UCL
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Outbreak characteristics and reproduction numbers of the 2017 measles outbreak in Guinea

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Année académique 2017-2018
Master en sciences de la santé publique
Finalité spécialisée

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Acronyms

ANSS: Agence Nationale de Sécurité Sanitaire (National Health Security Agency)

AVW: African vaccination week

CFR: case-fatality rate

ELISA: enzyme-linked immunosorbent assay

EPI: expanded programme on immunization

EVD: Ebola virus disease

GAM: global acute malnutrition

GT: generation time

IgM: immunoglobulin M

IDSR: Integrated Diseases Surveillance and Response, a comprehensive regional framework for strengthening national public health surveillance and response systems in Africa

MCH: maternal and child health

MCV: measles-containing vaccine; first dose = MCV1, second dose = MCV2

MLE: maximum likelihood estimate

ORI: outbreak response immunization

R: effective (instantaneous) reproduction number averaged across a time period

R_0: basic reproduction number

R_t: effective (instantaneous) reproduction number at time t (for $t > 0$)

SD: standard deviation

SI: serial interval

SIA: supplementary immunization activities

UNICEF: United Nations Children’s Fund

VC: vaccination coverage

VE: vaccine efficacy

VPD: vaccine-preventable disease

WHO: World Health Organization

WHO-AFRO: African Regional Office of the World Health Organization

I. Background

Measles

Measles is a highly contagious vaccine-preventable disease (VPD) caused by the measles virus (*Measles morbillivirus)* in the family Paramyxoviridae. Humans are the only known reservoir, although non-human primates have been infected experimentally.(1) In the pre-vaccine era, the disease caused an estimated 2.6 million deaths each year worldwide.(2) The first measles vaccine was introduced in 1963 and subsequent widespread vaccination efforts have significantly reduced measles-related morbidity and mortality.(3) However, measles remains a major cause of child mortality in developing countries.(4)

Endemic measles transmission was eliminated from the Americas in 2016 after 22 years of directed surveillance and vaccination strategies led to sufficiently high levels of vaccination coverage (VC) in the region.(5) Other countries and regions are making progress towards measles elimination by improving health and surveillance systems to increase VC.(4) However, in many countries humanitarian emergencies may result in the breakdown of the health and surveillance systems needed to support routine vaccination and promote progress towards measles elimination. In particular, interruptions to routine vaccination in emergency situations create immunity gaps that increase the number of susceptible individuals in a population.(6)

In 2016, measles incidence ranged from 0.02 cases per million population in the Americas (from imported or import-related cases) to 31 and 36 cases per million population in the Western Pacific and African regions. Between 2000 and 2016, measles vaccination led to an 87% decrease in reported measles incidence and an estimated 84% reduction in measles mortality worldwide, preventing an estimated 20.4 million deaths over that time period.(4) In 2016, worldwide reported measles deaths fell below 100,000 for the first time, with 89,780 deaths recorded, mostly for children under 5 years of age. The decrease in measles mortality is one of five main contributors to worldwide reduction in child mortality.(2)

The measles virus is transmitted from host to host via aerosolized droplet nuclei or direct contact with respiratory secretions from infected individuals. It has a short survival time (< 2 hours) in the open air and is rapidly inactivated. Once a person is infected, a primary viremia occurs 2–3 days after initial infection of the respiratory epithelium of the nasopharynx, and a second viremia occurs 5–7 days after initial infection as viral replication spreads. Prodrome may include one or more of the “3 Cs”—cough, conjunctivitis, or coryza—as well as fever and often Koplik spots. Rash occurs approximately 2–4 days after prodrome, 14 days after exposure, and persists for 5–6 days. Those infected shed the virus from onset of prodrome until 3–4 days after rash onset.(7) Although immunity for vaccinated or naturally infected individuals is considered lifelong, population dynamics (i.e. births) introduce new susceptible individuals on a continual basis.

Palliative treatment is the only option for those infected. While most people recover within 2–3 weeks, infection can cause serious complications among malnourished children and persons with reduced immunity. Complications include diarrhea, otitis media, pneumonia, encephalitis, seizures, and death. Wild-type measles infection also causes "immune amnesia"—or profound immunosuppression. Prevention of immune amnesia through vaccination against measles is an important public health intervention, as it reduces morbidity and mortality from other infections. Measles outbreaks occur when a sufficiently high proportion of susceptible individuals remains in the population.

Outbreak setting

Guinea is a low-income coastal country in tropical western Africa with a total population estimated to be between 11.2–12.4 million in 2016, up to 12.7 million in 2017.(8,9) It is 245,857 km^2 with 300 kilometers of coastline and stretches 800 kilometres from east to west and 500 kilometres from north to south. It shares borders with 6 countries—Côte d'Ivoire, Senegal, and Mali to the north and east, Liberia and Sierra Leone to the south, and Guinea-Bissau to the northwest. The Atlantic Ocean borders it to the west. Guinea gained its independence from France and joined the United Nations in 1958.(10)

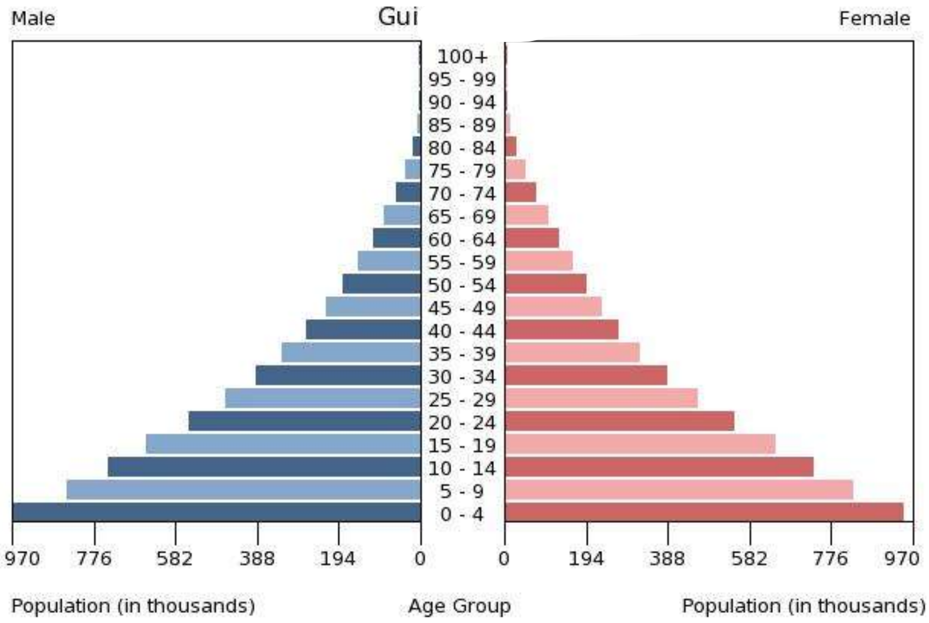
The country is divided into 8 administrative regions with 33 prefectures and one special administrative zone (the capital, Conakry). The prefectures are subdivided into 303 subprefectures. The most densely populated prefectures are Conakry, Coyah, Labé, and N'Zérékoré.(8) The population is 62% rural and 38% urban.(9) The climate, generally hot and humid, is influenced by a monsoonal-type rainy season from June to November and a dry season from December to May. April is generally the hottest month, although temperatures are high throughout the year. In temperate climates such as that of tropical Guinea, measles infections occur mainly in late winter and early spring. Over half of the land is agricultural (58.1%) and three-quarters (76%) of employment is agriculturally-related. An additional 26.5% of the land is forested.(10)

The four natural zones of Guinea include Lower Guinea (maritime Guinea), Middle Guinea, Upper Guinea, and Forest Guinea. Lower Guinea includes the capital, Conakry, and encompasses the alluvial basins of numerous coastal rivers spread along the Atlantic Ocean. Agriculture, small-scale fishing, and various commercial and mining activities provide employment and attract migratory flows. Middle Guinea has many mountains, plateaus, and rivers. The tropical climate is modified by mountain microclimates, rainfall is less abundant, agro-pastoral activities dominate, and there is emigration to urban centers from demographically pressured areas. Upper Guinea is a drier region of savannahs and plateaus watered by the Niger and its tributaries. The dry season is 6–7 months, and the geography is favorable to flooded agriculture and livestock-rearing. Harmattan desert winds approach from the north, and in the dry season upper Guinea is at risk of fires. Large deposits of gold and diamonds attract migratory flows. In Forest Guinea, abundant rainfall supports dense and moist forest. Commercial agriculture, logging, and mining iron are important sources of employment.(11)

Guinea is a high birth rate country, with an estimated crude birth rate of 35.9 per 1,000 population in 2016, and women had an average of 4.9 children. The death rate is much lower, estimated at 9.3 per 1,000 population. Life expectancy was 59.5 years for males and 60.5 years for females.(9) More than half of the population is under 20 years of age, with a larger proportion of the very young in rural areas.(11) Children under five accounted for an estimated 17.6%(8) or 16.0%(9) of the total population in 2016, depending on the reporting source. Health-related indicators are improving. The maternal mortality ratio decreased from 976 to 679 maternal deaths per 100,000 live births between 2000 and 2015.(12) Likewise, though under-five mortality remains relatively high, it decreased from 166 to 89 deaths per 1,000 live births between 2000 and 2016.(13)

One quarter (26%) of children 0–59 months are chronically malnourished in Guinea, and about one-third of the population is food insecure.(14) A 2015 Standardized Monitoring and Assessment of Relief and Transitions (SMART) survey revealed a global acute malnutrition (GAM) rate in Guinea of 8%, of which 2% was severe and 6% was moderate. Overall prevalence of stunting was 25.9% and underweight was 16.3% among children 0–5 years.(14) Malnutrition is associated with a more severe course of illness and higher risk of complications for children infected with measles.(15–19)

Figure 1. Population pyramid of Guinea, 2016



Source: Adapted from *The World Factbook* produced by the Central Intelligence Agency(10)

