Impact of mass vaccination campaigns on measles transmission during an outbreak in Guinea, 2017

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Highlights

- Low vaccination levels in Guinea facilitated a nationwide measles outbreak in 2017.
- Most cases were among young children born during or following the Ebola epidemic.
- Modeling transmission by vaccination timing can evaluate response effort success.
- Mass vaccination during the outbreak maintained transmission below epidemic levels.

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Running title: Impact of vaccination on measles spread in Guinea, 2017

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Summary

Objective: To estimate the time-dependent measles effective reproduction number (R_t) as an indicator of the impact of three outbreak response vaccination (ORV) campaigns on measles transmission during a nationwide outbreak in Guinea.

Methods: R_t represents the average number of secondary cases generated by a single primary case in a partially immune population during a given time period. Measles R_t was estimated using daily incidence data for 3,952 outbreak-associated measles cases in Guinea in 2017 for the time periods prior to, between, and following each of three ORV campaigns using a simple and extensible mathematical model.

Results: R_t was estimated to be above the threshold value of 1 during the initial growth period of the outbreak until the first ORV campaign began on March 13 (R_t =1.60, 95% CI: 1.55–1.67). It subsequently dropped below 1 and remained < 1 through the end of the year (range: 0.71–0.91), although low levels of transmission persisted.

Conclusions: Reduction in R_t coincided with implementation of the ORV campaigns, indicating success of the campaigns at maintaining measles transmission intensity below epidemic growth levels. However, persistent measles transmission remains an issue in Guinea due to insufficient levels of herd immunity. Estimation of R_t should be further leveraged to help decision makers and field staff understand outbreak progress and the timing and type of vaccination efforts needed to halt transmission.

Keywords: Epidemiology; Infectious diseases; Measles; Mathematical model; Disease outbreaks; Vaccination campaign

Introduction

Widespread vaccination has significantly reduced measles-related morbidity and mortality worldwide, yet measles remains a disease of global public health concern due to its highly transmissible nature, propensity to rapidly develop into outbreaks among children in resource-scarce settings, and rising levels of vaccine hesitancy.[1,2] Although primarily spread between humans via direct contact (e.g., droplets from coughing or sneezing), the measles virus (MeV) can become aerosolized and persist in an airspace or on surfaces for several hours.[3] Symptomatic disease begins with a high fever followed by rash, and typically includes cough, conjunctivitis, and/or coryza. Disease transmissibility is quantified by the basic reproduction number R_0, which estimates the number of secondary cases produced by a single infectious individual in a completely susceptible population during their entire infectious period—from approximately four days prior to four days after rash onset.[3] The R_0 of measles is high relative to other human diseases,[4] although factors such as population location and density influence contact structures, producing a wide variation in reported estimates.[5,6] A systematic review of the measles R_0 found that among African countries the median measles R_0 was 12.8 (range: 4.6–203.3), and for least-developed countries overall was 15.9 (range: 3.6–203.3).[6]

As vaccination and immunity gained from natural infection render a proportion of individuals immune to measles, MeV transmission is more accurately quantified by the time-dependent effective reproduction number R_t, which estimates the average number of secondary cases produced by a single infectious individual within a partially immune population at a given time or time period t. When R_t is less than the threshold value of 1, the number of new infections decreases with each generation, outbreaks taper off, and extended reduction in transmission can lead to disease extinction.[7] The goal of vaccination, therefore, is to reduce the pool of susceptible individuals and maintain $R_t < 1$. Targeted vaccination coverage for

measles containing vaccine (MCV) in order to achieve herd immunity and eventual measles elimination, a goal of the World Health Organization (WHO) Regional Office for Africa since 2012, is generally estimated at 95%.[8,9]

In Guinea, the 2013–2016 West African Ebola virus disease (EVD) epidemic weakened the already fragile health system,[10] hampering routine administration of a first dose of MCV to children born just before and during the epidemic.[11–13] Massive disruption of daily life, healthcare worker shortages and deaths,[10,14] fear of contracting EVD in health facilities,[15] implementation of cautionary measures against spread of EVD in routine healthcare,[12] vaccine shortages,[13,16] increased distrust of vaccines,[17] and lack of recognition that vaccination can prevent measles[16] all contributed to reduced MCV coverage in Guinea, which reached a 10-year low of 28% in 2014, and was approximated at 48% between 2015–2017.[18] In the wake of the EVD crisis, five million Guinean children ages 6 months–10 years were vaccinated against measles via mass vaccination campaigns amidst small, intermittent measles outbreaks in order to increase population immunity and prevent measles-related morbidity and mortality among this susceptible age group.[19,20] Nonetheless, in early 2017 a nationwide outbreak sparked that continued through the end of the year.

Initial localized response was succeeded by three outbreak response vaccination (ORV) campaigns interspersed between March 13 and May 1, 2017 that non-selectively targeted a combined two million children ages 6 months–10 years across 28 health districts (HDs).[20] ORV campaigns are cost-effective, mortality-preventing interventions for outbreaks in low- and middle-income countries[21,22] and have been part of the World Health Organization (WHO) strategy for response to measles outbreaks in settings with measles mortality-reduction goals since 2009.[23] Previous studies have assessed the impact of ORV campaigns using before and after estimates of case incidence or attack rates.[24–28] However, R_t has rarely been used to assess the impact of vaccination during outbreaks[29] and provides an easily interpretable and (when calculated in real time) actionable estimate of transmission. The aim of this evaluation was to calculate the measles R_t with respect to the three ORV campaigns held in 2017 to assess the impact of the campaigns on measles transmission in Guinea.

