Malaria epidemiology and key control interventions in the Democratic Republic of Congo

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The Dean of Faculty

To the Almighty Lord

To my parents

To my lovely wife Lisa and my adorable sons Dylan David and Allan Daniel

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List of Acronyms

ACT	Artemisinin-based Combination Therapy;
ADB	Asian Development Bank
AL	Artemether plus Lumefantrine
ALU	Artemether plus LUmefantrine (ALU).
AS-AQ	ArteSunate plus AmodiaQuine
ANC	Ante Natal Care
CDC	Centre for Disease Control
CI	Confidence Interval
CRF	Case Report Form
DFID	Department For International Development
DHIS2	District Health Information System 2
DHS	Demographic and Health Survey
DRC	Democratic Republic of the Congo
EKBB	EthikKommission Beider Basel
GF	Global Fund
GFATM	Global Fund to fight AIDS TB and Malaria
GIS	Geographic Information System
GPS	Global Positioning System
HA	Health Area
Hb	Haemoglobin
HMIS	Health Monitoring Information System
HZ	Health Zone
IDW	Inverse Distance Weighting
INFORM	Information for Malaria
IPTp	Intermittent Preventive Treatment in pregnancy
ITN	Insecticide-Treated Net
IV	Intravenous
JICA	Japanese International Cooperation Agency

KOICA	Korean International Cooperation Agency
KSPH	Kinshasa School of Public Health
LLIN	Long Lasting Insecticidal Net
MAP	Malaria Atlas Project
MATIAS	MAlaria Treatment with Injectable ArteSunate
MICS	Multiple Indicators Cluster Survey
MIS	Malaria Indicators Survey
MMV	Medicines for Malaria Venture
MMWR	Morbidity and Mortality Weekly Report
MoH	Ministry of Health
MSH	Management Science for Health
NGO	Non-Governmental Organization
NMCP	National Malaria Control Programme
NMSP	National Malaria Strategic Plan
OR	Odds Ratio
PCT	Parasite Clearance Time
PMI	President's Malaria Initiative
PNLP	Programme National de Lutte contre le Paludisme
PSI	Population Services International
RDT	Rapid Diagnostic Test
SP	Sulfadoxine-Pyrimethamine
UK	United Kingdom
UNICEF	United Nations International Children's Emergency Fund
USAID	United States Agency for International Development
USD	United States Dollar
WHO	World Health Organization

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Summary

Malaria remains a major global public health problem causing over 400,000 deaths annually, mainly among children in sub Saharan Africa. The Democratic Republic of Congo (DRC), the second largest and the fourth most populated country in Africa, is one of the most malarious countries in the world. An estimated 97% of its 71 million inhabitants live in high transmission areas. Together with Nigeria, DRC accounts for about 40% of the total estimated malaria cases worldwide, and for more than 35% of the total estimated malaria deaths. The national malaria control programme (NMCP) is committed to reducing malaria and the associated morbidity and mortality in DRC through the implementation of specific proven interventions. The aim of this thesis was to contribute to the improvement of malaria control activities in the DRC, through the provision of new evidence on the epidemiology of malaria and key control interventions, to support evidence-based policy making.

Kinshasa, the capital of DRC, has been expanding very rapidly in the past 20 years (going from an estimated 3 million inhabitants to a current estimate of 10 million) and available evidence has shown that urbanization had a significant impact on the ecosystems and disease patterns, including malaria. However, in the context of scaling up of interventions, data on malaria distribution in Kinshasa are scarce; the latest epidemiological study was conducted in 2000. We conducted two cross-sectional surveys to update malaria risk stratification in Kinshasa, identify factors contributing to the distribution patterns, and update information on malaria control activities. Geo-referenced data for key parameters were mapped at the level of the health area (HA) by means of a geographic information system (GIS). The overall standardized malaria prevalence was 11.7%, showing a decline compared to previous studies. The spatial distribution showed higher malaria risk in the peri-urban areas compared to the more urban central areas. Compared to the Demographic and Health Survey 2007 (DHS-DRC, 2007), coverage of malaria control measures showed considerable progresses in a pattern inversely proportional to the malaria risk distribution: low LLIN coverage in the peri-urban areas and higher coverage in the centre of the city. The analysis of drivers of malaria in both children less than five years and individuals aged older than five years highlighted the variation of the effect of age and reported history of fever by level of endemicity. In low endemicity strata, a shift in the peak of malaria prevalence towards the older age groups was observed, while the history of fever in the last two weeks increased the risk of malaria in all age groups and regardless of the level of endemicity. Individual use of LLIN was associated

with reduced risk malaria infection among children less than five years. The risk of malaria was lower among children less than five years of the wealthiest socio economic group. This risk map constitutes a strong basis for the planning of malaria control interventions in Kinshasa.

Following the publication of the results of two large open-label randomized controlled trials (SEAQUAMAT, AQUAMAT) that demonstrated the benefits of injectable artesunate over quinine in the treatment of severe malaria, and in line with the updated WHO guidelines, the NMCP changed the policy for treating severe malaria in children and adults from injectable quinine to injectable artesunate in 2012 A transition period of 3 years was set, including the need for operational research to support the national deployment. We conducted an operational comparative study of quinine and injectable artesunate for the treatment of severe malaria (MATIAS study) with the aims of assessing the operational feasibility of this introduction, providing national cost estimates, and assessing the acceptability of the new drug among both health care providers and patients. Our findings showed that all the operational parameters measured (time to discharge, interval between admission and the start of intravenous treatment, personnel time spent on patient management, and parasite clearance time) were equal or in favour of injectable artesunate. The mean total cost per patient treated for severe malaria in hospitals and health centres was also lower with injectable artesunate. There was a high acceptability by both health care providers and patients. These findings support the rapid scale up of injectable artesunate in the country.

Mass distribution campaigns of LLIN are accepted as the best approach to rapidly increase coverage and use. To promote correct and consistent use of distributed LLIN, the WHO recommends the integration of door-to-door visits with “hang up” activities into mass distribution campaigns. Integrating hang-up activities requires obviously additional human and financial resources. Since published data on the effects and cost of door-to-door visits with hang up activities on LLIN use are scarce, more evidence is still required to optimize the efficiency of national LLIN programmes. We used a LLIN mass distribution campaign in the province of Kasai Occidental that used two different approaches, a fixed delivery strategy and a door-to-door strategy including hang-up activities, to evaluate comparatively household LLIN ownership, access and individual use, and examine factors associated with LLIN use. We also compared the two delivery strategies with regard to the LLIN coverage achieved and the cost of implementation. Results showed that the mass distribution campaign was effective at achieving high LLIN ownership and use. Having sufficient numbers of LLIN to cover all

residents in the household was the strongest determinant of LLIN use. Compared with the door-to-door strategy, the fixed delivery strategy achieved a higher LLIN coverage at lower delivery cost, and seems to be a better LLIN delivery option in the context of DRC.

Information on the number and distribution of malaria cases and deaths is fundamental for the design, implementation and evaluation of malaria control programmes. In many endemic areas, health facility-based data remain the only consistent and readily available source of information on malaria. Because of known inherent limitations, this source of date can underestimate the total burden of disease by a considerable fraction. In DRC, the use of rapid diagnostic tests has been expanded since 2010, leading to a marked increase in suspected malaria cases receiving a diagnostic test. Together with other management measures, this should improve the quality of the incidence rates obtained through the Health Monitoring Information System (HMIS). Based on household survey data, the Malaria Atlas Project (MAP) of the University of Oxford has produced estimates of clinical incidence of malaria for the years 2000-2015 for all African countries, providing something like a reference value on incidence rates. We compared the malaria incidence rates obtained from the HMIS data in the DRC from 2010 to 2014 to the MAP modelled incidence rates for the same time period, in order to assess the relative reporting of the HMIS system. Our preliminary results showed that due to the expansion of parasitological diagnosis, the number of confirmed malaria cases reported and hence the fraction of incident cases captured by the HMIS data had increased substantially over time. By contrast, the number of incident malaria cases predicted by the MAP model had progressively decreased. Because of inconsistencies in reporting, it has been difficult to establish trends in malaria morbidity, but the unchanged high values of test positivity rates suggest malaria transmission remains high and stable over time.

Résumé

Le paludisme reste un problème mondial de santé publique causant plus de 400,000 décès par an, essentiellement chez les enfants en Afrique sub-saharienne. La République Démocratique du Congo (RDC), le deuxième plus vaste et le quatrième plus peuplé pays d'Afrique, est l'un des pays qui paie le plus lourd tribut au paludisme dans le monde. Environ 97% des 71 million d'habitants de la RDC vit dans des régions à forte transmission du paludisme. Avec le Nigeria, la RDC représente près de 40% de tous les cas de paludisme recensés dans le monde et plus de 35% de tous les décès. Le Programme National de Lutte contre le Paludisme (PNLP) est engagé à réduire la morbidité et la mortalité palustres en RDC à travers la mise en œuvre d'interventions spécifiques. L'objectif de cette thèse était de contribuer à l'amélioration des activités de lutte contre le paludisme en RDC en apportant un complément d'évidence sur l'épidémiologie du paludisme ainsi que sur les interventions clés pour une prise de décision basée sur les évidences.

Kinshasa, la capitale de la RD C, a connu une expansion rapide dans les 20 dernières années (de 3 millions d'habitants à 10 millions) et les évidences ont montré que l'urbanisation a un impact significatif sur l'écosystème et la transmission des maladies, dont le paludisme. Cependant, dans un contexte de mise à échelle des interventions, les données sur la distribution du paludisme à Kinshasa sont rares ; les dernières études épidémiologiques datent des années 2000. Nous avons conduit deux études transversales pour identifier les facteurs contribuant à la distribution observée et mettre à jour les informations sur les activités de lutte contre le paludisme. Les données géo-référenciées sur les paramètres-clé ont été cartographiées au niveau des Aire de Santé (AS) au moyen d'un système d'information géographique. La prévalence standardisée du paludisme était de 11.7%, montrant une baisse comparée aux études précédentes. La distribution spatiale a montré que le risque du paludisme était plus élevé dans les zones périurbaines comparées aux zones plus urbanisées du centre. Comparé à l'enquête démographique et de santé 2007, la couverture des mesures de contrôle a montré des progrès considérables, avec une tendance opposée au risque d'infection : une couverture en moustiquaire faible dans les zones périurbaines et élevée dans le centre de la ville. L'analyse des déterminants du paludisme chez les enfants de moins de 5 ans et les sujets de plus de 5 ans a révélé la variation de l'effet de l'âge et de l'histoire de fièvre par niveau d'endémicité. Dans la strate de faible endémicité, nous avons observé un shift du pic de prévalence du paludisme vers les groupes d'âge plus élevés, alors que

l'histoire de fièvre durant les 2 dernières semaines augmentait le risque du paludisme dans tous les groupes d'âge et indépendamment du niveau d'endémicité. L'utilisation de la moustiquaire était associée à un risque réduit du paludisme chez les enfants de moins de 5 ans. Le risque du paludisme était plus faible chez les enfants du niveau socio-économique le plus riche.

Suivant la publication des résultats de deux grands essais randomisés (SEAQUAMAT, AQUAMAT) qui ont démontré la supériorité de l'artesunate injectable comparé à la quinine dans le traitement du paludisme sévère, et en ligne avec les recommandations de l'OMS, le PNLP a changé la politique de prise en charge du paludisme sévère en RDC en 2012 de la quinine à l'artesunate injectable. Une période de transition de 3 ans a été instaurée incluant un besoin en recherche opérationnelle pour appuyer le déploiement du nouveau médicament à l'échelle nationale. Nous avons conduit une étude comparative opérationnelle entre la quinine et l'artesunate injectable avec pour but d'évaluer la faisabilité de l'introduction de l'artesunate injectable en RDC, fournir des estimations des coûts, et évaluer l'acceptabilité du nouveau médicament par les prestataires et les patients. Nos résultats ont montré que tous les paramètres opérationnels mesurés (durée d'hospitalisation, intervalle entre l'admission et le début du traitement, temps du personnel pour la surveillance du patient, temps de clearance parasitaire) étaient en faveur de l'artesunate. Le coût total moyen par patient traité dans les hôpitaux et les centres de santé était aussi plus bas avec l'artesunate injectable. Ces résultats ont plaidé pour une mise à échelle rapide de l'artesunate injectable dans le pays.

Les campagnes de distribution de masse des moustiquaires imprégnées d'insecticide à longue durée d'action (MILD) sont reconnues comme la meilleure approche pour augmenter rapidement la couverture et l'utilisation de la MILD. Pour promouvoir l'utilisation correcte et systématique de la MILD, l'OMS recommande l'intégration des visites porte-à-porte avec des activités de «hang-up» dans les campagnes. L'intégration de ces activités requiert des évidemment des ressources humaines et financières additionnelles. Actuellement, les publications sur l'effet de ces activités sur l'utilisation de la MILD ainsi que le coût d'implémentation sont peu nombreuses. Plus d'évidences sont nécessaires pour permettre au PNLP de distribuer les MILD de la manière la plus efficiente et efficace possible. Nous avons utilisé le cadre de la campagne de distribution des MILD dans la province du Kasaï Occidental avec deux stratégies de distribution, la stratégie fixe et le porte à porte avec activités de «hang-up», pour évaluer l'impact sur la possession, l'accès et l'utilisation de la MILD, et évaluer les facteurs associés à l'utilisation de la MILD. Nous avons aussi comparé

les deux stratégies en rapport avec le niveau de possession en MILD atteint, ainsi que le coût d'implémentation. Les résultats montrent que la campagne a permis d'atteindre des niveaux élevés de couverture et d'utilisation de la MILD. Avoir un nombre suffisant de MILD pour couvrir tous les membres du ménage était le plus important déterminant d'une bonne utilisation de la MILD. Comparée à la stratégie porte à porte, la stratégie fixe a atteint des couvertures plus élevées à plus faible cout. Elle semble donc être la meilleure option de distribution des MILD dans le contexte de la RDC.

Connaitre le nombre et la distribution des cas et des décès du paludisme est fondamental pour la mise en œuvre et l'évaluation d'un programme de lutte contre le paludisme. Dans plusieurs pays endémiques, les données des formations sanitaires demeurent la seule source d'information sur le paludisme rapidement accessible. A cause des limites y inhérentes, cette source de données peut sous-estimer d'une fraction considérable le fardeau total de la maladie. En RDC, l'utilisation des tests de diagnostic rapide a été étendue depuis 2010, entrainant une augmentation du nombre de cas suspects de paludisme testés. Avec d'autres mesures de gestion améliorée, ce développement a le potentiel d'améliorer la qualité des taux d'incidence obtenus à travers le système national d'information sanitaire (SNIS). A partir des données d'enquêtes ménages, le Malaria Atlas Project (MAP) de l'université d'Oxford a produit des estimations de l'incidence du paludisme clinique pour tous les pays africains pour les années 2000-2015, offrant au moins une valeur de référence permettant d'évaluer les taux d'incidence rapportés par le SNIS. Nous avons comparé les taux d'incidence obtenus des données SNIS à ceux projetés par le projet MAP pour la RDC de 2010 à 2014. Les résultats préliminaires ont montré que suite à l'expansion du diagnostic parasitologique, le nombre de cas confirmés rapportés et partant la fraction de cas incidents captée par le SNIS a augmenté significativement avec le temps, alors que le nombre de cas projetés par le projet MAP a diminué. A cause des incohérences dans les données, il a été difficile d'établir des tendances claires pour la morbidité palustre, mais les valeurs constantes et élevées des taux de positivité suggèrent que la transmission du paludisme reste forte et stable dans le temps.

1 Introduction

1.1 Malaria parasite and disease

Malaria is a protozoan parasitic infection caused by a single-celled parasite of the genus *Plasmodium.* Four species have been identified to be responsible for human malaria: *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae* and *Plasmodium ovale.* Recently, *Plasmodium knowlesi*, a simian parasite, was found to also occur in humans in Asia (Cox Singh *et al.* 2008). *P. falciparum* and *P. vivax* are the most important parasites to humans. *P. falciparum* is the main cause of malaria morbidity and mortality and it is the most prevalent species in sub-Saharan Africa (Marsh *et al.* 1995).

The parasite life cycle is complex and unfolds in two stages: an asexual reproduction stage in the human host and a sexual reproductive stage inside the mosquito definitive host. When an infected *Anopheles* mosquito bites a human, the parasite is introduced in the body in the form of a sporozoite. Shortly after inoculation into the blood circulation, sporozoites enter hepatocytes where they develop asexually (schizogony) into pre-erythrocytic schizonts. *P. vivax* and *P. ovale* have a dormant stage, named hypnozoite that may remain in the liver for many years before resuming the pre-erythrocytic schizogony, resulting in relapses of malaria infection. A pre-erythrocytic schizont contains thousands of small offsprings (merozoites) which are released into the blood stream and which invade new red blood cells. Within the erythrocyte, the merozoite develops asexually through the ring, trophozoite and schizont stages (erythrocytic schizogony). The infected erythrocyte eventually ruptures and releases the newly formed merozoites that invade new erythrocytes. After some times, a small proportion of merozoites differentiate into male or female gametocytes, which will be taken up by the mosquito in her blood meal. In the gut of the mosquito, male and female gametocytes will fuse (sexual reproduction) to form a zygote. The zygote matures into new sporozoites which then migrate to the salivary glands of the female *Anopheles* mosquito, ready to be expelled when the mosquito takes the next blood meal.

The massive destruction of erythrocytes associated with the accumulation of toxic wastes in the blood leads to the clinical symptoms of malaria. Depending on many factors including host/parasite genetics, age of the patient and intensity of transmission, clinical presentation of malaria varies from asymptomatic to a severe or even fatal condition (Reyburn *et al.* 2005).

Uncomplicated malaria is characterized by non specific symptoms including fever and any of the following symptoms: headache, body and joint pains, cold, shivering, occasionally diarrhoea, nausea, vomiting, splenomegaly (Warrell *et al.* 2002). The clinical manifestations of severe/complicated malaria result from vital organ dysfunctions. They include cerebral malaria which is associated with impairment of consciousness, abnormal behaviour, seizures, coma or other neurological abnormalities; severe anaemia; acute respiratory distress syndrome; prostration; shock; acute kidney injury; clinical jaundice; abnormal bleeding (WHO 2013a).

1.2 Global malaria distribution, burden and population at risk

Malaria is a major global public health problem and a leading cause of morbidity and mortality in many countries. According to the World Health Organization (WHO), in 2015 approximately 3.2 billion people - nearly half of the world's population - were at risk of malaria and 97 countries and territories had ongoing malaria transmission. There were globally an estimated 214 million new malaria cases and 438,000 deaths (WHO 2015b). Although this represents a decrease in malaria case incidence and mortality of 37% and 60% since the year 2000, the African Region continues to experience the heaviest malaria burden. About 88% of all malaria cases and 90% of malaria deaths are estimated to have occurred in the WHO African Region, mainly in children under 5 years. The Democratic Republic of Congo (DRC) and Nigeria together account for more than 35% of the total of estimated malaria cases and deaths (WHO 2015b).

Malaria is linked with poverty in a vicious circle, as higher case incidence and mortality rates are reported in countries with lower gross national income per capita, and the highest burden of disease is shouldered by resource constrained settings. Malaria is thought to be responsible for a 1.3% reduction in economic growth in affected countries (Sachs *et al.* 2002). The disease may account for as much as 40% of public health expenditures, and households in Africa lose up to 25% of their income to the disease (RBM 2000a; RBM 2000b).

In 2015, 15 countries mainly in sub Saharan Africa accounted for 80% of malaria cases and 78% of deaths globally. In these countries, the decline in malaria incidence was slower than in other countries. The slower reduction in malaria in high burden countries is a challenge that needs to be addressed if global progress is to be achieved (WHO 2015b).

Lowering malaria burden in sub Saharan Africa may pave the way for economic growth, both at household level and at large scale by the reallocation of public health expenditure to other parts of the health system.

1.3 Malaria vector

Malaria parasites are transmitted by female mosquitoes belonging to the genus *Anopheles*. There are about 400 species of *Anopheles* mosquitoes. Approximately 60–70 species worldwide can transmit malaria; of these, about 40 are vectors of major importance (Bruce-Chwatt 1985; Hay *et al.* 2010). The main properties of mosquitoes that influence their ability to transmit malaria efficiency are: (1) the susceptibility to malaria parasites; some vectors transmit all *Plasmodium* species equally well, while others are somewhat specific; (2) the longevity, expressed as the probability that a mosquito will survive through one day; (3) anthropophily, defined as the preference of mosquitoes for human blood; (4) mosquito population density. The main properties of vectors that are important for vector control are: (1) exo or endophagy, i.e. preference to feed outside or inside houses; (2) exo- or endophily, i.e. preference to rest outdoor or indoor during blood digestion; (3) anthropophily or zoophily; (4) biting time; and (5) predilection to rest at a particular height on a wall. The *Anopheles gambiae* complex in Africa includes seven species, of which *Anopheles gambiae sensu stricto and Anopheles arabiensis* are the most important vectors. *Anopheles funestus* is probably the best malaria vector because of its close association with humans. These species combine high parasite susceptibility, a high daily survival rate, anthropophily and the ability to use different types of breeding sites. On the other hand, the indoor biting and resting characteristic of these vectors makes them susceptible to indoor vector control measure using insecticides (i.e treated mosquito nets and indoor residual spraying).

1.4 Malaria prevention

The primary focus of malaria prevention is to reduce contacts between mosquitoes and human hosts, largely through vector control methods. Currently, by far the most effective measures of controlling malaria transmission are Long-Lasting Insecticidal Nets (LLIN) and Indoor Residual Spraying (IRS). LLINs reduce human vector contact at individual level via the physical barrier they provide, and also via the repellency of the insecticide imbedded or bound to its fibers. LLINs also kill mosquitoes in large numbers, thus reducing their

population density through reduced longevity. In addition to the individual protection for net sleepers, LLINs provide a community effect by which the overall transmission reduction offers protection from malaria infection even to those not sleeping under a net, particularly when use rates are high (Binka *et al.* 1998; Hawley *et al.* 2003; Killeen *et al.* 2007). Evidence of the efficacy of insecticides treated nets has been established in various large randomized trials, (D'Alessandro *et al.* 1995; Binka *et al.* 1996; Phillips-Howard *et al.* 2003; Ter Kuile *et al.* 2003) summarized in a Cochrane Review showing a substantial decrease in the occurrence of clinical cases of malaria by about 50% and child mortality by about 20% (Lengeler 2004). These results laid the foundation for the scale-up of LLINs as the primary method of vector control. Over the USD 1.6 billion spent in 2014 on malaria control commodities, LLIN accounted for 63% of total expenditure with 189 million nets delivered (WHO 2015b). Although the number of distributed LLINs is still insufficient to achieve universal coverage in all endemic settings, the current success in malaria control owes a lot to the massive rollout of LLINs and other effective prevention and treatment tools. LLINs have been estimated to contribute about 70% to the decline in malaria prevalence, and 70% of the 6.5 million clinical malaria cases averted in Africa from 2000 to 2015 (Bhatt *et al.* 2015). However, these gains are threatened by the development and spread of insecticide resistance in many countries (Coetzee *et al.* 2006; Ranson *et al.* 2011). This situation calls for urgent and coordinated action to monitor the spread of resistance, maintain effectiveness of current vector control interventions and develop new and innovative vector control tools (WHO 2012a; Hemingway *et al.* 2016).

1.5 LLIN distribution channels

To rapidly and equitably reach universal coverage, LLINs are mostly distributed through mass distribution campaigns designed to reach the entire population. Based on an agreed average LLIN lifespan of 3 years, mass distribution campaigns are repeated every 3-4 years. These campaigns have proven to be highly cost-effective in quickly achieving high coverage in countries where they have been implemented (Willey *et al.* 2012). However, under field conditions LLINs durability is highly variable, with a gradual process of loss beginning immediately after a campaign (Kilian *et al.* 2008; Kilian *et al.* 2011; Allan *et al.* 2012; Massue *et al.* 2016). Moreover, during the interval between campaigns, new sleeping spaces are created as new children are born or people move. The result is that repeated campaigns cannot maintain consistently high coverage and the WHO recommends therefore that mass

distribution campaigns be complemented by continuous or routine distributions through multiple channels" in order to maintain universal coverage (WHO 2013b). These continuous distribution channels include antenatal consultations, immunization and child health clinics, school based distribution, social marketing, commercial sales and other channels currently under consideration.

Although mass distribution campaigns have been widely accepted as the best approach to rapidly increase ITN coverage, there is a gap between LLIN ownership and use, mainly attributed to the lack of ability or willingness to hang the LLIN (Rickard *et al.* 2011; MacIntyre *et al.* 2012; Bowen 2013) . To promote correct and consistent use of LLIN, door-to-door visits with "hang up" and interpersonal communication activities have been integrated in to LLIN mass distribution campaigns, with varying effects on LLIN ownership and use (Thwing *et al.* 2008; Thawani *et al.* 2009; MacIntyre *et al.* 2012; Smith Paintain *et al.* 2014; Zegers de Beyl *et al.* 2016). Including hang-up activities requires additional human and financial resources, with implications on the cost of implementation. Published data on the effects of door-to-door visits with hang up activities are limited. A recent cluster randomised controlled trial conducted in Uganda showed that door-to-door visits and additional hang up activities did not provide any additional impact on net use and were therefore not cost-effective (Kilian *et al.* 2015). As funding for malaria control interventions might become more restricted in the future (WHO 2012b), more evidence is needed to support national programmes in delivering LLIN as efficiently and effectively as possible.

1.6 Malaria treatment: severe malaria

Severe malaria is the most serious form of *Plasmodium falciparum* infection, and it can be fatal in the absence of prompt recognition of the disease and appropriate patient management (WHO 2013a). Reducing this burden is currently the highest priority for malaria control, as evidenced by the Roll Back Malaria (RBM) target of near-zero deaths by 2015 (Roll Back Malaria Partnership 2011). For many decades, quinine has been the mainstay for the treatment of severe malaria. Two large open-label randomized controlled trials conducted in malaria endemic countries in Southeast Asia (SEAQUAMAT) and in Africa (AQUAMAT), as well as additional small trials, demonstrated the benefits of injectable artesunate compared to quinine for the treatment of severe malaria in both children and adults (Dondorp *et al.* 2005; Dondorp *et al.* 2010; Sinclair *et al.* 2012).

These results with a high quality of evidence led to a rapid change in the WHO guidelines for the treatment of severe malaria (WHO 2011b). WHO now recommends injectable artesunate for the treatment of severe malaria in children and adults and countries are adopting the new policy. However, because of reported cases of delayed anaemia associated with the use of injectable artesunate (Rolling *et al.* 2013; CDC 2013; Rolling *et al.* 2014), the long term safety profile of the drug needs still needs to be monitored.

In early 2012, following the new WHO guidelines, the National Malaria Control Programme (NMCP) of the Democratic Republic of Congo (DRC) changed the national policy for the treatment of severe malaria in both children and adults from intravenous quinine to injectable artesunate (PNLP 2012). A transition period of three years was set to allow clinical and operational adaptations. Operational research to establish the feasibility and acceptability of the new drug in the context of the routine care is needed to support this policy change.

The cost effectiveness of artesunate in the management of severe malaria has been shown in modelling studies, with an incremental cost per death averted of approximately US$150 (Lubell *et al.* 2009; Lubell *et al.* 2011). Cost estimates for the DRC are lacking and studies are required to establish procurement and operational costs.

1.7 The Democratic Republic of Congo: administrative and health organisation

The Democratic Republic of the Congo (DRC) is located in central Africa and is the second largest country by area in Africa (after Algeria). With a surface area of 2.345.000 km^2 it is the equivalent of two-thirds of the European Union. The country shares 9.165 km of border with nine countries, and it is bordered by the Atlantic Ocean to the west. With an estimated population of 71 million people (National Statistic Institute 2015), the majority of whom are living in rural areas, the DRC is the fourth most populated country in Africa (after Nigeria, Ethiopia and Egypt). Current population estimates are derived from the last census conducted in 1984 - which recorded 30.7 million inhabitants - by applying a fixed yearly growth rate (3%) without consideration of changes in fertility, mortality or displacement.

The DRC lies on the equator between latitudes 6°N-14°S, with one third of the landmass to the north and two thirds to the south. Temperatures are hot and humid in the central region, cooler and drier in the southern highlands, and cooler and wetter in the eastern highlands. Low ambient temperatures affect the likelihood of malaria transmission in mountainous regions (about 3% of total area).

Administratively, the DRC is a highly decentralized state which until recently had 11 provinces. Following a constitutional reform in 2006, the country has engaged in reform that led to the creation of 26 provinces (Figure 1-1). Kinshasa, the capital city, is a megacity of more than 10 million inhabitants and is divided into 24 communes.

The DRC is one of the poorest countries in the world, ranking second from the bottom (186th out of 187 countries) in terms of the 2014 human development index (HDI) (UNDP 2014). An estimated 80% of the population lives on less than $1 per day and capita gross national income was at US$ 410 in 2015 (World Bank 2016). According to the 2013-14 Demographic and Health Survey (DHS), the under-five mortality rate is currently 104/1,000 live births, a significant reduction from the previous rate of 158/1,000 in 2010 (UNICEF 2010).

The health system organization in DRC has a pyramidal structure with three levels: central, intermediate and peripheral. Policy decisions are made at central level: the office of the minister of health (MoH), the general secretary and the directorates of national disease specific programs. The intermediate (provincial) level performs the functions of technical support and monitoring, and comprises 26 provincial health divisions (11 until 2013). The peripheral level comprises 516 Health Zones (HZ), which are the operational unit for planning and implementing the national health policy. The HZ operate as autonomous decentralised entities with their own management. A HZ includes a general referral hospital and 15-20 health centres, and covers an average population of 150.000 in rural health zones and 250.000 in urban health areas. The 516 Health Zones are further divided into 8504 Health Areas (HA). Each HA serves between 5000 and 10,000 people. The health system also includes community health workers providing treatment at community level in the frame of the integrated community case management (iCCM).

Figure 1-1: Administrative map of the Democratic Republic of Congo showing the 11 old provinces and the 26 new provinces

1.8 Epidemiology of malaria in the Democratic Republic of Congo

The DRC is one of the most malarious countries in the world. Together with Nigeria, DRC accounts for about 40% of the 214 million new cases of malaria reported worldwide in 2015, and for more than 35% of the total estimated malaria deaths (WHO 2015b). Malaria is reported by the MoH as the principal cause of morbidity and mortality, accounting for more than 40% of all outpatient visits, and for 19% of all deaths among children less than 5 years. The DHS 2013-2014 and the supplemental malaria report showed a national malaria prevalence in children aged 6-59 months ranging from 23% to 34% (22.7% for microscopy, 30.9% from RDTs and 34.1% for PCR). The prevalence increased with age and was higher in rural areas compared to urban areas (DHS 2014).

1.8.1. The parasite

Four *Plasmodium* species are reported in the DRC, with *Plasmodium falciparum* being the predominant species, accounting for approximately 95% of all infections either in mono-infections (90.4%) or in co-infection with *Plasmodium malariae* (4.9%) or *Plasmodium ovale* (0.6%)(Ngimbi *et al.* 1982; Taylor *et al.* 2011). A number of studies have reported the presence of *Plasmodium vivax* in the DRC (Ngimbi *et al.* 1982; Guerra *et al.* 2010). Because of the possible confusion between *P. vivax* and *P. ovale* by microscopy (Rosenberg 2007) and the presence of Duffy negative trait preventing endemic *P.vivax* transmission in much of sub-Saharan Africa, it is difficult to interpret these data. However, evidence of the transmission of a parasite with *P. vivax* characteristics among Duffy negative individuals has been reported in some African countries and among travellers to central and west Africa (Gautret *et al.* 2001; Ryan *et al.* 2006; Culleton *et al.* 2009; Dhorda *et al.* 2011). Further investigations on the epidemiology of *P. vivax* infections in the DRC should be undertaken.

The last therapeutic efficacy trial of Artemisinin-Based Combination Treatments (ACT) conducted in 2012 showed an adequate clinical and parasitological response rates of 93% for both artemether-lumefantrine (AL) and artesunate-amodiaquine (AA). The latterhas been extensively used in the DRC since its introduction in 2006 (Onyamboko *et al.* 2014).

1.8.2. Vectors

The confirmed dominant vectors of malaria in the DRC include *Anopheles gambiae s.l.* and *Anopheles funestus s.l.*, with several secondary vectors present in different parts of the country, including *Anopheles nili*, *Anopheles moucheti*, *Anopheles paludis* and *Anopheles hancocki* (Coene 1993; Karch & Mouchet 1992; Karch *et al.* 1992).

In 2009, reduced kill rates of *Anopheles gambiae* were observed with DDT and with pyrethroids (deltamethrin, permethrin) in four sites in the country (Basilua Kanza *et al.* 2013). In 2010, *Anopheles gambiae* was shown to be resistant to both DDT and permethrin in the region of Kinshasa, with mortality rates of 27.3% and 75.8%, respectively (Bobanga *et al.* 2013). Results of insecticide resistance monitoring in seven sentinel sites from 2013 to 2015 using *Anopheles gambiae* suggested that deltamethrin and permethrin showed signs of resistance while *Anopheles gambiae* was sensitive to carbamates (PMI, 2014).

1.8.3. Risk stratification

The stratification used to describe the epidemiology of malaria in the DRC is based on the concepts of eco-faciae developed by Mouchet and Carnevale in the nineties and widely used across Francophone Africa (Mouchet *et al.* 1993). This stratification has been used in the DRC since 2002 and defines three principal areas:

1) **Equatorial facies** (central African forests and post forest savannas) where malaria transmission is intense and perennial, with an EIR of up to 1000 infected bites per person per year, resulting in an early acquisition of clinical immunity.

2) **Tropical facies** (African humid savannas) where transmission is seasonal with a peak in the rainy season during five to eight months, and where people might receive 60 to 400 infected bites per person per year. Semi-immunity appears later.

3) **Mountain facies** (between an altitude of 1000 and 1500 m) where the transmission period is very short and there may even be years without transmission. Semi-immunity is low or even absent, resulting in a risk of malaria epidemics.

It is estimated that 97 percent of the Congolese population lives within the first two epidemiological ecotypes, and hence lives in areas of high transmission intensity.

Using polymerase Chain Reaction (PCR) analysis of dried blood spots samples from the 2007 DRC Demographic and Health Survey (DHS-DRC, 2007), Messina *et al.* generated the first malaria risk map based on the intensity of transmission as measured by parasite prevalence, (Messina *et al.* 2011). Low prevalence rates were recorded in the Centre and East-Central regions and near the urban areas of Kinshasa and Lubumbashi. High prevalence rates were recorded in the Northern regions of the country, and in the rural areas close to Kinshasa and Lubumbashi.

Recent collaborative work from the INFORM project assembled data from available households surveys to stratify the spatial extent of malaria transmission intensity across the DRC for 2013 (PNLP *et al.* 2014). The results showed that over two thirds of the population live in areas where the population adjusted prevalence was >=50%. Areas of lowest transmission were located in the higher altitude Eastern provinces where the low ambient temperatures limit sporogony in vector populations. This work also highlighted the need to generate more data to improve the precision of predictions at lower levels (Health Zone), and

provide a baseline for updated predictions of malaria risk, and for more effective control planning and monitoring.

1.9 Malaria control in the DRC

The Congolese national malaria control programme (NMCP) was created in 1998, and is committed to reducing malaria and the associated morbidity and mortality in DRC through the implementation of proven interventions. Key strategies and activities in line with global and African policies are defined in the National Malaria Strategic Plan. The National Malaria Strategic Plan is continuously updated to follow WHO and RBM recommendations (PNLP 2016). Key strategies include:

1) **Malaria prevention** with an emphasis on individual and collective protection through LLIN, IRS, the treatment of mosquito breeding sites, and the prevention of malaria in pregnancy through intermittent preventive (IPTp). LLIN are distributed through free mass distribution campaigns and routinely through ANC and immunisation clinics. To cover the entire country, the NMCP carries out distribution cycles. The first distribution cycle was completed in 2012 and covered the whole country over a period of 5 years. The second cycle was initiated in 2013 and completed in early 2016. The country has now started the third distribution cycle. Limited IRS activities are only undertaken by the Tenke-Fungurume mining company. IPTp consists in administrating a single dose of Sulfadoxine-Pyrimethamine (SP) at every ANC visit after the first trimester. In 2014, only 14% of pregnant women received at least 2 doses of SP as IPT (DHS 2014).

2) **Improved case management** by promoting diagnostic confirmation of malaria and appropriate treatment at all levels of the health system. Parasitological confirmation is recommended for all suspected cases of malaria seen at all levels of the health system using Rapid Diagnostic Test (RDT).The use microscopy is only recommended in case of treatment failures and severe malaria cases. Artemether-lumefantrine and artesunate-amodiaquine are recommended for the treatment of uncomplicated malaria. Injectable artesunate is recommended for all cases of severe malaria in replacement of quinine during a transition phase of three years, and rectal artesunate for pre-referral treatment is recommended for pre-referral treatment at community level.

3) **Improving epidemiological surveillance** and strengthening monitoring and evaluation efforts. The main source of information for malaria surveillance in the DRC is reports of malaria cases, malaria inpatients and malaria deaths obtained from health facilities in the frame of the Health Monitoring Information System (HMIS). These data consist of monthly counts of malaria cases, inpatients and deaths collected at community (iCCM) and health facility level. Paper forms go through different levels of the DRC health system where they are checked. The entire system is progressively being made electronic by the scaling up of the District Health Information Software 2 (DHIS2), but at present many HZ continue to use paper forms for the collection of routine malaria data. The data quality, reporting completeness and timeliness still need to be improved. This source of data is complemented by weekly data collected by the MoH on potential outbreaks, and data from malaria surveillance sentinel sites, although both systems are not yet fully functional.

Several donors are contributing to the malaria control efforts in DRC, with the Global Fund, The World Bank, the US President's Malaria Initiative (USAID/PMI) and the UK Department for International Development (DfID) being the most important. Additional donors include UNICEF, KOICA, the Sweden International Development Agency, and the Canadian International Development Agency. Each donor is covering a number of HZs. Currently, partner support to the 516 HZ is being restructured according to the 26 new provinces, with a given partner covering entirely a given province.

With support from its donors, the NMCP has been scaling up key interventions over the past decade, especially LLINs. The household ownership of at least 1 LLIN, the LLIN use among children and pregnant women have increased from 9%, 6% and 7% in 2007 to 70%, 56% and 60% in 2014, respectively. However, because of the scarcity of epidemiological data and the low quality of routine health facility data, the impact of these interventions has not been clearly established.

In this thesis we present the results of a number of studies that aimed at better understanding the epidemiology of malaria in the DRC and improving the implementation of key control interventions.

2 Goal and objectives of the present thesis

2.1 Goal

To contribute to the improvement of malaria control activities in the Democratic Republic of the Congo, through the provision of quality evidence on the epidemiology of malaria and key control interventions.

2.2 Objectives

1. To establish a comprehensive and representative risk map of malaria transmission in the Greater Kinshasa area.
2. To estimate the malaria associated risk factors among different subgroups of the population of greater Kinshasa.
3. To investigate through limited scope implementation studies how injectable artesunate may be best implemented as the preferred treatment for severe malaria in the Democratic Republic of the Congo.
4. To estimate LLIN ownership, use and cost of implementation after a mass distribution campaign in the Kasaï Occidental Province.
5. To determine the fraction of all malaria cases reported by the Health Monitoring Information System.

3 A comprehensive malaria risk map in Kinshasa, Democratic Republic of Congo

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3.1. Abstract

Background

In Kinshasa, malaria remains a major public health problem but its spatial epidemiology has not been assessed for decades now. The city's growth and transformation, as well as recent control measures, call for an update. To identify highly exposed communities and areas where control measures are less critically needed, detailed risk maps are required to target control and optimise resource allocation.