Measles infectivity and vaccination coverage in Guinea

Guinea follows the World Health Organization (WHO) Expanded Programme on Immunization (EPI) vaccine schedule, which recommends administration of the first dose of measles-containing vaccine (MCV1) at 9 months of age in locations where risk of measles mortality is high.(3) Estimates of seroconversion following MCV1 administration at 9 months is estimated at 86% (CI 84–93%),(20) and increases when vaccination occurs at later ages (VE = 95% at 12 months and 98% at 15 months) due to interference by maternal antibodies and immaturity of the immune system at younger ages.(21) In other parts of the world, MCV1 administration is recommended at 12 months to increase vaccine efficacy (VE). VE further increases when individuals receive a second dose of measles-containing vaccine (MCV2).(22)

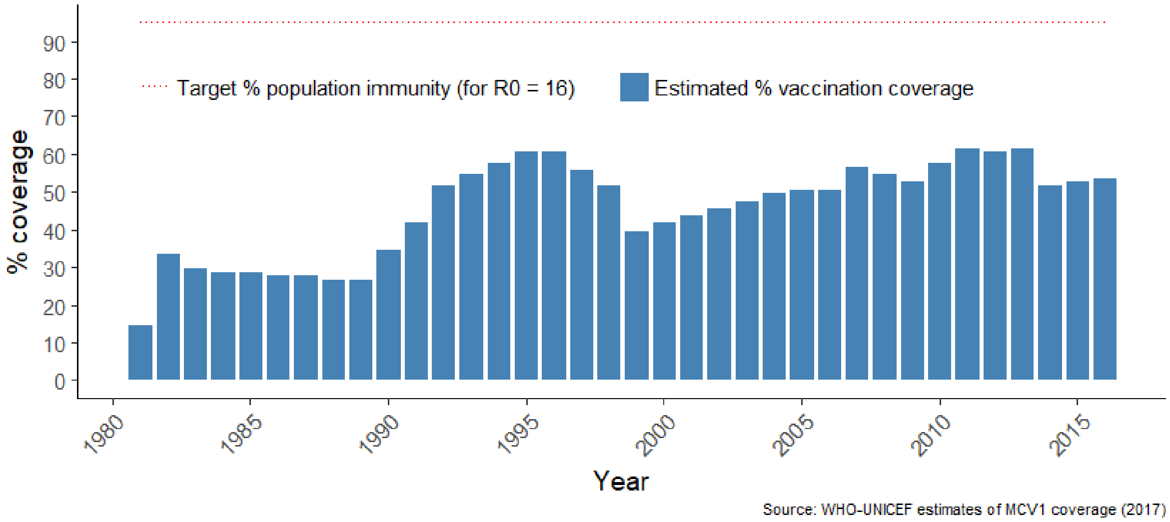
In 2016, approximately 85% of the world's children received MCV1 by their first birthday through routine health services—up from 72% in 2000. WHO and United Nations Children’s Fund (UNICEF) joint estimates of MCV1 coverage for the WHO African Region (WHO-AFRO) increased from 53% in 2000 to 72% in 2016(4) compared to 42% to 54% for Guinea in the same time period.(23,24) Guinea is among the countries with the lowest VC in the region.(25)

In the pre-vaccine era, the estimated basic reproduction number (R_0) of measles—the average number of secondary cases arising from a typical case in a totally susceptible population(26)—ranged from 6.1 to 27.0, with a median of 11.1.(27) In the post-vaccine era, morbidity and mortality have decreased due to the reduction in the number of susceptible individuals. However, the measles virus remains highly infectious. Estimates of R_0 in the post-vaccine era indicate that one infected person will infect 16 susceptible contacts (range: 3.7–203.3).(27) R_0 is not only an intrinsic characteristic of the pathogen, but is context-dependent and varies based on the contact patterns of the population in which it is measured. The lower median value of R_0 for studies conducted in the pre-vaccine era may be because the studies were from developed European and North American countries, while most studies providing estimates in the post-vaccine era are from least developed or developing countries in Asia and Africa, resulting in a skew in the median R_0.(27)

Assuming the estimated median post-vaccine era R_0 of 16, the critical proportion of immune individuals needed to interrupt transmission in a population (p_c) is approximately 94% given the control relation $p_c = (1 - 1/R_0)$.(28) This is also the estimated threshold for herd immunity and eventual measles elimination in a randomly mixing population. In Guinea, the current level of VC is much lower than this herd immunity threshold (Figure 2). As high birth rates in Guinea introduce approximately 400,000–450,000 new susceptible individuals to the population each year,(8,9) high VC (particularly from routine vaccination) is an important step towards decreasing child mortality.

In countries with higher birth rates, measles transmission tends towards annual dynamics.(29) However, Guinea likely experiences powerful seasonal forcing of transmission due to the rainy season and agricultural seasonality.(30) In industrialized countries, school schedules are also a powerful driver of seasonal forcing.(31,32) Other social determinants of contact patterns include cultural practices, nutrition, infection control measures, transnational contact clusters, and road/transportation networks.(27,33)

Figure 2. Estimated national vaccination coverage in Guinea by year, 1981–2016



Source: WHO-UNICEF estimates of MCV1 coverage (2017)

The WHO African Region (WHO-AFRO) targeted regional measles elimination for 2020, though it remains endemic in 2018. Elimination strategies rely heavily on vaccination, and most countries in the African region have yet to achieve MCV1 vaccination coverage above 90%.(25) In 2016, the average estimated vaccination coverage among 47 African countries was (79%), ranging from 20% in South Sudan to 90% in Comoros. Countries with high measles incidence and low MCV1 coverage are targeted by the WHO to conduct supplementary immunization activities (SIAs). “Follow-up” SIAs are periodic mass vaccination campaigns conducted every 2–4 years to reduce the number of susceptible children born since the previous SIA, to reach the unreached, and to reach those who did not gain immunity from previous vaccination. The frequency of follow-up SIAs depends upon current population demographics and VC from routine vaccination activities, as well as the percentage of the target population vaccinated in the most recent SIA.

Official statistics and local data are typically combined to establish realistic population figures.(34) During follow-up SIA campaigns, all children in the target age group and geographic area are eligible to receive a dose of MCV regardless of whether they have been previously immunized or have a known history of clinical measles. Even children who received a routine dose of MCV a few days earlier are eligible for a dose from an SIA campaign.(35)

Immunity to measles virus infection in Guinea is due to a combination of routine immunization, SIAs, outbreak response immunization (ORI), and catch-up campaigns, as well as through natural infection. Each year Guinea organizes two ACD (Atteindre Chaque District, or “reach every district”) catch-up campaigns during African Vaccination Week and

Maternal and Child Health (MCH) week in all health districts. All vaccines are administered to children and pregnant women who attend, and attendees are also provided with vitamin A supplementation, deworming, and screening and treatment of malnutrition as needed. Vitamin A supplementation also often accompanies ORI campaigns, as it can reduce measles morbidity in children.(36–38) SIA and ORI campaigns from the last ten years Guinea are described in Table 1.

Table 1. Ten years of vaccination from supplementary immunization activities (SIAs), outbreak response immunization (ORI), and other outbreak response campaigns in Guinea, 2006–2017

Year	Extent of campaign	Age group (months)	Target	Vaccinated	% vaccinated	Campaign type	Reporting source*
Dec 2006	Nationwide	9–59	1,755,122	1,707,633	97	Follow-up SIA	WHO (39)
Nov 2009	Nationwide	9–59	1,964,471	1,977,225	101	Follow-up SIA	WHO (39)
Jun–Jul 2012	Nationwide	9–59	2,209,623	2,098,829	95	Follow-up SIA	WHO (39)
Feb 2014	Sub-national*	6–119	1,425,296	1,411,043	99	ORI	WHO (39)
Feb–Apr 2015	Sub-national	6–119	1,389,810	1,259,690	91	ORI	WHO (39)
Feb 2015	Gaoual, Koundara	6–119	99,476	89,052	89	Outbreak response	UNICEF(40)
Apr 2015	13 districts†	9–119	1,391,775	1,358,034	98	Outbreak response	UNICEF (41)
Apr 2015	Lola	6–59	53,720	49,422 (estimated)	92	Outbreak response	Suk et al. (42)
Feb 2016	Nationwide	9–59	2,350,712	2,412,923	103	Follow-up SIA	WHO (39)
Oct–Dec 2016	Five districts§	9–59	23,612	21,678	92	Outbreak response	MoH (43)
Mar 2017	N'Zérékoré	9–119	142,270	148,344	104	Outbreak response	MoH (43)
Apr 2017	Conakry	9–119	686,568	662,733	97	Outbreak response	MoH (43)
Apr–May 2017	22 districts**	6–59	1,414,880	1,407,631	100	ORI	WHO (39)

Sources: World Health Organization (WHO), United Nations Children's Fund (UNICEF), Guinea's Ministry of Health (MoH) and Suk et al.

* Conakry (Dixinn, Kaloum), Coyah, Dubréka, Boké, Fria, Boffa, Forécariah, Mamou, Kissidougou, Mandiana, and Lélouma

† Beyla, Dinguiraye, Gueckédou, Kankan, Kouroussa, Lola, Macenta, Mali, Mandiana, N'Zérékoré, Siguiri, Télimélé, and Yomou

‡ Only Boké, Dubréka, and Forécariah were unable to participate due to their ongoing Ebola response.

§ Dubréka, Gueckédou, Kindia, Matoto, and N'Zérékoré

** Boffa, Boké, Coyah, Dalaba, Dinguiraye, Dubréka, Faranah, Forécariah, Fria, Gaoual, Gueckédou, Kankan, Kindia, Kissidougou, Kouroussa, Mamou, Mandiana, Macenta, Pita, Siguiri, Télimélé, et Yomou.

Outbreak response vaccination in 2017 targeted children ages 6 months to 10 years—an age range which represents approximately 32.1% of the total Guinean population.(11) Cumulative coverage rates from national vaccination campaigns (Table 1) combined with the national estimates of coverage (in Guinea introduce approximately 400,000–450,000 new susceptible individuals to the population each year,(8,9) high VC (particularly from routine vaccination) is an important step towards decreasing child mortality.

) provide insight into the number of susceptibles in the population.