Methods

Outbreak data

Guinea is divided into eight administrative regions and 38 health districts (HDs)—one for each of 33 prefectures, and five in the capital region of Conakry. During the 2017 measles outbreak, HD teams

collected and reported case data to the Guinea Ministry of Health on a weekly basis. The outbreak began the first week of 2017 and was officially declared on February 8. The ORV campaigns took place March 13–19 (N'Zérékoré HD; 148,344 vaccinated), April 7–15 (Conakry HDs; 662,733 vaccinated), and April 21–May 1 (Boffa, Boké, Coyah, Dalaba, Dinguiraye, Dubréka, Faranah, Forécariah, Fria, Gaoual, Gueckédou, Kankan, Kindia, Kissidougou, Kouroussa, Macenta, Mamou, Mandiana, Pita, Siguiri, Télimélé, and Yomou HDs; 1,315,918 vaccinated). The campaigns were reported to have reached between 97–104% of their respective target populations of children 9 months–10 years (N'Zérékoré and Conakry HDs) and 6 months–5 years (22 other HDs), although low denominator (underestimated target population) and high numerator (children outside of target group vaccinated) biases may have affected these estimates, resulting in values higher than 100%. Vaccination was provided to children in the targeted age group and geographic region regardless of their vaccination status.[20]

Outbreak cases were defined and classified using national Integrated Disease Surveillance and Response guidelines, and include laboratory confirmed, epidemiologically confirmed, and suspected cases.[30] All case classifications were included in the analysis with equal weight. Suspected cases had clinical onset of fever plus maculopapular (non-vesicular) generalized rash as well as cough, coryza, and/or conjunctivitis or were otherwise suspected to have measles by a clinician. Epidemiologically confirmed cases were suspected cases with illness onset less than one incubation period apart from a confirmed case in the same HD (weeks 1–11) or village (weeks 12–52). Laboratory confirmation was determined by detection of measles-specific immunoglobulin M (IgM) antibodies, though testing was not performed for cases epidemiologically linked to the outbreak. To improve case identification and better target case management efforts, the geographic delimitation for epidemiologic linkage was changed at 12 weeks from HD to village level.

The dataset contained information on date of illness onset, date of consultation with a healthcare worker, and date of notification to a health authority, allowing for investigation of the temporal distribution of the outbreak. Date of illness onset was known for 5,275 cases (88.9%). For the remaining 657 cases (11.1%), date of illness onset was imputed from date of consultation when available using the mean delay between date of onset and date of consultation. If date of consultation was also missing, onset was imputed from the mean delay between date of onset and date of notification. Vaccination status was determined based on vaccination card and caregiver-reported history. The dataset was checked for logical inconsistencies, omissions, and improbable data. Cleaning and analysis were conducted using R 3.5.2.[31] Individual consent was not necessary because the study used data that were previously collected as part of Guinean routine surveillance and outbreak response activities and deidentified for analysis. The study was approved by the Medical Ethics Committee at Hokkaido University.

Model

We estimated the effective reproduction number R_t as a function of time using a pulse time-dependent R_t where

$$R_t = \begin{cases} R_1, & \text{for t} < t_0 \\ R_2, & \text{for } t_0 \leq t < t_1 \\ R_3, & \text{for } t_1 \leq t < t_2 \\ R_4, & \text{otherwise.} \end{cases}$$

The time period $t < t_0$ refers to the initial epidemic growth period and implicitly includes localized response measures (e.g., case isolation) implemented prior to the ORV campaigns. The cutpoints t_0, t_1, and t_2 represent ORV campaign start or buffer period end dates, with the latter set to two weeks after the former, as cases with illness onset during a buffer period were likely exposed to MeV prior to the start of the relevant ORV campaign. Buffer periods are considered as measles seroconversion is expected to occur approximately two weeks (i.e. one incubation period) after vaccine receipt.[3,24-26]

We used daily incidence data to calculate the expected number of cases at calendar time t following the renewal equation

$$E(i_t) = R_t \sum_{i=1}^{t-i} i_{t-s}\, g_s$$

in which the sum of observed cases i at time t was varied by the distribution of the generation time (the time between infection of an infector and infectee) g_s, where s refers to the infection age. As time of infection is unknown for all cases, values for the generation time were derived as the daily difference of the cumulative distribution function of a discrete gamma distribution with a mean of 12 days and standard deviation of 3.4 days.[32,33] R_t was estimated from the negative logarithm of the likelihood and 95% confidence intervals were derived from the profile likelihood. The final model was selected based on Akaike information criterion (AIC) values, with the lowest value preferred.

In addition, to gain insight into area-specific dynamics we calculated the epidemic growth rate from incidence data stratified by each ORV campaign area. We employed the equation $E(C(t)) = ae^{rt}$, where E(C(t)) describes the expected number of new infections (i.e. incidence) at calendar time t, a is the initial number of cases, and r denotes the growth rate over time t, optimizing the model using the likelihood-based approach and Gaussian distribution.[34] Confidence intervals were estimated from the profile likelihood.

Results

The outbreak began the first epidemiological week of 2017 and incidence peaked in March (week 10). Of the 5,932 cases, 16.1% were laboratory confirmed, 79.6% were epidemiologically confirmed, and 4.3% were suspected to have measles. Age at symptom onset was available for 99.0% of cases. Most cases (73.4%) were under 5 years of age (Figure 1) and the median age at infection was 2 years (interquartile range [IQR]: 1–5). Nearly one-tenth of cases (8.8%) were too young to be targeted for routine vaccination (< 9 months). The majority of these very young cases were from the capital region of Conakry (Table 1). Just under half (47.5%) of all cases were female.

