Exploring the epidemiology of malaria and the impact of malaria control interventions in malaria-endemic and Ebola-epidemic West Africa

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Dekan

« Il n’y a pas de réussite facile ni d’échecs définitifs. »

Marcel Proust

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Summary

Despite significant advances in the number and type of control measures available, malaria remains one of the leading causes of death worldwide, with the majority of burden concentrated in sub-Saharan Africa. Long-lasting insecticide treated bed nets, antimalarial treatment using artemisinin combination therapies, mass drug administrations, indoor residual spraying and seasonal malaria chemoprevention, are used individually and in combination, supported by community education programs and early detection and treatment protocols. Despite these advances, little evidence exists on how to utilize these interventions effectively in hyperendemic settings or during emergencies.

This thesis focuses on malaria control and surveillance in West Africa, particularly Guéckédou Prefecture, the Republic of Guinea and Monrovia, Liberia. Issues that malaria control programs face and the impact that such programs can have in hyperendemic settings and other challenging environments, specifically, the West Africa Ebola epidemic are explored. The evidence presented here builds a case for placing a stronger emphasis on implementing and sustaining control measures in areas of hyperendemicity. Additionally, the need to develop alternative strategies for managing the burden of malaria in both hyperendemic settings and during outbreaks is emphasized.

A multi-component malaria control intervention that was implemented in program conditions from 2011-2014 in Guéckédou Prefecture. In Chapter 4, both intervention coverage and the impact of the malaria control intervention on malaria parasite prevalence are quantified using data from biannual population based cross-sectional surveys. Over time, intervention coverage increased while rapid diagnostic test confirmed malaria parasite prevalence decreased in areas where the control activities were implemented. Yet, in the comparison area where activities were not implemented there was no significant change. Nevertheless, while the decrease in malaria parasite prevalence measured during the period of intervention was encouraging, the overall decline was relatively small and suggests a need to develop new or modify currently available control strategies in order to have a greater impact on malaria burden in similar areas.

During the study period, the area of intervention became the initial epicenter of the 2013-2016 Ebola Virus Disease (EVD) outbreak. Malaria control activities were reduced because of the outbreak in Guéckédou and all activities related to the multi-component malaria control intervention ceased. In Chapter 5 data collected from the cross-sectional surveys was used to parameterize a stochastic malaria transmission model to assess the impact of the sudden cessation of malaria activities in this context. The model predicted the monthly incidence of malaria cases according to two scenarios, i) a counterfactual scenario that assumes no reinforced malaria interventions occurred between 2011 and 2014, and ii) a scenario with reinforced malaria interventions that ceased at the start of the Ebola outbreak. Interrupted time series analysis was used to assess the impact of malaria control activity cessation on malaria incidence from April 2014. The incidence of uncomplicated malaria was estimated to have resurged to levels higher than that predicted to have occurred in the counterfactual scenario within 8 months of activity cessation in Guéckédou (April 2014). The models show that gains made in malaria control are not sustained and resurgence becomes a significant risk. In areas where malaria is highly endemic, advances made during control activity implementation are quickly negated when activities stop.

Upon arrival in Guéckédou in 2010, data from health facility based surveillance was deemed unreliable due to underreporting. Consequently, concurrent with the cross-sectional surveys, community-based sentinel site mortality surveillance was implemented in the same areas in order to monitor malaria attributable mortality. As described in Chapter 6, data on mortality from 43,000 individuals under surveillance was collected for 36 months. The ability of the surveillance system to capture mortality, health-seeking behavior and quantify malaria attributable mortality is described. No early warning system was in place prior to the Ebola outbreak, consequently it was detected 4 months after it began. Data collected through the community-based mortality surveillance system was evaluated retrospectively for its ability to detect outbreaks, specifically of Ebola, when adapted to syndromes. Indeed, two of the suspect Ebola deaths captured through the surveillance system were among the first laboratory confirmed cases from the 2013-2016 outbreak. Although challenging, this demonstrates that prospective community-based mortality surveillance using sentinel sites can provide a means to document mortality and facilitate outbreak detection in low resource settings.

As the Ebola outbreak evolved into a multi-country epidemic, the response moved from vertical programming to a more holistic response that incorporated the innovative use of classic malaria control strategies. One of these strategies included the first mass drug administration (MDA) of malaria chemoprevention carried out during an Ebola outbreak. In post distribution surveys of individuals attending the distributions reported in Chapter 7, the incidence of self-reported fever decreased from 4.2% in the month prior to the first distribution to 1.5% after the first distribution. Yet, only 52% of household members initiated treatment after round 1 and only 22% after round 2. While the reduction in self-reported fever cases suggests that MDA may be effective in reducing cases of fever during Ebola outbreaks, the low treatment initiation suggests the need for longer-term interventions to prevent malaria and to improve access to healthcare.

All of these different aspects combined provide a unique perspective on malaria control in normal and emergency settings in malaria endemic areas of West Africa. Malaria control programs implemented in hyperendemic settings in program conditions can result in a decrease in malaria parasite prevalence and malaria attributable mortality. Yet, malaria morbidity can be expected to resurge quite quickly if activities are not sustained. In areas where health facility surveillance is weak, community-based surveillance can be implemented to both capture malaria related mortality and detect outbreaks. Finally, in order to mitigate the mortality that is inherent with both malaria and Ebola infections, particularly during outbreaks, the ability to differentiate between the two (in light of their common features) need to be improved. These lessons need to be translated into improved surveillance and response strategies in order to detect and respond to both diseases, potentially resulting in a synergistic decrease in mortality.

Acronyms and abbreviations

ACT	Artemisinin based Combination Therapies
ASAQ	Artesunate-Amodiaquine
ASAQ-CP	Artesunate-Amodiaquine Chemoprevention
CCL	Chairmen and Community Leaders
CDC	Centers for Disease Control and Prevention (USA)
CMR	Crude Mortality Rate
CHW	Community Health Worker
CV	Community Volunteer
DHA-PQP	Dihydroartemisinin-Piperaquine
DHS	Demographic and Health Survey
DOT	Directly Observed Treatment
EIR	Entomological Inoculation Rate
ETC	Ebola Treatment Center
EVD	Ebola Virus Disease
FDC	Fixed dose combination (refers to ASAQ)
FHF	Filovirus Hemorrhagic Fever
GBD	Global Burden of Disease Study
HDSS	Health and Demographic Surveillance System
HRP2	Histidine-rich protein 2
IPT	Intermittent Preventive Treatment
IPTi	Intermittent Preventive Treatment for infants
IPTp	Intermittent Preventive Treatment for pregnant women
IRS	Indoor Residual Spraying
ITN	Insecticide Treated Net
LLIN	Long Lasting Insecticide treated Net
LMIS	Liberia Malaria Indicator Survey
MDA	Mass Drug Administration
MOH	Ministry of Health
MSF	Médecins Sans Frontières
PNLP	Programme National de Lutte contre le Paludisme
R	Round
RBM	Roll Back Malaria (Organization)
RDT	Rapid Diagnostic Test
sEVD	Suspect Ebola Virus Disease
SMC	Seasonal Malaria Chemoprevention
U5MR	Under 5 Mortality Rate
VA	Verbal Autopsy
WHO	World Health Organization
Yrs	Years (of age)

1. Introduction

1.1. Epidemiology and control of malaria

1.1.1. Epidemiology of malaria in Africa

Malaria remains one of the principle causes of morbidity and mortality in developing countries. In 2015, the World Health Organization estimated that there were 214 million (range 149-303 million) new cases of malaria and approximately 438,000 (range 236,000-635,000) deaths due to malaria worldwide. The African continent has the highest proportion of its population at risk of malaria. Consequently malaria burden is high and the African continent is where the majority (88%) of the global malaria cases and malaria related deaths (90%) occur (World Health Organization Global Malaria Programme, 2015b). Notwithstanding, the global incidence of new malaria cases fell by 37% between 2000 and 2015 and by 42% in Africa specifically. Similar reductions were seen in malaria mortality rates which decreased by 60% globally and by 66% in Africa over the same period (Bhatt *et al.*, 2015; GBD 2015 Mortality and Causes of Death Collaborators, 2016; Gething *et al.*, 2016). Children under 5 years of age (children under 5) remain particularly vulnerable to malaria infection and subsequent death. In 2015, malaria is reported to have resulted in the deaths of approximately 306,000 children under 5 globally, 292,000 (96%) of which were African. While the number of malaria-related deaths remains high, similar to the reductions seen in the number of malaria cases, the malaria related mortality rate for children under 5 fell by 65% globally and by 71% in Africa from 2011 to 2015 (World Health Organization Global Malaria Programme, 2015b). Recent epidemiological observations made during the same period support the overall declines, demonstrating country specific evidence of declines in malaria prevalence (Bhattarai *et al.*, 2007; Okiro *et al.*, 2007; Otten *et al.*, 2009; D'Acremont, Lengeler and Genton, 2010).

As of 2015 malaria elimination is now within reach for many (33) countries around the world. To be considered eligible for malaria elimination a country needs to have less than 1 malaria case (local and imported)/1000 population in one year. In 2000 only 13 countries appeared to be moving towards elimination while in 2015 the number of countries on the road to elimination had more than doubled. As of 2015 three countries in Africa are either in pre-elimination (Cabo Verde, Swaziland) or elimination phase (Algeria). One, Morocco, has been malaria free since 2010. Eight countries known as the Malaria Elimination 8 (Botswana, Namibia, South Africa, Swaziland, Angola, Mozambique, Zambia and Zimbabwe), comprise a regional initiative to eliminate malaria by 2015 – however four of these, Botswana, Namibia, South Africa and Swaziland reported increases in the number of malaria cases from 2014 to 2015. It is uncertain however, if the reported increases may be a result of increased diagnostic capacity (World Health Organization Global Malaria Programme, 2015b).

Changes in the malaria burden in Africa are multifactorial and are evident when the uptake of key malaria prevention and control activities are analysed. The proportion of the population sleeping under an insecticide treated net (ITN) increased in sub-Saharan Africa from less than 2% in 2000 to 55% in 2015, likely related to increased access to ITN's. This proportion varies between countries and may be a reflective of lower ITN use in countries with lower malaria burden. In comparison, the proportion of the population in sub-Saharan Africa at risk of malaria who are protected by indoor residual spraying was

just 6% in 2014. In the 36 African countries where intermittent preventive treatment of malaria in pregnancy (IPTp) has been incorporated into the malaria control program policy, only 52% of all eligible pregnant women received at least one dose of IPTp in 2014. Levels of malaria diagnostic testing, primarily using rapid diagnostic tests (RDTs) have increased in Africa. In 2005, 36% of suspect malaria cases were tested while in 2014 65% were tested; 71% of those were tested with a rapid diagnostic test (RDT). Despite the increase in the number of cases tested, the proportion of children under 5 with *Plasmodium falciparum* malaria who received an ACT remained significantly below universal access (100%) for malaria case management, increasing from 1% in 2005 to 16% in 2014 (World Health Organization Global Malaria Programme, 2015b).

Despite an increase in the uptake of key malaria control interventions, improved access to diagnostics, increased use of ACTs and the promising declines in malaria case incidence, further evidence is needed to confirm if these reductions can be maintained. In order to continue making gains, additional work is required to attain international targets for universal coverage of and access to key malaria control interventions. High-burden countries have slower rates of decline in malaria incidence and mortality. Conversely, in some countries malaria prevalence remains static or is even on the rise despite implementation of malaria control strategies which have been shown to reduce malaria prevalence in other countries (Roca-Feltrer *et al.*, 2012; Mawili-Mboumba *et al.*, 2013; GBD 2015 Mortality and Causes of Death Collaborators, 2016). Many of the data sources for the World Health Organization World Malaria Report are based on routinely collected health facility data. These data often rely on presumptive diagnosis and as a result do not necessarily reflect the actual situation in the community. However it may also be that in some cases the prevalence of malaria has been previously overestimated rather than underestimated when diagnosed presumptively without laboratory confirmation (Choge *et al.*, 2014).

With the exciting progress that has been made in reducing malaria parasite prevalence in order to control and subsequently eliminate malaria it is easy to forget about countries where controlling malaria remains a struggle. While struggling to control malaria, elimination is far from being a reasonable goal. In countries or regions with a high burden of malaria, prevalence can vary widely (Gething *et al.*, 2016) thus the impact of blanket malaria control strategies may not be appropriate to address the burden. In high burden areas a better understanding of malaria epidemiology and improved or context specific malaria control measures will be needed in order to guide future interventions and make controlling malaria a reasonable goal.

1.1.2. Epidemiology of malaria in West Africa

1.1.2.1. Guinea

In the Republic of Guinea (Guinea) malaria is highly endemic and is among the primary causes of morbidity and mortality for the population. Malaria prevalence varies widely throughout the country from 3.2% in Conakry to 64.7% in Kankan, and is due to a variety of factors including topographic variation (Measure DHS, 2012). Despite the variation, the entire country is considered to be an area of high *Plasmodium falciparum* malaria transmission (World Health Organization Global Malaria

Programme, 2015b) which is primarily transmitted by *Anopheles gambiae, funestus, melas and arabiensis*.

In 2010 the estimated malaria incidence in Guinea was 101 cases/1000 people/year in all age groups (Measure DHS, 2012). Routinely collected data available is insufficient for evaluation of countrywide trends in malaria incidence, however; statistical modeling predicts that there has been a decrease in malaria case incidence from 2000 to 2015 (World Health Organization Global Malaria Programme, 2015b; GBD 2015 Mortality and Causes of Death Collaborators, 2016). The predicted decrease is likely due to an increase in the implementation of malaria control interventions. In 2014 access to ITNs was reported to exceed 50% yet the number of antimalarial medicines procured and delivered to public health facilities was sufficient for treating less than 40% of patients with malaria infections (World Health Organization Global Malaria Programme, 2015b).

Figure 1-1: Map of the Republic of Guinea.

In Guéckédou Préfecture, located in the forested region of south-western Guinea (Figure 1-1, black circle) the rainy season occurs from May to December and yearly average temperatures range from 24°C to 28°C. Malaria is hyperendemic in this region and *Plasmodium falciparum* is the predominant parasite species. According to préfectoral health data from 2009, malaria incidence for this region was estimated at 50 cases/1000 people/year. When compared to the national estimate this figure is likely to be an underestimate of the actual malaria incidence as the coverage of the health structures in the region is low, estimated at around 25% (World Health Organization Global Malaria Programme, 2014b). Since 2005, in accordance with the National Malaria Control Program Treatment Guidelines, the first line treatment for uncomplicated malaria is artesunate-amodiaquine (ASAQ) (World Health Organization

Global Malaria Programme, 2014b) Therapeutic efficacy remains high with a median treatment failure rate of less than 10% (World Health Organization Global Malaria Programme, 2015b).

1.1.2.2. Liberia

As in Guinea, malaria in the Republic of Liberia (Liberia) is among the most common causes of outpatient consultations and inpatient deaths in the general population. It is also the main killer of children under five (Measure DHS, 2011; World Health Organization, 2015f; GBD 2015 Mortality and Causes of Death Collaborators, 2016). Malaria is endemic in Liberia, transmission occurs year round and the entire country is considered to have high levels of malaria transmission. The predominate malaria vector is *Anopheles gambiae* and the majority of reported malaria cases are caused by infection with the *Plasmodium falciparum* parasite (World Health Organization Global Malaria Programme, 2015b).

Malaria transmission in Liberia peaks around July corresponding with the summer months (Lussiana, 2016). Malaria prevalence varies across the different regions of the country. In Monrovia, the capital of Liberia (Figure 1-2, black circle), the Liberia Malaria Indicator Survey (LMIS) reported a malaria prevalence according to microscopy of 7.1% in children under five while it was 49% in south eastern Liberia. At the same time, fever was reported in 44.8% of children under five in the two weeks prior to the survey and by 38% of surveyed population (all age groups) in the previous four weeks (Measure DHS, 2011). Overall the LMIS indicates a decreasing trend of malaria prevalence from 2005 to 2011 (Measure DHS, 2011) an estimate supported by statistical modeling which projects a 50-75% decrease in malaria case incidence from 2000 to 2015 (World Health Organization Global Malaria Programme, 2015b; GBD 2015 Mortality and Causes of Death Collaborators, 2016).

Figure 1-2: Map of the Republic of Liberia.

Similar to Guinea, access to ITNs has improved in Liberia and was reported to exceed 50% in 2014. At the same time the number of antimalarial medicines procured and delivered to public health facilities was only sufficient to treat less than 20% of patients with malaria infections (World Health Organization Global Malaria Programme, 2015b). Artesunate-amodiaquine (ASAQ) is currently used as the first-line treatment for malaria in Liberia (Liberia Ministry of Health and Social Welfare, 2009) and has been proven to be efficacious in children (6-59 months old), safe and well tolerated (Birgit Schramm *et al.*, 2013).

1.1.3. Malaria control strategies

In order to address the worldwide malaria burden, WHO and Roll Back Malaria (RBM) have encouraged and supported malaria endemic countries to implement malaria control strategies which incorporate Artemisinin based Combination Therapies (ACTs) as first line treatment for malaria episodes, distribution of insecticide treated bed nets (ITNs), intermittent preventive treatment of pregnant women (IPTp) intermittent preventive treatment of infants (IPTi) and indoor residual spraying (IRS). The RBM global malaria action plan also promotes the use of reliable rapid diagnostic tests (RDT) to diagnose cases of simple malaria in addition to community-based management of malaria (Roll Back Malaria Partnership, 2008).

Both ACTs and vector control measures have been demonstrated to be efficacious malaria control strategies (Bhattarai *et al.*, 2007; Smithson *et al.*, 2015). Epidemiological studies have credited ACTs with enhancing treatment efficacy and providing strong action against young gametocytes thereby reducing transmission and transmission intensity of malaria (Mayxay *et al.*, 2004; Okell *et al.*, 2008; Sagara *et al.*, 2012). Subsequent trials have demonstrated that the use of ITNs and/or IRS can reduce mortality in African children under five years of age (Abdulla *et al.*, 2001; Lengeler, 2004; Hemingway, 2014; Bhatt *et al.*, 2015).

New strategies to address malaria burden have been supported by the World Health Organization (WHO). Since March 2012 the WHO recommends the use of Seasonal Malaria Chemoprevention (SMC) as a control strategy in areas with seasonal malaria transmission. SMC is defined as “the intermittent administration of a full treatment course of an antimalarial during the malaria season to prevent malarial illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malaria risk” (World Health Organization Global Malaria Program, 2012). Currently the SMC strategy is recommended for 15 African countries, 6 of which have adopted the strategy (World Health Organization Global Malaria Programme, 2015b). SMC has been deemed appropriate for areas where malaria transmission has distinct seasonal peaks; specifically where ≥60% of malaria infections occurs during a defined (generally 4 consecutive month) period. As per WHO policy recommendation this approach targets only children under 5 years of age (World Health Organization Global Malaria Program, 2012).

Strategies such as SMC that involve administering therapeutic antimalarial regimens to large numbers of people at the same time, regardless of symptoms or laboratory confirmation, have been a component of malaria control programs for more than a decade (Poirot *et al.*, 2013; von Seidlein and Dondorp, 2015).

After becoming an integral component of malaria elimination programs in the 1950s, the WHO stopped recommending MDAs based on concern surrounding their ability to disrupt transmission and the perceived risk of increasing drug resistance to the limited number of antimalarials available (Poirot *et al.*, 2013; von Seidlein and Greenwood, 2003). Since then evidence has accumulated which support the use of drug regimens, particularly artemisinin-based combination therapies (ACT), for their ability to reduce malaria parasitemia as well as malaria morbidity and mortality when administered over a restricted amount of time (Poirot *et al.*, 2013; von Seidlein and Greenwood, 2003; Newby *et al.*, 2015).

One of the many challenges in controlling malaria is that there is no "one size fits all" approach. Malaria epidemiology, endemicity, transmission, vector dynamics and population mobility vary widely between and within countries. Advances have been made in the development of control strategies though despite being efficacious their impact has been heterogeneous (Cook *et al.*, 2011; De Beaudrap *et al.*, 2011; Roca-Feltrer *et al.*, 2012; Mawili-Mboumba *et al.*, 2013; Giardina *et al.*, 2014). This heterogeneity in addition to the degree to which malaria related factors (e.g. rainfall, altitude, vector density) vary within and between countries demonstrate a clear need to develop alternative and/or complementary strategies that are adapted to the context and can be utilized in addition to classic strategies. In many cases these strategies need to be context specific and extrapolatable to different contexts.

Due to the lack of malaria response strategies specific to complex settings, classic malaria control strategies as used by national malaria control programs in non-emergency settings frequently need to be adapted during both complex and humanitarian emergencies. These situations evolve rapidly and often unpredictably. In order to mount an appropriate response including case-management activities during an emergency, malaria control strategies need to be adapted and knowledge of the epidemiology of malaria in the affected areas is essential (World Health Organization, 2013). As the areas malaria epidemiology is better understood classic control strategies (for example SMC) may be adapted to the context and used as punctual interventions (instead of as long term control strategies) during an emergency. While this may lead to innovative deployment of such strategies, due to the sometimes hectic nature of an emergency this innovative use is rarely documented and even less frequently monitored and evaluated particularly if the period of intervention is short.

1.1.4. Modeling and malaria

In 1911 the first mathematical model explaining the relationship between malaria incidence in humans and the number of mosquitoes was published (Ross, 1915). Since then the number of models and their complexity has increased, now allowing for consideration of numerous factors including latent period of infection, asymptomatic infections, seasonality of infection and entomological inoculation rate among others (Mandal, Sarkar and Sinha, 2011). Less complex mathematical models are used to investigate changes in important factors that contribute to malaria transmission in order to quantify progress towards malaria control goals (World Health Organization Global Malaria Programme, 2015b; GBD 2015 Mortality and Causes of Death Collaborators, 2016). Regardless of the models' complexity, they are generally parameterized by data provided by Ministries of Health originating from health facility surveillance or less frequently community-based survey data. While increasing in number and complexity, models remain limited by the quality and availability of data with which to parameterize

them. Despite the limitations, mathematical models can aid our understanding of population level malaria transmission dynamics and be used to inform planning and implementation of malaria control interventions (malERA Consultative Group on Monitoring Evaluation and Surveillance, 2011; World Health Organization Global Malaria Programme, 2015a). Model predictions are particularly helpful in hard to reach, understudied areas and emergency situations.

Models can be used to inform policy, planning and guide research for malaria control, elimination and eradication at global policy, national and local levels. Models can also be used to predict future trends after being fit to past data (generally time series data) (Mandal, Sarkar and Sinha, 2011). Malaria specific models such as OpenMalaria, stochastic simulation models of malaria transmission based on infection in individuals, allow users to simulate the impact of different malaria control strategies individually or in combination, including vaccination, on malaria epidemiology and transmission in a given area (Smith *et al.*, 2006; Penny and Smith, 2012; Stuckey *et al.*, 2012, 2016; Penny *et al.*, 2015). These models can also predict the impact of the cessation of previously successful malaria control interventions on malaria prevalence in the absence of post-intervention surveys or surveillance data and help inform the choice of response interventions by predicting their potential epidemiological impact (Griffin *et al.*,2010; Smith *et al.*, 2008).

1.2. Médecins Sans Frontières and malaria control in Guinea

Médecins Sans Frontières (MSF), an international, independent, medical humanitarian organization has been active in the Republic of Guinea since January 2001 and established a malaria project in Guéckédou Préfecture from August 2010 to April 2014. In the area of intervention consultations for malaria constituted between 20% and 45% of all medical consultations (MSF program data). The primary goal of the MSF intervention in Guéckédou was to reduce malaria related morbidity, mortality and transmission in the intervention area. To do this, in collaboration with the Ministry of Health, MSF implemented a multi-component intervention in three areas selected for intervention. The intervention included strategies which have all been previously proven to be effective, including; preventive components such as public sensitizations (radio and in mass) and mass distribution of mosquito nets as well as curative strategies including the reinforcement of health structures (training health staff and improvements in facility infrastructure) and ensuring consistent access to malaria diagnostics and adequate treatment.

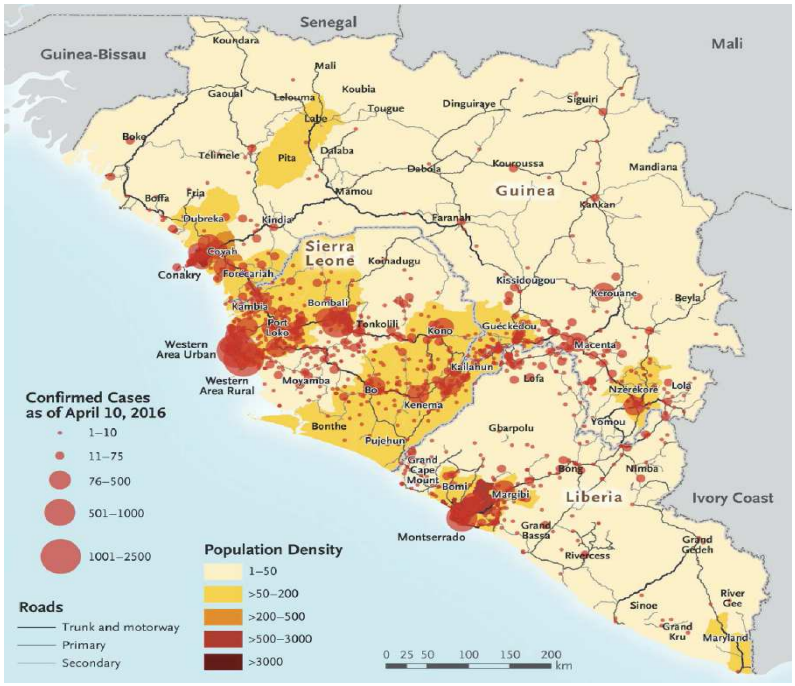
Improving the populations' access to testing and treatment for malaria was an important component of the MSF intervention and was ensured by a network of community health workers (CHWs). Fifty-four CHWs were nominated by their village and trained by MSF to perform rapid diagnostic tests, provide treatment for simple malaria and to identify, refer cases of severe malaria to the closest health facility after pre-referral treatment and to provide community sensitizations. In addition to providing referrals for patients with severe malaria, the CHWs also referred patients with conditions which they could not treat or which required more advanced follow-up. All RDTs and ACTs were needed by the CHWs to carry out their duties were provided by their closest health facility, supplied by MSF.

1.3. West Africa Ebola epidemic 2013-2016

The first outbreak of Ebola Virus Disease (EVD or Ebola) in West Africa was discovered, laboratory confirmed and officially declared by the World Health Organization (WHO) on March 23, 2014. The initial epicenter of the outbreak was Guéckédou, Guinea (World Health Organization, 2014b), the same region in which MSF had been intervening since 2010. Unfortunately the virus had been circulating in the region since December 2013 (Baize *et al.*, 2014) and due to Guéckédou's proximity to Sierra Leone and Liberia the outbreak quickly spread into the neighboring countries. The first case in Liberia was confirmed in mid-March 2014 (week 12), and in Sierra Leone in the end of May 2014 (week 21) (World Health Organization, 2015a). Formal declaration of the outbreak was made on March 30, 2014 in Liberia and on May 25, 2014 in Sierra Leone (World Health Organization, 2015g). MSF was present in Guéckédou Préfecture, involved in malaria control in the epicenter of the initial Ebola outbreak. After the outbreak was discovered, MSF's malaria control activities stopped and all staff, program activities, and resources were directed at combating the Ebola outbreak as of April 2014.

From its discovery in March 2014 Ebola continued circulating in the three countries eventually affecting 30 of 33 sous-préfectures in Guinea, 14 of 14 districts in Sierra Leone and 15 of 15 counties in Liberia (Figure 1-3, source: WHO Ebola Response Team, 2016). Overall, a total of 28,616 cases (suspected, probable confirmed) of Ebola and 11,310 Ebola related deaths occurred in Guinea, Sierra Leone and Liberia during the 2013-2016 epidemic. The epidemic was officially declared to be over on June 1, 2016, 42 days (two incubation periods) after the last confirmed case (WHO Ebola Response Team, 2016; World Health Organization Regional Office for Africa, 2016).

Figure 1-3: Distribution of confirmed Ebola cases in Guinea, Sierra Leone and Liberia December 2013 to April 10, 2016.



Unfortunately the impact of the epidemic extends beyond the number of individuals infected by Ebola to the palpable effect it had on the health system. Across the three most affected countries, health care systems were overwhelmed and many health care workers lost their lives during the response (World Health Organization, 2015e). Health facilities were closed or if they were open, their activities were greatly reduced (Bolkan *et al.*,2014; Gignoux and Hurum, 2014; Plucinski *et al.*, 2015). The initial, non-specific presentation of Ebola in patients during the early phase of the their illness resulted in their Ebola illness sometimes being confused by health care workers with other common morbidities (World Health Organization, 2014a). Unlike in Uganda and the Democratic Republic of the Congo, health care workers and communities in West Africa had never seen cases of Ebola prior to the 2013-2016 epidemic (Baize *et al.*, 2014).

1.3.1. Ebola and malaria in West Africa

The consequences of the Ebola epidemic extend beyond Ebola specific morbidity and mortality and include its impact on other common morbidities such as malaria and the efforts made to control it. In particular there were concerns around the overlap in symptoms between malaria and Ebola (World Health Organization Global Malaria Programme, 2014a; de Wit *et al.*, 2016). Malaria may have been misdiagnosed as Ebola and Ebola as malaria if unable to be differentiated in the absence of or while waiting for testing. Due to the potential for misdiagnosis and increased risk of Ebola infection resulting from high risk exposure to blood and body fluids, activities which may have been common prior to the epidemic, testing patients for malaria in the community or public health facilities, were temporarily suspended due to concerns for increased risk of Ebola infection (World Health Organization Global Malaria Programme, 2014a). In order to avoid leaving malaria infections untreated in MSF Ebola Treatment Centers, every patient hospitalized with suspect Ebola infection systematically received presumptive antimalarial treatment with an ACT at admission, generally artemether-lumefantrine (Sterk, 2008).

