Mathematical modelling of malaria control interventions to support strategic planning in Tanzania

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Table of contents

List of figures

List of tables

List of abbreviations

ACT	Artemisinin Combination Therapy
ALu	Arthemeter Lumefantrine
ANC	Antenatal Care
BCC	Behaviour Communication Change
BMGF	Bill & Melinda Gates Foundation
Bti	*Bacillus thuringiensis israelensis*
Bs	*Bacillus sphaericus strain*
CM	Case Management
CHAI	Clinton Health Access Initiative
DDT	*Dichlorodiphenyltrichloroethane*
DHS	Demographic Health Survey
DHIS2	Demographic Health Information System 2
DFID	UK Department for International Development
EIR	Entomological Inoculation Rate
EMIRA	Ecologic Malaria Reduction for Africa
FAO	Food and Agriculture Organisation
GIS	Geographic Information System
GFATM	Global Fund to Fight AIDS, TB and Malaria
GMAP	Global Malaria Action Plan
GMP	Global Malaria Programme
GTS	Global Technical Strategy
HBHI	High Burden to High Impact
ibpa	infectious bites per person per annum
iCCM	Integrated Community Case Management
ICER	Incremental Cost-Effectiveness Ratio
IPTp	Intermittent Preventive Treatment in Pregnant Women
IPTi	Intermittent Preventive Treatment in Infants
IPTsc	Intermittent Preventive Treatment in School Children
IMCI	Integrated Management of Childhood Illnesses
IRS	Indoor Residual Spraying
ITN	Insecticide-Treated Nets
IVM	Integrated Vector Management
LLIN	Long-Lasting Insecticidal Nets
LSM	Larval Source Management

MARA	Mapping Malaria Risk in Africa
MAP	Malaria Atlas Project
MBG	Model-Based Geostatistics
MDA	Mass Drug Administration
MDG	Millennium Development Goals
MIS	Malaria Indicator Survey
MICS	Multiple Cluster Indicators Survey
MMC	Malaria Modelling Consortium
MoHSW	Ministry of Health and Social Welfare
MoHCDGEC	Ministry of Health, Community Development, Gender, Elderly and Children
MoEVT	Ministry of Education and Vocational Training
MORU	Mahidol Oxford Research Unit
mRDT	Malaria Rapid Diagnostic Test
MRC	Mass Replacement Campaign
MSP	Malaria Strategic Plan
MTR	Mid-Term Review
NBS	National Bureau of Statistics
NIMR	National Institute for Medical Research
NIR	National Intake Ratio
NMCP	National Malaria Control Program
NMEP	National Malaria Elimination Program
NMSP	National Malaria Strategic Plan
OCGS	Office Of Chief Government Statistician
OM	OpenMalaria
PBO	*Piperonyl Butoxide*
*Pf*PR	*Plasmodium Falciparum* Parasite Rate
PMI	United States Agency for Aid and Development, President's Malaria Initiative
PMO-RALG	Prime Minister's Office, Regional Administration and Local Government
PPF	*Pyriproxyfen*
RCD	Reactive Case Detection
RDT	Rapid Diagnostic test
hsRDTs	highly sensitive rapid diagnostic test
RCH	Reproductive and Child Health
SDG	Sustainably Development Goals
SMC	Seasonal Malaria Chemoprevention

SMPS	School Malaria Parasitaemia Survey
SMMSP	Supplementary Malaria Midterm Strategic Plan
SNP	School Net Program
s.l.	*sensu lato*
s.s.	*sensu stricto*
SP	sulfadoxine-pyrimethamine
SWOT	Strengths, Weaknesses, Opportunities and Threats
Swiss TPH	Swiss Tropical and Public Health Institute
TACAIDS	Tanzania Commission for AIDS
TB	Tuberculosis
TDHS-MIS	Tanzania Demographic Health Survey – Malaria Indicator Survey
TMA	Tanzania Meteorological Agency
TPR	Test Positivity Rate
U5CC	Under-Five Catch Up Campaign
UCC	Universal Coverage Campaign
UMRC	Universal Mass Replacement Campaign
UMCP	Urban Malaria Control Program
USAID	United States Agency for International Development
WHO	World Health Organisation
XML	eXtensible Markup Language

Summary

In 2018, 219 million cases and an estimated 435 000 deaths due to malaria occurred in 92 countries worldwide (WHO, 2018). The deployment of control interventions at large scale and improvements in case management led to significant reductions between 2000 and 2010. Unfortunately, this trend stalled in most and even rebound in some countries between 2012 and 2016 (WHO, 2018), associated with emerging biological, environmental, and epidemiological challenges as well as stagnating funding (Brooke and Sridhar, 2019; Zelman et al., 2014). The core vector control interventions are not as effective anymore as in the past, with increasing heterogeneity in the effectiveness due to variations in risk factors and changing epidemiology. These developments call for more strategic and localised control efforts with resources targeted to the needs at local level (WHO, 2015a).