Coverage estimates may mask disparities when disaggregated by health district. In a 2016 evaluation, WHO found that only 8% of prefectures were performing to par for SIA and routine EPI vaccinations (Mamou, Koubia, and Koundara), while 13% of prefectures were performing for SIA but not routine EPI vaccinations (Fria, Dalaba, Boffa, Lélouma, and N'Zérékoré), 21% of prefectures were performing well for routine EPI but not SIAs (Tougué, Gueckédou, Mali, Pita, Beyla, Dabola, Faranah, Kaloum), and 58% of prefectures were not performing well for SIAs or routine EPI (Boké, Dinguiraye, Yomou, Coyah, Matam, Kankan, Kindia, Télimélé, Gaoual, Matoto, Dixinn, Ratoma, Dubréka, Lola, Labe, Macenta, Mandiana, Kissidougou, Siguiri, Kérouané, Kouroussa, Forécariah).(43)

The availability of sufficient qualified personnel is an indispensable factor for proper surveillance and management of common conditions and endemics. Most basic health facilities do not have sufficient and qualified staff to cover priority conditions, let alone adequately develop preventive activities, including immunization. In Guinea, there is approximately 1 physician and 1 nurse per 10,000 inhabitants.(8) Low nurse density is associated with lower MCV vaccination coverage in developing countries.(44) Cold chain management in resource-poor settings is also a challenge.(45)

Effects of the West African Ebola epidemic on routine vaccination

Measles outbreaks often follow humanitarian crises and become heralds of a broken health system.(46,47) Warnings of impending measles outbreaks in the wake of the 2014–2015 Ebola virus disease (EVD) epidemic in West Africa filtered into public attention as the EVD epidemic waned.(48,49) During the EVD response, economic, social, humanitarian, and security threats in Guinea, Liberia, and Sierra Leone became apparent.(50) Response efforts overwhelmed the local health system and increased public mistrust of healthcare systems, in addition to causing social instability and weakening food security.(48) During the outbreak, well residents were wary of seeking healthcare, and the already fragile healthcare system was further weakened by the re-allocation of limited resources to Ebola response.(51–55)

The original chain of transmission of EVD in West Africa began in late December 2013 in Gueckédou, Guinea and cases were reported through 2015, until Guinea was declared free of Ebola virus transmission on December 29, 2015.(56) Over the two-year period, Guinea reported a total of 3,804 EVD cases (3,351 laboratory confirmed) with 2,536 associated deaths—a case-fatality of 67%.(57) Routine vaccination was significantly reduced during the EVD outbreak, with declining trends continuing in the post-outbreak period. Local vaccine stock was also affected.(58) Persons suspected of EVD or exposed to EVD were not to be vaccinated.(59) Guinean communities increased routine vaccination efforts once they had not reported a case of EVD for 42 days. However, during post-Ebola recovery, there were gaps in administration of all vaccine types. For example, in Macenta District vaccine administration had not yet reached pre-Ebola levels even by mid-2016.(60)

Prior to the EVD outbreak, Guinea had planned an SIA campaign to continue to address gaps in routine immunization coverage. However this campaign never materialized.(49) Due to ongoing EVD transmission, the SIA follow-up monitoring campaign was not initiated until 2016. The prefectures most affected by EVD (Forécariah, Dubréka, and Boké) were unable to participate in MCH week vaccinations in June 2015.(61) The length of the Ebola response and reduction in routine vaccination was such that a large cohort of susceptible children may have entered the population. Takahashi et al. estimated that the susceptible population of children aged 9–59 months could have been as great as 1.1 million after 18 months of disruption in Guinea, Liberia, and Sierra Leone combined.(6)

Recent measles outbreaks in Guinea

Guinea conducts routine surveillance for measles at the community, district, and national levels and met WHO surveillance performance indicator targets in 2016.(62) A suspected outbreak of measles is defined by WHO-AFRO as at least 5 suspected cases found within a health facility or a health district in the same area within one month, with plausible means of transmission. An outbreak is confirmed when there are 3 or more cases with detected measles immunoglobulin M (IgM) positive) found within a health facility or district within one month.(63)

A measles outbreak occurred in Lola Prefecture, Guinea at the tail end of the Ebola outbreak, with 702 measles cases reported between January 1 and June 30, 2015. High measles susceptibility in the region is believed to have driven the outbreak.(42) At least 24% of children in Lola Prefecture were believed to be unvaccinated for measles.(64) In 2014, the year before the outbreak began, national VC was estimated at 52%, a reduction of 10% from the previous year estimate of 62%.(25)

A large-scale outbreak began in WHO epidemiologic week 1 of 2017. The Minister of Health declared the outbreak on February 8, 2017, and it continued into 2018. By the end of 2017, all prefectures had at least one reported suspect case. In response to this 2017–2018 outbreak, the Guinea National Health Security Agency (Agence Nationale de Sécurité Sanitaire, ANSS) and EPI commenced vaccination campaigns targeting children 6 months to 10 years of age in N'Zérékoré and the 5 communes of Conakry during March and April. ANSS and EPI program worked with Médecins Sans Frontières (MSF) in Conakry and ALIMA in N'Zérékoré. Outbreak response vaccination campaigns were later implemented in 21 other districts, with a target age group of 6 months to 5 years of age (Table 1). At the time, national vaccination coverage was not homogeneous in the different districts due in part to the quasi-suspension of the routine EPI during the Ebola outbreak, and many of the children in the targeted age group had likely received no dose of measles-containing vaccine since birth.(6)

Reproduction numbers and generation time

R_0 is a key epidemiologic parameter describing the transmissibility of a disease. It is often used to help design effective public health interventions, by determining the necessary level of VC to prevent outbreaks. It can also be leveraged to estimate the proportion of a population that will experience infection by the end of an outbreak.(65) However, R_0 assumes a completely susceptible population and cannot be directly estimated from incidence data when a proportion of the population may already be immune or will become immune. Instead, the effective reproduction number R is calculated.

R represents the actual number of secondary cases per primary case at time t for $t > 0$, and includes time-dependent variation due to the decline in susceptible individuals through natural infection or implementation of control factors such as vaccination campaigns (in the case of VPDs), isolation of infectious individuals, and dissemination of information through mass media leading to public recognition of an outbreak and increased caution regarding disease transmission.(66,67) The relationship between R and R_0 is described by the equation $R_0 = R/(1 - I)$ where I represents the prevalence of protected individuals in the population.(49) R will increasingly diverge from R_0 as the susceptible population becomes depleted, and can dip below 1. If R is maintained below 1, then sustained endemic transmission of the infection cannot occur.

Wallinga and Teunis demonstrated that there is a direct relationship between an epidemic curve (number of cases by date of symptom onset) and the distribution of R over time that allows for estimation of R after marginalization over all possible chains of transmission based on the distribution of the generation time (GT)—the time between infection of a primary case and its subsequent infection of another, secondary case.(68,69) Although GT differs from the serial interval (SI), which is the time from symptom onset in a given case to symptom onset in secondary cases, the mean SI and mean GT have the same value, provided the incubation times of the infectee and infector are independent and identically distributed.(70) Based on data mostly collected in the pre-vaccine era, the mean GT/SI of measles is estimated to range between 10–14 days.(70)

Gaps in knowledge

Measles continues to be a major health concern worldwide, and Guinea is off-track in meeting MCV coverage and measles disease incidence targets needed for WHO-AFRO to achieve measles elimination by 2020.(4) Further characterization of outbreaks can help health district staff and policy-makers better understand local disease dynamics in order to tailor response strategies and set VC targets. Worldwide measles elimination is the end goal, and context-specific R_0 estimates can help determine the feasibility of local elimination efforts.(27)

Estimates of R_0 for measles vary greatly even in the post-vaccine era.(27) In part, this is because R_0 reflects the population and setting within which it transmits and is not solely an intrinsic characteristic of virus. Compounding this, methods of calculation vary between studies, and reports of R_0 vary by data source.(27) Reports containing estimates of R are also limited.(71)

Few reports present R_0 and/or R using data from African countries.(72–74) Population densities, migration and local differences in vaccination coverage within African cities play an important role in the forecast impact of control measures once an epidemic has begun. A relatively low R and long duration were reported for an outbreak in Niger during 2003–2004.(74) Country-specific R and R_0 estimates based on national data are important given the variation in reported R_0. Ideally, outbreak studies should employ one or two simple methods to calculate R_0 so that values can be compared across epidemics.(27,75)

Major aims, specific objectives

The aim of this thesis is to better understand the transmission dynamics of measles in the first year of the 2017–2018 outbreak in Guinea through analysis of national outbreak-related case incidence data. The thesis objectives are as follows:

1. Describe the epidemiology of the first year of the 2017–2018 measles outbreak in Guinea (ongoing as of the writing of this thesis).
2. Calculate the effective reproduction number (R) of the outbreak. R represents the average across a time period of the actual number of secondary cases per primary case at calendar time t (for $t > 0$). Calculation of R represents one of the goals for the use of measles surveillance data as stated by WHO in order to target chains of transmission for interruption.(75)
3. Calculate the basic reproduction number (R_0) of the outbreak. R_0 is the mean number of secondary infections per infectious agent that occurs during the infectious period in a population that is completely susceptible at calendar time 0.

II. Methods

Data sources, collection, and handling

Measles is a notifiable infectious disease in Guinea. In accordance with national policy, measles case data from health centres and health facilities must be reported to their health district on a weekly basis. The health districts in turn must report it at the same frequency to the regional and central levels. With the support of WHO, the outbreak linelist data used here were collected by health district teams from the measles case investigation forms sent by health facilities. This linelist was reported weekly to the national level. Laboratory confirmation was performed at the

Guinea National Laboratory of Virology using enzyme-linked immunosorbent assay (ELISA) methods to detect immunoglobulin M (IgM), and information relevant to measles testing were compiled in the laboratory database for each case. Vaccination status of cases was typically determined by the health facilities based on the child's vaccination card and/or log book (Mory Keita, personal communication, 2018). The finalized outbreak dataset was compiled by ANSS and provided to WHO. The datasets are the property of ANSS and WHO.