Methods

In 2009 (end of the dry season) and 2011 (end of the rainy season), two cross-sectional surveys were conducted in Kinshasa to determine malaria prevalence, anaemia, history of fever, bed net ownership and use among children 6–59 months. Geo-referenced data for key parameters were mapped at the level of the health area (HA) by means of a geographic information system (GIS).

Results

Among 7,517 children aged 6–59 months from 33 health zones (HZs), 6,661 (3,319 in 2009 and 3,342 in 2011) were tested for both malaria (by Rapid Diagnostic Tests) and anaemia, and 856 (845 in 2009 and 11 in 2011) were tested for anaemia only. Fifteen HZs were sampled in 2009, 25 in 2011, with seven HZs sampled in both surveys. Mean prevalence for malaria and anaemia was 6.4% (5.6–7.4) and 65.1% (63.7–66.6) in 2009, and 17.0% (15.7–18.3) and 64.2% (62.6–65.9) in 2011. In two HZs sampled in both surveys, malaria prevalence was 14.1% and 26.8% in Selembao (peri-urban), in the 2009 dry season and 2011 rainy season respectively, and it was 1.0% and 0.8% in Ngiri Ngiri (urban). History of fever during the preceding two weeks was 13.2% (12.5–14.3) and 22.3% (20.8–23.4) in 2009 and 2011. Household ownership of at least one insecticide treated net (ITN) was 78.7% (77.4–80.0) and 65.0% (63.7–66.3) at both time points, while use was 57.7% (56.0–59.9) and 45.0% (43.6–46.8), respectively.

Conclusions

This study presents the first malaria risk map of Kinshasa, a mega city of roughly 10 million inhabitants and located in a highly endemic malaria zone. Prevalence of malaria, anaemia and reported fever was lower in urban areas, whereas low coverage of ITN and sub-optimal net use were frequent in peri-urban areas.

Keywords: Malaria, Anaemia, mosquito nets, DRC, Democratic Republic of Congo, Kinshasa

3.2. Background

Malaria is the leading cause of morbidity and death in children under five years in the Democratic Republic of Congo (DRC), accounting for an estimated 40% of outpatient visits and 40% of overall mortality (Roll Back Malaria 2014) Malaria is also a major public health issue in the capital city Kinshasa; an issue that has been studied since colonial times(Ngimbi *et al.* 1982). After Cairo and Lagos, Kinshasa is Africa's third largest city, with an estimated population of more than 10 million (Nations). In 1979–1980, the average malaria parasite rate in a representative sample of children was 33% (Ngimbi *et al.* 1982). Around the same time, malaria admissions comprised 29.5% of consultations in 1983, then 38.2% in 1985–86 (Greenberg *et al.* 1989). In 1986–1987, the mean prevalence rate of malaria in six districts of Kinshasa was 50%, with a higher prevalence in the peripheral districts (Mulumba *et al.* 1990). This reflected the distribution pattern of the main vector Anopheles gambiae, which was less present in the city centre than in the periphery (Karch *et al.* 1992; Coene 1993). The latest study in 2000 confirmed the general prevalence distribution pattern, with lower prevalence in the city centre (parasite rate 4%) than in peri-urban areas (46%) (Kazadi *et al.* 2004).

A first insecticide treated net (ITN) distribution campaign in 2007 achieved a 15.9% rate of ITN ownership and a 12.6% rate of use among children under five (DHS 2007). In 2008, the World Bank financed the acquisition and distribution of two million ITNs in Kinshasa through the PURUS project (*Programme d'Urgence de Réhabilitation Urbaine et Sociale*). The National Malaria Control Programme (NMCP), along with technical and logistic support from Population Services International (PSI), distributed two ITNs per household. Eight months after that distribution, the Kinshasa School of Public Health (KSPH) conducted a survey on basic malaria indicators to assess the impact of the intervention in 15 health zones (HZ) of the city. In 2011, the Swiss Tropical and Public Health Institute (Swiss TPH), in collaboration with the KSPH, conducted a second survey to evaluate the coverage and use of key malaria indicators, parasitaemia, anaemia and fever in the 23 HZ excluded from the 2009 survey. Kinshasa has expanded very rapidly in the past 20 years, thus updating and consolidating these data was urgently required for general malaria control purposes and for planning specific further research projects. Using geo-referenced prevalence data, this study aimed to generate the first map of malaria risk among children 6–59 months in Greater Kinshasa, down to the lowest level of the health system in DRC, the health area (HA).

These maps will enable researchers and implementers to identify HZs of high priority for malaria control in Kinshasa.

3.3. Method

Study area

The study was conducted in Kinshasa, the capital of the DRC. The city is located along the southern bank of the Congo River, directly opposite the city of Brazzaville, capital of the Republic of the Congo. The climate is hot and humid (AW4 according to the Koppen classification), with a rainy season lasting from October to May (Kottek *et al.* 2006). Characterised in the north by the Pool Malebo and by a marshy area in the north east along the river Congo, Kinshasa extends across a plain delimited to the south by hills with heights varying between 350 and 750 meters. The plain is crossed by three rivers (Ndjili, Nsele and Mai-Ndombe) and many smaller streams (D'Ascenzo 2010; de Maximy *et al.* 1975). The northern and central parts of the city include the old colonial neighbourhoods (*ville*), some of which represent the most industrialised and commercial areas. To the south lies the *cité*, consisting of more recent, large, residential districts. The land use pattern is heterogeneous, with densely populated areas separated by large semi-rural areas where urban agriculture is practiced. The most heavily inhabited area of Kinshasa covers 583 square km (Demographia, 2014), of which 80% is actually semi-rural. Administratively, Kinshasa has the status of a province, divided into four districts, which are further divided into 24 municipalities. The organisation of the health system differs from the administrative system and comprises six health districts, divided into 35 health zones (HZ). These represent the primary operational units of the health system in DRC. An HZ usually covers a population of 100,000 to 150,000 inhabitants in rural areas and 200,000 to 250,000 in urban centres. They include a general referral hospital, some health centres and a dozen lower-level health facilities. Each HZ is further divided into 15 health areas (HA), on average, which represent the lowest level of the health system. Each HA is clearly delimited and defined by the Ministry of Health and usually includes a population of 10,000 to 15,000 inhabitants. In Kinshasa Province, the three most eastern HZ are completely rural in nature, while the remaining 32 HZ are semi-rural or urbanised (http://www.kinshasa.cd). The study area only consisted of the 32 non-rural HZ because of the practical issues involved in including the three eastern HZs. Details of the sampled HZ can be found in Table 3-1.

Study design and sampling procedure

Two cross-sectional household surveys were conducted. The first survey was carried out at the end of the dry season between mid-September and end of October 2009 in 15 HZ, eight months after the first large ITN distribution campaign. The second survey was conducted at the end of the rainy season from mid-April to early June 2011 and covered 25 non-rural HZ. Seven HZ were sampled in both studies, including five HZ for which malaria prevalence was not measured in 2009 and two HZ for which prevalence was measured previously in 2009. The detailed list of HZ surveyed in 2009 and 2011 is presented in Table 3-1. For both surveys, a multi-stage cluster sampling design was adopted to select households for inclusion, using the HZ as a primary sampling stage and the HA as a secondary sampling stage.

2009 survey

Fifteen HZ were selected using a probability proportional to size (PPS) sampling method, so that more populated HZ had a higher probability of being selected. Of these 15 HZ, 10 were selected by simple random sampling for the determination of malaria by rapid diagnostic test (RDT). In the remaining five HZ, only haemoglobin (Hb) was measured and malaria preventive measures were investigated using a pre-tested, structured questionnaire. In each HZ, data collection took place in half of the HA, selected again with PPS. In case of an odd number of HAs per HZ, (n +1)/ 2 HAs were selected. In a third stage, a list of all streets with their approximate population number was obtained for each selected HA. Streets with fewer than 200 inhabitants were excluded and three streets were selected by simple random sampling. Households with at least one child aged 6–59 months were listed by community health workers (CHW) for each of the three streets. From this list, 25 eligible households were randomly selected, proportional to the size of each street. The target sample size of 325 children was calculated based on an estimated prevalence of anaemia of 69.2% in children aged 6–59 months. Assuming 1.3 children aged 6–59 months per household, a sample size of 260 households was set as the target per health zone (DHS 2007).

2011 survey

From mid-April to early June 2011, the remaining 23 HZ were sampled, including the five HZ for which malaria prevalence had not been measured in the 2009 survey. In all 23 HZ, a questionnaire was administered to households and malaria parasite prevalence and the Hb concentration were measured in children aged 6–59 months. Two additional HZ already investigated in 2009 were re-sampled in 2011 among children 6-59 months for both malaria and anaemia. To obtain the epidemiological age profile for all age groups in these latter HZ only, all individuals older than five were also included. In all, 25 HZ were sampled in the 2011 survey. The primary outcome measure was documented malaria in study children, as measured by RDT. The sample size was calculated based on the prevalence estimate for 2009 survey (6.4%) during the dry season, and increased to 10% to take into account the seasonal variation. In each HZ, the aim was to measure children's malaria with a precision of ± 8 absolute percent. The sample size calculation indicated the need for 55 children in each HZ. With a design effect accounting for clustering of two, this number increased to 110. With an average 1.3 children under five years in households in Kinshasa, 87 households needed to be selected (DHS 2007). To account for losses in the study process, we aimed for 100 households in each of the 25 HZ. Hence, the total number of households sampled in Kinshasa in 2011 was 2,500, including 3,250 children aged 6–59 months. HA and household selection followed the same methodology applied in the 2009 survey (described above). An average of 25 households was set per HA.

Table 3-1: List of the Health Zones in Gretaer Kinshasa surveyed in 2009 and 2011 and their corresponding populations.

Health zone	Environment	Population	Year survey
Bandalungwa	Urban	147.252	2011
Barumbu	Urban	115.780	2011
Binza Meteo	Urban	325.446	2009†/2011
Binza Ozone	Urban	317.731	2011
Biyela	Urban	174.232	2009†/2011
Bumbu	Urban	316.188	2009
Gombe	Urban	22.732	2011
Kalamu I	Urban	112.915	2011
Kalamu II	Urban	100.782	2011
Kasa-Vubu	Urban	102.856	2009
Kikimi	Urban	198.997	2011
Kimbanseke	Urban	217.772	2011
Kingabwa	Urban	162.323	2009
Kingasani	Urban	171.538	2011
Kinshasa	Urban	135.665	2011
Kintambo	Urban	81.026	2011
Kisenso	Urban-rural	335.265	2009
Kokolo	Urban	336.086	2009
Lemba	Urban	249.292	2009†/2011
Limete	Urban	145.331	2009†/2011
Lingwala	Urban	66.595	2011
Makala	Urban	238.088	2011
Maluku I	Urban	149.040	Excluded
Maluku II	Rural	54.158	2009
Masina I	Urban	258.687	2011
Masina II	Urban	214.401	2009†/2011

Matete	Urban	223.248	2009
Mont Ngafula I	Urban-rural	196.810	2011
Mont Ngafula II	Urban-rural	111.921	2011
N'djili	Urban	249.310	2009
Ngaba	Urban	140.861	2011
Ngiri Ngiri§	Urban	125.634	2009/2011
Nsele	Rural	387.486	Excluded
Police	Urban	93.910	2011
Selembao§	Urban	269.498	2009/2011

***** KSPH/ NMCP 2009, KSPH/ Swiss TPH 2011; † Surveyed for malaria preventive indicators and prevalence of anaemia; § surveyed for malaria prevalence in both years and for all age groups in 2011.

Data collection

Household survey questionnaire

In 2009, survey data were collected using a paper-based questionnaire. In 2011, survey data were collected using smartphone technology. For the 2011 survey, a validated electronic semi-quantitative questionnaire was developed on an HTC smartphone running Google's Android operating system. Eight teams of three field workers (one interviewer, one laboratory technician, one community liaison person) were trained in using the electronic questionnaire, in general interviewing skills and in administering informed consent during simulated interviews sessions. Each of the eight teams visited, on average, 25 households per day in each selected HA. The 2011 questionnaire was a simplified version of the one used in 2009, which was adapted from the standard Malaria Indicator Survey Household Questionnaire from the Roll Back Malaria Partnership (www.RBM.org). All questions retained from the 2009 survey form were kept as they were in 2011 to ensure comparability between both surveys. The questionnaire was developed in French with oral translation into Lingala (the second *lingua franca* in Kinshasa) and field tested prior to the survey.

Prior to administering the questionnaire, a signed informed consent form was obtained from the head of the household or his/her representative. Participation was entirely voluntary. Respondents were asked about demographic information of usual residents, educational level, factors indicating the household's socio-economic status, household construction material, presence and type of mosquito bed net (verified by direct observation), use of mosquito bed net and ITN in the night prior to the survey, history of fever (past 2 weeks), whether fever was present on the day of the survey and health seeking behaviour in case of a fever episode. During the 2011 survey, the coordinates (longitude and latitude) of all investigated households were recorded on-site using the integrated Global Positioning System (GPS) of the data collection devices. Households were revisited if no one was available for interview on the first attempt; if no one was available after two attempts, the interviewer continued to the next randomly selected household on the list until the desired number of households was obtained.

Blood testing

For each selected participant who gave signed informed consent, the same laboratory procedures as in 2009 were adopted during the 2011 survey. They included measuring axillary temperature with a digital thermometer, collecting peripheral blood by standard finger prick to test for malaria parasites with an RDT for *Plasmodium falciparum*-specific histidine rich protein 2 (HRP2) and other *Plasmodium species* (Pan pLDH for *P. vivax, P. malariae* and *P. ovale*) (Paracheck pf in 2009 and SD Bioline Malaria Antigen P.f/Pan in 2011) and assessing Hb level using a blood haemoglobin photometer (HemoCue 201 plus, Ängelholm, Sweden). In two HZ in 2011, Selembao and Ngiri Ngiri, individuals of all ages (not only children) were surveyed. RDT were used for on–site diagnosis of malaria and treatment with artesunate-amodiaquine, the official first-line malaria treatment at the time of the survey, was offered as needed. The HemoCue was validated by running a weekly high and low Hb liquid control (HemoCue – HemoTrol).

Statistical analysis

To ensure consistency and integrity of data collected during the 2009 survey, all paper forms were rechecked by team supervisors in the field at the end of each day. Incomplete entries were sent back to be filled the next day. Questionnaires were first checked for completeness, and the information was manually coded and entered using EpiData and crosschecked using EpiInfo (v. 6.04). Statistical analyses were performed using SPSS software for Windows (version 16.0), NCSS, and STATA (version 10).

Data collection devices used in the 2011 survey (HTC phones) were equipped with Open Data Kit (ODK) software (University of Washington & Google Foundation) to allow for data entry in the field. ODK programming also allowed for systematic range and consistency checks. Data in xml format were downloaded every evening from the HTC smartphones and then converted on the ODK Aggregate Server into tabular format (ODK aggregate).

Statistical analyses were performed using Stata version 12.1 (Stata Corp, College Station, Tx, USA). Analysis and mapping for the 2011 survey were based on geo-referenced prevalence data at the level of the HA. Since households could not be georeferenced in 2009, HA spatial coordinates were assigned to the HA's mean malaria prevalence. Maps were produced using ArcGIS version 10.0 (Environmental Systems Research Institute Inc. Redlands, USA).

A centroid for every HA was first generated (for 2009 the centroid was generated at the centre of the HZ, since GPS coordinates of the households were not collected). The standardized prevalence data were then assigned to the centroids of the surveyed health zone. The next step involved using the IDW interpolation to get prevalence estimates at un-surveyed HZ. Lastly, the interpolated prevalence estimates were extracted using the centroids (points data) of the HZ. These estimates were subsequently used map out the prevalence at HZ level (polygons data). Boundaries (shape files) were initially available at the level of the HZ only, from the Health Monitoring Information System Unit of the Ministry of Health (MoH). By using images developed by the Japan International Cooperation Agency (JICA) and through collaborating with a team of experts from the *Institut géographique du Congo* (IGC), it was possible to develop shape files at the level of the HA. The most eastern rural HZ (Maluku I and II and Nsele) were excluded from the final map due to the great effort that drawing boundaries in remote HA would have entailed. This was beyond the means and the scope of this study.

Ethical consideration

For both surveys, ethical clearance was obtained from the Ethics Committee of the KSPH, at the University of Kinshasa. In addition, the 2011 survey received authorization from the ethical committees in Basel (Ethikkommission beider Basel, Basel-Stadt) as well as clearance from Swiss TPH's internal research commission.

Signed informed consent to participate was obtained from parents or guardians on behalf of the enrolled children or by the adult participants themselves. Precautions to minimise the risk of secondary infection during blood collection were taken. All tested participants with a positive RDT but no evidence of severe illness were diagnosed as having uncomplicated malaria and given a voucher for treatment, free of charge, as per the DRC national malaria treatment policy (artesunate-amodiaquine or artemether-lumefantrine), at the nearest health facility. Drugs were provided to the relevant facilities one day before the household visits started in the area, to ensure drug availability for treatment. Participants diagnosed with severe anaemia and those with severe illnesses were excluded from the study and immediately referred to the nearest health facility for diagnosis and management, as recommended by national guidelines.

3.4. Results

Characteristics of the study population

Household and individual characteristics of the study populations in 2009 and 2011 are shown in Table 3-2. A total of 3,896 households distributed throughout 15 HZ were included in the 2009 survey, while 2,512 household in 25 HZ were sampled in 2011. The age distribution of individuals was similar between surveys, as were the proportions of men and women. Overall, 27,371 people were surveyed in 2009, including 12,761 men and 14,610 women. Of these, 47.1% were under 15 years of age, while the percentage of children 6–59 months was 24%. In addition, 302 pregnant women also participated. The 2011 survey included 15,005 people; 6,770 men and 8,235 women. Of these, 44.7% were under 15 years of age, while the percentage of children 6–59 months was 24.9%.

Table 3-2: Characteristics of study households and individuals in the 2009 and 2011 surveys, Kinshasa, Democratic Republic of Congo.

	Survey	**Survey**
Household characteristics		
Number of households sampled	3896	2512
Mean (SD) household size	7.1	5.9 (2.1)
Individual characteristics		
Number of persons in sampled households	27371	15005
Median Age years (90% central range)	-	17
Age groups		
< 6 months	-	0.9
6-59 months (%)	24.0	24.9
5-9 years (%)	13.1	10.9
10-14 years (%)	10.0	8.9
15-19 years (%)	9.2	8.1
≥ 20 years (%)	43.7	46.2
Proportion of females (%)	53.4	54.9

Prevalence of *P. falciparum* by health zone

Table 3-3 gives the proportion of children 6–59 months who tested positive for malaria with RDT, by sampled HZ. A total of 3,319 children 6–59 months in 10 HZ were tested for malaria by RDT in the 2009 survey, whereas 3,342 were tested in 25 HZ in 2011. Prevalence of confirmed malaria was 6.4% (5.6–7.4) at the end of the 2009 dry season, ranging from 1.0% (0.3–2.6) in Ngiri Ngiri (urban centre) to 14.1% (10.6–18.2) in Selembao (peri-urban). At the end of the 2011 wet season, malaria prevalence was 17.0% (15.7–18.3), ranging from 0.7% (0.0–4.1) in Kinshasa and Lingwala (urban centre) to 46.0% (37.1–55.1) in Biyela (peri-urban). *P. falciparum* accounted for 52% (95% CI: 47.4-55.8) of infections in 2011 survey, non-falciparum infections for 0.3% (95% CI: 0.0-1.3) while mixed infection (were not distinguished) prevalence was 48% (95% CI: 43.9-52.3).

In the two HZ sampled in both 2009 and 2011, prevalence of malaria in children aged 6–59 months was 1.0% (0.3–2.6) and 0.8% (0.0–4.2) in Ngiri Ngiri, and 14.1% (10.6–18.2) and 26.8% (19.9–34.7) in Selembao. Age-specific rates (Figure 3.1) show that prevalence in Ngiri Ngiri in 2011 was highest among individuals aged 15–19 years (14.0%), followed by the groups aged 5–9 years (4.8%), > 20 (4.2%), 10–14 (1.4%) and 6–59 months (0.0%). In Selembao, malaria prevalence was highest among the groups aged 5–9 (34.2%) and 15–19 (28.3%) years, followed by those 6–59 months (26.2%), 10–14 years (25.0%) and over 20 years (17.6%). All-ages malaria prevalence was 3.8% (2.4–5.8) in Ngiri Ngiri and 23.8% (20.4–27.6) in Selembao.

To prepare the data for mapping, direct standardisation was used to make prevalence rates of malaria comparable between surveys, accounting for the two different years and seasons. The standardisation was done according to the following formula:

$$P_s = \frac{p_1 n_1 \bar{p}_1 \sum n_1 + p_2 n_2 \bar{p}_2 \sum n_2}{(\sum n_1 + \sum n_2)}$$

where, P_s is the overall standardized prevalence for surveys 2009 and 2011, p_1 is the prevalence rate in survey 1 (2009), p_2 is the prevalence rate in survey 2 (2011), n_1 is the number of study participants in survey 1, n_2 is the number of study participants in survey 2, $\bar{p}1$ is the overall prevalence rate for survey 1, $\bar{p}2$ is the overall prevalence rate for survey 2 and $\sum$ is the total number of study participants (per survey).

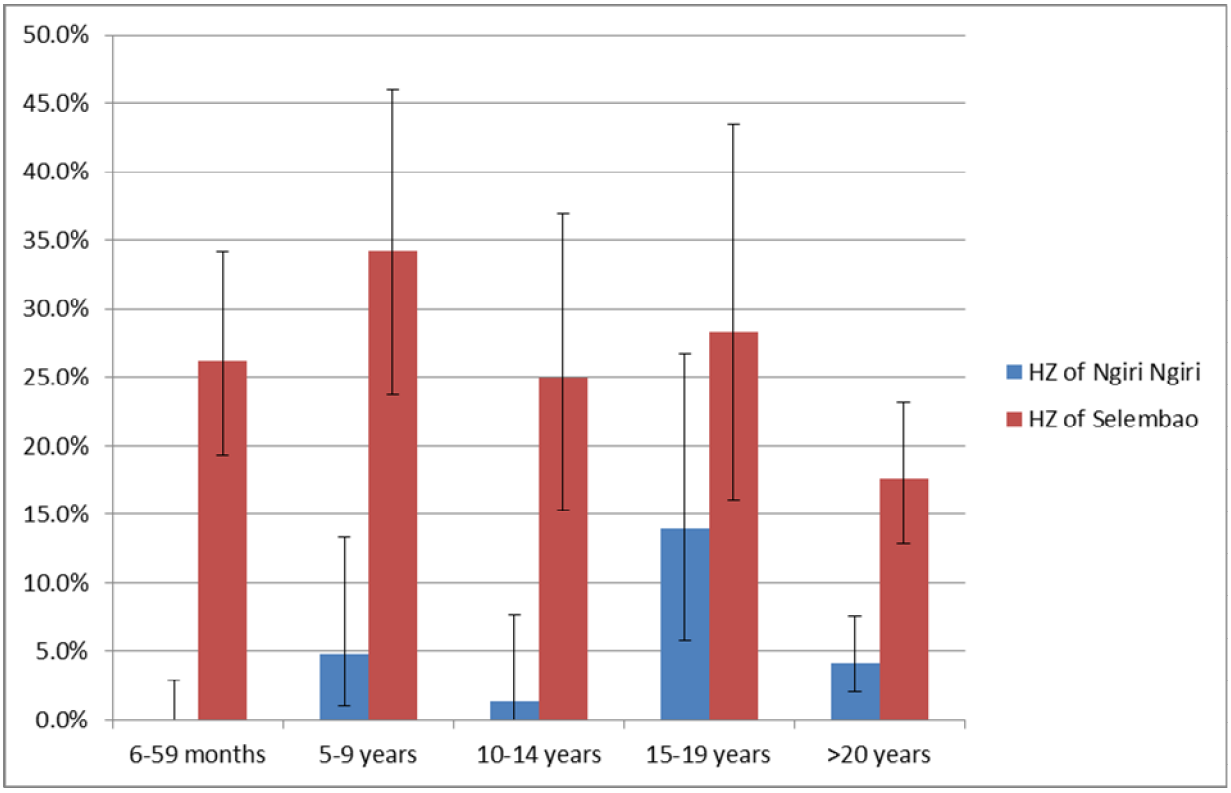

Figure 3-1: *Plasmodium falciparum* malaria prevalence (RDT positivity) by age group for the health zones of Selembao and Ngiri Ngiri

Geographical distribution of *P. falciparum* malaria

Results from the two surveys were used to produce a representative and standardised map of risk for malaria in children aged 6–59 months. Figure 3-2 shows the spatial distribution of the standardised prevalence rates of *P. falciparum* from the 2009 and 2011 surveys, at the level of the HA. Interpolated standardised prevalence rates are presented in Figure 3.3. Based on this risk map, three zones could be approximately defined; low risk in the central north part of the city, where prevalence rates were generally low (≤ 5%); intermediate risk in the central southern part of the city, where prevalence rates were between >5% and ≤30%; and high risk in the south western and eastern zones, where prevalence rates were higher (>30%) and, in general, more homogeneously distributed.

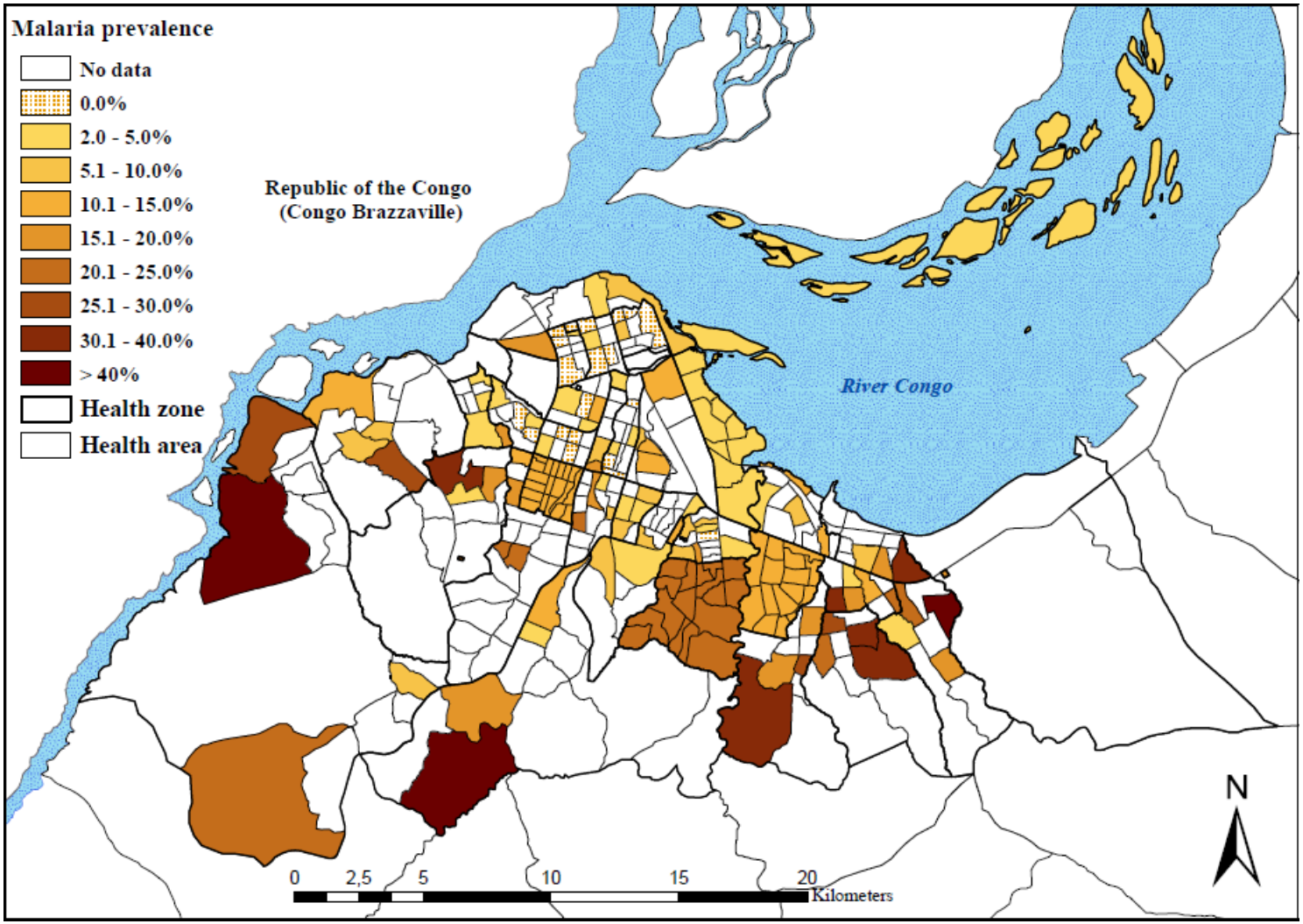

Figure 3-2: Standardized *Plasmodium falciparum* malaria prevalence in children aged 6-59 months, by health area.

The 2009 data for the health zones of Bumbu, Kingabwa, Kisenso, Kokolo and Ndjili were only available at the level of the health zones.

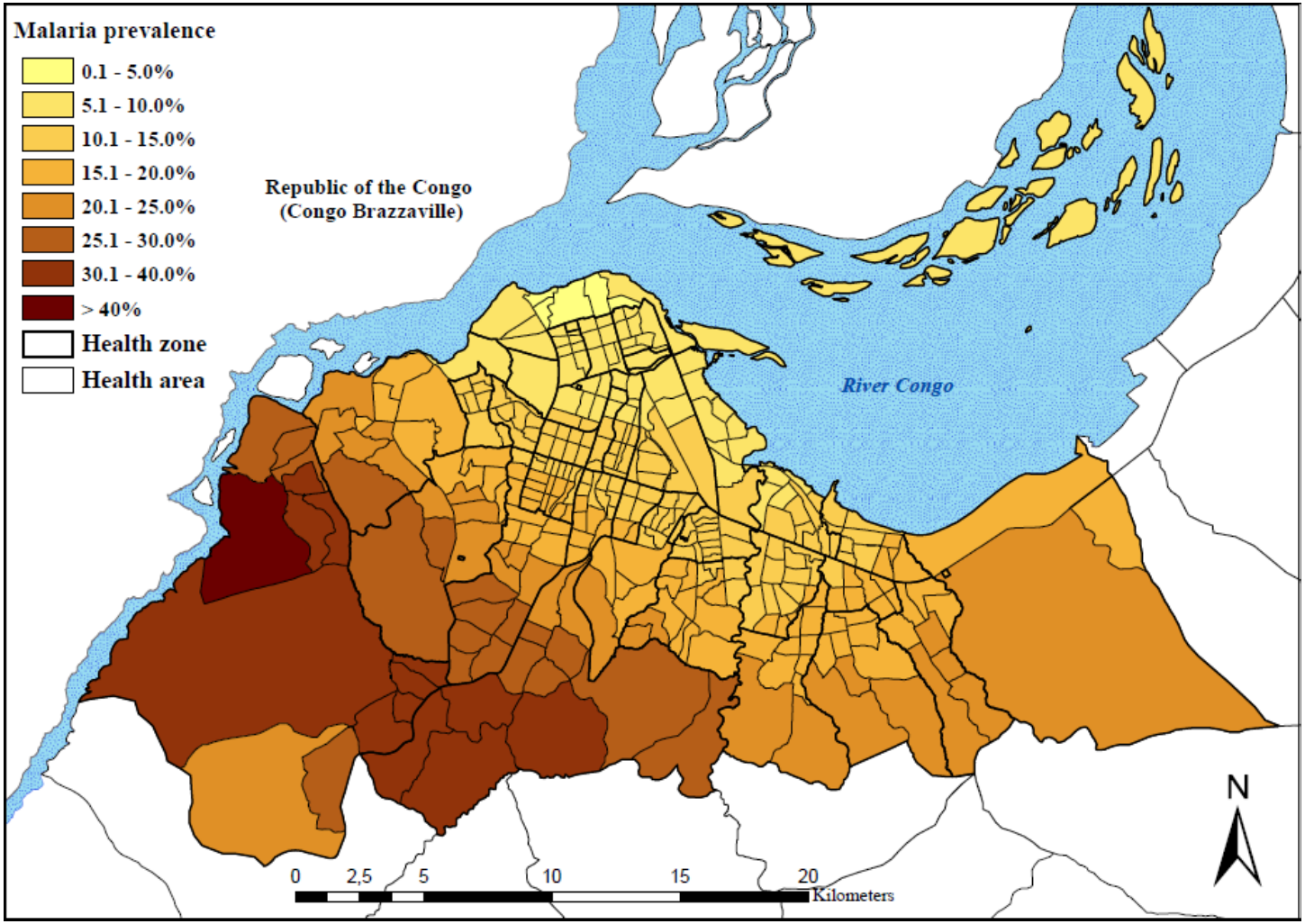

Figure 3-3: Interpolation results for standardized *Plasmodium falciparum* malaria prevalence in children aged 6-59 months, by health area.

Note: The data of Figure 3-2 were used for an inverse distance weighting (IDW) interpolation and then a mean prevalence value was calculated for every health area.

Geographical distribution of anaemia

A total of 4,164 and 3,353 children aged 6–59 months were tested for anaemia in the 2009 and 2011 surveys, respectively. The mean prevalence of anaemia (Hb < 11g/dl) was similar between surveys: 65.1% (63.7–66.6) in 2009 and 64.2% (62.6–65.9) in 2011. Results also show that the prevalence of moderate (7.0-9.9 g/dl) and severe (< 7.0 g/dl) anaemia was 34.2% and 1.9% in 2009, and 30.1% and 1.9% in 2011 (Table 3).

The formula given above was used to standardise the prevalence of anaemia and of severe anaemia. The spatial distribution of the standardised prevalence of anaemia for both surveys is shown in Figure 3-4. The risk of anaemia was consistently high across the entire study area, with maximal mean prevalence rates (> 70%) in the HZ of Kingabwa, Matete and Biyela. A map showing the standardised prevalence of severe anaemia is presented in Figure 3-5.

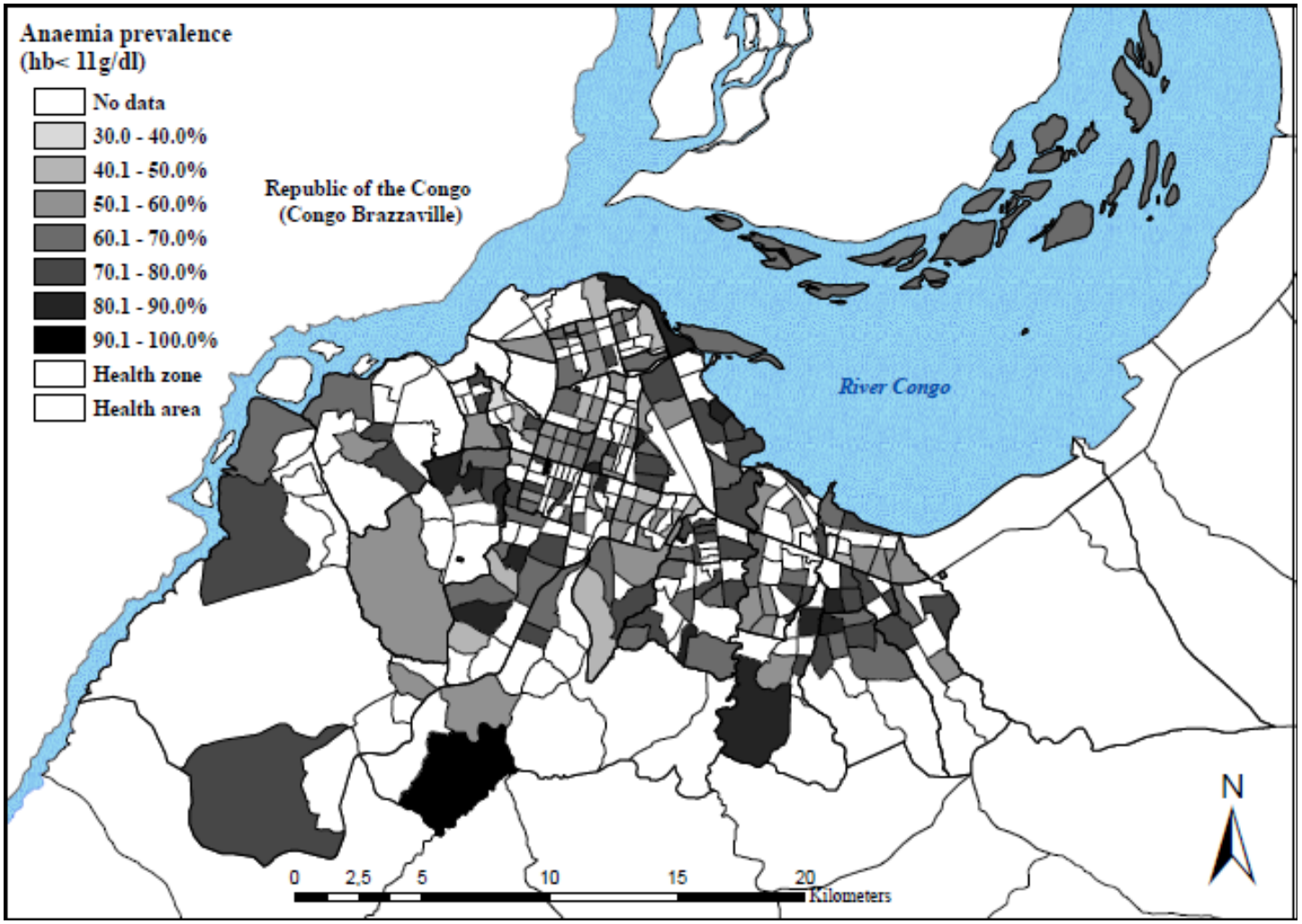

Figure 3-4: Standardized prevalence of anaemia (Hb<11g/dl) in children aged 6-59 months, by health area, surveys 2009 and 2011.