These developments and challenges recognised in malaria-endemic countries globally were also observed in Tanzania. Although malaria is endemic throughout the country, high variations in transmission risk and burden appear at sub-national level (NMCP et al., 2013). Since the year 2000, the National Malaria Control Programme (NMCP), embedded within the Ministry of Health, Community Development, Gender, Elderly and Children (MoHCDGEC), defined three national malaria control strategies to 1) introduce, 2) scale-up and 3) consolidate case management and vector control interventions (MoHCDGEC, 2002, 2008, 2014). As a result, significant reductions in disease burden and transmission were achieved. Between 2007 and 2012, the malaria prevalence declined from 17.7% to 9.2% nationally (MoHCDGEC et al., 2017a; TACAIDS et al., 2013). When a rebound to 14.4% was recorded in 2016 (MoHCDGEC et al., 2016) the appropriateness of the current national malaria strategy to address pressing challenges was questioned. As a response, the NMCP decided to revise the strategic plan with new intervention mixes targeted to malaria risk at council level. While the epidemiological malaria country profile from 2013 includes high-resolution risk maps (NMCP et al., 2013), prevalence estimates representative for the population at council level are missing, as the Malaria Indicator Surveys (MIS) are only representative at regional level and the health information system only captures subpopulations that seek care. Moreover, the impact of new intervention mixes at national and at council level is unknown and mathematical tools exist (Ross, 1911; Reiner et al., 2013; Smith et al., 2018) that allow to model malaria transmission and epidemiology and can provide estimates on likely impact across different setting and custom intervention mixes.

This thesis aims to contribute to a stronger basis for the rational development of malaria strategies for maximum progress towards control and elimination targets in Tanzania. The objectives were to (1) map the malaria prevalence at district level and the description of malaria risk factors among

school children, using data from the School Malaria Parasitaemia Survey introduced in 2014/15 (MoHCDGEC, 2018) (2) develop a model calibration and parameterisation workflow for district-specific impact predictions at council level, (3) apply the model workflow to assist the programme in strategic planning by predicting the impact of malaria control interventions, and (4) determine the optimal deployment of larviciding by describing how variations in deployment factors affect predicted entomological outcomes and malaria prevalence.

To achieve the objectives, multiple tools were applied. First, the data obtained from the first national malaria school survey was mapped and children's responses together with environmental covariates were analysed using hierarchical multivariate regression models to determine risk factors of malaria. The mapped malaria prevalence enabled an assessment of the malaria transmission risk at sub-regional level for the whole country. The results from the regression analysis found low ITN use among other factors as a main risk factor among school children, a neglected age group with high parasitaemia. Secondly, the individual-based dynamic transmission model "*OpenMalaria*" (Swiss TPH, 2020) was used to predict the impact of multiple intervention scenarios over long timeframes. The OpenMalaria model was initially developed for vaccines (Smith et al., 2006a) but extended for drug based interventions, including case management (Tediosi et al., 2006), reactive case management (Reiker et al., 2019), and mass drug administration (Pemberton-Ross et al., 2017), as well as vector control interventions, mainly insecticide treated bed nets and indoor residual spraying (Briët et al., 2013; Chitnis et al., 2012; Smith et al., 2008; T. Smith et al., 2012). Since its development, OpenMalaria was used in several research studies for a better understanding of transmission and disease dynamics and intervention impact including (Chitnis et al., 2008a; Crowell et al., 2012; Penny et al., 2016, 2015; Ross et al., 2008, 2006; Ross and Smith, 2010; Stuckey et al., 2014b, 2014a), among others. While the models' fundamental biological transmission and disease parameters are based on malaria therapy and epidemiological and clinical trials, country specific use requires reparameterization of location specific parameters. The model was parameterised with data from Tanzania and calibrated to all 184 councils in Tanzania using a Bayesian model to fit geospatial model-based prevalence estimates to OpenMalaria predicted prevalence. Thirdly, a cost-effectiveness analysis was performed based on the simulated cases averted and added costs to determine a more cost-effective intervention allocation at council level. Lastly, the modelling approach was extended to include a set of simulations with varying larviciding applications, different transmission intensities and seasonality patterns to assess the influence of deployment on malaria measures.

The results of this work provide a methodological framework for the successful use of mathematical modelling to support NMCPs in the planning of national malaria strategies. The malaria school survey provided the first national epidemiological prevalence map representative at sub-regional level in Tanzania, among children aged five to sixteen years. The prevalence map enabled a better description of the geographical pattern in malaria transmission as a basis for properly targeted interventions and feed into geospatial modelling to derive a prevalence map at higher resolution. These prevalence estimates together with prevalence estimates from Malaria Indicator Surveys and incidence data from health facilities, were used for intervention impact monitoring and evaluation as part of the midterm review of the national malaria strategic plan (NMSP) (MoHCDGEC et al., 2017b). Calibrated to the prevalence at sub-regional level, mathematical model predictions confirmed the results of the midterm review of the strategic plan, suggesting that it would not be possible to achieve the national target with the current intervention by 2020. The model predictions further showed that interventions could be allocated more efficiently, i.e. achieving higher reduction in burden for the same or less investment. The database of predictions could be re-used to promptly visualise the impact of intervention scenarios of interest for the country. The results directly fed into interactive discussions on the selection of interventions and contributed to the Supplementary Malaria Midterm Strategic Plan 2018-2020 (MoHCDGEC, 2019). The long-term collaboration with NMCP staff facilitated knowledge transfer between modellers and program managers, which allowed for an increased mutual understanding of the needs in the planning of malaria control strategies as well as influencing factors when making decisions. Besides, the simulations of larviciding demonstrated the usefulness of modelling to address specific operational questions of the deployment of larviciding in different transmission and seasonality areas, which still constitute a significant challenge for reaching high impact in the field.