Outbreak case definition

Cases in the outbreak presented here were defined and classified using national Integrated Disease Surveillance Response (IDSR) guidelines and WHO reference documents. The WHO clinical case definition for measles is: "any person in whom a clinician suspects measles infection, or any person with fever and maculopapular rash (i.e. non-vesicular) and cough, coryza (i.e. runny nose) or conjunctivitis (i.e. red eyes)."(63) Cases were classified as laboratory confirmed, epidemiologically confirmed, or clinically compatible. To determine classification, the following case definitions were utilized:

- **Case confirmed by laboratory:** Any person for whom a health worker suspects measles with detectable measles virus-specific IgM antibodies following an ELISA test.
- **Case confirmed by epidemiological link (epi-link):** Any person for whom a health worker suspects measles whose infection has not been confirmed by a laboratory, but the case is geographically and temporally related to a laboratory-confirmed case (i.e. case lived in the same village as a confirmed case).
- **Clinically compatible:** Any person for whom a health worker suspects measles who has fever, maculopapular (non-vesicular) generalized rash, and at least one of cough, coryza, or conjunctivitis for which no adequate clinical specimen was taken and which have not been linked epidemiologically to a laboratory-confirmed case of measles or to laboratory-confirmed case of another communicable disease.

At the beginning of the outbreak, once a health district was declared part of the outbreak, all suspected cases in the district were presumed confirmed by epi-link. Therefore, for the first 12 weeks of 2017, cases confirmed by epi-link were residents in an affected health district with clinical symptoms compatible with measles. The epi-link criterion was reviewed in epi-week 13 when cases began to decrease after the beginning of the response vaccination campaign, and epilinkage was thereafter restricted to the village level, rather than by health district per WHO recommendations (Mory Keita, personal communication, 2018).

The cases presented here are believed to represent approximately 80% of all cases during the year 2017. Private health structures are not yet all integrated into the epidemiological surveillance system and are therefore not all reporting epidemic prone-diseases to the health districts. Moreover, the data transmitted along the surveillance system, from the lower levels to central level, are not without the potential for error (Mory Keita, personal communication, 2018). To promote consistency of information in the database, WHO reclassified some cases whose final status was not completed, considering the information available in the database and WHO case definitions (Appendix, Figure 8). As of June 2018, the outbreak was considered ongoing in certain health districts, however this analysis has an upper limit of cases with illness onset reported by the end of 2017.

Mathematical models for calculation of effective reproductive numbers

Mathematical modelling of infectious diseases has been gaining traction in recent years and numerous methods are available. The more traditional approach for measles modelling is to fit a compartmental model to available data.(76) Well known compartmental models include the susceptible-infected-recovered (SIR) and susceptible-exposed-infected-recovered (SEIR) models. Various other model types exist, including time-since-infection(77,78), Bayesian,(79) maximum likelihood,(68,80) and branching process(81,82) models.

In this paper, likelihood-based estimation was used to infer the temporal pattern of R from an observed epidemic curve as described by Wallinga and Teunis and implemented in the R software by Obadia, Haneef, and Boëlle.(68,83) This method was preferred as incidence (case-count) data was the primary model input. The methods rely on the probabilistic reconstruction of transmission trees and count the number of secondary cases per infected individual. They are briefly redescribed here:

In the model, p_{ij} is the relative likelihood that case i has been infected by case j, given their difference in time of symptom onset $t_i – t_j$ of generation interval w. The probability compares the relative likelihood that case i has been infected by case j normalized by the likelihood that case i has been infected by any other case k—i.e. the average across all possible transmission networks of the outbreak curve.

$$p_{ij} = \frac{N_i w(t_i - t_j)}{\sum_{i \neq k} N_i w(t_i - t_j)}$$

R for case *j* is the sum over all cases *i*, weighted by the relative likelihood that case *i* has been infected by case j, $R_j = \sum_i p_{ij}$, and is averaged as $R_t = \frac{1}{N_t} \sum_{\{t_j = t\}} R_j$ for a single day over all cases with that same date of onset. The method is beneficial in the absence of detailed contact tracing data. Using this MLE method, it is also possible to account for not-yet-observed secondary cases.(83)

As infector-infectee pairs were not reported in the outbreak dataset, GT could not be calculated empirically. Instead, the model assumed a gamma-distributed GT with a mean of 12 days and a standard deviation (SD) of 2.0 days, based on findings from Klinkenburg and Nishiura, among others.(70,84–86) The models were run across 10,000 simulations. The estimate for *R* is the average of daily estimates of R_t for a given time period. The 95% confidence intervals (CI) were obtained through simulations.(44) All calculations using the models described hereafter were conducted using R version 3.4.3.(87)

Estimation of basic reproduction numbers from effective reproduction numbers

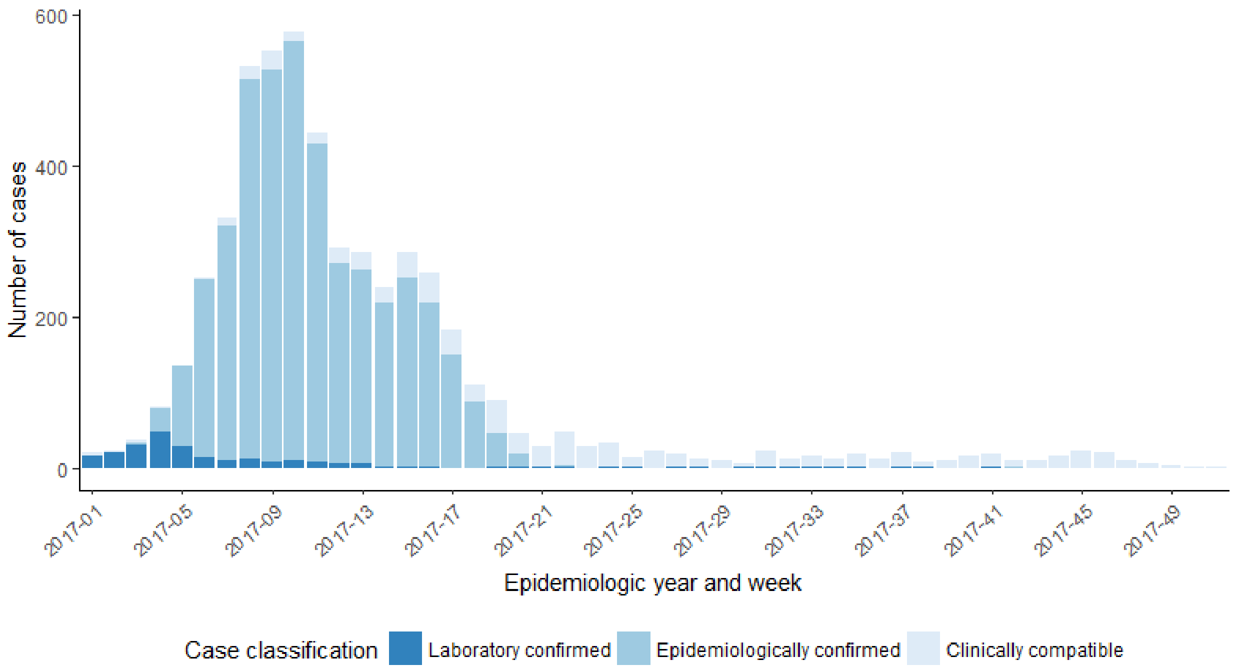
The relationship between R_0 and *R* was established using the equation $R_0 = R/(1 - I) = R/(1 - VE)$, where *V* represents VC and *E* represents VE.(88) R_0 was calculated using VC values of 54% (the WHO/UNICEF estimate for 2016) and 64% (the official estimate for 2016). VE was estimated at 86% and 95%, and 98%, which are the estimates of VE for MCV1 administration at 9, 12, and 15 months of age. Although Guinea recommends routine immunization at 9 months, due to the EVD outbreak many susceptible children likely received a first dose at > 9 months from the various vaccination campaigns conducted in 2015 and 2016 (**Table 1**). Due to the long nature of the outbreak (> 1 year), the smoothed R_t for epi-week 1 was used to calculate R_0, as otherwise transmission dynamics were likely affected by the seasonal variation in transmission(89), vaccination campaigns, and natural immunization from illness.

III. Results

Outbreak description

According to the WHO, the outbreak began the first epidemiologic week of 2017. The outbreak has continued through 2018. Between January 2 and December 31, 2017, there were a total of 5,931 measles cases reported to ANSS and recorded in the outbreak linelist. Cases had reported illness onsets between January 2 and December 25, 2017, though one-tenth (11.1%) of cases were missing date of illness onset in both the outbreak and laboratory datasets. Less than 5% of cases were laboratory-confirmed. Most (79.6%) met the clinical case definition and were epidemiologically linked to a confirmed case, while an additional 16.1% were considered clinically compatible suspect cases (Table 3). Testing dates for laboratory-confirmed cases were clustered towards the beginning of the year, with none identified among cases with onsets between October 12 and December 31. Most cases with illness onset towards the end of 2017 were classified as clinically compatible (Figure 3).

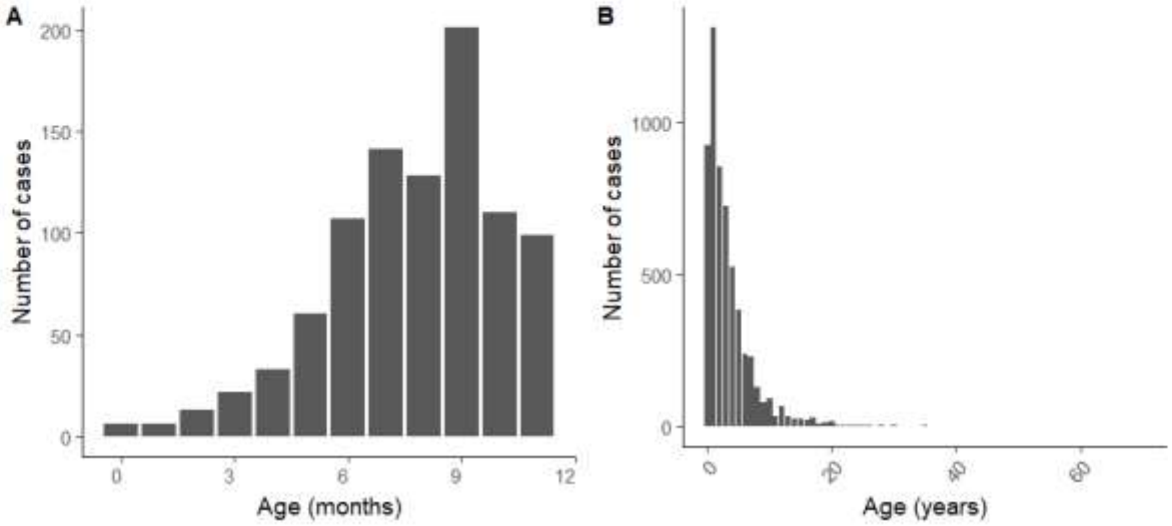
Figure 3. Epidemic curve of measles cases in outbreak by epidemiologic week of symptom onset—Guinea, 2017



Among cases for whom age was known, three-quarters (74.1%) were children under 5 years of age. The median age was 2 years (IQR: 1–5 years). Among cases < 1 year of age (n=988), only 14% were under the age of 6 months—an age where they are too young to be targeted for vaccination and are generally considered to be protected by maternal antibodies. Only 2.8% of cases were over the age of 15 years. Just under half (47.4%) of the cases were female (Table 3).