Differentiating symptoms of malaria from those of Ebola was not only problematic for health care workers but also for community members who were sick and needed to seek healthcare. Fear of Ebola and being infected in health facilities was rampant in the communities and resulted in a reduction in health seeking behavior at public health facilities (Bolkan *et al.*, 2014; Vygen *et al.*, 2016). An additional concern was that due to the reduced access to public health facilities, those individuals who were sick with malaria would present at Ebola Treatment Centers (ETCs) and be hospitalized inside the center while they were tested for Ebola and malaria, thus increasing their risk for nosocomial Ebola infection. At the same time, healthcare workers in public health facilities were also fearful of being infected by patients, consequently patients were sometimes turned away unless they were able to present proof that they were Ebola free, generally a certificate of discharge Ebola negative from an Ebola Treatment Center (unpublished observation).

In order to mitigate the impact of the Ebola epidemic on malaria control measures, the WHO Global Malaria program released guidance on malaria control measures to be taken in Ebola-affected countries for the duration of the epidemic. These measures included changes in testing practices, changes in LLIN distribution strategies to avoid crowding and contact at distribution point, in addition to mass drug

administrations of ACTs in areas where malaria transmission was high and access to treatment low (World Health Organization Global Malaria Programme, 2014a). Nevertheless, the end of or significant reduction of malaria activities, both curative and preventive, delivered both by non-governmental organizations and through health systems by Ministries of Health, likely resulted in an increase of malaria cases and deaths (Plucinski *et al.*, 2015). Consequently the Ebola epidemic is likely to have had a much greater impact on morbidity and mortality in the three most affected countries than that which can be measured by Ebola case fatality rates alone, a consequence of its effects on the health system and health seeking behavior. In malarious areas like Guéckédou that were also hit hard by the Ebola epidemic, any progress in controlling malaria that had been made prior to the epidemic may have been reversed.

Modelling exercises have attempted to quantify the indirect health effects of the Ebola epidemic on common infectious diseases such as malaria considering the lack of quality general surveillance data and the significant decrease in health facility consultations. As reported by Walker et al., when assuming that the Ebola epidemic led to complete disruption of malaria related activities, the subsequent increase in untreated malaria cases was found to be 3.5 million additional untreated cases in the three most affected countries for a total of 11.5 million untreated cases and 10,900 additional malaria deaths, more than the reported number of Ebola deaths alone during the same period (Walker *et al.*, 2015). As patients recommence seeking care at health facilities, the excess number of malaria cases will place an additional burden on health systems that are getting back on their feet.

1.4. Disease surveillance in sub-Saharan Africa

Throughout sub-Saharan Africa, with the exception of South Africa, there is little systematic, formal, recording of health and demographic indicators such as birth and deaths (Mathers *et al.*, 2005). Furthermore, most of the population does not have access to a formal system of medical care. Population denominators are difficult to come by and are frequently estimations based on a census which may or may not have occurred many years prior to the period of enquiry (Cooper *et al.*, 1998). Consequently, basic health indices such as death rates or causes of death are difficult to ascertain with any degree of certainty.

The most reliable data on health indices in sub-Saharan Africa come from health and demographic surveillance systems (HDSSs). In HDSS sites, communities in low- and middle-income countries where health and demographic surveillance has been implemented, data including health, socio-economic indicators in addition to population movements are monitored longitudinally for a defined population over a prolonged period of time (Streatfield *et al.*, 2014). Barriers to HDSS site implementation include both the cost of implementation in addition to the need for a long-term commitment to sustain such initiatives. Nevertheless, as of 2016 over 3,800,000 people in Africa, Asia and Oceania reside in one of 49 HDSS sites. In Africa alone there are 38 HDSS sites, home to 2,977,149 individuals under surveillance (INDEPTH Network, 2016) among an estimated population of 1.2 billion people (United Nations Population Division, 2015).

In HDSS sites, cause of death is attributed according to verbal autopsy (VA), the recommended method for determining cause of death in places where vital registration systems are weak. VA uses data from

interviews with lay respondents on the signs and symptoms of the decedent before death to attribute cause of death. While currently the gold standard, VA accuracy can be impacted by the need for both trained individuals to carry out the interviews and multiple physicians for VA questionnaire review (World Health Organization, 2015h). An additional limitation for malaria endemic regions in particular is the difficulty of distinguishing a death due to malaria from other common (co-)morbidities (Garenne and Fauveau, 2006).

In countries without the resources to implement HDSS sites, civil registration and vital registration systems are frequently inadequate and the data provided from these systems, if they exist, varies in completeness. Consequently, health facility based surveillance/reporting is frequently the source of country-wide disease specific surveillance data (Cooper *et al.*, 1998). Compounded with low facility attendance, lack of qualified staff and commodity stock outs, health facility based malaria data are suspected to provide to either an over- or under-estimation of malaria burden caused by problems of misdiagnosis (Amexo *et al.*, 2004). In both HDSS and non-HDSS sites, the majority of deaths tend to occur outside health facilities (Amexo *et al.*, 2004; Kouanda *et al.*, 2013; Tiffany, Moundekeno, Traoré, Haile, Sterk, Guilavogui, Serafini, *et al.*, 2016), consequently surveillance data from health facilities when taken together is neither able to provide nationally representative estimates of cause-specific morbidity and mortality nor accurate estimations of community mortality (Cooper *et al.*, 1998).

1.5. Project rationale

Malaria control is challenging in the best of situations. Never-the-less control programs aiming to reduce malaria related morbidity and mortality employ intervention(s) that have been proven to be effective. However, depending on the malaria epidemiology and the situation, the implementation of some strategies may not be recommended, further complicating malaria control. Strategies to control and respond to malaria need to be flexible and able to be adapted to different contexts as should our ability to use surveillance to detect malaria morbidity and mortality and by extension that of outbreaks of other diseases.

This thesis aims to investigate the impact of malaria control interventions on the epidemiology of malaria in two West African countries under distinctly different circumstances. The first, a deployment of classic control strategies during a 'normal' situation in Guéckédou, Guinea (prior to Ebola) in addition to the novel deployment of a classic malaria control strategy during an 'emergency' situation, the Ebola outbreak in Monrovia, Liberia.

This thesis will provide new insights into malaria intervention implementation and impact in difficult settings during both normal and emergency situations. For Guéckédou in particular, these findings will highlight the impact of a multi-component malaria control program and its cessation on the malaria parasite prevalence in the area of intervention. In Liberia, the impact of the novel deployment of a malaria control measure in the midst of a large Ebola outbreak will be discussed. Lessons learned will be drawn in order to inform future implementation of similar interventions (or intervention packages) in these situations. Additionally the importance of simple, community-based surveillance and its ability to both capture malaria related mortality and detect outbreaks particularly of Ebola virus disease will be

explored. Finally, this thesis will demonstrate that in order to mitigate the mortality that is inherent with both malaria and Ebola infections, particularly during outbreaks, the ability to differentiate between the two (in light of their common features) need to be improved and those lessons translated into improved surveillance, in order to detect and respond to both diseases, potentially resulting in a synergistic decrease in mortality.

2. Goal and objectives

2.1. Goal

To explore the impact that malaria control interventions had in two West African countries during a normal and an emergency situation and provide insight into the impact of malaria intervention implementation and cessation.

2.2. Objectives

This thesis has 4 different but closely related objectives:

Objective 1

Assess the impact of a multi-component malaria control intervention and its impact on malaria parasite prevalence in sous-préfectures of Guéckédou, Guinea after 2.5 years of implementation.

Objective 2

Model the impact of a cessation of a malaria control program as a result of an outbreak of Ebola in Guéckédou, Guinea.

Objective 3

Investigate the use of prospective sentinel site community-based mortality surveillance for documenting malaria related mortality and evaluate the systems utility for outbreak detection.

Objective 4

Assess the scale of a Mass Drug Administration of malaria chemoprevention carried out in Monrovia, Liberia during an Ebola outbreak, evaluate its acceptance by the population and estimate the effectiveness of the intervention on reducing the incidence of self-reported fever.

3. Methods

The general approach was to conduct operational research to assess the impact of multicomponent malaria control programs on malaria related morbidity and mortality in different situations, during large scale deployment.

3.1. Study design

3.1.1. Impact of a multi-component malaria control program on hyperendemic malaria in Guinea.

Intervention

A multi-component malaria control program was implemented in 3 sous-préfectures of Guéckédou Préfecture, the Republic of Guinea. Components of the intervention included: 1) improved detection of clinical malaria cases with RDTs, 2) provision of ACTs for community health workers and public health facilities, 3) introduction of injectable artesunate for treatment of severe malaria in the hospital, 4) mass distribution of LLINs, 5) provision of sulfadoxine-pyrimethamine for intermittent preventive treatment of malaria for pregnant women in health facilities, 6) health promotion to reinforce messages regarding the importance of testing and treatment for malaria and 7) training community health workers to use and interpret RDTs, treat RDT positive patients and pre-treat and refer cases of severe malaria.

Method of evaluation

Data was collected during a series of community-based cross-sectional cluster surveys carried out every six months for 2.5 years. Surveys were carried out in the 3 sous-préfectures of intervention and 1 sous-préfecture where the malaria control program was not implemented.

Sample size

1,650 individuals of all ages per sous-préfecture, 6,600 individuals total, 55 per cluster (30 clusters per sous-préfecture per survey).

Primary outcome

Sous-préfecture specific changes in malaria parasite prevalence during the period of data collection, survey 1 (April 2010) to survey 5 (February 2013).

3.1.2. The impact of a reduction in malaria control activities due to an outbreak of Ebola virus disease in Guéckédou, Guinea; a modeling study of malaria resurgence.

Data from the surveys carried out in 3.1.1 was used to parameterize a stochastic model of malaria transmission to reflect the trends seen in malaria parasite prevalence (above) during the intervention period. Changes in malaria interventions according to the timeline of implementation were accounted for in the model and estimates of the relationship between parasite prevalence and malaria case incidence were provided by the model. By using the observed effect of the interventions, estimates of the parasite prevalence under hypothetical scenarios without interventions (counterfactual) was possible. As of April 2014, the interventions were removed from the model to represent the cessation of malaria control activities. The model predicted the impact of the cessation of malaria control interventions. Using interrupted time series analysis, the model predictions were then compared to the counterfactual scenario.

3.1.3. Community-based surveillance to monitor malaria mortality in a malaria endemic and Ebola epidemic rural Guinea.

During implementation of 3.1.1, prospective community-based sentinel site surveillance was implemented concurrently in 46 sentinel sites in the sous-préfectures mentioned above. Key informants

collected data on malaria (fever) related mortality. The systems utility for outbreak detection was also evaluated through retrospective analysis of this routinely collected data.

Study population

All permanent residents of the sentinel sites were included in the surveillance system, 43,000 in total.

Procedures

Deaths were recorded by community nominated key informants in each sentinel site and classified as due to malaria or another cause. Malaria deaths were those reported as due to malaria or fever in the 3 days before death with no other known cause. Suspect Ebola virus disease (sEVD) deaths were those due to select symptoms in the Ebola case definition. Deaths were aggregated by sous-préfecture and analyzed by a 6-month period.

3.1.4. Impact of and lessons learned from mass drug administration of malaria chemoprevention during an Ebola outbreak in Monrovia, Liberia.

A systematic investigation of intervention coverage, treatment initiation and incidence of self-reported fever was carried out in systematically selected households in four zones of Monrovia, Liberia. These zones were selected to participate in the MDA of malaria chemoprevention based on their high incidence of Ebola.

Main outcomes

- Attendance, treatment compliance and adherence
- Community acceptance of the MDA and reasons for non-compliance and -adherence
- ASAQ side effects and their impact on treatment adherence
- Effectiveness of the MDA

Study population and sample size

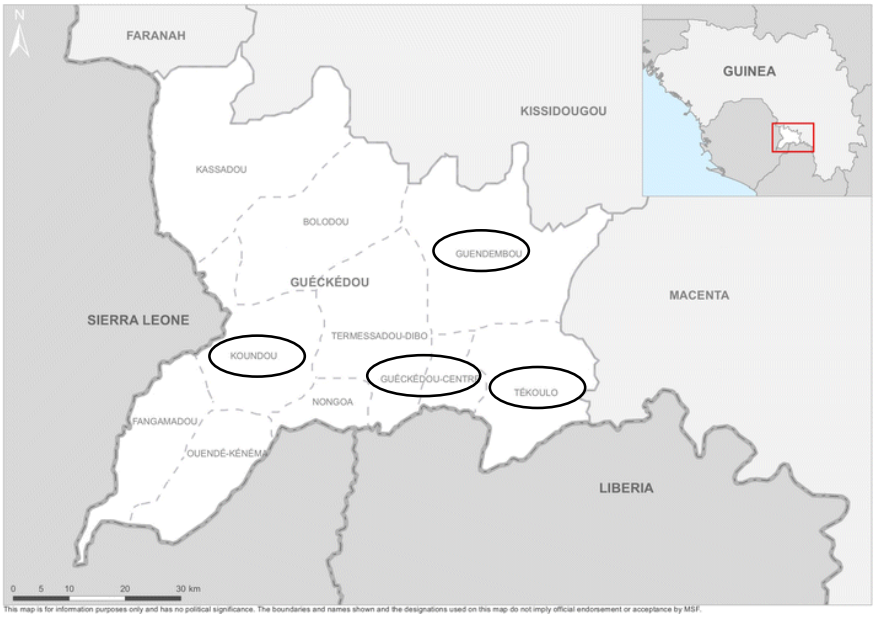
A total of 222 households comprised of 1,236 household members of all ages were included in the follow-up and subsequent analysis.

3.2. Study area and setting

Study area in Guéckédou, Guinea

Bordered by Sierra Leone and Liberia, the area of intervention, Guéckédou Préfecture, consists of 13 sous-préfectures; the 4 communes in the urban area and the rural area that is subdivided into 9 sous-préfectures. Data collection for the malaria parasite prevalence study and community-based sentinel site malaria mortality surveillance was carried out in the sous-préfectures of intervention, Guéckédou City (semi-urban), Tekoulo (rural) and Guendembou (rural) in addition to a fourth sous-préfecture that did not receive the malaria intervention, Koundou (Figure 3-1).

Figure 3-1: Map of Guéckédou Préfecture. *Study sous-préfectures denoted by a black circle.*



Together, the four sous-préfectures have an estimated population of 297,919 individuals (Table 3-1) spread among a geographic area of 1,779 km^2 with difficult access, particularly during the long rainy season when many roads become impassable.

Table 3-1: Population size and administrative subdivision of the study areas in Guéckédou Préfecture.

Sous-préfecture	Population size*	Number of administrative units	Strata	Sentinel sites selected	Median population per administrative unit (range)
Guéckédou City	149,905	40 neighborhoods	6	24	523 (33-20564)
Guendembou	48,731	117 villages	2	8	370 (32-1273)
Tekoulo	59,920	176 villages	2	8	281 (16-5368)
Koundou	39,363	185 villages	1	6	149 (16-1024)
Total:	297,919	518	11	46	

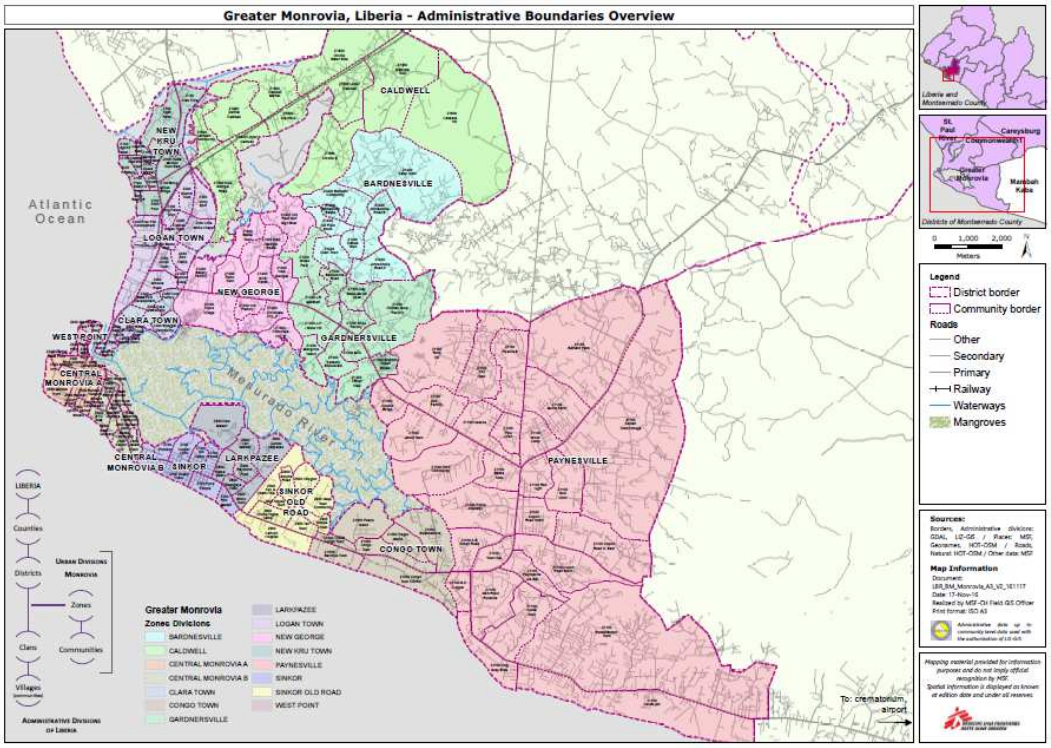
*2010 sous-préfectoral estimate

Study area in Monrovia, Liberia

Monrovia, located in Montserrado County, is the economic and political capital of the Republic of Liberia located on the West coast of Africa. As of the 2008 census the population of Monrovia was estimated at 1,010,970 people, or 29% of the population of Liberia. The study area was comprised of four zones (neighborhoods) of Monrovia targeted for the MDA based on their high Ebola incidence, high population density, precarious living conditions and limited access to healthcare. The population of these zones,

New Kru Town, Clara Town, Westpoint and Logan Town as seen in Figure 3-2 was initially estimated at 300,000 through a census carried out by MSF in collaboration with community leaders.

Figure 3-2: Zones of Monrovia, Liberia selected for mass drug administration.



4. Encouraging impact following 2.5 years of reinforced malaria control interventions in a hyperendemic region of the Republic of Guinea.

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Keywords: *Plasmodium falciparum*, malaria, prevalence, symptomatic, Guinea, hyperendemic, cross sectional surveys

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4.1. Abstract

Background

Malaria is one of the principle causes of morbidity and mortality in the Republic of Guinea, particularly in the highly endemic regions. To assist in malaria control efforts, a multi-component malaria control intervention was implemented in the hyperendemic region of Guéckédou Préfecture. We assessed the coverage of the intervention package and its impact on malaria parasite prevalence.

Methods

Five cross-sectional surveys using cluster based sampling and stratified by area were conducted from 2011-2013 in 3 sous-préfectures of Guéckédou Préfecture that received the intervention: Guéckédou City, Tekoulo and Guendembou in addition to one comparison sous-préfecture that did not receive the intervention, Koundou. Surveys were repeated every six months, corresponding with the dry and rainy seasons. Rapid diagnostic tests (RDT) were used to diagnose malaria infection. In each selected household, bed net use and ownership were assessed.

Results

A total of 35,123 individuals participated in the surveys. Malaria parasite prevalence declined in all intervention sous-préfectures from 2011 to 2013 (56.4% to 45.9% in Guéckédou City, 64.9% to 54.1% in Tekoulo and 69.4% to 56.9% in Guendembou) while increasing in the comparison sous-préfecture (64.5% to 69%). It was consistently higher in children 5-14 years of age followed by those 1-59 months and ≥15 years. Indicators of intervention coverage, the proportion of households reporting ownership of at least one bed net and the proportion of survey participants with fever who received treatment from a health facility or community health worker also increased significantly in the intervention areas.

Conclusions

Implementation of the multi-component malaria control intervention significantly reduced the prevalence of malaria in the sous-préfectures of intervention while also increasing the coverage of bed nets. However, malaria prevalence remains unacceptably high and disproportionately affects children <15 years of age. In such situations additional vector control interventions and age specific interventions should be considered.

4.2. Background

Malaria is endemic with perennial transmission in the Republic of Guinea (Guinea) where it is among the primary causes of morbidity and mortality for the population, responsible for 34% of all medical consultations in 2012 (Measure DHS, 2012). Malaria prevalence is estimated to be 44% nationally, although there are important regional differences in endemicity, with transmission highest in the heavily forested southern part of the country (Measure DHS, 2012). In Guinea the National Malaria Control Program recommends the use of artemisinin combination therapy (ACT) for treatment for uncomplicated malaria. (Ministere de la Santé et de l'Hygiene Publique - Republique de la Guinée, 2014). Malaria rapid diagnostic tests (RDT) and ACTs are free of charge for the population in health facilities while microscopy services and other medications incur a fee.

Historically, epidemiological data are either inaccurate or sparse in Guinea, posing a challenge to use of health facility data for disease surveillance and monitoring program impact. Prior to receiving support to surveillance from external partners and improved data collection from 2014 onwards, reporting of malaria cases was weak and consequently the malaria burden may have been severely underestimated in the country. In 2012, only 211,157 cases and 108 deaths due to malaria were reported in a population of 11.75 million (World Health Organization Global Malaria Programme, 2014b). This lack of reliable data hinders prevention and treatment efforts and requires improved data collection over longer periods in order to document trends and better understand the malaria burden in Guinea and, by extension, similar settings.

Impact from malaria control programs results from the additive effects of multiple interventions and, when implemented with high coverage, they are expected to have greater impact than any one intervention alone (Bhatt *et al.*, 2015). Many controlled trials have been carried out to assess the efficacy of different malaria control interventions including insecticide treated nets (Lengeler, 2004), indoor residual spraying (Pluess *et al.*, 2010) and malaria intermittent preventive treatment in pregnancy (Wilson *et al.*, 2011; Kayentao *et al.*, 2014). While curative interventions such as community case management of malaria have been documented to be effective (Chanda *et al.*, 2011) few have been tested in controlled trials. Additionally, little research has been carried out to investigate the additive or potentially synergistic effects of several interventions when implemented together under trial conditions (Hamel *et al.*, 2011; West *et al.*, 2014) or outside of trial conditions.

In collaboration with the Ministry of Health and National Malaria Control Program, Médecins Sans Frontières (MSF) reinforced malaria control activities in Guéckédou Préfecture beginning in 2011. Guéckédou Préfecture was chosen to benefit from the reinforced activities based on the populations' relatively poor access to health care and the (suspected) disproportionately high malaria burden in the region. All sous-préfectures within Guéckédou Préfecture were to be covered by the intervention package with implementation occurring in a stepwise manner. However, due to operational constraints implementation was ultimately restricted to the 3 sous-préfectures that received the intervention during the first phase of project rollout. In 2014 all activities were to be handed over to the Ministry of Health for continuation and expansion however the program ended earlier than anticipated due to an outbreak of Ebola Virus Disease in the region.

The data presented here represent the first published description of the burden of malaria in Guéckédou Préfecture and evaluation of the impact of a malaria control intervention package on malaria burden in the same area.

The data presented here represent the first published description of the burden of malaria in Guéckédou Préfecture and evaluation of the impact of a malaria control intervention package on malaria burden in the same area.

4.3. Methods

Nature of the intervention

The malaria intervention in Guéckédou was intended to cover a geographic area of 1,779 km2 with difficult access, particularly during the long rainy season when many roads to outlying villages become impassable. Activities were carried out from 2011 to 2014 in 3 sous-préfectures of Guéckédou Préfecture (intervention sous-préfectures): Guéckédou City (semi-urban), Tekoulo (rural) and Guendembou (rural) as seen in Figure 4-1. The total population in these areas in 2010 was estimated at 224,399 individuals (sous-prefectoral estimates).

Figure 4-1: Map of Guéckédou Préfecture.

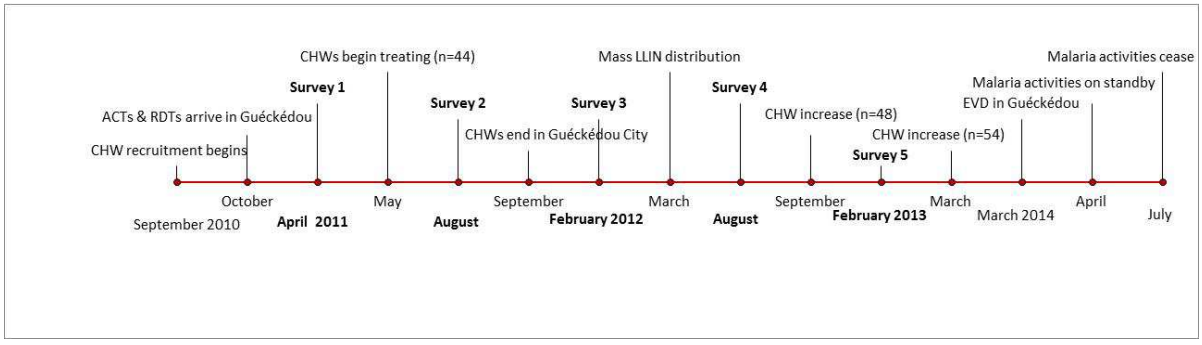
In line with strategy recommendations from the Roll Back Malaria Partnership, the malaria control activities (intervention package) implemented in Guéckédou Préfecture involved both curative and preventive components (Roll Back Malaria Partnership, 2008). Curative components included improving

detection of clinical malaria cases and timely treatment with an artemisinin-based combination therapy (ACT). This was done by ensuring malaria rapid diagnostic tests (RDT) and ACTs were available and free of charge in all 21 MSF supported public health facilities in the intervention sous-préfectures. Additionally, community health workers (CHW) were trained to use and interpret RDTs, treat RDT positive patients with an ACT and pre-treat and refer cases of severe malaria. Injectable artesunate was also introduced in the hospital as treatment for cases of severe malaria. Preventive activities included community health promotion designed to reinforce messages regarding the importance of being tested and treated for malaria. Long-lasting insecticide-treated nets (LLINS) were distributed in April 2012 during a mass campaign. LLINs were also provided to pregnant women during antenatal visits throughout the intervention period. MSF also ensured supply of sulfadoxine-pyrimethamine (SP) for malaria intermittent preventive treatment in pregnancy (IPTp) in all health facilities through September 2013. From October 2013, IPTp was replaced by intermittent screening and treatment for pregnant women in urban facilities while rural facilities continued with IPTp.

Study design and target population

Five cross-sectional surveys were conducted from April 2011 to February 2013 to evaluate the impact of the malaria intervention package. Surveys were carried out during the peak of the rainy season (July/August) and dry season (February/April) in order to document any seasonal heterogeneity in malaria parasite prevalence. In addition to the 3 intervention sous-préfectures, a fourth sous-préfecture that did not receive the intervention package was selected to serve as a comparison sous-préfecture. The first survey was carried out in April 2011 in all four sous-préfectures while preparation for implementation of the intervention package was underway. The first survey was followed by four surveys in the same sous-préfectures in August 2011, February 2012, August 2012 and February 2013 (Figure 4-2).

Figure 4-2: Timeline of intervention implementation and cross-sectional surveys 2010-2014.



Households were selected using two-stage cluster sampling, stratified by sous-préfecture. Thirty clusters, villages (rural) or neighborhoods (urban), were randomly selected in each stratum (sous-préfecture) with probability proportional to population size. Households were selected using the EPI method (Henderson and Sundaresan, 1982) within each cluster. Cluster selection carried out independently for each survey round. All household residents >1 month of age were included in the survey until at least 55 individuals

were surveyed per cluster. Rapid diagnostic tests based on detection of the Histidine Rich Protein II (Malaria Antigen P.f. SD Bioline®) were performed for all participants.

Sample size was estimated based on a hypothesized RDT malaria parasite prevalence of at least 50% in each sous-préfecture. Detecting a change of at least 10% in malaria prevalence after 1 year of intervention with alpha of 5%, 80% power and a design effect of 2 required that 814 individuals be surveyed per sous-préfecture (strata). A stratified analysis by age required two times this number for a total sample size of 1,650 individuals per strata or 6,600 individuals in total, requiring a minimum of 55 individuals to be surveyed per cluster.

Training and data collection

Each survey was conducted over 21 days by seven teams, each composed of one nurse and one laboratory technician who were accompanied by a driver. All team members underwent 5 days of training prior to the survey: three days of role-specific training followed by one day of joint team training and one day to pilot and practice the survey questionnaire, procedures and laboratory materials.

Data were gathered through face-to-face interviews for participants ≥15 years of age, primary caregivers were interviewed on behalf of children <15 years of age. Selected households that were found to be empty (but not abandoned) on the first visit were visited a second time later in the same day; if the occupants could not be found on the second visit or if they refused to participate, the household was skipped and replaced with another household.

A standardized questionnaire was used to collect the following information for each individual: name, gender, age, household size and residence (Préfecture and village/neighborhood. Malaria-related indicators included: reported history of fever/malaria, LLIN availability and use. Additional clinical data included: axillary temperature, thick blood smears and RDT malaria diagnosis. The same questionnaire was used for all survey rounds.

All interviews were conducted in French or the local language according to the preference of the participants, and data collection was supervised and monitored daily by one of two team leaders.

Data entry and analysis

Data were double entered using EpiData (version 3.1, Odense, Denmark) and statistical analysis was performed using Stata (version 12.1, College Station, Texas). A symptomatic malaria infection was defined as a survey participant with a positive malaria rapid diagnostic test and an axillary temperature ≥37.5°C on the day of the survey and/or a self-reported history of fever in the 24 hours prior to the survey. Intervention coverage was estimated as: 1) the proportion of survey participants reporting an episode of fever in the month prior to the survey and seeking treatment from a health facility or CHW, and 2) the proportion of survey participants reporting LLIN ownership.

Malaria parasite prevalence (*P.falciparum*) according to RDT was calculated as the proportion of participants with positive RDT results among all participants tested. The proportion of participants

fulfilling the definition of symptomatic (above) was calculated among all participants tested. Both variables were calculated separately for each survey round, sous-préfecture and by age group (1-59 months, 5-14 years, ≥15 years) using the Horvitz-Thompson estimator. Variance of the estimates was computed using the linearization method (Levy Paul S & Lemeshow Stanley, 2008). Proportions of participants seeking treatment from a health facility or CHW, in addition to the proportion of participants that reported owning an LLIN were estimated by sous-préfecture and by survey (April 2011 and February 2013).