Current developments in malaria policy include the recently launched the High Burden to High Impact initiative (WHO and RBM Partnership to End Malaria, 2019), serving as a “Wake-up” call to become more strategic in malaria policy planning in countries, in pursuance of getting back on track for achieving the Global Technical Strategic Goals which define specific impact and outcome targets globally for 2020, 2025 and 2030 (WHO, 2015a). Moreover, the Lancet Commission on malaria stated that eradication would be feasible by 2050 (Feachem et al., 2019), pushing further for global commitment, whereas the World Health Organisation was more careful with setting a target year just yet, to avoid donor fatigue as observed after global malaria eradication efforts around the 60ties (WHO Strategic Advisory Group on Malaria Eradication, 2019). Nevertheless, both sources largely agree on the same agenda and emphasise the need for strong political leadership and management,

data-driven decision making and better coordination of stakeholders and partners, including the private sector, as well as strengthening of health systems and surveillance.

This PhD covers malaria risk description using school survey data (Chapter 2), intervention allocation and impact prediction (Chapter 3), cost-effectiveness of alternating intervention mixes nationally at sub-regional level (Chapter 3), impact predictions of selected intervention mixes targeted to malaria risk strata (Chapter 4), interaction between modellers and stakeholders in the application of modelling for strategic planning (Chapter 5), and assessed intervention deployment strategies on the example for larviciding (Chapter 6), which constitute critical steps in the development of national malaria control strategies. The results demonstrate the advantages of adding modelling to the analytical toolbox for evidence-based decision making. The developed model calibration workflow, with direct application in strategic planning, as well as the critical reflection of the process provides valuable guidance on how to use modelling for national malaria policy. However, in order to make modelling an intrinsic part of the strategic planning process, the critical roles of capacity building, long-term collaboration and continued yet flexible funding need to be recognised. Overall, this PhD provides a fundamental first step towards integrating modelling into national malaria policymaking in Tanzania and may serve as a role model for other countries. The next steps towards strengthening the rational development of malaria strategies will require strengthening of analytical skills and capacities in control programmes. This process aims to ensure that interventions are deployed where there are needed most and ultimately strives for maximum effectiveness and prevention of drawbacks in our efforts towards malaria control and elimination in Tanzania as well as other countries suffering from malaria.

Zusammenfassung

Im Jahr 2018 traten in 92 Ländern weltweit insgesamt 219 Millionen Krankheitsfälle und schätzungsweise 435 000 Todesfälle aufgrund von Malaria auf (WHO, 2018). Der Einsatz grossflächiger Kontrollmassnahmen, sowie Verbesserungen im Managment von Malaria Krankheitsfällen, führte zu einem erheblichen Rückgang der Krankheits- und Todesfälle zwischen 2000 und 2010. Leider hat dieser Trend nicht angehalten und der Rückgang in Malaria stagnierte in den meisten Ländern zwischen 2012 und 2016, in einigen wenigen Ländern waren die Fallzahlen sogar wieder gestiegen (WHO, 2018). Diese Entwicklung wurde mit biologischen, umweltbezogenen, und epidemiologischen Herausforderungen, sowie mit stagnierender Finanzierung in Zusammenhang gebracht (Brooke and Sridhar, 2019; Zelman et al., 2014). Die Wirksamkeit der Massnahmen, die zur Kontrolle von Malariamücken eingesetzt werden, nimmt aufgrund steigender Heterogenität in der Effektivität ab, welche auf Schwankungen in den Risikofaktoren und Veränderungen der Epidemiologie zurückzuführen sind. Daher sind strategischere Kontrollmassnamen auf lokaler Ebene gefordert die eine bessere Ressourcenverteilung, zugeschnitten auf die lokalen Bedürfnisse, ermöglicht (WHO, 2015a).

Diese Entwicklungen und Herausforderungen, beobachtet in malaria-endemischen Ländern weltweit, wurden auch auf dem Festland von Tansania festgestellt. Obwohl Malaria im ganzen Land endemisch ist, variiert das Übertragungsrisikos und die Krankheitslast geographisch auf subnationaler Ebene (NMCP et al., 2013). Seit dem Jahr 2000, wurden drei nationale Strategien zur Malariakontrolle definiert, mit dem Ziel geeignete Kontrollmassnahmen 1) einzuführen, 2) zu erweitern und 3) zu stärken (MoHCDGEC, 2002, 2008, 2014). Infolgedessen wurden signifikante Rückgänge in den Malariafällen und im Übertragungsrisiko erreicht und die nationale Malariaprävalenz ging zwischen 2007 und 2012 von 17,7% auf 9,2% zurück (TACAIDS et al., 2008, 2013). Als in 2016 ein Anstieg der Prävalenz auf 14,4% zu verzeichnen war (MoHCDGEC et al., 2016), wurde die Angemessenheit und Effektivität der aktuellen Strategie in Frage gestellt. Daraufhin beschloss das nationale Malariakontrollprogram (NMCP) die Strategie zu überarbeiten und die Interventionspakete auf das lokale Malariarisiko zuzuschneiden. Obwohl geographische Karten mit höher Auflösung in dem epidemiologische Malaria Profil von Tanzania (NMCP et al., 2013) vorhanden sind, fehlen Malaria Prävalenzschätzungen welche für die Bevölkerung auf lokaler Ebene repräsentativ sind. Malaria Umfragen und Datenerhebungen von Malariaindikatoren (Malaria Indicator Surveys) sind ausgelegt um die Bevölkerung nur auf regionaler Ebene zu repräsentieren und das Gesundheitsinformationssystem erfasst nur symptomatische Malaria Infektionen und nur dann wenn die betroffenen Personen Behandlung aufsuchen.

