third, small-scale targeted serological surveys designed to be representative and requiring novel sample

collection to ground-truth local population immunity (eg, as currently done in Madagascar to evaluate the HIV situation among specific groups) could provide an important further line of evidence. Such surveys could either be deployed in particular scenarios (eg, towards suspected regions of vulnerability), or routinely (eg, associated with 'vaccination weeks', brief campaigns occurring biannually and an important part of the vaccine delivery system in Madagascar[7]). Mathematical models suggest that obtaining data on the immunity status of even a small fraction of the population could yield critical information as to outbreak risk,[13] noting, however, that the added value of a serological survey relative to existing information should be seriously evaluated.[14] Finally, the themes addressed so far focus on approaches to anticipating and thus mitigating the outbreak by ensuring population immunity. Another important aspect is in readiness for outbreak response. On the logistical side, an important barrier to the response was lack of coordination across core partners. In the wake of both this outbreak and the recent plague outbreak, Madagascar has taken steps to address this with the development of a special committee including governmental, non-governmental and technical partners with remit to manage outbreak responses.

MEASLES CONTROL IN MADAGASCAR: NEXT STEPS

Madagascar experienced up to a decade of low measles circulation prior to this outbreak (figure 1). Most cities and towns in Madagascar are below the 'Critical Community Size'—a threshold population size that measles requires to persist without stochastic extinction[15]—making local measles extinction likely, particularly with growing vaccination coverage (figure 1). These features make measles elimination in Madagascar seem relatively tractable. Furthermore, as an island, risks of measles reintroduction following elimination are also reduced.[16] Beyond these general features, the current context may be particularly propitious for measles elimination. Following the 2018–2019 measles outbreak, population immunity will be high (since so many people were infected, and with the large-scale vaccine catch up efforts). The population is also likely to be sensitised to the risks of measles given the high burden recently imposed. It could be a propitious time to add a second dose of measles-containing vaccine to Madagascar's childhood immunisation schedule (as suggested by WHO[1]).

However, it is increasingly recognised that effective control or elimination efforts need community support, particularly for communities whose experience of vaccination efforts may otherwise seem divorced from the realities of their needs (eg, following polio elimination efforts). Given this context, expanding local capacity to integrate available data streams and generate high-resolution maps of risk will make it possible to deploy much more effectively vaccination efforts by targeting specific regions and/or age groups rather than as homogeneous national campaigns.[17] As well as reducing costs, such targeting could limit repeated revaccination of already immunised individuals, and are likely be easier to communicate to communities. Developing national capacity for such analyses will have benefits for pathogens beyond measles, and is an important direction for future investment and innovation in Madagascar. The foundations for this are being laid, as currently evidenced by integration of public health data-streams within the District Health Information System 2, to innovation emerging from academic and non-governmental organisations partners in Madagascar like the Malagasy-led development of a COVID-19 dashboard (www.covid19mg.org). Although there have been large global and national gains in measles control and elimination, delayed vaccination campaigns, interrupted routine services and downscaling of laboratory/virological surveillance, especially in the context of the current COVID-19 pandemic, make developing strategies to strengthen prediction of outbreaks and identify optimal strategies to combat them a policy priority.