Chi-squared test was used to test differences between proportions. A t-test or non-parametric test was applied to continuous variables when appropriate. Logistic regressions models were used to analyze temporal trends in malaria parasite prevalence. All test results were corrected to account for clustering in the sample design.

Ethical considerations

The study proposal was reviewed and approved by the Médecins Sans Frontières Ethics Review Board (1028) and the Ethical Review Board of Guinea (02/CNERS/11). Participation was voluntary and written consent was obtained from each respondent or their caregiver before conducting the survey. If the participant was not literate, they were asked to make a cross instead of a signature. All personal data was anonymized and kept confidential, no individual identifiers were entered in the final database. Participants who tested RDT positive on the day of the survey were treated with an ACT according to the national malaria treatment protocol.

4.4. Results

Individual and household characteristics

In total, 35,123 individuals participated in all surveys, approximately 7,024 per survey. The median number of residents per household was 8 and survey participants were predominately female (Table 4-1). The level of education of the head of household (HH) was generally low, with the majority reporting no formal education. Most survey participants (91%) lived in dwellings with mud brick walls and a tin roof. There were no significant differences in demographic indicators across sous-préfectures or survey round.

Table 4-1: Household and individual characteristics of study population by sous-préfecture and survey period.

Household characteristics										
Area	**N**	**April 2011**	**N**	**August 2011**	**N**	**February 2012**	**N**	**August 2012**	**N**	**February 2013**
Median household size, n (range)										
Guéckédou City	1,762	7 (1-22)	1,908	8 (3-30)	1,694	8 (3-20)	1,729	7 (2-17)	1,733	8 (1-17)
Tekoulo	1,690	7 (2-30)	1,829	8 (3-26)	1,684	8 (3-25)	1,690	7 (3-22)	1,694	7 (2-15)
Guendembou	1,798	8 (2-20)	1,880	8 (2-19)	1,661	7 (1-20)	1,730	6 (1-30)	1,763	8 (3-16)
Koundou (comparison)	1,697	8 (2-24)	2,016	8 (3-29)	1,687	8 (4-21)	1,750	7 (2-25)	1,730	8 (1-25)
Education level+, n (%)										
Guéckédou City	272	165 (61%)	297	152 (51%)	317	186 (59%)	301	153 (51%)	275	124 (45%)
Tekoulo	262	149 (57%)	285	196 (69%)	318	215 (68%)	285	181 (64%)	281	154 (55%)
Guendembou	287	169 (59%)	325	177 (54%)	323	230 (71%)	293	135 (46%)	271	147 (54%)
Koundou (comparison)	260	173 (67%)	320	219 (68%)	305	239 (78%)	282	192 (68%)	291	186 (64%)
House structure*, % (95% CI)										
Guéckédou City	272	239 (88%)	297	298 (100%)	317	265 (84%)	301	289 (96%)	275	250 (91%)
Tekoulo	262	241 (92%)	285	283 (99%)	318	279 (88%)	285	259 (91%)	281	198 (70%)
Guendembou	287	270 (94%)	325	321 (99%)	323	303 (94%)	293	273 (93%)	271	259 (96%)
Koundou (comparison)	260	224 (86%)	320	319 (99%)	305	250 (82%)	282	253 (90%)	291	234 (80%)
Individual characteristics										
Area	**N**	**April 2011**	**N**	**August 2011**	**N**	**February 2012**	**N**	**August 2012**	**N**	**February 2013**
Median age – median, (interquartile range)										
Guéckédou City										
Overall	1,762	11 (21.5)	1,908	10 (19.5)	1,694	18.2 (20.6)	1,729	18.6 (19.9)	1,733	18.2 (20.2)
1-59 months	505	0.3 (0.3)	504	0.36 (0.2)	499	0.36 (0.3)	391	0.36 (0.3)	512	0.36 (0.3)
5 – 14 years	555	9 (5)	732	9 (4)	464	9 (6)	592	8 (5)	447	8 (5)
≥15 years	701	29 (24)	672	29 (24)	731	30 (30)	746	30 (28)	774	30 (28)
Tekoulo										
Overall	1,690	10 (27.5)	1,829	10 (29.5)	1,684	18.6 (19.9)	1,690	19.6 (20.5)	1,694	18.5 (20.1)
1-59 months	495	0.36 (0.3)	556	0.35 (0.32)	512	0.36 (0.3)	403	0.36 (0.3)	475	0.36 (0.2)
5 – 14 years	495	8 (4)	513	8 (5)	420	8 (4)	525	8 (4)	481	7 (4)

≥15 years	700	34 (25)	760	35 (21.5)	752	35 (20)	762	35 (26)	737	34 (24)
Guendembou										
Overall	1,798	9 (29.5)	1,880	8 (24.5)	1,661	19.3 (20.7)	1,730	19.2 (20.6)	1,763	18.2 (20.3)
1-59 months	628	0.36 (0.3)	633	0.36 (0.3)	562	0.36 (0.3)	464	0.28 (0.3)	542	0.36 (0.3)
5 – 14 years	432	8 (5)	549	7 (4)	314	7 (4)	493	8 (4)	459	7 (3)
≥15 years	738	34.5 (20)	698	32 (23)	785	36 (22)	773	35 (24)	761	35 (24)
Koundou (comparison)										
Overall	1,697	11 (29.5)	2,016	17.2 (29.5)	1,687	19.6 (20.8)	1,750	19.2 (20.9)	1,730	19.8 (20.7)
1-59 months	522	0.36 (0.3)	567	0.36 (0.3)	466	0.36 (0.3)	460	0.36 (0.2)	450	0.36 (0.3)
5 – 14 years	426	8 (5)	610	8 (5)	475	7 (4)	524	7 (4)	493	7 (4)
≥15 years	749	35 (23)	839	32 (21)	746	38 (24)	766	35 (27)	787	35 (24)
Sex, n (% male)										
Guéckédou City	1,762	742 (42%)	1,908	800 (42%)	1,694	689 (41%)	1,729	739 (43%)	1,733	698 (40%)
Tekoulo	1,690	798 (47%)	1,829	890 (49%)	1,684	772 (46%)	1,690	774 (46%)	1,694	757 (45%)
Guendembou	1,798	741 (41%)	1,880	844 (45%)	1,661	707 (43%)	1,730	790 (46%)	1,763	749 (42%)
Koundou (comparison)	1,697	767 (45%)	2,016	949 (47%)	1,687	800 (47%)	1,750	865 (50%)	1,730	737 (43%)

+ Highest education attained by the head of household, % none

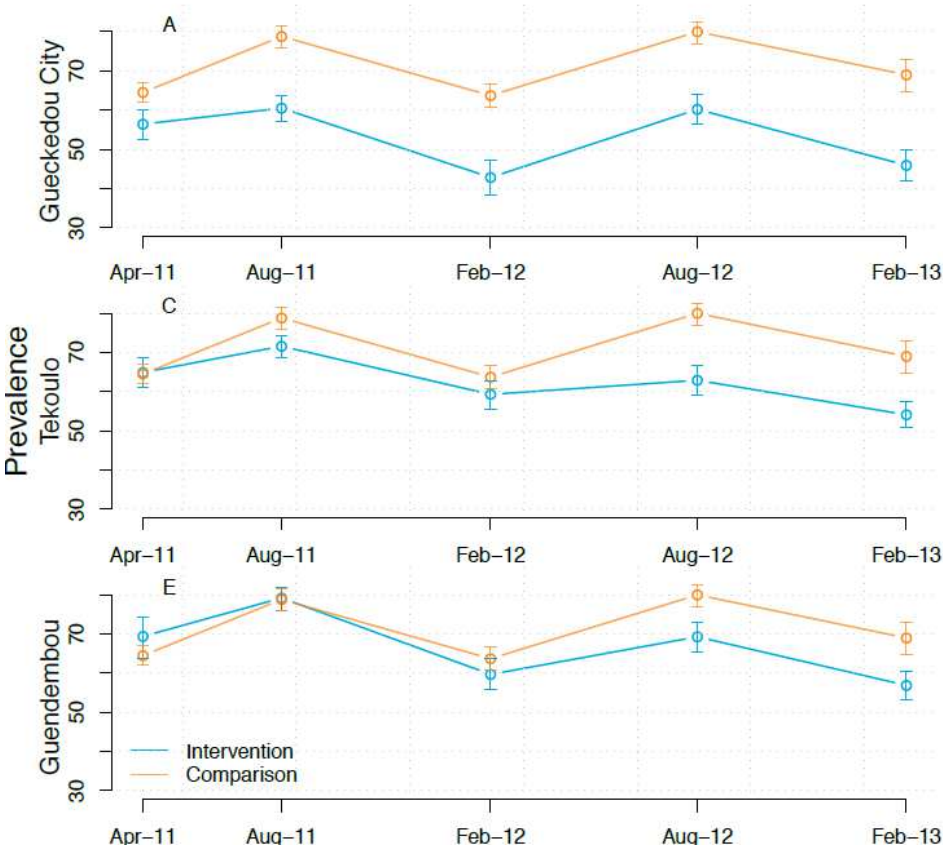
**Walls made of mud brick & roof made of iron sheet vs. other*

Malaria parasite prevalence

In April 2011, the prevalence of P. falciparum malaria infection according to RDT was over 55% in all sous-préfectures surveyed. In the first survey (April 2011), malaria parasite prevalence was significantly higher in the rural comparison sous-préfecture Koundou (64.5%, 95% CI: 62-66.9) than in urban Guéckédou City (56.4%, 95% CI: 52.6-60.1), p<0.001. There was no significant difference between Tekoulo or Guendembou and the comparison sous-préfecture (Figure 4-3).

As seen in Figure 4-3, after 2.5 years of the intervention, malaria parasite prevalence decreased significantly in all intervention sous-préfectures; Guéckédou City (45.9%, 95% CI: 42.0-49.8, p<0.01), Tekoulo (54.1%, 95% CI: 50.9-57.3, p<0.01) and Guendembou (56.9%, 95% CI: 53.1-60.5, p<0.01), while it increased insignificantly in the comparison sous-préfecture (69%, 95% CI: 64.7-73.0, p=0.06).

Figure 4-3: Malaria parasite prevalence according to rapid diagnostic test by sous-préfecture and survey period.



Malaria parasite prevalence was consistently higher in children 5-14 years of age, followed by children 1-59 months of age and individuals ≥15 years of age in all sous-préfectures (Table 4-2). From April 2011 to February 2013, malaria parasite prevalence decreased significantly across all intervention sous-préfectures for children 1-59 months and 5-14 years. However, there was no significant change in

malaria parasite prevalence for adults ≥15 years in any of the intervention sous-préfectures. No significant changes in malaria parasite prevalence by age group were seen in the comparison sous-préfecture during the same period (Table 4-2).

Table 4-2: Malaria parasite prevalence according to rapid diagnostic test by age group, sous-préfecture and survey period.

	April 2011 % (95% CI)	**August 2011** % (95% CI)	**February 2012** % (95% CI)	**August 2012** % (95% CI)	**February 2013** % (95% CI)
Guéckédou City					
1-59 months	54.8 (49.7-59.9)	60.7 (55.3-66.0)	40.0 (34.0-46.0)	54.4 (48.7-60.1)	44.3 (39.2-49.3)
5 – 14 years	78.3 (74.5-82.2)	75.9 (72.1-79.7)	65.9 (59.6-72.2)	80.2 (76.1-84.2)	67.3 (62.2-72.4)
≥15 years	40.3 (34.6-46.0)	43.6 (39.5-47.6)	29.9 (25.7-34.1)	47.4 (42.2-52.6)	34.6 (29.9-39.2)
Tekoulo					
1-59 months	67.9 (63.0-72.6)	75.3 (70.8-79.8)	63.0 (58.0-68.1)	61.7 (55.3-68.2)	54.3 (48.4-60.2)
5 – 14 years	89.4 (86.7-92.2)	92.0 (89.2-94.7)	84.5 (80.0-88.9)	88.3 (85.4-91.2)	78.3 (73.4-83.2)
≥15 years	45.4 (39.6-51.1)	55.1 (51.3-58.8)	42.6 (37.6-47.7)	46.0 (40.8-51.2)	38.3 (34.2-42.5)
Guendembou					
1-59 months	79.2 (74.8-83.7)	84.3 (81.3-87.4)	67.2 (61.8-72.7)	73.4 (67.2-79.6)	56.0 (49.8-62.2)
5 – 14 years	93.0 (90.4-95.6)	95.0 (92.8-97.3)	86.9 (82.8-91.0)	91.1 (88.2-93.9%)	85.8 (82.0-89.6)
≥15 years	47.1 (39.5-54.8)	62.0 (57.3-66.7)	43.5 (39.0-48.0)	52.5 (48.1-58.8)	40.0 (36.1-44.0)
Koundou (comparison)					
1-59 months	73.9 (69.0-78.8)	85.1 (81.2-89.1)	68.2 (63.3-73.1)	88.0 (84.3-91.7)	78.0 (72.8-83.1)
5 – 14 years	89.4 (86.2-92.5)	93.7 (91.4-96.0)	91.1 (88.0-94.2)	95.2 (93.3-97.1)	90.4 (87.1-93.7)
≥15 years	43.7 (38.1-49.4)	63.7 (60.1-67.3)	43.5 (39.3-47.7)	64.7 (60.4-69.0)	50.4 (44.9-55.9)

Symptomatic malaria infections

In April 2011 over 45% of RDT positive participants had a symptomatic malaria infection: 46.3% (95% CI: 38.1-54.4) in Koundou, 47.6% (95% CI: 38.8-56.4) in Guéckédou City, 50.5% (95% CI: 41.6-58.8) in Tekoulo and 49.6% (95% CI: 42.4-56.8) in Guendembou. Compared to February 2013, there were no significant changes in the proportion of symptomatic malaria infectious by sous-préfecture or among children under 5 years of age. Overall, the proportion of symptomatic participants generally deceased with increasing age as seen in Table 4-3.

Table 4-3: Proportion of symptomatic malaria rapid diagnostic test positive participants by age, survey period and sous-préfecture.

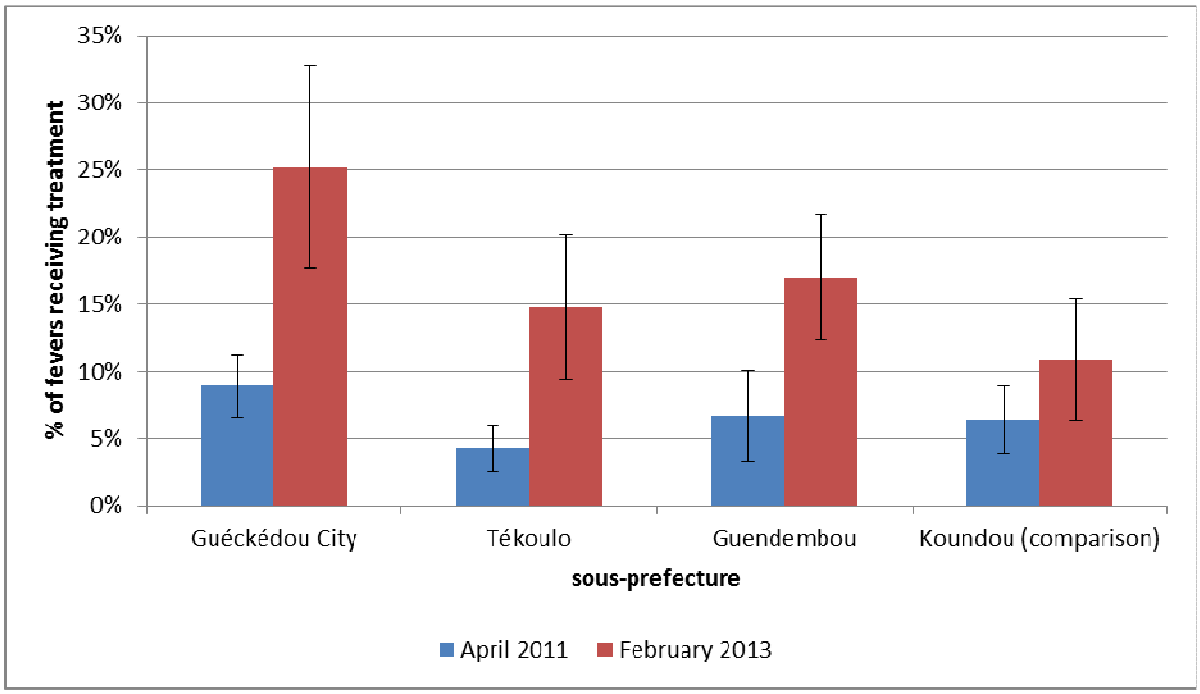
	April 2011 % (95% CI)	**August 2011** % (95% CI)	**February 2012** % (95% CI)	**August 2012** % (95% CI)	**February 2013** % (95% CI)
Guéckédou City					
Overall	47.6 (38.8-56.4)	55.0 (43.5-66.5)	44.9 (35.7-54.1)	30.4 (18.8-41.9)	47.4 (35.1-59.8)
1-59 months	51.6 (41.5-61.6)	58.1 (47.2-69.1)	45.0 (34.0-55.9)	39.4 (26.9-51.9)	53.7 (40.9-66.5)
5 – 14 years	48.5 (37.8-59.1)	54.8 (42.4-67.2)	48.6 (37.8-59.5)	26.7 (15.2-38.2)	45.1 (31.5-58.7)
≥15 years	42.4 (33.3-51.4)	52.2 (38.0-66.3)	39.7 (30.4-49.0)	29.9 (16.4-43.4)	44.7 (30.5-59.0)
Tekoulo					
Overall	50.5 (42.6-58.8)	51.6 (42.5-60.7)	50.2 (41.6-58.8)	35.5 (21.9-49.0)	33.8 (24.2-43.5)
1-59 months	51.4 (42.2-60.7)	60.6 (52.0-69.2)	54.1 (44.5-63.7)	46.9 (33.0-60.8)	36.4 (26.8-46.0)
5 – 14 years	48.5 (39.4-57.5)	47.2 (35.9-58.5)	54.0 (43.4-64.7)	34.4 (19.7-49.1)	32.0 (20.4-43.6)
≥15 years	52.2 (42.8-61.5)	47.7 (37.8-57.6)	42.0 (31.6-52.4)	28.7 (15.7-41.8)	33.9 (22.7-45.1)
Guendembou					
Overall	49.6 (42.4-56.8)	52.7 (42.3-63.2)	45.7 (35.9-55.5)	31.6 (22.1-41.0)	41.5 (31.2-51.9)
1-59 months	51.6 (43.9-59.2)	55.8 (46.0-65.5)	41.1 (31.6-50.4)	41.9 (31.3-52.5)	42.7 (30.3-55.1)
5 – 14 years	49.7 (40.8-58.6)	51.7 (39.0-64.3)	52.7 (41.8-63.6)	29.3 (18.6-39.9)	39.8 (28.1-51.5)
≥15 years	46.8 (37.5-56.0)	50.3 (37.4-63.1)	45.3 (32.2-58.3)	25.7 (14.6-36.8)	42.6 (30.4-54.8)
Koundou (comparison)					
Overall	46.3 (38.1-54.4)	47.2 (38.2-56.1)	53.6 (42.9-64.3)	44.0 (34.6-53.5)	45.3 (34.6-53.5)

1-59 months	48.4 (38.4-58.4)	56.3 (48.2-64.4)	52.5 (41.3-63.6)	53.3 (44.0-62.5)	48.7 (37.4-59.9)
5 – 14 years	48.2 (39.3-57.2)	45.4 (34.5-56.3)	57.9 (45.4-70.4)	40.2 (29.2-51.3)	42.6 (29.7-55.4)
≥15 years	41.4 (30.8-52.0)	40.9 (30.9-50.9)	48.9 (37.7-60.0)	40.3 (30.1-50.5)	45.3 (32.5-58.1)

Fevers and treatment seeking behavior

As seen in Figure 4-4, the proportion of participants who reported a history of fever in the month prior to the interview and who sought treatment at a health facility or from a CHW was low in April 2011: 6.4% (95% CI: 3.9-8.9) in Koundou, 8.9% (95% CI: 6.6-11.1) in Guéckédou City, 4.3% (95% CI: 2.6-5.9) in Tekoulo and 6.7% (95% CI: 3.9-8.9) in Guendembou. By February 2013, there was a significant increase in treatment seeking in the intervention sous-préfectures, Guéckédou City (25.2%, 95% CI: 17.7-32.6, p<0.001) Tekoulo (14.8%, 95% CI: 9.4-20.2, p<0.001) and Guendembou (17.0%, 95% CI: 12.3-21.7, p=0.001), while there was no significant change in the comparison sous-préfecture (10.9%, 95% CI: 6.4-15.5, p=0.08).

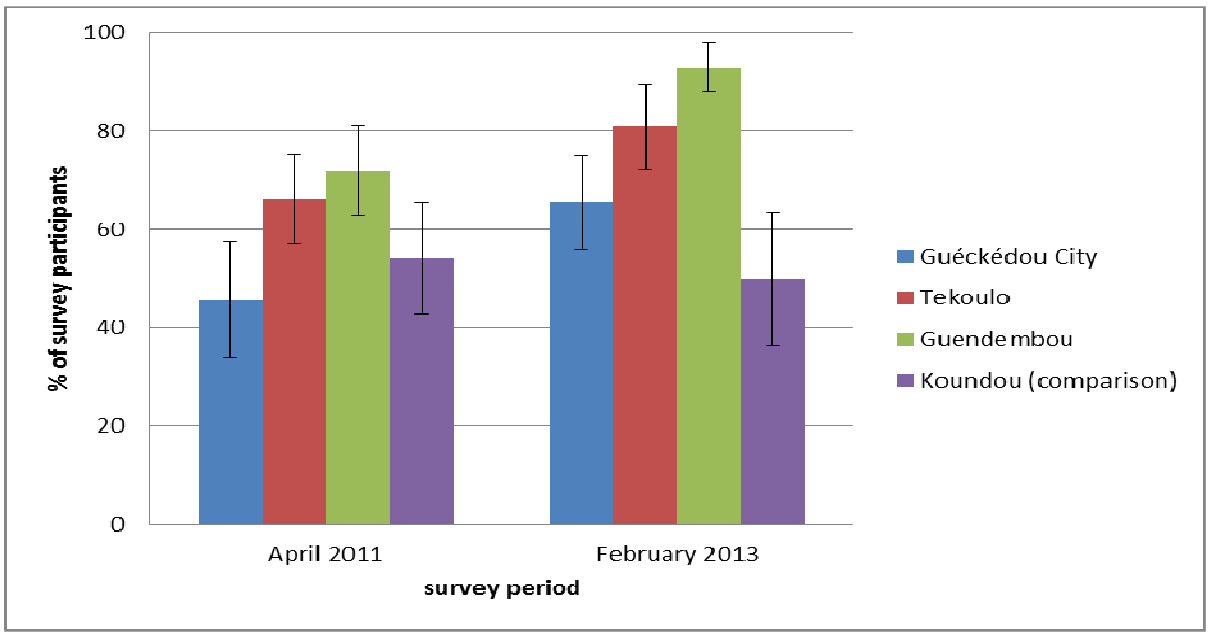
Figure 4-4: Treatment seeking behavior by sous-préfecture and survey period.



LLIN ownership and use

Over 40% of survey participants reported owning a LLIN in April 2011. Reported LLIN ownership was higher in the rural sous-préfectures than in the urban sous-préfecture (Figure 4-5). After the mass LLIN distribution was carried out in the intervention sous-préfectures in April 2012 the proportion of respondents who reported owning an LLIN in February 2013 increased significantly in all intervention sous-préfectures (45.7% to 65.4% in Guéckédou City, p=0.01; 66.2% to 80.8% in Tekoulo, p=0.02; 72.0% to 92.9% in Guendembou, p<0.001). No significant change in reported LLIN ownership was observed in Koundou (54.1% to 49.8%, p=0.63). Among participants who reported owning an LLIN in April 2011, reported LLIN use was over 94% in all areas (range 94.5-99.4%) and increased to over 98% (range 98.0-99.4%) in all sous-préfectures in February 2013.

Figure 4-5: Reported LLIN ownership by sous-préfecture and survey period.



4.5. Discussion

Data from repeated cross-sectional surveys was used to assess the impact and coverage of a multi-component malaria control intervention in a hyperendemic region of Guinea. These results document improved coverage and a reduction in *P. falciparum* malaria parasite prevalence in the intervention sous-préfectures during the study period, April 2011 to February 2013. This contrasts with the comparison sous-préfecture where an increase in *P. falciparum* malaria parasite prevalence was observed during the same period.

Outside of trial conditions making direct comparisons between individual intervention sous-préfectures and the comparison sous-préfecture is difficult because malaria transmission dynamics likely vary across sous-préfectures and are not easily controlled. Indeed results from the first survey in April 2011 showed that malaria parasite prevalence was significantly different between urban Guéckédou City and the rural

comparison sous-préfecture. However, despite not being directly comparable, the difference in the direction of the trends, an increase in malaria parasite prevalence in the comparison area and a decrease in Guéckédou City, remains indicative of the impact of the intervention package in the latter. Studies investigating the impact of multiple malaria control interventions have been carried out in other comparable settings, however implementation was frequently over smaller geographic areas, without a comparison group or used health facility-based surveillance data rather than malaria-specific surveys for evaluation (Nyarango *et al.*, 2006; Alba *et al.*, 2011; Thiam *et al.*, 2012; Linn *et al.*, 2015).

Despite these encouraging findings, malaria parasite prevalence remains high in this region and is considerably higher in children than adults. While none of the interventions specifically targeted children, malaria parasite prevalence in both groups of children (1-59 months and 5-14 years of age) decreased significantly over the study period in all intervention sous-préfectures albeit with seasonal fluctuations. Yet, there was no significant change in malaria parasite prevalence in individuals ≥15 years likely due to the presence of acquired protective immunity (Doolan, Dobano and Baird, 2009). In the comparison sous-préfecture neither the overall change in malaria parasite prevalence nor age specific changes were significant suggesting that decreases in malaria parasite prevalence in the intervention sous-préfectures were related to the intervention package. Nevertheless after 2.5 years of implementation malaria parasite prevalence remained over 44% in children 0-59 months and 67% in children 5-14 years of age. While this suggests that health interventions, including those for malaria, that focus on children under-5 are justified in targeting this particularly vulnerable group it also demonstrates that interventions that focus on under 5's alone will be insufficient to control malaria transmission and that consideration should be given to enlarging the target age range (Lalloo, Olukoya and Olliaro, 2006; Walldorf *et al.*, 2015).

Estimates of malaria parasite prevalence varied depending on whether RDT or microscopy was used for evaluation. Although acknowledged that RDTs are less specific than microscopy for evaluation of malaria parasite prevalence (Kyabayinze *et al.*, 2008; Nankabirwa *et al.*, 2015), the difference in prevalence according to RDT and microscopy may also have resulted from the experience of the laboratory technicians and the condition of the slides when they were read. Notwithstanding, when repetitive testing and treatment of participants takes place, use of HRP2 tests should be discouraged due to their time to become negative [23] as their use may result in the unnecessary treatment of malaria negative participants.

We cannot discount the impact that treating at least 22,387 individuals over 2.5 years may have had on malaria parasite prevalence. While treating so many people may have contributed to the decrease in malaria parasite prevalence documented here, surveys were carried out in newly selected clusters every 6 months. In this hyperendemic area it is unlikely that this focal, punctual administration of malaria treatment had a sustained impact on malaria parasite prevalence. In the absence of continued mass treatment it is unlikely that local transmission would not have been re-established in the 6 months between surveys.

Unlike previously reported decreases of symptomatic malaria infections after malaria control intervention implementation (Linn *et al.*, 2015), there was no significant change in the prevalence of symptomatic infections in the intervention sous-préfectures. Although our definition of symptomatic episodes is commonly used, this indicator may have been impacted in part by the self-reported nature of 'history of fever'. Previous studies have shown that a caregivers determination of a febrile episode is frequently inaccurate (Whybrew, Murray and Morley, 1998; Diallo *et al.*, 2001) making self-reported data less reliable than biomarkers such as measured temperature the day before the survey, gathered directly from participants. Furthermore, experiencing a febrile episode does not systematically indicate malaria infection as other common morbidities in the region also present with fever (Mazigo *et al.*, 2011; D'Acremont *et al.*, 2014). Nevertheless despite its limitations, using fever or a history of fever as an indicator of uncomplicated malaria in areas of high endemicity is not without precedent (Rooth and Bjorkman, 1992; Olaleye *et al.*, 1998; Okiro and Snow, 2010).

Community health workers were recruited and trained to facilitate timely testing and treatment of cases of uncomplicated malaria and to refer cases of complicated malaria to the nearest health facility after administration of pre-referral treatment. Reported treatment seeking from a health facility or CHW, an indicator of intervention coverage, increased over time in all intervention sous-préfectures but was greatest in Guéckédou City, likely reflecting better access to health facilities in urban areas (Bruce-Chwatt, 1983; Alba *et al.*, 2010; Hay *et al.*, 2011). The increase in treatment seeking from a health facility or CHW supports results from previous studies demonstrating that the availability of medication influences treatment seeking behavior for febrile illness (Amuge *et al.*, 2004; Alba *et al.*, 2010). Despite the increase in treatment seeking behavior during the study period, it remains low, particularly in the rural sous-préfectures and suggests that additional activities targeting behavior change may be needed to achieve and sustain greater impact.

In April 2011 none of the study sous-préfectures reported LLIN ownership of 80% (2010 RBM target) (Roll Back Malaria Partnership, 2004). After the April 2012 mass distribution, LLIN ownership had reached 80% only in the two rural intervention sous-préfectures when measured in February 2013 not unlike the heterogeneity in coverage levels reported after a LLIN distribution in Ethiopia (Deressa *et al.*, 2011).