Das Ziel dieser Dissertation ist es die Grundlage einer rationalen Entscheidungsfindung für Malaria Strategien zu stärken, und damit zum maximalen Fortschritt in Richtung von Kontroll- und Eliminierungszielen in Tansania beizutragen. Die spezifischen Ziele waren folgende: (1) die Malariaprävalenz auf Distriktebene und die Beschreibung der Malariarisikofaktoren bei Schulkindern unter Verwendung von Daten aus der 2014/15 eingeführten Datenerhebung von Malariaindikatoren in Schulen (MoHCDGEC, 2018) abzubilden, (2) eine Methode zur Modelkalibrierung- und parametrisierung zu entwickeln, um damit lokale Vorhersagen über den Effekt von Kontrollmassnahmen zu generieren, (3) die entwickelte Methode anzuwenden um mit den Vorhersagen zum Effekt von den Kontrollmassnahmen das NMCP beim strategischen Planen zu unterstützen, (4) den optimalen Einsatzes von *larviciding* (Insektiziden gegen Mückenlarven) zu ermitteln durch das Beschreiben von Variationen in der Anwendung und assoziertem Effekt auf entomologische Ergebnisindikatoren sowie auf die Malariaprävalenz.

Um die genannten Ziele zu erreichen, mehrere Methoden wurden angewendet. Zunächst wurden die Daten der ersten nationalen Malariaerhebung in Schulen geographisch abgebildet und Risikofaktoren für Malaria unter Schulkindern mit einem hierarchischen multivariablen Regressionsmodell analysiert. Die resultierende Karte der Malariaprävalenz ermöglichte eine Einschätzung des Übertragungsrisikos auf sub-regionaler Ebene für das gesamte Land. Die Ergebnisse der Regressionsanalyse beschrieben die geringe Nutzung von Mückenschutznetzen als einen wichtigen Risikofaktor bei Schulkindern, einer ohnehin vernachlässigten Altersgruppe mit hoher Malariaparasitämie. Als nächtes wurde das dynamische Übertragungsmodell „OpenMalaria“ (Swiss TPH, 2020) verwendet, um die Auswirkungen mehrerer Interventionsszenarien über lange Zeiträume vorherzusagen. Das OpenMalaria-Modell wurde ursprünglich für die Einschätzung des Effekts einer Malariaimpfung in der Bevölkerung entwickelt (Smith et al., 2006a), seitdem jedoch erweitert für medikamentöse Interventionen Krankheitsbehandlung (Tediosi et al., 2006), für reactive Behandlung von Malaria Fällen (Reiker et al., 2019), für Massenverabreichung von Anti-malaria Medikamenten (Pemberton-Ross et al., 2017), sowie für Malariavekto Kontrollmassnahmen, hauptsächlich Mückenschutznetze und Besprühen von Haushaltswänden mit Insektiziden (Briët et al., 2013; Chitnis et al., 2012; Smith et al., 2008; T. Smith et al., 2012). Seit der Entwicklung, OpenMalaria wurde in mehreren Forschungsstudien genutzt um ein bessers Verständnis über die Übertragung und Krankheitsfaktoren sowie Effekt von Kontrollmassnahmen zu erlangen (Chitnis et al., 2008a; Crowell et al., 2012; Penny et al., 2016, 2015; Ross et al., 2008, 2006; Ross and Smith, 2010; Stuckey et al., 2014b, 2014a). Das Model wurde mit lokalen Daten parametrisiert und für alle 184 *councils* in Tansania, unter Verwendung von geographisch-statistischen Analyseverfahren vorhergesagte und simulierte Malariaprävalenze, kalibriert. Anschliessend wurde eine Kosten-Nutzen-Analyse

durchgeführt, um eine kostengünstigere Verteilung von Interventionen auf lokaler Ebene zu ermitteln. Schliesslich wurde der Ansatz um eine Reihe von Simulationen mit unterschiedlichen Anwendungen von *larviciding* erweitert, unter Berücksichtigung von unterschiedlichen Intensitäten im Übertragungsrisiko und Saisonalitäten, um den Einfluss auf die Mückenpopulation und Malariainfektionen in Menschen zu analysieren.