Vital status was missing for 12.0% of cases. A total of 29 deaths were reported, of which 22 were among children under five years old. There was one death among cases < 9 months (Table 1)—a child with unknown vaccination status. The overall and children under five years old case-fatality ratios (CFR) were equivalent, at 0.5%. Most deceased cases were unvaccinated (89.7%) and the CFR for unvaccinated cases was 0.6%. Mean age at death was 3 years (range: 8 months–14 years). Kindia HD had only 3.1% of all cases but 31.0% of all deaths and the highest CFR of all the HDs (4.9%).

Less than one-sixth of cases (13.4%) had previously been vaccinated. Most cases were unvaccinated (74.7%) or had unknown vaccination status (11.9%). A small proportion of cases (2.4%) were < 6 months of age and therefore unlikely to have been vaccinated through routine or supplementary vaccination—although 6.4% of cases < 6 months were reported to have received at least one dose of MCV. The largest proportion of unvaccinated cases ≥ 9 months of age were from Conakry (Table 1).

Accounting for changes in the measles R_t at the beginning of each ORV campaign provided the model fit that best captured peak timing of the outbreak (Figure 2) and minimized AIC (Table 2). In this selected model, R_t was estimated to be 1.60 (95% CI: 1.55–1.67) during the initial growth period of the outbreak, then dropped below 1 following the first ORV campaign and remained < 1 for the rest of the year (Table 2, Figure 2). R_t followed a similar pattern using cutpoints set to the end of the campaign buffer periods, wherein R_t was 1.23 (95% CI: 1.19–1.27) during the initial growth period of the outbreak then dropped below 1 and remained < 1 for all subsequent time periods (Table 2).

Estimates of the growth rate *r* of the outbreak for each of the time periods determined by our selected model (Table 2) are presented in Table 3. In all campaign areas, the growth rate *r* converted from positive to negative values between the *r1* (pre-campaign) and *r2* (post-Campaign 1) time periods. In the Campaign 1 and 2-targeted HDs, the estimated growth rate remained negative in *r3* and *r4*—although the

confidence intervals spanned zero. The wide confidence intervals for the Campaign 1 HD (N'Zérékoré HD) during the third and fourth time periods (*r3* and *r4*) reflect the lack of cases in that area during the latter part of the outbreak. For the Campaign 3-targeted HDs, there was a resurgence in growth in those HDs prior to the ORV campaign (*r3*), but the growth rate again became negative following implementation of the campaign (*r4*).

Discussion

The model presented here captured the peak timing of the 2017 measles outbreak in Guinea and demonstrated that ORV campaign implementation coincided with the decrease and maintenance of R_t to < 1 (Figure 2). The low median age at infection (2 years) of cases indicates that measles transmission during the outbreak was largely driven by a substantial number of susceptible children born during and following the EVD epidemic, as previously predicted.[11] Despite vaccination of over seven million children via supplementary mass vaccination campaigns in 2014–2017, the post-EVD epidemic pocket of susceptible children increased to beyond pre-EVD levels, with only 39.5% of Guinean children 12–23 months surveyed in 2018 vaccinated against measles, compared to 61.8% in 2012.[20,35]

Despite low levels of population immunity, synchronicity of the reduction in R_t with the timing of the ORV campaigns indicates that the campaigns succeeded at elevating herd immunity in real time, likely preventing additional measles cases and measles-related deaths.[36,37] Estimation of R_t to assess the transmission dynamics of measles, whether in real time[38,39] or retrospectively,[40] can serve as a useful indicator of the impact of control measures such as quarantine[41] or vaccination campaigns (as presented here). Although it is expected that R_t will decrease following implementation of the ORV campaigns, the trend need not be linearly decreasing as there may be hotspots of transmission activity in other areas. The increase in R_t following Campaign 2 (Conakry HDs) may be related to the positive growth in the Campaign 3-targeted HDs during that time period (Table 3). The subsequent reduction in R_t from the third to fourth time periods may indicate that having campaigns in more than one area was critical to maintaining control of the outbreak (Table 2). While transmission was successfully reduced following the ORV campaigns, routine vaccination remains critical to attaining a level of herd immunity capable of preventing future outbreaks in Guinea.

Over 95% of measles-related deaths occur in countries with low per-capita incomes and weak health infrastructure, such as Guinea.[1] Mass vaccination campaigns can importantly help to reach children from less wealthy households[42] who are less vaccinated compared to children in higher wealth quintiles.[35] However, successful routine vaccination is needed to assure sufficient reduction of susceptible individuals

in the population. Caregivers, religious leaders, and healthcare personnel in Guinea understand the need for and benefits of vaccines, but lack of knowledge about vaccines is a concern for caregivers, and community health workers do not always have the appropriate knowledge, attitude, and skills to serve the communities they seek to vaccinate.[43] The higher CFR noted in Kindia HD (4.9%) compared to Guinea overall (0.5%)—all fatalities among children 1–5 years of age—is concerning, and requires further investigation to explain.