Conakry was the most affected region, with 2,142 cases (36.1% of all cases). N'Zérékoré and Kindia regions were also greatly affected, accounting for 1,564 and 1,269 cases respectively (26.4% and 21.4% of all cases). In these three regions, more than 85% of cases were epidemiologically confirmed.

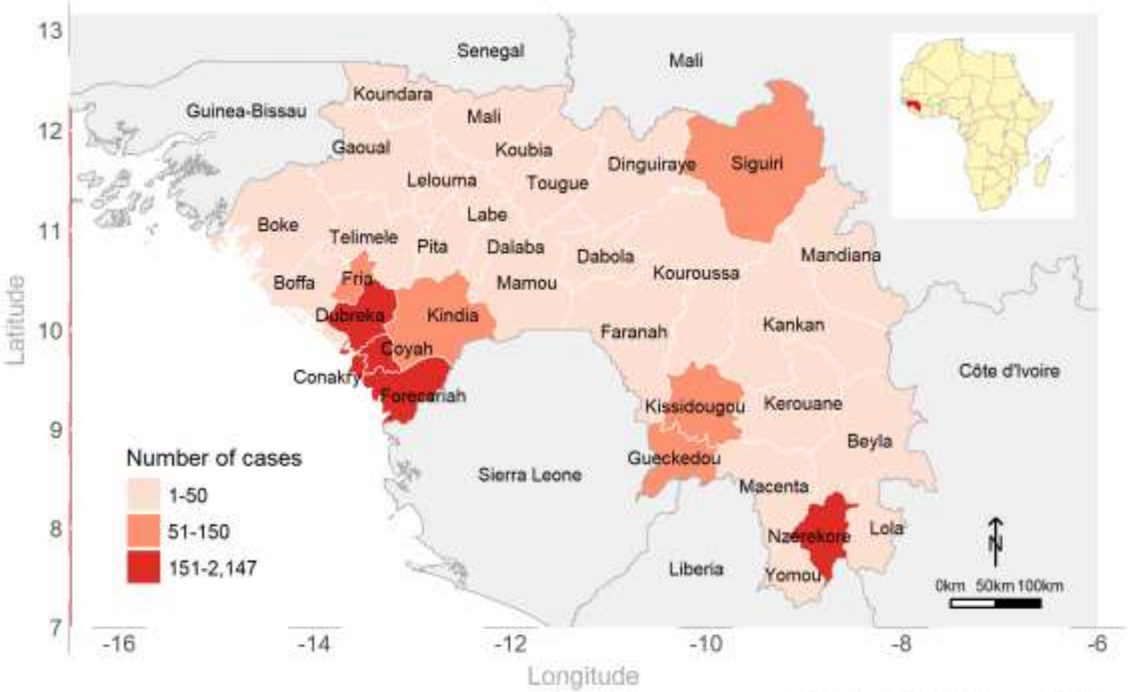
Figure 4. Frequency of measles cases by age—Guinea, 2017



A: Case age in months for cases < 1 year of age; **B**: Case age in years for all cases

Of the 5,931 cases, there were 29 deaths (case-fatality rate [CFR] of 4.9 per 1,000 cases). All fatalities were among children under 15 years of age. Most fatalities (72%) were among children under 5 years of age. Kindia Prefecture had the highest number of deaths at 9 deaths (**Table 3**), as well as the highest CFR (48.9 deaths per 1,000 cases). Information on date of death for deceased cases was not included in the outbreak dataset.

Figure 5. Cases in measles outbreak by prefecture—Guinea, 2017



Projection: WGS84; Source: WHO

Vaccination status of cases

The proportion of cases with known vaccination history was 88.1% (n = 5,226), of whom only 13.5% were listed as being previously vaccinated. Descriptive characteristics of cases by vaccination status are presented in (Table 2). Among cases ≥ 9 months–4 years of age, a slightly higher proportion of cases were vaccinated compared to unvaccinated (72.6% versus 67.1%). A larger proportion of cases ≥ 5 years of age were vaccinated compared to unvaccinated cases. A lower proportion of deceased cases were vaccinated (0.1%) compared to unvaccinated cases (0.7%). In addition, a larger proportion of clinically compatible cases were vaccinated compared to unvaccinated (28.5% versus 15.5%) and a larger proportion of laboratory confirmed cases were vaccinated compared to unvaccinated cases (7.8% versus 4.6%). In contrast, among epidemiologically confirmed cases a smaller proportion were vaccinated compared to unvaccinated (63.7% versus 80.0%).

Nearly one-tenth of cases (8.7%) were infants under 9 months of age. Of those, 72.9% were between 6–8 months of age, and vaccination status was available for 329 of them (87.5%), with only 11.2% reported as vaccinated. For cases among whom vaccination status is known, the regions of Kindia and Conakry had the lowest proportion of vaccinated cases. The Labe and Mamou regions had the highest proportion of vaccinated cases, but also had the least number of cases (Table 3).

Table 2. Descriptive characteristics of cases overall < or ≥ 9 months of age and by vaccination status for cases ≥ 9 months of age—Guinea, 2017

Characteristic	Cases < 9 months	Cases ≥ 9 months	Vaccination status, cases ≥ 9 months		
			Previously vaccinated	Not previously vaccinated	Unknown
Number of cases	516	5,353	752	3,992	609
Age in years (%)					
< 1	516 (100)	410 (7.7)	74 (9.8)	291 (7.3)	45 (7.4)
1–4	—	3,423 (63.9)	430 (57.3)	2,605 (65.3)	388 (63.7)
5–9	—	1,068 (20.0)	195 (25.9)	751 (18.8)	122 (20.0)
10–14	—	262 (4.9)	31 (4.1)	197 (4.9)	34 (5.6)
≥ 15	—	190 (3.5)	22 (2.9)	148 (3.7)	20 (3.3)
Sex (%)					
Female	233 (45.2)	2,558 (47.8)	359 (47.7)	1,920 (48.1)	279 (45.8)
Male	278 (53.8)	2,789 (52.1)	392 (52.2)	2,068 (51.8)	329 (54.0)
Unknown	5 (1.0)	6 (0.1)	1 (0.1)	4 (0.1)	1 (0.2)
Case classification (%)					
Laboratory confirmed	11 (2.1)	245 (4.6)	59 (7.8)	182 (4.6)	4 (0.7)
Epidemiologically confirmed	430 (83.3)	4,241 (79.2)	479 (63.7)	3,193 (80.0)	569 (93.4)
Clinically compatible	75 (14.6)	867 (16.2)	214 (28.5)	617 (15.5)	36 (5.9)
Vital Status (%)					
Alive	466 (90.3)	4,673 (87.3)	657 (87.4)	3,492 (87.5)	524 (86.0)
Deceased	1 (0.2)	28 (0.5)	1 (0.1)	26 (0.7)	1 (0.2)
Unknown	49 (9.5)	652 (12.2)	94 (12.5)	474 (11.9)	84 (13.8)
Region of residence (%)					
Boké	11 (2.1)	298 (5.6)	100 (13.3)	196 (4.9)	2 (0.3)
Conakry	230 (44.6)	1,861 (34.8)	164 (21.8)	1,418 (35.5)	279 (45.8)
Faranah	15 (2.9)	181 (3.4)	43 (5.7)	116 (2.9)	22 (3.6)
Kankan	30 (5.8)	256 (4.8)	46 (6.1)	209 (5.2)	1 (0.2)
Kindia	112 (21.7)	1,148 (21.4)	46 (6.1)	1,096 (27.5)	6 (1.0)
Labé	1 (0.2)	51 (1.0)	22 (2.9)	29 (0.7)	0 (0.0)
Mamou	14 (2.7)	97 (1.8)	36 (4.8)	51 (1.3)	10 (1.6)
N'Zérékoré	103 (20.0)	1,461 (27.3)	295 (39.2)	877 (22.0)	289 (47.5)