Die Ergebnisse dieser Arbeit stellen ein methodisches Beispiel für den erfolgreichen Einsatz mathematischer Modelle zur Unterstützung von NMCPs bei der Planung von nationalen Strategien zur Malariakontrolle dar. Die Datenerhebung in Schulen lieferte die erste landesweite Prävalenzkarte auf subregionaler Ebene für Tansania. Die Karte ermöglichte eine bessere Beschreibung des geografischen Musters von der Malariaübertragung und dient als Grundlage für gezielte Kontrollmassnahmen. Die Vorhersagen aus dem mathematischen Modell bestätigten die Ergebnisse der Evaluation des Strategieplans, wonach das nationale Ziel bis 2020 nicht erreicht werden könnte wenn gegenwärtige Massnahmen beibehalten werden. Die Modellvorhersagen zeigten zudem, dass Interventionen wirksamer zugeteilt werden könnten. Der generierte Datensatz konnte wiederverwendet werden, um die Auswirkungen von Interventionsszenarien, die für das Land von Interesse sind, unmittelbar zu visualisieren. Die Ergebnisse hatten einen direkten Einfluss in interaktiven politischen Diskussionen über die Auswahl von Interventionen, die im Jahr 2019 zu der neuen mittelfristigen Malariakontrollstrategie für 2018-2020 beitrugen (MoHCDGEC, 2019). Die langfristige Zusammenarbeit mit dem NMCP ermöglichte den Wissenstransfer zwischen Anwendern von mathematischen Modellen und dem NMCP. Dies ermöglichte insbesondere ein besseres Verständnis der Bedürfnisse bei der Planung von Kontrollmassnahmen und der Einflussfaktoren bei Entscheidungsprozessen. Die Simulationen von *larviciding* haben zudem die Nützlichkeit von mathematischen Modellen um spezielle Fragen zum Einsatz von *Larviciding*, welche in der Praxis immer noch eine erhebliche Herausforderung darstellt, gezeigt.

Zu den aktuellen Entwicklungen in der Malariapolitik gehört die kürzlich gestartete Initiative "*High Burden to High Impact*" (WHO and RBM Partnership to End Malaria, 2019), die als "Auffwachruf" dient, bei der Planung der Malariapolitik in den Ländern strategischer vorzugehen, um die Ziele der globalen technischen Strategie, welche spezifische Ziele setzt für die Jahre 2020, 2025 und 2030, zu erreichen (WHO, 2015a). Darüber hinaus erklärte die Lancet-Kommission für Malaria, dass die Ausrottung bis 2050 möglich sein werde (Feachem et al., 2019), um das weltweite Engagement voranzutreiben, während die Weltgesundheitsorganisation (WHO) eher vorsichtig ist und noch kein Zieljahr festlegt, und die generelle Ermüdung der globalen Geldgeber, wie sie nach den weltweiten Bemühungen in den 60er Jahren zu beobachten war, zu vermeiden (WHO Strategic Advisory Group

on Malaria Eradication, 2019). Dennoch sind sich beide in der Agenda grösstenteils einig, und heben die Wichtigkeit von stärkerer politischer Führung, daten-basierenden Entscheidungen, besserer Koordination zwischen Akteuren und Partnern, dem privaten Sektor inbegriffen, sowie Stärkung des Gesundheits- und Meldesystem hervor.

Diese Doktorarbeit adressiert viele der entscheidende Schritte für die Entwicklung neuer nationaler Malariakontrollstrategien. Die Ergebnisse demonstrieren die Vorteile von mathematischen Modellen, als zusätzliche Methode zu den bereits existierenden analytischen Methoden, zur Verbesserung von evidenzbasierte Entscheidungsfindung. Die entwickelte Model-kalibrierungsmethode, welche in der strategischen Planung direkt angewendet wurde, sowie eine kritische Reflektion des Prozesses, liefern wertvolle Informationen für die generelle Anwendung dieser Methode in der nationalen Malariapolitik. Allerdings müssen die analytischen Kapazitäten in dem Malariaprogram, sowie die langfristige Zusammenarbeit mit Forschung-institutionen gestärkt werden, und zudem langfristige, jedoch flexiblen Finanzierung ermöglicht werden, um die Anwendung von mathematischen Modellen zu einem wesentlichen Bestandteil des strategischen Planungsprozesses zu machen. Diese Arbeit setzt einen ersten grundlegenden Schritt zur Integration von mathematischen Modellen als eines der Standardmethoden zur Anwendung in der nationalen Malariapolitik. Der nächste Schritt erfordert eine Stärkung der analytischen Fähigkeiten und Kapazitäten in Kontrollprogrammen. Dieser Prozess zielt darauf ab, sicherzustellen, dass Interventionen dort eingesetzt werden, wo sie am dringendsten benötigt werden, und strebt eine maximale Wirksamkeit und Vermeidung von Nachteilen bei den Bemühungen zur Malariakontrolle und -eliminierung in Tansania sowie in anderen Ländern, die an Malaria leiden, an.