In countries with high birth rates and low vaccination coverage, children as young as 6 months are targeted in mass vaccination campaigns, as was the case during the 2017 ORV campaigns in Guinea. Vaccination of children 6–8 months of age in settings of low vaccination coverage may help prevent transmission in this vulnerable age group[44] as well as provide a survival advantage.[45,46] Nearly one-tenth (8.8%) of the 2017 measles cases were under 9 months of age, and 72.9% of cases < 9 months were between 6–8 months of age. Vaccination status was available for 329 (87.5%) infants ages 6–8 months, with 36 (10.9%) were reported as vaccinated with at least one dose of MCV. Seroconversion from vaccination at 6–8 months ranges from 30–90%, but reduced vaccine efficacy due to early MCV1 administration can largely be ameliorated with administration of additional doses.[1,47] Vaccination of women of childbearing age with no previous history of disease or vaccination and other susceptible individuals expected to have contact with an infant can also contribute to the protection of children too young to be vaccinated.[48]

Investigation into factors behind the persistence of measles transmission and low MCV coverage in Guinea indicated that one quarter (25.4%) of caregivers surveyed experienced a failed attempt to vaccinate their children. In some cases, there was a shortage of healthcare personnel or vaccine at the time they attempted to vaccinate. In other cases, concern about vaccine wastage led to missed opportunities for vaccination.[16] Vaccine effectiveness may also have been impacted by vaccine failure associated with early administration age (and no follow-up dose) or problems with cold chain assurance.[49]

Persistence of measles transmission is also highly influenced by surveillance system strength, as early detection of outbreaks and implementation of response activities may diminish the growth of an outbreak, as was suspected to have been the case in N'Zoo during the 2015 measles outbreak in Lola HD.[38] On the other hand, a weak surveillance system and low involvement by private health facilities, as was the general situation in post-EVD epidemic Guinea, likely resulted in underreporting of measles cases during the 2017 outbreak. Such suspected underreporting is a limitation of this study, which depends on cases being reported, and as a result the expected number of cases and R_t reported here may be underestimates.

Moreover, imputation of date of illness onset for 11.1% of cases may have affected our results if cases were assigned to the wrong time period.

Another limitation of this study is that it uses only ORV campaign timing to assess impact on R_t and does not include data from any smaller, localized public health interventions that may have occurred as such data were not available. This may be reflected in that the lowest AIC score was obtained for the model that used start-of-campaign rather than end-of-buffer-period cutpoints for estimation of R_t (Table 2), even though the latter is more sensible epidemiologically.[24–26] The result may indicate that implementation of localized response activities and reduction in the pool of susceptible individuals due to infection, as well as the change in epidemiologic linkage criteria in March, induced some level of decline in R_t independent of the ORV campaigns (Table 2), though disentanglement of these factors is beyond the scope of this study.

Furthermore, although presentation of the growth rate r by ORV campaign-targeted area (Table 3) provides some insight into area-specific dynamics, assumptions about transmission cannot be drawn directly from the growth rate estimates. The model presented here assumes a homogenously mixing population and did not account for geographic- or age-related heterogeneity that may provide further insight into the outbreak dynamics. Nonetheless, our results provide a unique overview of the relationship between R_t and ORV campaigns at the national level in Guinea in 2017, and offer insight into practical application of the renewal equation model, which is highly adaptable and readily modified to other settings or diseases, such as cholera or diphtheria outbreaks.[50]

Our results demonstrate that R_t was reduced to and maintained < 1 following implementation of the ORV campaigns, however measles transmission remains a persistent issue in Guinea due to low population levels of immunity. Timing of ORV campaigns is one key to minimizing the number of severe measles cases and deaths,[51] and calculation of R_t from case count data using simple modeling methods can help decision makers and those in the field understand the progress of an outbreak[38] and guide them on the timing type of vaccination efforts needed.

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References

1. World Health Organization (WHO). Measles Fact Sheet. https://www.who.int/news-room/fact-sheets/detail/measles. Accessed March 28, 2019.

2. World Health Organization (WHO). Ten threats to global health in 2019. https://www.who.int/emergencies/ten-threats-to-global-health-in-2019. Accessed August 15, 2019.

3. Centers for Disease Control and Prevention (CDC). Measles. In: *Epidemiology and Prevention of Vaccine-Preventable Diseases, 13th Edition*.; 2015:209-229. http://www.cdc.gov/vaccines/pubs/pinkbook/meas.html.

4. Anderson RM, May RM. *Infectious Diseases of Humans: Dynamics and Control*. Vol 28.; 1991. http://arxiv.org/abs/Infectious Diseases of Humans: Dynamics and Control.

5. Smith RJ, Li J, Blakeley D. The failure of R0. *Computational and Mathematical Methods in Medicine*. 2011. doi:10.1155/2011/527610

6. Guerra FM, Bolotin S, Lim G, et al. The basic reproduction number (R0) of measles: a systematic review. *The Lancet Infectious Diseases*. 2017;17(12):e420-e428. doi:10.1016/S1473-3099(17)30307-9

7. Chowell G, Hyman JM, Bettencourt LMA, Castillo-Chávez C. *Mathematical and statistical estimation approaches in epidemiology*.; 2009:1-363. doi:10.1007/978-90-481-2313-1

8. Nokes DJ, Anderson RM. The use of mathematical models in the epidemiological study of infectious diseases and in the design of mass immunization programmes. *Epidemiology and Infection*. 1988;101(1):1-20. doi:10.1017/S0950268800029186

9. Funk S, Knapp JK, Lebo E, et al. Target immunity levels for achieving and maintaining measles elimination. *bioRxiv*. 2018. doi:10.1101/201574

10. Shoman H, Karafillakis E, Rawaf S. The link between the West African Ebola outbreak and health systems in Guinea, Liberia and Sierra Leone: A systematic review. *Globalization and Health*. 2017;13(1):1-22. doi:10.1186/s12992-016-0224-2

11. Takahashi S, Metcalf CJE, Ferrari MJ, et al. The growing risk from measles and other childhood infections in the wake of Ebola. *Science*. 2016;347(6227):1240-1242.

12. World Health Organization (WHO). Guidance for immunization programmes in the African region in the context of Ebola, 30 March 2015 revision. 2015. https://www.who.int/csr/resources/publications/ebola/ebola-immunization-afro/en/. Accessed April 11, 2019.