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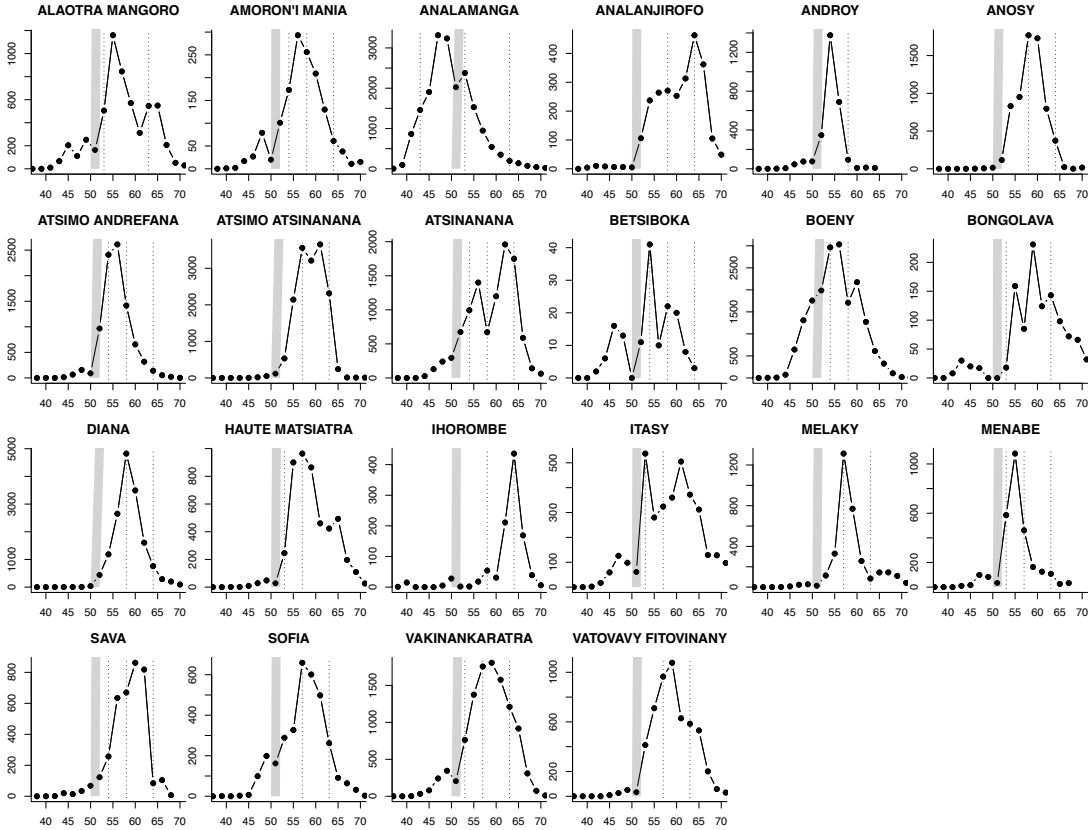

Figure S2: A) Measles age-specific seroprevalence by province in 2014-2015 based on residual febrile/rash samples. B) Total number of measles suspected cases by age in the 2018-19 outbreak by province.

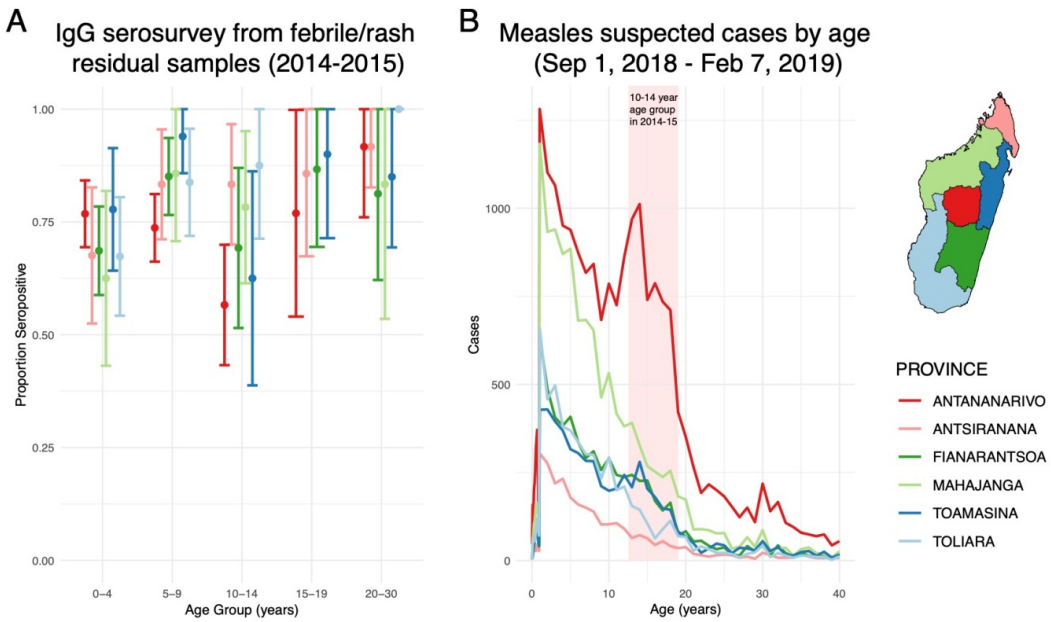

Figure S3: The age range of reported cases is relatively invariant over the course of the outbreak (x axis is time in weeks since the start of 2018, y axis is age in years, colour indicates the proportion of cases concentrated at each age over time, vertical black line indicates Christmas 2018). A fitted generalized additive model of age as function of week for each region (or province) revealed only very slight changes in age over the course the outbreak, associated with very small fractions of the variation explained (<1% across scenarios). Cases occur in individuals aged >10 years, the upper range targeted by vaccination (horizontal grey line).