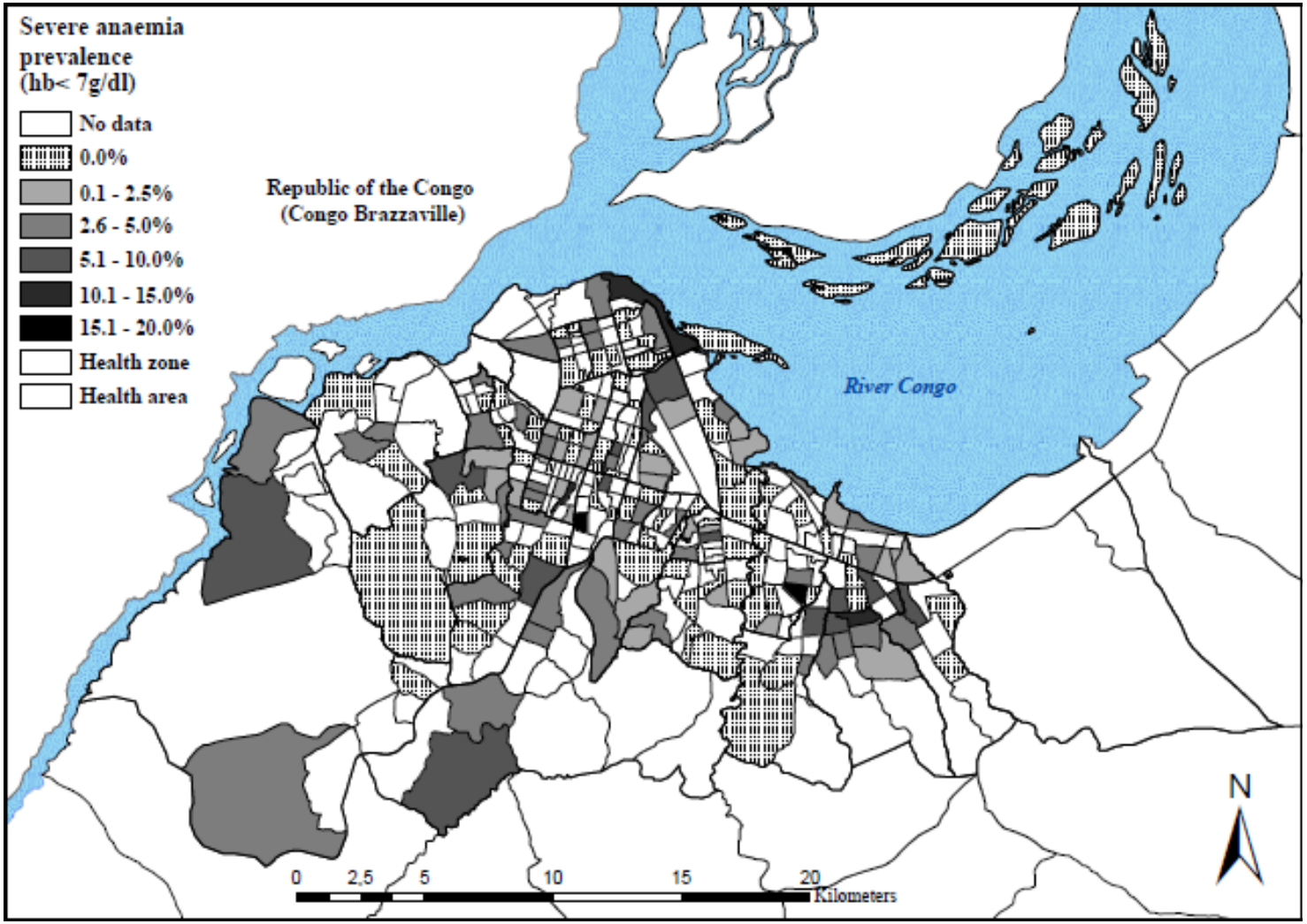

Figure 3-5: Standardized prevalence of severe anaemia (Hb<7g/dl) in children aged 6-59 months, by health area, surveys 2009 and 2011.

History of fever

The proportion of children aged 6–59 months reporting a history of fever in the two weeks preceding the survey was 13.2% (12.5–14.3) in 2009 and 22.3% (20.8–23.4) in 2011. On the day of the 2011 survey (data not available for 2009), 3.2% (106/3348) were febrile (defined as temperature > 37.5 C). The positive predictive value (PPV) of history of fever among children with a positive RDT was 29.7% (26.3–32.7) in 2011. Health seeking behaviour in case of fever was high in 2011 (data not available for 2009): overall, 91.4% (770/842) of children sought some type of care. In all, 53.9% sought modern treatment at home by a family member, whereas 36.1% were taken to a health facility. Very few (0.5%) made use of traditional medicine. Private facilities were the most common provider of treatment among those who sought care outside the home, covering 65.4% of the cases, whereas 22.9% consulted a public facility and 11.8% consulted a confessional structure. In case of home treatment, drug outlets represented the principal source of treatment (96.3%). Unfortunately, only 4.3% of the antimalarials purchased were the recommended combination of artesunate-amodiaquine. As a result, only 3.6% received the recommended treatment at home within the 24 hours. In 66.5% of fever cases, treatment was sought within 24 hours regardless of whether treatment was recommended or not.

Table 3-3: Clinical outcomes, by health zones

Health zone	Malaria prevalence in children aged 6-59 months							Anaemia prevalence in children aged 6-59 months						Children <5 years with a fever episode in the 2 weeks before the survey			
	Survey 2009 (dry season)			Survey 2011 (wet season 2011)			Standardised prevalence	Survey 2009 (dry season)			Survey 2011 (wet season 2011)			Survey 2009 (dry season)		Survey 2011 (wet season 2011)	
	%	[95% CI]	N	%	[95% CI]	N	%	% severe (<7g/dl)	% any (<11g/dl)	N	% severe (<7g/dl)	% any (<11g/dl)	N	%	N	%	N
Bandalungwa				1.5	[0.2-5.3]	134	1.0				0.7	51.5	134			22.8	149
Barumbu				2.4	[0.5-6.9]	125	1.7				0.8	57.8	128			19.6	143
Binza Météo				24.8	[17.0-34.0]	109	17.1	1.3	70.6	238	1.7	65.3	118	20.4	339	24.4	131
Binza Ozone				19.1	[12.9-26.7]	136	13.2				1.5	66.2	136			19.0	158
Biyela				46.0	[37.1-55.1]	126	31.7	4.5	64.9	313	2.4	78.6	126	9.5	422	24.7	150
Bumbu	7.4	[4.7-10.9]	299				13.6	3.6	69.2	308				9.3	407		
Gombe				11.5	[6.7-18.0]	139	7.9				3.6	65.5	139			29.6	159
Kalamu I				16.2	[8.4-27.1]	68	11.2				0.0	73.5	68			28.8	73
Kalamu II				2.5	[0.8-5.7]	200	1.7				1.5	56.7	203			19.5	221
Kasa Vubu	2.8	[1.2-5.4]	286				5.1	1.6	55.4	242				10.2	352		
Kikimi				32.8	[24.9-41.6]	131	22.6				2.3	64.9	131			18.5	151
Kimbanseke				36.1	[27.9-44.9]	133	24.9				2.3	75.9	133			22.7	154
Kingabwa	2.6	[1.2-4.9]	345				4.8	1.5	74.3	315				9.8	386		
Kingasani				25.0	[18.3-32.7]	152	17.2				3.3	76.2	151			24.6	175
Kinshasa				0.7	[0.0-4.0]	136	0.5				1.5	61.2	134			30.7	150
Kintambo				11.7	[7.0-18.1]	145	8.1				1.5	68.2	132			24.8	165
Kisenso	11.2	[8.0-15.1]	331				20.5	1.0	69.3	267				8.3	348		
Kokolo§	9.3	[6.5-12.9]	353				17.0	0.6	66.7	36				10.3	39		
Lemba				7.7	[3.8-13.7]	130	5.3	1.8	59.4	276	3.1	53.8	130	25.8	357	15.3	150

Limete				17.3	[11.3-24.8]	133	11.9	1.8	69.5	334	3.0	72.2	133	14.3	399	29.1	148
Lingwala				0.7	[0.0-4.1]	135	0.5				0.7	63.0	135			27.3	154
Makala				17.9	[11.8-25.5]	134	12.3				4.5	69.4	134			20.6	155
Maluku II*	8.0	[5.0-12.0]	261				14.7	1.2	54.2	260				11.1	342		
Masina I				12.3	[7.3-19.0]	138	8.5				0.7	66.7	138			20.2	163
Masina II				24.8	[17.7-33.0]	133	17.1	2.5	57.6	321	2.3	60.9	133	15.6	458	21.7	161
Matete	3.5	[1.8-6.0]	344				6.4	2.1	74.0	334				6.6	394		
Mont Ngafula I				33.6	[25.7-42.2]	134	23.2				3.7	69.4	134			20.8	154
Mont Ngafula II				35.3	[27.3-44.1]	133	24.4				3.0	68.4	133			19.0	158
Ndjili	6.3	[4.0-9.3]	366				11.5	2.4	61.3	287				16.7	412		
Ngaba				7.5	[3.6-13.3]	134	5.2				1.5	50.7	134			28.8	153
Ngiri Ngiri	1.0	[0.3-2.6]	387	0.8	[0.0-4.2]	124	1.5	1.3	62.4	314	0.8	58.8	131	15.3	428	12.9	140
Police§				17.0	[11.1-24.5]	135	11.7				0.7	53.3	135			13.4	164
Selembao	14.1	[10.6-18.2]	347	26.8	[19.9-34.7]	145	23.6	1.9	67.1	319	1.3	65.3	150	15.2	387	19.1	162
TOTAL	**6.4**	**[5.6-7.4]**	**3319**	**17.0**	**[15.7-18.3]**	**3342**	**11.7**	**1.9**	**65.1**	**4164**	**1.9**	**64.2**	**3353**	**13.2**	**5470**	**22.3**	**3841**

* The HZ of Maluku II although surveyed in 2009 was excluded from the final risk map since the choice was to map only HZs of non-rural character.

§ The HZs Kokolo and Police consist of military and police camps scattered in the city.

Coverage of malaria control measures

Eight months after the 2009 distribution campaign, ITN coverage (measured by the possession of at least one ITN per household) reached 78.7% (77.4–80.0). In 2011, it was 57.7% (56.0–59.9). In 2009, coverage ranged from 51.7% in Biyela (peri-urban) to 92.7% in Maluku II (peri-urban) (Table 3-4), with a mean number of 2.0 ITNs per household. In 2011, ITN coverage ranged from 34.4% in Biyela to 81.8% in Kinshasa, with a mean number of 1.9 ITN per household (1.1).

The most common reasons for not owning an ITN, as given by households in both the 2009 and 2011 surveys, included not having obtained the ITN during the mass distribution campaign (38.7% and 23.8%), either because they were absent (26.6%, 2009) during the campaign or because the stock had been sold out (3.8% and 18.8%). A high proportion of respondents reported having discarded or destroyed their ITN because of rumours (7.4% and 23.8%). Other reasons given were heat (2.4% and 10.6%) and the absence of mosquitoes at home (9.4% in 2009).

The proportion of respondents who reported that their child slept under an ITN the night before the survey decreased from 65.8% (63.5–66.0) in 2009 to 45.0% (43.6–46.8) in 2011. Figures 3-6 and 3-7 show the geographical distribution of ITN usage among children under five, geo-referenced and mapped at the level of the HA for both surveys. Use rate decreases progressively towards the periphery in both surveys, with markedly lower use rates (<30%) in the south-eastern and western health zones of Biyela (30.8%, 2009; 17.3%, 2011), Selembao (53.3% 2009; 28.4% 2011), Kikimi (27.2% 2009) and Kimbanseke (20.1% 2011). A higher proportion of pregnant women, 83.1% (77.5–87.7), reported using an ITN in 2009, than in 2011, were reported use decreased to 43.1% (37.5–48.9). Again, the HZ on the outskirts of the city showed the lowest use rates.

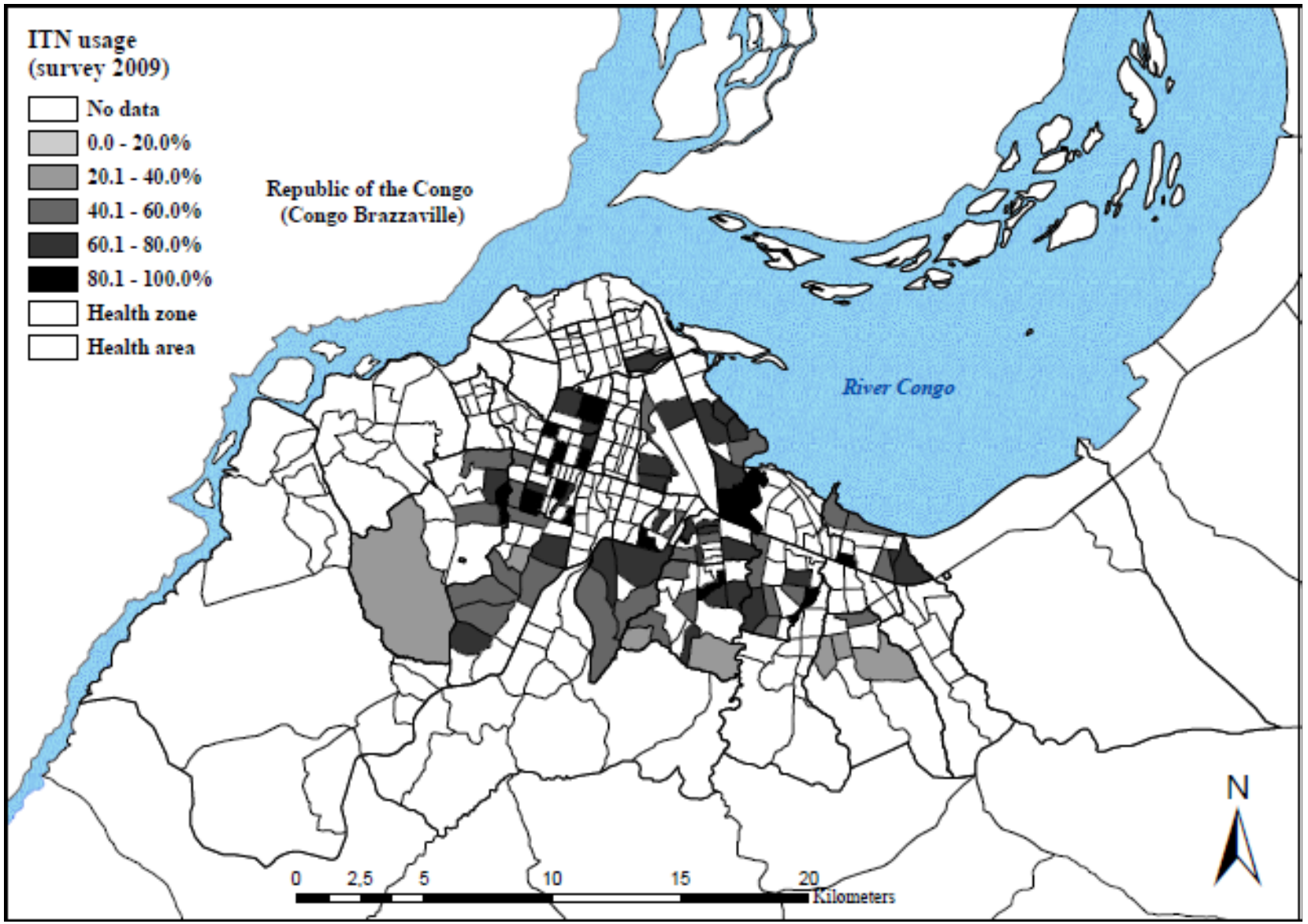

Figure 3-6: Percentage of children <5 years having slept under an ITN the night before the survey in 2009, by health area.

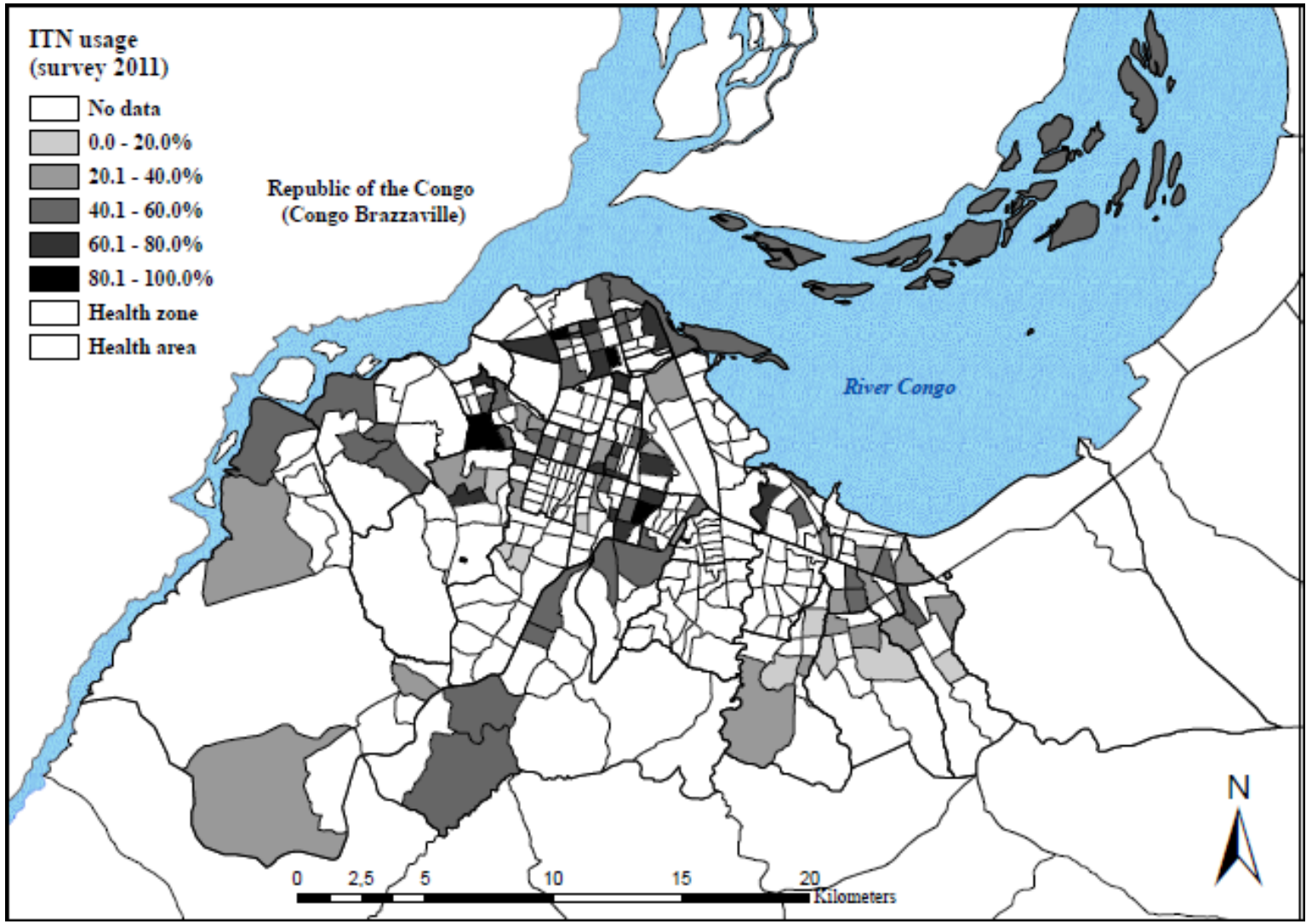

Figure 3-7: Percentage of children < 5 years having slept under an ITN the night before the survey in 2011, by health area

3.5. Discussion

Kinshasa falls within the perennial transmission in the classification of the Mapping Malaria Risk in Africa (MARA) project. This study created the first malaria risk map at the scale of a health area, the lowest level of the health system in DRC. Although the mean endemicity level seems to have declined over the last 30 years in Kinshasa, the results from the 2009 and 2011 cross-sectional surveys show that malaria was still a public health concern (Ngimbi *et al.* 1982; Mulumba *et al.* 1990; Kazadi *et al.* 2004). The geographic pattern of endemicity is comparable to that identified in earlier studies done in Kinshasa (Ngimbi *et al.* 1982; Mulumba *et al.* 1990; Kazadi *et al.* 2004). Prevalence is clearly highest in the more densely populated and less urbanised districts in the periphery, although marked variations in rates are apparent, even over a few kilometres. These findings are consistent with a recent meta-analysis that used data on the prevalence of malaria parasitaemia to document an analogous situation in other cities in Sub-Saharan Africa (Pond 2013). A similar reduction in the annual *P. falciparum* entomological inoculation rates (APfEIR) has been observed in the more urbanised central areas, with a tendency to increase gradually towards the peri-urban areas (Hay *et al.* 2000; Robert *et al.* 2003; Keiser *et al.* 2004). The relative reduction in the APfEIR in urban areas was also reported in Kinshasa and in Brazzaville (Trape 1987; Karch *et al.* 1992; Coene 1993). Trape JF *et al.* suggested a relationship between levels in transmission in certain districts of Brazzaville and prevalence of malaria reported (Trape 1987). The existence of a linear correlation between APfEIR and prevalence was also confirmed by Hay SI *et al.* (Hay *et al.* 2005).

In this study, the overall standardised malaria prevalence was 11.9% in children 6–59 months, ranging from 0.5% in the downtown health zones of Kinshasa and Lingwala, to 31.7% in Biyela, a semi-rural peripheral district extending south east. Results also show that spatial heterogeneity is high in the central and northern urbanised HZ, whereas in the western and south-eastern HZs, more homogeneous levels of high risk can be found (Figure 3-2). It is likely that the proximity to productive breeding sites could account for the uneven distribution of malaria risk, together with socio-economic stratification and level of control measures (Machault *et al.* 2009; Clark *et al.* 2008). Kazadi *et al.* observed that initial urbanisation might increase levels of malaria transmission through increased human density and the creation of breeding sites favourable to *Anopheles gambiae,* the main local vector (Coene 1993; Kazadi *et al.* 2004). In a second phase, the densification of human habitations reduces potential mosquito breeding sites and hence transmission levels.

In Kinshasa, the increase in the density of dwellings in older urban districts has progressively eliminated the last remaining open spaces, contributing to the scarcity of *Anopheles* breeding sites through elimination and pollution. However, exceptions exist, especially where urban agriculture and gardens persist. In particular, the districts extending towards the south-east and west maintain a semi-rural character. Various studies have documented the presence of higher prevalence or transmission rates in areas close to agriculture fields (Afrane *et al.* 2004; Matthys *et al.* 2006; Clark *et al.* 2008; Klinkenberg *et al.* 2008; Stoler *et al.* 2009; Yadouléton *et al.* 2010). Kinshasa is crossed by rivers from north to south, creating large flood zones where much of the gardening is practised. This characteristic is particularly evident in the large semi-rural areas south west of the *boulevard* Lumumba, encompassing the health zones of Kingasani, Biyela, Kimbanseke and Kikimi. The areas favour *Anopheles sp.* breeding sites and are consistent with the more homogeneous transmission pattern observed in the areas on the outskirts of the city, compared to the more urbanised zones.

Additional factors, such as the use of personal protection against mosquitoes or socio-economic status, should also be considered as important determinants explaining the distribution of disease prevalence. A spatial regression analysis linking malaria prevalence to risk factors for malaria in Kinshasa will be published separately (Ferrari *et al.* 2016).

Not surprisingly, the age groups with the highest prevalence, independent from the level of endemicity in both urban and semi-rural areas (Ngiri Ngiri and Selembao), were those aged 5–9 and 15–19. Hence, in Kinshasa, malaria infections seem to occur more frequently late in childhood. This could be in part explained by the age specific ITN usage across age groups, with highest use in younger children in the low endemicity setting (percent of usage in Ngiri Ngiri 49% compared to 28% in Selembao) as compared to lower and similar utilization rates among age groups in the high transmission setting (Ferrari *et al.* 2016). Higher malaria prevalence rates in older children were also found in school surveys carried out in the 1980s in Kinshasa and in Brazzaville. At that time, the finding was attributed to the increased use of antimalarials in early childhood (Trape 1987; Kazadi *et al.* 2004).

A concerted effort to scale-up ITN coverage through a free distribution in Kinshasa led to an ITN ownership rate of 78.7% of households in 2009. This represented a 395% increase in household possession of $\geq$1 ITN over the 2007 estimate of only 15.9% (DHS 2007). However, 24 months after the distribution campaign, ITN ownership had decreased to 57.7% of households.

Clearly, this points to the need for stronger programmes for routine ITN distribution as it occurs in most endemic settings, in addition to the campaigns, (Grabowsky *et al.* 2007).

The prevalence of anaemia was high in 2009 (65.1% in children 6 to 59 months) and in 2011 (64.2%). This is consistent with the 69.2% prevalence reported by the DHS 2007 (DHS 2007). Furthermore, the distribution of anaemia across Kinshasa was highly heterogeneous as shown in Figure 4, and the absence of a spatial trend seems in favour of the role of additional factors other than malaria in the aetiopathogenesis of this condition. Multiple factors account for anaemia and their contributions can vary according to the setting (Hall *et al.* 1982). In Kinshasa, 23% and 9% of children suffer from chronic and severe forms of malnutrition (DHS 2007) and sickle cell anaemia is widespread (Tshilolo *et al.* 2009).

The maps we present for different variables reflect survey results from two distinct time periods and seasons. Since malaria transmission is neither constant throughout the year nor between years, this has likely introduced some mistakes. To account for these differences, we tried standardising prevalence rates, but that is an imperfect means of accounting for such differences. Moreover, surveys were based on detection of cases of uncomplicated malaria and, therefore, it is not possible to draw strong conclusions about the prevalence of anaemia, which is more often related to severe malaria.

3.6. Conclusions

This study provides the first comprehensive risk map of malaria at the level of the health areas in Kinshasa, a mega-city in a highly endemic malarious zone. Overall malaria prevalence has undoubtedly decreased over the last 30 years, but it is impossible to quantify the effect given the lack of representative historical data. As expected, prevalence rates were lower in the central urban districts compared to the more peripheral and more rural districts (Kazadi *et al.* 2004). The penetration of malaria control measures, especially ITN, remains insufficient and is less successful in less developed and less accessible HZ on the outskirts of the city. Hopefully, this gap can be closed in the years to come with renewed efforts by the National Malaria Control Programme and its partners. Despite the methodological limitations, the risk map provides a good baseline assessment against which to assess the effect of future control efforts.

4 Identifying risk factors for *Plasmodium* infection and anaemia in Kinshasa, Democratic Republic of Congo

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4.1 Abstract

Background

There is little data on the risk factors for malaria infection in large cities in central Africa and in all age groups. There may be different associations with the risk factors for areas with different malaria transmission intensities such as the effect of fever or age. This study aimed at identifying risk factors associated with *Plasmodium* infection and anaemia among children 6-59 months and individuals aged older than five years in Kinshasa, a large city with heterogeneity in malaria prevalence.

Methods

This study analysed data from 3342 children aged 6-59 months from 25 non-rural health zones (HZ) and for 816 individuals aged older than five years from two HZ in Kinshasa (non-rural), collected during a cross sectional malaria survey in 2011. Logistic regression with random effects was used to investigate predictors for malaria and anaemia. Differences in risk factors in areas with a prevalence of less than 10% and 10% or greater were investigated.

Results

There was evidence of a different age-pattern in the two transmission settings. For children under five years, the highest prevalence of malaria was observed in the 48-59 months group in both transmission settings but it increased more gently for the lower transmission HZs ($p=0.009$). In a separate analysis in children over five years in two selected HZ, the peak prevalence was in 5-9 years old in the higher transmission setting and in 15-19 years old in the lower transmission setting. Reported fever was associated with malaria in both transmission strata, with no evidence of a difference in these associations ($p=0.71$); however in children older than five years there was a significant interaction with a stronger association in the low transmission HZ. Insecticide-treated net (ITN) use was associated with a lower risk of malaria infection in children 6-59 months in the high transmission HZ. Similar estimates were found in children over five years and the lower transmission HZ but the associations there were not significant. There was no evidence of a difference in these associations by strata. The risk of anaemia decreased with increasing age in all strata, whereas it increased with malaria infection and reported fever. ITN use did not show evidence of protection against anaemia. Low socio-economic status was associated with malaria in high transmission setting in children 6-59 months and anaemia in low transmission setting.

Conclusions

This study shows that in areas of low transmission in Kinshasa, the peak prevalence occurs in older age groups however ITN use was highest in children under five years. Targeted distribution of ITN to all age groups should be continued. For most risk factors, there was no evidence of an interaction with transmission intensity however the associations with age and with fever in the last two weeks did vary significantly.

Keywords: Malaria, Malaria risk, Anaemia, Fever, ITN use, ITN ownership, Democratic Republic of Congo, Kinshasa

4.2 Background

Urbanization, widespread use of malaria control measures and effective treatment in recent years have had a significant impact in reducing the prevalence of malaria in many African cities, as well as contributing to the more heterogeneous risk in malaria observed in many urban areas (Staedke *et al.* 2003; Keiser *et al.* 2004; Caldas de Castro *et al.* 2004; Wang *et al.* 2005; Matthys *et al.* 2006). In Kinshasa, the capital of the DRC malaria has considerably decreased during the past thirty years. A survey conducted in 2011, showed a prevalence of 17% among children 6-59 months of age, and the existence of a gradient of prevalence from the centre (lower risk) to the periphery (higher risk) (Mulumba *et al.* 1990; Ngimbi *et al.* 1982; Kazadi *et al.* 2004; Ferrari *et al.* 2016). Moreover, traditionally attention has focused on high risk groups, and little attention has been put on older children and adults. Understanding the complex heterogeneity of risk factors that can contribute to increased risk of malaria in urban settings across different age groups will enable a more effective use of control measures.

In addition, many studies have shown that control of malaria can reduce the prevalence of childhood anaemia (Premji *et al.* 1995; Premji *et al.* 1995; Korenromp *et al.* 2004; Lengeler 2004; Mathanga *et al.* 2010). Anaemia, in particular due to iron deficiency, is a major public health challenge in paediatric populations in sub-Saharan Africa, and in DRC it is among the top five leading causes of years lived with disability (YLDs) (GBD 2010). In Kinshasa the current rate of anaemia (Hb<11 g/dl) among pre-school aged children was 65% in 2011 (Ferrari *et al.* 2016).

The present study investigated individual and household risk factors for *Plasmodium falciparum* infection and anaemia in Kinshasa in children aged 6-59 months in 25 non-rural HZ, as well as in individuals aged five years and older in a separate analysis in two HZ.

4.3 Methods

Study area and recruitment of study participants

This study used cross-sectional data from a survey conducted in 2011 in Kinshasa, the capital city of the DRC, which is described in detail in Ferrari *et al.* 2016 (Ferrari, *et al.* 2016). In summary, data collection took place from April to June 2011, before the end of the rainy season and included 2512 households selected through a multi stage sampling procedure to obtain a sample of 3342 children aged 6 to 59 months from 25 health zones (HZ) and 816 individuals aged five years or older from two HZ selected out of the 25 (Ngiri Ngiri and Selembao). The HZ represents the primary operational unit of the health system in DRC, and covers about 150.000 inhabitants. It includes a general referral hospital, health centres and lower-level health facilities. Each HZ is further divided in health areas. In Kinshasa malaria transmission is ensured by *Anopheles gambiae s.l.*, and usually peaks during the long rainy season from September to May (Coene 1993). From each participant a finger-prick blood sample was collected to test for malaria by rapid diagnostic test (RDT) (SD Bioline Malaria Antigen P.f/Pan), providing an immediate on-site diagnosis. The level of haemoglobin (Hb) was measured with a HemoCue 201 plus+ photometer (Ångelholm, Sweden). Axillary temperature was measured using a digital thermometer and the individual's history of fever in the preceding two weeks was also recorded. A standardized electronic survey questionnaire was administered to all heads of eligible household using an HTC smartphone running with Android OS. The survey questionnaire was an adaptation of the standard Malaria Indicator Survey Questionnaire from the Roll Back Malaria Partnership (www.RBM.org) created with the Build component of the Open Data Kit (ODK) software (University of Washington & Google Foundation). Respondents were asked about demographic information of the residents, educational level, assets owned (such as television and bicycle), presence of insecticide treated bed net (ITN) and use of ITN the night prior to the survey.

Assessing risk factors of *Plasmodium* infection and anaemia

The analysis was stratified according to malaria transmission intensity, based on the prevalence of malaria infection measured in 2011 among children 6-59 months (Ferrari *et al.*, 2016). The prevalence ranged from 0.7 % to 46% in children aged 6 to 59 months. Two strata were defined at the HZ level: a prevalence of infection below 10% or prevalence above 10%. The 10% prevalence cut-off was an arbitrary selection to allow enough observations in each stratum. *Plasmodium* infection and anaemia were assessed for their association with a number

of variables. For individuals aged older than five years, data collection took place in only two HZ with different transmission intensities (Ngiri Ngiri, 0.8% and Selembao, 26.8% in children younger than 5 years); these data were analysed separately.

The primary outcomes of the study were the presence or absence of *Plasmodium* malaria as measured by rapid diagnostic test (RDT) and the anaemia test results. A child aged 6 to 59 months was defined as anaemic if his/her Hb was below 11.0 g/dl. Therefore, the outcomes variables were dichotomous. Recorded explanatory variables were: age, gender, educational level of the respondent, occupation of the respondent, insecticide mosquito-net use and reported fever during the last two weeks and wealth index. A wealth index, calculated according to the method of Filmer *et al.* (2001), was constructed for each household based on ownership of household assets (having a television, a radio, etc.) and house characteristics (having electricity, drinking water, toilet type, roof and ground material) (Filmer *et al.*, 2001). Three categories were generated to classify households ranging from the poorest to the least poor in the community.

Statistical methods

The proportions with malaria infection and with anaemia were analysed using a logistic regression model with random effects to take account clustering by health zone and health area. All analysis were performed separately for children (6 to 59 months) and individuals older than five years since they were sampled from different HZ. The analysis was carried out using STATA version 13 (Stata Corporation College Station, TX, USA).

Ethics approval and consent to participate

Ethical approval of the study was obtained from the ethics committee of the Kinshasa School of Public Health University of Kinshasa, in DRC, as well as the ethical committee in Basel (Ethikkommission beider Basel, Basel-Stadt). Individual written informed consent was obtained by parents or guardian on behalf of their children (until the age of 10) or by the adults study participants themselves. In addition, assent was obtained from children over 10 years of age. Every precaution to minimize the risk of infection during blood sampling was taken. All patients who tested positive for malaria by RDT were treated for free by the nationally recommended therapy combination with artemisinin, artesunate plus amodiaquine (ASAQ), previously placed at the health centre of reference of the corresponding health area.

4.4 Results

Data collection took place in 2512 households, in the 25 HZ that were visited. A total of 3342 children aged 6-59 months were included in the analysis, 1118 and 2224 in the low and high transmission setting respectively. A similar number of males (50%) and females were included; the median age was 30 months (90% central range 9–55). Table 4-1 shows the number of children examined, by HZ and by transmission strata. For individuals above 5 years, data collection took place in two HZ only and included 816 individuals, of which 34% were males and the median age was 22 years (90% central range 6–62).

Table 4-1: Number of children 6 to 59 months examined and prevalence of *Plasmodium spp* in Kinshasa, by health zone and strata, 2011

Health zone	**Malaria prevalence in children aged 6-59 months [95% CI]**					
	<10%			**>10%**		
	%		**N**	**%**		**N**
Bandalungwa	1.5	[0.2-5.3]	134			
Barumbu	2.4	[0.5-6.9]	125			
Binza Météo				24.8	[17.0-34.0]	109
Binza Ozone				19.1	[12.9-26.7]	136
Biyela				46.0	[37.1-55.1]	126
Gombe				11.5	[6.7-18.0]	139
Kalamu I				16.2	[8.4-27.1]	68
Kalamu II	2.5	[0.8-5.7]	200			
Kikimi				32.8	[24.9-41.6]	131
Kimbanseke				36.1	[27.9-44.9]	133
Kingasani				25.0	[18.3-32.7]	152
Kinshasa	0.7	[0.0-4.0]	136			
Kintambo				11.7	[7.0-18.1]	145
Lemba	7.7	[3.8-13.7]	130			
Limete				17.3	[11.3-24.8]	133
Lingwala	0.7	[0.0-4.1]	135			
Makala				17.9	[11.8-25.5]	134
Masina I				12.3	[7.3-19.0]	138
Masina II				24.8	[17.7-33.0]	133
Mont Ngafula I				33.6	[25.7-42.2]	134
Mont Ngafula II				35.3	[27.3-44.1]	133
Ngaba	7.5	[3.6-13.3]	134			
Ngiri Ngiri	0.8	[0.0-4.2]	124			
Police				17.0	[11.1-24.5]	135
Selembao				26.8	[19.9-34.7]	145
TOTAL N			1118			2224

Risk factors for *Plasmodium* infection in children aged 6-59 months (25 HZ)

The risk factors for *Plasmodium* infections in children 6-59 months are shown in Table 2. There was an increase in the proportion with malaria infection with age in both transmission strata. The greatest risk was in children 48-59 months: an odds ratio (OR) of 5.86 (95% confidence interval (CI) 1.62-21.17) for the 36-47 months group and an OR of 15.53 (95% CI 4.26-56.64) for the 48-59 months group, compared to the youngest age group. The effect was also seen in higher transmission strata, although the OR was lower: an OR of 1.73 (95% CI 1.36-2.20) for the 36-47 months group and an OR of 2.54 (95% CI 1.93-3.35) for the 48-59 months group compared to the youngest age group. The interaction between age and transmission intensity was significant (p=0.009).

Treated net use was found to significantly lower malaria infection risk in the higher transmission strata with 38% protection (OR=0.62, 95% CI 0.50 – 0.77), however the effect was not significant in the lower transmission strata. Children who reported fever in the last two weeks had a significantly elevated risk of malaria infection in both strata.

Higher education levels showed a trend towards being protective in both transmission settings (Table 4-2). However there was no evidence of an association with the occupation of the respondent. Finally, children living in the wealthiest tertile were significantly less likely to have a malaria infection compared to the children from the poorest tertile in strata of high transmission (OR=0.27, 95% CI 0.20-0.38, p<0.001). No evidence was found in the HZ with less than 10% prevalence (OR=0.82, 95% CI 0.31-2.13, p=0.83), however the interaction between socioeconomic status and transmission was not significant (p=0.14).

Table 4-2: Univariate and multivariate analysis of risk factors associated with malaria in children between 6 and 59 months of age in Kinshasa, stratified by malaria transmission zone

	< 10% prevalence								> 10% prevalence								
			Univariate analysis			Multivariate analysis					Univariate analysis			Multivariate analysis			Interaction by transmission
Variable	***n***	**(%)**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**	***n***	**(%)**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**	***P*-value**
Sex																	
Male	521	3.1	1			1			1141	23.6	1			1			
Female	527	2.7	0.86	0.42-1.8	0.687	0.87	0.41-1.88	0.731	1162	23.3	1.01	0.84-1.23	0.886	0.98	0.80-1.21	0.857	0.670
Age																	
6-35 months	446	0.7	1			1			958	17.8	1			1			
36-47 months	416	3.1	4.76	1.35-16-		5.86	1.62-		872	25.5	1.57	1.26-1.97		1.73	1.36-2.20		
48-59 months	186	7.5	12.0	3.41-	< 0.001	15.5	4.26-	< 0.001	473	31.1	2.08	1.61-2.68	< 0.001	2.54	1.93-3.35	< 0.001	0.009
Reported treated bed net																	
No	446	3.6	1			1			1342	27.6	1			1			
Yes	596	2.3	0.65	0.31-1.34	0.240	0.82	0.38-1.76	0.606	961	17.6	0.56	0.46-0.69	< 0.001	0.62	0.50-0.77	< 0.001	0.705
Fever in the last two																	
No	798	1.6	1			1			1744	18.3	1			1			
Yes	245	6.9	4.50	2.15-9.41	< 0.001	5.53	2.52-	< 0.001	559	39.4	2.89	2.34-3.56	< 0.001	2.94	2.36-3.68	< 0.001	0.254
Education of the																	
No education	24	8.3	1			1			220	32.3	1			1			
Primary	390	3.6	0.41	0.09-1.92		0.35	0.07-1.82		1135	26.5	0.76	0.55-1.03		0.90	0.65-1.26		
Secondary	471	2.8	0.31	0.07-1.47		0.28	0.05-1.50		740	19.7	0.52	0.37-0.72		0.78	0.54-1.14		
Superior and above	163	0.6	0.07	0.01-0.78	0.080	0.05	0.00-0.68	0.084	208	10.6	0.25	0.15-0.42	< 0.001	0.47	0.26-0.86	0.056	0.754
Occupation of the																	
Without occupation	720	2.8	1			1			1523	23.2	1			1			
Manual labour	86	2.3	0.83	0.19-3.63		0.98	0.21-4.47		212	27.8	1.27	0.92-1.76		1.29	0.91-1.84		
Self employed	104	3.8	1.40	0.47-4.18		1.58	0.49-5.11		275	24.7	1.08	0.80-1.46		1.01	0.74-1.38	0.236	
Employed	138	2.9	1.04	0.35-3.11	0.931	1.79	0.51-6.31	0.742	293	20.1	0.83	0.61-1.13	0.229	1.35	0.95-1.94		0.860
Wealth tertile																	
Poorest	196	4.1	1			1			1175	31.6	1						
Middle	298	3.0	0.73	0.28-1.93		0.72	0.26-2.04		575	19.5	0.52	0.41-0.67		0.54	0.42-0.70		
Wealthiest	546	2.4	0.57	0.23-1.40	0.488	0.82	0.31-2.13	0.828	540	9.44	0.23	0.17-0.31	< 0.001	0.27	0.20-0.38	< 0.001	0.142

Risk factors for *Plasmodium* infection in individuals older than 5 years (2 HZ)

The risk factors for *Plasmodium* infection in individuals aged older than five years are shown in Table 4-3. The association between age and malaria infection was strong. The highest prevalence was observed in the 15-19 years age group in the low transmission HZ of Ngiri Ngiri with an OR of 7.11 (95% CI 1.17-43.05) compared to the 5-9 years-old. In the higher transmission HZ of Selembao however, OR were lower and more homogeneously distributed across all age groups, compared to the 5-9 years-old group which showed the highest prevalence. The interaction between age and transmission intensity however was not significant (p=0.11).