13. Delamou A, El Ayadi AM, Sidibe S, et al. Effect of Ebola virus disease on maternal and child health services in Guinea: a retrospective observational cohort study. *The Lancet Global Health*. 2017;5(4):e448-e457. doi:10.1016/S2214-109X(17)30078-5

14. Delamou A, Beavogui AH, Kondé MK, Van Griensven J, De Brouwere V. Ebola: Better protection needed for Guinean health-care workers. *The Lancet*. 2015;385(9967):503-504. doi:10.1016/S0140-6736(15)60193-3

15. Delamou A, Hammonds RM, Caluwaerts S, Utz B, Delvaux T. Ebola in Africa: Beyond epidemics, reproductive health in crisis. *The Lancet*. 2014;384(9960):2105. doi:10.1016/S0140-6736(14)62364-3

16. Agence Nationale de Sécurité Sanitaire (ANSS). *Rapport de l'enquête sur les facteurs liés à la persistance de la rougeole en Guinée - 2018*.

17. Lazuta J. Vaccination teams defeat 'Ebola effect' in Guinea. 2015. https://reliefweb.int/report/guinea/vaccination-teams-defeat-ebola-effect-guinea. Accessed June 8, 2018.

18. World Health Organization (WHO). *Guinea: WHO and UNICEF estimates of national immunization coverage: 2017 revision*.; 2018. https://www.who.int/immunization/monitoring/surveillance/data/gin.pdf.

19. Suk JE, Jimenez AP, Kourouma M, et al. Post-ebola measles outbreak in Lola, Guinea, January–June 2015. *Emerging Infectious Diseases*. 2016;22(6):1106-1108. doi:10.3201/eid2206.151652

20. World Health Organization (WHO). WHO Supplementary Immunization Activities, 2000–2019. https://www.who.int/immunization/monitoring/surveillance/data/Summary/Measles/SIAs2000/2019.xls. Accessed March 21, 2019.

21. 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. *Journal of Infectious Diseases*. 2011;204(Suppl 1):S35-S46. doi:10.1093/infdis/jir072

22. Damme W van, Lerberghe W van. Strengthening health services to control epidemics: empirical evidence from Guinea on its cost-effectiveness. *Tropical Medicine and International Health*. 2004;9(2):281-291.

23. World Health Organization (WHO). *Response to measles outbreaks in measles mortality reduction settings*. Vol WHO/IVB/09.; 2009. http://whqlibdoc.who.int/hq/2009/WHO/IVB/09.03/eng.pdf.

24. Goodson JL, Wiesen E, Perry RT, et al. Impact of measles outbreak response vaccination campaign in Dar es Salaam, Tanzania. *Vaccine*. 2009;27(42):5870-5874. doi:10.1016/j.vaccine.2009.07.057

25. Goodson JL, Sosler S, Pasi O, et al. Impact of a measles outbreak response immunization campaign: Maroua, Cameroon, 2009. *Journal of Infectious Diseases*. 2011;204(Suppl 1):S252-9. doi:10.1093/infdis/jir151

26. Isere EE, Fatiregun AA, Adeyemo A. Measles outbreak and response immunisation in a south-western district of Nigeria: January to June 2013. *Southern African Journal of Infectious Diseases*. 2015;30(1):36-40. doi:10.1080/23120053.2015.1103964

27. 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 Medicine*. 2013;10(11):1-4. doi:10.1371/journal.pmed.1001544

28. Ntshoe GM, McAnerney JM, Archer BN, et al. Measles outbreak in South Africa: Epidemiology of laboratory-confirmed measles cases and assessment of intervention, 2009–2011. *PLoS ONE*. 2013;8(2):2009-2011. doi:10.1371/journal.pone.0055682

29. Gastañaduy PA, Funk S, Paul P, et al. Impact of public health responses during a measles outbreak in an Amish community in Ohio: Modeling the dynamics of transmission. *American Journal of Epidemiology*. 2018;187(9):2002-2010. doi:10.1093/aje/kwy082

30. World Health Organization Regional Office for Africa (WHO-AFRO). Integrated Disease Surveillance and Response in the African Region. 2010.

31. R Development Core Team. R: A Language and Environment for Statistical Computing. 2019. https://www.r-project.org/.

32. Vink MA. The generation interval of infectious diseases. 2010:1-44.

33. Klinkenberg D, Nishiura H. The correlation between infectivity and incubation period of measles, estimated from households with two cases. *Journal of Theoretical Biology*. 2011;284(1):52-60. doi:10.1016/j.jtbi.2011.06.015

34. Nishiura, H, Chowell, G, Heesterbeek, H, Wallinga, J. The ideal reporting interval for an epidemic to objectively interpret the epidemiological time course. *J R Soc Interface*, 2010;*7*(43), 297-307. doi.org/10.1098/rsif.2009.0153

34. Nishiura, H, Chowell, G, Heesterbeek, H, Wallinga, J. The ideal reporting interval for an epidemic to objectively interpret the epidemiological time course. *J R Soc Interface*, 2010;*7*(43), 297-307. doi.org/10.1098/rsif.2009.0153

35. Institut National de la Statistique (INS). *Enquête Démographique et de Santé (EDSG V)*.; 2019. https://dhsprogram.com/pubs/pdf/PR111/PR111.pdf.

36. Lessler J, Metcalf CJE, Cutts FT, Grenfell BT. Impact on epidemic measles of vaccination campaigns triggered by disease outbreaks or serosurveys: A modeling study. *PLoS Medicine*. 2016;13(10):1-14. doi:10.1371/journal.pmed.1002144

37. Mina MJ, Metcalf CJE, Swart R, Osterhaus ADME, Grenfell BT. Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. *Science*. 2015;348(6235):694-700.