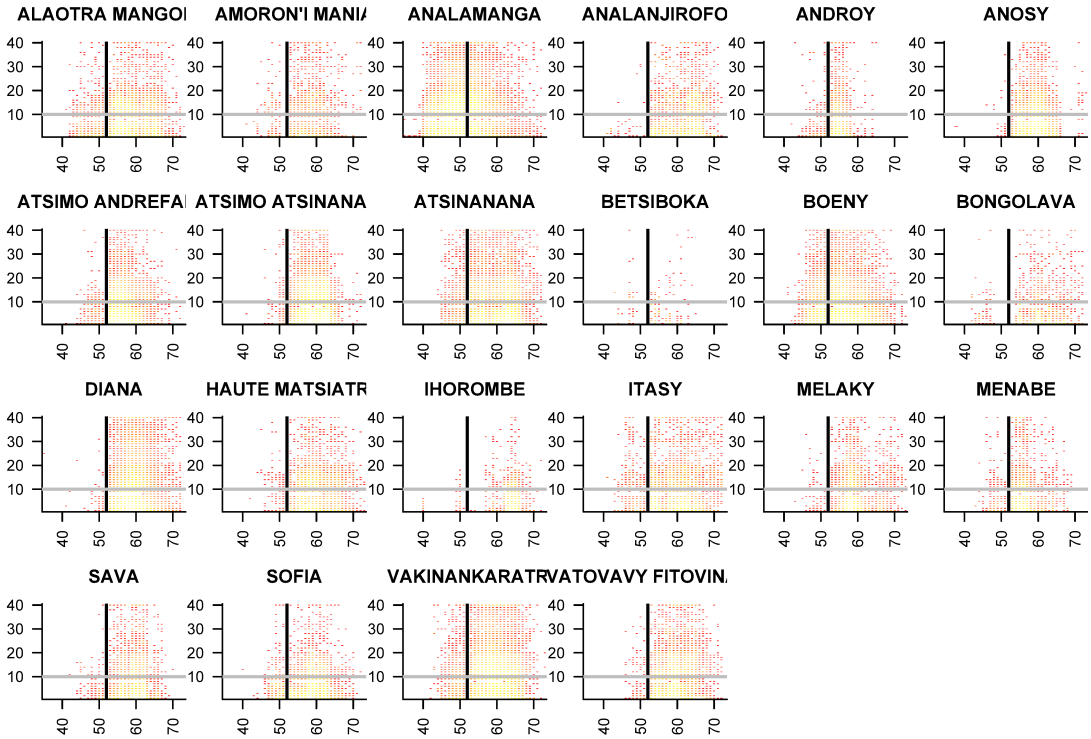

Table S1: **Expected coverage by region in each of the three waves of vaccination.** All districts within each of the regions of Madagascar were ultimately targeted (i.e., by April), with a known subset of districts targeted within each wave of vaccination. To understand the degree to which vaccination might have been concentrated early/late within each region, and in the absence of more fine scale information, we assumed that vaccination coverage reached the same fraction of the target population within each district. From this assumption, the fraction of each region reached within each wave can be captured by knowing the fraction of the population of that region that lives in the districts targeted in each wave (ignoring the nuance of age distributions, given all the other sources of uncertainty). We used estimates of the population size distribution across districts from worldpop.org.uk to obtain the proportion of each region targeted in each wave.