ITN use was not found to significantly lower the prevalence of malaria infection, although the estimates were in the direction of being protective. Individuals aged five years and older who reported fever in the last two weeks had an elevated risk of having malaria infection in both sites, and the association was stronger for the lower transmission: OR = 38.71 (95% CI 11.08-135.23), and OR = 2.05 (95% CI 1.07-3.95) in Selembao, with a highly significant interaction term (p<0.0001). There was no evidence of an effect of higher education levels, occupation of the respondent or socio-economic status.

Table 4-3: Univariate and multivariate analysis of risk factors associated with malaria in individuals aged > 5 years in Kinshasa, stratified by malaria transmission zone, 2011

	Ngiri Ngiri: 0.8% prevalence								Selembao: 26.8% prevalence								
			Univariate analysis			Multivariate analysis					Univariate analysis			Multivariate analysis			Interaction by transmission zone
Variable	***n***	**(%)**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**	***n***	**(%)**	**OR**	**95% CI**	***P*-**	**OR**	**95% CI**	***P*-**	***P*-value**
Sex																	
Male	142	5.6	1.0			1.0			143	28.7	1.0			1.0			
Female	257	4.3	0.75	0.29-1.91	0.548	0.74	0.23-2.37	0.616	274	20.1	0.62	0.39-	0.050	0.66	0.40-1.08	0.102	0.733
Age																	
5-9 years	62	4.8	1.0			1.0			76	34.2	1.0			1.0			
10-14 years	68	1.5	0.29	0.03-2.90		0.22	0.01-3.39		68	25.0	0.64	0.31-		0.79	0.37-1.72		
15-19 years	48	14.6	3.36	0.82-13.75		7.11	1.17-43.05		46	28.3	0.76	0.34-		0.85	0.37-1.96		
> 20	221	3.6	0.74	0.19-2.87	0.022	1.09	0.21-5.72	0.009	227	17.6	0.41	0.23-	0.021	0.45	0.24-0.83	0.042	0.105
Reported treated bed net use																	
No	244	6.1	1.0			1.0			315	25.7	1.0			1.0			
Yes	155	2.6	0.40	0.13-1.24	0.089	0.33	0.09-1.21	0.075	102	14.7	0.50	0.27-	0.017	0.57	0.30-1.09	0.078	0.746
Fever in the last two weeks																	
No	366	2.2	1.0			1.0			361	21.6	1.0			1.0			
Yes	33	33.3	22.38	8.17-61.27	< 0.001	38.71	11.08-135.23	< 0.001	54	33.3	1.81	0.98-	0.066	2.05	1.07-3.95	0.036	< 0.001
Education of the respondent																	
No education	8	12.5	1.0			1.0			35	34.3	1.0			1.0			
Primary	120	5.0	0.37	0.04-3.50		0.18	0.01-2.49		186	26.9	0.70	0.33-		0.82	0.36-1.87		
Secondary	189	4.8	0.35	0.04-3.16		0.27	0.02-3.48		145	18.6	0.44	0.19-		0.49	0.20-1.19		
Superior and above	82	3.7	0.27	0.02-2.91	0.802	0.17	0.01-2.87	0.647	51	13.7	0.30	0.11-	0.041	0.32	0.09-1.13	0.115	0.865
Occupation of the																	
Without occupation	244	5.7	1.0			1.0			200	26.0	1.0			1.0			
Manual labourer	37	2.7	0.46	0.06-3.58		0.82	0.09-7.91		64	23.4	0.87	0.45-		1.17	0.58-2.37		
Self employed	27	3.7	0.63	0.08-5.00		1.33	0.13-13.64		56	16.1	0.55	0.25-	0.398	0.56	0.24-1.28	0.425	
Employed	91	3.3	0.56	0.16-2.00	0.696	0.59	0.11-3.20	0.913	97	20.6	0.74	0.41-		1.12	0.56-2.23		0.911
Wealth tertile																	
Poorest & middle [a]	162	4.9	1.0			1.0			201	25.4	1.0			1.0			
Wealthiest	237	4.6	0.94	0.37-2.38	0.891	1.31	0.18-9.64	0.618	99	19.2	0.74	0.42-	0.293	0.91	0.48-1.73	0.779	0.676

[a] Combined due to low number of observations

Risk factors for anaemia in children aged 6-59 months (25 HZ)

The risk of having anaemia was found to decline progressively with increasing age (Table 4-4) in both low and high transmission strata ($p<0.001$). Although there was no evidence that malaria infection increased the risk of having anaemia in the low transmission strata (OR=2.01, 95% CI 0.89-4.51), this effect was significant in the higher transmission strata (OR=3.40, 95% CI=2.60–4.44). There was no evidence that reported ITN use was protective for the anaemia status in either stratum. There was also no evidence of an association neither with fever nor with education or occupation. Belonging to the wealthiest tertile was borderline significantly associated with the risk of having anaemia in both low transmission (OR=0.68, 95% CI=0.47-0.99) and high transmission strata.

Table 4-4: Univariate and multivariate analysis of risk factors associated with anaemia in children between 6 and 59 months of age in Kinshasa, stratified by malaria transmission zone, 2011

	< 10%								> 10%								
			Univariate analysis			Multivariate analysis					Univariate analysis			Multivariate analysis			Interaction by transmission zone
Variable	***n***	**(%)**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**	***n***	**(%)**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**	***P*-value**
Sex																	
Male	521	55.5	1.0			1.0			1161	69.0	1.0			1.0			
Female	526	59.7	1.19	0.93-1.52	0.167	1.21	0.93-1.58	0.160	1142	66.5	0.89	0.75-1.07	0.210	0.93	0.77-1.12	0.355	0.064
Age																	
6-35 months	445	73.0	1.0			1.0			957	80.6	1.0			1.0			
36-47 months	416	50.5	0.38	0.28-0.50		0.38	0.28-0.51		873	61.6	0.39	0.31-0.48		0.35	0.28-0.43		
48-59 months	186	36.6	0.21	0.15-0.31	< 0.001	0.19	0.13-0.28	< 0.001	473	53.3	0.28	0.22-0.35	< 0.001	0.23	0.18-0.29	< 0.001	0.473
Education of the respondent																	
No education	24	70.8	1.0			1.0			220	75.0	1.0			1.0			
Primary	390	62.1	0.67	0.27-1.66		0.64	0.24-1.70		1135	69.4	0.76	0.54-1.05		0.83	0.58-1.20		
Secondary	471	57.7	0.56	0.23-1.38		0.57	0.21-1.50		740	64.9	0.62	0.44-0.86		0.78	0.53-1.15		
Superior and above	162	44.4	0.33	0.13-0.84	< 0.001	0.35	0.13-0.99	0.037	208	61.5	0.53	0.35-0.81	0.004	0.80	0.49-1.31	0.629	0.412
Occupation of the respondent																	
Without occupation	720	60.7	1.0			1.0			1523	68.8	1.0			1.0			
Manual labourer	86	39.5	0.42	0.27-0.67		0.41	0.25-0.68		212	69.3	1.03	0.75-1.40		0.97	0.69-1.36		
Self-employed	104	60.6	1.00	0.65-1.52		1.03	0.65-1.63		275	65.1	0.85	0.64-1.11		0.77	0.58-1.03		0.010
Employed	137	50.4	0.66	0.46-0.95	< 0.001	0.94	0.61-1.44	0.005	293	63.8	0.80	0.62-1.04	0.268	0.92	0.68-1.24	0.313	
Net use																	
No	446	57.2	1.0			1.0			1341	68.3	1.0			1.0			
Yes	595	57.5	1.01	0.79-1.30	0.922	0.91	0.70-1.20	0.515	962	67.0	0.94	0.79-1.13	0.524	1.09	0.90-1.32	0.512	0.653
Malaria infection																	
No	1017	57.3	1.0			1.0			1762	63.1	1.0			1.0			
Yes	30	66.7	1.49	0.69-3.21	0.302	2.01	0.89-4.51	0.078	540	83.1	2.89	2.26-3.69	< 0.001	3.40	2.60-4.44	< 0.001	0.119
Fever in the last two weeks																	
No	798	54.6	1.0			1.0			1744	65.0	1.0			1.0			
Yes	244	66.4	1.64	1.22-2.21	< 0.001	1.30	0.93-1.80	0.197	559	76.4	1.74	1.40-2.17	< 0.001	1.32	1.04-1.67	0.039	0.755
Wealth tertile																	
Poorest	196	62.2	1.0			1.0			1176	72.9	1.0			1.0			
Middle	298	65.8	1.17	0.80-1.70	0.423	1.14	0.76-1.71		574	64.1	0.66	0.54-0.82	0.000	0.78	0.62-0.99		
Wealthiest	545	51.9	0.66	0.47-0.92	0.013	0.68	0.47-0.99	0.003	540	60.7	0.58	0.46-0.71	0.000	0.77	0.60-0.99	0.073	0.022

ITN use

There were some age-specific differences in ITN usage (Figure 4-1), with highest use in younger children (p-value=0.006) in the low transmission strata. In areas of high transmission, ITN usage although lower appeared more homogeneously distributed across age groups (Figure 4-1). No significant differences in the utilization were found among individuals age more than five years, in both low and high transmission strata (Figure 4-1).

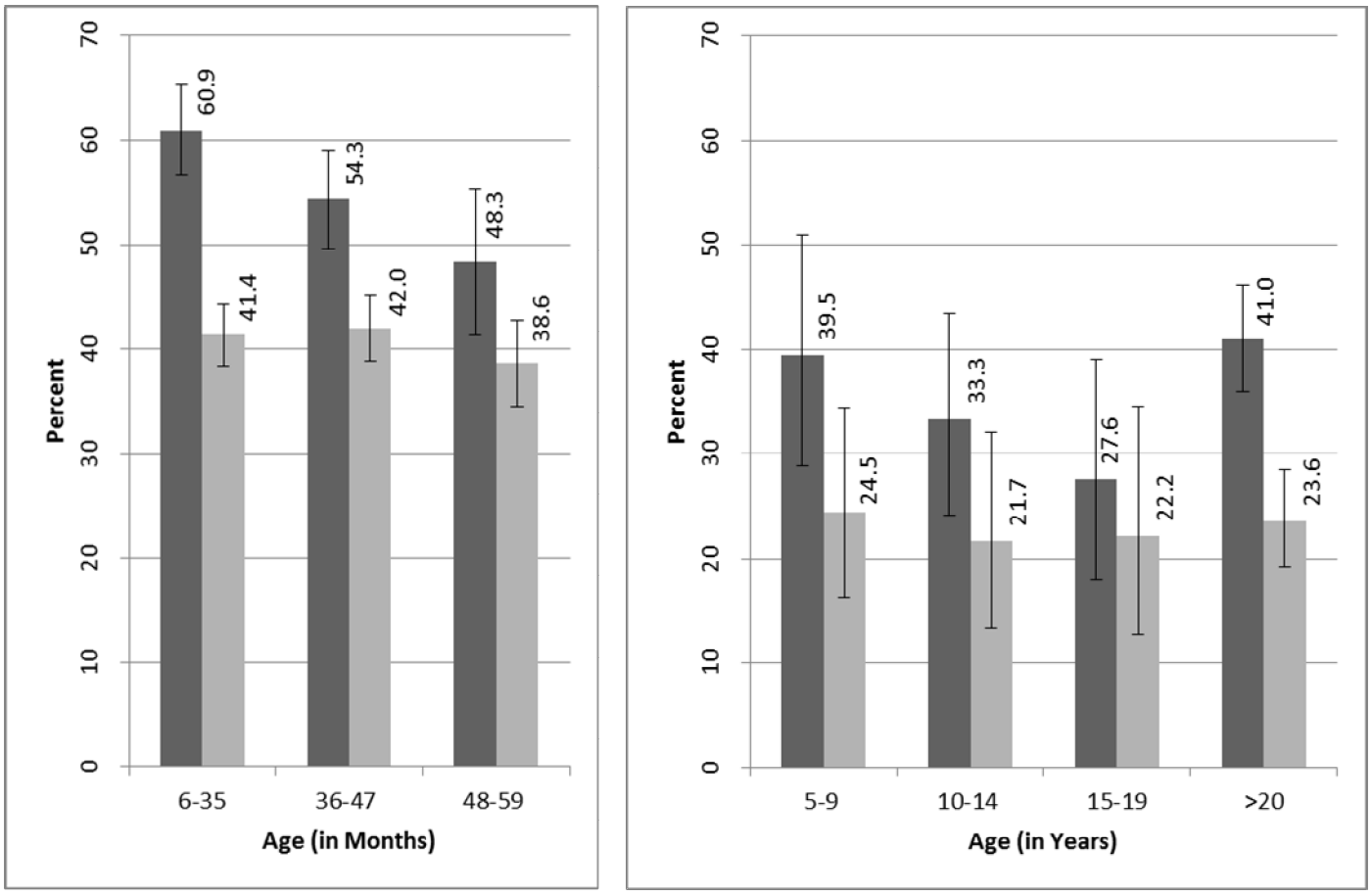

Figure 4-1: Left panel: ITN usage among children 6 to 59 months by transmission intensity. Right panel: ITN usage among individuals older than five years in Ngiri Ngiri (0.8%) and Selembao (26.8%) in Kinshasa, 2011. Light grey bars represent proportions of reported ITN usage in high transmission strata, and dark grey bars in low transmission strata. Error bars indicate 95% CI.

4.5 Discussion

The identification of risk factors for malaria infection and anaemia, provides information on the local malaria epidemiology and has the potential to lead to a more effective and targeted use of malaria control measures. This study presents the results of an analysis of the association of a number of variables that alone or in combination could affect the risk of acquiring *Plasmodium* infection and anaemia, in a city with diverse malaria transmission patterns. The key results from this analysis are the association between malaria infection and age, with older age groups being exposed to higher risk of malaria in low transmission settings and a lower and more homogeneous risk across all age groups in high transmission settings. Shift in the age of peak prevalence towards the older groups has been described for malaria and other infectious diseases and is consistent with exposure-related acquired immunity (Woolhouse 1998; Snow & Marsh 2002). In zones of low transmission, children are less exposed to infective malaria, hence delaying the age of the first infection and the acquisition of immunity (Winskill *et al.* 2011). Clearly, in Kinshasa the risk of *Plasmodium* infection seems to occur later in childhood, which is consistent with areas of rather low levels of transmission. The prevalence rates by HZ shown in Table 1 (range: 0.7-46.0), with most HZs below 30% confirm that Kinshasa overall has a moderate endemicity level. Recent school surveys done in Kimbanseke, a relatively high prevalence HZ southeast of Kinshasa, found similar results, showing children aged 10-13 at higher risk of malaria and a high prevalence of asymptomatic infections (Matangila *et al.* 2014).

The relationship of ITN use by the different age groups could also influence the age pattern of risk that was observed: children in the youngest age group, 6-35 months, were significantly more likely to sleep under an ITN in the low transmission setting, whereas utilization was similar among age groups in high transmission setting. A similar shift in age of peak of prevalence towards the older children has been observed elsewhere with an increase in net coverage (Wang *et al.* 2006). Only 44% of children 6-59 months used an ITN the night preceding the survey, which is still far from universal coverage. In individuals > 5 years, overall ITN use was even lower, with only 38% and 23.3% using an ITN in Ngiri Ngiri and Selembao, respectively. In addition, less than 58% of HHs owned enough ITNs to cover all household members in 2011. These low values are of concern.

Higher malaria prevalence in older children has also been attributed to increased use of antimalarials in early childhood (Trape 1987).

In case of fever in Kinshasa, it is common practice by the caregivers to initially treat their child at home (54% of the cases) although only 4.3% of the children treated for fever receive a recommended combination therapy containing artemisinin (unpublished data).

Results indicated that sleeping under an ITN the previous night reduced the risk of *Plasmodium* infection by 38% (OR=0.62, 95% CI 0.50 – 0.77) among children 6-59 months of age in areas of high transmission, consistent with the vast body of evidence supporting the efficacy and effectiveness of ITN in protecting against malaria(Lengeler 2004). In low transmission areas, however, there was no evidence of such an association, presumably because the overall risk of infection was lower.

Reported history of fever was associated with malaria infection overall. There was evidence of a difference in this association with transmission level among individuals aged older than five years ($p<0.001$). The weaker association of reported fever with malaria in areas of high transmission could be explained by differences in the levels of acquired immunity.

The data confirm that anaemia is frequent in urban Kinshasa, with 65% prevalence among children 6-59 months, 30% moderate (7.0-9.9 g/dl) and 1.9% severe (< 7.0 g/dl). ITN use in Kinshasa did not appear to be associated with benefits in lower anaemia risk, contrary to what has been documented in other settings (Premji *et al.* 1995; Korenromp *et al.* 2004; Lengeler 2004; Mathanga *et al.* 2010). These findings are consistent with a Kenyan study that found only a small difference in prevalence of anaemia between villages with and without ITNs (Mathanga *et al.* 2010). Anaemia has many causes in addition to malaria (nutrition (UNICEF, 2010), soil transmitted infections (STH) and schistosomes), and in Kinshasa these are likely to also be contributors to this morbidity. A recent study revealed a high prevalence of STH infections among primary school children in Kinshasa (32.8%) (Matangila *et al.* 2014). Nevertheless, the estimated odds of anaemia in zones of high transmission were 3.5 times (95% CI 2.70-4.62) higher in malaria infected children.

In this study, the risk of anaemia was shown to decrease with increasing age in both low and high transmission strata. These results are consistent with studies conducted in West Africa, showing a significant reduction in the mean haemoglobin level in children aged 2-5 years compared to children aged 1-2 (Soares Magalhães *et al.* 2011).

This study also showed differences in the effect in malaria risk or anaemia risk by socioeconomic status, consistent with previous studies carried out in sub-Saharan Africa (De Beaudrap *et al.* 2011; Gahutu *et al.* 2011; Winskill *et al.* 2011; Ayele *et al.* 2012), and as documented in a multi country analysis of DHS data (Balarajan *et al.* 2011).

This study however has some limitations. Foremost, the analysis draws on cross-sectional data; hence the causal nature of associations should be viewed with a certain caution. A second most important limitation of the study relates to the smaller sample size for individuals over five years compared to that of children 6-59 months, limiting our ability to potentially detect important differences and interactions between risk factors and transmission. Furthermore, the low proportion of males for this survey (34%) may have triggered a gender-response bias, with consequences on the prevalence and associations found. The direction and magnitude of a possible bias remain unknown. Lastly, RDTs are limited in sensitivity to detect low density parasitaemia and their use may have led to an underestimation of the true proportion of people infected with *Plasmodium falciparum*. The underestimation may have differed with acquired immunity affecting the age pattern (Alves *et al.* 2002; Nicastri *et al.* 2009; Harris *et al.* 2010; Wu *et al.* 2015).

4.6 Conclusions

For the most part, there was no evidence of an interaction between malaria infections and the risk factors with transmission intensity; however the associations with age and with fever in the last two weeks did vary significantly. The results also show that school-aged children are the least protected with ITN, across the different transmission settings, hence representing an important reservoir for infection. The observation of a shift in the peak age of risk for malaria to older groups is consistent with areas of low transmission and highlights the need for a more equal distribution of ITN in Kinshasa to target all age groups and not only the traditional high-risk group of young children.

5 An operational comparative study of quinine and artesunate for the treatment of severe malaria in hospitals and health centres in the Democratic Republic of Congo: The MATIAS study

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5.1 Abstract

Background

The Democratic Republic of the Congo (DRC) has the highest number of severe malaria cases in the world. In early 2012, the National Malaria Control Programme (NMCP) changed the policy for treating severe malaria in children and adults from injectable quinine to injectable artesunate. To inform the scaling up of injectable artesunate nationwide, operational research is needed to identify constraints and challenges in the DRC's specific setting.

Methods

The implementation of injectable quinine treatment in 350 patients aged two months or older in eight health facilities from October 2012 to January 2013 and injectable artesunate in 399 patients in the same facilities from April to June 2013 was compared. Since this was an implementation study, concurrent randomised controls were not possible. Four key components were evaluated during each phase: 1) clinical assessment, 2) time and motion, 3) feasibility and acceptability, and 4) financial cost.

Results

The time to discharge was lower in the artesunate (median = 2, 90% central range 1 – 9) compared to the quinine group (3 (1 – 9) days; p <0.001). Similarly, the interval between admission and the start of intravenous (IV) treatment (2 (0 – 15) compared to 3 (0 – 20) hours; p <0.001) and parasite clearance time (23 (11 – 49) compared to 24 (10 – 82) hours; p <0.001) were lower in the artesunate group. The overall staff pre-administration time (13 (6 – 38) compared to 20 (7 – 50) minutes; p <0.001) and the personnel time spent on patient management (9 (1 – 24) compared to 12 (3 – 52) minutes; p <0.001) were lower in the artesunate group. In hospitals and health centres, the mean (standard deviation, SD) total cost per patient treated for severe malaria with injectable artesunate was USD 51.94 (16.20) and 19.51 (9.58); and USD 60.35 (17.73) and 20.36 (6.80) with injectable quinine.

Conclusions

This study demonstrates that injectable artesunate in the DRC is easier to use and that it costs less than injectable quinine. These findings provide the basis for practical recommendations for rapid national deployment of injectable artesunate in the DRC.

5.2 Background

The Democratic Republic of the Congo (DRC) has the highest severe malaria burden in the world (WHO 2011c). The combination of artesunate plus amodiaquine (AS-AQ) was adopted as a first-line treatment for uncomplicated malaria in 2005, with a second ACT, artemether plus lumefantrine (AL), added in 2010. Meanwhile, injectable quinine remained the recommended first-line drug for cases of treatment failure and for severe malaria.

In 2010, the AQUAMAT trial demonstrated that treating severe malaria with artesunate reduced the case fatality rate in African children (<15 years) by 22.5% compared to treatment with injectable quinine (Dondorp *et al.* 2010). Previously, the benefit of artesunate compared to quinine had been demonstrated in adults in the SEAQUAMAT trial carried out in Southeast Asia (Dondorp *et al.* 2005). These results led to the recommendation of injectable artesunate as the treatment of first choice for severe malaria in children and adults in the WHO guidelines in 2011 (WHO 2011b).Nevertheless, cases of delayed haemolytic anaemia secondary to injectable artesunate administration were reported and the causative role of artesunate is still controversial. Its long-term safety profile is under evaluation. In addition to its efficacy, injectable artesunate offers a number of programmatic advantages over quinine, such as eliminating the need for rate-controlled infusions or cardiac monitoring, and the risk of induced hypoglycaemia (WHO 2011b).

In 2012, the National Malaria Control Programme (NMCP) of the DRC, with support from the relevant ministry departments, decided to adopt the revised WHO severe malaria treatment guidelines, which strongly recommended injectable artesunate in preference to quinine or artemether as first-line treatment for severe malaria. An implementation period of three years to scale up injectable artesunate was included in the national strategic plan.

This transition will require many operational and clinical adaptations. To support this process, there is a need for locally derived operational experience addressing constraints and challenges, something that all implementing countries will have to consider. These data are essential for three reasons: 1) better planning of the implementation of the new treatment based on quantified operational parameters; 2) identifying constraints and pitfalls to guide the training of health care providers; and, 3) providing strong and locally relevant arguments in situations where the health staff are reluctant to accept the change of treatment.

The present MATIAS study ('MAlaria Treatment with Injectable ArteSunate') aims to support the national introduction of injectable artesunate as the first-line treatment of severe malaria in the DRC by assessing four key components: 1) clinical safety, 2) time and motion, 3) feasibility and acceptability, and 4) cost.

5.3 Methods

Study design

The MATIAS study was an observational implementation study of patients aged two months and older with severe malaria and included two successive phases. In the first phase, between October 2012 and January 2013, severe malaria patients were treated with intravenous (IV) quinine. Then, between April and June 2013, severe malaria patients were treated with IV artesunate.

Four components were evaluated in each phase: 1) clinical safety, assessed on the basis of limited routine patient information; 2) time and motion parameters; 3) feasibility and acceptability; and 4) financial costs. The results of the feasibility and acceptability component required additional in-depth studies and are reported elsewhere (Ntuku *et al.*, personal communication).

Participants (population, inclusion, exclusion criteria)

The study population consisted of patients admitted with severe malaria to one of the study sites between October 2012 and June 2013. Patients were included in the study if they were older than two months, fulfilled the WHO criteria of severe *Plasmodium falciparum* malaria (WHO 2013a), had either a positive rapid diagnostic test (RDT) for *P. falciparum* (SD Bioline Malaria Antigen P.f/Pan Standard Diagnostics Inc, Yongin, South Korea) and/or a positive Giemsa-stained thick blood smear on admission, and they or their relative or guardian gave informed written consent. Patients were excluded if they had a known serious adverse reaction to quinine and/or artemisinin derivatives, or if there was a history of adequate anti-malarial treatment for more than 24 hours before admission.

Women with known or suspected pregnancy in all trimesters during the second (artesunate) phase were not included and were treated with quinine according to the national guidelines (PNLP, 2012). Pregnancy status was determined by details from the patient's history and/or by a positive pregnancy test.

Signed informed consent for participation was obtained in French or in the local language from all participants or from their relatives or guardians. Because of the life-threatening nature of the disease, an initial consent was obtained from the accompanying relative or guardian on behalf of the patient, if necessary, and final consent was solicited as soon as the patient was able to decide and respond. Since this was an observational study, investigators did not intervene in patient management, which was left to the discretion of the attending physicians. Ethical clearance for the study was obtained from the Ethics Committee of both Cantons of Basel, Switzerland (EKBB, Ref No 201/12) and from the Ethics Committee of the Kinshasa School of Public Health (KSPH Ethics Commission, Ref No 057/12), University of Kinshasa, DRC. The study was registered in ClinicalTrials.gov (Identifier: NCT01828333).

Study settings

The study sites consisted of three hospitals and five health centres in one urban and three rural health zones (HZ) in the DRC, representative of typical health facilities in the country (Figure 5-1). The sample included a large public health hospital (Institut Médical Evangélique, Kimpese, Bas Congo); one medium-sized, non-profit, missionary hospital (St Luc Kisantu); and a medium-sized, government hospital (Centre Hospitalier Roi Baudouin). In addition, five rural health centres were selected within the same HZ (Health Centre Bita, Health Centre Menkao, Health Centre Ngeba, Health Centre CECO, Health centre La Famille) (Figure 5-1 and see additional file 1).

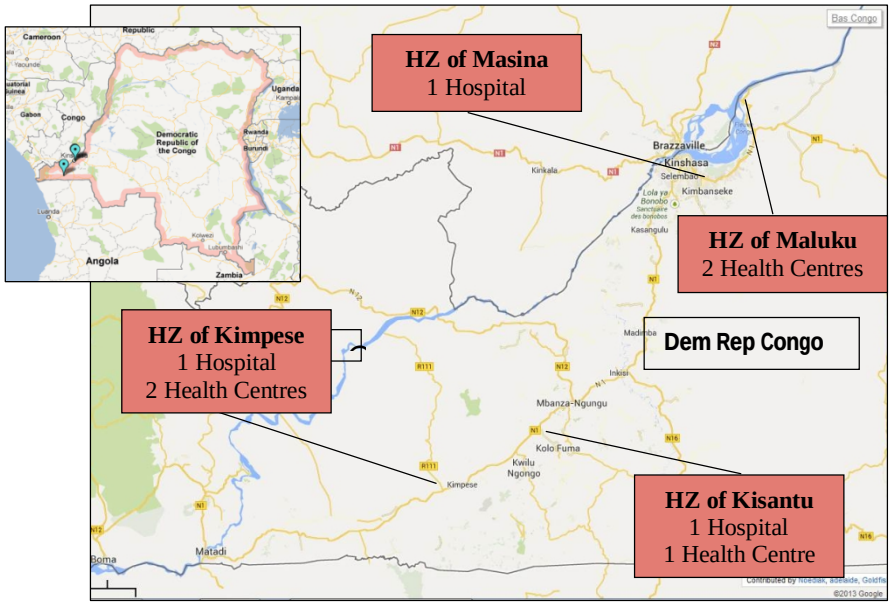

Figure 5-1: Map showing the location of the study sites and the selected health zones

Interventions

During the first phase, patients receiving IV quinine were treated according to the national treatment guidelines. An initial loading dose of 20 mg of quinine salt/kg in 5 – 10 ml isotonic glucose solution (5%) per kg body weight was infused over four hours. Following a rest period of eight hours and 12 hours after administration of the loading dose began, a maintenance dose of 10 mg of quinine salt/kg was given. The maintenance dose was repeated every 12 hours until the patient was able to swallow the oral treatment (WHO 2013a; PNLP 2012). Patients receiving artesunate (Guilin Pharmaceuticals, Shanghai, China) received doses intravenously at 2.4 mg/kg on admission, at 12 and 24 hours, and then once daily until oral treatment could be swallowed (WHO 2013a). The content of each 60 mg vial of artesunate powder was dissolved in 1 ml of sodium bicarbonate and then diluted with normal saline solution or dextrose 5% before IV injection (WHOPARs). At least three doses of artesunate had to be given before switching to a full course of oral treatment. The drugs used for the study were provided for free by the manufacturer (Artesunate, Guilin Pharmaceutical Co. Ltd, Shanghai, China) and by the funding agency, Medicines for Malaria Venture (MMV) (quinine).

Study outcomes

Outcome measures were defined for each of the four study components. For the clinical assessment component, the outcomes were: 1) duration of hospitalisation, defined as the time from hospital registration to discharge, (this was the primary study endpoint); 2) time from hospital admission to start of parenteral treatment; 3) time from initiation of parenteral treatment to initiation of oral treatment; 4) parasite clearance time (PCT), defined as the time from the initiation of a patient's parenteral treatment until the patient's first negative blood film; and 5) clinical status at discharge. For the time and motion component, the main outcome measure was the cumulative staff time required for all steps of drug preparation, administration and patient management. For the feasibility and acceptability component, the main outcomes were health-provider perceived feasibility of patient management, perceived ease of applying drug treatment, and perceived quality of case management by patient/caretaker. These results are reported separately (Ntuku *et al.* 2016). For the financial cost component, the main outcome was the total financial cost of patient management, including treatment.

Sample size calculation

The study sample size was calculated based on seven centres, a mean hospitalisation of 2.23 days (standard deviation of 1.64) (Dondorp *et al.* 2005), 80% power and an assumed 20% shorter hospital stay with injectable artesunate. This calculation yielded 25 patients per centre and study period. Under the assumption of an effect variation by centre with a standard deviation of 0.05, the required number per centre was corrected to 27. This effect was presumed to be moderate, as each centre acted as its own control in the study. The two-phase study design was selected to fit the implementation strategy in this area. To ensure a safety margin and to aid disaggregation of the data by centre, the number of patients to be recruited was finally set to 50 patients of all ages from each centre and per study phase. One of the sites initially selected was removed due to difficulties in initiating the study. However, due to recruitment numbers slightly below expectations during the quinine phase, two additional study centres were added. This amendment increased the number of treatment centres to eight.

Statistical methods

Continuous outcomes were described using their mean and standard deviation, or median and 90% central range if the distribution was skewed. Dichotomous outcomes were summarised as proportions. Clinical characteristics are presented by age groups <five years and ≥five years. Skewed data, such as the time to event outcomes, were compared using the non-parametric Wilcoxon rank sum test. The paper-based questionnaires were double-entered and validated in EpiData version 3.1 software (The EpiData Association, Odense, Denmark) and analysed in Stata version 12.1 (Stata Corp, College Station, TX, USA).

Key procedures

Prior to the first study phase, all investigators and staff involved in the study in each hospital/health centre participated in a three-day training on study procedures. Laboratory technicians received a refresher course on thick blood smear preparation/reading and, before the second phase, a refresher course on haemoglobin (Hb) measurement with the HemoCue 201 plus system (Angelholm, Sweden). Simulated interviews were conducted to practice obtaining informed consent. Local principal investigators took part in practical sessions on filling in the case report forms (CRF). Nurses and doctors attended a separate training on reporting serious adverse events (SAE). Nurses also participated in piloting the time and motion study tool, which included observing and timing the activities related to drug preparation/administration prior to the first data collection. Upon completion of the first phase, hospital and health centre personnel involved in the study convened in Kinshasa for a two-day training on preparing and administering injectable artesunate. Job aids and training tools developed by MMV were used for this training. In addition, each site received ten doses of injectable artesunate for training purposes, allowing health care providers to become familiar with the new drug prior to patient recruitment. Weekly supervision visits to each site throughout the duration of the study ensured regular monitoring of the study team.

Patient assessment

Demographic information and limited routine clinical history data were collected for each patient and local study physicians (hospitals) or nurses (health centres) performed basic routine clinical assessments. A Giemsa-stained thick blood smear was performed and examined every 12 hours during the first 24 hours and then every 24 hours until negative or until patient discharge. For PCT calculations, thick blood smears were later reread for quality control by experienced microscopists at the KSPH, blinded to the results of the first reading and to the RDT results. Hb levels were systematically assessed with a HemoCue 201 plus+ photometer (Angelholm, Sweden) during the second study phase, at hospital admission, at discharge and at follow-up visits on days 7, 14, 21, and 28. The HemoCue testing resulted in a change in study protocol because of reports of haemolytic anaemia following artesunate treatment(Centers for Disease Control and Prevention (CDC) 2013). The results of that extension are presented elsewhere (Burri *et al.* 2014). To ensure the proper functioning of the photometer, high and low Hb liquid controls (HemoCue Eurotrol HemoTrol) were run weekly at each site. Given the observational nature of the study, laboratory tests were not systematically performed and were left to the discretion of the physician or treating nurse, except for parasitological tests required for inclusion in the study and the Hb assessment during the second phase. Time of admission, time of start and end of parenteral treatment, and time to discharge were also recorded for every patient during both phases.

Parenteral treatment was completed by administering a full course of the recommended first-line, oral, combination therapy AS-AQ or AL in the artesunate phase, or with quinine tablets or the standard treatment practiced by the centre in the quinine phase. The first dose of the oral treatment was administered at the health facility in the presence of the nurse responsible. Subsequent doses were administered at home, according to the instructions given to parents and guardians. Patients were discharged at the discretion of the attending physician/nurse, after a final clinical assessment. During the first study phase, patients were asked to return to the hospital/health centre for follow-up seven days after discharge to assess their clinical status and their adherence to oral therapy. In the second study phase, patients were asked to return on days 7, 14, 21, and 28 after discharge to assess the clinical status and adherence to oral therapy and to determine their Hb levels at these time points.

Time and motion

The time and motion methodology consisted of 1) dividing a process into key tasks, and 2) observing each task to assess the average time required to perform it. The sum of the average times spent on each task was used to compute the total average time to complete the process. In each of the three participating hospitals, an external study nurse supervised the time and motion component and was present throughout the study. In the five health centres, the health centre personnel were responsible for the measurements. Therefore, the number of patients followed up was limited as a second nurse was not always available. Observed activities included: 1) pre-administration tasks (preparation of all materials and injectable solution, searching for the vein, setting the infusion in case of quinine), 2) drug administration, and 3) all other activities related to patient management. Observations were made by the nurses using digital stopwatches and a checklist to record the time taken for each task. Inter-observer agreement was not formally assessed. Materials required for all tasks were also recorded on the same observer checklist and this information was used later to calculate financial costs.

Cost of treatment component

A financial cost analysis was carried out from the provider's perspective, accounting only for costs incurred by the hospitals and the health centres. Complete unit cost data on resources used were recorded for 386 patients under quinine and for 333 patients under artesunate. To estimate the mean unit cost, the 2014 average exchange rate (USD 0.00107 to the Congolese Franc) was adopted (OANDA n.d.). Health care costs were divided into four main categories: 1) drug costs (parenteral quinine and artesunate, oral therapy), 2) diagnostic costs (blood smear), 3) administration equipment costs (infusion set, IV solution, syringes), and 4) in-patient costs (consultation cost, bed occupancy, blood transfusion, and nursing care). Administration equipment, blood smear and parenteral quinine unit costs were estimated from the hospital/health centre price lists, as well as in-patient costs. The full dose costs for both parenteral quinine and artesunate were applied, since the recommendation given in the study was to avoid re-using the drug once it was opened, and hence partially used ampoules had to be discarded. Artesunate was used in the 60-mg vial, the WHO pre-qualified formulation at the time. Costs of oral treatment with AS-AQ/AL were included in the analysis despite being subsidised by the Global Fund to Fight AIDS, TB and Malaria (GFATM) in the selected health facilities.

Costs of artesunate and of AS-AQ/AL were obtained from the Management Sciences for Health (MSH) *International Drug Price Indicator Guide* (MSH, 2014).

Additional treatments and diagnostic costs, other than the parenteral drug and the thick blood smear, were not included in the analysis. Specific costs associated with co-morbidities, with the exception of blood transfusions (severe anaemia), were not considered in the analysis because they would have required a level of clinical monitoring that was not possible in this study. In two sites (referral hospital Saint Luc and Health Centre Ngeba), a lump sum health care payment system was in place, thus unit costs were unavailable. The decision was made to reflect as closely as possible the local practice and to generate nationally relevant data rather than internationally, fully costed estimates. Hence, the lump sum estimates were taken for this analysis. However, the two sites were analysed separately to take these differences into account, since lump sums are likely to underestimate the full cost of treatment, especially if there is a central subsidy by an external donor, as in the case of these two facilities.

5.4 Results

Clinical assessment

A total of 749 patients were recruited from eight sites, 399 in the quinine group from October 2012 to January 2013 (study phase one), and 350 in the artesunate group from April to July 2013 (study phase two). The quinine group consisted of 248 (62%) children between two and 59 months, and 151 (38%) individuals aged five years and above. The artesunate group consisted of 215 (61%) children between two and 59 months and 135 (39%) individuals aged five years and above. The demographic and baseline characteristics were similar for the two study groups (Table 5-1). All patients tested positive for malaria, either by thick blood smear or RDT on the day of inclusion. Overall mortality was 2.8% (21/749), with 3.8% for patients treated with quinine (15/399) and 1.7% for patients treated with artesunate (6/350) (p=0.110). The majority of deaths (13 of 21, 62%) occurred within the first 24 hours after admission, of which nine of 15 were in the quinine group (with two dying before receiving the treatment) and four of six were in the artesunate group (zero before receiving the treatment). Of the eight deaths that occurred after 24 hours, six occurred in the quinine group and two in the artesunate group.