38. Graham M, Suk JE, Takahashi S, et al. Challenges and opportunities in disease forecasting in outbreak settings: A case study of measles in Lola Prefecture, Guinea. *American Journal of Tropical Medicine and Hygiene*. 2018:0-3.

39. Akhmetzhanov AR, Lee H, Jung S-M, et al. Real time forecasting of measles using generation-dependent mathematical model in Japan, 2018. *PLoS Currents*. 2018:1-14.

40. Fonnesbeck CJ, Shea K, Carran S, et al. Measles outbreak response decision-making under uncertainty: A retrospective analysis. *Journal of the Royal Society Interface*. 2018;15(140). doi:10.1098/rsif.2017.0575

41. Cauchemez S, Boëlle P-Y, Thomas G, Valleron AJ. Estimating in real time the efficacy of measures to control emerging communicable diseases. *American Journal of Epidemiology*. 2006;164(6):591-597. doi:10.1093/aje/kwj274

42. Portnoy A, Jit M, Helleringer S, Verguet S. Impact of measles supplementary immunization activities on reaching children missed by routine programs. *Vaccine*. 2018;36(1):170-178. doi:10.1016/j.vaccine.2017.10.080

43. Gil Cuesta J, Whitehouse K, Kaba S, et al. "When you welcome well, you vaccinate well": A qualitative study on improving vaccination coverage in urban settings in Conakry, Republic of Guinea. *International Health* (accepted for publication).

44. Woudenberg T, Maas NAT van der, Knol MJ, Melker HE de, Binnendijk RS van, Hahné SJM. Effectiveness of early measles, mumps, and rubella vaccination among 6–14-month-old infants during an epidemic in the Netherlands: An observational cohort study. *Journal of Infectious Diseases*. 2017;215(8):1181-1187. doi:10.1093/infdis/jiw586

45. Aaby P, Whittle HC, Martins CLV, Garly ML, Rodrigues A, Benn CS. The optimal age of measles immunisation in low-income countries: a secondary analysis of the assumptions underlying the current policy. *BMJ Open*. 2012;2(4):e000761. doi:10.1136/bmjopen-2011-000761

46. Hansen JS, Thysen SM, Rodrigues A, Martins CLV, Fisker AB. Is early measles vaccination associated with stronger survival benefits than later measles vaccination? *BMC Public Health*. 2018;18(1):1-10. doi:10.1186/s12889-018-5866-y

47. Lochlainn L, Gier B de, Maas N van der, et al. Measles vaccination below 9 months of age: Systematic literature review and meta-analyses of effects and safety. 2015. https://www.who.int/immunization/sage/meetings/2015/october/2_MCV1_below_9_months_Effect_safety_28092015.pdf.

48. Gans HA, DeHovitz R, Forghani B, Beeler J, Maldonado Y, Arvin AM. Measles and mumps vaccination as a model to investigate the developing immune system: Passive and active immunity during the first year of life. *Vaccine*. 2003;21(24):3398-3405. doi:10.1016/S0264-410X(03)00341-4

49. Haralambieva IH, Ovsyannikova IG, Pankratz VS, Richard B. The genetic basis for interindividual immune response variation to measles vaccine: new understanding and new vaccine approaches. *Expert Review of Vaccines*. 2013;12(1):57-70. doi:10.1586/erv.12.134.The

50. Matsuyama R, Akhmetzhanov AR, Endo A, et al. Uncertainty and sensitivity analysis of the basic reproduction number of diphtheria: a case study of a Rohingya refugee camp in Bangladesh, November–December 2017. *PeerJ*. 2018;6(December 2017):e4583. doi:10.7717/peerj.4583

51. Grais RF, Radiguès X de, Dubray C, Fermon F, Guerin PJ. Exploring the time to intervene with a reactive mass vaccination campaign in measles epidemics. *Epidemiology and Infection*. 2006;134(4):845-849. doi:10.1017/S0950268805005716

Table 1: Descriptive characteristics of measles cases by age group and vaccination status during a nationwide outbreak in Guinea, 2017

Characteristic	Cases < 9 months[a]	Cases ≥ 9 months	Vaccination status, cases ≥ 9 months		
			Not previously vaccinated	Previously vaccinated	Unknown
Number of cases[b] (%)	516 (100)	5,356 (100)	3,997 (100)	747 (100)	612 (100)
Age in years (%)					
< 1	516 (100)	410 (7.7)	291 (7.3)	74 (9.9)	45 (7.4)
1–4	—	3,426 (64.0)	2,609 (65.3)	428 (57.3)	389 (63.6)
5–9	—	1,068 (19.9)	752 (18.8)	193 (25.8)	123 (20.0)
10–14	—	262 (4.9)	197 (4.9)	31 (4.1)	34 (5.6)
≥ 15	—	190 (3.5)	148 (3.7)	21 (2.8)	21 (3.4)
Sex (%)					
Female	233 (45.2)	2,559 (47.8)	1,922 (48.1)	356 (47.7)	281 (45.9)
Male	278 (53.8)	2,791 (52.1)	2,071 (51.8)	390 (52.2)	330 (53.9)
Unknown	5 (1.0)	6 (0.1)	4 (0.1)	1 (0.1)	1 (0.2)
Case classification (%)					
Laboratory confirmed	11 (2.1)	247 (4.6)	184 (4.6)	59 (7.9)	4 (0.7)
Epidemiologically linked	430 (83.3)	4,242 (79.2)	3,194 (79.9)	479 (64.1)	569 (93.0)
Clinically compatible	75 (14.6)	867 (16.2)	619 (15.5)	209 (28.0)	39 (6.3)
Vital status (%)					
Alive	466 (90.3)	4,676 (87.3)	3,497 (87.5)	652 (87.3)	527 (86.1)
Deceased	1 (0.2)	28 (0.5)	26 (0.7)	1 (0.1)	1 (0.2)
Unknown	49 (9.5)	652 (12.2)	474 (11.9)	94 (12.6)	84 (13.7)
Region of residence (%)					
Boké	11 (2.1)	298 (5.6)	196 (4.9)	100 (13.4)	2 (0.3)
Conakry	230 (44.6)	1,864 (34.8)	1,421 (35.6)	164 (22.0)	279 (45.6)
Faranah	15 (2.9)	181 (3.4)	116 (2.9)	43 (5.8)	22 (3.6)
Kankan	30 (5.8)	256 (4.8)	211 (5.3)	44 (5.9)	1 (0.2)
Kindia	112 (21.7)	1,148 (21.4)	1,096 (27.4)	46 (6.2)	6 (1.0)
Labé	1 (0.2)	51 (1.0)	29 (0.7)	19 (2.5)	3 (0.5)
Mamou	14 (2.7)	97 (1.8)	51 (1.3)	36 (4.8)	10 (1.6)
N'Zérékoré	103 (20.0)	1,461 (27.3)	877 (21.9)	295 (39.4)	289 (47.2)