Low levels of reported LLIN ownership could be due to the manner in which the LLINs were distributed, at fixed points requiring individuals to leave their village in order to receive them. It may also be due to repurposing of LLINs. Indeed observations by the authors and anecdotal reports from survey teams described nets distributed in April 2012 for sale in markets and used as garden fencing and fishing nets. As the LLINS that were distributed by MSF were distinctive in size and color it is unlikely that there was confusion between these LLINS and other nets. Yet, these experiences are not unique to this distribution (McLean *et al.*, 2014). Finally, the quality of the LLINs distributed could partially explain the elevated prevalence of malaria parasitemia that persisted after 2.5 years of malaria control interventions. However, unlike reports of substandard LLINs distributed in Rwanda (Mwema Bahati, 2015), the LLINs distributed in Guéckédou were procured by MSF and used by both the community and in MSF households and supported facilities. We are not aware of any reports of problems with the quality of the

LLINs distributed. Nevertheless, in contrast to the relatively low LLIN coverage, reported use of LLINS was consistently high both prior to and after the LLIN distributions. For logistical reasons, implementation of the different components of the intervention package was heterogeneous and resulted in a key intervention, the mass distribution of LLINs, occurring over 12 months after implementation had begun. Admittedly a larger impact of the intervention package on malaria parasite prevalence may have been seen had LLINS been distributed at the beginning of the intervention.

The intervention package was constantly reviewed as it would be in 'real life' resulting in modifications of some activities. Consequently these results describe the impact of a multi-component malaria intervention implemented over a large geographic area and outside of trial conditions where extraneous factors are more easily controlled. The evaluation was not designed to quantify the impact of individual components of the intervention. Any indicator specific survey to survey variation is likely due to uncontrollable differences in implementation, the area of intervention and intervention components. While this variation presents a challenge for analyzing program impact, this approach also reflects the obstacles that malaria control programs encounter with unavailable materials, etc, and highlights the difficulties of implementation on a large scale outside of trial conditions (Salam *et al.*, 2014).

This study has a number of limitations, particularly related to the realities of field implementation. First, information on all activities related to the intervention package in the study sous-préfectures was not systematically collected and intervention implementation was heterogeneous over time. Additionally, indicators that are known to impact malaria transmission, rainfall, village altitude, proximity to water, forest density and condition of LLINs, among others were not collected. Although it is difficult to know or record all changes in the intervention or these indicators in any field setting, similar studies in the future could attempt to more systematically collect this data. Second, the cross-sectional design of this study did not permit accounting for short term fluctuations in parasitemia however we believe this effect to be small and not to have substantially impacted the overall results. Additionally here we present malaria parasite prevalence according to RDT and microscopy that show some variation in the two sets of estimates. The difference between the two measures could be due to the limitations of RDT performance (Nankabirwa *et al.*, 2015) in addition to the prolonged time to become negative for HRP2 tests (Kyabayinze *et al.*, 2008). Third, because of the selection of new clusters for each survey round we were unable to analyze spatial variations in malaria or determine particular parasite foci. Future studies could consider collecting data from the same geographic areas in order to account for spatial distribution. Finally, one indicator of intervention coverage was measured using an indicator heavily reliant on self-reported episodes of fever that encompasses more than malaria morbidity. Additionally, households were not purposefully visited in order to verify the information provided by the respondent concerning reported LLIN ownership. However, it is assumed that during the period of intervention other causes of common morbidities remain unchanged; reports of fever should provide a reliable indicator of malaria morbidity. As there were no major interventions aside from this intervention during the study period that could have led to the prevention of new fever cases this is a reasonable assumption.

4.6. Conclusions

This study, which took place from 2011 to 2013 in Guéckédou, Guinea, shows an encouraging decrease in malaria parasite prevalence and an increase in treatment seeking and ownership of LLINs. These results provide support for the RBM recommended malaria control interventions and add to a growing body of evidence that suggests that multi-component malaria interventions have a greater impact than singular interventions alone, at least in the short term.

While this malaria control intervention was ambitious and challenging to implement in a large, hyperendemic area with difficult access, our results show that wide-spread coverage can be obtained and intervention programs can be monitored and adapted over time.

Although malaria parasite prevalence decreased, it remained unacceptably high even after 2.5 years of intervention, particularly in children ≤14 years of age. These results demonstrate the importance of reinforcing malaria control activities in hyperendemic areas such as Guéckédou in the long term. They also highlight the need for development and implementation of age specific interventions and vector control measures to further reduce transmission.

Competing interests

The authors declare they have no competing interests.

Authors' contributions

The study was conceived and designed by AT, MS, BG, ES and RFG. Substantial contributions to acquisition of the data were made by FPM, ATr, TG and MH. Initial analysis and interpretation of the data was done by AT and BG. The manuscript was drafted by AT, BG and RFG. All authors were involved in the revision of the manuscript for intellectual content and approved the final version.

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5. The impact of a reduction in malaria control activities due to an outbreak of Ebola virus disease in Guéckédou, Guinea; a modeling study of malaria resurgence.

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5.1. Abstract

Introduction

The 2013-2016 Ebola epidemic in West Africa greatly hit the health care systems in the most affected countries and resulted in a significant reduction of malaria control activities as resources were diverted to the Ebola response. We assessed the impact of a cessation of malaria control activities in Guéckédou, Guinea as a result of an outbreak of Ebola virus disease in March 2013.

Methods

Data from 3 sous-préfectures where malaria control activities had been implemented from 2011 to 2014 was used to calibrate an individual-based stochastic malaria model (OpenMalaria). Estimates of the incidence of uncomplicated malaria cases from January 2010 to October 2017 were produced by the model for two scenarios: i) a counterfactual scenario that assumes no reinforced malaria interventions occurred between 2011 and 2014, and ii) a scenario with reinforced malaria interventions that began in April 2011 and ceased at the start of the Ebola outbreak (April 2014). Interrupted time series analysis was used to assess the impact of malaria control activity cessation on malaria incidence by comparing the two scenarios.

Results

There was a 10.5% (95% CI: 8.3-12.2) increase in the incidence of malaria after declaration of Ebola outbreak as a result of cessation of malaria control activities when compared to the counterfactual scenario produced by the model. The increase in incidence was heterogeneous and varied by sous-préfecture. Via multivariate interrupted time series analysis, the change in trend after activity cessation was statistically significant after the Ebola outbreak was declared in all sous-préfectures where reinforced malaria control interventions had been implemented.

Conclusions

These findings suggest that Guéckédou likely experienced a resurgence of uncomplicated malaria cases as a result of the 2013-2016 Ebola epidemic. Further modeling work will indicate the likely age structure of these increases in cases and which age group bore the brunt of malaria resurgence. This will indicate if emergency responses should prioritize targeting more vulnerable age groups. Health facility data from the sous-préfectures investigated, or a cross-sectional survey of malaria parasite prevalence will be needed to confirm the model results presented here. While the Ebola epidemic provided an opportunity to investigate malaria resurgence, the risk of resurgence is a concern for any disease control program that stops suddenly due to lack of funding, commitment or deprioritization during an emergency. In areas where malaria is highly endemic, progress made during the intervention is quickly negated when activities stop. The impact of activity cessation extends beyond the emergency and will be costly to address in the long-term.

5.2. Introduction

On March 23, 2014, the first outbreak of Ebola virus disease (Ebola) was declared in the Republic of Guinea (Guinea). The epicenter of the outbreak was located in the forested préfecture of Guéckédou where malaria is hyperendemic and where, since 2011, Médecins Sans Frontières (MSF) and the Ministry of Health implemented a multi-component malaria control intervention. Community-based cross-sectional surveys were carried out in order to monitor the implementation of the intervention. After declaration of the Ebola outbreak, malaria control activities supported by the Ministry of Health were significantly reduced and all malaria control activities implemented by MSF ceased and transitioned to responding to the Ebola outbreak.

Treatment seeking for fever related illness at health facilities in Guéckédou Préfecture was low prior to the outbreak (Tiffany, Moundekeno, Traoré, Haile, Sterk, Guilavogui, Genton, *et al.*, 2016) and was noticeably reduced after declaration of and during the Ebola outbreak (Plucinski *et al.*, 2015; Moisan *et al.*, 2016). The decline in visits to public health facilities during this period likely resulted in numerous malaria infections going untreated (Plucinski *et al.*, 2015; Walker *et al.*, 2015). Health facility attendance only began increasing after Guéckédou had been declared Ebola free (Moisan *et al.*, 2016). Consequently, health facility data during the period of the outbreak in Guéckédou is unlikely to represent the true burden of malaria during the Ebola and post-Ebola periods due to the decrease in patient visits. If testing for malaria remained infrequent after the outbreak for any reason, any estimates derived from health facility data would likely provide an underestimate of the true burden.

It can be expected that the cessation of malaria control activities resulted in an increased number of malaria cases in Guéckédou. Indeed, estimates of the impact of the Ebola outbreak on malaria related morbidity and mortality suggest that the burden of malaria increased (Plucinski *et al.*, 2015; Walker *et al.*, 2015). In order to investigate the possibility and magnitude of resurgence of malaria cases, an individual-based stochastic model of malaria transmission, OpenMalaria (Smith *et al.*, 2012; *OpenMalaria Microsimulation.*, 2016) was used to predict the impact of the cessation of malaria control activities. The model was informed by previously reported data from the prefectures on prevalence, intervention coverage and reported clinical incidence (Tiffany *et al.,* 2016). The number of cases that occurred in both an intervention and counterfactual (non-intervention) scenario were estimated by month. An interrupted time series analysis was used to describe the impact of the cessation of malaria control activities as a consequence of the Ebola outbreak in Guéckédou, Guinea on the incidence of uncomplicated cases of malaria.

Study Area

Bordered by Sierra Leone and Liberia, the prefecture of Guéckédou is one of 33 préfectures in the Republic of Guinea (Guinea), which is itself comprised of 13 sous-préfectures, 9 in the rural area and 4 urban communes (Ministere de la Santé et de l'Hygiene Publique - Republique de la Guinée, 2014). The area is heavily forested and malaria is hyperendemic with perennial transmission. Community level malaria parasite prevalence measured by microscopy in a 2011 community-based cross sectional survey was estimated to be 63.8% with mild seasonal variation (Tiffany, Moundekeno, Traoré, Haile, Sterk,

Guilavogui, Genton, *et al.*, 2016). Transmitted by *Anopheles gambiae, Plasmodium falciparum* is the predominate malaria parasite species in the country (World Health Organization Global Malaria Programme, 2015b).

A reinforced malaria control program was implemented in three sous-préfectures (Guéckédou City, Tekoulo and Guendembou) of Guéckédou Préfecture beginning in 2011. Activities were implemented by Médecins Sans Frontières in collaboration with the Ministry of Health. The components of the intervention package were based on WHO recommendations and the Roll Back Malaria Strategy and have been described elsewhere (Tiffany, Moundekeno, Traoré, Haile, Sterk, Guilavogui, Genton, *et al.*, 2016) in detail. Briefly, the intervention had both curative and preventive components including ensuring access to malaria RDT's and artemisinin-based combinations (ACT) for treatment of uncomplicated malaria cases in health facilities and by community health workers. A one-time community-wide mass distribution of long lasting insecticide treated nets (LLINs) was also carried out. Coverage levels of each intervention are detailed in Appendix 1.

In order to monitor the reinforced control intervention, five community-based cross-sectional cluster surveys were carried out from 2011 to 2013 in the three sous-préfectures that received the intervention (Guéckédou City, Tekoulo, Guendembou). The same surveys were also carried out in a fourth sous-préfecture (Koundou) where reinforced malaria control activities were not implemented.

5.3. Methods

Experiment design

A previously described OpenMalaria simulation (Penny and Smith, 2012; Smith *et al.*, 2012) was used to simulate malaria transmission in Guéckédou, Guinea from January 2010 through October 2017. Model runs were performed at the level of sous-préfecture, the third-level administrative division, and the output used to estimate the effect of a cessation of malaria control activities on the monthly incidence of uncomplicated malaria. For each sous-préfecture the model was fitted to biannual estimates of microscopy diagnosed malaria parasite prevalence for all ages from the community-based cross-sectional surveys (Appendix 1).

The model predicted malaria incidence following the cessation of interventions in each of the sous-prefectures and allowed for an evaluation of the impact of the reinforced malaria control intervention. Entomological inoculation rate, access to effective treatment at baseline, the change in access to effective treatment following intervention, the proportion of indoor to outdoor biting mosquitos (estimated only for Guéckédou due to the its semi-urban population), LLIN usage, and the proportion of active outdoor biting mosquitos were parameterized or fitted to represent the specific situation in each sous-prefecture. The LLIN parameter accounted for attrition of nets as well as for reduction in net efficacy over time, assuming that nets are no longer effective 3 years after distribution. However the vector bionomics remained unclear in these areas. As a result, in order to reflect this uncertainty, the predictions included varying levels of mosquito biting behavior (Appendix 2). Seasonality was fitted to

parasite prevalence data from Koundou, a sous-préfecture that never received the reinforced malaria control interventions.

The model was used to estimate the monthly number of uncomplicated cases of malaria that occurred from January 2010 through October 2017 for each sous-préfecture. The model simulated the impact of the interventions on the incidence of malaria; however, the model also simulated the hypothetical scenario of an absence of interventions (counterfactual) for each sous-préfecture. Comparisons of model predictions between these two scenarios allowed for estimation of the impact of the cessation of malaria control activities in Guéckédou on the incidence of malaria. Simulations were repeated with multiple random seeds to address stochasticity in model predictions and model outputs were validated against a subset of cross-sectional surveys.

Statistical analysis

The primary outcome was the predicted incidence of uncomplicated clinical cases of malaria by month. Three periods were considered: the pre-intervention period (Jan 2010-March 2011), the reinforced malaria control intervention period, prior to Ebola, (April 2011-March 2014) and the malaria control activity cessation period, during and post-Ebola (April 2014-October 2017). April 2014 was determined to be the point when malaria control activities ceased.

Firstly, the predicted mean number of uncomplicated malaria cases occurring per month per 1,000 inhabitants in the intervention and counterfactual scenarios was calculated for each period. The relative percent difference in the number of uncomplicated cases was estimated by period for each sous-préfecture as: (cases in the counterfactual scenario - cases in the intervention scenario)/(cases in the counterfactual scenario) *100.

Second, interrupted time series analysis (segmented generalized linear model with robust Poisson distribution) was used to analyze changes in the trend of uncomplicated malaria cases during the different periods, by sous-préfecture. The population was included as a log offset. The model was adjusted by trend, seasonality and month. Stata 12 (StataCorp, College Station TX) was used to perform the analysis.

Trends in the number of uncomplicated malaria cases were analyzed by period. Changes over time were analyzed by intervention and counterfactual scenarios, and assessed by a relative percent change.

Role of the funding source

No specific funding was obtained for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

5.4. Results

The predicted impact of the implementation of the reinforced malaria control intervention and the cessation of control activities, estimated as the mean number of cases per 1,000 inhabitants per month is presented in Table 5-1. All intervention areas (Guéckédou City, Guendembou, Tekoulo) experienced a

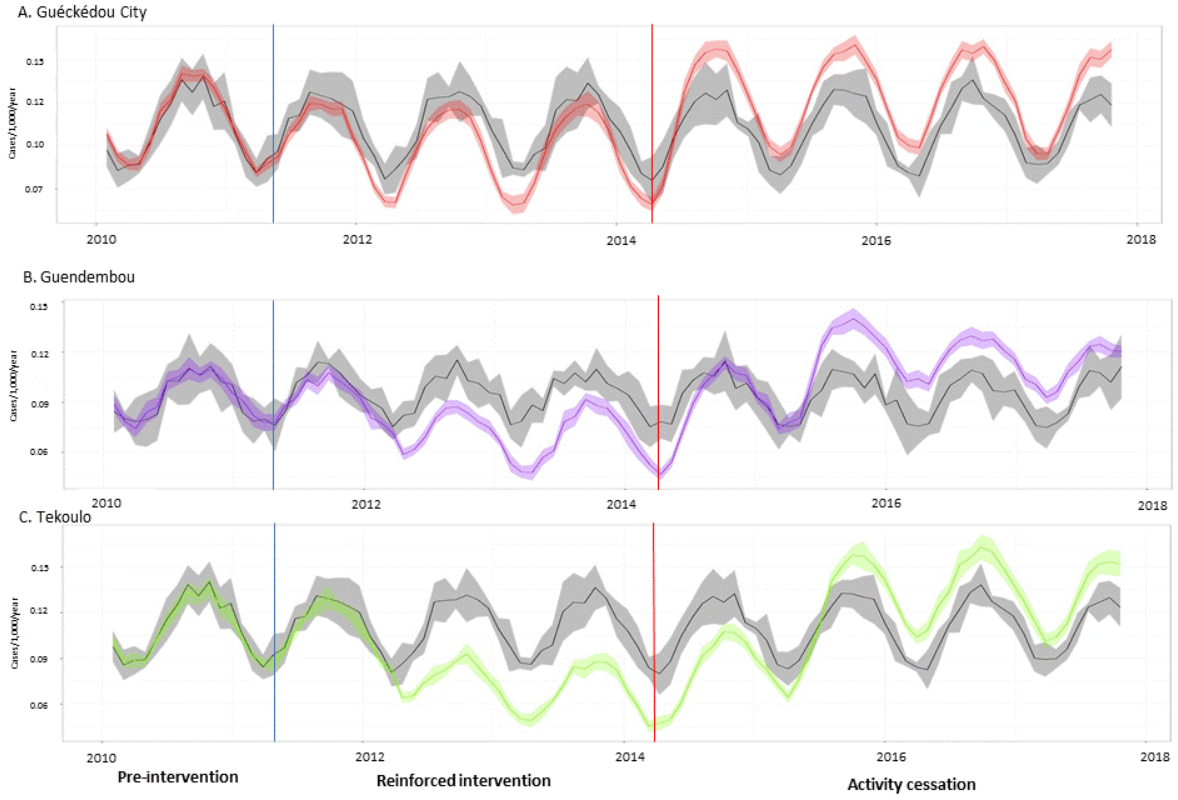
decrease in the incidence of malaria after implementation of the reinforced malaria control program (reinforced intervention period) which, after activity cessation, was followed by an increase in the number of uncomplicated malaria cases during the activity cessation period as illustrated in Figure 5-1. The relative increase in the number of malaria cases predicted by the model during the activity cessation period was 13.1% (95% CI: 12.2-13.9) in Guéckédou City, 12.6% (95% CI: 10.7-14.1) in Guendembou and 5.3 % (95% CI: 1.7-8.5) in Tekoulo when comparing the counterfactual scenario with the intervention scenario. Analyzed over time, overall the number of cases per month in the intervention scenario eventually surpassed that in the non-intervention scenario 8 months after activities ceased. This occurred earlier in Guéckédou City (July 2014) than in Guendembou (September 2014) and in Tekoulo (August 2015).

Table 5-1: Population estimates of uncomplicated clinical malaria cases from 2010-2017, by period, in Guéckédou, Guinea.

	Pre-intervention (Jan 2010-March 2011*)	**Reinforced intervention** (April 2011-March 2014)	**Activity cessation** (April 2014- Oct 2017*)
	Population estimate		
Guéckédou City	141,419	152, 153	181,216
Guendembou	45,973	49,476	58,968
Tekoulo	56,529	60,819	72,437
Koundou	37,134	39,953	47,585
	Uncomplicated clinical malaria cases per 1,000 inhabitants per month (95% CI)		
Guéckédou City			
Intervention	111.0 (99.8-122.2)	99.4 (92.3-106.6)	127.6 (120.1-135.1)
Counterfactual	108.7 (98.3-119.2)	111.9 (106.0-117.7)	110.8 (105.4-116.2)
Guendembou			
Intervention	92.3 (52.7-131.8)	77.7 (72.1-83.2)	107.8 (101.2-114.1)
Counterfactual	91.3 (84.3-98.2)	96.2 (92.2-100.1)	94.2 (90.4-97.9)
Tekoulo			
Intervention	107.4 (97.6-117.2)	83.5 (75.7-91.4)	117.1 (107.2-127.0)
Counterfactual	108.7 (98.3-119.2)	111.9 (106.0-117.7)	110.8 (105.4-116.2)
Koundou			
Comparison	91.3 (84.3-98.2)	96.2 (92.2-100.1)	94.2 (90.4-90.0)

* *January 2010-March 2011, April 2014-2017 intervention and all counterfactual estimates based on model predictions. March 2011-March 2014 intervention estimates are based on cross-sectional survey data.*

Figure 5-1: Model predictions of the number of uncomplicated cases of clinical malaria per 1,000 inhabitants and month with 95% confidence intervals from January 2010 to October 2017, by sous-préfecture. *Colored line and shading represents the intervention scenario and its 95% confidence interval while the gray line and shading represents the counterfactual scenario and its 95% confidence interval. The blue dividing line corresponds to reinforced malaria control activity implementation (April 2011) while the horizontal red solid line represents the point at which control activities ceased (April 2014).*



The impact of the cessation of malaria control activities on the number of uncomplicated malaria cases was also analyzed through an interrupted time series analysis (Figure 5-1). In the multivariate interrupted time series analysis, the change in the trend after activity cessation was statistically significant after the Ebola outbreak was declared in all sous-préfectures where reinforced malaria control interventions had been implemented (Table 5-2) except in Koundou where no activities had been implemented.

Table 5-2: Segmented generalized linear model with robust Poisson distribution.

	IRR	(95% CI)	p-value
Guéckédou City			
Annual cycle (sine curve)	0.78	0.76-0.79	0.000
Annual cycle (cosine curve)	1.09	1.07-1.12	0.000
Change in level after intervention	0.87	0.81-0.92	0.000
Change in trend after intervention	0.99	0.98-0.99	0.000
Change in level after activity cessation	1.14	1.03-1.27	0.010
Change in trend after activity cessation	1.00	1.00-1.01	0.001
Guendembou			
Annual cycle (sine curve)	0.83	0.80-0.85	0.000
Annual cycle (cosine curve)	1.07	1.04-1.10	0.000
Change in level after intervention	0.93	0.85-1.02	0.177
Change in trend after intervention	0.98	0.98-0.99	0.000
Change in level after activity cessation	1.34	1.14-1.57	0.000
Change in trend after activity cessation	1.01	1.01-1.02	0.000
Tekoulo			
Annual cycle (sine curve)	0.81	0.78-0.84	0.000
Annual cycle (cosine curve)	1.13	1.09-1.17	0.000
Change in level after intervention	0.99	0.89-1.10	0.938
Change in trend after intervention	0.97	0.97-0.98	0.000
Change in level after activity cessation	1.44	1.20-1.73	0.000
Change in trend after activity cessation	1.03	1.02-1.03	0.000
Koundou			
Annual cycle (sine curve)	0.84	0.83-0.85	0.000
Annual cycle (cosine curve)	1.02	1.01-1.04	0.000
Change in level after intervention	0.99	0.95-1.03	0.751
Change in trend after intervention	0.99	0.99-0.99	0.000
Change in level after activity cessation	0.99	0.92-1.06	0.827
Change in trend after activity cessation	1.00	0.99-1.00	0.632

5.5. Discussion

The results presented here predict the impact of an abrupt cessation of malaria control activities on the incidence of malaria in Guéckédou Prefecture, the initial focus of the 2013-2016 Ebola outbreak. The increase is likely a consequence of the escalating trend in malaria cases after control activities ceased. The extent to which the number of cases in each sous-préfecture changed was heterogeneous, larger in semi-urban Guéckédou City, when compared to the rural sous-préfectures of Tekoulo and Guendembou and reflects the micro-epidemiological variation in access to effective treatment, malaria parasite prevalence and EIR present within Guéckédou Préfecture.

The impact of the reinforced control program on malaria cases waned and incidence reached pre-intervention levels an average of eight months after activities ceased. This is a result of increased population infection as the vectorial capacity returned to pre-intervention levels in each sous-préfecture,

in addition to decreased access to effective treatment. Moreover, incidence levels are anticipated to have resurged past the pre-intervention level, a result of delay in acquisition of immunity and thus an age shift in clinical cases.

The relatively rapid increase in the incidence of malaria in Guéckédou City may reflect the high population density in addition to the frequent movement of people in and out of the city. We demonstrate that despite a substantial investment in malaria control in the areas of intervention, a reduction in malaria incidence is not sustained for long after control activities cease, and resurges to a prior equilibrium. In the case of Guéckédou City, this point was predicted by the model to have occurred only 4 months after malaria control activities ceased. Malaria resurgence has been documented previously and classified as occurring as a result of three main causes: weakening of malaria control programs including purposeful cessation, increased in the potential for malaria transmission and technical problems including drug and parasite resistance (Cohen *et al.*, 2012).

Previously published estimates of the impact of the Ebola epidemic on the number of clinical malaria cases was estimated at the level of country (Guinea) and region (Walker *et al.*, 2015). Unlike the estimates presented here, their estimates, particularly for the region of N'zerekore, do not account for intra-regional variation in malaria epidemiology, nor were they informed by prevalence surveys or intervention coverage data. They were also unable to consider the incremental impact over time of the implementation of the reinforced malaria control intervention, including increased access to effective and free antimalarial treatment, prior to the epidemic. Nevertheless, the increase documented here is in the same direction as the region specific increase reported by Walker et al.

A worst case scenario is assumed in the data presented here, namely that all malaria activities stopped and access to treatment ceased in Guéckédou when the Ebola outbreak was discovered in 2014. Yet, donations of commodities were made to local health facilities when the MSF project closed. Consequently, RDTs and ACTs may have been available in health facilities after activities ceased though the number of people seeking care at the health facilities was reduced (Plucinski *et al.*, 2015; Moisan *et al.*, 2016). Currently the model assumes that control activities ceased and did not resume, even by the Ministry of Health, even after Guéckédou had been declared Ebola free. Consequently, the estimates provided by the model may overestimate the number of cases that have occurred in Guéckédou since activities ceased.

Interventions have been proposed to address the increased burden of malaria in Ebola affected areas. Mass Drug Administrations (MDA) of malaria chemoprevention were carried out in neighboring Sierra Leone and Liberia however their impact on the incidence of malaria or the incidence of fever was short-lived (Aregawi *et al.*, 2016; Kuehne *et al.*, 2016). Yet, MDAs have been suggested for this and other Ebola affected areas to address the increased malaria burden (Walker *et al.*, 2015). Unfortunately, without a significant scale up of malaria control activities during or immediately after the MDA campaigns it is likely that the effect of the MDA would be short lived. Instead, ensuring a mass distribution of LLINs to replace those that have reached the end of their effective period should be considered as use of LLINs is likely to provide prolonged protection to the population if used correctly. Nevertheless the increase in

the number of malaria cases during the period of the Ebola epidemic is likely to have had residual impacts. The increase in malaria cases immediately following program cessation could be expected to have resulted in patients presenting to an Ebola treatment center or local health facility with malaria-related fever. In the short term, systematic administration of antimalarials to contacts of patients with Ebola virus disease or to residents of villages or neighborhoods where cases of Ebola were found could have mitigated this, particularly for contacts with a higher risk of infection.

The main limitation of this analysis is that it is not extrapolatable to other sous-préfectures, although similar findings have been documented at the regional level (Walker *et al.*, 2015). Nonetheless, the relatively small geographical scale of our study area presents some advantages. First, the data collection system and study population has remained relatively stable over time without major variations. Although the population is highly mobile, we are unaware of any mass population movements from Guéckédou Préfecture that would have significantly affected population numbers during the Ebola outbreak. Second, malaria parasite prevalence was well characterized prior to the cessation of control activities and allowed for better understanding of the seasonality of malaria in the area. This is relevant for impact studies as season-to-season variation can have a large influence on the estimates. Third, the long follow-up period after introduction of the reinforced malaria control activities allows for characterization of how rates changed over time. However, data collection prior to the commencement of reinforced malaria control activities was not carried out, and would have allowed us to be sure to accurately quantify malaria parasite prevalence with only Ministry of Health activities. Finally, in this model it was assumed that malaria parasite prevalence prior to the reinforced malaria control activities corresponded to the sous-préfecture specific prevalence measured during the first survey (April 2011). Additionally, the model predictions were not validated against the number of cases observed in the community or in health facilities. Here the models only provide predictions of cases at the community level and in order to accurately estimate impact, results should be calibrated to case data from health facilities when available. Additional work will be carried out to validate the model predictions with local data.

Here we predict a resurgence of uncomplicated malaria cases in a hyperendemic malarious area in which an outbreak of Ebola resulted in the cessation of malaria control activities. While the Ebola outbreak provided an opportunity to investigate malaria resurgence, this is not just an Ebola related issue. The risk of resurgence is a reality for any disease control program that stops due to lack of funding, commitment or deprioritization. For malaria in particular, projects need to carefully consider exit strategies. Abrupt activity cessation without assurance of continuation by partners or Ministries of Health may cause more damage in terms of morbidity and mortality than that which was prevented. When gains made in malaria control are not sustained, resurgence becomes a real risk. In areas where malaria is highly endemic, advances made during control activity implementation are quickly negated when activities stop. The impact of activity cessation extends beyond the time frame of the disaster. The efforts that will be required to return to levels at the end of the control program or the start of emergency are expensive both in terms of financial cost and excess morbidity and mortality.

6. Community-based surveillance to monitor mortality in a malaria endemic and Ebola epidemic setting in rural Guinea.

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Keywords: malaria, surveillance, Ebola, proportional mortality, outbreaks

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6.1. Abstract

Multiple community-based approaches can aid in quantifying mortality in the absence of reliable health facility data. Community-based sentinel site surveillance was used to document mortality and the systems utility for outbreak detection was evaluated. We retrospectively analyzed data from 46 sentinel sites in 3 sous-préfectures with a reinforced malaria control program and 1 sous-préfecture without (Koundou) in Guinea. Deaths were recorded by key informants and classified as due to malaria or another cause. Malaria deaths were those reported as due to malaria or fever in the 3 days before death with no other known cause. Suspect Ebola virus disease (sEVD) deaths were those due to select symptoms in the EVD case definition. Deaths were aggregated by sous-préfecture and analyzed by 6 month period. 43,000 individuals were monitored by the surveillance system, 1,242 deaths were reported from July 2011-June 2014. 55.2% (n = 686) were reported as due to malaria. Malaria attributable proportional mortality decreased by 26.5% (95% CI: 13.9-33.1, $p < 0.001$) in the program area and by 6.6% (95%CI: -17.3-30.5, $p=0.589$) in Koundou. Sixty-eight deaths were classified as sEVD and increased by 6.1% (95% CI: 1.3-10.8, $p = 0.021$). Seventeen sEVD deaths were reported from November 2013 through March 2014 including the first two laboratory confirmed EVD deaths. Community surveillance can capture information on mortality in areas where data collection is weak, but determining causes of death remains challenging. It can also be useful for outbreak detection if timeliness of data collection and reporting facilitate real-time data analysis.