Prostration was the most frequent manifestation of severe malaria at admission in children between two to 59 months in the quinine (204/248, 82%) and artesunate groups (171/215, 80%), as well as in individuals five years and above (122/151, 81% and 120/135, 90%). Respiratory distress and convulsions were also frequent symptoms at admission in both groups. The total number of patients who received a blood transfusion was 214 (29%), with 128 (32%) and 88 (25%) in the quinine and artesunate groups, respectively. Five per cent of the patients under the quinine regimen had persistent symptoms at discharge, compared to 3% under the artesunate regimen (Table 5-2). A decrease in Hb levels at one of the follow-up visits was a frequent SAE reported during the artesunate regimen (Burri *et al.* 2014). A seven-day oral quinine course was the most frequently prescribed oral medication to complete treatment after the initial injectable quinine regimen (92%), whereas AS-AQ was the most prescribed oral medication (97%) after injectable artesunate for all ages. Patient adherence was assessed by the duration of oral treatment and the reported number of tablets taken. Following injectable quinine and injectable artesunate, 236 (85%) and 308 (99%) patients fully adhered to the treatment, respectively.

The time to discharge was slightly lower in the artesunate group compared to the quinine group, with a median of two (90% central range 1 – 9) *versus* three (1 – 9) days, respectively ($p < 0.001$). Given that mortality was slightly higher in the quinine group, this would have led to a shorter hospital stay but the effect would be minimal because of the low case fatality rate. The interval between admission and start of parenteral treatment was significantly shorter in the artesunate group compared to the quinine group, two (0 – 15) *versus* three (0 – 20) hours ($p < 0.001$). The interval from beginning parenteral treatment initiating oral treatment was slightly longer in the artesunate group (45 (32 – 56) *versus* 39 (12 – 67) hours in the quinine group, $p < 0.001$). Parasite clearance time was 23 (11 – 49) hours for artesunate *versus* 24 (10 – 82) hours for quinine ($p < 0.001$) (Table 5-3).

Table 5-1: Characteristics and clinical presentation of patients at recruitment

	Quinine		**Artesunate**	
	2-59 months	**>5 years**	**2-59 months**	**>5 years**
Sex				
Female	122 (49%)	72 (48%)	115 (53%)	71 (53%)
Age	24 (7-53)	10 (5-48)	24 (7-48)	8 (5-48)
Medical history (past 30 days)				
Other malaria episode	18 (7%)	7 (5%)	16 (7%)	16 (12%)
Fever (N=398)	90 (37%)	78 (52%)	59 (27%)	76 (56%)
Pre-treatment with anti-malarial	31 (12%)	20 (13%)	20 (9%)	20 (15%)
Other treatment(s) received	113 (46%)	75 (50%)	98 (46 %)	83 (61%)
Other major health problem(s)	6 (2%)	3 (2%)	0 (0%)	4 (3%)
Episode of convulsion (N=394)	34 (14%)	10 (7%)	13 (6%)	11 (8%)
Known hypersensitivity to other drugs	0 (0%)	5 (3%)	2 (1%)	5 (7%)
Signs and symptoms on admission				
Fever	220 (89%)	129 (85%)	197 (92%)	121 (90%)
Fever before enrolment (days and	3 (2-4)	3 (2-5)	3 (1-7)	3 (1-7)
Vomiting	100 (40%)	78 (52%)	113 (53%)	78 (58%)
Coma	23 (9%)	12 (8%)	5 (2%)	11 (8%)
Reported convulsions	72 (29%)	19 (13%)	59 (27%)	14 (10%)
Blantyre coma score (8-24 months)	3 (2-5)	-	4 (3-8)	-
Glasgow coma score (>2 years)	10.5 (5-13)	10 (8-15)	7.5 (4-5)	NA
Pallor	NA	NA	77 (36%)	20 (15%)
Jaundice	3 (1%)	4 (3%)	7 (3%)	2 (1%)
Shock	10 (4%)	2 (1%)	2 (1%)	2 (1%)
Respiratory distress	128 (52%)	58 (38%)	96 (45%)	64 (47%)
Severe anaemia (<5 g/dl) (N=326 Q; 334 A)	8.1 (3%)[a]	9.1 (2%)[a]	15 (7%)[b]	1 (1%)[b]
Parasite count (per µl); geometric mean (95 % CI)	17068 (12119-24038)[c]	12022 (7040-20527)[c]	22289 (15498-32057)[c]	12346 (7812-19511)[c]
Prostration	204 (82%)	122 (81%)	171 (79%)	120 (89%)
Urine colouration (N=391)	2 (1%)	2 (1%)	10 (5%)	8 (6%)
Clinical examination on admission				
Weight (kg and SD)	11.1 (3.0)	33.2 (17)	11.2 (4)	27.6 (15)
Temperature (°C and SD) (N=398)	38.1 (1)	38.3 (1)	38.1 (1)	38.4 (1)
Pulse	125 (70-180)	102 (64-148)	119 (60-171)	94 (60-140)
Respiratory rate per minute	42.5 (28-72)	39.0 (24-60)	40 (24-72)	40 (20-58)
Co-morbidity	82 (34%)	51 (34%)	80 (37%)	58 (43%)

Data are summarised as numbers (%), median (90% central range) or mean (SD); NA = Not available;

[a] Clinical assessment only; [b] HemoCue; [c] The initial parasitaemia was calculated only for those patients for whom the biological confirmation was done by thick blood smear

Table 5-2: Clinical examination at discharge

	Quinine		**Artesunate**	
	2-59 months	**>5 years**	**2-59 months**	**>5 years**
Weight (kg)	11.1 (3.0)	32.8 (16.7)	11.2 (4.3)	27.2 (14.9)
Temperature (°C)	36.7 (0.5)	36.6 (0.5)	36.7 (0.4)	36.5 (0.4)
Pulse	100 (70-128)	90 (41-120)	90 (64 - 124)	85.4 (18.8)
Respiratory rate per minute	35 (22-40)	28 (16-48)	31.8 (6.6)	29.2 (8.0)
Persistence of signs at discharge	12 (5.4%)	6 (4.3%)	7 (3.4%)	4 (3.0%)

Data are summarised as numbers (%), median (90% central range) or mean (SD).

Table 5-3: Key time intervals

	Quinine	**Artesunate**	**p-value**
Time to discharge (days)	3 (1-9)	2 (1-9)	<0.001
Interval between admission and beginning of parenteral treatment (hours)	3 (0-20)	2 (0-15)	<0.001
Interval between beginning of parenteral treatment and oral treatment (hours)	39 (12-67)	45 (32-56)	<0.001
Parasite clearance time (hours)	24 (10-82)	23 (11-49)	<0.001

Median and 90% central range

Time and motion study

Administration times by task are shown in Tables 5-4 and 5-5. There was a reduction in the staff time required for all tasks during the artesunate phase. The total median personnel time for pre-administration and patient management tasks was 33 (10 – 60) for artesunate and 36 (13 – 92) minutes for quinine. The median cumulative staff time for observed drug pre-administration tasks per patient per drug session was 13 (6 – 38) for artesunate and 20 (7 – 50) minutes for quinine. Cumulative median personnel time spent for patient management was 9 (1 – 24) for artesunate and 12 (3 – 52) minutes for quinine.

Table 5-4: Personnel time (in minutes) required to complete pre-administration tasks, by drug type

Quinine (N = 832)		**Artesunate (N = 795)**	
Material preparation	6 (2-18)	Material preparation	4 (1-10)
Drug preparation	4 (1-14)	Reconstitution	3 (1- 8)
Search for the vein	5 (1-14)	Dilution	2 (1-10)
Perfusion regulation	4 (1-10)	Dose verification	2 (1-6)
-		Search for the vein	3 (1-10)

Median and 90% central range

Table 5-5: Overall cumulative personnel time (in minutes)

	Quinine	**Artesunate**	**p-value**
Overall personnel pre-administration time	20 (7-50)	13 (6-38)	<0.001
Overall personnel patient management time	12 (3-52)	9 (1-24)	<0.001
Overall personnel time	36 (13- 92)	33 (10-60)	<0.001

Median and 90% central range

Cost analysis

In hospitals and health centres, the mean (SD) total costs per patient treated for severe malaria with injectable artesunate were USD 51.94 (16.20) and 19.51 (9.58); and USD 60.35 (17.73) and 20.36 (6.80) with injectable quinine. Costing details for individual study sites are given in Table 5-6.

Table 5-6: Mean cost (with SD) for treating one episode of severe malaria in patients admitted to hospitals and health centres in the Democratic Republic of Congo

Hospital/ Health centre	Mean length of stay, days (SD)		Blood smear unit cost		Mean injectable drug cost		Mean oral drug cost[a]		Mean administration cost		Mean inpatient cost		Mean total cost per patient	
	QNN	**ART**	**QNN**	**ART**	**QNN**	**ART**	**QNN**	**ART**	**QNN**	**ART**	**QNN**	**ART**	**QNN**	**ART**
Kimpese referral hospital Centre	7.12 (4.43)	6.26 (5.01)	2.94	2.94	0.45 (0.22)	7.72 (3.28)	0.66 (0.38)	0.48 (0.06)	1.89 (0.83)	1.39 (0.48)	49.56 (18.04)	47.25 (19.82)	61.58 (18.72)	59.57 (20.97)
Hospitalier Roi Baudouin	4.09 (3.41)	3.72 (2.17)	3.21	3.21	0.78 (0.17)	3.24 (1.51)	0.97 (0.30)	0.56 (0.21)	6.59 (1.56)	0.90 (0.83)	38.60 (12.99)	38.76 (8.32)	53.29 (7.86)	46.58 (8.55)
Hôpital St Luc Kisantu	3.13 (1.06)	6.68 (4.00)	NA	NA	NA	3.87 (1.72)	0.70 (0.23)	0.50 (0.18)	NA	NA	NA	NA	50.34 (9.98) [b]	55.44 (11.81) [b]
Health Centre CECO	3.96 (2.35)	4.28 (3.36)	1.07	1.07	0.57 (0.14)	7.19 (2.51)	1.00 (0.49)	0.48 (0.13)	2.10 (0.34)	1.62 (0.45)	40.28 (10.32)	41.62 (14.47)	32.53 (14.25) [c]	28.21 (9.41) [c]
Health Centre La Famille	3.80 (1.54)	2.58 (1.50)	1.07	1.07	0.94 (0.43)	7.26 (3.95)	1.58 (0.59)	0.66 (0.30)	3.89 (1.59)	1.22 (0.45)	10.48 (3.63)	8.19 (3.21)	19.35 (4.46)	18.21 (5.02)
Health Centre Bita	2.18 (0.68)	1.99 (0.11)	1.07	1.07	1.49 (0.33)	7.30 (2.68)	1.99 (0.78)	0.49 (0.17)	6.48 (1.23)	1.51 (0.23)	6.71 (2.07)	6.39 (0.30)	21.97 (2.73)	16.56 (2.87)
Health Centre Menkao	1.78 (0.97)	1.27 (1.34)	1.07	1.07	1.81 (0.72)	9.12 (5.09)	1.05 (0.45)	0.63 (0.24)	5.10 (1.19)	2.60 (0.73)	3.15 (1.29)	2.49 (1.76)	13.92 (2.59)	15.66 (5.84)
Health Centre Ngeba	4.6 (2.59)	2.7 (0.98)	NA	NA	NA	5.87 (1.95)	0.97 (0.30)	0.43 (0.04)	NA	NA	NA	NA	6.86 (0.84) [b]	4.47 (0.10) [b]

In 2014 USD; NA = Not available

[a] Mean cost for oral quinine and AS-AQ

[b] Unit costs not available. Lump sum payment system. All exams and drugs other than anti-malarial are included. Patients pay a part of the total costs; the rest is supported by a partner.

[c] Among health centres, blood transfusion was only performed in CECO. To allow cost comparison with the other health centres, costs of blood transfusion were not included in the total costs. Total costs for CECO under ART and QNN are USD47.47 (9.41) and USD51.79 (14.25) respectively if blood transfusion is included.

5.5 Discussion

This study is the first to quantify key operational parameters in the management of patients with severe malaria treated with injectable artesunate. Injectable artesunate was superior to quinine for almost all of the parameters assessed. Furthermore, from the provider's perspective, overall costs were lower for injectable artesunate in hospitals and similar in health centres. The aim of the study was to assess operational aspects rather than safety and efficacy. However, there was no indication for any of the outcomes obtained from available clinical charts that patients fared worse with injectable artesunate compared to parenteral quinine, concurring with available data on the efficacy and safety of the use of injectable artesunate in the DRC (Dondorp *et al.* 2010).

A major reason for conducting the study in two phases was the need for comparative operational data between the new regimen and the old regimen. Because many aspects in health services are setting-specific, it was thought that the best controls would be the facilities themselves. The strongest study design would include a randomised concurrent control trial with enough health facilities to account for inter-facility variability, however, time and logistical reasons precluded such an approach for the current study. The design outlined here was the best suited to the Ministry of Health's current plan for scaling up artesunate. The operational parameters of treating severe malaria are unlikely to be sensitive to seasonal effects, and also unlikely to change much in a given facility over time periods equal to that of the study. Hence, although not randomised, this design allowed a reasonable comparison of the two regimens in real-world implementation settings. Although injectable quinine has been the mainstay for treating severe malaria for many years, there are virtually no existing data in the literature quantifying the operational parameters of interest.

In this study, patients admitted with severe malaria experienced a median delay of three hours before receiving their initial quinine dose compared to two hours with artesunate (Table 5-3). This time delay depended on several factors that should be further investigated. In particular, it could reflect the difficulties of promptly and safely administering quinine via IV. Although comparable in its preparation, quinine is a difficult drug to administer because of its unfavourable safety profile; it requires correct dose calculation, taking into account previous quinine treatment to avoid overdosing and serious consequences for the patient.

In the AQUAMAT trial (Dondorp *et al.* 2010), the risk of children dying while waiting to receive quinine was almost four times higher than the risk in children treated with artesunate.

This delay adds to the time needed for referral, during which the condition of the patient can deteriorate (WHO, 2010). In this study, two patients died before receiving quinine compared to none in the artesunate group. Although this delay is still critical for both regimens, it can be expected to decrease further for injectable artesunate as skills and confidence are acquired through repeated administration and preparation by health personnel.

The well-known difficulties in administering quinine may also explain the difference observed in the time interval between the beginning of the parenteral treatment and the initiation of oral treatment. Lack of confidence or uncertainty in reconstructing the history of previous treatments with quinine could potentially limit the number of doses a patient receives. According to the national DRC directives on the treatment of severe malaria (PNLP 2012), the number of doses of quinine administered should be minimised until the patient can tolerate an oral medication. Under the artesunate regimen in this study, the WHO's recommendations of a minimum of three injections during the first 24 hours, irrespective of the patient's ability to tolerate oral medication were strictly followed. This is one possible explanation for the prolonged time interval to the initiation of oral therapy.

The artesunate regimen achieved parasite clearance faster than the quinine regimen, which likely accounts for the shorter hospital stay. The reduction in median hospital stay by a day reduces costs of malaria treatment and minimises socio-economic impacts on patients and their families. This is especially important for poorer and more vulnerable segments of the population.

The estimated costs of treating a patient with severe malaria in this study are similar to those calculated in previous studies (Lubell *et al.* 2009; Lubell *et al.* 2011), although lower than those reported by Kyaw *et al.*, which used a more detailed cost analysis approach (Kyaw *et al.* 2014). The costs were highly variable, depending on the level and type of facility (public, private or missionary). The mean pooled estimate total cost was found to be similar for artesunate compared to quinine in health centres, USD 19.51 (9.58) and 20.36 (6.80), while lower in hospitals, USD 51.94 (16.20) to USD 60.35 (17.73). Inpatient costs were the major driver costs for the difference observed between hospitals and health centres. Less standardized inpatient costs are established by each hospital and health centre and take into account a number of parameters, which include cost of labour, and the organisation of the health service.

Since it was not possible to analyse all patient costs, particularly the cost related to supportive measures and the presence of co-morbidities, the total treatment costs are clearly underestimated. For the purpose of this study, a new vial of quinine was used for every dose, but this is not necessarily the case in the real world. As a result, drug costs were likely overestimated. However, not all sessions of drug preparation and administration were included due to understaffed health centres and the inability to reliably observe the most severe cases in need of prompt treatment.

The results show that the overall time spent on pre-administration tasks and on direct post-treatment patient care was slightly lower in the artesunate compared to the quinine group. Although statistically significant, this time difference is smaller than expected considering that artesunate is easier to use. This could be explained by the fact that health personnel had a limited time to get used to preparing and administering artesunate before starting patient enrolment in the second phase. Therefore, it could be that the overall difference in the pre-administration times will increase over time, in favour of artesunate. The overall personnel time spent on patient care was lower with artesunate administration compared to quinine. This is likely to have resulted in more time to care for other patients, leading to a positive effect on the overall quality of care. This was consistent with health care providers' higher satisfaction when using artesunate, as described elsewhere (Ntuku *et al.* 2016).

5.6 Conclusions

This study provides for the first time descriptive evidence of the effectiveness and practicability of using injectable artesunate for treating severe malaria in hospitals and health centres in the DRC. For most operational and cost parameters, injectable artesunate was found to be superior to injectable quinine. Combined with its higher efficacy, these findings support the rapid switchover in the country. These findings also provide some useful operational and cost data for national authorities and for local health care managers involved in planning the transition.

Training health personnel is obviously a key factor for a successful transition, including a change in the attitudes and behaviours of providers.

The MATIAS study has contributed further evidence that injectable artesunate is a better treatment option than injectable quinine for patients with severe malaria. The findings suggest that transition to the new drug should be accelerated as quickly as possible. The Ministry of Health of the DRC is currently scaling up the use of injectable artesunate in the public sector, with the support of the GFATM and the other partners, which will enable 100% coverage of in-patient cases within a three-year period.

6 Feasibility and acceptability of injectable artesunate for the treatment of severe malaria in the Democratic Republic of Congo

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6.1 Abstract

Background

The Democratic Republic of the Congo (DRC) changed its national policy for the treatment of severe malaria in both children and adults in 2012 from intravenous quinine to injectable artesunate. The country is now planning to deploy nationwide injectable artesunate as the preferred treatment for the management of severe malaria. To support this process, the feasibility and acceptability of the use of injectable artesunate in the context of the DRC was assessed, from the perspective of both health care providers and patients/caretakers.

Methods

Questionnaires and observations were used to collect information from health care providers and patients/caretakers in eight health facilities in the Province of Kinshasa and in the Province of Bas-Congo.

Results

A total of 31 health care providers and 134 patients/care takers were interviewed. Seventy five percent (75%) of health care providers found it less difficult to prepare injectable artesunate compared to quinine. None of them encountered problems during preparation and administration of injectable artesunate. The large majority of care providers (93%) and patients/caretakers (93%) answered that injectable artesunate took less time than quinine to cure the symptoms of the patients. Twenty-six (84%) health care providers reported that the personnel workload had diminished with the use of injectable artesunate. Seven (22.6%) health workers reported adverse drug reactions, of which a decrease in the haemoglobin rate was the most common (71.4%). All care providers and the vast majority of patients/caretakers (96%, N=128) were either satisfied or very satisfied with injectable artesunate.

Conclusions

These findings show that the use of injectable artesunate for the treatment of severe malaria is feasible and acceptable in the context of DRC, with appropriate training of care providers. Both care providers and patients/caretakers perceived injectable artesunate to be effective and safe, thus promoting acceptability.

6.2 Background

In the Democratic Republic of the Congo (DRC), malaria is one of the leading causes of death in children under five years of age, with an estimated 9,000,000 cases and 22,000 deaths reported in 2012 (PNLP 2013a). As a result, the DRC is the second country in the world in terms of burden of malaria (WHO 2013c; PNLP 2013b). For severe malaria, the case fatality is reaching 10% (Likwela *et al.* 2012). Severe malaria is obviously a medical emergency, and reducing its burden is currently the highest priority of malaria control, as evidenced by the Roll Back malaria (RBM) target of near-zero deaths by 2015 (Roll Back Malaria Partnership 2011).

For the management of severe malaria cases, comparative clinical trials between quinine and injectable artesunate have demonstrated that the treatment with artesunate was associated with a substantial reduction of case fatality in both children and adults (Dondorp *et al.* 2005; Dondorp *et al.* 2010; Sinclair *et al.* 2012). In addition, intravenous artesunate offers a number of programmatic advantages over quinine in terms of not requiring rate-controlled infusion or cardiac monitoring (WHO 2013a). These results led to a change in the WHO guidelines for the treatment of severe malaria in 2011, recommending intravenous artesunate as the preferred treatment for severe malaria in children and adults (WHO 2011b). As a result of this change, an additional 195,000 deaths could be averted every year in Africa (MMV 2012). Following the new WHO guidelines, the National Malaria Control Programme (NMCP) of the DRC changed the national policy for the treatment of severe malaria in both children and adults from intravenous quinine to injectable artesunate in 2012 (PNLP 2012). However, this policy change requires a number of clinical and operational adaptations, as quinine has been the treatment of choice for many decades. The national strategic plan set up an implementation period of three years to scale up injectable artesunate.

The handling of injectable artesunate is reported to be easier compared to quinine, however a number of operational issues such as dosing and preparation of the drug may hinder its use.
One important element for a successful transition, besides logistical aspects, is ensuring that there is a high acceptability of the new treatment by the health care providers, as well as by the patients. Finally, there is also a need to determine the perceived effectiveness and safety of the new treatment. These factors are a prerequisite for achieving a successful rollout and therefore high public health impact.

Here we investigate the feasibility and acceptability of the use of injectable artesunate in the context of the DRC, to identify arising issues and propose solutions before the start of the national rollout.

Although a number of studies have investigated the efficacy of injectable artesunate for the treatment of severe malaria as well as some issues related to its use (Burri *et al.* 2014), none has focused so far on the feasibility of the implementation of the new IV/IM anti-malarial drug from the perspective of care providers, as well as its acceptability from the perspective of patients/caretakers.

6.3 Methods

Study sites

This study was conducted as part of the MATIAS study (*Treatment of severe malaria – An operational comparative study for the treatment of severe malaria between quinine and artesunate in Hospitals and Health Centres of Kinshasa and Bas Congo province).* The MATIAS study was a non-controlled operational comparative study conducted in children and adults admitted with severe malaria to hospital and health centres (Ferrari *et al.* 2015).

The study was implemented in eight health facilities (three hospitals and five health centres) in Greater Kinshasa, the capital of the DRC (Referral Hospital Roi Baudoin, Health Centre Bita, Health Centre Menkao) and in the Province of Bas Congo (Referral Hospital Saint Luc Kisantu, Health Centre Ngeba, Referral hospital of Kimpese, Health Centre Ceco, Health Centre La Famille). Figure 6-1 shows the location of the study sites. Selected health facilities were representative of typical health facilities in the country including a large public health hospital; a medium-sized, non-profit, missionary hospital; a medium-sized, government hospital (Centre Hospitalier Roi Baudouin) and rural health centres.

Kinshasa sites serve urban and semi-rural populations, whereas the Bas-Congo sites serve a largely rural population. All sites are hyper to holoendemic for malaria and transmission is perennial with seasonal variation (MAP 2010). At the time the study started, injectable artesunate had not been deployed to public health facilities and was not available in the private sector.

The MATIAS study was conducted in two consecutive phases. In the first phase, in the eight selected study sites, a target number of 350 patients were recruited over three months, from October 2012 to January 2013, with intravenous quinine as the treatment drug.

In the second phase, following the introduction of injectable artesunate, the same target number of patients were recruited over the three months period, from April to July 2013. A three-month interval was kept between the two phases in order to train the healthcare providers from the study sites in the preparation and administration of the new drug.

With regard to the use of injectable artesunate in hospitals, clinicians were responsible for prescribing the drug, specifying the dose needed and the schedule of dosing and evaluating patients' progress while nurses prepared and administered the drug. In health centres, nurses were responsible for all aspects of drug use.

The MATIAS study included four key components: (1) clinical assessment of patients, (2) a time and motion study, (3) financial costs, (4) feasibility and acceptability assessments through providers and patients/caretakers questionnaires. The results of the first three components are reported elsewhere (Ferrari *et al.* 2015), while the results of the fourth component are reported here.

All interviews for the feasibility and acceptability assessment were conducted during the second phase (artesunate phase) between April and July 2013, since the aim was chiefly to compare assessments of quinine *versus* artesunate.

Participants belonged to two groups with separate questionnaires: (1) Health care providers who prescribed or administered injectable artesunate during the MATIAS study and whose verbal consent was obtained. A purposive sample of four health care providers per health facility was interviewed, which represents the mean number of personnel trained in the use of injectable artesunate per health facility. (2) patients/caretakers of patients who were treated with injectable artesunate in each study site. A convenience sample of one third of all patients/caretakers of patients attending follow up visits were interviewed. Patients/caretakers of patients were eligible for interview if they had personal past experience with quinine treatment or have taken care of another member of the family in the past treated with quinine and they must give verbal consent. Patients or caretakers of patients were randomly selected.

Training and implementation of injectable artesunate

In preparation for the first part of the study (quinine treatment), a three-day training on study procedures was given to all investigators and staff involved in the patient's clinical management in each hospital and health centre. The training included an update of knowledge on malaria diagnosis and management. Before starting the second phase, a two-day training on the preparation and administration of injectable artesunate was given to all staff involved in clinical management in the study sites.

During these sessions a new training tool kit developed and provided by the Medicines for Malaria Venture (MMV) product development partnership was used. This kit consisted of a very detailed user guide; an explicit and straightforward job aid (Figure 6-2), and a practical training video. Prior to patient recruitment, health care providers were allowed some time to become familiar with the handling of the new drug under supervision.

Injectable artesunate (Guilin Pharmaceutical Co, Ltd, Shanghai, China) was packed in boxes each containing one vial of 60 mg of artesunate powder for injection, one ampoule of sodium bicarbonate and one ampoule of sodium chloride. The following steps were required prior to drug injection: (1) calculation of the number of vials required based on patient weight, (2) reconstitution of artesunate solution with sodium bicarbonate solution, (3) dilution of the solution with sodium chloride.

Artesunate was given intravenously at a dose of 2.4mg/kg bodyweight at 0, 12 and 24 hours, and then once a day until the patient was able to take oral treatment. In line with the WHO recommendations (WHO 2013a), parenteral treatment was given for a minimum of 24 hours, irrespective of the patient's ability to tolerate oral medication. After completion of the injectable treatment, the patient was given a full course of the recommended oral artemisinin-based combination therapy, AS-AQ or AL. Alternatively, parenteral artesunate was given for a maximum of seven days, until oral treatment could be taken reliably.

Patients were followed up at day 7, day 14, day 21 and day 28 after discharge. Artesunate was provided free of charge by the manufacturer (Guilin Pharmaceuticals, Shanghai, PDR China) while the costs of quinine were covered by the study. In each study site, patients were managed by local clinicians (hospitals) or nurses (health centres), while the research team carried out a weekly supervision at each study site throughout the duration of the study.

The NMCP provided policy support. All authorizations for drug importation were obtained from the Ministry of Health through the National Drug Authority. All relevant authorities were actively involved in the planning of the study and preliminary results of the study were shared and discussed during stakeholders meetings. Unpublished preliminary results of the study were used by the NMCP to develop training manuals for healthcare providers and communication tools in prevision of the deployment of injectable artesunate.

Data collection

Two questionnaires were used to collect data. Interviews were conducted by nine trained interviewers recruited from the local community. Two of them were physicians, four were nurses and three were social workers. The two physicians were recruited from Kinshasa and conducted interviews with all study physicians. Two nurses and one social worker were recruited in Kinshasa and conducted interviews respectively with nurses and patients/caretakers in Kinshasa sites. Two nurses and two social workers were recruited in Bas Congo and conducted interviews respectively with nurses and patients/caretakers in Bas Congo sites. These interviewers were supervised by study field scientists. A three-day training was given to all interviewers prior to data collection. The training included familiarization with the study tools and practicing interviews. Basic techniques of probing and recording responses were also discussed during the training. Interview guides were developed and pre-tested prior to use.

Interviews with *care providers* focused on ease of application and drug handling, perceived safety of the treatment, quality of the patient management, perception of old versus new treatment on staff work load, and level of satisfaction with the new treatment. The core questions of the interviews compared injectable artesunate and quinine. While obviously there could have been a recall bias due to the fact that the interviews were done during the artesunate phase of the study, about 3-6 months after the quinine phase, this should not have been too much of an issue since quinine has been used for decades in the DRC, and all health care providers were very familiar with its use.

Interviews with *patients/caretakers* took place during the follow up visits and focused on the perception of the effectiveness and safety of injectable artesunate, especially with regard to adverse events. Here, recall bias could have been more of an issue since patients were less familiar with quinine adverse events. In order to minimize this problem, one inclusion criterion for the interviews of patients/caretakers was a past experience with quinine treatment, either for themselves or for one member of the family.

According to the interviewee's preference, interviews were conducted in French, the official language in DR Congo or in Lingala and Kikongo, the languages spoken in Kinshasa and Bas–Congo, respectively. Interviews typically lasted between twenty and thirty minutes. Multiple choice closed-ended questions were followed by open-ended questions to collect narrative responses. All answers were recorded in French by the interviewers.

Ethics

The MATIAS study protocol was reviewed and approved by the ethics committee of the Kinshasa School of Public Health (University of Kinshasa) and by the ethics commission of both cantons of Basel, EKBB (*Ethikkommission beider Basel)* in Switzerland. Informed verbal consent was obtained from health care providers, patients and caretakers who participated in the study.

Data processing and analysis

Quantitative data were entered electronically using Epi data 3.1 (Epidata Association; Odense, Denmark). After standard quality control checks, data were transferred to Stata version 12 (Stata Corporation; College Station, Texas) for analysis. Categorical variables were compared using pearson's Chi square test or fisher's exact test in case the expected value of any of the cells of the table was less than 5. A p-value ≤ 0.05 was considered statistically significant. Qualitative data were summarized in emerging themes which were coded and entered using Epi data 3.1. They are presented as proportions of different variables. Some answers are reported as narratives.

6.4 Results

Health care providers

Key results of interviews with health care providers are summarized in Table 6-1. A total of 31 health care providers were interviewed, whereby medical doctors and nurses accounted for 22.6% (7/31) and 77.4% (24/31) of the interviewed personnel, respectively. The median number of providers interviewed per health facility was four, ranging from three to five per facility. The majority of the personnel interviewed (28/31, 90.3%) had more than three years of working experience, whilst three individuals (9.7%) had one to three years experience. None of the health care providers interviewed had used injectable artesunate before the beginning of the study.

Table 6-1: Summary of interviews with health care providers

Question / Parameter	Frequency	Percentage
Did you find more or less difficult to prepare artesunate compared to quinine (N=24)?		
More difficult	3	12.5
Same difficulty	3	12.5
Less difficult	18	75
Have you noticed any adverse effect that you think could be related to artesunate (N=31)?		
Yes	7	22.6
No	24	77.4
Do you think that the workload has reduced with artesunate compare to quinine (N=31)?		
The workload has diminished	26	83.9
The workload is the same	4	12.9
The workload has increased	1	3.2
What is your level of satisfaction with injectable artesunate (N=31)?		
Satisfied	12	38.7
Very satisfied	19	61.3

Ease of use

Questions related to the handling of the drug were only asked to the 24 nurses who were responsible for the drug preparation and administration. Compared to quinine, eighteen (75%) of all interviewed nurses reported to have spent less time to prepare and administer injectable artesunate, three (12.5%) spent more time and three (12.5%) said to have spent the same amount of time (Table 6-1). Eighteen (75%) found it less difficult to prepare injectable artesunate compared to quinine, three (12.5%) found it more difficult and three reported to have experienced the same level of difficulty (Table 6-1). All those who found it more difficult to prepare injectable artesunate compared to quinine specified that too many steps were needed in artesunate preparation. For patients above 50 kg body weight, a minimum of 3 vials are needed for a single dose and obviously this increased the time spent in drug preparation since each vial must be opened and reconstituted separately.

All interviewed nurses involved in the administration of the treatment found it less difficult to administer artesunate compared to quinine.

The most important reasons cited by the respondents were the rapid means of administration (62.5%), no accidents related to infusion (45.8%) and the reduced patient monitoring time (20.8%) (Table 6-1). None of the nurses interviewed encountered problems during drug preparation and drug administration.

Perceived effectiveness and safety

Regarding the time to observe clinical effects, twenty nine (93.6%) health workers reported that it took less time compared to quinine, one (3.2%) estimated it took the same time and one (3.2%) estimated it took more time (Table 6-1). Thirty (96.7%) health care providers reported to be very satisfied with the capacity of injectable artesunate to cure the symptoms of their patients compared to quinine, one (3.2%) experienced the same satisfaction level, and none found injectable artesunate less satisfactory.

Seven (22.6%) health workers reported to have noticed adverse drug reactions: The most common ones mentioned were a decrease of haemoglobin rate (71.4%), shivering following the drug injection (42.9%) and loss of weight (14.3%). However, all the seven health care providers who reported adverse drug reactions answered that they were less frequent than those observed with quinine (Table 6-1).

Patient management

The majority (96.8%) of health care providers reported to have dedicated less time for patient monitoring after administration of artesunate compared to quinine. This proportion was not significantly different according to the type of health facility (hospitals *vs* health centres; p=0.388 Fisher's exact test). Of all health care providers interviewed, twenty six (83.9%) reported that the personnel workload had diminished with the use of injectable artesunate, four (12.9%) reported the workload to be the same, while one (3.2%) reported that the workload had increased (Table 6-1). The most important reasons for reported workload reductions were reduced patient monitoring time (88.5%), saving of time by health personnel (80.7%) and shorter treatment duration (15.4%). A reason reported by one health care provider from Ngeba Health Centre for workload increase was increased patient monitoring time.

Care providers general satisfaction

When health care providers were asked about their level of satisfaction with injectable artesunate they were either satisfied (38.7%, 12/31) or very satisfied (61.3%, 19/31) with the new treatment, with nobody giving negative feedback (Table 6-1). Reasons for being satisfied/very satisfied were lack of adverse events (54.8%), rapid action of the drug (48.4%), the easy way the drug is prepared and administered (29%), injectable artesunate being more effective (29%) compared to quinine and workload reduction (25.8%). The level of satisfaction towards injectable artesunate was not significantly different among type of health facility (hospitals *vs* health centres; p=0.452 Fisher's exact test) and health care providers (medical doctors vs. nurses; p=0.384 Fisher's exact test).

A nurse said about injectable artesunate : *" …I am very satisfied, it makes work easier, we have good time management, patient monitoring has been improved, there are no side effects, it has reduced mortality rate among children treated, the drug has attracted many patients to come to our health facility".*

A medical doctor stated: *"very satisfied ... it responds well, no side effects, but there's a risk of a high cost because it is so precise and easier to use that such a product can only be more expensive than quinine... Good outcome after treatment."*

Patients or caretakers

Results of interviews with patients/caretakers are summarized in Table 6-2. A total of 134 patients/caretakers were interviewed (124 caretakers and 10 patients aged 12 years or older). There were more female (73.3%, 96/134) than male (26.7%, 35/134) respondents (p-value<0.05). Of the 124 caretakers interviewed, seventy six (61.3%) were mothers of patients, thirty three (26.6%) were fathers, fourteen (11.3%) were other members of the family and the remaining one (0.8%) was another member of the neighbourhood who accompanied a two-year old female patient at Ceco Health Centre.

Effectiveness and safety

With regards to the time needed for injectable artesunate to cure the symptoms of the patients, the large majority of respondents (93.3%, N=125) felt that it took less time compared to quinine, while eight (6%) respondents said it took the same time and one (0.7%) more time.

Forty-six (34.6%) respondents reported to have noticed adverse events; asthenia (63 %) and loss of appetite (15.2%) were the most common ones, while eighty-seven (65.4%) did not report any complication. The proportion of patients/caretakers reporting adverse events was not significantly different from that of care providers (X2 =1.593, p-value=0.207). Statistical analysis showed no significant difference in the occurrence of adverse events between patients less than and more than five years of age (X2 =0.162, p-value=0.687). Of those who reported to have noticed adverse events, thirty two (69.6%) considered that they were less than those observed with quinine, while seven (15.2%) and one (2.1%) said respectively they are the same and more than those observed with quinine. Six (13.1%) did not know. The point made above on recall bias calls for some caution in the interpretation of these results.

Satisfaction

Regarding general satisfaction towards the ability of injectable artesunate to cure the symptoms that motivated the patients' consultation, the vast majority of patients/caretakers (95.5%, N=128) reported to have been either satisfied or very satisfied (Table 6-2). Six (4.5%) reported being less satisfied than with quinine, of whom three reported persistent fever as a main reason for their dissatisfaction, while two (33.3%) reported asthenia and dizziness. One respondent said he did not know what could be the long-term side effects of this new drug. Patients/caretakers level of satisfaction was not significantly different among type of health facility they consulted (p-value=0.46, Fisher's exact test) and patient's age (p-value=0.77 Fisher's exact test). When asked if they would choose or recommend injectable artesunate over quinine again next time for themselves or a family member, the majority of respondents (97.7%) said they would choose injectable artesunate. The most important reasons for choosing artesunate were rapid action (47%), no or less adverse events (44.5%), shorter treatment course and a shorter hospital stay (26.5%) (Table 6-2).

A mother said: "*This is a short duration treatment, the symptoms disappear quickly. There is less manipulation compared to quinine, where you have to be in bed for 4 hours of infusion but with this treatment, just a few minutes of injection. This drug takes less time compared to quinine and there are no side effects. I think it is better suited to malaria treatment for children*"

A young mother said: "*Very satisfied - After the first injection, my child was doing fine already. The fever had dropped quickly. The treatment duration is very short. We stayed for a short time at the hospital*".

Table 6-2: Summary interview with patients/caretakers

Question / Parameter	Frequency	Percentage
Have you noticed any side effect that you think could be related to artesunate?		
Yes	46	34.3
No	88	65.7
If you had to make the choice in the future between quinine and artesunate, which one would you choose? (N=121)		
Quinine	4	3.3
Artesunate	117	96.7
Most important reasons for choosing injectable artesunate instead of injectable quinine (N=117)		
Rapid action	55	35.3
No side effects	38	24.4
Short treatment course	24	15.4
Less side effects	14	9.0
Rapid way of administration	13	8.3
Short hospital stay	7	4.5
More efficacious	5	3.2
What is your level of satisfaction towards injectable artesunate?		
Dissatisfied	6	4.5
Satisfied	66	49.2
Very satisfied	62	46.3

6.5 Discussion

This study was designed to assess the feasibility and acceptability of the implementation of IV/IM artesunate from the perspective of care providers, as well as its acceptability (versus quinine treatment) from the perspective of the patients / caretakers. Results clearly show that use of injectable artesunate for the treatment of severe malaria in the context of the DRC is both feasible and well accepted. Patients/caretakers were very receptive to the new drug as they perceived it as being highly effective. Despite a few number of health providers reporting that several steps were needed in the preparation of artesunate, the handling of the drug was perceived to be easy. The vast majority of providers reported to have spent less time in this task. This is consistent with the results of quantitative measures of time and motion reported by Ferrari *et al.*, which showed that the overall cumulative staff time dedicated to drug pre-administration tasks was 20 minutes for quinine compared to 13 minutes for artesunate. This difference is expected to improve in favour of the latter with health personnel gaining more experience (Ferrari *et al.* 2015).

Drug formulation had a significant impact on the duration of the preparation and administration. The drug used in the study was packaged in vials of 60 mg which, when reconstituted, was equivalent to 6 ml of solution for the intravenous route. For an average 60 kg body weight adult, this equates to prepare three vials and repeating three times all steps of preparation, resulting in a longer preparation time.