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1 Introduction

Malaria is an infectious disease caused by *Plasmodium* parasites and transmitted by female *Anopheles* mosquitoes. Malaria parasite infection leads to febrile illness with potentially life-threatening symptoms. Although malaria is treatable and preventable, the global burden and estimated deaths, especially in young children, are still high and mostly concentrated in Sub-Saharan Africa. This chapter provides background information on malaria globally, the burden, past achievements, and current challenges in controlling the disease. This is followed by a description of the malaria epidemiology, including main prevention and control methods. The section on surveillance with relevant malaria indicators and methods for country stratification leads to the development of national malaria control strategies. Finally, the use of mathematical modelling for strategic planning process is described, before outlining current trends of malaria in Mainland Tanzania and how mathematical modelling can support the planning of future control strategies in the country.

1.1 Global malaria burden, achievements, and challenges

In 2017, 219 million malaria cases and an estimated 435 000 deaths due to malaria occurred worldwide in 93 countries (WHO, 2018). The malaria burden is highest in Sub-Saharan Africa (SSA), contributing 70% to the estimated number of cases globally and 90% to the estimated number of malaria deaths. Although the cases and deaths were reduced by 18% between 2000 and 2015, and by almost 10% between 2010 and 2017, no significant progress has been observed since 2015 (WHO, 2018). The substantial reductions between 2000 and 2012 were attributed to the large-scale deployment of control interventions and case management. However, starting from 2012, emerging resistance, changes in malaria epidemiology and entomology, as well as increasing funding gaps led to stagnating trends and rebounds (WHO, 2018, 2015a). In 2017, around US$ 3.1 billion international funds were available for malaria, which constitutes only around 50% of the estimated funding required to achieve global targets in malaria control (WHO, 2018).

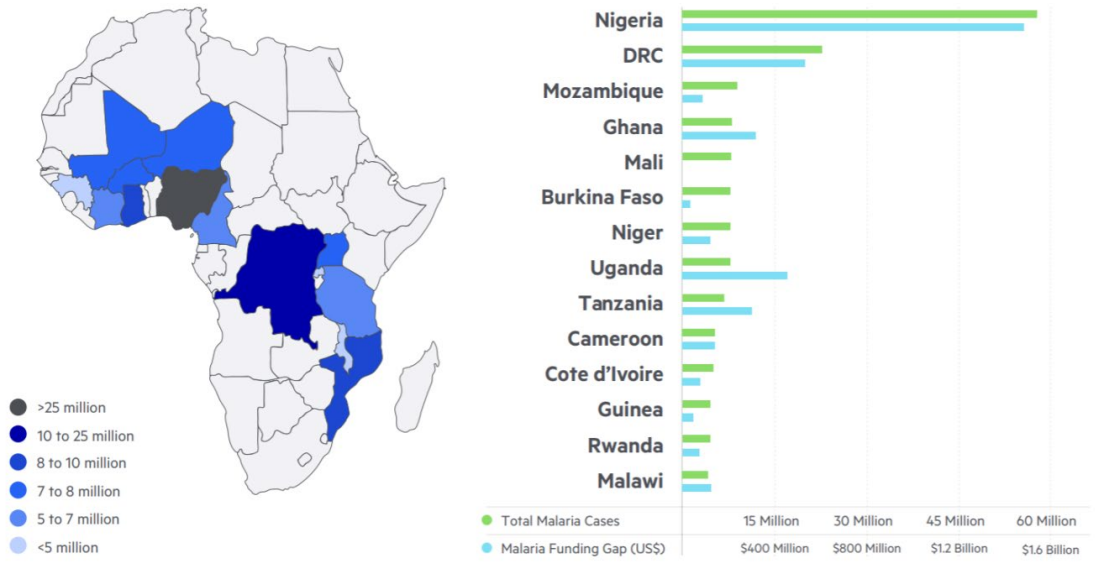
Global malaria policies 1955 to today

The Global Malaria Eradication Program (GMEP) from 1955 to 1979 was the first worldwide malaria campaign (Nájera et al., 2011). Although targeting all malaria-endemic countries, the GMEP mostly focussed on South Africa, Southern Europe, and the Mediterranean (Nájera et al., 2011). The program mainly relied on indoor residual spraying and was discontinued when malaria resurgence and a rapid decline in funding challenged achieved gains (Cohen et al., 2012). Although being described as disappointing in SSA countries, the program has taught important lessons for future

strategies, such that one single tool will not be sufficient to eliminate malaria everywhere. After a few years, malaria returned to the global health agenda when the Millennium Development Goals and Roll Back Malaria (RBM) Initiative were launched around 2000 (WHO, 1999). From 2000 multiple stakeholders started investing in the fight against malaria and vector control interventions and case management were scaled up to achieve universal health coverage (United Nations, 2015). The Global Fund To Fight Aids (GFTAM) was created to channel financial contributions from different country governments to provide more efficient support to malaria-endemic countries. Another global initiative worth noting is the creation of the Bill and Melinda Gates Foundation in 2006, leading to further mobilisation of funding and global attention. In 2015 the efforts reached a "critical juncture" when emerging challenges haltered the downward trend (WHO, 2015a).