Table 3. Case characteristics by region of residence—Guinea, 2017

Characteristic	National	Boké	Conakry	Faranah	Kankan	Kindia	Labé	Mamou	N'Zérékoré
Number of cases	5,931	309	2,142	197	287	1,269	52	111	1,564
Age in years (%)									
< 1	926 (15.6)	29 (9.4)	413 (19.3)	31 (15.7)	47 (16.4)	195 (15.4)	1 (1.9)	21 (18.9)	189 (12.1)
1–4	3,423 (57.7)	160 (51.8)	1,301 (60.7)	119 (60.4)	181 (63.1)	765 (60.3)	20 (38.5)	46 (41.4)	831 (53.1)
5–9	1,068 (18.0)	80 (25.9)	268 (12.5)	34 (17.3)	45 (15.7)	211 (16.6)	17 (32.7)	34 (30.6)	379 (24.2)
10–14	262 (4.4)	18 (5.8)	65 (3.0)	3 (1.5)	6 (2.1)	46 (3.6)	6 (11.5)	10 (9.0)	108 (6.9)
≥ 15	190 (3.2)	22 (7.1)	44 (2.1)	9 (4.6)	7 (2.4)	43 (3.4)	8 (15.4)	0 (0.0)	57 (3.6)
Unknown	62 (1.0)	0 (0.0)	51 (2.4)	1 (0.5)	1 (0.3)	9 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Sex (%)									
Female	2,814 (47.4)	149 (48.2)	958 (44.7)	105 (53.5)	121 (42.2)	611 (48.1)	26 (50.0)	59 (53.2)	785 (50.2)
Male	3,098 (52.3)	160 (51.8)	1,174 (54.8)	92 (46.7)	166 (57.8)	649 (51.1)	26 (50.0)	52 (46.8)	779 (49.8)
Unknown	19 (0.03)	0 (0.0)	10 (0.5)	0 (0.0)	0 (0.0)	9 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Case classification (%)									
Laboratory confirmed	258 (4.4)	16 (5.2)	61 (2.8)	32 (16.2)	26 (9.1)	79 (6.2)	5 (9.6)	14 (12.6)	25 (1.6)
Epi-link confirmed	4,270 (79.6)	229 (74.1)	1,961 (91.5)	28 (14.2)	1 (0.3)	1,106 (87.2)	1 (1.9)	0 (0.0)	1,394 (89.1)
Clinically compatible	953 (17.1)	64 (20.7)	120 (5.6)	137 (69.5)	260 (90.6)	84 (6.6)	46 (88.5)	97 (87.4)	145 (9.3)
Previously vaccinated (%)									
No	4,428 (74.7)	205 (66.3)	1,616 (75.4)	129 (65.5)	236 (82.2)	1,206 (95.0)	30 (57.7)	62 (55.9)	994 (60.4)
Yes	798 (13.5)	102 (33.0)	185 (8.6)	45 (22.8)	49 (17.1)	49 (3.9)	22 (42.3)	38 (34.2)	308 (19.7)
Unknown	705 (11.9)	2 (0.6)	341 (15.9)	23 (11.7)	2 (0.7)	14 (1.1)	0 (0.0)	11 (9.9)	312 (19.9)
Vital Status (%)									
Alive	5,191 (87.5)	302 (97.7)	1,970 (92.0)	115 (58.4)	209 (72.8)	1,152 (90.8)	49 (94.2)	111 (100.0)	1,283 (82.0)
Deceased	29 (0.5)	1 (0.3)	4 (0.2)	1 (0.5)	1 (0.3)	11 (0.9)	0 (0.0)	0 (0.0)	11 (0.7)
Unknown	711 (12.0)	6 (1.9)	168 (7.8)	81 (41.1)	77 (26.8)	106 (8.4)	3 (5.8)	0 (0.0)	270 (17.3)

Reproduction number calculations

Estimations were calculated from 5,270 cases with available dates of symptom onset. The dataset was truncated after day 346 (December 13, 2017, epi-week 50), as there was a gap in cases of 11 days, with only one case with onset on December 25, and no cases thereafter. The model estimated $R = 1.02$ (95% CI 0.39–2.03) for all cases with onsets between January 2 and December 13, 2017. R dropped below unity ($R = 1$) at day 60 (March 2, epi-week 9). Although spatial patterns are not considered in the models, the data were stratified by region for areas where there were > 1,000 cases to assess temporal transmission in each region.

Weekly smoothed R for all Guinea and for the three regions with the most cases are plotted in Figure 6. The overall weekly smoothed estimate of R for epi-week 1 was 3.01 and was highest in week 2 at 3.24. $R < 1$ was not maintained, even though vaccination control measures were implemented beginning day 71 with the ORI in N'Zérékoré, followed by an ORI initiated in Conakry on day 96, and in Kindia and other regions on day 110. After dropping below unity at day 60 (before the ORI campaigns began), R rose back above unity at day 86 (just around when vaccinations from the ORI campaign in N'Zérékoré would begin to give protection). The fluctuation of R_t later in the year reflects the fluctuations in the epidemic curve (Figure 7).

The weekly R estimates are truncated for the three regions (Conakry, Kindia, and N'Zérékoré) based on the time when a gap in cases occurred that was > 9 days, as the model will become biased when the gap in cases exceeds the mean GT ± SD. Truncation was performed after day 192 for Conakry, day 173 for Kindia region, and day 103 for N'Zérékoré region (Figure 6). R calculated for Conakry, Kindia, and N'Zérékoré during the time periods prior to implementation of the ORI vaccination campaigns were estimated at 1.87 (1.06–2.06) for N'Zérékoré during days 1–71, 1.61 (0.78–2.57) for Conakry during days 1–96, and 1.36 (0.58–2.28) for Kindia during days 1–110. The value of R_0 necessary to generate the outbreak was 5.62 (3.17–8.50) based on WHO/UNICEF estimates of VC in 2016. The estimate of R_0 using official data (a 10% increase in the VC estimate) was 6.69 (3.78–10.12). Results of the model are summarized in (Table 4).

Figure 6. Instantaneous reproduction numbers (R_t) smoothed by week in Guinea and three regions for cases with illness onset between January 2–December 13, 2017

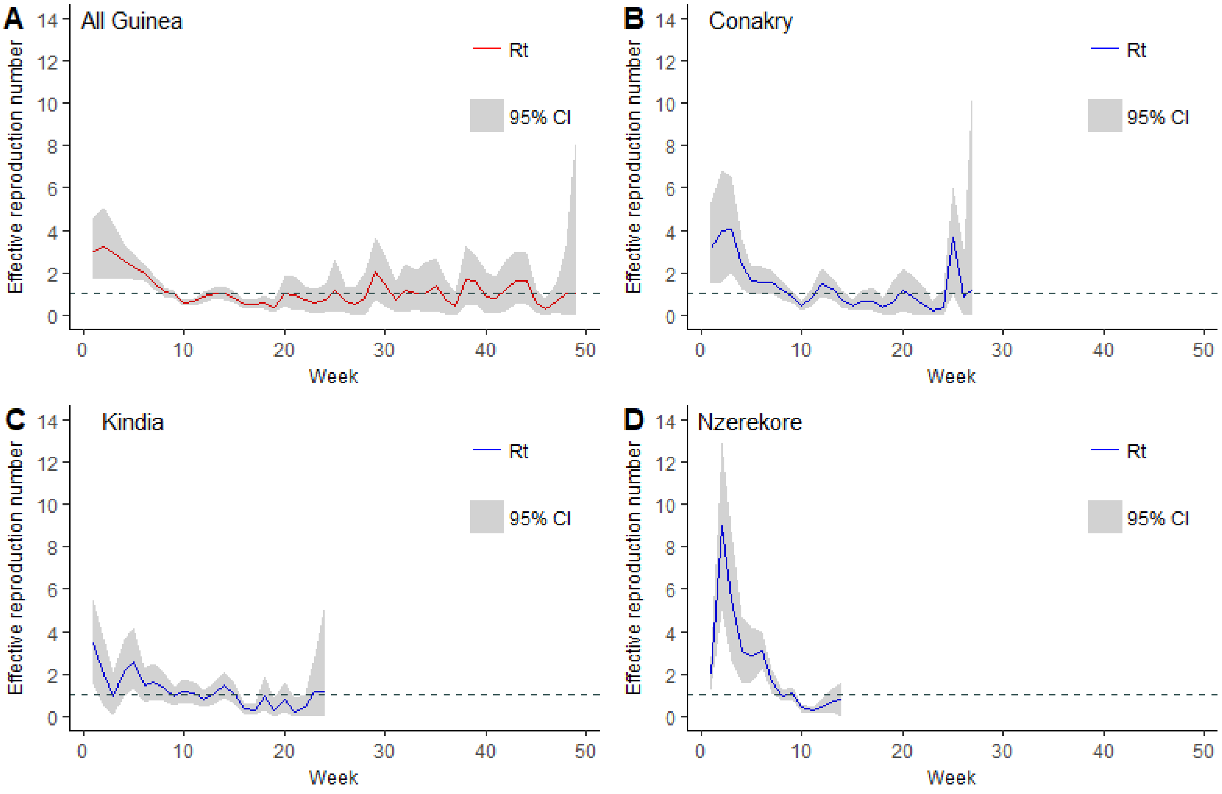


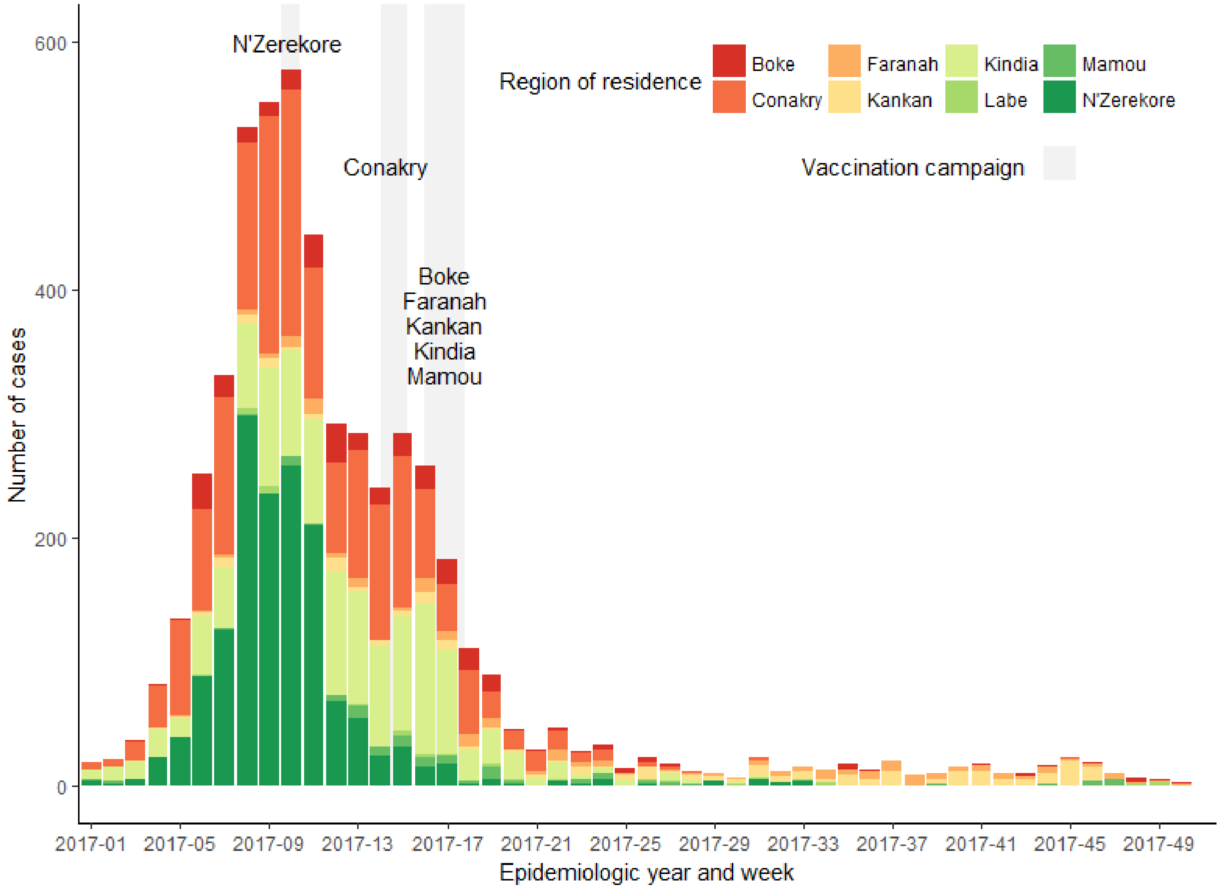
Table 4. Reproduction numbers for different parameters and time periods for measles outbreak cases in Guinea with illness onset between January 2–December 13, 2017