Region	Jan wave	Feb wave	Mar/April wave
ALAOTRA MANGORO	0.84	0	0.16
AMORON I MANIA	0.37	0.28	0.35
ANALAMANGA	0.90	0	0.10
ANALANJIROFO	0	0.51	0.49
ANDROY	0	1.00	0
ANOSY	0	0.40	0.60
ATSIMO ANDREFANA	0.11	0.78	0.12
ATSIMO ATSINANANA	0	0.94	0.06
ATSINANANA	0.40	0.30	0.30
BETSIBOKA	0.51	0.42	0.07
BOENY	0.50	0.50	0
BONGOLAVA	0.72	0	0.28
DIANA	0	0.85	0.15
HAUTE-MATSIATRA	0.16	0.84	0
IHOROMBE	0	0.65	0.35
ITASY	0.41	0.59	0
MELAKY	0	0.61	0.39
MENABE	0.20	0.67	0.13
SAVA	0.23	0.51	0.25
SOFIA	0	0.54	0.46
VATOVAVY FITOVINANY	0	0.72	0.28
VAKINANKARATRA	0.67	0.11	0.22

Supplementary text.

Many lines of evidence suggest the outbreak was driven by late age immunity gaps. An alternative possibility is that later aged suspected cases (Figure 2A) have another aetiology (e.g., rubella virus), a question requiring attention since a large fraction of suspected cases serologically tested for measles IgM (a short term marker of infection) were seronegative (46% out of n=3094 of the most recent data). However, rates of laboratory confirmation did not vary over age ($p>0.1$ for age as an explanatory variable of measles seropositivity using a generalized additive model) confirming that older aged susceptible individuals played a large role in the outbreak. Furthermore, the ages where infection is concentrated approximately map to the age groups identified by the earlier febrile/rash-based serological survey for measles susceptibility (Figure S2).

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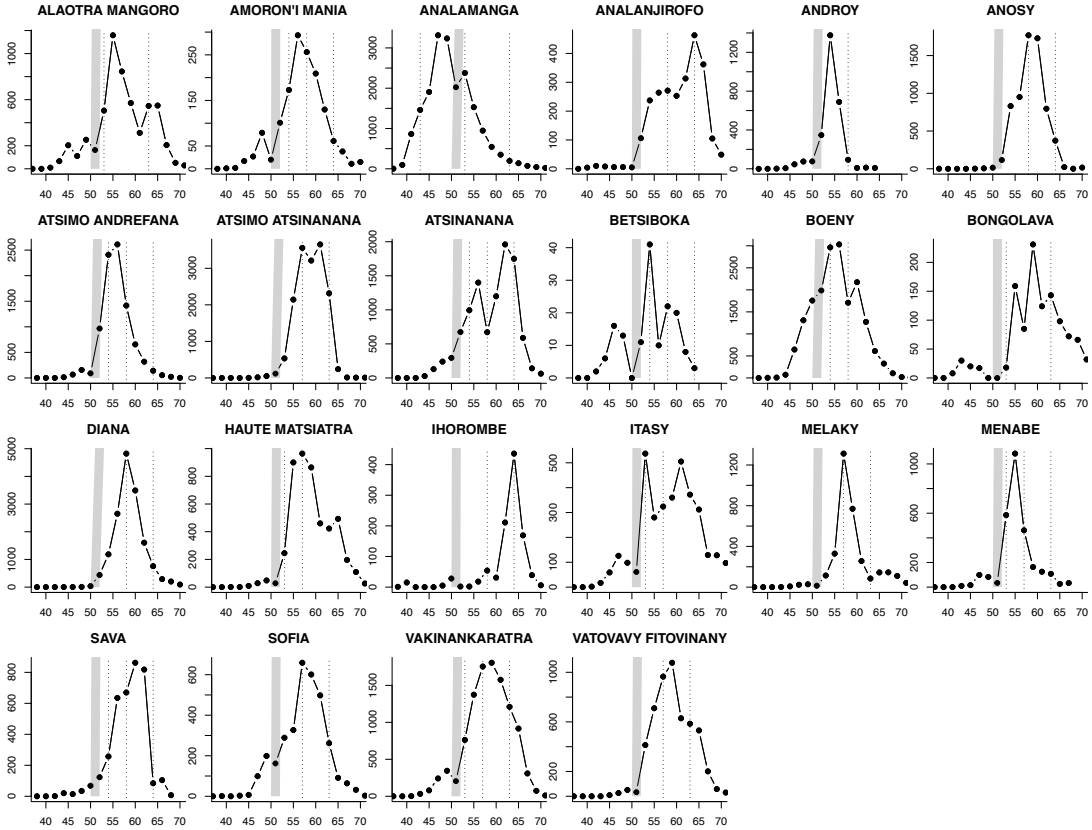