On the other hand, this drug formulation may cause significant drug wastage especially in small children who need small quantities. As the reconstituted solution is only stable for one hour, and since an opened vial cannot be reused, it is possible to lose up to more than half of the vial. In the context of limited resources, it is important that drug manufacturers develop adapted and easy-to-use forms of injectable artesunate.

Contrary to artesunate, the administration of quinine requires special precautions because of its potential toxicity, and close monitoring of the patient as the risk of incorrect dosage and severe side effects is high (Wolf *et al.* 1992; Taylor & White 2004; AlKadi 2007; WHO 2013a). This leads to a reduced patient monitoring time with the use of injectable artesunate which may explain the reported reduction of personnel workload which in turn has the potential to improve the quality of care.

The superior efficacy of injectable artesunate compared to intravenous quinine in the management of severe malaria has been demonstrated in clinical trials (Dondorp *et al.* 2005; Dondorp *et al.* 2010; Sinclair *et al.* 2012). Because of its small-scale nature based on purposive sampling, this study cannot draw a conclusion on the effectiveness of injectable artesunate. However, both health care providers and patients/caretakers perceive artesunate to be highly effective.

The findings from this study are consistent with what is known so far about the better short-term safety of artesunate compared to quinine (Sinclair *et al.* 2012; Sam-wobo *et al.* 2012). Patients/caretakers did not report significant adverse event, the commonly reported adverse events (asthenia and loss of appetite) may be disease induced.

The most common adverse events reported by health workers was a decrease in haemoglobin, a fact supporting recent findings on the occurrence of delayed anaemia after parenteral artesunate for severe malaria (Rolling *et al.* 2013; Rolling *et al.* 2014; Burri *et al.* 2014). However, the training received by health workers before the implementation of artesunate had an emphasis on the monitoring of adverse events and especially a drop in haemoglobin, and this may have influenced the frequency of reporting. The results of this study cannot be used to draw conclusion on the safety of intravenous artesunate, but rather only as supportive evidence to the acceptability of the new treatment.

The design with a lack of concurrent controls, the relatively small scale of the study and the purposive sampling constitute a limitation to the generalizability of the findings. The majority of interview questions were comparative between quinine and artesunate and the time between interviews and prior experience with quinine treatment was not recorded, this could have led to a recall bias, especially for interviews with patients/caretakers. Courtesy bias in respondents' answers could be possible as the drug cost was free for patients and interviewed health care providers were involved in the MATIAS project. In order to minimize this, interviews were conducted by independent interviewers recruited from the local community.

One of the major challenges in switching from quinine to injectable artesunate may be the reluctance of health care workers to switch to a new treatment (MSF 2011). In this study, the majority of health care providers were not aware of the latest evidence on safety and efficacy, and they are very familiar with quinine treatment. Hence, it is important to promote the benefits of injectable artesunate among health workers and train them well in the use of the new treatment.

The new treatment guidelines should be included as soon as possible in the training curricula in medical and nursing schools, and public awareness of the new drug should be raised through effective communication channels.

6.6 Conclusions

The findings from this study showed that the use of injectable artesunate for the management of severe malaria in hospitals and health centres of the DRC is feasible and acceptable to both care providers and patients/caretakers. Injectable artesunate was perceived to be very effective and safe. Training of health personnel is a key factor for a successful implementation. This study provides for the first time operational evidence to support the roll out of injectable artesunate in the DRC.

7 Long-Lasting Insecticidal Net (LLIN) ownership, use and cost of implementation after a mass distribution campaign in Kasaï Occidental Province, Democratic Republic of Congo

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7.1 Abstract

Background

Long-Lasting Insecticidal Nets (LLIN) are a highly effective means for preventing malaria infection and reducing associated morbidity and mortality. Mass free distribution campaigns have been shown to rapidly increase LLIN ownership and use. Around 3.5 million LLIN were distributed free of charge in the Kasaï Occidental Province in the Democratic Republic of Congo (DRC) in September-October 2014, using two different approaches, a fixed delivery strategy and a door-to-door strategy including hang-up activities.

Methods

Repeated community based cross sectional surveys were conducted two months before and six months after the mass distribution. Descriptive statistics were used to measure changes in key malaria household indicators. LLIN ownership and use were compared between delivery strategies. Univariate and multivariate logistic regression analyses were used to identify factors associated with LLIN use before and after the mass distribution. A comparative financial cost analysis between the fixed delivery and door-to-door distribution strategies was carried out from the provider's perspective.

Results

Household ownership of at least one LLIN increased from 39.4% pre-campaign to 91.4% post-campaign and LLIN universal coverage, measured as the proportion of households with at least one LLIN for every two people increased from 4.1% to 41.1%. Population access to LLIN within the household increased from 22.2% to 80.7%, while overall LLIN use increased from 18.0% to 68.3%. Higher LLIN ownership was achieved with the fixed delivery strategy compared with the door-to-door (92.5% [95% CI: 90.2%-94.4%] versus 85.2% [95% CI:78.5%-90.0%]) while distribution strategy did not have a significant impact on LLIN use (69.6%[95% CI:63.1%-75.5%] versus 65.7%[95% CI:52.7%-76.7%]). Malaria prevalence among children aged 6-59 months was 44.8% post-campaign. Living in a household with sufficient numbers of LLIN to cover all members was the strongest determinant of LLIN use. The total financial cost per LLIN distributed was 6.58 USD for the fixed distribution strategy and 6.61 USD for the door-to-door strategy.

Conclusions

The mass distribution campaign was effective for rapidly increasing LLIN ownership and use. These gains need to be sustained for long term reduction in malaria burden. The fixed delivery strategy achieved a higher LLIN coverage at lower delivery cost compared with the door-to-door strategy and seems to be a better distribution strategy in the context of the present study setting.

Keywords Malaria, LLIN ownership, LLIN use, mass distribution campaign, LLIN cost, delivery strategy, malaria prevalence, Democratic Republic of Congo.

7.2 Background

Long-Lasting Insecticidal Nets (LLIN) are a highly effective means of preventing malaria infection and reducing associated morbidity and mortality, particularly in endemic areas (Lengeler 2004; Lim *et al.* 2011). Accross sub-Saharan Africa, the use of LLIN has been shown to be associated with an average parasite prevalence reduction of 20% (Lim *et al.* 2011). Sustained high coverage of LLIN and other effective interventions is essential to achieve and maintain such gains in reduction of malaria burden, and therefore achieve the joint target of the new action and investment to defeat malaria (AIM) and the global technical strategy for malaria (WHO 2015a; Roll Back Malaria 2015). Mass free distribution campaigns have been shown to rapidly increase LLIN ownership and use in several countries (Bonner *et al.* 2011; Bennett *et al.* 2012; Larson *et al.* 2014). Accross Africa, different distribution strategies such as fixed or door-to-door delivery have been used with varying effects on LLIN coverage and use. Furthermore, despite overall LLIN scale up, several other factors still influence LLIN use including demographic characteristics; individual's knowledge and beliefs related to malaria and LLIN; dwelling construction, family size, sleeping arrangements; LLIN characteristics; environmental factors; community and cultural characteristics; distribution strategy and household net density (Thwing *et al.* 2008; Atieli *et al.* 2011; MacIntyre *et al.* 2012; Auta 2012; Bennett *et al.* 2012; Larson *et al.* 2014).

The Democratic Republic of Congo (DRC), through its National Malaria Control Programme (NMCP) is in the midst of unprecedented efforts to rapidly scale up coverage of malaria interventions. As recommended by the World Health Organisation (WHO) to achieve universal coverage of LLIN, the NMCP has adopted a combined strategy of: free mass distribution campaigns every three years and routine distribution through antenatal care visits and immunisation services (WHO 2014a). While the mass distribution has been shown to be the best approach to achieve rapid scale up (aiming to achieve at least 80% of people sleeping under a LLIN), routine distribution is important for maintaining high levels (WHO 2013b) (PNLP 2013a) .

Since the adoption of free of charge LLIN policy in 2006, over 75 million LLIN have been distributed across the country, leading to a tremendous increase in ownership and use (PNLP 2013b). For example, the overall proportion of households with at least 1 LLIN increased from 9% in 2007 to 70% in 2014 (DHS 2007; DHS 2014). However, the scale up of these interventions has not been achieved across all geographic areas of the DRC.

Results of the 2013-2014 Demographic and Health Survey (DHS) showed a strong coverage gradient between provinces with Orientale and Kasaï Occidental Provinces having the lowest ownership rate at 47% and 58%, respectively. Furthermore, the lowest LLIN use in children less than five years of age was reported in Kasaï Occidental at 36% (DHS 2014).

Consequently, as part of a larger effort by many partners to accelerate the progress towards the goal of increasing coverage and use of LLIN, a mass distribution campaign was organised in 2014, distributing approximately 3,5 million LLIN in Kasaï Occidental using two different approaches, a fixed strategy and a door-to-door strategy with hang up activities. The aim of this research was to measure changes in key malaria household indicators before and after the LLIN mass distribution campaign, as well as malaria morbidity after mass distribution and to identify factors associated with LLIN use. This study also compared the two distribution strategies in terms of LLIN ownership, use and associated cost.

7.3 Methods

Study site

This study was conducted in the Kasaï Occidental Province, located in the centre of the Southern part of the DRC (Figure 7-1). Kasaï Occidental spans over 170,000 square kilometres and has an estimated 7.3 million inhabitants. The province has two districts (Lulua and Kasaï) and one large city in each- Kananga and Tshikapa respectively. On the health front it is divided into 44 Health Zones (HZ) grouped into 5 Health Districts. The HZ represents the primary operational unit of the health system in DRC. It usually covers a population of 100,000–150,000 in rural areas and 200,000–250,000 in urban centres. It includes a general referral hospital, some health centres and about a dozen lower level health facilities. Each HZ is further divided into 15 health areas (HA) on average, which represent the lowest level of the health system. Each HA is clearly delimited and defined by the Ministry of Health and usually has 10,000–15,000 inhabitants. In Kasaï Occidental Province, malaria is endemic with stable transmission throughout the year. The DHS 2014 reported an average malaria prevalence of 45% in children less than 5 years (DHS 2014), one of the highest in the world. A previous mass distribution campaign in the province was organised in 2011.

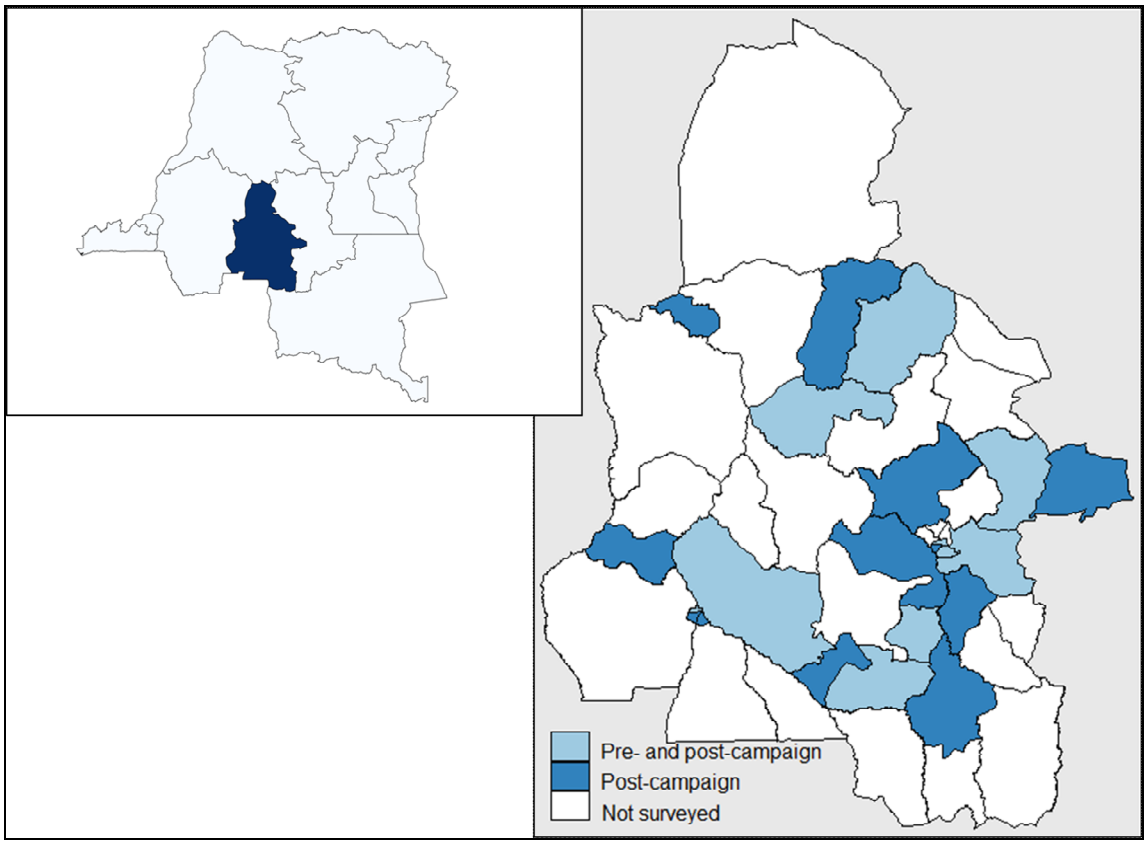

Figure 7-1: Map showing the location of the study sites

Mass distribution campaign

A free LLIN distribution campaign took place in all HZ of Kasaï Occidental Province in 2014 using two different strategies: a) Fixed delivery strategy; b) door-to-door (hang up) strategy.

- *Fixed strategy*: This strategy was used to distribute nets in 35 of the 44 HZ in Kasaï Occidental Province. Specially selected community volunteers were mobilised and trained to visit each household before the campaign. The volunteers registered the number of residents per household, issued a numbered coupon to be exchanged for LLIN on distribution day, and delivered educational messages on malaria and the importance of sleeping under a treated net. LLIN distribution was done at fixed sites at the 'health area' level and each household presented their coupon in exchange for LLIN. The number of LLIN to be allocated per household was calculated according to household size as follows: 1–2 persons=1 LLIN; 3–5 persons=2 LLIN; 6-8 persons=3 LLIN; 9 and more persons=4 LLIN.

- *Door-to-door (hang up) strategy*: This strategy was used to distribute nets in 9 of the 44 HZ in Kasaï Occidental Province. Teams of 3 to 4 community volunteers visited each household sequentially at the moment of distribution. They were responsible for household registration (recording number of people, sleeping spaces, nets, etc.), giving nets and hanging them with the head of the household or another household member. Community volunteers were provided hammers, string and nails for this purpose. Contrary to the fixed strategy, the number of LLIN per household here was calculated based on the number of sleeping spaces. Community volunteers were also trained in the use of smartphones to collect household data (socio-demographic, health seeking behaviour, use of malaria prevention measures, etc.) and delivered educational messages about malaria and the importance of net use.

Study design and sample size

A cross-sectional household based survey was conducted 2 months before and repeated 6 months after the mass LLIN distribution campaign. Sample size calculation was based on LLIN coverage of 55% before the campaign and 85% after the campaign, a precision of 5% and 80% power. The resulting number of HZ to be sampled was calculated as 10 for the pre-campaign survey and 22 for the post-campaign survey (of which the 10 HZ from the pre-campaign survey were kept). In both surveys, 51 households were sampled per HZ.

A multi-stage cluster sampling method was used to select households. Health Zones were randomly selected from a complete list. To ensure sufficient representation from the door-to-door strategy (conducted in 9 of the 44 HZ), 2 of the 10 pre-campaign HZ and 5 of the 22 post-campaign HZ were selected from those 9 that received the door-to-door strategy. In each selected HZ, 3 HA were randomly selected from a complete list. In each HA, an exhaustive list of streets (for urban areas) and villages (for rural areas) with their corresponding populations was drawn up and 3 streets or villages were randomly selected from this list. A total of 17 households were sampled in each HA (to give a total of 51 households per HZ) and the number of households to be surveyed in each of the 3 selected villages/streets from the HA was proportional to the size of the street or village. Households were identified by systematic random sampling. A total of 509 households were surveyed in the pre-campaign and 1121 in the post-campaign.

Data collection

Household survey questionnaire

In all selected households the head or another responsible member of the household was interviewed after written informed consent was obtained. Interviewees were asked questions on all household members (sex, education level, occupation, whether they slept under net previous night), on all nets in the household (type, source, location and if it was slept under the previous night) as well as general information about the house including number of sleeping spaces and malaria knowledge. LLIN ownership and use were established by respondent self-report, however data collectors also requested to observe all nets available in the household at the time of the visit. The survey teams recorded the presence of material goods in the household such as radios, electricity and various types of livestock, and also noted types of toilets, types of roof and wall construction. From this, a composite household wealth index was created using a principal components analysis (PCA) to determine households' socioeconomic status (Vyas & Kumaranayake 2006). Longitude and latitude coordinates of all surveyed households were recorded on-site using the integrated Global Positioning System (GPS) of the data collection devices. Data were collected using a standardised questionnaire electronically programmed on tablets (Samsung Tab 3) running Google Android operating system and equipped with Open Data Kit software (ODK, University of Washington & Google Foundation). This questionnaire was adapted from the standard Malaria Indicator Survey household questionnaire from the Roll Back Malaria (RBM) partnership (WHO PMI UNICEF RBM Measure Evaluation 2013). It was developed in French with oral translation into local language and dialects, and pre-tested prior to use in the field. After daily quality control checks by field supervisors, completed data were sent regularly to the central server housed at the Swiss Tropical and Public Health Institute (Swiss TPH) for distant access and verification by members of the coordination team.

Blood testing

During the post-survey only, all eligible children aged 6 to 59 months present in surveyed households were tested for malaria using the SD Bioline three bands *P. falciparum*/Pan malaria Rapid Diagnostic Test (RDT) (Standard Diagnostics, Kyonggi, Republic of Korea) and had haemoglobin levels measured using a blood haemoglobin photometer (HemoCueHb201+ Ängelholm, Sweden). Children with positive malaria tests were given free treatment with an artemisinin-based combination therapy (ACT), in particular Artesunate-Amodiaquine (AS-AQ), the official first-line malaria treatment at the time of the survey in

the DRC. For children with signs of complicated malaria or low haemoglobin levels, parents were advised to visit the nearest health facility.

Collection of cost data

A comparative financial cost analysis between the fixed delivery and door-to-door distribution strategies was carried out from the provider's perspective, which was defined as the cost incurred by implementation agencies. Cost components of each distribution strategy were identified using the ingredients approach. Costs were collected retrospectively using financial expenditure records to capture financial costs from the accountant service of the implementing agencies using a standardised spreadsheet developed by the NMCP. Costs related to research activities were excluded. The procurement cost of LLIN including purchase cost, shipment and custom clearance were included in the analysis. For the fixed delivery strategy, costs were collected in Great British Pound (GBP) and converted into US Dollars (USD) applying the 2015 average exchange rate of USD 1.5283 to the GBP (OANDA n.d.). For the door-to-door strategy, costs were collected in USD. For each distribution strategy the delivery cost per LLIN (i.e. total cost per net delivered) was calculated. Calculations of 'per LLIN' costs under each distribution strategy were based on the total number of LLIN recorded as distributed per strategy. Costs are presented in 2015 USD.

Measurements and indicators' definition

Standard malaria household survey indicators were measured as recommended by the RBM Monitoring and Evaluation Reference Group (MERG) (WHO PMI UNICEF RBM Measure Evaluation 2013) as follows: Prevention indicators: 1) Proportion of households with at least one LLIN; 2) Proportion of households with at least one LLIN for every two people; 3) Proportion of population with access to an LLIN within their household (calculated as previously described by Kilian *et al* (Kilian *et al.* 2013)); 4) Proportion of population that slept under an LLIN the previous night; 5) Proportion of children under five years old who slept under an LLIN the previous night; 6) Proportion of pregnant women who slept under an LLIN the previous night; 7) Proportion of existing LLIN used the previous night. Case management indicators: 8) Proportion of children less than five years old with fever in the last two weeks who had a finger or heel stick; 9) Proportion of children less than five years old with fever in the last two weeks for whom advice or treatment was sought; 10) Proportion receiving an ACT (or other appropriate treatment), among children less than five years old with fever in the last two weeks who received any antimalarial drugs. Morbidity indicators:

11) Malaria prevalence, defined as the proportion of children aged 6-59 months with a positive RDT; 12) Anaemia prevalence, defined as the proportion of children aged 6-59 months with haemoglobin rate <8g/dl.

Data management and analysis

Data were extracted from the ODK aggregate server using the ODK Briefcase in the CSV format and imported into STATA version 13 (Stata Corporation College Station, TX, USA) for statistical analysis. Dichotomous outcomes were summarized as proportions with 95% confident intervals. Continuous outcomes were described using their mean and standard deviation, or median and 90 % central range if the distribution was skewed. The Pearson chi square was used to compare proportions. Bivariate associations between the primary outcome and hypothesized explanatory variables were first done to guide subsequent model building; odds ratios and 95% confidence intervals were produced using logistic regression. After testing individual bivariate associations, a backward selection procedure was used to create an optimal multivariate model while adjusting for potential confounders. To take into account clustering by HZ and HA, a multi-level mixed effects logistic regression model was used to assess the association between the outcome and explanatory variables. Results are presented as adjusted odds ratios with their 95% confidence intervals.

7.4 Results

Households characteristics

Table 7-1 displays the characteristics of all surveyed households. During the pre-campaign survey, a total of 509 households were visited across 10 HZ including 3,227 people of which 51.5% were female. The median (90% central range) number of persons per household was 6 [2-12]; the median number of children less than five years of age per household was 1 [0-3]. In the post-distribution survey, 1,121 households were sampled of which 868 were from HZ that received LLIN through the fixed delivery strategy and 253 were from HZ that received LLIN through the door-to-door strategy. In total, 6,157 people were surveyed, 4,886 in HZ with fixed strategy and 1,271 in HZ with door-to-door strategy and in both strategies, about half (50.5%) of the surveyed people were female (fixed: 50%; door-to-door:52.5%). The median number of persons per household was 5 [2-10] (fixed: 5 [2-10]; door-to-door: 5 [2-9]) and the median number of children less than five years of age per household was 1 [0-3] (fixed: 1 [0-3]; door-to-door: 1 [0-2]).

Table 7-1: Characteristics of surveyed households

Characteristics	Survey		Post survey by delivery strategy	
	Pre	Post	Fixed	Door-to-door
Number of households	509	1121	868	253
Number of individuals in sampled households	3227	6157	4886	1271
Percent female	51.5	50.5	50.0	52.5
Median (90% central range) number of people per household	6 [2-12]	5 [2-10]	5 [2-10]	5 [2-9]
Median (90% central range) number of children under 5 per household	1 [0-3]	1 [0-3]	1 [0-3]	1 [0-2]
Median (90% central range) number of nets per household	0 [0-2]	2 [0-4]	2 [2-4]	2 [2-4]

Households' LLIN ownership and intra household access to LLIN

Table 7-2 shows key malaria household indicators before and after the campaign. Table 7-3 shows post-distribution indicators by distribution strategy. The proportion of households owning at least one LLIN increased from 39.4% [95% CI: 32.2%-47.0%] before the distribution to 91.4% [95% CI: 88.8%-93.4%] after the distribution (Table 7-2). Household ownership of at least one LLIN after the distribution was significantly higher in HZ with fixed delivery strategy compared to those with door-to-door strategy with a mean of 92.5% [95% CI: 90.2%-94.4%] versus 85.2% [95% CI: 78.5%-90.0%] respectively ($\chi 2$=5.71 p=0.026) (Table 7-3).

LLIN universal coverage, measured as the proportion of households with at least one LLIN for every two people increased from 4.1% [95% CI: 2.5%-6.5%] in the pre-campaign to 41.1% [95% CI: 36.1%-46.2%] in the post-campaign (Table 7-2). After the distribution, the proportion of households owning at least one LLIN for every two people was significantly higher in HZ with fixed delivery strategy compared to HZ with door-to-door strategy with a mean of 44.1% [95% CI: 38.7%-49.7%] versus 30.9% [95% CI: 22.7%-40.6%] respectively ($\chi 2$=5.14 p=0.034) (Table 7-3). The average number of LLIN in the surveyed households was approximately one for every 2.5 people (Fixed: 1 LLIN: 2.4; door-to-door: 1 LLIN: 3).

To assess the performance of each delivery strategy, the proportion of households reached during the campaign (proportion of households with at least 1 LLIN from the campaign) was calculated while the proportion of households with sufficient LLIN (1 LLIN for every two people) was calculated among those households that received at least 1 LLIN from the campaign to assess the efficiency of each allocation method. The proportion of households with at least 1 LLIN from the campaign (households reached) was significantly higher in HZ that received LLIN through fixed delivery strategy compared to those that received LLIN through the door-to-door strategy with a mean of 91.4% [95% CI: 89.1%-93.7%] versus 79.0% [95% CI: 70.2%-87.8%] respectively ($\chi 2$=13.87 p<0.001). Among households reached, the proportion of those that received enough LLIN (1 LLIN for 2 people) did not significantly vary by net allocation method (net per person: 50.0% [95% CI: 45.6%-54.5%]; net per sleeping space: 42.7% [95% CI: 29.2%-56.2%]; $\chi 2$=1.90 p=0.186).

In households containing more than four people, regardless of the delivery strategy, the mean number of LLIN received from the campaign was consistently lower than the WHO recommendation of one LLIN for every two people (figure 7-2).

Population access to LLIN within the household increased from 22.2% [95% CI: 17.9%-27.3%] pre-campaign to 80.7% [95% CI: 76.8%-84.6%] post campaign (Table 7-2). The post distribution access to a LLIN within the household did not vary by distribution strategy (fixed: 85.0% [95% CI: 81.1%-88.2%]; door-to-door: 75.8% [95% CI: 65.3%-83.9%]; $\chi 2$=2.45 p=0.131) (Table 7-3).

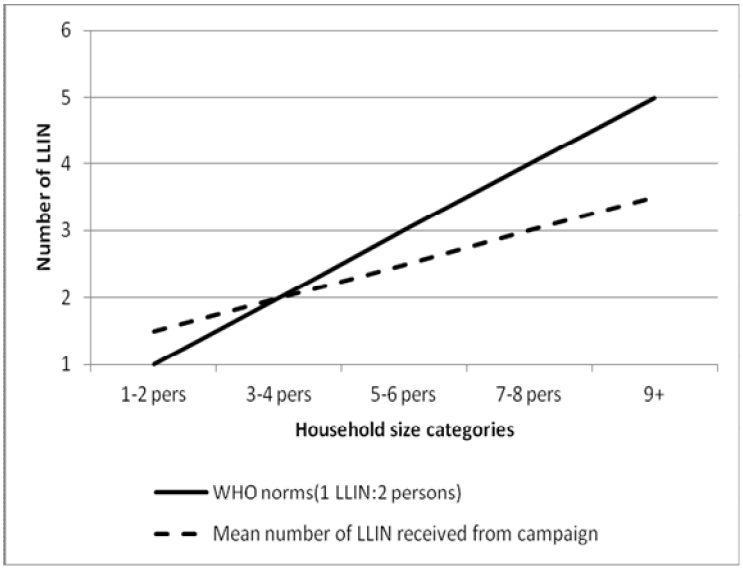

Figure 7-2: Number of LLIN received from the mass distribution campaign by household

LLIN use

Overall LLIN use increased from 18.0% [95% CI: 14.5%-22.2%] in the pre-distribution survey to 68.3% [95% CI: 62.9%-73.3%] after distribution. The overall use of LLIN was not statistically different between HZ with different distribution strategies (fixed: 69.60% [95% CI: 63.1%-75.5%]; door-to-door: 65.7% [95% CI: 52.7%-76.7%]; $\chi 2$=0.07 p=0.791) (Table 7-3).

Before the mass distribution campaign, LLIN use was lowest among the poorest wealth quintile and progressively increased with increasing wealth with a concentration index of 0.12 [95% CI:0.02-0.22]. After the distribution no specific pattern was observed in the LLIN use with regard to the socio economic status of the household with a concentration index of 0.02 [95% CI:0.00-0.02]. Figure 7-3 presents the Lorenz concentration curve describing the equity in LLIN use before and after the campaign.

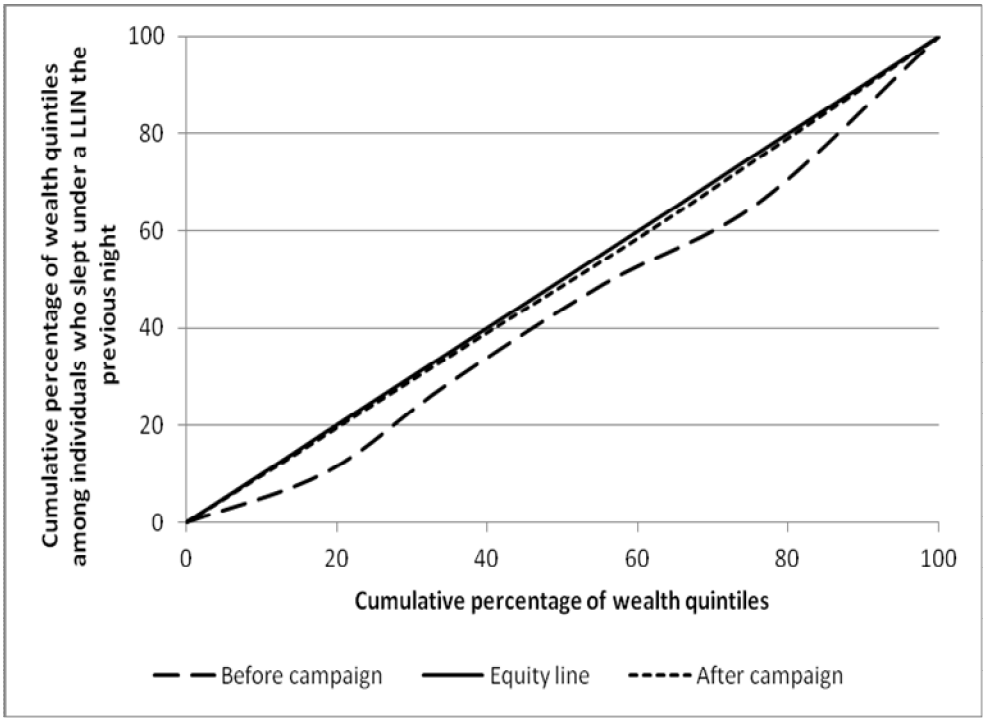

Figure 7-3: Lorenz concentration curve showing equity in LLIN use before and after the campaign

After the mass distribution, LLIN use was significantly higher in households with universal coverage (1 LLIN for 2 people) with a mean of 82.0% [95% CI: 76.6%-87.4%] versus 58.4% [95% CI: 52.2%-64.6%] ($\chi 2$=44.70 p<0.001). During both pre- and post-distribution surveys, at least 80 %(pre: 81.1%; post: 84.6%) of the population with access to a LLIN within their household slept under it the previous night (Figure 7-4).

Approximately one quarter (23.8%) of children less than five years of age slept under a LLIN before the distribution while there were three quarters (73.7%) after the distribution (Table 7-2). The post-distribution use of LLIN by children less than five years of age did not vary by distribution strategy (Fixed: 74.8% [95% CI: 67.9%-80.7%]; door-to-door: 71.6% [95% CI: 57.2%-82.6%]) (Table 7-3).

In both pre- and post-distribution surveys, the use of LLIN varied strongly across different age groups, with the lowest use rate observed in the age group of 5-19 years old (Figure 7-5A). Even in households with universal coverage (1 LLIN for 2 people), age specific use of LLIN consistently showed the same pattern (Figure 7-5B).

Use of LLIN by pregnant women increased from 20.9% [95% CI: 12.7%-32.4%] to 74.0% [95% CI: 63.9%-82.2%] before and after the distribution respectively (Table 7-2).

The latter did not vary by distribution strategy (Fixed: 79.6% [95% CI: 64.0%-89.6%]; door-to-door: 65.0% [95% CI: 34.4%-86.9%]) (Table 7-3).

After the distribution campaign, on average 66.7% [95% CI: 61.5%-71.5%] of existing LLIN were used the previous night. This proportion was slightly higher in HZ with door-to-door strategy compared to those with fixed strategy with a mean of 76.9% [95% CI: 68.0%-83.9%] versus 63.7% [95% CI: 58.3%-68.8%] ($\chi 2$=9.01 p=0.007) (Table 3). On average, 2.4 sleepers shared the same LLIN the previous night. Overall, around 60% of existing LLIN used the previous night had one or two sleepers, considered as appropriate coverage while the rest had more than two sleepers.

About 60% of interviewed household members reported to have heard or seen a message on malaria or LLIN in the last thirty days. The most commonly mentioned sources of messages were community health workers (46.2%), health centres (33.7%) and radio (32.3%), TV and other mass media channels were mentioned by about 10 % of respondents. The most commonly recalled message content were “nets prevent malaria” (66.6%) and “use a net every night” (67.6%).

LLIN characteristics

During the post-distribution survey, a total of 2,479 LLIN were recorded in surveyed households; 2,121 (85.6%) of which were observed. Of the 2,121 LLIN observed, 70.6% [95% CI: 64.7%-76.4%] were hung at the time of the interview. The proportion of LLIN hung per strategy was significantly higher in HZ with door-to-door strategy compared to the fixed delivery strategy with a mean of 90.1% [95% CI: 86.0%-94.2%] versus 67.5% [95% CI: 61.6%-73.3%] respectively ($\chi 2$=8.56 p=0.008). Nearly all (98%) of the LLINs observed in households during the post-distribution survey were marked Permanet® and were obtained from the mass distribution campaign.

Overall, 60% of households reported to have hung their LLIN the same day or the day following its reception but this proportion was higher in HZ with door-to-door strategy than in HZ with fixed delivery strategy (90.1% versus 52.6%). In HZ with fixed strategy, nearly all households (98.7%) reported their LLIN were hung by a household member, whereas in HZ with door-to-door strategy, over half of the households (56.5%) reported their LLIN were

hung by a member of the distribution team and 43.5% by a household member. Nearly all households (97.7%) encountered no problems hanging their LLIN in both strategies.

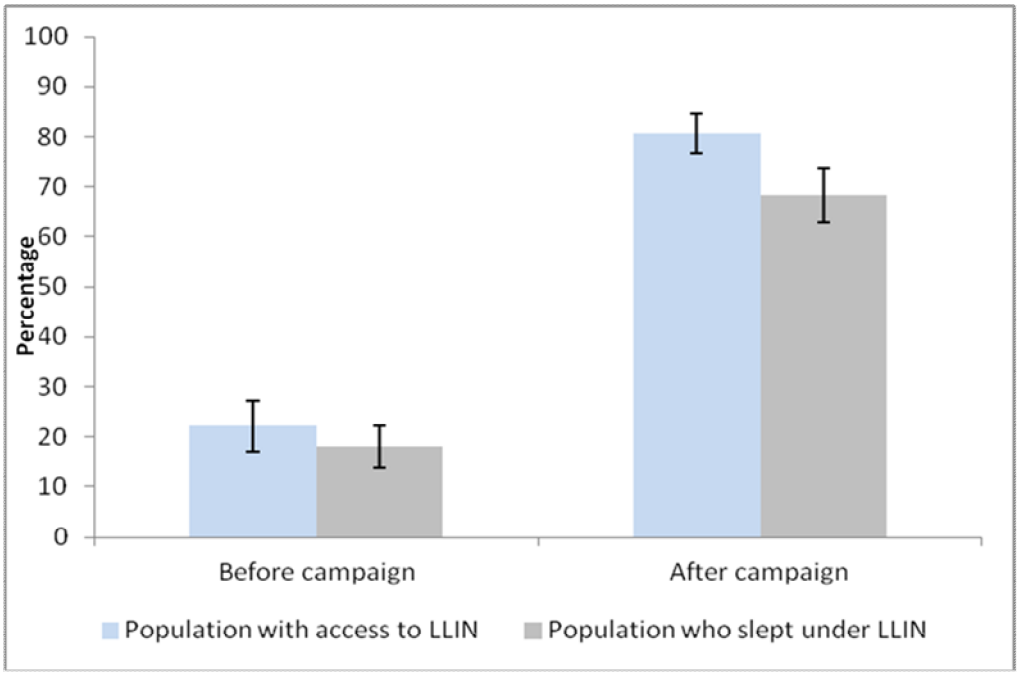

Figure 7-4: Population access and use before and after the mass distribution campaign

Health seeking behaviour and malaria morbidity

Data on health seeking behaviour and malaria morbidity were collected only during the post-distribution survey. More than one third (37.7% [95% CI: 29.5%-46.0%]) of children less than 5 years old had fever in the two weeks preceding the survey. Advice or treatment was sought for 31.0% [95% CI: 23.1%-38.9%] of them and a quarter (26.1%; [95% CI: 20.5%-31.6%]) had a finger or heel prick. Among these children less than 5 years of age who had fever in the two weeks before the survey and who received any antimalarials, 32.6 % [95% CI: 15.7%-49.4%] received an ACT (Table 7-2).

Malaria prevalence among children less than 5 years old was 44.8 % (95% CI: 34.7%-55.0%) and the proportion of children aged 6-59 months with a haemoglobin measurement of <8 g/dl was 37.7% [95% CI: 29.5%-46.0%] (Table 7-2). Malaria and anaemia prevalence was not significantly different between distribution strategies (Table 7-3).