Region	Parameter	Data*/Time†	Estimate (95% CI)
All regions	R_0	WHO/UNICEF data	5.62 (3.17–8.50)
		Official data	6.69 (3.78–10.12)
All regions	$R_{t=week1}$	Epidemic week 1	3.01 (1.70–4.55)
	R	All	1.02 (0.39–2.02)
	$R_{t=1:71}$	Days 1-71	1.99 (1.24–2.85)
	$R_{t=71:134}$	Days 71-134	0.69 (0.43–0.98)
N'Zérékoré‡	$R_{t=1:71}$	Days 1–71	1.87 (1.06–2.06)
Conakry	$R_{t=1:96}$	Days 1–96	1.61 (0.78–2.57)
Kindia	$R_{t=1:110}$	Days 1–110	1.36 (0.58–2.28)

* WHO/UNICEF vaccination coverage estimate is based on the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) estimate of 54% vaccination coverage in 2016(25); the official data estimate was 64% for 2016. R_0 is estimated from the weekly-smoothed R of epidemic week 1 using the equation $R_0 = R/(1\text{-}VE)$, where V = vaccination coverage and E = vaccine efficacy at 9 months (86%).

† Day 71 = March 13, the first day of the outbreak response immunization campaign in N'Zérékoré.
Day 96 = April 7, the first day of the outbreak response immunization campaign in Conakry.
Day 110 = April 21, the first day of the outbreak response immunization campaign in 21 districts, including in Kindia.
Day 134 = May 15, two weeks after the last day of the outbreak response immunization campaign targeting 21 districts.

Figure 7. Epidemic curve of measles outbreak cases by epidemiologic week and region of residence—Guinea, 2017



IV. Discussion

In 2017, measles outbreaks spiked in many parts of the world. Europe saw a 4-fold increase in measles cases compared to 2016,(90) and four countries in the Americas—the first (and only) WHO region to declare measles eliminated—reported over 200 imported or import-related cases.(91,92) Achieving and maintaining sensitive surveillance systems and high VC worldwide is critical to measles elimination efforts. A decrease in VC or uptick in disease incidence in any one region increases the risk of case importation in other regions. In order to understand the VC necessary to achieve and maintain elimination, context-specific reproduction number estimates are necessary.

The factors that relate to sustained transmission in outbreaks tie back to the susceptibility of individuals in a population. Guinea was estimated to be particularly vulnerable to measles outbreaks in the time following the West African EVD epidemic—a biological disaster that was even declared a Public Health Emergency of International Concern.(93) A regional measles outbreak between Guinea, Sierra Leone, and Liberia based on a large connected cluster of unvaccinated children could have developed into 127,000–227,000 cases,(6,49) but was likely prevented by vaccination efforts that occurred in response to national level measles outbreaks during the EVD emergency,(94) as well as SIA and ORI campaigns that followed (Table 1). The 2017–2018 measles outbreak is the largest Guinea has seen in at least the last 5 years. Low VC was likely a factor in local transmission, and was itself a result of interruptions to routine vaccination and reduced healthcare availability and access in the wake of the EVD epidemic.(6,95)

The intent of this thesis was to explore the temporal distribution of transmission of measles using the epidemic curve of the outbreak from cases reported in 2017. In developing countries, high-quality datasets are often not available, so models that rely on fewer assumptions and require less information can be useful to assisting developing countries in meeting WHO targets for surveillance indicators.(75)

As the estimates for R in the first epi-week of 2017 were > 1, it can be assumed that R in Guinea had been > 1. Analyses of the effective and basic reproductive numbers for the first 364 days of the outbreak resulted in an estimated R of 1.02 (95% CI 0.39–2.03). That the value of R is close to 1 is unsurprising given that the date range captures extrinsic interventions (i.e. ORIs and other public health responses such as isolation of infectious cases) as well as the intrinsic natural depletion of susceptible individuals.

Context of reproduction numbers

Standardized methods for calculating R_0 have not been established. For the same disease, R_0 may differ considerably between affected populations based on the characteristics of the population as well as the data sources and calculation methods used. Further, R_0 depends on the duration of the infectious period, the probability of infecting a susceptible individual during one contact, and the number of new susceptible individuals contacted per unit of time. It is also sensitive to dispersal of transition times (i.e. recovery, isolation, or death) and progression of the disease.(96) High birth rates and population densities, common for urban centers in low-income countries, have been associated with high R_0.(27) In a recent systematic review of published measles R_0 conducted by Guerra et al., the median R_0 among least-developed countries in the post-vaccine era was 15.9. The median R_0 among studies conducted in the WHO-AFRO region was 12.8.(27)

The value of R_0 necessary to generate the outbreak was 5.62 (3.17–8.50) based on WHO/UNICEF estimates of VC in 2016 (Table 4), which is lower than the pre-vaccine era commonly cited estimates of 12–18 and post-vaccine era median estimate of 16 found by Guerra et al. in a systematic review of measles R_0.(27) The estimate of R_0 using official data (a 10% increase in the VC estimate) was 6.69 (3.78–10.12). VE was set at 86%, but R_0 would be higher if VE were presumed greater due to the likelihood that additional doses and doses at a later age were administered during the 2016 SIA and outbreak response campaigns. Increasing VE to 95% and 98% for the WHO/UNICEF estimates of 54% VC results in R_0 estimates of 6.18 and 6.40. R_0 estimates in Guinea lower than the post-vaccine era median of 16 may not be surprising given the wide range of R_0 in the literature and lower median R_0 noted in the WHO-AFRO region compared to other WHO regions.(27)

Quality of disease surveillance and immunization data

Known problems with disease surveillance in Guinea may include: low involvement in the community-based surveillance process in certain areas, low participation from private health facilities, and limited laboratory availability to rapidly confirm disease—an essential factor for a rapid response (Mory Keita, personal communication, 2018). The performance of measles surveillance in selected health districts is assessed through the timeliness and completeness of weekly data provided by public structures at the national level. The promptness and completeness of sending the databases are close to 100%. However, the completeness and quality of the data and indicators need improvement.(43) During the outbreak, the change in epi-link criteria beginning epidemiologic week 13 may have also influenced identification of true cases compared to the previous weeks.

Strengths, limitations, and interpretation of model results

To the best of our knowledge, the method presented by Wallinga and Teunis and coded for R by Obadia, Haneef, and Boëlle have not been used to assess *R* for a measles outbreak, although it has been used to calculate *R* for other acute diseases with relatively short serial intervals such as Ebola.(97) Daily incidence data were available for this analysis, which is a time scale smaller than the mean GT—a prerequisite for the MLE procedure.(83) In addition, gaps in reported cases (consecutive days with 0 cases reported) for the overall model never exceeded the maximum GT, reducing the potential for bias in the model.(83) For region-specific models where bias was possible due to gaps in cases, the models were truncated to the last date with illness onset prior to a gap in cases greater than the mean GT ± SD.

Estimates of R and R_0 depend greatly on the distribution of the GT,(98) which could not be empirically calculated from the available datasets as infector-infectee pairs were not tracked. Instead, the models assume that the GT was known throughout the time periods of the outbreak being analysed (calculated as gamma-distributed with values based on past studies). However, the distribution of GT could change during the outbreak due to interventions in later periods and an inability to account for these changes could lead to some bias in the estimates of R presented here.(83) The R value of 1.02 (95% CI 0.39–2.03) was obtained by averaging R_t for the entire time period. After initial growth and decrease, the curve of R fluctuated in later periods in sync with the epidemic curve. This is typical of how an outbreak in a first geographic area is stamped out, but later many other geographic locations experienced outbreaks.

In the epidemic curve, most cases were in Conakry, Kindia, and N'Zérékoré during the growth phase of the outbreak, but towards the end most cases were Kankan region residents (Figure 7). Although R is presented as stratified by region, the MLE procedure used in this thesis only considers the temporal pattern of R and does not adjust for spatial patterns. As measles transmission patterns are rooted in human interactions across spatial scales,(33) accounting for spatial dynamics could produce different estimates. Additionally, the outbreak took place over a long period of time, so it was by no means in a closed population. High birth rates continued to introduce susceptible individuals to the population. However, the MLE method does not depend on population estimates to estimate transmission.