6.2. Background

Malaria is endemic in the Republic of Guinea (Guinea) and was the cause of 34% of all medical consultations in public health facilities in 2012 (Measure DHS, 2012). There are, however, important regional differences in malaria endemicity in Guinea; prevalence in children under-5 ranges from 3% in Conakry, the urban capital, to over 55% in the southern, more heavily forested areas of the country (Measure DHS, 2012). Since 2008, every case of uncomplicated malaria should receive oral antimalarial treatment with an artemisinin based combination therapy (ACT) and in 2013 malaria rapid diagnostic tests (RDT) were made available free of charge in health facilities (Ministere de la Santé et de l'Hygiene Publique - Republique de la Guinée, 2014). However, in the 2012 Demographic and Health Survey (DHS), 45% of respondents with a self-reported episode of malaria in the 6-months prior to the survey neither sought care nor received treatment (Measure DHS, 2012).

In areas where civil registration and vital registration systems are inadequate and where health care seeking at public health facilities is infrequent, surveillance data from health facilities may not accurately reflect community mortality. At present, the majority of reliable data on community mortality comes from locations where Health and Demographic Surveillance Systems (HDSS) have been implemented. These systems monitor health and socio-economic indicators in addition to migration, births and deaths in a defined population over time (Streatfield *et al.*, 2014). Cause of death is attributed according to verbal autopsy (VA) which is the recommended method for determining cause of death in places where vital registration systems are weak. VA uses data from interviews with lay respondents on the signs and symptoms of the decedent before death to attribute cause of death (World Health Organization, 2015h). However the accuracy of the VA result can be hindered by the need for both trained individuals to carry out the interviews and multiple physicians for VA questionnaire review. An additional limitation for malaria endemic regions in particular is the difficulty of distinguishing a death due to malaria from other common (co-)morbidities (Garenne and Fauveau, 2006). With limited resources, VA is limited by the availability of qualified human resources and HDSS site implementation and follow-up is expensive and difficult to sustain making adoption and implementation of similar systems by governments or local authorities unlikely.

Compounded with weak health facility surveillance in Guéckédou, the reliability of routine health facility-based data was further compromised during the 2013-2016 Ebola virus disease (EVD) epidemic that originated in Guéckédou Préfecture (Baize *et al.*, 2014; World Health Organization, 2015c). While the majority of health facilities remained open during the epidemic, health care workers were infected and there was fear of EVD in in the community (Bogus *et al.*, 2015). Consequently patients stayed away from health facilities (Plucinski *et al.*, 2015) decreasing the reliability of data collected in health facilities during this period. Diagnosis of malaria infections was further complicated during the epidemic due to the overlap of malaria and EVD symptoms (World Health Organization, 2014a); malaria testing was suspended during the EVD epidemic unless the health care workers had and used appropriate personal protective equipment (World Health Organization Global Malaria Programme, 2014a).

Multiple approaches can be used to quantify mortality rates in the absence of reliable data however their accuracy in cause of death determination is limited. These approaches include retrospective

mortality surveys which are used to monitor mortality in emergencies (Valenciano *et al.*, 2004; Carrión Martín *et al.*, 2014), yet they do not provide information on changes over time unless they are repeated. Furthermore when the recall period is short, large sample sizes are needed to achieve acceptable precision for the estimate (Checchi and Roberts, 2008). Another approach is prospective community-based surveillance which allows for real-time monitoring of trends and can serve as an early warning system for certain diseases depending on the timeliness of data collection, reporting and evaluation. However such systems can be labor intensive, expensive and take time to implement (Checchi and Roberts, 2005). In areas where there is no HDSS and health facility surveillance and vital registration systems are weak or non-existent, a lack of reliable data hinders the ability to monitor changes in mortality. For organizations working in such areas, alternative means to monitor mortality need to be developed. For the purposes of this project we aimed to implement a system that was simple and resource light, where data collection occurred in the community by community members and could continue with limited supervision. The primary aim of this project was to monitor community mortality, specifically assessing malaria attributable mortality in a predominately rural population of the Republic of Guinea using data collected through community-based prospective sentinel site surveillance. Secondarily we also assessed the ability of community-based sentinel site surveillance to retrospectively detect suspect EVD (sEVD) cases during the 2014-2015 outbreak.

6.3. Methods

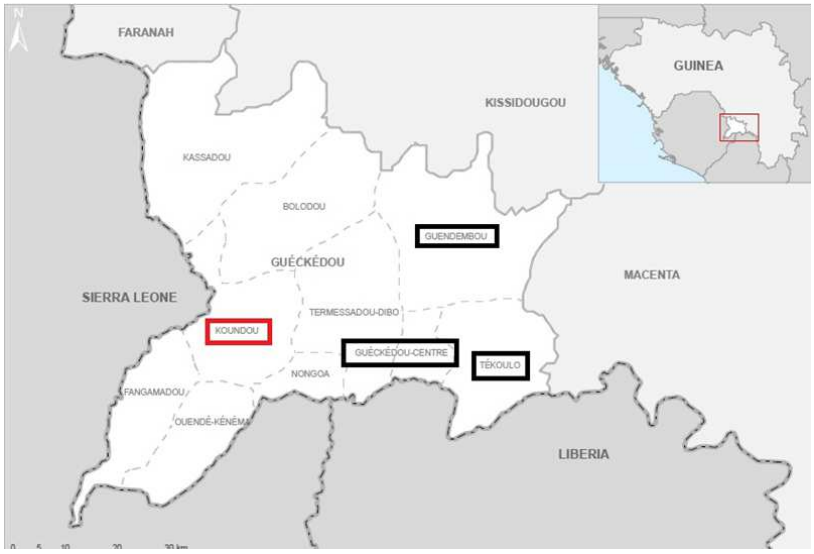
Area and study population

Guéckédou Préfecture is one of 33 préfectures in Guinea and borders Sierra Leone and Liberia. It is subdivided into 10 sous-préfectures, 9 rural and 1 urban, with a total area of 4,400 km2 and a population of 517,572 individuals (2010 estimate). The majority of the inhabitants of this area are subsistence farmers, growing rice and corn in addition to perennial crops such as coffee and kola nuts. The préfecture has 1 hospital in its capital, Guéckédou City, 13 health centers (1 in each sous-préfecture and 4 in Guéckédou City) and 46 health posts.

Study setting

This study was carried out in the Préfecture of Guéckédou in the sous-préfectures of Guéckédou City (Centre), Tekoulo, Guendembou and Koundou as indicated in Figure 6-1. These sous-préfectures have a combined area of 1,779 km2 and a population of approximately 297,919 individuals (2010 estimate). Aside from Guéckédou City, Tekoulo, Guendembou and Koundou are predominately rural, forested sous-préfectures with small villages connected by dirt roads or paths.

Figure 6-1: Map of Guéckédou Préfecture. *Boxes represent sous-préfectures where community-based sentinel site surveillance was implemented. Black boxes are those sous-préfectures with the reinforced malaria control program; the red box is the sous-préfecture that did not receive the reinforced malaria control program.*



Reinforced malaria control program

The reinforced malaria control program began in 2010 as a collaboration between Médecins Sans Frontières and the Ministry of Health of Guinea. Planning and recruitment of staff began in 2010; implementation of activities began in 2011 and continued until April 2014. While information on the program and its impact on malaria parasite prevalence has previously been published (Tiffany, Moundekeno, Traoré, Haile, Sterk, Guilavogui, Genton, *et al.*, 2016), briefly, the reinforced malaria control program consisted of interventions in both health facilities and in the community. These interventions included improving detection of clinical malaria cases using rapid diagnostic tests and timely treatment with artemisinin-based combination therapy through health facilities and community health workers, referral of severe cases with pretreatment in addition to a mass distribution of long lasting insecticide treated nets.

The implementation of the reinforced malaria control program began in Guéckédou City, Tekoulo and Guendembou (n=3) and roll out was to continue for three years in a progressive stepwise manner until all sous-préfectures in Guéckédou Préfecture were receiving the control program (N=10). Koundou was the next sous-préfecture in which implementation was planned after the 3 previously mentioned, for this reason data was collected in Koundou to serve as its pre-implementation measurement. Unfortunately, implementation of the program did not move beyond the initial three sous-préfectures due to logistical constraints. Nevertheless, data collection continued in Koundou due to the engagement of the local authorities.

Study design

The present project was part of a larger study that examined the impact of the reinforced malaria control program on malaria attributable morbidity, transmission and mortality in the areas of implementation.

Concurrently, prospective community-based sentinel site (villages or neighborhoods) surveillance was implemented in the three sous-préfectures of Guéckédou Préfecture with the reinforced malaria control program (program area) in addition to the sous-préfecture of Koundou, where the program was to be implemented. Data collected in Koundou served as documentation of mortality in an area where the reinforced malaria control program had not been implemented.

Sample size considerations

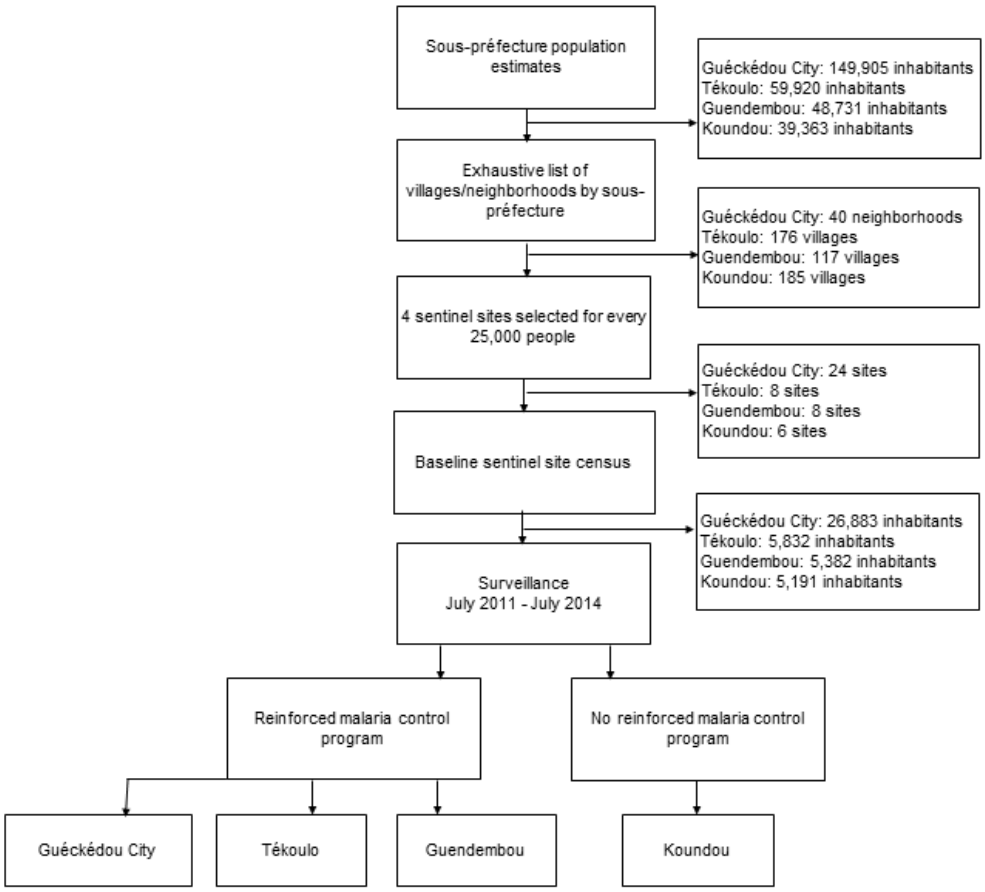
Sample size was calculated based on a hypothesized malaria attributable mortality of 30% in each sous-préfecture prior to implementation of the reinforced malaria control program. Detecting a decrease of at least 10% in malaria attributable mortality after one year of intervention with alpha of 10% and 80% power required a minimum of 251 deaths reported per sous-préfecture.

Based on an average village size of 350 people in the rural sous-préfectures we aimed for each sentinel site to include 400 individuals. With a crude mortality rate of 9.46 deaths/1,000 people/year (Central Intelligence Agency, 2015) we anticipated that at least 4 deaths/month (48 per year) would occur in each sentinel site of 400 individuals. In order to ensure a sufficient number of deaths captured by the surveillance system, at least 251 deaths in 1 year, a minimum of 6 sentinel sites per sous-préfecture were required.

Sentinel site selection

Population estimates were obtained for each sous-préfecture. As seen in Figure 6-2, sentinel site selection by sous-préfecture followed with sites chosen from a sampling frame consisting of an exhaustive list of administrative units (villages or neighborhoods). Implicit stratification was used to improve precision (Levy Paul S & Lemeshow Stanley, 2008). Accordingly, before selection the administrative units were sorted by sous-préfecture according to urban versus rural and then by driving distance from the nearest health facility. For every 12,500 inhabitants in each sous-préfecture two sentinel sites were systematically selected from the sampling frame. Forty-six sentinel sites were included in the surveillance system. A baseline census was conducted in each sentinel site to ensure its population was at least 400 inhabitants. Villages with less than 400 inhabitants were grouped with a neighboring village (or more if necessary) and their populations pooled to form one sentinel site.

Figure 6-2: Schematic representation of sentinel site surveillance.



Implementation

Each sentinel site was visited prior to implementation. The implementation team met with village members and leaders and informed them of the project and its objectives. Village members nominated a key informant, a volunteer who was a full-time village resident and could read and write in French, to collect data. The village leader provided consent for their village to participate and a pre-census estimate of the population. One supervisor of key informants (supervisor) was hired in each sous-préfecture.

Data collection

Information on mortality was collected regarding all permanent residents of the sentinel sites. Key informants collected data only when a death occurred. Supervisors visited each sentinel site and collected data from the key informants at least twice per month. Data collection was paper-based as many areas of Guéckédou Préfecture were without mobile phone coverage at the time of implementation.

Name, age (<5, 5-14, 15-44, ≥45), sex, cause of death (see below), place of death and health-seeking behavior prior to death were collected from the family of the deceased. Data was recorded as reported by the family of the deceased. Data on births and in- and out-migration were not collected as the population was understood to be quite stable. Population estimates were updated every year during an exhaustive census of each sentinel site carried out by the community leader(s), key informant and their supervisor. VA were not used because this method was too resource demanding (human and financial) in the context of this program

Data management

Supervisors transported the data collection forms to the MSF office in Guéckédou on a monthly basis. The data manager verified and entered the data in a Microsoft Excel spreadsheet and referred any questions regarding inconsistencies to the supervisor and key informants for correction or further precision. Monthly reports were produced and shared within MSF and with the local Ministry of Health officials. Once verified, the data was anonymized and entered in to a project specific Epi Info (version 3.5.4) data mask.

Population and outcomes

A permanent resident of a sentinel site was considered to be any person who would be counted during the annual sentinel site census. Causes of death were classified as due to a) "corps chaud"/malaria/fever (considered as a death due to malaria); b) fever and another specified cause; c) another specified cause. A death due to 'malaria' was defined as: 1) death due to malaria or naa dialuntouvo/naa hoiyo/yo wo tchouanduni as reported by the family of the deceased; or 2) an individual with a history of fever in the 3 days prior to death without another known (specified) cause. A death due to 'another cause' was one that was either reported as: 1) due to another cause, specified by the family member; or 2) due to another cause with fever prior to death; or 3) a death with no known cause or fever prior to death. 'EVD suspect deaths' were those reported as not due to malaria and having been due to symptoms listed in the EVD case definition: diarrhea, vomiting, vomiting blood, vomiting and diarrhea and/or hiccups (Baize *et al.*, 2014; WHO Ebola Response Team, 2014).

Analysis

The database was cleaned and statistical analysis performed using Stata (version 12.1, StataCorp, College Station, Texas). All data were analyzed retrospectively after being aggregated into periods corresponding with the rainy and dry seasons. Period 1: July 2011 – December 2011 (rainy), period 2: January 2012 – June 2012 (dry), period 3: July 2012 – December 2012 (rainy), period 4: January 2013 – June 2013 (dry), period 5: July 2013 – December 2013 (rainy), and period 6: January 2014 – June 2014 (dry).

All estimates are reported by sous-préfecture and period. Proportional mortality attributable to malaria was calculated as the number of deaths reported as due to malaria over all the deaths reported in the sous-préfecture. The proportion of sEVD deaths was calculated as the number of deaths classified as sEVD deaths over all deaths reported. Descriptive analysis was performed and the results expressed as

frequencies and percentages. Differences in reported place of death, proportional mortality and the proportion of sEVD deaths, from period 1 to period 6, were compared using a z-test for a difference in proportions. Differences between health seeking behavior and sEVD deaths by period and sous-préfecture were compared using chi squared or fisher's exact test, as appropriate. All results are presented with their 95% confidence intervals and statistical tests were considered significant at $p \leq 0.05$.

Ethical considerations

The project was carried out with the support of the National Malaria Control Program in Guinea; the surveillance protocol was presented to and approved by both the prefectoral and sous-préfectoral health authorities. Results presented here consist of retrospective analysis of routinely collected program data; as such they represent a standard component of program monitoring and are considered to be exempt from the Médecins Sans Frontières Ethical Review Board. Nevertheless, these data were collected in accordance with standards presented in the Declaration of Helsinki and following receipt of verbal informed consent from village leaders. No identifying information was recorded in the database and all individuals were free to refuse contributing information to the surveillance system. During the EVD outbreak, supervisors were included as part of the epidemiological investigation teams and key informants were trained to provide health promotion messages regarding EVD and the prevention of transmission to their and surrounding communities. During the EVD outbreak data collection continued using strict infection prevention and control procedures which prohibited entrance into households of the individual being interviewed and also limited direct contact between the key informant and the family of the deceased and the supervisor and the key informant.

6.4. Results

Population under surveillance

For 36 months 43,000 individuals were monitored by the surveillance system and 1,242 deaths were reported. No households refused to take part in the surveillance system and no families refused to have mortality data collected. Deaths of children < 5 years of age and individuals ≥ 45 years of age represented 34.9% (434/1,242) and 36.5% (454/1,242) of all deaths reported through the system, respectively (Table 1). Children < 5 years of age were more frequently reported to have died from malaria (73.5%, 95% CI: 69.3-77.6%) than individuals ≥ 5 years of age (45.4%, 95% CI: 41.9-48.8) (difference 28.1%, 95% CI: 21.0-35.1, $p < 0.001$).

Health seeking behavior

Family members frequently reported that the deceased sought care for their illness prior to their death. 70.1% (871/1,242) of all decedents were reported to have sought care from a public health center or post during the course of the illness that resulted in their death. 72.1% (495/686) of decedents whose cause of death was reported to be malaria were reported to have sought care at a public health center or post prior to death. Regardless of age, decedents whose cause of death was classified as malaria frequently sought care for their illness at a public health center or post (< 5 years: 78.6%, 95% CI: 74.1-

83.1; 5-14 years: 61.9%, 95% CI: 47.0-76.7; 15-44 years: 74.7%, 95% CI: 67.0-82.5; ≥ 45 years: 62.3%, 95% CI: 55.6-69.0). There was no significant difference in the number of malaria deaths that sought treatment at a public health center or post by period (p = 0.274), however individuals in Guendembou sought care less frequently (51.4%) at a public health center or post than the other sous-préfectures (Guéckédou City: 74.5%, Tekoulo: 71.0%, Koundou: 74.5%).

Reported place of death

The majority (75.2%) of all deaths reported through the surveillance system occurred at home while 17.8% occurred in a health center, health post or Guéckédou Hospital (Table 6-1). From period 1 to period 6 the proportion of deaths occurring at home increased from 68.6% to 79.7% (difference 11.1%, 95% CI: 2.5-19.7, p = 0.011) while the proportion of deaths occurring in a health center, health post or Guéckédou Hospital decreased from 22.0% to 11.7% (difference 10.3%, 95% CI: 3.0-17.6).

Table 6-1: Administrative division, deaths captured and location of deaths as reported through sentinel site surveillance by sous-préfecture.

	Guéckédou City	**Tekoulo**	**Guendembou**	**Koundou**	**Total**
Population estimate (2010)	149,905	59,920	48,731	39,363	297,919
Number of sentinel sites	24	8	8	6	46
Sentinel site census					
2011	26,883	5,832	5,382	5,191	43,288
2012	26,751	6,009	5,474	5,200	43,434
2013	26,524	5,943	5,405	5,474	42,999
Deaths captured, N (% malaria)	594 (56.4)	204 (50.4)	208 (51.9)	236 (59.3)	1,242 (55.2)
<5, n (% malaria)	167 (71.3)	63 (87.3)	96 (66.7)	108 (75.0)	434 (73.5)
5-14, n (% malaria)	23 (60.8)	14 (78.5)	12 (50.0)	18 (61.1)	67 (62.7)
15-44, n (% malaria)	167 (47.3)	47 (34.0)	29 (24.1)	44 (47.7)	287 (42.9)
≥45, n (% malaria)	237 (51.9)	80 (26.2)	71 (43.7)	66 (40.9)	454 (44.5)
Location of death					
At home, n (% N)	406 (68.3)	169 (82.8)	178 (85.6)	181 (76.7)	934 (75.2)
Guéckédou Hospital, n (% N)	147 (24.7)	7 (3.4)	6 (2.9)	25 (10.6)	185 (14.9)
Public Facility, n (% N)	6 (1.0)	2 (1.0)	8 (3.8)	20 (8.5)	36 (2.9)
Other , n (% N)	35 (5.9)	26 (12.7)	16 (7.7)	10 (4.2)	87 (7.0)

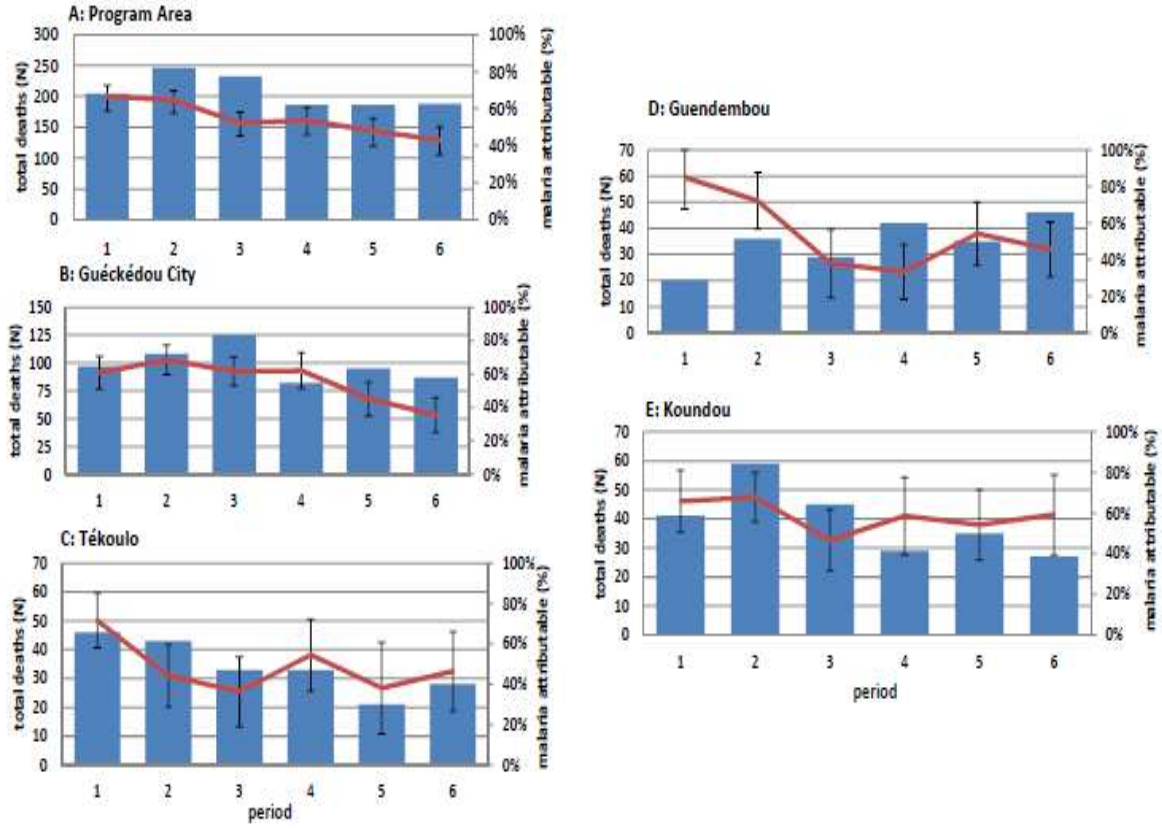
Proportional mortality

Malaria was the most frequently reported cause of death during the surveillance period, 55.2% overall. By sous-préfecture, malaria attributable mortality accounted for 56.4% of all deaths in Guéckédou City, 50.4% in Tekoulo, 51.9% in Guendembou and 59.3% in Koundou (Table 6-1).

Overall, proportional mortality attributable to malaria decreased steadily from period 1 to period 6 in the program area by 26.4% (95% CI: 15.9-37.0, p < 0.001) (Figure 6-3, panel A). From period 1 to period 6 proportional mortality attributable to malaria decreased by 25.1% (95% CI: 11.1-39.2, p < 0.001) in

Guéckédou City, 25.3% (95% CI: 2.3-48.2, p = 0.031) in Tekoulo, 39.3% (95% CI: 17.6-61.0, p < 0.001) in Guendembou and 6.5% (95% CI: -17.8%-30.5%, p = 0.589) in Koundou (Figure 6-3, panels B-E).

Figure 6-3: Overall and malaria attributable mortality by period and sous-préfecture.



Ebola virus disease

Suspect EVD deaths July 2011 through June 2014

As seen in Table 6-2, 5.5% (68/1,242) of all deaths reported through the surveillance system were retrospectively classified as sEVD deaths. The number of sEVD deaths increased from period 1 to period 6 however the difference in period specific estimates was not significant (p = 0.132). EVD suspect proportional mortality increased by 6.1% (95% CI 1.3-10.8, p = 0.011) from period 1 to period 6 while exhibiting fluctuations likely due to the small number of sEVD deaths per period (range 6-17). The largest number of EVD suspect deaths was reported during period 6 and coincided with the apparition of EVD in Guéckédou.

Table 6-2: Deaths retrospectively classified as EVD suspect by reported cause and period. Guéckédou, 2011-2014.

	Period 1 July – December 2011	Period 2 January – June 2012	Period 3 July – December 2012	Period 4 January – June 2013	Period 5 July – December 2013	Period 6 January – June 2014	Total
Diarrhea, n (%)	4 (66.7)	8 (57.1)	6 (66.7)	8 (66.7)	2 (20.0)	8 (47.0)	36 (52.9)
Vomiting, n(%)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Vomiting blood, n(%)	2 (33.3)	4 (28.5)	2 (22.2)	4 (33.3)	7 (70.0)	2 (11.1)	21 (30.8)
Vomiting and diarrhea, n(%)	0 (0.0)	1 (7.1)	1 (11.1)	0 (0.0)	0 (0.0)	4 (23.5)	6 (8.8)
Hiccups, n(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (5.8)	2 (2.9)
Ebola, n(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.7)	2 (2.9)
Total:	**6 (100)**	**14 (100)**	**9 (100)**	**12 (100)**	**10 (100)**	**17 (100)**	**68 (100)**
EVD suspect mortality, % (95% CI)	2.9 (0.6-5.2)	5.6 (2.7-8.6)	3.8 (1.3-6.3)	6.4 (2.8-10.0)	5.3 (2.1-8.6)	9.0 (4.9-13.1)	5.4 (4.2-6.7)

Suspect EVD deaths November 2013 through March 2014

During November 2013 to March 2014, the period during which EVD emerged in Guéckédou Préfecture, 131 deaths were reported through the surveillance system. Seventeen (12.9%) were retrospectively classified as sEVD deaths due to the symptoms reported before death for each individual. Fifty-two (39.6%) were reported as due to malaria. The reported causes for deaths classified as sEVD are found in Table 6-3 and include diarrhea, diarrhea and vomiting, hemorrhagic symptoms and hiccups. Two of the sEVD deaths captured through this surveillance system were among the first laboratory confirmed Ebola Zaire cases from the 2013-2016 outbreak (Baize et al., 2014). Fourteen deaths occurred in the community, 1 occurred in Guéckédou Hospital while and two occurred in the Guéckédou Ebola Treatment Center and were verified with the EVD patient line listing.

Table 6-3: Characterization of EVD suspect deaths occurring between November 2013 and March 2014. Guéckédou, 2011-2014.

	Guéckédou City	Tekoulo	Guendembou	Koundou
Vomiting blood	1	0	0	2
Hiccups	2	0	0	0
Persistent diarrhea	0	0	1	1
Diarrhea	3	1	1	0
Diarrhea and cough	1	0	0	0
Vomiting and diarrhea	4	0	0	0
Total	11	1	2	3

6.5. Discussion

In low resource settings the absence of reliable surveillance data and vital registration systems makes it difficult to monitor mortality and determine cause of death, activities that are essential to understanding disease burden (World Health Organization, 2015h) and implementing appropriate prevention and control measures. Ascertainment of cause specific mortality without use of VA poses an additional challenge to surveillance and is further complicated in malaria endemic areas where malaria is frequently characterized by non-specific signs including fever (Rowe *et al.*, 2007). In countries without the means to establish an HDSS or maintain health facility based surveillance, alternative methods of data collection are needed. Here we demonstrate that data from prospective community-based mortality surveillance using sentinel sites can provide a means to document mortality and facilitate outbreak detection in low resource settings, although this remains challenging.