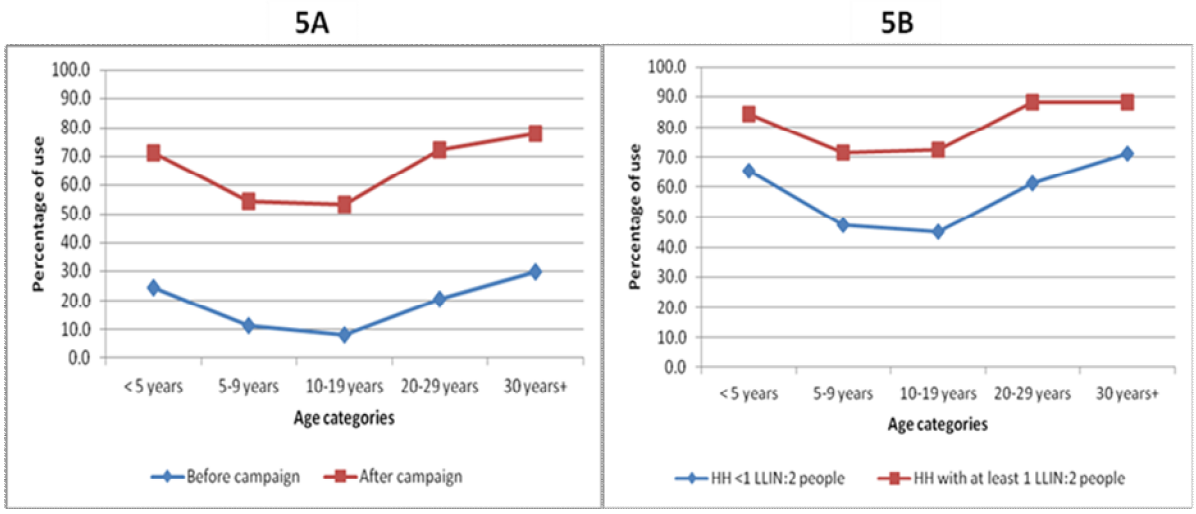

Figure 7-5: Age specific use of LLIN. Before and after the mass distribution campaign (5A). By coverage level after the mass distribution campaign (5B)

Table 7-2: Key malaria household survey indicators before and after the mass distribution campaign

Indicators	Pre (% CI)	Post (% CI)
Proportion of households with at least one ITN	39.4 [32.2-47.0]	91.4 [88.8-93.4]
Proportion of households with at least one ITN for every two people	4.1 [2.5-6.5]	41.1 [36.1-46.2]
Proportion of population with access to an ITN in their household	22.2 [17.9-27.3]	80.7 [76.8-84.6]
Proportion of the population that slept under an ITN the previous night	18.0 [14.5-22.2]	68.3 [62.9-73.3]
Proportion of children <5 y who slept under an ITN the previous night	23.8 [18.0-30.6]	73.7 [67.8-78.9]
Proportion of pregnant women who slept under an ITN the previous night	20.9 [12.7-32.4]	74.0 [63.9-82.2]
Proportion of existing ITNs used the previous night	82.2 [75.9-87.2]	66.7 [61.5-71.5]
Proportion of children <5 y with fever in the last two weeks		37.7 [29.5-46.0]
Proportion of children <5 y with fever in last two weeks who had a finger or heel stick		26.1 [20.5-31.6]
Proportion of children <5 y with fever in the last two weeks for whom advice or treatment was sought		31.0 [23.1-38.9]
Proportion receiving an ACT (or other appropriate treatment), among children under five years old with fever in the last two weeks who received any antimalarial drugs		32.6 [15.7-49.4]
Proportion of children aged 6-59 months with malaria infection		44.8 [34.7-55.0]
Proportion of children aged 6-59 months with a hemoglobin measurement of <8 g/dl		14.6 [11.0-18.3]

Table 7-3: Key malaria household survey indicators by distribution strategy

Indicators	Fixed (% CI)	Door-to-door (% CI)	χ^2	p-value
Proportion of households with at least one ITN	92.5 [90.2-94.4]	85.2 [78.5-90.0]	5.71	0.026
Proportion of households with at least one ITN for every two people	44.1 [38.7-49.7]	30.9 [22.7-40.6]	5.14	0.034
Proportion of population with access to an ITN in their household	85.0 [81.1-88.2]	75.8 [65.3-83.9]	2.45	0.131
Proportion of the population that slept under an ITN the previous night	69.6 [63.1-75.5]	65.7 [52.7-76.7]	0.07	0.791
Proportion of children under five years old who slept under an ITN the previous night	74.8 [67.9-80.7]	71.6 [57.2-82.6]	0.12	0.729
Proportion of pregnant women who slept under an ITN the previous night	79.6 [64.0-89.6]	65.0 [34.4-86.9]	1.08	0.310
Proportion of existing ITNs used the previous night	63.7 [58.3-68.8]	76.9 [68.0-83.9]	9.01	0.007
Proportion of Children Aged 6-59 Months with Malaria Infection	37.8 [25.9-51.5]	64.9 [39.6-83.9]	2.78	0.110
Proportion of Children Aged 6-59 Months with a Hemoglobin Measurement of <8 g/dL	13.4 [10.1-17.6]	11.6 [6.6-19.6]	0.29	0.597

Determinants of LLIN use

The contribution of different factors associated with LLIN use before and after the distribution is shown in tables 7-4 and 7-5. During the pre-distribution survey, there was no evidence of association between use of LLIN and gender, while significant heterogeneities were observed in LLIN use among age groups. Compared to children less than 5 years of age, individuals aged 5-19 years were significantly less likely to sleep under a LLIN (OR = 0.26 [95% CI: 0.19, 0.34]) and those aged 30 years and above were significantly more likely to use a LLIN (OR = 1.40 [95% CI: 1.06, 1.86]). A higher educational level of the head of the household was associated with increased odds of sleeping under a LLIN (OR = 2.67 [95% CI: 1.15, 6.19]). Individuals living in households whose head was employed were also significantly more likely to use a LLIN than those of other occupations (OR = 1.81 [95% CI: 1.06, 3.09]). There was no evidence of an association between LLIN use and the number of persons per sleeping space, the knowledge of malaria transmission or the exposition to a sensitisation message on malaria/LLIN., The wealthiest socio-economic quintile (compared with the poorest) was associated with significant increased odds of sleeping under a LLIN (OR = 2.79 [95% CI: 1.54, 5.07]).

Following the mass distribution, no association was found between gender and the use of LLIN as before. The age specific use of LLIN showed the same pattern as before the distribution, with the 5-19 years olds having the lowest odds of LLIN use (OR = 0.39 [95% CI: 0.33, 0.46]) and the 30 years and above being more likely to use a LLIN (OR = 1.46 [95% CI:1.21, 1.78]) compared with children less than 5 years. As before the distribution, occupation and educational level of the head of the household were significantly associated with the use of LLIN. There was no evidence of association between the use of LLIN and the distribution strategy. Individuals living in households whose head knew the cause of malaria (OR = 1.39 [95%CI: 1.16, 1.68]) or have heard about malaria or LLIN in the last month (OR = 1.57 [95%CI: 1.34, 1.84]) were more likely to sleep under a LLIN. The socio-economic status of the household was not associated with LLIN use. Individuals living in households owning at least one LLIN for every two people had the highest odds of sleeping under a LLIN (OR = 3.79 [95%CI: 3.21, 4.49]).

Table 7-4: Logistic regression model showing determinants of LLIN use before the mass distribution campaign

			Univariate analysis			Multivariate analysis		
Variable	***n***	**(%)**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Sex								
Male	1413	17.7	1			1		
Female	1582	19.1	1.17	0.96-1.43	0.118	1.15	0.93-1.42	0.190
Age								
<5 years	576	24.3	1			1		
5-19 years	1328	9.3	0.26	0.19-0.35		0.26	0.19-0.34	
20-29 years	383	20.6	0.73	0.52-1.02		0.80	0.56-1.13	
>=30 years	708	29.5	1.2	0.92-1.57	<0.001	1.40	1.06-1.86	<0.001
Education of the head of the household								
No education	73	15.1	1			1		
Primary	640	11.3	1.06	0.50-2.22		1.20	0.55-2.63	
Secondary	2,066	18.2	1.8	0.89-3.64		1.59	0.74-3.42	
Superior and above	216	43.1	3.8	1.78-8.13	<0.001	2.67	1.15-6.19	0.010
Occupation of the head of the household								
Without occupation	187	13.4	1			1		
Farmer	1,160	12.4	0.87	0.53-1.42		0.83	0.49-1.41	
Merchant	927	15.3	1.14	0.70-1.85		0.93	0.54-1.60	
Employed	721	33.4	2.42	1.51-3.90	<0.001	1.81	1.06-3.09	<0.001
Persons per sleeping space								
2 or less	1,752	19.18	1			1		
More than 2	1,243	17.38	0.79	0.64-0.97	0.025	1.04	0.58-1.88	0.889
Wealth quintile								
Poorest	558	10.6	1			1		
Second	496	20.4	2.67	1.78-4.00		2.38	1.54-3.68	
Middle	624	17.8	2.54	1.66-3.88		2.23	1.40-3.54	
Fourth	637	15.2	1.93	1.23-3.02		1.82	1.06-3.11	
Wealthiest	680	27.1	3.23	2.00-5.23	<0.001	2.79	1.54-5.07	<0.001
Knowledge transmission								
No	775	13.7	1			1		
Yes	2,220	20.1	1.29	0.98-1.29	0.064	1.20	0.89-1.60	0.226
Heard a message on malaria/ITN last month								
No	1,113	16.4	1			1		
Yes	1,882	19.6	1.14	0.90-1.45	0.274	0.97	0.74-1.26	0.798

Table 7-5: Logistic regression showing determinants of LLIN use after the mass distribution campaign

			Post distribution					
			Univariate analysis			Multivariate analysis		
Variable	***n***	**(%)**	**OR**	**95% CI**	***P*-value**	**AOR**	**95% CI**	***P*-value**
Sex								
Male	2746	66.4	1			1		
Female	2913	67.2	1.05	0.93-1.18	0.458	1.05	0.93-1.20	0.422
Age								
<5 years	1308	71.6	1			1		
5-19 years	2164	54.1	0.41	0.35-0.49		0.39	0.33-0.46	
20-29 years	706	72.5	1.03	0.83-1.28		0.97	0.77-1.23	
>=30 years	1481	78.4	1.49	1.24-1.79	<0.001	1.46	1.21-1.78	<0.001
Education of the head of the household								
No education	397	58.2	1			1		
Primary	1599	62	1.35	1.04-1.74		1.28	0.97-1.69	
Secondary	3265	68.8	2.08	1.63-2.66		1.92	1.46-2.52	
Superior and above	398	78.1	2.95	2.06-4.23	<0.001	2.29	1.52-3.45	<0.001
Occupation of the head of the household								
Without occupation	355	63.9	1			1		
Farmer	2748	63.8	0.91	0.70-1.19		1.40	0.94-2.09	
Merchant	1397	64.3	1.06	0.81-1.39		1.62	0.94-2.79	
Employed	1159	77.8	1.95	1.47-2.59	<0.001	3.73	1.75-8.38	<0.001
Persons per sleeping space								
2 or less	3722	70.0	1			1		
More than 2	1937	65.2	0.84	0.74-0.96	0.010	0.97	0.66-1.41	0.862
Distribution strategy								
Fixed	4577	67.2	1			1		
Door-to-door	1082	65.3	0.87	0.47-1.61	0.655	0.80	0.40-1.62	0.538
Wealth quintile								
Poorest	1114	63.6	1			1		

Second	1081	66.2	1.04	0.84-1.27		0.94	0.71-1.25	
Middle	1137	64.6	1.47	1.14-1.88		1.51	0.98-2.33	
Fourth	1105	68.3	1.72	1.33-2.23		1.84	0.98-3.37	
Wealthiest	1222	70.8	1.49	1.12-2.00	<0.001	1.53	0.67-3.46	0.061
Knowledge transmission								
No	1,121	62.1	1			1		
Yes	4,538	68.0	1.47	1.25-1.73	<0.001	1.39	1.16-1.68	<0.001
Heard a message on malaria/ITN last **month**								
No	2,110	61.4	1			1		
Yes	3,549	70.0	1.74	1.51-2.00	<0.001	1.57	1.34-1.84	<0.001
At least 1 LLIN/2 people								
No	3,730	58.79	1			1		
Yes	1,929	82.27	3.35	2.89-3.88		3.79	3.21-4.49	<0.001

Cost analysis

Costing details for both strategies are shown in table 7-6. The total financial cost of the campaign from the provider perspective was USD 22.84 million (USD 18.71 million for the fixed delivery strategy and USD 4.13 million for the door-to-door strategy). The total financial cost per LLIN distributed was USD 6.59 (USD 6.58 for the fixed distribution strategy and USD 6.61 for the door-to-door strategy). Overall, LLIN transport and storage comprise around 80% (87.3% for the fixed delivery strategy and 70.3% for the door-to-door strategy) of the total financial cost.

Table 7-6: Financial costs of the LLIN distribution by cost category and delivery strategy

	Door-to-door		**Fixed**		**Combined**	
Number of LLIN distributed	624,532		2,843,442		3,467,974	
Total financial cost (2015 USD)	4,130,050		18,706,824		22,836,874	
Financial cost per LLIN delivered (USD)	6.61		6.58		6.59	
Cost of LLIN Campaign (2015 USD) per category	**Cost**	**%**	**Cost**	**%**	**Cost**	**%**
LLINs	2,287,500	55.4	11,858,176	63.4	14,145,676	61.9
Transport and storage	613,92	14.9	4,477,243	23.9	5,091,163	22.3
Personnel	567,484	13.7	555,023	3.0	1,122,507	4.9
Trainings	140,997	3.4	660,994	3.5	801,991	3.5
Office, supplies and equipment	438,654	10.6	566,167	3.0	1,004,821	4.4
IEC	20,995	0.5	469,3	2.5	490,295	2.1
M&E	60,500	1.5	119,921	0.6	180,421	0.8

7.5 Discussion

Concerted efforts to scale up LLIN coverage through a free mass distribution campaign in the Kasaï Occidental province have rapidly increased ownership and use of LLIN. In terms of coverage, RBM targets of 80% of households owning at least 1 LLIN and 80% of population having access within their household have been achieved. Universal coverage (defined as households with at least 1 LLIN for every 2 people) though below the 80% target, has shown a remarkable tenfold increase. These findings are consistent with what is known about the effectiveness of mass distribution campaigns to quickly scale-up LLIN coverage in low coverage areas (Bonner *et al.* 2011; Bennett *et al.* 2012; Renggli *et al.* 2013; Larson *et al.* 2014). However, there had been a previous mass distribution campaign in 2011 with high coverage values; hence the level of indicators found in the pre-distribution survey was surprisingly low.

Following a universal free mass distribution campaign, the fact that less than half of surveyed households had at least 1 LLIN for every 2 people can be surprising. This highlights a limitation of the distribution campaign in quantifying the number of LLIN allocated per household, in particular for households of more than 4 members. A study conducted in Sierra Leone six months after a mass distribution campaign also showed that when limiting the maximum number of LLIN one household can receive, households with more than 5 residents were less likely to have sufficient LLIN to cover all occupants (Bennett *et al.* 2012).

Despite a dramatic increase in LLIN access and use overall, significant heterogeneities were observed in LLIN use among age groups, with the lowest use rate observed in the age group of 5-19 years old. The age specific pattern we observed has been reported by other researchers in different contexts including DRC, (Auta 2012; Loha *et al.* 2013; Kateera *et al.* 2015; Ferrari *et al.* 2016). Interestingly, in this study, the same pattern was observed even in households possessing sufficient numbers of LLIN to cover all residents, suggesting a behavioural gap in LLIN use among older children and adolescents. The lower LLIN use rate obviously put this age group at higher risk of malaria prevalence as reported in other studies (Nankabirwa *et al.* 2014; Ferrari *et al.* 2016).

Findings from this study also showed that both before and after the campaign, at least 80% of those with access to a LLIN used it the previous night.

Nevertheless, as access to LLIN has tremendously increased, it is important that the NMCP focus on developing behaviour change communications strategy and plan to promote LLIN use in the general population as well as in specific group such as older children and adolescents.

Contrary to what could be expected, results of this study showed that the fixed delivery strategy reached a much higher proportion of households compared to the door-to-door strategy. However, among those households reached, having enough LLIN did not vary by net allocation method. A multi country comparison of LLIN delivery strategies based on 14 surveys from five African countries did not find a significant association between delivery strategy and ownership of a net from the campaign but found a positive association between sleeping space allocation and enough LLIN in the household (Zegers de Beyl *et al.* 2016).

Only half of surveyed households in areas where the hang up approach was implemented reported their LLIN was hung by a member of the distribution team. However, of those that were hung by a member of the distribution team, a higher proportion were still hung and used the previous night compared to those not hung by a member of the distribution team as also noted by other researchers (MacIntyre *et al.* 2012; Bennett *et al.* 2012). However this did not necessarily result in higher LLIN use rates among the population. A cluster randomised controlled trial conducted in Uganda showed that additional hang up activities following a mass distribution campaign did not provide any additional impact on net use (Kilian *et al.* 2015)

As could be expected after a free LLIN mass distribution campaign that targeted the entire population at risk for malaria, equity in household LLIN coverage and individual use of LLIN has been improved as demonstrated by the Lorenz curve meeting the equity line as well as the concentration index shifting from positive to close to zero values. These findings corroborate results from other mass distribution campaigns showing equitable LLIN ownership and use (Noor *et al.* 2007; Thwing *et al.* 2008; Ye *et al.* 2012; Renggli *et al.* 2013).

Despite higher coverage and reported use of LLIN six month after a free mass distribution of LLIN, malaria rates remain high in the province. Although lower in LLIN users compared with non users, the overall malaria prevalence among children aged 6-59 months found in this study was higher than the national average of 31% prevalence reported by the DHS (DHS 2014). This high malaria rate calls for further investigation of possible contributors. As an attempt to identify factors explaining high malaria rates in northern Ghana, Monroe *et al* found that under-usage of LLINs at times when they could confer maximum protection as well as a variety of outdoor night-time activities, including outdoor sleeping were factors that could potentially contributed to high rates of malaria in that setting (Monroe *et al.* 2015).

In this study, the prevalence of anaemia was high and consistent with findings of other researchers (Ferrari *et al.* 2016), however additional factors common in this setting such as malnutrition (DHS 2014) and sickle cell anaemia (Tshilolo *et al.* 2009) play a role in the occurrence of this condition.

Access to diagnostic testing and malaria treatment is very low; efforts should be made to increase availability of RDT and ACT in both public and private sectors.

For both fixed delivery distribution and door-to-door strategies, the average cost per LLIN distributed was consistent with findings of other researchers (White *et al.* 2011). As expected, the highest proportion of cost was attributable to the purchase cost of the LLIN. Compared to the fixed strategy, the average cost per LLIN distributed was slightly higher in the door-to-door strategy with the personnel cost being the second highest single cost position after LLIN. This is consistent with the additional cost associated with hang up activities as reported by other researchers (Smith Paintain *et al.* 2014; Kilian *et al.* 2015).

This study has limitations. Although interviewers were required to observe LLIN owned by households, most net results reported in this study relies on data reported by respondents, thus they are prone to recall and information bias. LLIN may be more subject to over-reporting due to social desirability bias. As RDT were used for malaria diagnostic and parasite antigens (detected by the test) often persist up to two weeks post-treatment, some children previously treated for malaria might have tested positive within 14 days after treatment.

7.6 Conclusions

This study demonstrates substantial improvements in LLIN coverage, use and equity. Although all RBM targets were not met, much progress has been made. In addition to antenatal and vaccination clinic programmes, other LLIN distribution strategies should be explored as part of a keep-up strategy in order to maintain high and equitable coverage over time. The very low ownership and use levels observed before the campaign in this study despite a previous mass distribution campaign in 2011 is a stark reminder of the need for a keep-up mechanism.

These results also suggest a revision of distribution guidelines especially with regard to LLIN quantification to better cover larger households and those not reached by the mass distribution campaign. Having sufficient numbers of LLIN to cover all residents in the household was the strongest determinant of LLIN use. As access to LLIN is increasing, results of this study suggest that behaviour change strategies should focus on interpersonal interventions to promote LLIN use in the general population and specific groups such as older children and adolescents. In the context of the present study setting, a fixed delivery strategy seems to be a better LLIN delivery option, as it was shown to be associated with higher levels of LLIN coverage and use indicators as well as lower delivery cost.

8 Malaria morbidity in the Democratic Republic of Congo from 2010 to 2014: What is really captured by the surveillance system?

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Working paper

8.1 Abstract

Background

Despite inherent challenges, health facility-based data remain the only consistent and readily available source of information on malaria in many endemic areas. In the Democratic Republic of Congo (DRC), the use of rapid diagnostic tests has been expanded since 2010, leading to a marked increase in suspected malaria cases receiving a diagnostic test. Together with other management measures, this should improve the quality of the incidence rates obtained through the Health Monitoring Information System (HMIS). Based on household surveys data, the Malaria Atlas Project (MAP) has produced estimates of clinical incidence of malaria for the years 2000-2015 for all African countries. Here we assess how well the two data sources (routine versus modelled) correlate.

Methods

Validated HMIS data from 2010 to 2014 were obtained through the National Malaria Control Programme (NMCP). Data on incidence cases of clinical malaria by province were downloaded from the MAP website. Trends in surveillance indicators were examined over a 5-year period. The number of reported confirmed malaria cases was compared to the MAP predicted incidence counts to determine the relative reporting of the HMIS system.

Results

While the incident cases predicted by the MAP model were progressively decreasing (from 27.7 million cases in 2010 to 20.1 million cases in 2014), the reported confirmed malaria cases increased from 2.4 million in 2010 to 9.8 million in 2014. As a result, the percentage of suspected malaria cases receiving a diagnostic test increased from 37.4% in 2010 to 90.1% in 2013. Over this time period the slide and RDT positivity rates have remained almost constant, with an average of 62.7% and 68.9%, and the reporting completeness rate as well as the total number of outpatients and the number of suspected cases have not shown marked changes either. When compared to the MAP predicted incidence cases, the fraction of incidence cases reported by the HMIS has been progressively increasing from 8.7% in 2010 to 48.7% in 2014.

Conclusions

Due to the expansion of parasitological diagnosis, the number of confirmed malaria cases reported and hence the fraction of incident cases captured by the HMIS data is increasing over time. Because of inconsistencies in reporting, it has been difficult to establish trends in malaria morbidity from nationally aggregated data, but the unchanged test positivity rates suggest malaria transmission remained high and stable over that time period.

8.2 Background

Information on the number and distribution of malaria cases and deaths is fundamental for the design, implementation and evaluation of malaria control programmes (WHO 2011a). As in many sub-Saharan African countries, the decision makers in the Democratic Republic of Congo (DRC) rely on two main sources of data: (1) routinely collected health facility-based data available through the Health Management Information System (HMIS); and (2) nationally representative surveys such as the Demographic and Health Surveys (DHS), Multiple Indicators Cluster Surveys (MICS), and Malaria Indicators Surveys (MIS) (PNLP 2013a). Nationally representative surveys provide reliable estimates for key malaria indicators that are important for: (1) planning control interventions, (2) for monitoring trends in population intervention coverage, and (3) for evaluating impact on malaria burden. They provide as well valuable information for interpreting data from other sources (Cibulskis *et al.* 2007). Recent collaborative work by the INFORM project assembled data from households surveys to produce an epidemiological profile of malaria in the DRC (Figure 8-1) (PNLP *et al.* 2014). However, nationally representative surveys are designed to produce precise estimates at national and at best at regional level. Using these data to provide sub-regional level estimates of outcome will therefore lead to low precision in the estimates. Since unsampled areas get an estimate on the basis of neighbouring sampled areas, the validity of such estimates also becomes an issue. DRC is the size of Western Europe and has a highly decentralised health system (Figure 8-2). The operational unit of the health system is the health zone (sub-provincial level). Given the low total number of parasite prevalence surveys done in the country (1400 time-space surveys since 1980), the validity and precision of the estimates at the level of the health zone is low. This, along with the long interval between surveys (usually 3-4 years) and their high cost constitute a clear limitation of such data sources for monitoring and planning purposes.

HMIS data have the advantage of being collected continuously from every health facility in the country. When such a system is working well, it can represent continuously with a high time-space resolution the evolution of malaria cases (Gething *et al.* 2007; Bennett *et al.* 2014). However, HMIS data have usually a number of limitations. Firstly, varying degrees of data quality and completeness are observed across the HMIS system and therefore trends in morbidity and mortality can vary over time for reasons that have nothing to do with the epidemiology of disease. Secondly, the reported cases in a HMIS are influenced by changes in health service utilization, in diagnostic technology, in medical procedures, and changes of regulations within the HMIS itself.

Thirdly, the HMIS only captures those members of the population that seek care at a formal health facility and represents therefore an incomplete sample of the morbidity and mortality experienced by communities. As a result of these limitations, a HMIS can underestimate the total burden of disease by a considerable fraction (Chilundo *et al.* 2004; Rowe *et al.* 2009). The World Health organisation (WHO) estimates that routine health information systems detect only 14% of the malaria cases estimated to occur globally. Further, case detection rates and the proportion of deaths reported are lowest in countries with the highest malaria disease burden As a result of this weak information system, it is not possible to reliably assess malaria trends using the data submitted to the WHO in 32 highly endemic countries, including DRC (WHO 2013c; WHO 2014b) Despite these inherent challenges, in many settings the HMIS data remain the only consistent and readily available source of information on malaria.

Due to an increase in the use of rapid diagnostic tests, there has been a marked increase in the proportion of suspected malaria cases receiving a malaria diagnostic test. Substantial improvements have also been observed in treatment seeking rates for malaria (DHS 2007; DHS 2014; UNICEF 2010; WHO 2013c; WHO 2015b; Battle *et al.* 2016), often thanks to donor-supported programmes. These trends have the potential to improve the case detection rate of HMIS data and hence the fraction of the actual community malaria incidence that is captured.

Based on parasite rate household surveys, the Malaria Atlas Project (MAP) has produced modeled estimates of clinical incidence of *Plasmodium falciparum* malaria for the years 2000-2015 for all African countries (Bhatt *et al.* 2015). Although these estimates come with uncertainties and some limitations, they constitute probably the best estimates of clinical malaria incident cases at present for countries with incomplete reporting systems. Even they do not constitute a Gold Standard, these modelled numbers provide at least a reference value to allow an estimation of how well the HMIS is reporting incidence rates. This study assesses the malaria incidence rates obtained from the HMIS data in the DRC from 2010 to 2014, and compares them to the modelled incidence rates from the MAP project for the same time period.

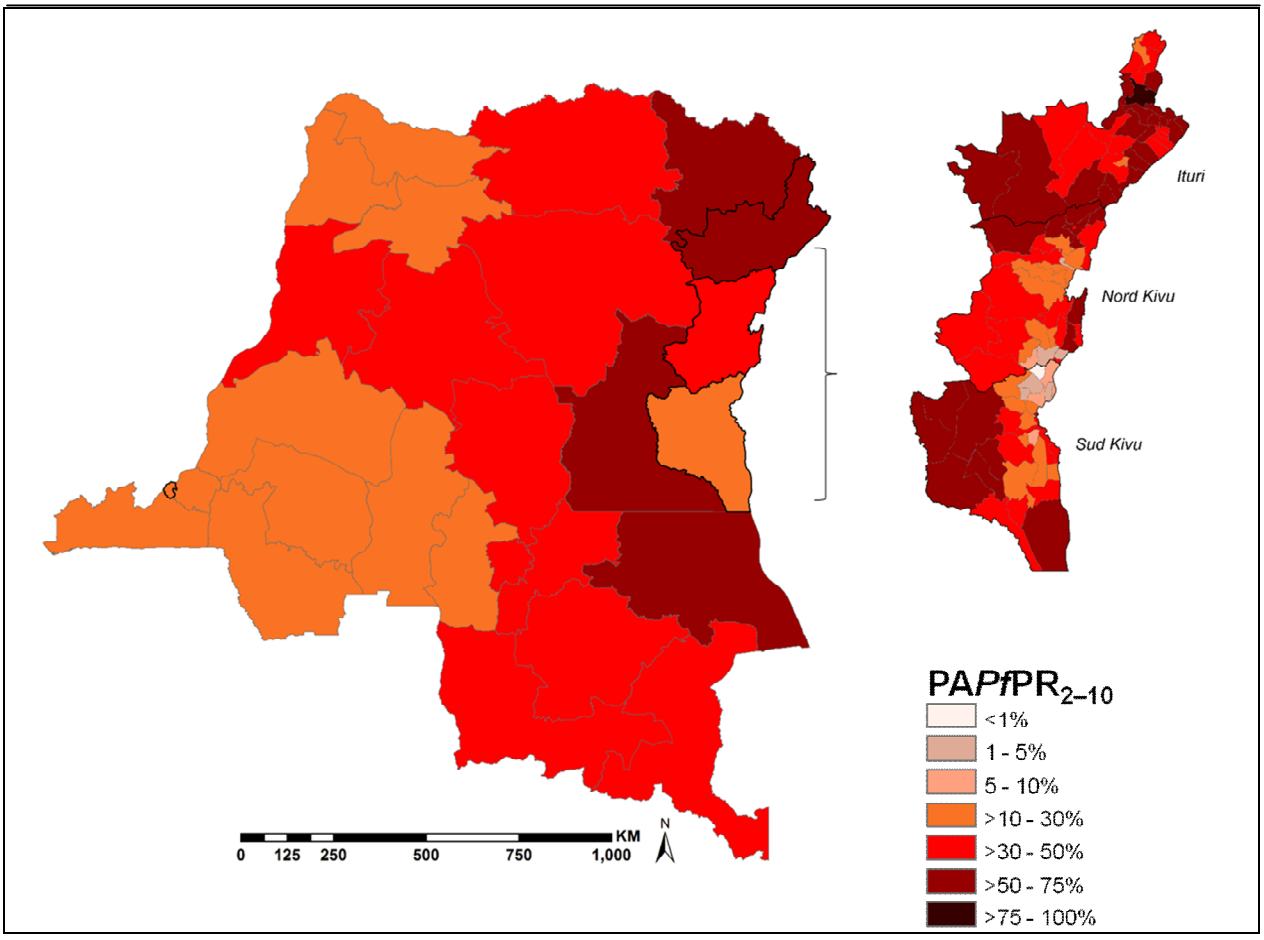


Figure 8-1: Population-adjusted Plasmodium falciparum parasite rate in 2-10 years olds, by region (large figure) and by health zones for three regions (detailed map for Ituri, Nord Kivu and Sud Kivu), 2013.

Source: INFORM Project.

8.3 Methods

Study site

The DRC is one of the most malarious countries in the world. Together with Nigeria, DRC accounts for about 40% of the total of estimated malaria cases worldwide, and for more than 35% of the total estimated malaria deaths (WHO 2015b). In total, 97% of the estimated 72 million inhabitants live in high malaria transmission areas. In 2014, the DHS reported an average malaria prevalence of 31% in children less than 5 years (DHS 2014).

The health system in DRC has a pyramidal structure with three levels (Figure 8-2): central, intermediate and peripheral level.

The central level includes the office of the minister of health (MoH), the general secretary of the MoH, and the directorates of national disease-specific programs. The intermediate level is composed of 26 provincial health divisions (previously 11 until 2013). The peripheral level comprises 516 Health Zones (HZ). The HZ is the actual operational unit of the health system and includes a general referral hospital and 15-20 health centres. A HZ is further divided into 15 Health Areas (HA) on average. The health system also includes community health workers providing treatment at community level in the framework of the integrated community case management (iCCM). The national guidelines for the management of malaria recommend parasitological confirmation for all malaria suspected cases seen at all levels of the health system using Rapid Diagnostic Test (RDT) or microscopy.

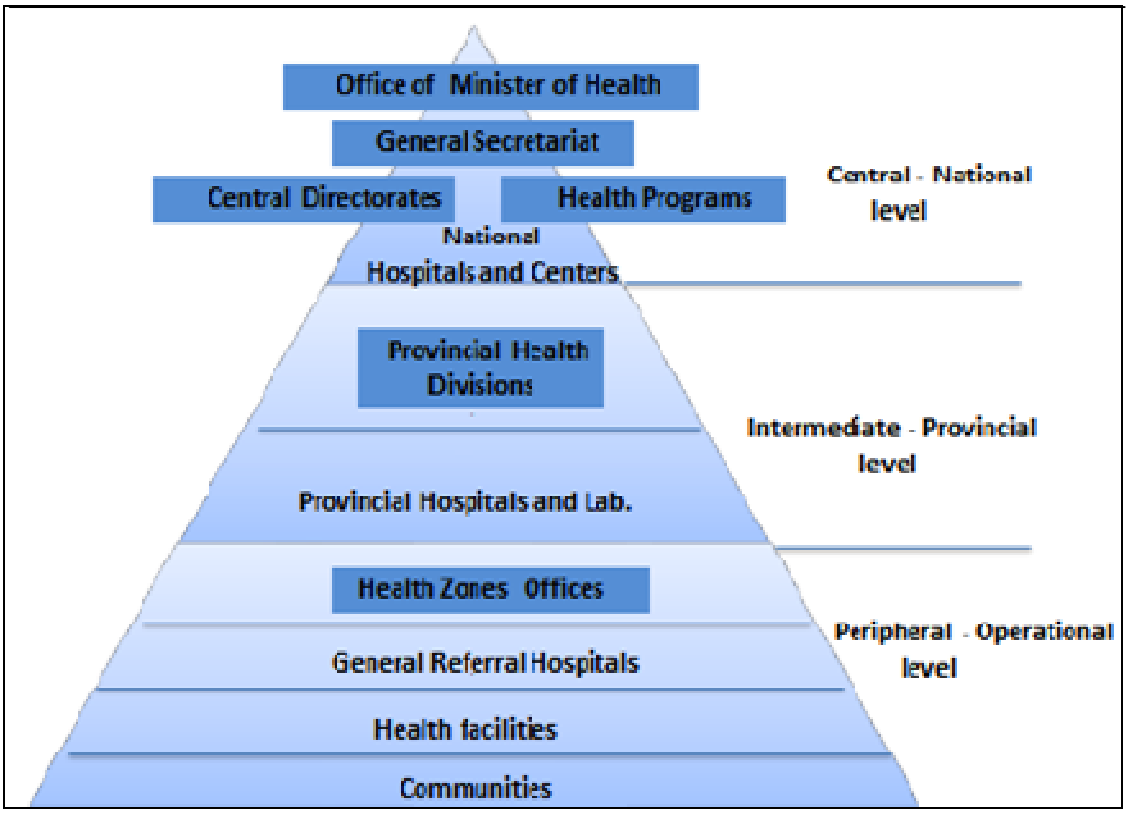


Figure 8-2: Health system structure in the DRC

Data assembly

HMIS data from 2010 to 2014 were obtained from the Monitoring and Evaluation division of the National Malaria Control Programme (NMCP). Monthly data from iCCM sites and health facilities as well as data from the general referral hospitals are transmitted to the HZ office, where they are analysed and validated during a monitoring meeting with nurses responsible for the different HA.

The data are then transmitted to the provincial level, which compile, analyse, validate, and transmit the consolidated data to the central level, where they are further consolidated, verified, analysed and validated. Aggregated data at country level are then used to produce the NMCP annual report and these data are transmitted to the WHO. While the entire system is progressively being made electronic by the scaling up of the District Health Information Software 2 (DHIS2), many HZ continue to use paper forms for the collection of routine malaria data. The data are then entered at provincial level.

Data on modelled incident cases of clinical malaria were downloaded from the MAP website (http://www.map.ox.ac.uk). These data are available for use on an open access basis. For the DRC, the modelled clinical incident cases of *Plasmodium falciparum* malaria are derived from a cartographic method based on parasite rate surveys, including the DHS 2014. Firstly, parasite prevalence data from 1995 to 2014 were assembled within a spatiotemporal Bayesian model, taking into account environmental and sociodemographic covariates, as well as data on use of insecticide treated nets (ITN) and access to treatment. The model predicted *P. falciparum* prevalence at a resolution of 5x5km^2. Secondly, an ensemble model was developed to predict malaria incidences as a function of parasite prevalence, and then applied to obtain estimates of malaria incidence cases at 5x5km^2. Data for each 5x5km^2 grid were thenaggregated to obtain national and regional estimates of malaria cases (Bhatt *et al.* 2015). Data on predicted malaria clinical incidence are available as annual incidence counts (total number of malaria cases) and annual incidence rates (cases per 1000 people per annum), for both country and provincial levels.

Analysis

National HMIS case data were obtained in XLS format from the NMCP and converted into STATA version 13 (Stata Corporation College Station, TX, USA) for analysis at both national and provincial levels. Overall trends at national and provincial level were produced over a 5-year period for the following key surveillance indicators: (1) number of confirmed malaria cases per 1000 population per year; (2) percentage of suspected malaria cases receiving a diagnostic test; (3) malaria test positivity rate (RDT and slide positivity rate) and (4) completeness of reporting (i.e number of monthly reports received out of the total expected). Incidence rates were calculated using as denominator population data from the National Health Development Plan. Unfortunately, these data are based on the 1984 census to which a yearly growth rate of 3% is applied (PNDS 2011-2016), and the numbers are likely to be subject to some (unknown) error.

To assess variation by geographical area, the incidence of reported confirmed malaria cases and test positivity rates were mapped at provincial level using quantum GIS version 2.0 (Quantum GIS Development Team, Open Source Geospatial Foundation).

Finally, the number of reported confirmed malaria cases was compared to the predicted incidence count to determine the representative fraction of HMIS data. Trends in this fraction were examined over the same time period.

Given large numbers of reported cases and hence large numerators and denominators, confidence intervals were very small; therefore they are not shown in the text.

8.4 Results

HMIS dataset were collected from the NMCP for the period 2010 to 2014. For each year, data were available for all 11 provinces; 2014 data were also presented for the 26 new provinces. Available data included, amongst other, the total population, the number of suspected cases, the number of microscopy slides performed with the number of positive slides, the number of RDTs performed with the number of positive RDTs, and the report completeness.

Completeness of reporting

Over the period considered, the completeness of reporting has been fluctuating with the highest value (92%) reported in 2010 and the lowest value (83.9%) reported in 2014 (Table 8-1).

The provinces of Equateur, Kasai Occidental and Katanga have reported the lowest rates of reporting completeness for the year 2014, with respectively 57%; 72% and 79%. Moreover, during the past five years, the provinces of Equateur and Katanga have reported some of the lowest rates of reporting completeness with 73% in 2013 and 2012 for the first and 67% in 2012 and 55% in 2011 for the second. The provinces of Bas Congo and Nord Kivu have reported consistently over 90% during the five-year period.

Reported suspected cases

From 2010 to 2014, the total number of outpatients did not show any particular trend. The same was found for the number of suspected malaria cases reported nationally, which ranged between 129 and 147 cases per 1000 population, with the highest value observed in 2013 and the lowest observed in 2014 (Table 8-1). Higher numbers of suspected malaria cases per 1000 population were reported in provinces with higher reporting completeness rate. The province of Bas Congo, with the highest reporting completeness (average 97% over the period considered), reported the highest number of suspected cases, showing a peak of 266 cases per 1000 population in 2013 (Figures 8-3).

Percentage of suspected malaria cases receiving a diagnostic test

Overall, the proportion of suspected malaria cases receiving a diagnostic test has been progressively increasing. From 37.4% in 2010, this percentage increased to 69.4% in 2011; 76.9% in 2012; 90.1% in 2013 and it was reported to be 147.6% in 2014 (Table 8-1). The observed increase in percentage of suspected malaria cases tested was seen across all provinces. When split by the types of diagnostic test used, the results showed that while the proportion of suspected cases tested by microscopy has remained almost constant throughout the study period with a slight decline during the past 3 years (36.8% in 2010; 41.0% in 2011; 43.5% in 2012; 36.4% in 2013 and 35.7% in 2014), the proportion of cases tested by RDT has progressively increased from 0.005% in 2010 to 53.7% in 2013 and 111.9% in 2014. A possible explanation of this proportion of more than 100% might be a misclassification of patients resulting in fewer reported suspected cases compared to the number of tests performed. At provincial level, the data showed the same patterns with constant or decreasing percentage of cases tested by microscopy, and increasing percentages of cases tested by RDT. The province of Equateur showed one of the lowest testing rates, increasing from 16.9% in 2010 to only 51.8% in 2013. For almost all provinces, the percentage of suspected cases tested by RDT in 2014 was above 90%, except Maniema (83%) and Kasai Oriental (82%). The lowest percentage of cases tested by microscopy was reported in Maniema Province (from 19% in 2010 to 10% in 2014), while the province of Bas Congo reported the highest percentage of cases tested by microscopy: 80% in 2010 and 2011; 87% in 2012; 88% in 2013 and 67% in 2014.

Table 8-1: Summary of malaria surveillance indicators at national level form 2010 to 2014

NATIONAL	2010	2011	2012	2013	2014
Population	64,420,000	66,352,600	68,343,178	70,393,473	72,505,278
Reporting completeness (%)	94	86	87	88	84
OPD	24,631,423	26,189,657	24,225,892	27,167,148	27,370,003
Suspected cases	9,252,959	9,442,144	9,128,398	10,408,506	9,378,589
Suspected /1000 population	143.6	142.3	133.6	147.9	129.4
Tested/Suspected (%)	37.4	69.4	76.9	90.1	147.6
Slide positivity rate (%)	64.6	63.9	61.4	63.3	60.2
RDT positivity rate (%)	78.3	63.9	64.2	67.3	70.8
Confirmed cases	2,417,780	4,561,981	4,791,598	6,715,223	9,823,673
Incidence rate/1000 population	37.5	68.8	70.1	95.4	135.5
MAP predicted number of cases	27,732,836	25,687,991	22,446,366	21,083,796	20,170,486
Fraction captured (%)*	8.7	17.8	21.3	31.9	48.7

Malaria test positivity rate

Neither the slide positivity rate nor the RDT positivity rate has shown marked changes over time during the period considered. The slide positivity rate has remained almost constant, with an average of 62.7% (64.6% in 2010; 63.9% in 2011; 61.4% in 2012; 63.3% in 2013 and 60.2% in 2014). The RDT positivity rate has shown a slight increase of 7 points from 2011 to 2014. The average RDT positivity rate was 68.9% (78.3% in 2010; 63.9% in 2011; 64.2% in 2012; 67.3% in 2013 and 70.8% in 2014) (Table 8-1).