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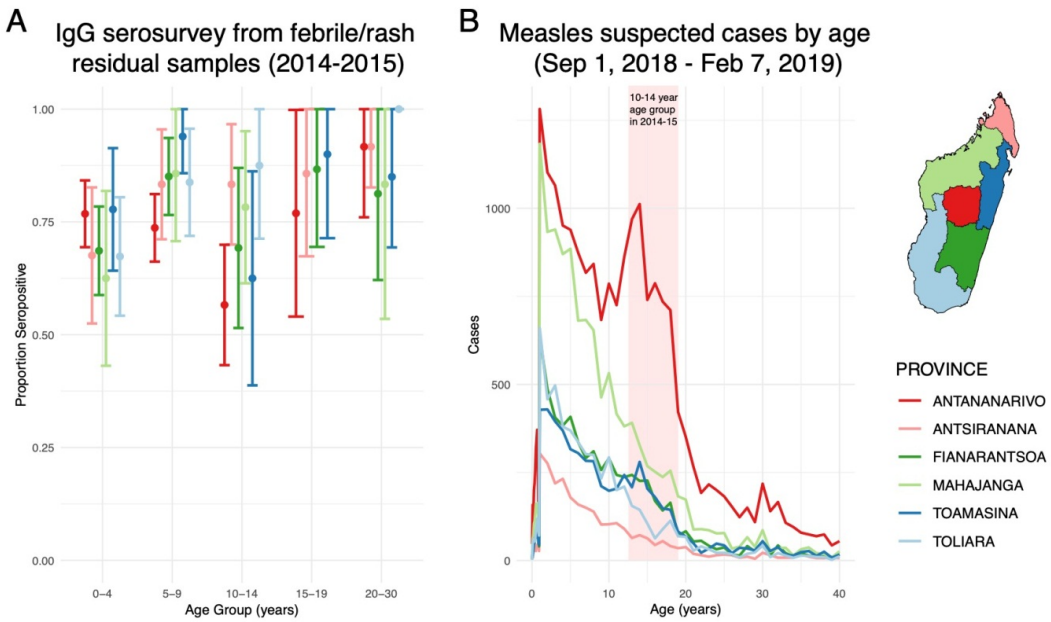

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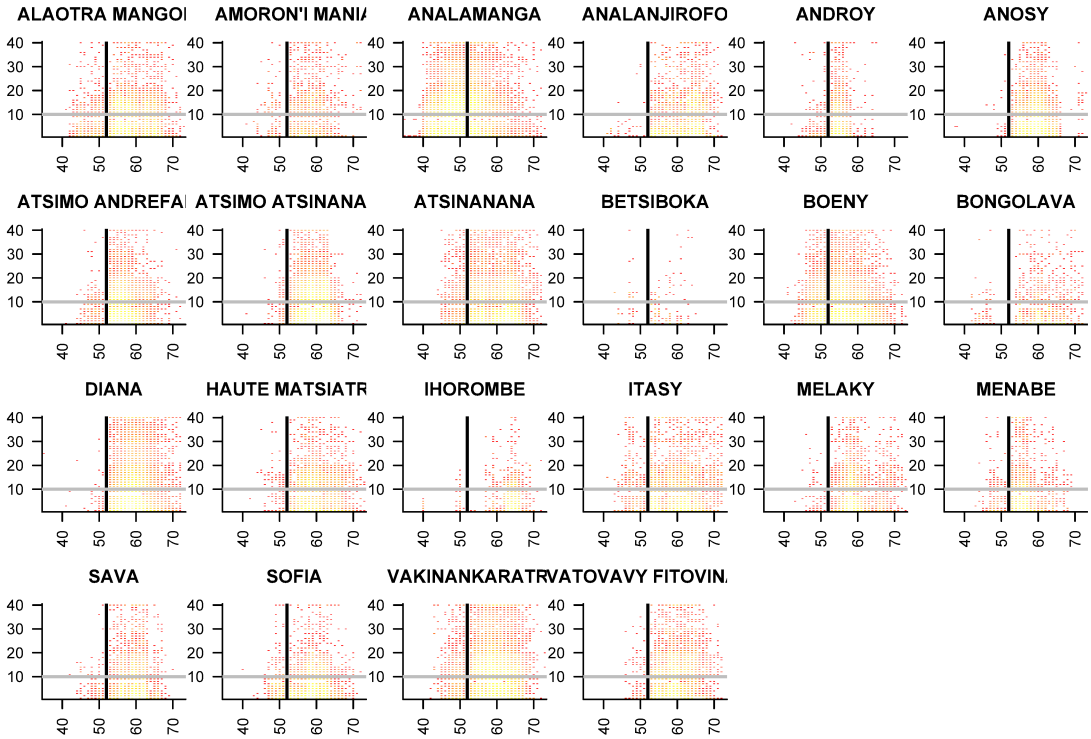