Getting back on track is crucial, and recent modelling predicted that malaria control and elimination would be feasibly by 2050 (Feachem et al., 2019), which leads to additional push globally and mobilisation of resources. As a response to the emerging challenges, the Global Malaria Program (GMP) at the World Health Organisation (WHO) launched The Global Technical Strategy (GTS) in 2015 (WHO, 2015a). The GTS reinstates the importance of universal coverage while also emphasising the importance of targeted interventions and data-driven decision making based on strong surveillance mechanisms. Moreover, the WHO emphasises the need for better coordination, a political will that translates into action, more strategic use of information, and technical guidance. Current global goals are the reduction of malaria mortality and case incidence by 40% in 2020, by 75% in 2025 and by 90% in 2030 (WHO, 2015a). Unfortunately, the progress towards the 2020 targets did not show significant improvements, and in 2017 the High Burden High Impact Initiative (HBHI) initiated a "massive wakeup call" to mobilise resources for intensified efforts in the ten highest-burden[1] countries (WHO and RBM Partnership to End Malaria, 2019) (Fig. 1.1).

[1] Contributing 66% to the malaria burden globally.



Fourteen highest malaria-burden countries (left panel) and financial gaps and the total number of cases of the fourteen countries with the highest malaria burden in Africa (right panel), of which the first ten are included in the HBHI initiative. Source: (RBM, 2018).

1.2 Malaria epidemiology

Malaria transmission involves the parasite, the human, and the mosquito which results in diverse transmission dynamics that are influenced by the climate, the environment, the health system, and behavioural factors, among other aspects (Protopopoff et al., 2009).

1.2.1 Disease and vulnerable populations

Malaria infections can be asymptomatic or symptomatic. Common symptoms of uncomplicated malaria infections are fever, chills, and headache, occurring after an incubation period of around 10-14 days (Ashley et al., 2018). A severe cause can be life-threatening or result in severe impairment. Vulnerable sub-populations are pregnant women, infants, and children under the age of five. Infants and young children are at higher risk, as their immune system is not accustomed to the malaria parasite (Doolan et al., 2009) and malaria in pregnant women contributes to maternal and neonatal mortality and morbidity (Desai et al., 2007; Guyatt and Snow, 2004). Partial immunity builds up with cumulative exposure to the parasite over the years, and older children are often asymptomatic (Coalson et al., 2016; Nankabirwa et al., 2013; Singh et al., 2014). Fewer infections in early childhood, i.e. due to effective prevention, lead to delayed acquisition of immunity and potentially to a shift of the malaria burden towards older children (Griffin et al., 2014; Wotodjo et al., 2018).

1.2.2 Transmission, parasites, and vectors

While multiple parasites exist*, Plasmodium falciparum* (*Pf*) causes the greatest burden, mostly concentrated in SSA (WHO, 2018). *P. vivax* (*Pv*) is less dangerous and more widely distributed in South America and Asia[2], although increasingly present in SSA. Malaria parasites are transmitted to human by mosquitoes of the *Anopheles* genus. Although around[3] 500 species are known only 41 are relevant malaria vectors (Hay et al., 2010) of which *Anopheles funestus sensu lato (sl)*, *An. gambiae sensu stricto (ss)* and *An. arabiensis* are of particular importance in SSA (Sinka, 2013).

Parasite

Plasmodium parasite sporozoites are injected into the human blood vessel at the bite of an infectious mosquito. Upon infection, the exo-erythrocytic cycle takes place in the liver, and after 10 to 14 days, the erythrocytic cycle is initiated. The latter has been associated with the onset of symptoms, as merozoites are released which feed on the haemoglobin of red blood cells. The erythrocytic cycle takes approximately 48 hours (Ashley et al., 2018) but reoccurs multiple times and, after several generations, produces gametocytes, female and male reproductive forms of the parasite. When another mosquito bites an infective person, the gametocytes enter the mosquito's stomach initiating the sporogonic cycle which leads to a release of sporozoites. The time from the blood meal until the sporozoites migrate to the salivary glands takes around 9-23 days (Beier, 1998). An understanding of the parasite and how it behaves within the human (to a lesser extent also how it behaves in the mosquito) is crucial for effective and safe treatment.

Vector

The mosquito's life cycle can be separated into the aquatic and the adult phase. In the aquatic phase, eggs develop into larvae, which can take 24-49 hours depending on climate (Service, 2012). The larvae swim on the surface and eat bacteria and algae and after five to seven days, become pupae. The pupae swim below the water surface, do not feed, and moult into adults after two to three days (Service, 2012). The female adult mosquitos survive on average three to four weeks. The main activities in the adult phase are mating, sugar feeding, host searching blood-feeding, resting, and egg-laying (oviposition). The mosquito behaviour throughout the life stages differs depending on the species (Killeen and Reed, 2018). Mosquitoes either feed and rest indoors (endophagic and endophilic) or outdoors (exophagic and exophilic) and are most active between dusk and dawn. In addition, some species feed on human while others prefer non-human hosts (Garrett-Jones et al.,

[2] This PhD thesis focuses on *Pf* infections in SSA and the used terminology applies to this context, if not stated otherwise.

[3] The numbers vary depending on taxonomy (465 formally named species, 528 discovered species (Sharma, 2013)) and literature source (e.g. 477 reported in (Service, 2012)).