The surveillance system as it was implemented in Guéckédou was intentionally simple and resource light, a model that would both serve the purposes of the project in Guéckédou while also allowing it to be adapted to different contexts. In some contexts, monitoring all population movements and attributing cause of death by VA may not be feasible due to limited financial resources or difficulties finding qualified human resources. Implementation of VA, the gold standard for cause of death attribution, requires review of interviews by two or more trained clinicians, individuals that are rare in rural areas in addition to being difficult to find in countries like Guinea where there are very few (World Health Organization, 2014c). An additional limitation to the use of VA is its ability to accurately attribute cause of death, particularly for malaria related deaths (Anker *et al.*, 1999). As a result, after investigating the communities understanding of malaria and the different terms they employ to signify malaria, cause of death was classified as reported by the deceased's next-of-kin. Using this method for cause of death attribution, deaths reported as due to fever or malaria were considered as a malaria attributable death. If no other cause was specified, deaths resulting from conditions unrelated to malaria that presented with fever (e.g. typhoid) with no other known cause were likely to have been classified as 'due to malaria'. While use of this proxy may have overestimated the number of malaria attributable deaths, the use of fever as a proxy for malaria is not without precedent (Rooth and Bjorkman, 1992; Olaleye *et al.*, 1998; Okiro *et al.*, 2007) and has also been proposed by the World Health Organization as the case definition for malaria to be used in community-based surveillance for individuals in malaria endemic areas (World Health Organization Regional Office for Africa., 2014).

The importance of data from community-based surveillance is apparent in areas like Guéckédou Préfecture where data collection in health facilities is weak and many deaths occur outside of health facilities. Indeed the majority of decedents were reported to have died at home and increased significantly from period 1 to period 6 while the proportion reported to have died in a public health center or post decreased. The increase may be due to community fear of visiting public health facilities during period 6 when the EVD outbreak was declared in Guéckédou, a consequence of the 2014-2015 EVD epidemic documented in Guinea (Plucinski *et al.*, 2015), Sierra Leone (Bolkan *et al.*, 2014) and Liberia (Ly *et al.*, 2016).

Notwithstanding, 72.1% of decedents classified as having died from malaria reportedly sought care for their illness at a health center or post prior to death. As the national malaria control guidelines emphasize systematic testing before treatment (Ministere de la Santé et de l'Hygiene Publique - Republique de la Guinée, 2014), an unknown number of these deaths may have been reported as due to malaria after receiving confirmation at the health facility; however we were unable to verify this data in health facility records. Although the confirmed cases of malaria should be reflected in the national statistics, had the surveillance system not been in place the deaths captured through the community surveillance system would not have been documented.

The deaths documented through the surveillance system occurred during the implementation of a reinforced malaria control program and were used to provide sous-préfecture specific estimates of the number of deaths occurring in addition to malaria attributable mortality. Yet, few deaths occurred each month requiring the data to be aggregated into 6 month periods and not providing enough power with which to make annual comparisons. Consequently, the estimates of malaria attributable mortality in the rural sous-préfectures fluctuated from period to period. In addition to the small number of deaths reported, the fluctuations may have been the result of factors that are difficult to quantify retrospectively including periodic population movements and variations in completeness of reporting. Seasonality of malaria may also have played a role in the fluctuations with periods 1, 3 and 5 encompassing the rainy season when more cases of malaria tend to occur. Nevertheless, from period 1 to period 6, proportional mortality attributable to malaria decreased in Guéckédou City, Tekoulo and Guendembou, the three sous-préfectures where the reinforced malaria control program was implemented. Although the decrease in malaria attributable proportional mortality reported here could also be due to changes in other causes of death that present with fever, we are unaware of any other large health interventions that addressed causes of febrile illness in this area during the surveillance period. Furthermore, this assertion is corroborated by results from a cross-sectional study of malaria prevalence in the same areas, during the same period which documented a significant increase in the coverage of malaria control interventions in addition to a decrease in malaria prevalence linked to the reinforced malaria control interventions (Tiffany, Moundekeno, Traoré, Haile, Sterk, Guilavogui, Genton, *et al.*, 2016). While the system seemed to adequately detect mortality, more work would need to be done to ensure improved cause of death attribution.

Cause of death attribution could be improved through use of refined syndrome definitions. Clusters of deaths presenting with similar syndromic presentations could be detected by community surveillance and provide valuable information for outbreak detection (Henning, 2004). Retrospective analysis of the data described above was conducted to ascertain if the EVD outbreak that was laboratory confirmed in Guéckédou in March 2014 (Baize *et al.*, 2014) could have been detected earlier if the data had been monitored for causes of death other than malaria. There was a statistically significant increase in the number of sEVD deaths, those with at least one of the symptoms found in the WHO EVD case definition (World Health Organization, 2014a), from period 1 to period 6 while differences in sEVD case numbers between periods other than 1 and 6 were not significant. Similar to malaria, the symptoms of Ebola aside from hiccups and bleeding of unknown origin which generally indicate severe illness are non-specific.

Despite using a sensitive sEVD case definition which captures both specific and non-specific EVD symptoms and led to the detection of numerous suspect cases prior to the outbreak, the number of sEVD cases identified per period were likely too small to detect a significant difference between periods. Consequently, to operationalize the use of such definitions, additional work would need to be done to determine the appropriate syndrome definition in addition to defining a threshold which determines when follow-up in the community would be required. The fact that despite the fact that this community-based surveillance was in place, EVD was not considered a possibility until additional later in time. Furthermore, to improve the utility of community surveillance data, timely reporting and analysis in addition to an improved understanding of the communities and their understanding of illness is essential. Similar surveillance systems, particularly for Ebola, are already in place but use predefined triggers or events that serve as an alert (Crowe *et al.*, 2015). While event based surveillance is useful for identifying events during an outbreak, community surveillance using syndrome definitions derived from case definitions is a proactive approach and may result in earlier outbreak detection.

There are several important limitations to this data. Causal inference between changes in mortality and the implementation of the reinforced malaria control program should be made with caution as the program components were implemented in field conditions and not as a controlled trial. Nevertheless, data from sentinel sites that did not receive the malaria control program was included for the purpose of comparison. When evaluating changes in mortality, data on pre-program mortality are not available in the sentinel sites themselves, thus the only comparison that can be made is between period specific mortality in the individual sous-préfectures themselves, which are further limited by the rare occurrence of death. These analyses also did not take into consideration population movements, births, arrivals and departures; however, the population in the area is quite stable and the impact of these movements on the overall denominator is probably quite small. The result of the annual census in each site confirms this supposition. We attempted to validate the data from the system using capture recapture(Roberts *et al.*, 2010) for the individuals who were reported to have died at health facilities; however when visiting the named health facility, we were unable to match a sufficient number of individuals, likely due to the fact that deaths are not always recorded in the register. Finally, despite information sessions with local community leaders in each sentinel site, due to the size of some of the urban sentinel sites, it is possible that the key informants were not aware of all deaths occurring in the site and may also have encountered difficulties enumerating the population of their site.

Mortality data from prospective, community-based sentinel site surveillance can be utilized to document community mortality. However improved methods for cause of death attribution are needed to enhance cause-specific mortality measurement in low resource settings. Here we suggest a derivation of prospective community-based sentinel site surveillance that could be useful for outbreak detection if timeliness of data collection and reporting were improved, facilitating real-time data analysis. In such cases, standard pre-defined profiles for specific causes of death of interest and thresholds of acceptability should be developed. Prospective mortality surveillance using sentinel sites is not only a manner in which to document community mortality, it can also compliment health facility surveillance particularly in areas where data collection is weak.

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7. Impact and lessons learned from mass drug administrations of malaria chemoprevention during the Ebola outbreak in Monrovia, Liberia, 2014.

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7.1. Abstract

Background

In October 2014, during the Ebola outbreak in Liberia healthcare services were limited while malaria transmission continued. Médecins Sans Frontières (MSF) implemented a mass drug administration (MDA) of malaria chemoprevention (CP) in Monrovia to reduce malaria-associated morbidity. In order to inform future interventions, we described the scale of the MDA, evaluated its acceptance and estimated the effectiveness.

Methods

MSF carried out two rounds of MDA with artesunate/amodiaquine (ASAQ) targeting four neighbourhoods of Monrovia (October to December 2014). We systematically selected households in the distribution area and administered standardized questionnaires. We calculated incidence ratios (IR) of side effects using Poisson regression and compared self-reported fever risk differences (RD) pre- and post-MDA using a z-test.

Findings

In total, 1,259,699 courses of ASAQ-CP were distributed. All households surveyed (n=222; 1233 household members) attended the MDA in round 1 (r1) and 96% in round 2 (r2) (212/222 households; 1,154 household members). 52% (643/1233) initiated ASAQ-CP in r1 and 22% (256/1154) in r2. Of those not initiating ASAQ-CP, 29% (172/590) saved it for later in r1, 47% (423/898) in r2. Experiencing side effects in r1 was not associated with ASAQ-CP initiation in r2 (IR 1.0, 95%CI 0.49-2.1). The incidence of self-reported fever decreased from 4.2% (52/1229) in the month prior to r1 to 1.5% (18/1229) after r1 ($p<0.001$) and decrease was larger among household members completing ASAQ-CP (RD=4.9%) compared to those not initiating ASAQ-CP (RD=0.6%) in r1 ($p<0.001$).

Conclusions

The reduction in self-reported fever cases following the intervention suggests that MDAs may be effective in reducing cases of fever during Ebola outbreaks. Despite high coverage, initiation of ASAQ-CP was low. Combining MDAs with longer term interventions to prevent malaria and to improve access to healthcare may reduce both the incidence of malaria and the proportion of respondents saving their treatment for future malaria episodes.

7.2. Introduction

In 2014 and 2015 the largest Ebola outbreak in history occurred in West Africa with more than 28,000 confirmed, probable and suspect Ebola cases reported in three countries with intense transmission – Guinea, Sierra Leone and Liberia (WHO Ebola Response Team, 2016). Between March 2014 and July 2015, more than 10,500 suspect Ebola cases were notified in Liberia (World Health Organization, 2015b). The majority of cases and deaths were identified in Montserrado County where the capital city Monrovia is located (Liberia Ministry of Health and Social Welfare (MOHSW), 2015).

As a consequence of the Ebola outbreak existing healthcare structures in Monrovia were rapidly overwhelmed. By October 2014 few health facilities in Monrovia were fully operational and those that were open seemed to offer limited services. Laboratory testing for any medical condition, including rapid diagnostic tests (RDTs) for malaria was largely unavailable outside Ebola treatment units (ETUs) and Liberian National Malaria Control Program (NMCP) recommended presumptive malaria treatment.

At the same time, malaria, the main killer of children under five years of age and among the most common causes of outpatient consultations and inpatient deaths in Liberia (Measure DHS, 2011), was circulating in the community. Malaria is endemic in Liberia and despite a seasonal peak in July (Mentor Initiative Liberia, 2014), transmission occurs year round (Measure DHS, 2011). In October 2011, microscopy confirmed malaria prevalence was estimated to be 7% in children under 5 years of age in Monrovia (Measure DHS, 2011). Since 2003, artesunate/amodiaquine (ASAQ) is the recommended first-line treatment for uncomplicated malaria in Liberia (Measure DHS, 2011).

Clinical presentation of Ebola and malaria cases is similar and differentiation without laboratory tests often impossible. In Liberia the case definition used for suspect Ebola cases (fever plus three unspecific symptoms) was highly sensitive in order to capture all Ebola cases. However, it also captured patients with malaria. As a result, an unknown number of malaria patients remained either unattended to due to the collapse of the healthcare system or were admitted to an ETU as a suspect Ebola case. Consequently, malaria patients were put at risk of exposure to Ebola and ETU resources were further strained by the admission of substantial numbers of non-Ebola patients. While the number of confirmed Ebola cases in Monrovia began to decline in October 2014 (Ministry of Health and Social Welfare (MOHSW) [Liberia], 2014), malaria transmission continued and healthcare for non-Ebola-illnesses including malaria remained limited (Médecins Sans Frontières unpublished operational data). Thus, Médecins Sans Frontières (MSF) initiated mass administrations of antimalarial drugs in cooperation with the Liberian NMCP in four administrative zones of Monrovia, to decrease malaria-associated morbidity and mortality in order to mitigate the reduced access to general healthcare and reduce admissions to ETUs for malaria-associated fever.

The administration of therapeutic antimalarial regimens to entire populations regardless of clinical symptoms or laboratory tests has been part of malaria control programs for more than a century (Poirot *et al.*, 2013; von Seidlein and Dondorp, 2015). After constituting a component of many malaria elimination programs in the 1950s, the World Health Organisation (WHO) stopped recommending MDAs due to uncertainty about their ability to interrupt transmission and concerns about their potential to

increase drug resistance (Poirot *et al.*, 2013; von Seidlein and Greenwood, 2003; Newby *et al.*, 2015). However, evidence accumulated indicating that drug regimens, specifically those including artemisinin-based combination therapies (ACT) in therapeutic doses, significantly reduced parasitaemia prevalence as well as malaria morbidity and mortality over time (Poirot *et al.*, 2013; von Seidlein and Greenwood, 2003). In November 2014, WHO recommended MDAs of ACTs regardless of malaria symptoms (World Health Organization Global Malaria Programme, 2014a) for the countries affected by the Ebola outbreak in West Africa in areas with high Ebola morbidity, high malaria transmission and limited access to treatment (World Health Organization Global Malaria Programme, 2014a).

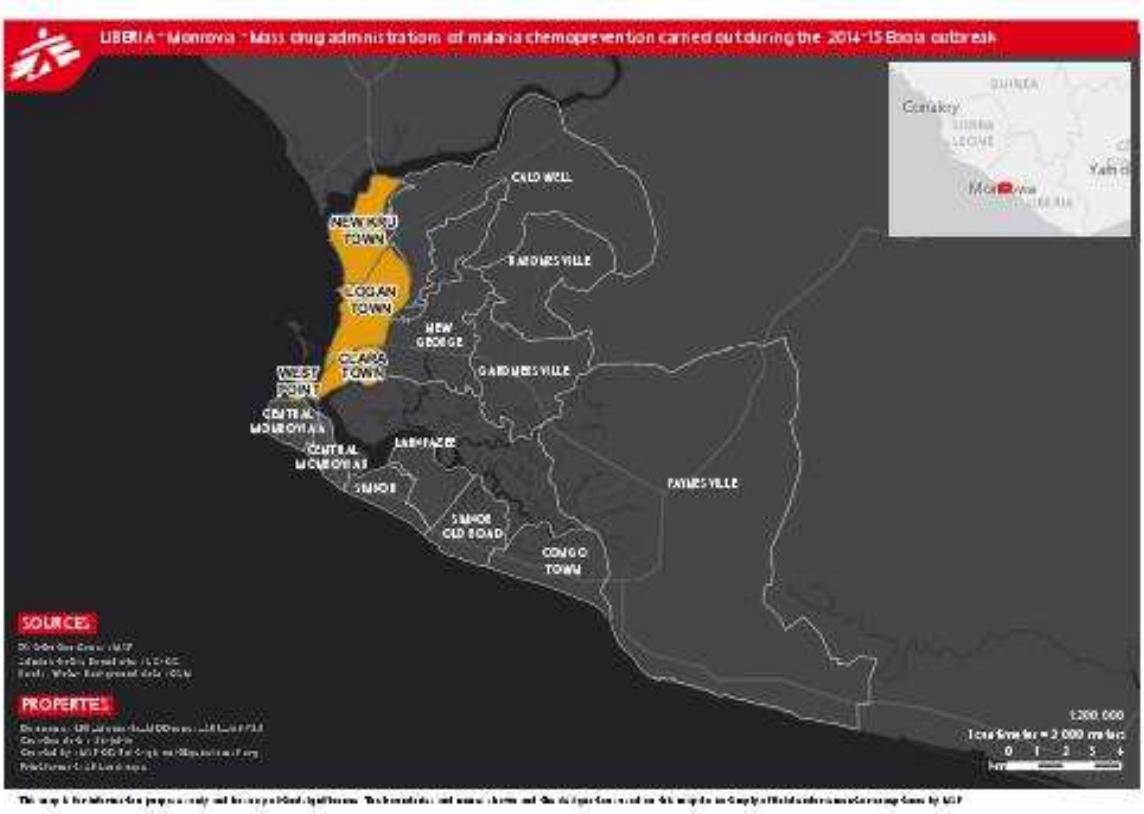
Mass administrations of antimalarial drugs to reduce the number of fever cases during an Ebola outbreak had never been carried out before. We aimed to describe the scale of the MDA, to evaluate community acceptance of the strategy, adherence to treatment, and estimate the effectiveness of the intervention with regards to the reduction of fever cases in order to inform future public health interventions targeting fever reduction in an Ebola context.

7.3. Methods

Design and implementation of the MDA

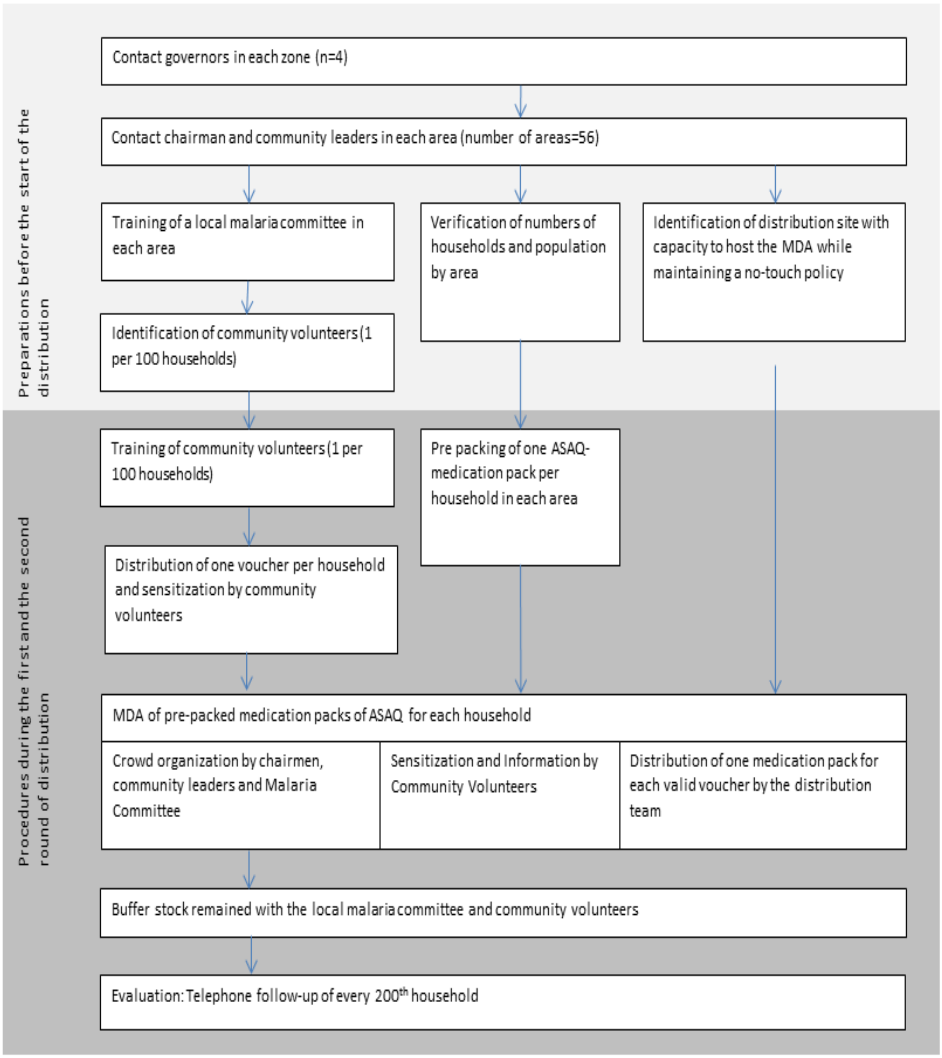
Four zones in Monrovia were targeted for the MDA based on their high Ebola incidence, high population density, precarious living conditions and limited access to healthcare. The population of these zones, New Kru Town, Clara Town, Westpoint and Logan Town (Figure 7-1), was initially estimated at 300,000 individuals (MSF census in collaboration with community leaders, unpublished programmatic data). Two rounds of MDA were carried out in a stepwise fashion at 56 fixed points of distribution between October and December 2014 with a one-month interval between rounds. The drug distributed was ASAQ and was specifically procured for the MDA. One course of ASAQ consists of three doses to be taken once a day over three consecutive days in age-specific, fixed-dose-combinations. ASAQ is used as treatment for uncomplicated malaria infections and the post-treatment prophylactic effect is thought to last for at least one month after the full course is taken (B Schramm *et al.*, 2013).

Figure 7-1: Areas of Mass Drug Administration of antimalarials, Monrovia, Liberia, 2014.



The distribution team met with the governor of each zone prior to the distribution (Figure 7-2). After agreement with the governor, the chairmen/chairwomen and community leaders (CCL) of all areas in the zone were contacted by the distribution team. Together with CCL a local malaria committee comprised of numerous community authorities including representatives of minority groups was established and population numbers were verified. In collaboration with the malaria committee, one community volunteer (CV) was identified per 100 households and trained by the distribution team to provide sensitization messages to the population. These messages included the information i) that preventive malaria treatment will be distributed, ii) age-specific doses will be provided, iii) doses should be taken with food, three days in a row. These messages were adapted regularly during the intervention. CVs went door-to-door (without entering the house) the day before the MDA explaining the purpose and content of the MDA to household members and distributing one voucher to each household. The voucher entitled one woman of the household to receive one pre-prepared medication pack for their household, from the designated distribution point, on the day of the MDA.

Figure 7-2: Steps of implementation of the mass drug administration (MDA) of artesunate/amodiaquine malaria chemoprevention (ASAQ-CP) during the Ebola outbreak, Monrovia, Liberia, 2014.



To avoid crowding, the MDAs were carried out at fixed points in the early morning during curfew for a maximum of two hours. Crowd-management and security were the responsibility of CCL and the malaria committee. Women attending the distribution were asked to stand in lines, CVs were present to re-emphasize sensitization messages and to ensure adherence to the no-touch policy. The set-up of the easy-to-carry and easy-to-disinfect distribution site was organized in a way that avoided crowding and ensured rapid distributions.

On the distribution day, women could exchange the voucher they received from the CV for a pre-prepared medication pack of ASAQ containing a full course of ASAQ-chemoprevention (ASAQ-CP) for

seven household members (two adults and five children of various age groups). Children below 6 months did not receive ASAQ-CP. The medication packs were pre-prepared to keep logistics light and to facilitate rapid distribution. A catch-up distribution was carried out if less than 85% of the expected households attended the distribution at the respective site. In addition to the MDA, a back-up stock of medication packs remained with designated members of the community after the MDA. Households that did not receive sufficient ASAQ for all household members had the possibility to collect the missing ASAQ-CP doses.

The distribution team documented the number of vouchers and medication packages distributed by area in each round and the number of necessary catch-up distributions.

Objectives and design of the evaluation

We used data collected by the distribution team to assess the target population size, the absolute numbers of vouchers and medications packages distributed during the MDA and the number of catch-up distributions carried out.

For further evaluation of the MDA, one in every 200 households that received vouchers in round 1 (r1) of the MDA was randomly selected for telephone follow-up through systematic sampling during voucher distribution.

The objectives of the evaluation were to:

1) Describe the scale of the MDA: We described the absolute numbers of vouchers and medication packs distributed and the number of catch-up distributions.

2) Estimate acceptance of the MDA and adherence to ASAQ: We estimated attendance at the MDA and described the attitude towards the distributions on household level. On individual level, we estimated the availability of ASAQ and compliance with initiation of and adherence to ASAQ-CP and identified reasons for non-compliance and non-adherence. Additionally, we estimated the rate of self-reported side effects and examined the association between side effects and ASAQ-CP initiation.

3) Estimate the effectiveness of MDA: We estimated the incidence of self-reported fever episodes before and after the first round of MDA.

Procedures and data collection of the evaluation

Every 200th voucher was marked by a triangle shaped punch cut into the plastic voucher. The CVs that carried vouchers informed each household that received a marked voucher about the purpose of the evaluation and asked the head of the household (or another adult, if not available) for consent. If they refused, the next household to whom the CV distributed a voucher was asked for consent. For logistical reasons, no information about households was collected by the CVs during telephone number collection. After consenting, the respondents provided their telephone number. One week after both MDA r1 and r2 had taken place in the area, a trained surveyor interviewed the respondents by telephone using a

structured questionnaire. The questionnaires collected information on MDA attendance and acceptance. The respondent provided information for every member of his/her household regarding availability of ASAQ-CP for all household members, initiation and completion of the ASAQ-CP course, side effects and fever in the previous month. A question regarding the availability of the appropriate age-specific dose was added during the first round.

To assess the feasibility of the evaluation and the composition of the medication packs, we conducted a pilot evaluation. This included households from the first five distribution days, approximately 20% of all households. Data from these households was excluded from the evaluation.

Operational definitions of the evaluation

A household was defined as a group of people living under the same roof and sharing the same meal at least three times a week regardless of family ties.

Self-reported fever was used as a proxy for malaria infection and defined as history of fever or malaria within the past month reported by the respondent. Reports could not be confirmed by laboratory testing due to the ongoing Ebola outbreak.

Reported side effects were defined as any sign or symptom reported as a side effect by the respondent.

Compliance with treatment initiation was defined as taking at least one of the three doses of ASAQ-CP as reported by the respondent.

Adherence was defined as taking all three doses of ASAQ-CP, thus completing the full course as reported by the respondent.

Data analysis for the evaluation

We described absolute population numbers and MDA attendance and number of catch-up distributions as collected by the distribution team.

For further evaluation, households that were reached for telephone interviews in both rounds of MDA were included in the analysis. As one individual was reporting for his or her whole household in both rounds, individual household members needed to be re-identified in the second round to allow for individual level analysis of data; re-identification was based on reported age and sex as data collection was anonymous and names were not recorded. First we re-identified individuals with identical ages in both rounds. Next, in order to account for imprecise age estimations by household members, we re-identified individuals ± 1 year (or months for infants below 12 months of age) during the second round followed by individuals ±2 years of age. Household members that were only reported in one of the two rounds were not included in the analysis as measures of associations cannot be calculated for them.

On household level, we calculated proportions. On an individual level we calculated proportions with 95% confidence intervals (95% CI) where appropriate, allowing for the potential cluster effect of the household on treatment availability, compliance with treatment initiation and adherence. Differences

between household members initiating and adhering to treatment and those that did not were calculated with chi squared tests.

We used poisson regression to calculate incidence ratios (IR) as a measure of association between reported side effects and treatment initiation, adjusting for possible confounders and also taking into account the cluster effect of the household.

As fever was reported for the past month, the evaluation after r1 captured self-reported fever incidence prior to the start of the MDA and the evaluation after r2 captured the self-reported fever incidence the month after r1. We calculated the difference in reported fever by subtracting the incidence of reported fever episodes after r2 from the incidence of reported fever episodes after r1 and presented risk differences (RD) with 95% CI. We compared the reported pre- and post-r1 incidences using a z-test for difference in proportions. Additionally, we compared the RD among household members that took the full course of ASAQ in r1 with the RD among household members that did not take the full course of ASAQ with a z-test for difference in proportions.

Analyses were conducted with STATA version 13 (Stata corporation, Texas, USA).

Ethical considerations

The data presented here are from an analysis of MSF programmatic data. The procedures conducted during the evaluation were in accordance with the ethical standards of the Helsinki Declaration. The CVs read a consent form to the head of the household and explained that participation was voluntary. Respondents provided verbal consent. No personal identifiers were collected and only aggregated data was reported. All evaluation documents were stored in a locked cabinet or a password protected computer.

7.4. Results

Scale of the MDA

In the four targeted zones of Monrovia a total population of 551,971 individuals in 102,372 households was verified with CCL and the malaria committee in round 1 and corrected to 558,483 individuals in 103,497 households during r2. 102,372 vouchers for a pre-packaged medication pack were distributed during round 1 and 103,497 during r2. The total number of vouchers exchanged for medication packs was 90,411 (94%) in r1 and 89,546 (93%) in r2. In total, 1,259,699 courses of ASAQ-CP were distributed.

At each of the 56 distribution points in both rounds, between 347 and 3,853 women received medications packs, depending on community size.

Catch-up distributions needed to be carried out in three (5%) of the 56 sites in r1. In r2, two catch-up distributions were deemed necessary but only one was carried out; in the other community, chairmen were reluctant to organize a new distribution as they were convinced that it was not necessary.

Response

The communities included in the evaluation (excluding the pilot evaluation) consisted of 426,760 individuals in 72,585 households of which every 200th was asked to participate.

We aimed to contact 365 selected households by phone in rounds 1 and 2. CVs reported that every selected household agreed to participate and had a phone. Of the 365 selected households, 222 (61%) were reached by phone in both rounds. The remaining 39% (143/365) of sampled households either i) did not answer their phone, or ii) had their phone turned off, or iii) the connection was too poor to collect any information during three tries. Of the 143 households that were not included in the evaluation, 47% (67/143) were only reached in one of the rounds of the MDA and 53% (76/143) were not reached in any round. All 222 households that were reached in both rounds had provided informed consent to the CV beforehand and agreed to be interviewed.

In total, 1,643 individuals were reported to live in the 222 households reached in both rounds (average household size: 7.4). Using household-code, sex and age, 1,236 (75%; 1236/1643) individuals could be re-identified in both rounds. The 1,236 individuals were principally female (54%, 667/1,236) with a median age of 16 (Interquartile range: 8-28 years). The 407 (25%) individuals who were unable to be re-identified were reported to have lived in the household during only one of the two rounds of MDA.