The provinces of Nord Kivu and Sud Kivu in the eastern part of the country reported the lowest slide positivity rates, with respectively an average of 50.0% (46.2% in 2010; 53.1% in 2011; 51.6% in 2012; 51.7% in 2013 and 47.6% in 2014) and 42.6% (44.7% in 2010; 45.5% in 2011; 42.1% in 2012; 40.4% in 2013 and 40.2% in 2014). The highest slide positivity rates were reported in the provinces of Bas Congo and Katanga with respectively an average of 69.2% (67.6% in 2010; 69.4% in 2011; 69.1% in 2012; 68.7% in 2013 and 70.9% in 2014) and 68.6% (71.6% in 2010; 68.5% in 2011; 67.7% in 2012; 64.2% in 2013 and 71.1% in 2014) (Figure 8-5A).

The provinces of Nord Kivu and Sud Kivu also reported the lowest RDT positivity rates with respectively an average of 45.0% (46.1% in 2011; 45.5% in 2012; 43.4% in 2013) and 38.6 %(29.6% in 2011; 37.8% in 2012; 48.6% in 2013). The highest RDT positivity rates were reported in the provinces of Katanga and Orientale, with respectively an average of 77.1% (86.6% in 2010; 75.5% in 2011; 75.8% in 2012; 78.3% in 2013 and 69.1 in 2014) and 75.6% (73.8% in 2010; 72.8% in 2011; 70.9% in 2012; 73.2% in 2013 and 87.6% in 2014) (Figure 8-5B).

When compared at national and provincial levels, the RDT positivity rates were consistently higher than the slide positivity rates over time, except for the provinces of Kinshasa and Nord Kivu (Figure 8-4). The greatest differences were observed in the provinces of Orientale, Equateur and Maniema. In most provinces, the slide positivity rate curves seem flatter than the RDT positivity rates curves.

Reported confirmed malaria cases

Overall, the number of reported confirmed malaria cases has been increasing over time. The reported malaria incidence rate has shown a 100 percent increase from 37.5 per 1000 population in 2010 to 135.5 per 1000 population in 2014. The biggest increases have been observed from 2010 to 2012, with a 30 percent increase, and from 2013 to 2014 with an increase of 40 percent (Table 8-1, Figure 8-3). Obviously, much of this increase is linked to the much higher testing rates.

For the year 2014, the highest confirmed malaria incidence rates have been reported in the provinces of Bas Congo with 319 cases per 1000 population and Kasai Oriental with 258 cases per 1000 population (Figure 8-3), whereas the lowest confirmed incidence rates have been reported in the provinces of Katanga with 118 cases per 1000 population and Equateur with 124 cases per 1000 population (Figure 8-3).

Except for the province of Bandundu, where an apparent decrease in confirmed malaria incidence was reported between 2011 and 2013 (82.7 per 1000 in 2011; 78.9 per 1000 in 2012 and 64.4 per 1000 in 2013) followed by an increase in 2014 (175.5 per 1000), in all provinces the data showed the same patterns as the national level: reported confirmed malaria incidence progressively increased over the period considered. The ascending curve was interrupted by a small drop in 2012 in four provinces (Bas Congo, Nord Kivu, Equateur and Kasai Oriental) and in 2013 in two provinces (Kinshasa and Maniema).

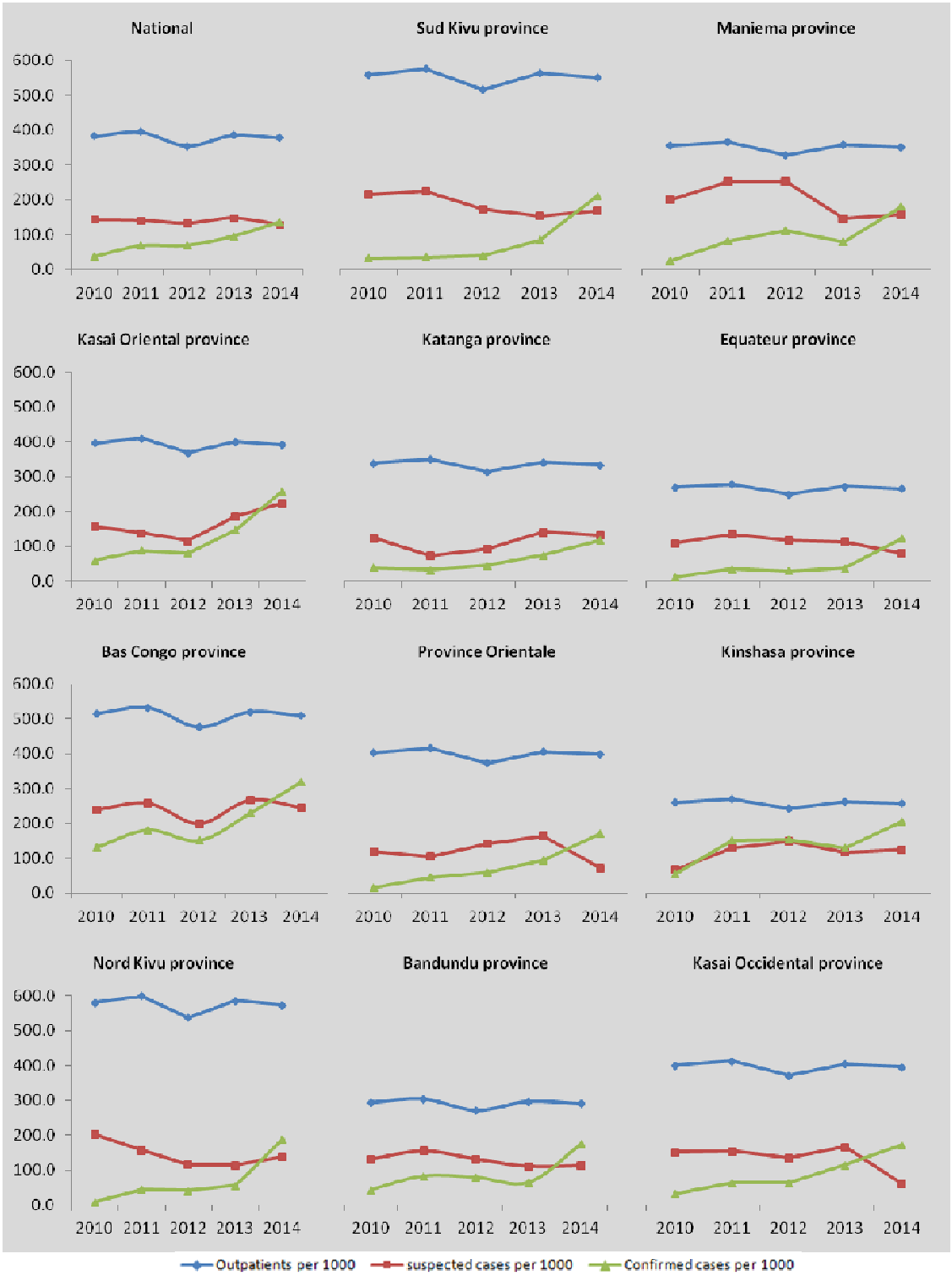


Figure 8-3: Total all-cause outpatients incidence, total suspected and confirmed malaria case incidence, per 1000 population, by province and year, 2010-2014, DR Congo

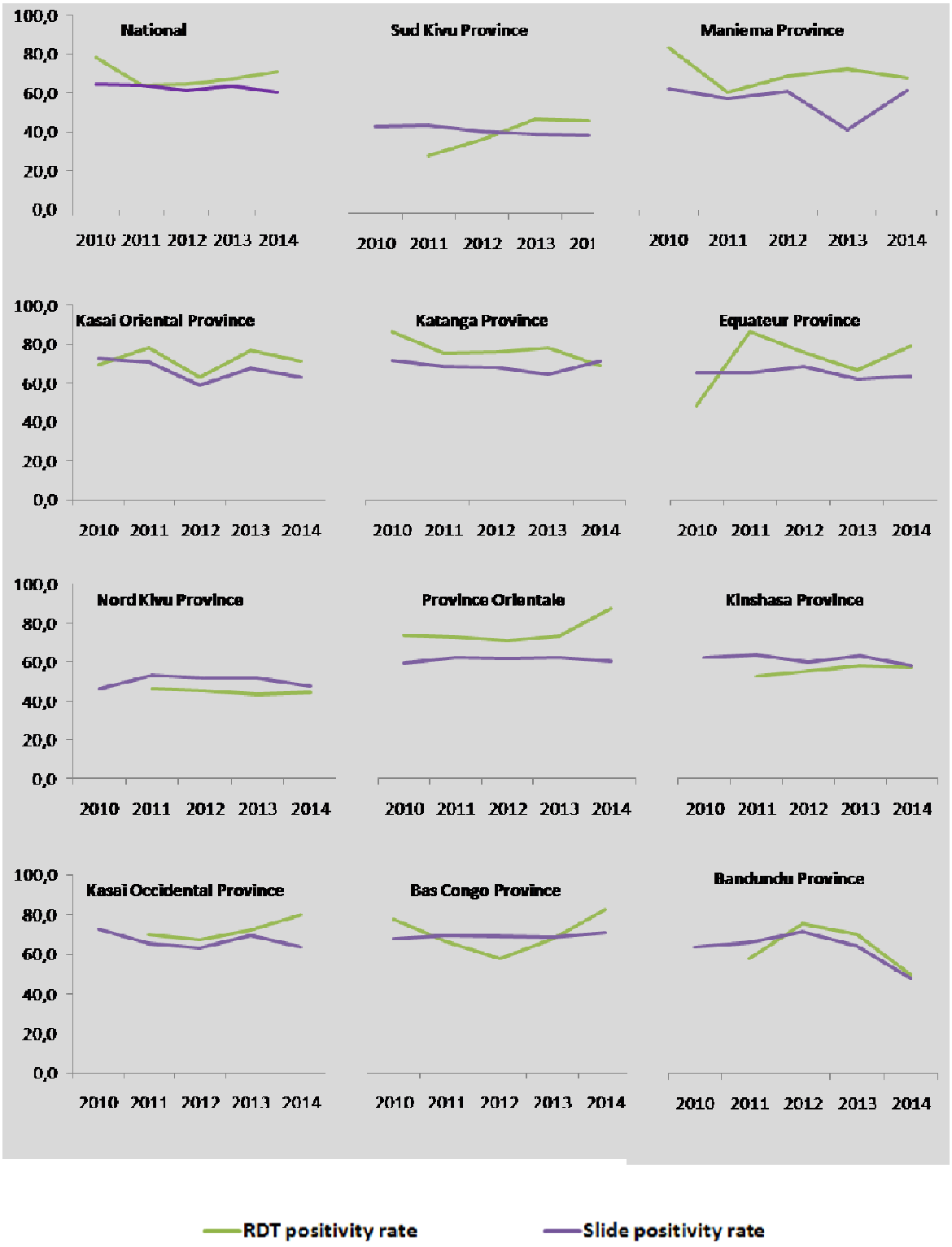


Figure 8-4: RDT and slide positivity rates, by province and year, 2010-2014, DR Congo

Relative fraction of HMIS data

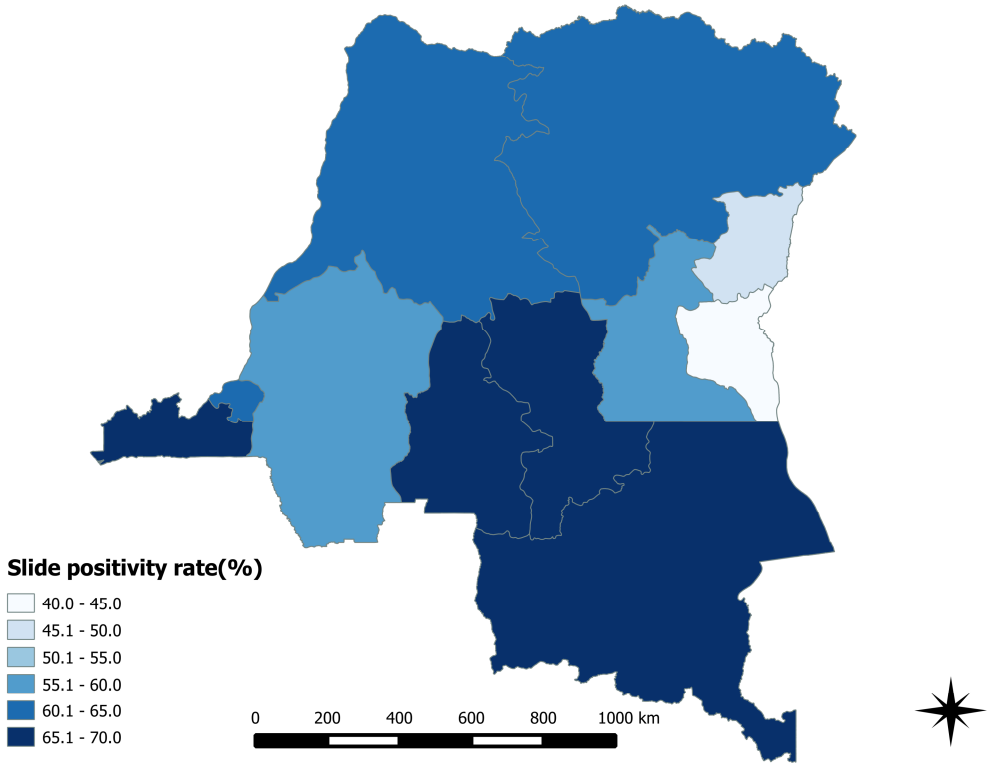
The number of reported confirmed malaria cases was compared to the predicted incidence counts estimated by the MAP project, to determine the fraction of all malaria cases reported by the HMIS.

The MAP predicted numbers of malaria cases for the period 2010 to 2014 were 27.7 million cases in 2010, 25.7 million cases in 2011, 22.4 million cases in 2012, 21.1 million case in 2013 and 20.1 million cases in 2014 (Table 8-1)

Over the period considered, trends in malaria incidence using the two different sources of data showed opposite patterns. While the MAP predicted incidence of cases progressively declined from 27.7 million predicted cases in 2010 to 20.1 million predicted cases in 2014 (mainly as a result of the predicted effect of key interventions such as LLIN), the reported confirmed HMIS number of malaria cases increased over time (from 2.4 million cases in 2010 to 9.8 million cases in 2014(Table 8-1). Obviously, as more cases were tested, the number of confirmed cases increased. The same pattern was observed across all provinces (data not shown).

When compared to the MAP predicted incident cases, the reported confirmed cases by the HMIS data in 2014 represented 48.7%. This fraction has been progressively increasing since 2010: it was only 8.7% in 2010, 17.8% in 2011, 21.3% in 2012, 31.9% in 2013 and 48.7% in 2014. The biggest increase in the fraction reported by the HMIS was observed from 2013 to 2014, with a 17 points increase (Table 8-1).

The same pattern of increasing representative fraction was observed in all provinces. The lowest representative fractions were observed in the provinces of Province Orientale (1.8% in 2010; 5.6% in 2011; 8.5% in 2012; 14.9% in 2012 and 29.2% in 2014) and Katanga (9.8% in 2010; 8.9% in 2011; 13.3% in 2012; 23.2% in 2013 and 38.3% in 2014). In the majority of provinces the number of confirmed malaria cases reported has markedly increased in the last year (2014), with a representative fraction of about 90% in two provinces; Kinshasa (93.3%) and Bandundu (90.4%). In four provinces, there were more confirmed malaria cases reported in the HMIS than those predicted by the MAP, leading a representative fraction over 100%; Bas Congo (126%), Nord Kivu (209.3%), Kasai Oriental (100.6%) and Sud kivu (176.1%).



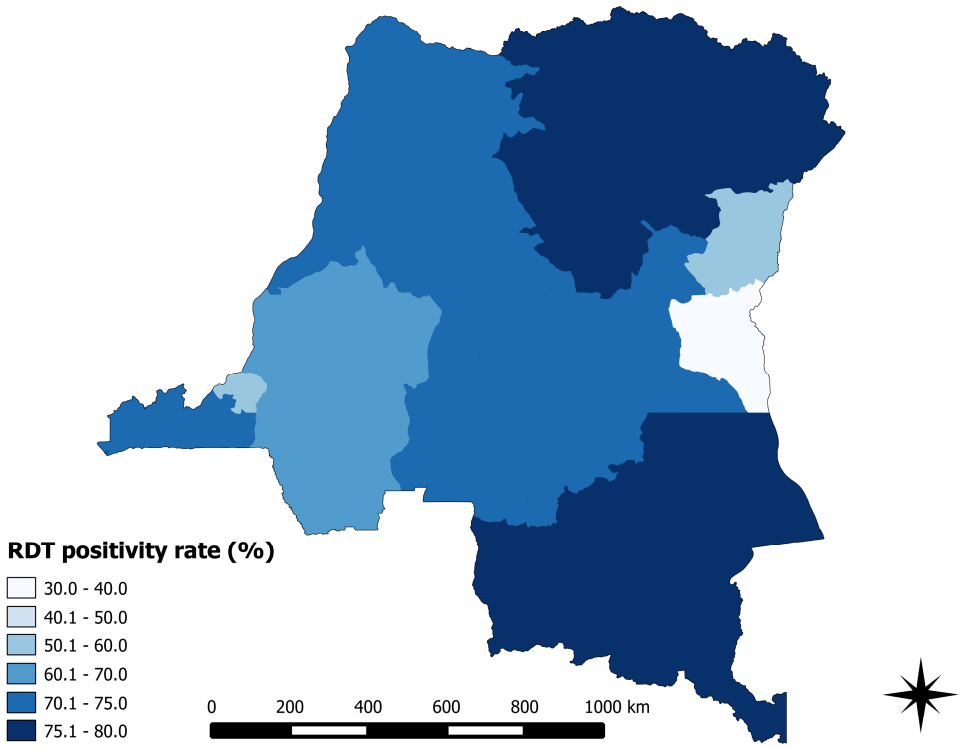


Figure 8-5 A and B: A: Average slide positivity rate, B: average RDT positivity rate. 2010-2014, DR Congo

8.5 Discussion

The two principal objectives of malaria surveillance systems are to provide programme managers with accurate and timely spatio-temporal information on malaria incidence trends to (1) track the epidemiological situation, and (2) guide interventions. Due to known biases and confounders in HMIS data, different methodological approaches have been used to improve the use of routine health system data for rigorous programme evaluations (Graves *et al.* 2008; Rowe *et al.* 2009; Bennett *et al.* 2014) . Using a simple analysis of HMIS datasets, results of this study showed that over the period considered, the number of confirmed malaria cases as well as the percentage of suspected malaria cases receiving a diagnostic test, as well asthe representative fraction of HMIS were increasing. At the same time the malaria test positivity rates remained almost constant at a very high level (62% for microscopy and 68% for RDT).

The number of confirmed malaria cases reported by the surveillance system is obviously highly sensitive to changes in a number of operational factors such as reporting rates, diagnostic practices and health facility utilization rates. The period considered in this study coincided with changes in diagnostic practices, especially the introduction of RDTs in 2010. This translated directly in an increasing proportion of suspected cases receiving a diagnostic test, hence leading to increasing numbers of reported confirmed malaria cases.

With the introduction of RDT, it could be expected that the proportion of suspected cases tested with microscopy would be decreasing, but this proportion remained almost constant. This, along with the fact that the proportion of suspected cases receiving a diagnostic test was over 100% in some provinces, might suggest the use of both RDT and microscopy for malaria diagnostic in many health facilities. Economic incentives work in favor of doing blood slides (paid for by patients) in addition to RDTs (provided for free to health facilities and hence in principle also free to the patient).

In contrast to trends in confirmed malaria cases, the malaria test positivity rate is less sensitive to changes in reporting rates, diagnostic practices and health facility utilization rates, and may therefore provide more reliable information on trends in malaria burden. In this study, both slide and RDT positivity rates have remained stable at high values over the study period. The stable and high test positivity rates despite scaling up of control measures are rather surprising. For example, during the same period, the household ownership of at least 1 ITN increased from 51% in 2010 to 70% in 2013-2014 (UNICEF 2010; DHS 2014).

In other settings the malaria test positivity rate has been used to estimate changes in malaria incidence (Jensen *et al.* 2009; Karema *et al.* 2012; Bi *et al.* 2012; Assele *et al.* 2015) following the scaling up of malaria interventions. It has been shown in recent work to be a valuable surveillance indicator especially in high transmission settings(Boyce *et al.* 2016). Although the test positivity rates are not immune to distortions due to bias and/or confounding (Francis *et al.* 2012), the consistency and stability observed here in both RDT and slide positivity rates are less likely to be explained solely by the poor quality of data. If true, these estimates suggest that the DR Congo remains one of the most endemic settings in the world.

While the routine surveillance system cannot be expected to detect all malaria cases in the community, it should be expected to reflect at least the relative changes in incidence over time, and between areas. Based on parasite prevalence data from nationally representative household surveys (DHS 2014), the current malaria stratification used for planning interventions in the new malaria strategic plan 2016-2020 (PNLP 2016) defines essentially two zones in the DRC: (1) the pre-elimination zone in the province of North Kivu (prevalence <5%) and (2) highly endemic zones in the rest of the country (prevalence 6-45%). However, the number of HMIS confirmed malaria cases per 1000 population reported in 2014 does not reflect the malaria distribution in the country on the basis of prevalence data. The highest malaria incidence rates were reported in the province of Bas Congo in the western part of the country, and the lowest values in the provinces of Katanga and Equateur - where some of the highest parasite prevalence rates were reported by the DHS. So this is clearly pointing towards under-reporting of cases by routine statistics.

By contrast, the test positivity rates followed the malaria distribution in the country rather well. Both RDT and slide positivity rates were consistent with the two zones defined by parasite prevalence data, with the Eastern part (Nord Kivu and Sud Kivu) having the lowest rates (<=50%) and the rest of the country having higher rates (>=50%).

The higher RDT positivity rates compared to microscopy positivity rates are consistent with reports from other researchers in similar transmission setting (Francis *et al.* 2012). A further analysis of the DRC DHS 2013-2014 suggested that RDTs, in particular HRP-2 based RDTs (the ones most used in DRC) generate frequent false-positive results which are likely due to the persistence of HRP-2 in the circulation after parasites had been cleared (DHS 2014).

With the progressive increase in the number of confirmed malaria cases reported by the HMIS data and the progressive decrease in the number of malaria cases predicted by the MAP, the fraction of incidence captured by the HMIS data is increasing. This is likely to be due primarily to the improvement in diagnostic practices with the introduction of RDTs. But the fact that in some provinces the total number of reported confirmed cases is higher than the total number of predicted cases points towards a low quality in HMIS reporting, hence also contributing to the observed trend. Furthermore, for a country of the size of DRC with a very low number of parasite prevalence surveys available, it would be appropriate to hypothesize that the small sample size and the low spatiotemporal density of prevalence surveys might have been contributing to uncertainty in outputs and hence a low precision in MAP estimates.

This study took a rather simple analysis approach and did not include trends in other factors that could influence trends in malaria cases seen at health facilities, such as health services utilisation rates and rainfall.

8.6 Conclusions

This study showed that due to the expansion of parasitological diagnosis, the number of confirmed malaria cases reported and hence the fraction of incident cases captured by the HMIS data has been increasing over time. Because of inconsistencies in reporting, it has been difficult to establish trends in malaria morbidity from nationally aggregated data. The test positivity rates suggest malaria transmission remained high and stable over time, despite a substantial increase in coverage of control interventions. Hence, health facility based data do not seem to reflect adequately the malaria distribution in the country at present, and the HMIS has not yet reached its full potential in monitoring disease trends. Improving the routine data system to provide robust, geographically detailed and timely data remains crucial for supporting the current malaria control efforts.

9 General discussion and conclusions

The present thesis aims to provide further evidence on the epidemiology of malaria and key control strategies in the DRC, in order to improve malaria control activities. This section synthetically discusses the main research findings presented in different chapters of this thesis, with implications for malaria control in Kinshasa, implementation of injectable artesunate, LLIN distribution and malaria surveillance at national level. Finally, we make recommendations for future research.

In Chapters 3 and 4, we updated the malaria risk stratification in Kinshasa and identified factors contributing to the estimated distribution patterns. Our findings showed that compared to previous studies (Ngimbi *et al.* 1982; Mulumba *et al.* 1990; Kazadi *et al.* 2004), the overall malaria prevalence has decreased and the risk was higher in the peri-urban areas of recent occupation. At the same time, the penetration of control measures showed the opposite pattern: lower LLIN coverage in the peri-urban areas and higher coverage in the centre of the city. This risk map constitutes a strong basis for the planning of malaria control interventions in Greater Kinshasa, a mega-city of more than 10 million people.

The analysis of drivers of *P. falciparum* infection in both children less than five years and individuals older than five years highlighted the variation of the effect of age and reported history of fever by the level of endemicity. In low endemicity strata (but not in high endemicity strata), a shift in the peak of malaria prevalence towards older age groups was observed, while a history of fever in the last two weeks increased the risk of malaria in all age groups regardless of level of endemicity. Individual use of LLIN was associated with a reduced risk of malaria infection among children less than five years. As expected, the risk of malaria was lower among children less than five years in the wealthiest socio economic status group.

In Chapter 5, we assessed the feasibility of the use of injectable artesunate for the management of severe malaria in hospitals and health centres of the DRC, in replacement of quinine. We also assessed the cost of implementation in order to provide the basis for practical recommendations for its rapid national deployment. We also assessed the perceived feasibility and acceptability of the implementation of the new drug from the perspective of both health care providers and patients (Chapter 6). Our findings showed that injectable artesunate can be successfully handled by health care providers in DRC, and is associated with a reduced cost compared to quinine. There's also a high acceptability by both health care providers and patients. These findings support the rapid switch to injectable artesunate in the country.

Following a LLIN mass distribution campaign in the province of Kasai Occidental using two different approaches (a fixed delivery strategy and a door-to-door strategy including hang-up activities), we evaluated the impact on household LLIN ownership and individual use, and examined factors associated with LLIN use. We also compared the two delivery strategies with regard to the LLIN coverage achieved and the cost of implementation (Chapter 7). Results showed that the mass distribution campaign was effective at achieving high LLIN ownership and use. Having sufficient numbers of LLIN to cover all residents in the household was the strongest determinant of LLIN use. Compared with the door-to-door strategy, the fixed delivery strategy achieved a higher LLIN coverage at a lower delivery cost. These findings provide importance guidance for future LLIN distributions in DRC.

In Chapter 8, we examined changes in the fraction of malaria community incidence (as predicted by the MAP model) captured by the reported routine health facility data from 2010 to 2014. Our findings showed that while the number of malaria cases predicted by the MAP model was progressively decreasing over time, the number of confirmed malaria cases reported by the routine system was increasing.Thus, the fraction of the actual community malaria incidence captured by the routine system was increasing. This was due mostly to the expansion of parasitological diagnosis with RDTs. Over the same period, both RDT and slide positivity rates have remained constant at high levels, suggesting high and stable malaria transmission in the country.

9.1 Implications for malaria control in Kinshasa

Results presented in Chapter 3 demonstrated the heterogeneity of malaria transmission in the city of Kinshasa, as reported in other urban settings across Africa (Matthys *et al.* 2006; Keiser *et al.* 2004; De Silva *et al.* 2012). Since malaria transmission in Kinshasa is focal, the implementation of control strategies needs to reflect this and take into account the specific context of each area, and all factors contributing to transmission. Because of differing levels of urbanisation and the uneven malaria distribution and service offers, the new strategic plan 2016-2020 defines the city of Kinshasa as a control stratum in its own right (PNLP 2016). In addition to the key interventions already implemented, “new” interventions should include environmental management, IRS and larval control. Although larviciding has proven to be cost-effective for urban malaria control (Maheu-Giroux & Castro 2014), its implementation requires a thorough update on vector distribution and behaviours. For memory, the last entomological studies in Kinshasa date back to the end of the 1980s (Coene 1993). Such entomological studies would also help understand factors that contribute to residual transmission, defined as transmission that occurs despite high coverage with LLIN or

IRS (Killeen 2014; Msellemu *et al.* 2016). These factors include earlier biting behaviour of *A. gambiae* or *A. funestus* (Cooke *et al.* 2015; Wamae *et al.* 2015) or human activity during peak biting hours (Monroe *et al.* 2015).

The observed shift in the peak of malaria prevalence towards the older age groups in low endemicity areas, combined with the low rate of LLIN use reported in that age group is of particular concern. As discussed in Chapter 3, a small fraction of asymptomatic carriers can maintain transmission during low transmission season (Trape *et al.* 2002; Smith *et al.* 2005; Clark *et al.* 2008). Further research is needed to understand the contribution of this age group to the overall malaria transmission, and identify appropriate measures to better target this population.

The low intervention coverage observed in peri-urban areas of Kinshasa might have changed since our survey. As of this writing, the NMCP with support from Population Services International (PSI) has completed a universal mass distribution campaign in Kinshasa in early 2014, with a particular focus on peripheral HZ. This campaign has reached high LLIN ownership (PSI, unpublished report). But as shown in Chapters 3 and 7, net attrition rates are high and begin a few months after distribution campaigns. Without effective keep-up mechanisms, the high coverage levels cannot be maintained and will return in 1-2 years to the levels we measured.

Mapping the distribution of malaria risk should be a dynamic process of evidence generation, constantly updated to guide and monitor progress towards strategic plan targets (Snow *et al.* 1996; Kleinschmidt *et al.* 2001). The next step would be to update the risk map once additional data are available. Including environmental covariates could improve the precision of the estimates.

9.2 Implications for the implementation of injectable artesunate

The DRC is one of the countries with the highest burden of severe cases of malaria. As a result, it is also the country where the second highest number of additional lives could be saved by the introduction of injectable artesunate. The results presented in Chapters 5 and 6 support the rapid nationwide scale-up of the new drug. As usual, different operational and systemic challenges need to be considered for achieving a successful rollout and a high public health impact of the new drug.

Ensuring availability of injectable artesunate is undoubtedly the key factor that will lead to the expected impact in saving lives of children. To this effect, the Ministry of Health of the DRC has received the support of the Global Fund to fight Aids, Tuberculosis and Malaria (GFATM) and of

other partners in the need quantification and procurement processes. As a result, it is currently scaling up the use of injectable artesunate in the public sector, aiming for 100% coverage of in-patient cases within a three-year period. Frequent stock-outs represent a major constraint in managing malaria and other diseases in the DRC. In our study, we could not investigate issues of drug stock-out since injectable artesunate vials were donated by Guillin Pharmaceuticals for study purposes and were consistently available. By contrast, the End-Use Verification survey (EUV) conducted by PMI in 2014 found 40% of health facilities with stockouts of antimalarials drugs and commodities for three days or more in the past three months (USAID/SIAPS 2014). Strengthening the supply chain will therefore be critical for a successful implementation.

The private sector plays an important role in delivering malaria treatments in DRC, accounting for 97% of all antimalarials distributed in Kinshasa in 2013 for example (ACT watch Group and ASF 2014). Findings presented in Chapter 3 showed that private facilities were the most common providers of treatment among those who sought care, covering 65.4% of the cases. Increasing access to injectable artesunate will therefore require a strong implication of the private sector.
Although findings from Chapter 6 indicate a high level of acceptability of the new drug by health care providers in study sites, health care providers' reluctance to change may hinder the nationwide implementation of injectable artesunate. It is important to promote the benefits of the new drug among health workers through effective communication channels and train them in the practical aspects of its use. In our study, the large majority of health care providers perceived the handling of injectable artesunate to be easy, and the new simplified three-dose intra-muscular regimen (once daily) has the potential to make the handling even simpler and more appropriate for remote health facilities (Kremsner *et al.* 2016).

Healthcare professionals should also be made aware of the possibility of delayed haemolytic anaemia for up to one month post treatment (Zoller *et al.* 2011; Cramer *et al.* 2011; Rolling *et al.* 2014; Burri *et al.* 2014; Kremsner *et al.* 2016). A sub-study conducted within the MATIAS study to assess the potential risk of delayed anaemia (Burri *et al.* 2014) and evidence from other researchers (Rolling *et al.* 2014) showed that all reported cases of delayed anaemia have been successfully managed, and the therapeutic benefits of injectable artesunate outweighed the risk of post-treatment complications. The detection of such post-discharge complications in a setting of low access to health care is challenging and points more generally to the absence of a functioning pharmacovigilance system. The current proposition to assess haematological parameters and serological markers of haemolysis on days 0, 3, 7, 14, 21, 28 post-treatment is clearly unrealistic given the low access to health facilities and laboratory capacities.

Possibly, clear instructions to caregivers to return for consultation if some danger signs become apparent (such as excessive pallor) could represent a more realistic approach to this issue. Moreover, it is important to strengthen generally the pharmacovigilance system, to better detect adverse events related to the use of artesunate. Hence, areas for further research could be the identification of predictors of post-treatment haemolysis to prevent its occurrence, and danger signs that could be identified by caretakers.

Finally, local quinine production represents an important challenge to speed up the introduction of injectable malaria treatment nationwide. A local Congolese manufacturer produces quinine since 1942, and this represents the principal economic activity of the company. The switch from quinine to injectable artesunate may have been seen as a threat to the viability of the company, and this factor needs also to be taken into account.

9.3 Implications for LLIN distributions

Distribution of LLIN is a key component of malaria control in the DRC. Since the adoption of a free-of-charge LLIN policy in 2006, over 75 million LLIN have been distributed across the country. The campaign round organised in 2014 was the second after the first round started in 2011. The results of the evaluation presented in chapter 7 highlighted a number of issues that need to be addressed for future LLIN distributions.

The low ownership and use levels observed before the campaign in this study area despite a previous mass distribution campaign in 2011 not only suggest an average physical lifespan of nets of less than 3 years (Hakizimana *et al.* 2014; Wills *et al.* 2013; Gnanguenon *et al.* 2014; Mutuku *et al.* 2013), but also revealed the limitations of the current routine distribution channels (ANC and immunisation) to maintain high LLIN coverage between mass campaigns. These findings constitute a stark reminder of the need for additional keep-up strategies (Networks 2014). The DRC has now revised distribution guidelines to organise mass campaigns every two years, and has adopted school and community channels for continuous distribution. The first pilot school distribution has been completed in the province of Kasai Occidental. However, more work is needed to estimate the appropriate timing of the continuous distribution in order to prevent oversupply or failure to reach targeted coverage levels. There's also a need to carry out LLIN quantification properly and most regularly update the costing of continuous distribution channels.

In a given setting, the durability of LLIN is influenced by household behaviour and living conditions (Kilian *et al.* 2015). By simply improving the way the nets are handled within

households, substantial gains can be made in median net lifespan (Helinski *et al.* 2015; Koenker *et al.* 2015). Behaviour change communication (BCC) messages on net care should be integrated into existing BCC programmes accompanying LLIN distributions. Our findings suggest that such BCC activities should prioritise interpersonal channels. Interpersonal communication could also promote proper LLIN use in targeted groups such as adolescents, who have currently the lowest use rates. Universal coverage, as defined by the proportion of households with at least one LLIN for every two people (WHO PMI UNICEF RBM Measure Evaluation 2013), remains the goal of LLIN distribution programmes. It is determined by the number of households reached and the number of LLIN delivered per household during the campaign. Completeness of household registration is the strongest determinant of the proportion of households receiving at least one LLIN from a given campaign (Zegers de Beyl *et al.* 2016). In addition, the net allocation strategy determines the households' likelihood of having enough LLINs for all residents. Results presented in Chapter 6 showed that among households that received at least one LLIN from the campaign, less than half received enough LLIN for all its residents. Since having enough LLIN to cover all residents in the household was the strongest determinant of LLIN use, net allocation strategies should be improved in term of respecting strictly the criteria required for reaching universal coverage: 1 LLIN for 2 people, with rounding up in case of an odd number of household members. Finally there should be no capping of the total number of nets per household.

As reported by other researchers (Smith Paintain *et al.* 2014; Kilian *et al.* 2015), the door-to-door delivery strategy with hang-up activities in the Kasai Occidental was associated with higher cost per LLIN delivered compared to the fixed point delivery strategy, and yet there was no difference in LLIN use. The main reason for this difference could be that distribution teams are less likely to reach the most remote inhabitants, while such populations are likely to come to a fixed distribution point. Therefore, in the context of the DRC, a fixed point delivery strategy with effective BCC activities and enough allocated nets should be sufficient to lead to high rates of LLIN ownership and use.

9.4 Implications for malaria surveillance

Results presented in Chapter 8 suggest that the malaria surveillance system in DRC does not fully play its role of identifying locations in which the incidence of malaria cases is the greatest, and for tracking changes in these incidence rates. Although the study was not designed to analyse the quality of health facility data, our findings have highlighted some of the issues that make it difficult, at the current stage, to use routine data for the planning, implementation and evaluation of malaria control programme.

The expansion of parasitological diagnosis with RDTs represents a golden opportunity for malaria surveillance to be based on better quality data (confirmed rather than suspected cases) at all levels of the health system. The increasing number of reported confirmed cases between 2010 and 2014 most likely reflects changes in diagnostic coverage rather than a real change in the incidence of malaria cases. Shortcomings in data recording and reporting still results in low quality of reported data, even though progress has clearly been made.

The lack of correspondence between the number of suspected cases and the number of confirmed cases points towards problems in the registration of cases. In most of the health facilities, information on patients are recorded in an outpatient register while results of malaria tests are recorded in a separate laboratory register. The reconciliation of the two data sources is problematic, and therefore misclassification of patients and double testing (using both RDT and blood slide) will lead to inconsistencies, as discussed in Chapter 8. Training and regular supervision visits need to be reinforced to improve data recording. A simple fool-proof system for reconciling patients' statistics between the clinical ledgers and the laboratory books should be designed and implemented. The implementation of the DHIS2 system has the potential to improve substantially data recording, since automatic consistency checks can be integrated into the software, and the timeliness of reporting should improve. Efforts to improve the completeness of reporting should also consider integrating private health facilities into the surveillance system.

While improving routine data systems to provide robust, geographically detailed and timely data remains one of the basic tools for supporting improved malaria control efforts, small-scale sentinel surveillance with enhanced supervision and rapid reporting mechanisms can be a viable alternative to, and an important complement of HMIS data (Cibulskis *et al.* 2007; Yukich *et al.* 2014). With the support from its partner, the NMCP is currently revitalising the network of existing sentinel sites to provide high quality and timely malaria surveillance data beyond the scope of the routine surveillance system.

9.5 Overall conclusions and outlook

This thesis has provided a wealth of new quality evidence on the epidemiology of malaria and the implementation of key control interventions in the DRC. Currently the second malaria-endemic country in the world, the DRC urgently needs to increase both its routine data surveillance system and increase its applied (operational) research portfolio. This will lead to improved programme management and to a sustained flow of resources for control activities through two key

mechanisms: (1) efficient implementation of the best possible interventions in an optimized combination, and (2) justifying politically the high cost of malaria control activities thanks to documenting continuously and with a high quality level the substantial positive health impact that malaria control interventions deliver. We plead therefore for more applied research activities in the country to reduce lastingly the unacceptable high burden of malaria in Congolese citizens.

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