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BONGOLAVA	0.72	0	0.28
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Many lines of evidence suggest the outbreak was driven by late age immunity gaps. An alternative possibility is that later aged suspected cases (Figure 2A) have another aetiology (e.g., rubella virus), a question requiring attention since a large fraction of suspected cases serologically tested for measles IgM (a short term marker of infection) were seronegative (46% out of n=3094 of the most recent data). However, rates of laboratory confirmation did not vary over age ($p>0.1$ for age as an explanatory variable of measles seropositivity using a generalized additive model) confirming that older aged susceptible individuals played a large role in the outbreak. Furthermore, the ages where infection is concentrated approximately map to the age groups identified by the earlier febrile/rash-based serological survey for measles susceptibility (Figure S2).

FINTINA

Taona maromaro tao aorian'ny naha-ambany ny tahan'ny kitrotro teto Madagasikara dia niverina indray izany valan'aretina izany tamin'ny volana septambra 2018 ary nanomboka teo amin'ireo faritra afovoany teo Madagasikara.

Niparitaka ary nahakasika ireo faritra 22 manerana ny nosy ny valan'aretina kitrotro. Olona mihoatra ny 100 000 no voan'ny kitrotro tamin'izany ary olona teo ho eo amin'ny 1 000 teo no matiny.

Ny hatanjak'ilay valan'aretina kitrotro, ny taonan'ireo olona narary, ny fivoaran'ny tahan'ny valan'aretina ary ny fomba nanaovana vaksiny teto Madagasikara dia mifanandrify amin'ilay posa-kevitra epidemiolojika iray atao hoe: "post-honeymoon outbreak". Ny "post-honeymoon outbreak" dia valan'aretina niseho tao aorian'ny taona maromaro izay nahitana fahombiazana (sarintsarim-pahombiazana) teo amin'ny ady amin'ny kitrotro.

Fanamby iray lehibe sy maika apetraka eto ny hamaritana ireo tranga na fambara ahafahana maminany io fotoana "post-honeymoon" io izay mahakasika ny valan'aretina kitrotro sy ireo aretina hafa azo sorohina amin'ny fanaovana vaksiny. Izany dia ahafahana mandray lesona avy amin'ity valan'aretina kitrotro nitranga ity mba ho fanatsarana ny fiomanana amin'ny fisorohana ny mety hisian'ny vala'naretina amin'ny ho avy sy ho fanatsarana ny paikady aroso.

Ny zava-nisy teto Madagasikara dia mampiseho fa zava-dehibe tokony hilofosana ny fananana antontan'isa mari-pototra sy mifanaraka ara-potoana tsara amin'ny zava-misy (manomboka amin'ny fanaraha-maso tsy tapaka ireo tranga ka hatramin'ny fanatanterahana ny vaksiny sy ny fitiliana ny singa ao anaty rà ahafahana manamarina fa mandaitra ilay vaksiny) mandritry ny dingana sy ny ezaka rehetra atao amin'ny ady amin'ny kitrotro mba ahafahana manao vaksiny ara-potoana ireo olona tokony hisitraka izany. Izany rehetra izany dia ahafahana misoroka ny fisian'ny valan'aretina sy ireo voka-dratsiny amin'ny ho avy.