Attendance, compliance and adherence

All 222 households attended the distribution during r1 (100%), accounting for 1,236 household members of which 1,233 were eligible for ASAQ-CP (i.e. household members older than six months). During r2, 212 (96%) households attended the MDA, accounting for 1,157 household members of which 1,154 were eligible for ASAQ-CP. Of the eight households that could not attend the MDA in r2, six were not in the distribution area during the distribution of medication packs, one did not receive a voucher and one lost the voucher.

Despite the availability of buffer stocks, some household members did not receive ASAQ-CP. In r1, 1,113 (90%) of 1,233 household members received sufficient ASAQ-CP, compared with 1,144 (99%) of 1,154 in r2 (Table 7-1).

Table 7-1: Reported compliance and adherence with artesunate/amodiaquine malaria chemoprevention (ASAQ-CP) among households targeted for mass drug administration (MDA) during the Ebola outbreak, Monrovia, Liberia, 2014.

Response for all household members		MDA round 1 (N=1233ϕ)			MDA round 2 (N=1154ϕ)		
		n	% of N	(95% CI)	n	% of N	(95% CI)
Household members who received sufficient ASAQ-CP	Unknown	48	3.9	(1.5; 9.8)	0	0.0	-
	No	72	5.8	(3.7; 9.0)	10	0.9	(0.3; 2.3)
	Yes	1113	90	(85; 94)	1144	99	(98; 100)
Household members who initiated ASAQ-CP	Unknown	8	0.7	(0.3; 1.6)	0	0.0	-
	No	462	38	(32; 43)	888	77	(71; 82)
	Yes	643	52	(46; 58)	256	22	(17; 28)
Household members who adhered to the full course of ASAQ-CP*	Unknown	0	0.0	-	0	0.0	-
	No	51	4.1	(2.3; 7.2)	3	0.3	(0.1; 1.3)
	Yes	592	48	(42; 54)	253	21	(17; 28)

ϕ 3 infants < 6 months were not included in the analysis

* includes household members that reported having just started the 3-day-course of chemoprevention and planning to complete the course of ASAQ-CP within the next two days

Among those household members that received any dose, the dose received was reported to be age appropriate for ≥98% of household members in both rounds. During r1, 98% (983/1,005) of household members for whom information was available, reported receiving the correct dosage of ASAQ-CP for their age, 21 (2%) did not know, and one (0.1%) reported receiving an incorrect dose. In r2, 100% (1,144) household members reported receiving the correct dose.

Compliance with ASAQ-CP initiation among those that attended the MDA was 52% (643/1233) in r1 and 22% (256/1154) in r2 (Table 7-1). There were no significant differences in age or gender between individuals who did and did not initiate ASAQ-CP in r1 and r2: In r1 44% of household members initiating ASAQ-CP were male, median age was 15 years. 47% of household members not initiating ASAQ-CP were male and median age was 17 years. In r2 44% of household members initiating ASAQ-CP were male, median age was 15 years. 45% of household members not initiating ASAQ-CP were male and median age was 16.5 years.

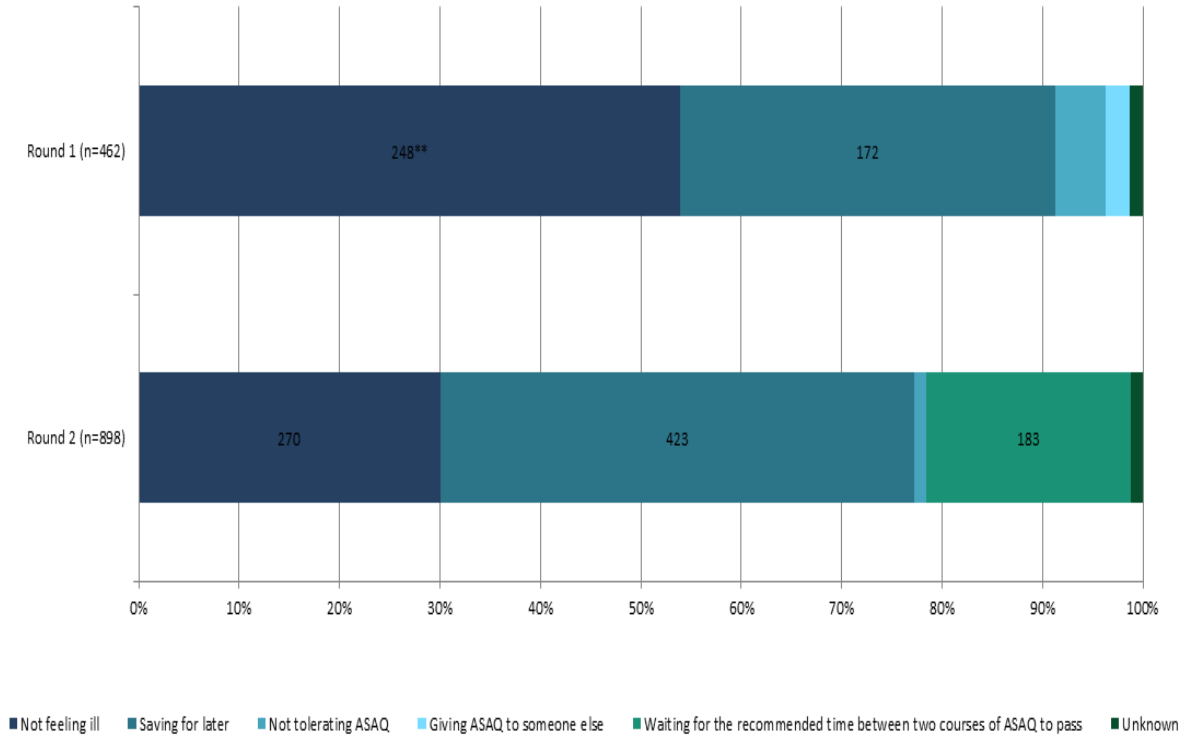
In r1 48% (592/1233) of all household members that received ASAQ-CP adhered to the full course, in r2 21% (253/1154) (Table 7-1). In r1, 51 individuals did not complete their treatment; 22 (43%) were male; median age 15 years. In r2 only 3 individuals did not complete their treatment; 1 (33%) was male; median age 10 years.

Community acceptance of the MDA and reasons for non-compliance and -adherence

After r1 all but one household approved of the way the distribution was carried out; the disapproving respondent mentioned that some people arrived with multiple vouchers and got more than one household-pack of ASAQ-CP. No complaints were reported after r2.

In r1, 248 (54%) of 462 household members not initiating the course of ASAQ-CP reported they did not feel sick, and 172 (37%) that they had saved ASAQ for later. In r2, 423 (48%) of 888 not compliant with ASAQ-CP initiation reported saving it for later, 270 (30%) reported not feeling sick and 183 (21%) that they waited for one month between the two rounds of chemoprevention (Fig 7-3).

Figure 7-3: Reported reasons for non-compliance with initiation of artesunate/amodiaquine malaria chemoprevention (ASAQ-CP) during the Ebola outbreak, Monrovia, Liberia, 2014*.



*includes only those household members that received sufficient ASAQ during the mass drug administration (MDA) in round 1 and 2
**absolute numbers of reported reasons are given for categories reported >50 times

Adherence to the three day ASAQ-CP course among those who initiated ASAQ-CP increased from 91% (592/643) in r1 to 99% (253/256) in r2 of MDA; those completing ASAQ-CP and those not completing ASAQ-CP did not differ in age and gender. In r1, 14 household members reported side effects as the reason for interruption, 12 did not understand the importance of completing a full course, eight shared their course with someone else and 17 reported other or unknown reasons. In r2, three household members did not complete the ASAQ-CP course; one reported side effects as the reason and two reported not understanding the importance of continuing the three-day course. Among the 605 household members who initiated ASAQ-CP in r1 and attended the MDA in r2, 406 (67%) decided not to initiate ASAQ-CP in the second round. The most frequently reported reasons were saving ASAQ for later (49%; 198/406), waiting for the recommended time between two ASAQ courses to pass (25%; 100/406) and not feeling ill (24%; 96/406).

Side effects of ASAQ and their impact on adherence during the MDA

Reported side effects among household members starting ASAQ-CP in each round included: drowsiness (r1: 10%; r2: 6%), dizziness (r1: 10%; r2: 5%), fever (r1: 2%; r2: 0.0%), nausea (r1: 1%; r2: 0.0%), headache (r1: 1%; r2: 0.0%), vomiting (r1: 1%; r2: 0.4%) and skin reactions (r1: 0.6%; r2: 0.0%). Overall attack rate of any reported side effect in the first and second round of MDA was 17% (107/643) and 6% (16/256), respectively. Among those household members that started ASAQ-CP, 15 (1.7%) of 899 ASAQ-CP courses during both rounds of MDA were reported to be interrupted for possible ASAQ side effects.

In r1, 23 (2%) of 1,113 household members that received sufficient ASAQ reported that they did not initiate ASAQ-CP because they feared side effects. In r2, 11 (1%) of 1,144 household members did not initiate due to ASAQ side effects. Yet, occurrence of side effects during r1 was not associated with ASAQ-CP initiation during r2 when adjusted for age and gender (Table 7-2).

Table 7-2: Association between experiencing side effects of artesunate/amodiaquine malaria chemoprevention (ASAQ-CP) in the first round of mass drug administration (MDA) with initiation of ASAQ-CP in the second round of the MDA, during the Ebola outbreak, Monrovia, Liberia, 2014 (Poisson regression).

Characteristics of household members*	(N=591)	Adjusted IR	(95% CI)	p-value
Household members reported experiencing side effects in round 1				
No	487	reference		
Yes	104	1.00	(0.61; 1.64)	0.99
Age				
Age in years	591	1.00	(0.99; 1.01)	0.40
Gender				
Male	258	reference		
Female	333	0.97	(0.77; 1.22)	0.76

* includes only household members that initiated ASAQ-CP in round 1 and received ASAQ-CP in round 2

Among household members that initiated ASAQ-CP in r1 and provided information on side effects in r1 and ASAQ-initiation in r2, the proportion of household members initiating ASAQ-CP in r2 was 32%, both among those that experienced side effects (33/104) and among those that did not experience side effects (158/487).

Effectiveness of the MDA

The incidence of self-reported fever episodes decreased significantly after r1 compared to the month prior to r1, from 4.2% to 1.5% ($p<0.0001$) (Table7-3).

Table 7-3: Incidence and risk difference (RD) of self-reported fever episodes among household members that attended the mass drug administration (MDA) of artesunate/amodiaquine malaria chemoprevention (ASAQ-CP) in rounds 1 and 2 during the Ebola outbreak.

Responses for all household members	Incidence of self-reported fever episodes (%) in the month prior to round 1	Incidence of self-reported fever episodes (%) in the month prior to round 2	RD (%) of self-reported fever episodes	(95% CI for RD)	p-value
All household members (N=1229[ϕ])	4.2	1.5	2.7	(1.4; 4.0)	<0.001*
Incidence of self-reported fever by ASAQ-CP adherence					
Household members who completed ASAQ-CP in round 1 (N=592[‡])	6.4	1.5	4.9	(2.7; 7.1)	<0.001*
Household members who did not start or complete ASAQ-CP in round 1 (N= 511[‡])	2.2	1.6	0.6	(-1.1; 2.2)	0.690
Incidence of self-reported fever by age group					
Household members >5 years old (N=1044)	3.8	1.6	2.2	(0.8; 3.6)	0.002*
Household members ≤5 years old (N=185)	6.5	1.1	5.4	(1.6; 9.2)	0.006*

[ϕ] 6 household members for whom incidence of self-reported fever is unknown were excluded
[‡] Further 126 household members for whom compliance with ASAQ-CP initiation or adherence was unknown were excluded from analysis
* Significant difference in incidence of self-reported fever between round 1 and 2 of the MDA

Reported fever incidence was initially higher in children than in adults: self-reported fever incidence was 6.9% in children ≤ 5 years of age and 3.8% in older household members and decreased to 1.1% and 1.6% respectively after the first round of the MDA. Incidence of self-reported fever was 4.9% lower after r1 among those household members who took a full course of ASAQ-CP and 0.6% lower among household members who did not start or not complete a full course of ASAQ-CP (Table 7-3). While reported incidence decreased in both groups, the RD was significantly bigger among the group that took the full course ($p<0.001$).

7.5. Discussion

The MSF lead MDA in Monrovia was a novelty and a challenge as MDAs have rarely been carried out on such large scale, never with ASAQ (Newby *et al.*, 2015; von Seidlein and Dondorp, 2015) and for the first time during an Ebola outbreak. Several challenges were encountered and lessons learned from the MDA which could help to inform future interventions (Box 1).

Box 1: Challenges and lessons learned from the mass drug administration (MDA) of artesunate/amodiaquine malaria chemoprevention (ASAQ-CP) during the Ebola outbreak, Monrovia, Liberia, 2014.

Lessons learned

- Verification of population estimates with local leaders prior to the distribution substantially increased the estimated population size but was necessary to ensure appropriate coverage.
- Use of fixed points for distribution of pre-packed medications using stringent infection prevention and control procedures was challenging but fast and feasible.
- Coordination of messages with relevant actors in the target area is important; adaptation of messages according to monitoring results can improve compliance and adherence.
- If DOT is impossible, treatment initiation can possibly be improved by distributing familiar and uniformly packed medication and by provision food and ORS at the same time.
- Occurrence of treatment related side effects did not affect compliance.
- Adherence to ASAQ-CP was high and no risk of drug resistance development was identified.
- No amplification of the Ebola outbreak in the target areas was observed during or after the intervention.
- Self-reported fever cases were significantly lower after the MDA, particularly among household members that initiated ASAQ-CP.
- Combining MDAs in malaria endemic areas with longer term interventions to prevent malaria and to improve access to healthcare may reduce the proportion of respondents saving their treatment for future malaria episodes.

Scale and challenges in implementation of the MDA

After discussions with CCL and the malaria committee in all 56 distribution sites the initial population estimate used to plan the distribution increased by 184% (300,000 to 551,971). While a challenge for planning, overcrowding and multiple families using the same shelter in shifts may explain the initial underestimation. An additional increase of approximately 7,000 people was noted from the first to second round and was due to the initial accidental exclusion of several small minority communities. These minority communities were not deemed part of their community by CCLs during planning for r1 and were only discovered by local MSF staff after the first distribution.

Engagement of local staff and close collaboration with both the local CCL and malaria committee ensured one woman per household would attend the distribution. Similar to other distributions where the importance of community engagement was highlighted as critical to ensuring high campaign coverage (Newby *et al.*, 2015; von Seidlein and Dondorp, 2015), these relationships proved essential in reaching more than 80% of the population in each target community (Newby *et al.*, 2015). Community sensitization was key however challenging. Different actors carried out distributions of various items during the same period in Monrovia with little coordination. Consequently, CVs, depending on the organization for which they were working, provided different sensitization messages and announced different distribution schedules and places. Additionally, the distributions took place during a period

when trust in international aid and the Ebola response was not high and rumors about the spread of Ebola by international actors were common.

Compliance with ASAQ-CP initiation may have been improved by utilization of directly observed treatment (DOT), a strategy cited as an essential component of successful MDAs in the past (Newby *et al.*, 2015). Indeed, WHO recommended door-to-door distributions with DOT for MDAs during the Ebola outbreak (World Health Organization Global Malaria Programme, 2014a). However, in the most populated areas of Monrovia with the highest Ebola incidence, door-to-door distributions and the DOT strategy were deemed unfeasible due to concerns for staff security and the risk of amplifying Ebola transmission. Use of fixed distribution points allowed us to mitigate the risks of Ebola transmission among staff and beneficiaries through use of rigorous crowd-management and a no-touch-policy. Furthermore, strict infection prevention and control procedures were implemented for distribution sites, staff and cars. These measures would not have been possible to implement during door-to-door distributions. Despite ongoing Ebola transmission in the distribution areas during the MDAs, no Ebola case associated with the MDAs presented at the MSF ETU in Monrovia or was brought to the attention of MSF, NMCP or other actors. Additionally, several Ebola transmission chains ended in the target area during that period. Thus, we identified no risk of fuelling the Ebola outbreak during the MDAs.

Acceptance, compliance, adherence – Lessons learned

Even though almost 100% of recipients reported a positive attitude towards the MDA, the majority did not initiate ASAQ-CP; most reported not feeling sick and saving ASAQ for later. In other MDA interventions with similar experiences, more than one third of respondents reported being reluctant to take the available drugs because they did not feel sick (Newby *et al.*, 2015). In Monrovia, this could be a consequence of national health messaging prior to the Ebola outbreak that emphasized the importance of being tested for malaria before initiating treatment. During the start of the distribution local staff reported that this message continued to be communicated by other actors in parts of the target areas.

Some of the ASAQ doses however, were procured from a manufacturer different to that manufacturer which provided the most commonly available ASAQ drugs in Monrovia prior to the outbreak. This may have led to confusion among recipients as the packaging was different and community members may have been less familiar with the drug name than the packaging itself. Due to issues with supply, the household medication packs were pre-prepared in plastic bags of varying colors. This may have caused some additional confusion among recipients who suspected that the contents of each bag were different based on its color.

Anecdotal reports from local nurses and CVs highlighted the role that the absence of food and oral rehydration solution (ORS) distributions concurrent with the drug distribution may have had on treatment initiation. Indeed, it was recommended to take ASAQ with food and to use ORS in case of vomiting or diarrhea – both unavailable to some recipients living in the most precarious areas of Monrovia. Finally, ASAQ-CP may have been saved more frequently during the second round because residents realized that MSF would not be carrying out a third MDA and health facilities had yet to reopen. The risk of future infection with malaria and the lack of available treatment in the continuous

absence of healthcare facilities or future MSF distributions may have been perceived as more important. Consequently, the best use of ASAQ would be as treatment when sick.

Although a concern, no evidence has been found in the past that MDAs of full course therapeutic treatment with combination drug regimens lead to increased drug resistance (von Seidlein and Greenwood, 2003; Newby *et al.*, 2015; von Seidlein and Dondorp, 2015). We were able to increase ASAQ-CP adherence to the three-day course from 90% to close to 100% between r1 and r2 thus minimizing the risk of amplification of resistant parasite strains. Increase in ASAQ-CP adherence may be the result of adapted messaging after preliminary analysis of the first round data. For the second round CVs were encouraged to stress the importance of adherence and the availability and location of the buffer stock for those household members who did not receive ASAQ-CP.

Side effects of ASAQ and their impact on adherence during the MDA

ASAQ was selected as CP due to its availability, proven efficacy (B Schramm *et al.*, 2013), safety, tolerability (Birgit Schramm *et al.*, 2013) and the communities' familiarity with it. During this intervention ASAQ-CP led to common but mild side effects that did not affect adherence in the two rounds of MDA. Interruptions of ASAQ-CP course due to reported side effects were rare. These findings are consistent with previous studies of ASAQ-CP related adverse events. Severe adverse events were recorded in only 3% of respondents and none of these led to treatment interruption or long-term impairment (Birgit Schramm *et al.*, 2013). Even though side effects were deemed a major challenge for compliance by some local actors, during the MDA, only 1.5% of household members refused to initiate ASAQ-CP for fear of side effects, even though, i) they were made aware of possible side effects by CVs, ii) many were familiar with side effects from prior experience, and iii) ASAQ side effects can potentially mimic Ebola symptoms. Also the risk of overdosing appears to have been well understood by the population; one fifth of those not initiating ASAQ-CP in the second round reported starting the first ASAQ-CP course late and needing to wait for one month before beginning the next round of ASAQ-CP.

Effectiveness of the MDA

The initial self-reported fever incidence in children under five years of age of 6.5% prior to the first round of MDA is low when compared with previously reported estimates of laboratory confirmed malaria prevalence in Monrovia (Measure DHS, 2011). Underreporting of fever and malaria in our study may have occurred due to stigmatization of Ebola patients and the similarity of malaria and Ebola symptoms. However, given that the first round of MDA was carried out close to the peak of the Ebola outbreak in Monrovia, the bias due to underreporting should be similar or reduced in r2 of MDA compared to r1. Nevertheless, it has been suggested that malaria maybe over-reported in the initial phase of study implementation and that reports decrease over time, possibly because respondents hope to receive more support with higher burden of disease initially (Alba *et al.*, 2011). However, the significant difference self-reported fever reduction for household members completing ASAQ-CP and those that did not would not be explained by the phenomenon of systematic under- or over-reporting.

The reduction in fever incidence among those completing the full course of ASAQ in the first round was significantly larger compared to those not initiating or not completing the ASAQ course. This decrease in incidence is coherent with previous knowledge as ASAQ has not been used in MDAs for chemoprevention previously but proved efficient as treatment in Liberia (B Schramm *et al.*, 2013) and previous MDAs of malaria chemoprevention have been shown to reduce malaria morbidity over limited time periods (Poirot *et al.*, 2013; von Seidlein and Greenwood, 2003; von Seidlein, Lorenz Walraven *et al.*, 2003; Song *et al.*, 2010; Newby *et al.*, 2015). To our knowledge, additional vector control measures by non-governmental or governmental organizations were not carried out in the distribution area during our intervention. Seasonal changes between the first round in October/November and the second round in November/December may have contributed to the reduction of fevers but cannot explain the significant difference between those that completed ASAQ-CP and those that did not.

With the observed adherence to a full course of ASAQ-CP of 48% in the first round, extrapolation of the overall reduction in incidence of self-reported fever from 4.2% to 1.5% in the sample to the population of the target zone (551,971 individuals) suggests that 14,821 (95% CI 4,801-24,840) fever episodes per month may have been averted as a result of the MDA in Monrovia. Mathematical modelling conducted in early 2015 suggested that in the absence of adequate healthcare provision, three rounds of ASAQ-MDA with coverage of 70% in the whole of Liberia from January 2015 would have had averted 300,000 to 700,000 malaria cases (Walker *et al.*, 2015). Given that this MDA targeted about 10% of the Liberian population and consisted of two rounds, our estimates are consistent with modelling results (Walker *et al.*, 2015) and indicate that self-reported fever is an adequate proxy for malaria in this particular setting.

In addition to the reduction in incidence of self-reported fever, the availability of left over ASAQ likely resulted in a reduction of movements to search for malaria treatment and may have reduced transmission of communicable diseases in health facilities.

Limitations of the evaluation

Potential selection biases may have occurred and affected the findings. First, our sample was based on households selected during voucher distribution, and completeness of voucher distribution could not be concluded from the data available. Therefore, no inference about coverage in the target area can be made. Second, 20% of the target community was included in the sampling frame for the pilot evaluation and could not be included in this evaluation. Third, 39% of sampled households were not reached in both rounds using the phone number provided. We do not know if those individuals that were not reached after three attempts differed systematically from those that were reached in both rounds. Comparing households that were reached in only one round with those reached in both, did not indicate differences in household composition, self-reported side effects or fever incidence. Nevertheless, there is possible sampling bias introduced by those households that were not reached in any of the rounds as they might have a more critical attitude towards the MDA and did not answer the phone for that reason. Additionally, individuals that did not respond may have died or lived in very remote corners of the MDA area without stable phone connections and might differ in other characteristics as well. Unfortunately, it was not possible to train all CVs in basic data collection and the no-touch policy heavily restricted

opportunities for direct interaction with the community, so no background information on sampled but not reached households could be obtained. On the other hand, CVs reported that all selected households agreed to participate and provided a phone number. This indicates a) high acceptability of the phone survey and b) a sufficiently good coverage of phone ownership even in disadvantaged areas of Monrovia.

Reporting bias may have been introduced as the prevalence of malaria parasitemia could not be established and self-reported episodes of fever were used as a proxy for malaria, leading to possible estimation-bias of malaria incidence, particularly in the first round (Alba *et al.*, 2011). Fever might be under-reported for fear of stigma or over-reported with the hope of receiving additional support. In addition, fever may be caused by other illnesses than malaria. However, the aim of the intervention was to reduce the number of fever cases in Monrovia; therefore, we believe, that the low specificity of fever as a symptom did not negatively impact the ability of the study to measure the effectiveness of the intervention. In addition, the coherence of our results with previous modelling results for malaria incidence indicates that fever may actually be an acceptable proxy for malaria in this context (Walker *et al.*, 2015).

Lastly, this analysis does not include fever incidence figures from non-MDA areas. It is therefore difficult to determine whether the observed differences in reported incidence were exclusively attributable to the intervention.

Conclusions

The apparent reduction in self-reported fever cases following the MDA of malaria chemoprevention suggests that the intervention may have been effective in reducing the number of fever cases during the Ebola outbreak in Monrovia. Despite high acceptance and coverage of the MDA and the small impact of side effects, initiation of malaria chemoprevention was low, possibly due to health messaging and behaviour in the pre-Ebola outbreak period and the ongoing lack of healthcare services. Stronger community involvement by dedicated local staff prior to the intervention and improved coordination with other actors in the target area may have been helpful in identifying relevant sensitization messages and hidden communities earlier, and could have possibly addressed misconceptions, fears and rumours more effectively. Combining MDAs during Ebola outbreaks with longer term interventions to prevent malaria and to improve access to healthcare might reduce the proportion of respondents saving their treatment for future malaria episodes.

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8. General discussion and conclusion

The aim of this thesis was to explore several aspects pertaining to the implementation of malaria control interventions in malaria endemic West Africa, in program conditions, prior to and during the 2013-2016 Ebola epidemic. In Chapter 4 changes in malaria parasite prevalence in a rural, hyperendemic area of the Republic of Guinea where reliable estimates of malaria parasite prevalence were previously unavailable is described. Additionally, the impact of a multi-component malaria control intervention on malaria parasite prevalence, when implemented in program conditions, is measured during a series of five cross-sectional cluster surveys.

All malaria control activities were reduced as a result of the Ebola outbreak and the MSF malaria project closed. In Chapter 5 we model the impact that a cessation of malaria control activities is likely to have had on malaria incidence in the areas where the multi-component intervention had been implemented. We used data collected from the cross-sectional surveys to parameterize a stochastic malaria transmission model in order to simulate impact in terms of cases (malaria incidence) that resulted from the reduction of malaria control activities in the areas where they had previously been implemented.

Data from health facility based surveillance in the areas where the intervention was implemented was deemed to be unreliable due to underreporting. In Chapter 6 the concurrent implementation of community-based sentinel site surveillance of 43,000 individuals and its ability to capture malaria related deaths and quantify malaria attributable mortality is described. As the multi-component malaria intervention came to an end, an outbreak of Ebola occurred in the intervention area. In Chapter 6 data collected through the community-based mortality surveillance system is evaluated for its ability to detect outbreaks, specifically of Ebola.

Finally, over time the Ebola outbreak evolved into a multi-country epidemic and the response moved from vertical programming to a more holistic response which incorporated innovative use of classic malaria control strategies. In Chapter 7 the impact of the first mass drug administration of malaria chemoprevention carried out during an Ebola outbreak is evaluated and lessons learned are documented in order to inform the deployment of similar strategies in the future.

All these different aspects combined provide a unique perspective on malaria control in normal and emergency settings in malaria endemic areas of West Africa.

8.1. Challenges in controlling malaria

There are 15 countries of the world, primarily located in sub-Saharan Africa, that account for more than 80% of the world-wide malaria burden (World Health Organization Global Malaria Programme, 2015b). Yet, estimates of malaria burden vary not only between but also within countries. In two of these, the Republics of Guinea and Liberia, country specific estimates of malaria incidence, 55/1000 and 62/1000, respectively, do not reflect the intra-country variations of endemicity (World Health Organization Global Malaria Programme, 2015b; Gething *et al.*, 2016). The variation in malaria prevalence measured in the 2012 DHS survey in Guinea highlights the regional heterogeneity, 3.2% in urban Conakry, 64.1% in N'Zerekore and 67.8% in Faranah (Measure DHS, 2012). Yet, aside from the regional estimate of malaria

parasite prevalence, little was known about the epidemiology of malaria when MSF began planning its intervention in Guéckédou. Consequently when the cross-sectional studies were conceived, the two rural areas of intervention (Guendembou and Tekoulo) and the rural comparison area (Koundou) were thought to be equivalent in terms of malaria parasite prevalence. Unlike the rural areas, it was anticipated that Guéckédou City would have a different parasite prevalence due to its semi-urban profile; however, all sous-préfectures were estimated to have a malaria parasite prevalence of at least 50%. This was found to be true during the first malaria prevalence survey however there was significant variation in the point estimates.

Malaria parasite prevalence demonstrated significant albeit small decreases over time when the reinforced intervention package was implemented on a large scale and in program conditions. This was not entirely unexpected however because the impact of malaria control interventions has been demonstrated to vary (Ceesay *et al.*, 2008; Beiersmann *et al.*, 2011; Okiro *et al.*, 2011; Roca-Feltrer *et al.*, 2012; Mawili-Mboumba *et al.*, 2013). Although intervention coverage in Guéckédou increased over time, the impact of the intervention package may have been influenced by environmental factors such as climatic variability (Arab, Jackson and Kongoli, 2014) and topography including vegetation coverage (Githeko *et al.*, 2006) that we did not measure but can influence the epidemiology of malaria. On one hand the observed decrease is encouraging as it demonstrates the impact that Ministries of Health can have on malaria parasite prevalence by investing in malaria control activities in high burden areas. Conversely, it is also illustrative of the difficulties that Ministries of Health and international actors have to control malaria in highly endemic settings. Improved understanding of malaria epidemiology at the Préfecture level in addition to human and financial resources will be required to progress towards control in Guéckédou and similar settings.

In addition to more resources, new or modified malaria control strategies are needed to address malaria in Guéckédou and similar settings. A success of the intervention in Guéckédou was that it was continuously being monitored and evaluated and interventions such as IPTp were added to the intervention package over time. Yet, had LLINs been distributed in 2011, an earlier and more significant decrease in malaria parasite prevalence may have been seen. In order to address specific parasite reservoirs, malaria control programs could consider incorporating IPTc as a control strategy and expanding the age range from 0-5 years to 0-10 or 14 years. Expanding the age range could reduce a significant proportion of the parasite reservoir which is likely to reduce transmission in the community (for those not included in the age range). Additionally, implementation of a few rounds of MDA could result in an immediate, yet temporal, reduction in the malaria burden if not followed by a sustained by a scale up of control activities. Furthermore, deployment of a malaria vaccine (RTS,S) for children 5-17 months of age in addition to reinforcing malaria control measures in high transmission settings could also be considered (World Health Organization, 2016b). In low to medium transmission settings with closed or stable populations, the addition of Ivermectin to a MDA with coverage <80% may also have an impact on transmission by reducing the mosquito population. The best package of interventions will vary according to the malaria epidemiology of the area of intervention.