[a] Routine measles vaccination in Guinea is recommended at 9 months. Cases < 9 months are not expected to be vaccinated, although some children may have received measles vaccine during mass vaccination campaigns, which target children as young as 6 months.
[b] Only includes cases for whom age was available (missing: n=60).

Table 2: The effective reproduction number of measles based on the timings of three outbreak response vaccination (ORV) campaigns in Guinea, 2017

		Effective reproduction number (95% CI)				
Timing	**k**[a]	**Before ORV**	**Campaign 1**[b]	**Campaign 2**[b]	**Campaign 3**[b]	**AIC**[a]
Start of campaign	Two	1.60 (1.55–1.67)	0.76 (0.74–0.79)	----------	----------	2564
	Three	1.60 (1.55–1.67)	0.75 (0.71–0.79)	----------	0.77 (0.73–0.80)	2566
	Four	1.60 (1.55–1.67)	0.75 (0.71–0.79)	0.91 (0.84–0.98)	0.71 (0.68–0.75)	2545
End of buffer period[c]	Two	1.23 (1.19–1.27)	0.79 (0.76–0.82)	----------	----------	3060
	Three	1.23 (1.19–1.27)	0.89 (0.84–0.94)	----------	0.71 (0.68–0.75)	3031
	Four	1.23 (1.19–1.27)	0.89 (0.84–0.94)	0.69 (0.63–0.76)	0.72 (0.68–0.77)	3033

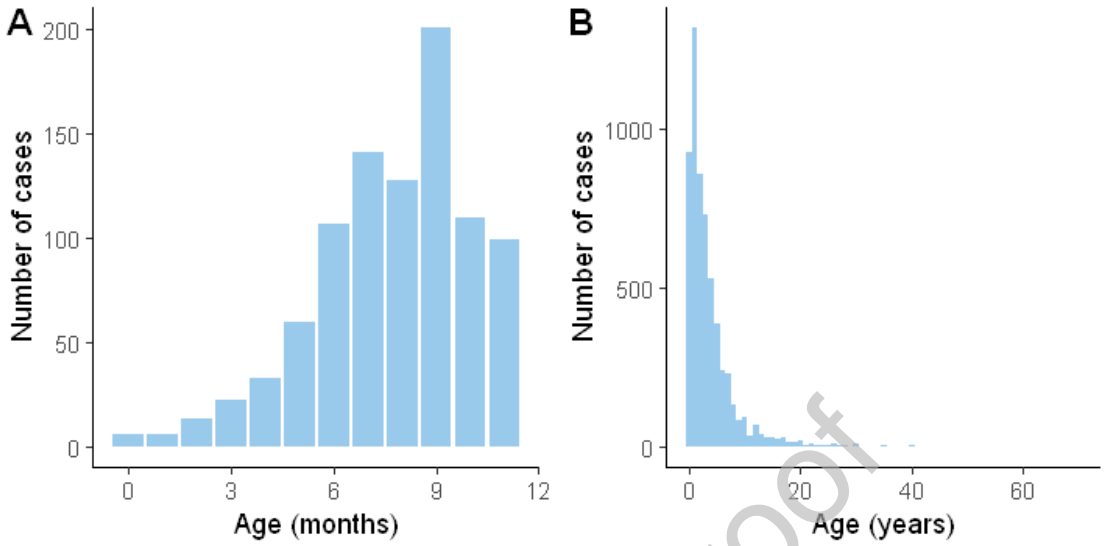
[a] Akaike information criterion (AIC) were calculated as *2k-2ln(L)*, where *-ln(L)* is the minimized value of the negative log likelihood and *k* represents the number of parameters—in this case, the number of estimates of the effective reproduction number.
[b] Campaign 1: N'Zerekore health district (HD); Campaign 2: Conakry HDs; Campaign 3: Boffa, Boké, Coyah, Dalaba, Dinguiraye, Dubréka, Faranah, Forécariah, Fria, Gaoual, Gueckédou, Kankan, Kindia, Kissidougou, Kouroussa, Macenta, Mamou, Mandiana, Pita, Siguiri, Télimélé, and Yomou HDs.
[c] The end of buffer period is defined as two weeks from the start date of a given ORV campaign.