The highest single value of R_t was for day 1 ($R_t = 5.77$). It is possible that value is an overestimation due to the outbreak not being observed from the first case. As Guinea also experienced an outbreak in October–December 2016 in Dubréka, Gueckédou, Kindia, Matoto, and N'Zérékoré prefectures, it is plausible that some initial cases for this outbreak were counted as cases in the preceding outbreak, and some of the "initial" cases in the 2017 outbreak are secondary cases that are imputed to too few index cases.(83)

As mentioned previously, cases reported in the dataset are estimated to account for ~80% of outbreak cases that presented to clinics over the year period. The calculations for *R* assume that all infected persons will present with overt clinical symptoms and that all cases will be reported. Underestimation of daily incident case counts could influence the estimations of *R* presented here if underreporting is not constant in time. However, when developing the procedure Wallinga and Teunis compared a model from real data with presumed complete reporting to a model with 0.5 probability of each case being reported and the resulting estimates were only slightly less accurate than the model with complete reporting.(68)

Vaccination coverage and reported vaccination status

Estimates of MCV1 coverage in Guinea differ greatly depending on the reporting source. The WHO/UNICEF estimate for MCV1 coverage in 2016 was 54%, while the official national estimate was 64%, the administrative estimate was 120%, and the average of subnational district estimates was 98%.(24,99) The WHO/UNICEF 2016 estimate was calibrated to a 2014 estimate based on the difference between reported administrative and official data. The official estimate was based on a national assessment of the most likely coverage based on any combination of data. The administrative estimate was based on aggregated administrative reports from health service providers on the number of vaccinations administered during a given period (numerator data) and reported target population data (denominator data), of which both sources may be biased by inaccuracies.(24,99)

Regular SIAs at high coverage levels can prevent measles outbreaks.(100) Guinea is able to achieve high coverage rates during SIAs (Table 1), however these rates may be biased by an inaccurate denominator.(35,101) The National Statistical Institute of Guinea estimated the 2017 Guinean population at 11.3 million, while the World Bank put the estimate at 12.7 million.(8,9) If the true population size is closer to the latter estimate, then the target populations defined for SIAs or ORIs using the lower National Statistical Institute estimate may underrepresent the true target, resulting in overestimation of the percentage of the target population that is vaccinated. Moreover, as SIAs do not consider vaccination history or known clinical infection, individuals may be revaccinated, resulting in additional overestimation of the percentage of the target (susceptible) population that was vaccinated during a campaign.

Most cases in this outbreak (75.1%) with age information available were among children under 5 years old with no previous vaccination reported. However, it should be noted that vaccination status as recorded in the outbreak dataset is generally based on the child's vaccination card and log book—items which can differ from provider sources(102) and may underrepresent the true number of vaccinated cases. The low proportion of cases (1.4%) among infants less than 6 months of age is likely due to passive immunity via the mother, which wanes over time.(103)

Continued susceptibility of individuals to VPDs largely relates to VC, as most individuals gain immunity through vaccination. Public distrust of vaccines in Guinea was exacerbated by communication failures at the beginning of the EVD outbreak. Circulating rumors that vaccines brought EVD to Guinea and the resemblance between some of the side effects of MCVs and the first symptoms of EVD increased wariness and distrust of MCVs and other vaccines.(104,105) Vaccination efforts need to develop the appropriate messages, involve all aspects of communities in spreading these messages, as well as consider the sway on opinion held by community leaders (Mory Keita, personal communication, 2018).

Timing of vaccination

The case-fatality rate was 5 per 1,000 among children aged < 5 years. The youngest death was of an 8-month old child for whom vaccination status was unknown. The three children who died at 10 months of age were all reported as unvaccinated. The WHO recommendation to set routine administration of MCV1 at 9 months of age in areas with high measles incidence is intended to minimize exposure to maternal antibodies and maximize VE. However, in the era of measles elimination, presence of maternal antibodies may endure for less than 3 months(103) and delaying vaccination to increase efficacy also increases the opportunity for infants to be exposed to infection—particularly in countries like Guinea where incidence of measles is relatively high and routine vaccination coverage is low. In fact, MCV1 coverage in Guinea was only 19% for children 9 months of age in 2005 (overall coverage was estimated at 51%).(25,106)

Decreasing the WHO recommended age of MCV1 receipt from 9 to 6 months for countries with high measles incidence could reduce morbidity in the youngest age groups, and potentially improve VC levels for children at 9 months of age by providing additional opportunities for vaccination at an earlier age. Although seroconversion at 6 months has been estimated to be low

(30%, 95% CI: 17–60%), early vaccination with MCV has not been shown to be detrimental.(107) Decreased VE from early MCV1 administration could be ameliorated through vaccination with MCV2 at 12 or 15 months.(22)

V. Conclusion

Measles is a highly contagious disease, but its transmissibility relates not only to inherent characteristics of the pathogen, but also to characteristics of the population in which the virus is circulating. Understanding local transmission conditions can assist responders in countering and preventing outbreaks by providing insight into the population immunity and vaccination coverage thresholds necessary to prevent and eliminate transmission in a given region. However, during complex emergencies and large-scale outbreak situations, readily available data may be insufficient to parameterize models that require many variables, and staff likely will not have time to develop specialized models. This is particularly of note for developing countries that are struggling to meet basic surveillance indicators. In these scenarios, it can be helpful to investigators to leverage existing tools that require no more than incident case count and knowledge of the generation time or serial interval of the disease in question.

Sensitive and effective surveillance and improvements to health structures to support routine vaccination efforts are necessary components for addressing measles outbreaks and eventual elimination of the disease. As well, response plans for disease outbreaks such as Ebola and other emergencies should include preparations for sustaining vaccination activities in order to prevent measles outbreaks that would further strain health systems and response resources. Despite large-scale outbreak response SIAs with high percentages of the target population vaccinated that likely prevented many cases, overall immunity levels in Guinea have not been sufficient to maintain $R < 1$. As Guinea continues to recover from the recent Ebola epidemic and re-establish routine vaccination, attention should be paid to regions where transmission persists.

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Acknowledgements

Mory Keita provided the linelist dataset and extract of the laboratory database, provided contextual information for the data, and gave recommendations. Maria Rodrigues Leal Moitinho De Almeida connected me with Mory Keita. Joris van Loenhout was involved in the projection conception, liaison with collaborators, draft proof-reading and revision, supervised the work process, and approved the final product for submission and defence. Hiroshi Nishiura provided suggestions for research aims and assisted in some interpretation of results. The Erasmus Mundus Master in Public Health Disasters (EMMPHID) program provided financial support to cover tuition and living expenses associated with this thesis and the associated Master of Science course.

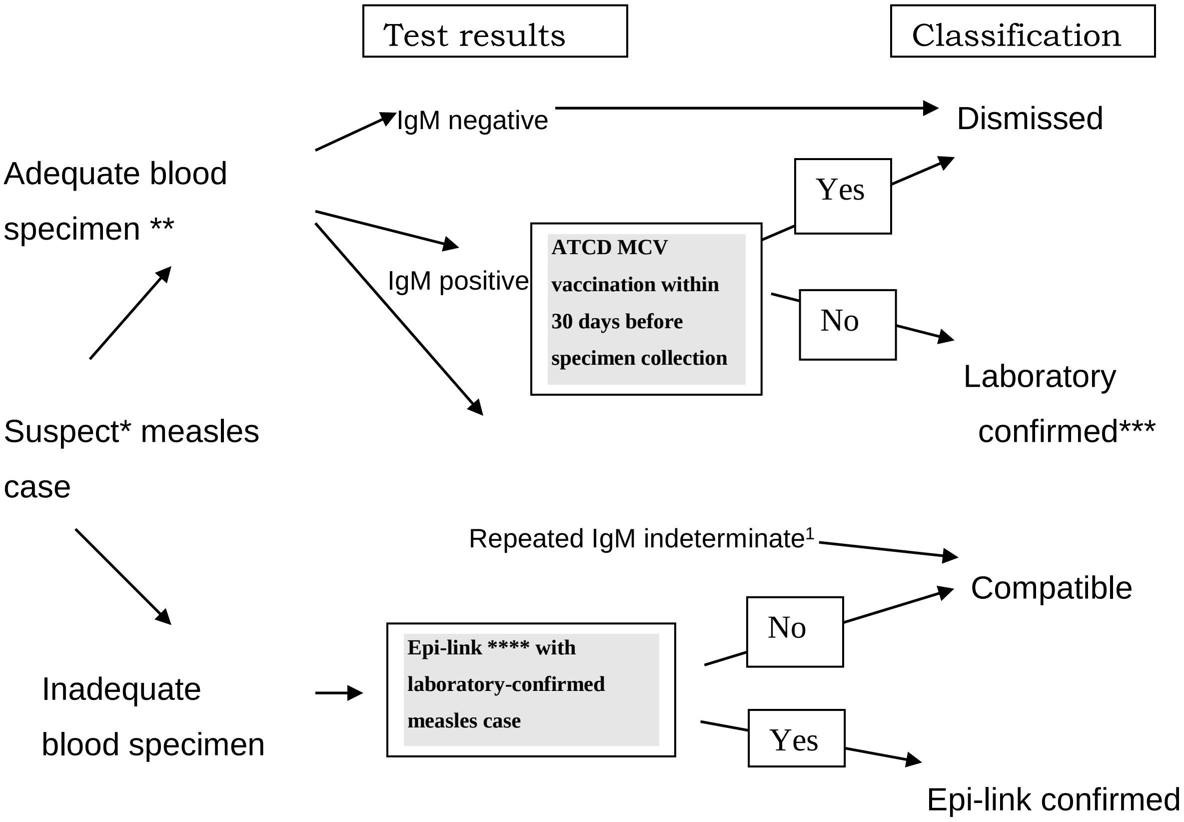
Statement of work

This thesis is my own work. All sources of information reported by others are indicated in the list of references.

Appendix

Figure 8. Classification diagram for suspect measles cases

For surveillance purposes, the World Health Organization (WHO) recommends the following scheme for the classification of measles cases.



Source: WHO African Region report—original document in French. Translated to English for reproduction in this thesis.

* Corresponds to the standard definition of measles case; fever and generalized maculopapular rash plus cough OR coryza OR conjunctivitis.

** An adequate specimen is one that is collected at first contact with a suspected case of measles **within the first 30 days after the onset of rash** and must be in **good condition**[2] (at adequate volume for the serological test, no leakage, no disturbed due to possible contamination, AND not dried up) until the arrival at the laboratory

*** Only if there is no history of measles immunization within 30 days before specimen collection.

******** Epidemiologic link (epi-link): corresponds to the definition of suspected case and has been in contact with a confirmed case (laboratory or epidemiological link) with eruption occurring in the previous 30 days (case living in the same district or in adjacent districts with plausible transmission).

[1] All serum specimens with indeterminate measles IgM results should be retested before being labeled "indeterminate" and classified as "Compatible".

[1] It is always recommended to avoid hemolysis by treating serum specimens in the field. However, hemolysis is not a reason to mark "bad" specimens when they are brought to the laboratory since it is known that hemolysis does not interfere with the IgM test for measles and rubella using the Behring test kit.

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