Malaria control interventions need to be flexible and adaptable to different contexts including complex

and humanitarian emergencies. The MDA of malaria chemoprevention in Monrovia illustrates an adaptation of a classic malaria control strategy for an emergency situation. Prior to the 2013-2016 Ebola epidemic in West Africa a MDA of malaria chemoprevention had never been carried out during an Ebola outbreak. As seen in Chapter 7, the primary objective of the 2 rounds of MDA carried out from October to December 2014 was to reduce malaria related morbidity and mortality as a consequence of reduced access to health care during the Ebola outbreak. The deployment of MDA during an Ebola outbreak was innovative and demanded adaptation of the traditional strategy in order to address the risks of carrying out a MDA in an Ebola context. The risks were not only related to distribution of an antimalarial medication (ASAQ) with known side effects such as nausea, abdominal pain, weakness and tiredness (Sanofi-Aventis, 2012) which mimic the symptoms of Ebola. There were also risks related to exposure to the virus through contact for both attendees and distribution staff. To mitigate the risks, the distribution strategy used fixed point distribution sites whose location varied according to the distribution area for the day. Additionally, distributions were carried out in the early hours of the morning before curfew was lifted and only one woman from each household was invited to attend the distribution. In order to minimise the amount of time each woman spent at the distribution point pre-packed medication packs were distributed. These packs were given to each woman in attendance in exchange for a voucher she had received the previous day. In order to ensure adequate coverage per family, buffer stocks were made available free of charge at health facilities if the contents of the medication pack were insufficient for the household. A strict “no touch” policy was enforced at all distribution points. The policy limited contact between women attending the distribution and between the women and distribution staff. Although the distribution strategy differed, the “no touch” policy was directly in line with the WHO guidance on temporary malaria control measures in Ebola-affected countries that was released after activities had begun in Liberia (World Health Organization Global Malaria Programme, 2014a). Despite all of the potential limitations the innovative deployment of the MDA resulted in a significant reduction in the incidence of self-reported fever.

The impact of the MDA in Liberia also extended beyond the reduction of fever episodes to reducing the number of patients presenting at ETCs with malaria related fever and consequently their risk for nosocomial infection. The experience in Liberia also served as an example for neighboring Sierra Leone where two rounds of door-to-door MDA were carried out and reached over 2.7 million people. Unlike in Liberia, the first dose was generally directly observed, in accordance with the WHO guidelines (World Health Organization Global Malaria Programme, 2014a). The deployment of MDA in Sierra Leone extended beyond the capital, Freetown, and involved no fewer than 6 partners to the Ministry of Health. A follow-up study in Sierra Leone analysed data from health facilities from October 2014 through February 2015 to demonstrate the impact of the MDA and found that the number of RDT confirmed malaria cases declined after each MDA round. In addition, the number of Ebola alerts at Ebola District Command Centers was found to have decreased (by 30%) in the first week after distribution. The impact of the MDA continued in the subsequent weeks. In Sierra Leone the MDA’s impact on reducing the number of clinical malaria cases waned about four weeks after each MDA round and malaria trends returned nearly to pre-MDA levels at about the same time (Aregawi *et al.*, 2016).

The impact of the MDA of malaria chemoprevention in both Sierra Leone and Liberia investigated from both a population and health facility perspective highlight the impact that innovative use of malaria control strategies can have as a short-term intervention. Yet using such strategies in hyperendemic areas and expecting to have a sustained impact on malaria burden is unrealistic. In hyperendemic settings use of MDA could be considered if immediately followed by a rapid scale up of (sustainable) malaria control activities.

To progress towards malaria control, malaria control strategies need to be implemented at an appropriate scale that is sustainable by Ministries of Health or their partners. While engagement of international actors will be important to control malaria in high burden areas, allowing major donors and implementers to pick and choose what and where they carry out their activities comes at a cost. As seen in Chapter 5 when the interventions are unable to be sustained, malaria parasite prevalence resurges very quickly to levels higher than that which were observed prior to the interventions. Consequently, the resurgence of (avoidable) cases of malaria causes a major setback for malaria control programs in high burden areas.

8.2. Improving of the management of malaria during Ebola outbreaks

In Chapters 5 and 7 we illustrate how the impact of an Ebola outbreak extends beyond Ebola related morbidity and mortality to other morbidities, specifically malaria. Outbreaks of Ebola in Africa have historically occurred in malaria endemic countries specifically: Uganda, the Democratic Republic of the Congo, Gabon, Sudan, and the Republic of the Congo. The latest epidemic in Guinea, Sierra Leone and Liberia was no exception. In previous outbreaks Ebola response activities have historically been implemented as vertical programs; however, vertical, disease-specific responses are not unique to Ebola. In Chapter 4 the impact of a vertical malaria control program on malaria parasite prevalence as implemented in Guéckédou prior to the Ebola outbreak is described. Yet, when control activities ceased so did their impact on malaria parasite prevalence. While Ebola was taking hold in Guéckédou and surrounding prefectures, the malaria burden was increasing as a consequence of the cessation of malaria control activities.

Guidelines for the response to and management of patients infected with filovirus hemorrhagic fevers (FHF) acknowledge the consequences of FHF outbreaks on health systems and the residual effects of outbreaks on non-FHF related morbidity during and after FHF outbreaks (Sterk, 2008; World Health Organization, 2016a). Nevertheless, despite the symptom overlap between Ebola, malaria, and other febrile illnesses, the epidemic's impact on non-Ebola morbidity and the health care system were only taken into consideration in late 2014 when the number of Ebola cases in West Africa was increasing with no signs of slowing down.

The MDA carried out in Monrovia is illustrative of an evolution in thinking and serves as an example of a response that moved beyond its focus on Ebola while also mitigating the impact of decreased access to health care. The decision to distribute artesunate-amodiaquine (ASAQ) during the MDA, the first line treatment for malaria in Liberia, Sierra Leone and Guinea, was pragmatic and based on the quantity available at the time of the distributions. Although generally not advisable to use the same antimalarial

for treatment and prevention (World Health Organization, 2015d), this decision may have inadvertently extended the impact of the MDA beyond its primary objectives to saving additional lives as a result of the practical choice of ASAQ. Indeed a small ecological study demonstrated patients with a confirmed Ebola infection who received artesunate-amodiaquine during their stay in an ETC had a reduced risk of death compared to those patients who received artemeter-lumafantrine (risk ratio 0.69; 95% CI, 0.54-0.89) regardless of their malaria status (Gignoux *et al.*, 2016). While promising, additional research is needed to confirm the association between amodiaquine and reduced Ebola mortality. If MDAs are to be deployed during future Ebola outbreaks, the use of an antimalarial with a longer half-life could be used to extend the duration of the prophylactic period. Dihydroartemisinin-piperaquine (DHA-PQ) is a potential candidate however the efficacy of piperaquine should be investigated in an appropriate animal model for demonstration of Ebola inhibition properties. In the absence of Ebola inhibition, the use of an antimalarial other than ASAQ would simply extend the prophylactic period and the potential benefit of using ASAQ due to its suspected impact on reducing mortality would be negated.

These results also suggest an additional element that could be incorporated into future Ebola response strategies and guidelines. With an objective similar to that of the MDA, systematic administration of a full course of an antimalarial to contacts of patients with confirmed Ebola infection could i) clear their malaria infection and/or prevent future malaria infections, ii) reduce the probability that they are taken to an ETC with malaria-related fever and iii) potentially reduce their risk of mortality if already infected with the Ebola virus (depending on antimalarial used). A modeling analysis has demonstrated that such a strategy would be cost effective and could reduce the probability of a contact being admitted into an ETC by 10-36% (Carias *et al.*, 2014). Incorporation of such a strategy into response guidelines should be considered and deployment at scale and impact as measured in the community need to be demonstrated.

8.3. Disease surveillance where there is little data

Disease surveillance where health facility surveillance is limited is challenging even outside of emergencies. In Chapter 6, we document mortality in the community during 3 years of community-based sentinel site surveillance in Guéckédou Préfecture; many of these deaths would have gone otherwise unreported. The success of the project was likely due to the way it was implemented in the field. Key informants were nominated by their communities to collect data on mortality in their community. The familiarity of the community with the key informant facilitated data collection during the familial mourning period. Data collection occurred soon after death before the details could be forgotten. Additionally, a resident of the sous-préfecture in which the data was collected was hired to supervise data collection in all sentinel sites in his sous-préfecture. The design of the project could have been improved however, and expanded beyond its vertical focus on malaria (fever) related mortality to include other causes of mortality. Indeed, when the data on non-malaria related causes of death was analysed retrospectively, it was found that the Ebola outbreak that began in Guéckédou Prefecture in 2013 may have been detected earlier had community-based surveillance which employed syndrome specific criteria (here based on the WHO case definition for a suspect Ebola case) been in place. While the amount of data was limited, the results did highlight the potential value of community-based

surveillance for outbreak detection. If the objective of the surveillance system been to detect outbreaks, instead of detecting clusters of deaths with a similar profile, the surveillance system could have also been designed to detect "events" designated as important, as was developed and used with limited success during the 2013-2016 Ebola epidemic (Crowe *et al.*, 2015; Ratnayake *et al.*, 2016).

Alternatively, community-based syndromic surveillance provides a compromise between event based and general mortality surveillance. Syndromic surveillance has been used with success in Africa when surveying for Influenza-like illnesses in Senegal in primary health care centers (Thiam *et al.*, 2015). Disease trends could be monitored using this approach if longitudinal data is collected and syndromes of interest are chosen and defined in advance (Henning, 2004; Thiam *et al.*, 2015). An advantage to this approach is that it doesn't require use of verbal autopsy to determine cause of death and a list of syndrome groups based on ICD-9-CM codes is available (Centers for Disease Control and Prevention, 2003). Additionally, if implemented systematically in numerous areas in a country, it could provide data complimentary to that which is used to estimate country specific disease burden. Improving the data used to parameterize models which are used to describe country specific disease burden (GBD 2015 Mortality and Causes of Death Collaborators, 2016) could provide more accurate estimations rather than relying on data from vital registration systems in countries where they are weak or do not function. Unfortunately, surveillance carried out in small, focal areas like Guéckédou won't contribute much to informing the modeling. However, if implemented more systematically, the country specific estimates may improve while also allowing for a better understanding of community specific morbidity and mortality. Syndromic surveillance could also provide a method through which to monitor program impact by monitoring cause (syndrome) specific morbidity.

It could be argued that the simplicity of the system implemented in Guéckédou limited its intrinsic value. However, simple community-based systems can provide vital information that is not captured through health facility surveillance; 75% of all deaths reported through the surveillance system in Guéckédou reportedly occurred at home. Yet, we overestimated the number of deaths that could be expected to occur each month by basing our estimation on the national mortality rate. Consequently, although 43,000 individuals were under surveillance, our ability to calculate mortality rates and trends over time was hindered by the small numbers of deaths reported. There may have been two ways to overcome this difficulty, i) combining the community-based mortality data with that reported from the health facilities in the same sous-préfecture or ii) increasing the number of people under surveillance. Had we been able to calculate mortality rates, we would have been able to provide more robust estimates of intervention impact. While we do not suspect the results to be impacted by underreporting, had the resources been available we could have carried out a retrospective mortality survey in the sentinel sites to corroborate the data. We attempted to triangulate our data through a capture-recapture exercise and visited health facilities where deaths reported through the surveillance system were reported to have occurred. However we were not able to locate many of the reported deaths in the patient register. The explanations for this were varied however we suspected the problem to be one of registration and not one of misreporting by the community.

Community-based sentinel site or syndromic mortality surveillance can also be used in emergency

settings to guide humanitarian response (Bowden *et al.*, 2012; Caleo *et al.*, 2012). However cause of death ascertainment remains difficult. For surveillance systems with more resources, ascertainment of cause specific mortality could be improved through use of a standardized verbal autopsy (VA) questionnaire such as the 2014 WHO verbal autopsy tool. In addition to reducing the number of questions and time it takes to complete an interview, automated interpretation of the data (i.e. InterVA, SmartVA-Analyze) could simplify use of verbal autopsy. Data could be collected on Android devices through use of Open Data Kit (ODK) Collect or similar data collection software. Use of a standardized data collection tool and automated analysis would both standardize cause of death attribution and improve estimations of cause specific mortality. Automating data collection and analysis is likely to facilitate deployment of such systems in areas where there are limited numbers of physicians for questionnaire review. In addition to verbal autopsies, variations on a conventional autopsy exist however their applicability to community surveillance is limited as they generally require taking of biological samples (i.e. post-mortem biopsies) for further analysis, an activity that is likely to be met with resistance in the community.

If community surveillance data is collected in a timely manner through an electronic platform or SMS the data could easily be monitored regularly. In areas where electronic transfer of data is possible, centralized internet-based platforms could facilitate the design and deployment of data collection tools. These tools could be developed specifically for surveillance and targeted to the indicator of interest. Electronic data collection would allow for automation of significant parts of the system, removing the potential for human error in data entry and interpretation. Electronic reporting and internet-based platforms could facilitate data interpretation if programmed to perform appropriate statistical analyses which allow for reducing uncertainty and bias if estimating incidence from raw data. Electronic platforms could also facilitate understanding by incorporating project specific dashboards that automatically generate figures and maps. When monitoring trends over time, aberrations from “normal” incidence or detection of signals of interest could serve as alerts which trigger follow-up by a specialized team.

In countries where vital registration systems are functional and the population regularly seeks care at health facilities, the added value of community-based surveillance may be limited. However, in areas where vital registration systems do not function well, community surveillance data can provide insight into community-level morbidity and mortality that might go otherwise unreported. In emergency situations, community-based surveillance data can compliment data collected in health facilities and help inform operational decisions. What is the “right” surveillance system for each context? Unfortunately, as with malaria control, it seems there is no hard and fast rule. Instead, lessons learned from this and other experiences should inform the design of future systems for areas with limited resources. In resource limited settings, improving cause of death determination with less focus on verbal autopsy implementation and working to understand communities and their perception of illness to inform specific syndrome definitions should improve the quality of data collected.

8.4. Mathematical modeling during emergencies and beyond

Mathematical models have been increasingly used for epidemic forecasting and determining where to allocate resources (human and monetary) during an outbreak response. In an effort to gain exposure to

mathematical modeling, in Chapter 5 we demonstrate that stochastic malaria transmission models can not only be used to predict the impact of malaria control interventions on malaria case burden but can also predict of the effect of control effort cessation. By providing data, modeling forecasts can help advocate for sustaining or reinitiating control activities when there is pressure to reduce them.

Mathematical modeling can be used to quantify disease specific mortality at both a global and local levels in addition to quantifying impact and forecasting trends over time (GBD 2015 Mortality and Causes of Death Collaborators, 2016). Model accuracy depends on whether factors that lead to the disease specific outcome of interest are well described and accounted for. Malaria transmission models have been used to predict the impact of malaria interventions as advanced as vaccines (Smith *et al.*, 2006) while models for Ebola are relatively new in comparison. Indeed, prior to 2013, few Ebola-specific models existed. Yet, in the first 18 months of the 2013-2016 epidemic, over 66 mathematical modeling studies of the EVD epidemic were published in the peer-reviewed literature (Chretien, Riley and George, 2015). Many of these papers aimed to predict the trajectory of the epidemic and identify interventions that could be effective in reducing transmission; however, their utility at the time of publication and the number of cases they predicted varied widely.

Of the mathematical modeling papers published after declaration of the Ebola epidemic in 2014, 11 attempted to forecast the number of cases that would occur by the end of 2014 while some also projected into 2015 (Table 8-1). Similarities between the papers in Table 8-1, except for the WHO model, include their use of publicly available data which was in some way derived from the WHO or country specific Ministry of Health situation reports.

Table 8-1: Mathematical modeling papers that forecasted the number of Ebola cases in 2014 under a no change scenario.

Author	Country	Public	Model type	Cases predicted
*Drake et al.	L	Yes	Mechanistic	Over 100,000 by end of 2014
*Fisman et al.	GLS	Yes	Phenomenological	Over 25,000 by end of 2014
Kiskowski et al.	GLS	Yes	Mechanistic	11,519 on Dec 1, 2014
Lewnard et al.	L	Yes	Mechanistic	170, 996 (95%CI: 81,909-361,793) by Dec 15, 2014
*Meltzer et al.	LS	Yes	Mechanistic	550,000-1.4 million by Jan 20, 2015
Nishiura et al.	GLS	Yes	Phenomenological	77,181 to 277,124 by end of 2014
Pandey et al.	L	Yes	Mechanistic	24,920 (range: 15,710-39,580) by Dec 30
Towers et al.	GLS	Yes	Mechanistic	4,400 new EVD cases during the last half of September 2014
*WHO et al.	GLSN	No	Phenomenological	20,000 by November 2, 2014

The accuracy of the model forecasts varied considerably and none accurately predicted the number of cases at the end of December 2014. Highlighting the models indicated by an asterisk in table 8.1, in September 2014 the World Health Organization (the “WHO model”) predicted that more than 20,000

cases would occur by November 2, 2014 at which point about 13,000 had been reported (WHO Ebola Response Team, 2014). A worst-case scenario prediction made by the Centers for Disease Control and Prevention (the "CDC model") around the same time estimated between 550,000 to 1.4 million cases in Liberia and Sierra Leone by January 20, 2015 if no additional control measures were implemented (Meltzer *et al.*, 2015). In contrast, using approaches different to those taken by CDC and WHO, both Fisman et al. and Drake et al. predicted over 25,000 cases by the end of 2014 (Fisman, Khoo and Tuite, 2014; Drake *et al.*, 2015), levels that would not be reached until mid-2015.

A limitation common to most mathematical models is the quality and accuracy of the data used to parameterize them. Many approaches were taken to model the trajectory of the 2013-2016 Ebola epidemic. The variation in the forecasts reflects the global communities' uncertainty about Ebola transmission dynamics and the lack of empirical data on how control measures affect transmission. Additionally, the variation highlights the potential benefit of employing different models at different points in an Ebola outbreak. A consensus modeling group could be formed to improve Ebola transmission models for the future and respond to specific research questions using the strengths of different models. Elucidation of missing parameters or areas where data is missing could help define avenues for additional research. Research protocols could be developed presumptively for investigation during the next outbreak or developed for retrospective analysis of datasets that have yet to be explored. Improving model forecasts will support improved implementation of public health activities during outbreaks, particularly those that aim to reduce transmission.

Before the next outbreak occurs, response strategies can be considered and modeled according to numerous scenarios. Such strategies include incorporation of systematic antimalarial distribution to contacts of EVD patients as part of contact tracing activities alone and concurrent with Ebola vaccination. The incorporation of antimalarials could be particularly pertinent for children under 13 years of age for whom vaccination is not yet recommended. When taken correctly, the probability that vaccinated individuals develop malaria-related fever while developing immunity to Ebola and beyond to the first weeks of vaccination could be reduced. Simulations could investigate the use of ACTs such as DHA-PQ for their prolonged prophylactic period. When additional information is available on the Ebola inhibition properties of amodiaquine, the complementarity of MDA with ASAQ and Ebola vaccination could be investigated further. Potential benefits of distributing the first line antimalarial treatment during an MDA could include high acceptance of the strategy by the population as a result of their familiarity with the molecule. Additionally, there may be fewer refusals to participate and it may open the door for additional response activities. Additional models developed could incorporate behaviour change and population acceptance for and as a result of such activities and their impact on the uptake of control activities.

The impact of extending activities (MDA, vaccination for Ebola and malaria, etc) beyond immediate contacts to include entire villages or communities could be investigated for future outbreaks that take place in malaria endemic areas. Moving towards community-level coverage, could be used with both MDA of antimalarials, Ebola vaccination and potentially the malaria vaccine, RTS,S. Contact tracing and follow-up activities would remain focused on immediate contacts.

In the early stage of an Ebola outbreak the focus needs to be on getting ahead of the outbreak. The potential benefits of deploying additional strategies need to be weighed against the resources (human and financial) they would divert from controlling the outbreak. For outbreaks of extended duration, as in West Africa, additional resources need to be devoted to the response in order to address the longer term impact. Deployment of strategies to mitigate the indirect effects of Ebola during an active outbreak in addition to maintaining key response activities needs to be considered carefully. This could include ensuring EPI activities are maintained. As the dengue vaccine and RTS,S malaria vaccine become more common, ensuring continued administration of such vaccines could also work to reduce the probability that community members present with febrile illness which may be confused with Ebola. Modeling potential scenarios now can help us inform the steps taken and the interventions employed during the next Ebola outbreak. The types of interventions have to be adapted to the size and scale of the outbreak and the indirect effects not forgotten.

8.5. Conclusion

This thesis provides insight into aspects of malaria control in both normal and emergency situations. Our findings show that when implemented in program conditions there are limitations to the impact that traditional malaria control interventions will have on malaria parasite prevalence in hyperendemic settings, even as coverage increases. We also demonstrate the limited duration of control intervention impact in hyperendemic settings when stopped suddenly, and that malaria parasite prevalence quickly returns to pre-intervention levels. In areas like Guéckédou where health facility based surveillance is weak, community surveillance data can be used to monitor program impact and has the potential to detect outbreaks if the system is designed appropriately. Finally, we demonstrate that the population's acceptance of the deployment of a mass drug administration of malaria chemoprevention during an Ebola outbreak in Monrovia, Liberia was high and that it resulted in a reduction of the incidence of fever immediately after implementation.

Controlling malaria in both normal and emergency settings requires flexibility and a strong commitment of all organizations involved. Here we provide insights into malaria intervention implementation and impact in difficult settings. To improve the impact that control strategies have they need to be adapted to the micro-epidemiology of the area of intervention. To progress towards malaria control in hyperendemic settings it will be essential to develop new or modify existing strategies to address the disproportionately high malaria burden. These strategies should be monitored and evaluated in real time allowing for changes to strategy during implementation, as appropriate. Finally during outbreaks of Ebola virus disease that tend to occur in malaria endemic settings, it is important not to forget about the cases of fever going untreated while responding to the epidemic.

9. Recommendations and areas for future research

9.1. Malaria control activity implementation

- Instead of employing a one-size-fits-all approach, malaria control strategies should be designed to fit the local context and be informed by data from epidemiological and entomological investigations. Prior to or immediately during the first phase of implementation risk assessments should be carried out in order to elucidate the epidemiology of malaria in the area of intervention.

- Measuring the impact of new malaria control interventions or variations on existing interventions such as a IPTc with an extended age range, or administration of RTS,S through EPI programs will be key to providing an evidence base for future implementation. Both the immediate and long-term impact of new strategies on malaria incidence needs to be documented in addition to the impact of activity cessation, when appropriate. In addition to the direct effects of malaria interventions, the indirect effects on community transmission or potential age shifts of malaria incidence, particularly those targeted by interventions in the early years of life, should also be measured in terms of incidence and mortality.

- The impact of malaria control interventions that have been studied and demonstrated in trial settings may lead to unrealistic expectations for deployment in program conditions. Consequently, the impact of interventions deployed in program conditions should be systematically monitored and evaluated in order to provide a realistic estimate of impact at scale. Lessons learned during implementation should be documented with enough detail to allow for replication of activities, not just documentation of research. Accordingly, documentation should improve deployment in other areas/by other actors and define avenues for further investigation.

- During emergencies in malaria endemic settings sustaining control efforts is important insofar as possible. If the system is too overwhelmed or under resourced, after the emergency ends, activity reinstatement needs to be prioritized in order to mitigate the risk of resurgence and to address any decreases in population access to health facilities during the emergency.

9.2. Surveillance in low resource settings

- In areas where health actors implement activities to complement Ministry of Health activities for a long duration, the systematic implementation of community-based surveillance systems should be strongly encouraged. If carried out in collaboration with public health facilities, particularly when utilizing syndromic surveillance, the system's ability to generate cause specific mortality estimates may be increased. Collaboration with public health facilities may also allow for verification of community data using health facility registers.

- Implementation of surveillance activities could begin in areas where the population has poor or limited access to public health facilities. These are generally vulnerable groups that may not seek care at health facilities as their first choice and instead visit traditional healers. In such

communities, incorporation of traditional healers as part of the surveillance system should also be considered.

- Syndromic surveillance could not only capture malaria related morbidity and mortality but also control and limit disease outbreaks through early detection in stable, low resource settings, and during emergencies. Syndromes of interest should be selected carefully and alert thresholds established in order to ensure resources are not used unnecessarily. Collaboration with public health facilities would encourage local engagement and facilitate development of response teams to investigate alerts generated by the system. Further investigation could include use of available RDTs (malaria, dengue, cholera, Ebola, etc) as appropriate for initial screening. When acceptable, this could be followed by microbiological investigation of the suspect cases where possible (i.e. stool sample in the case of suspect cholera) to inform an appropriate response.

- Implementation of syndromic surveillance needs to be systematically documented with enough detail to allow the surveillance system to be replicated in different contexts.

9.3. Malaria chemoprevention during Ebola outbreaks

- The deployment of MDAs during prolonged Ebola epidemics could be used to mitigate the number of malaria related fevers that present to and are admitted to ETCs. The ACT of choice should be informed by i) the duration of post-administration protection from infection and ii) scientific evidence regarding the effect (experimental or demonstrative) of the accompanying drug on the Ebola virus. ASAQ may be preferable if the Ebola inhibitory properties of amodiaquine are confirmed.

- During Ebola outbreaks of both short and long duration, administration of malaria chemoprevention to all contacts of individuals with confirmed Ebola virus infection should be considered. Incorporation of this activity into contact tracing activities should ensure at least one daily dose is directly observed. Expansion of this strategy to entire households or communities should be explored and Ebola vaccination included, when available.

9.4. Avenues for future research

- Antimalarial distribution to contacts for prophylactic use may become a standard activity in future Ebola outbreaks. Currently available antimalarials should be screened for Ebola virus inhibition properties. Screening results should be considered along with the length of protection from malaria infection they provide in order to determine the best antimalarial for distribution.

- In vitro experiments have showed the efficacy of amodiaquine in inhibiting Ebola virus activity however in vivo studies using an appropriate animal model are needed to confirm this. Subsequent population based studies will be needed to confirm the relationship if such strategies are implemented in future outbreaks.

- Implementation of any community-based surveillance system comes at a financial cost. Further research is needed in order to evaluate the benefit of introducing community-based syndromic

surveillance versus the cost of reinforcing health facility based surveillance.

- Syndromic community-based surveillance is likely to be carried out by community health workers or individuals with low levels of education. Qualitative research should be carried out in the community prior to implementation to better understand how the community perceives and describes the illnesses of interest. Community feedback could inform definitions of the syndromes of interest.

- Until now the RTS,S malaria vaccine has been investigated for its direct effect on malaria related morbidity and mortality when deployed as a unique intervention. The incremental impact of RTS,S malaria vaccine on reducing malaria related morbidity and mortality when deployed in conjunction with traditional malaria control interventions needs to be documented. These results will inform implementation as part of a malaria control package outside of trial conditions. In emergency situations, vaccination of high risk populations (migrants, IDPs, etc) should be considered, especially if relocating from areas of low to high endemicity.

- Ring vaccination with Ebola vaccine may only be operationally feasible when contact tracing is functional and the number of cases is small. When the ability to contact trace is limited, vaccination according to geographic area (i.e. communities/neighborhoods where the cases are found) may be appropriate. In such cases, the efficacy of ring vaccination when deployed in such a way will need to be investigated.

10. References

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11. Appendices

Appendix 1: Sous-préfecture specific cross-sectional data points used for model validation and fitting of OpenMalaria parameters.

	Guéckédou City	Tekoulo	Guendembou	Koundou
Malaria parasite prevalence				
April 2011	67.2% (2.5-71.9)	68.3% (62.7-73.9)	70.6% (64.9-76.4)	71.8% (67.3-76.4)
August 2011	59.0% (54.5-63.5)	72.8% (69.8-75.9)	73.1% (68.6-77.5)	73.4% (70.3-76.4)
February 2012	43.0% (39.2-46.7)	58.9% (54.8-62.9)	60.5% (57.0-64.0)	65.0% (61.3-68.8)
August 2012	57.6% (53.3-61.9	60.6% (57.3-63.9)	66.1% (63.0-69.2)	77.7% (74.8-80.5)
February 2013	43.4% (40.0-46.8)	52.3% (48.4-56.2)	59.2% (54.5-63.8)	64.2% (60.4-67.9)
LLIN coverage pre and post distribution				
February 2012	46.1 (37.5-54.7)	47.1 (37.2-57.0)	52.7 (41.9-63.5)	60.4 (51.2-69.6)
August 2012	86.1 (79.2-92.9)	90.5 (83.6-97.3)	95.0 (92.3-97.7)	25.0 (16.2-33.7)
Proportion of fevers receiving treatment				
April 2011	8.9 (11.2-6.6)	4.3 (6-2.6)	6.7 (10.1-3.3)	6.4 (8.9-3.9)
February 2013	25.2 (32.7-17.7)	14.8 (20.2-9.4)	17.0 (21.7-12.3)	10.9 (25.4-6.4)

Appendix 2: Scenario variables and parameter values by sous-préfecture

	Treatment access pre intervention	Treatment access during intervention	EIR	EIR Outdoor during intervention	LLIN coverage during intervention	Proportion active outdoor biting mosquitoes during intervention	Seeds
GKD City							
Intervention	15	38	25	2,5,10,50,100	83.8	70	5
Counterfactual	15	1	25	n/a	0	n/a	5
Guendembou							
Intervention	1	50	64	n/a	93	60, 70, 80	5
Counterfactual	1	1	64	n/a	0	n/a	5
Tekoulo							
Intervention	1	25	32	n/a	90	60,70,80	5
Counterfactual	1	1	32	n/a	0	n/a	5
Koundou							
Counterfactual	1	1	64	n/a	0	n/a	5