Table 3: Growth rate of the measles outbreak by time period and outbreak response vaccination (ORV) campaign targeted area in Guinea, 2017

Parameter[a]	Nationwide[b] (95% CI)	ORV campaign targeted area[c]		
		Campaign 1 (95% CI)	Campaign 2 (95% CI)	Campaign 3 (95% CI)
a	8.96 (7.40, 10.70)	2.37 (1.84, 2.98)	3.86 (2.73, 5.21)	2.62 (1.94, 3.42)
r1	0.03 (0.03, 0.04)	0.04 (0.04, 0.05)	0.03 (0.03, 0.04)	0.03 (0.03, 0.04)
r2	-0.04 (-0.05, -0.04)	-0.14 (-0.17, -0.12)	-0.02 (-0.03, -0.01)	-0.01 (-0.02, -0.01)
r3	0.02 (-0.004, 0.03)	-0.10 (-0.54, 0.34)[d]	-0.02 (-0.05, 0.002)	0.03 (0.02, 0.05)
r4	-0.05 (-0.06, 0.03)	-0.03 (-0.37, 0.31)[d]	-0.04 (-0.06, -0.03)	-0.05 (-0.06, -0.05)

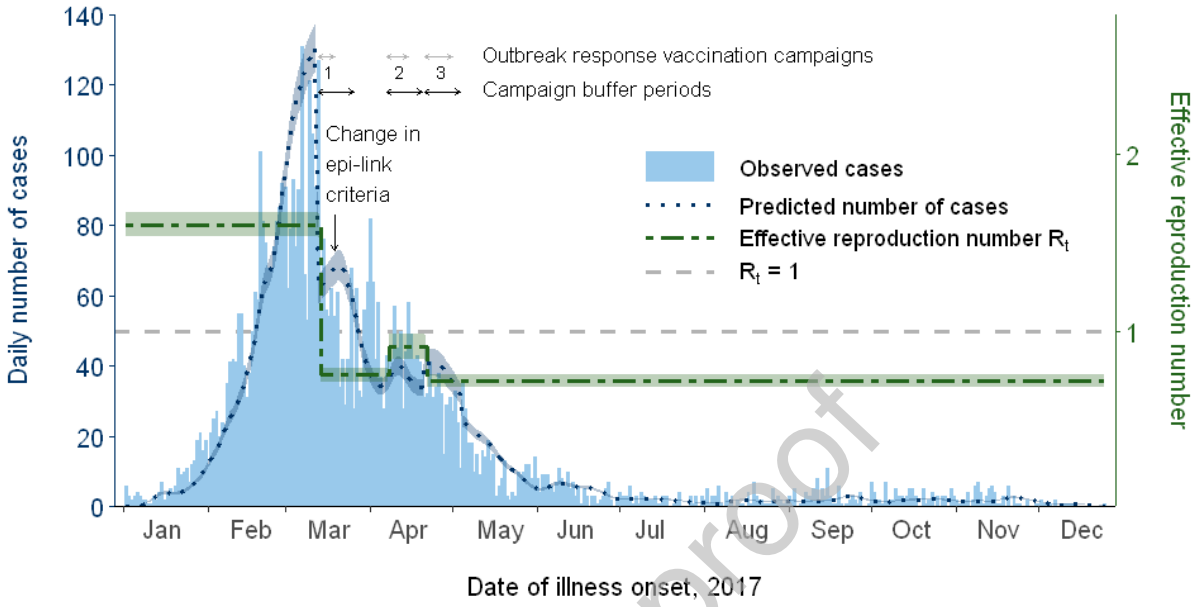
[a] The parameter *a* is the initial number of cases while *r* denotes the growth rate over the four time periods. The parameter *r1* corresponds to the time period prior to the outbreak response vaccination (ORV) campaigns, *r2* covers the time period following ORV campaign 1 and before campaign 2, *r3* describes the time period after ORV campaign 2 and before campaign 3, while *r4* indicates the time period following implementation of all three ORV campaigns. CI: confidence interval.
[b] Nationwide: all HDs, including ten that were not targeted in any of the ORV campaigns (Beyla, Dabola, Kérouané, Koubia, Koundara, Labé, Lélouma, Lola, Mali, and Tougué HDs)
[c] Campaign 1: N'Zérékoré health district (HD); Campaign 2: Conakry HDs; Campaign 3: Boffa, Boké, Coyah, Dalaba, Dinguiraye, Dubréka, Faranah, Forécariah, Fria, Gaoual, Gueckédou, Kankan, Kindia, Kissidougou, Kouroussa, Macenta, Mamou, Mandiana, Pita, Siguiri, Télimélé, and Yomou HDs.
[d] Due to the low number of cases, an asymptotic confidence interval is presented.

Figure 1: Reported measles cases in nationwide outbreak by age at illness onset, Guinea, 2017



((Editorial note: color not needed))

Figure 2: Measles outbreak cases and effective reproduction number, Guinea, 2017



The outbreak response vaccination (ORV) campaigns took place across 28 of 38 health districts (HDs) during (1) March 13–19 (N'Zérékoré HD), (2) April 7–15 (Conakry HDs), and (3) April 21–May 1 (Boffa, Boké, Coyah, Dalaba, Dinguiraye, Dubréka, Faranah, Forécariah, Fria, Gaoual, Gueckédou, Kankan, Kindia, Kissidougou, Kouroussa, Mamou, Mandiana, Macenta, Pita, Siguiri, Télimélé, and Yomou HDs). There was a change to the outbreak case definition criteria for epidemiological linkage (epi-link) criteria beginning in week 12, after which geographic linkage of new cases was restricted to cases with onset less than one incubation period apart from another confirmed cases within the same village (for weeks 1–11 geographic linkage was delimited by HD). R_t values were calculated using ORV campaign start dates as cutpoints.

((Editorial note: Color not needed, but it would look best with color))