1980; Killeen et al., 2017a). These classifications are not very strict, as most mosquitoes have a mix of behaviours depending on the species, local microclimate, and vector control (Ngowo et al., 2017; Thomsen et al., 2017). An understanding of the mosquito's life cycle and behaviour provides clues for effective vector control interventions as well as monitoring measures.

1.2.3 Malaria prevention and treatment

The WHO releases regular evidence-based guidelines on interventions to prevent transmission and treat infections (WHO, 2019a). This section describes the main interventions relevant in this work, whereas many other vector control interventions or preventive therapies exist that are either still in the development phase, or do not fulfil the requirements to be yet included in the recommendations but may play a critical role in the near future.

Case management and preventive therapies

Malaria is treatable and antimalarial drugs are used to reduce the burden and progression to severe disease or death. Treatment will also clear parasites and prevent onward transmission. In most countries, artemisinin combination therapies (ACT) are used as first-line treatment (WHO, 2015b). Malaria infections can be diagnosed with either microscopy or malaria-specific rapid diagnostics tests (mRDT) Active surveillance and case detection methods, such as reactive case detection (RCD), can be implemented to identify asymptomatic infections and cases not captured through health facilities. Another method to clear parasites from the population is mass drug administration (MDA), which treats the whole population or a specific subgroup regardless of the infection status (WHO, 2015c). Active case detection methods and MDA are recommended in low transmission areas and targeted to local foci of transmission[4] (WHO, 2015b).

Preventive therapies

Preventive therapies include intermittent preventive treatment (IPT) and seasonal chemoprevention (SMC) to protect vulnerable subpopulations from adverse consequences of malaria infections (WHO, 2012). By administering full doses of antimalarial drugs, those therapies clear present infections and prevent new infections. IPT in pregnant women and infants is recommended in all malaria-endemic countries in SSA but might be less cost-effective at low transmission, and SMC is recommended in areas with high seasonality during the transmission season (WHO, 2012) while IPTsc is currently not included in the WHO recommendations. Advances in preventive therapies, such as vaccines, are in development and are not yet included in the toolbox of interventions against malaria.

[4] "A defined circumscribed area situated in a currently or formerly malarious area that contains the epidemiological and ecological factors necessary for malaria transmission" (WHO, 2016).

Vector control interventions

Multiple vector control tools target different life stages of the mosquito and are the most scalable approach to interrupt transmission (WHO, 2019b). The core interventions are (long-lasting) insecticide-treated bed nets, in the following abbreviated as ITNs, and indoor residual spraying (IRS). Bed nets provide a physical barrier to prevent bites, and when treated with insecticides, they also kill mosquitoes. IRS is the application of insecticides on the wall of houses and kills resting mosquitoes (WHO, 2019b). Both interventions target indoor biting and resting mosquitoes and can be complemented with larval source management (LSM), which affects larvae before emerging to adult mosquitoes (WHO, 2019b). Other vector control interventions include house screening, space spraying, swarm spraying, attractive sugar baits, auto-dissemination of larvicide, and genetically modified mosquitoes.

ITNs are delivered to households via mass campaigns, to pregnant women via health programs at health facilities (e.g. reproductive child health programs (RCH), or to children through school net programs (SNP)). The ITN distribution schemes are not mutually exclusive; mass campaigns increase the access of the whole population to achieve community protection, while SNPs aim to keep up high coverage levels (Grabowsky et al., 2007; Lalji et al., 2016) and the RCH programs mostly serve the personal protection of pregnant women and infants. Bed nets distribution campaigns aim for universal coverage[5] of the whole populations at risk (WHO, 2019b). The longevity and physical appearance of the bed nets affect its efficacy and the WHO recommends mass campaigns every three years based on estimates on attrition of bed nets in the population. Moreover, the effectiveness of the intervention depends on the regular use of the bed nets every night during the transmission season.

The efficacy of IRS largely depends on the insecticides used and the characteristics of the walls on which it is applied, while its effectiveness depends on the spraying performance and coverage in the community. IRS campaigns are conducted once or twice a year, ideally before the peak in transmission, hence shortly before the rainy season in most areas (WHO, 2019b). The four insecticide classes are *carbamates, organochlorines, organophosphates* and *pyrethroids* (WHO, 2015d). Of those, *carbamates* (e.g. *bendiocarb, propoxur*), and organophosphates (e.g. *pirimiphos-methyl*) are preferable since *organochlorines* (e.g. DDT) were found to have adverse effects on the environment. Pyrethroids are not ideal for IRS as those commonly are used in most ITNs, and the extensive use of the same insecticides facilitates the development of insecticide resistance[6] in mosquitoes. In

[5] "*Access to and use of appropriate interventions by the entire population at risk of malaria*",

[6] "Property of mosquitoes to survive exposure to a standard dose of insecticide" (WHO, 2019b)

addition, the insecticides used in annual IRS campaigns should be rotated to mitigate resistance. IRS campaigns are recommended in high transmission areas but may also be conducted as outbreak response in low transmission areas, but also only in areas with confirmed pyrethroids resistance or insufficient ITN coverage due to marginal impact in combination with high ITN coverage (WHO, 2019b).

LSM aims to reduce the emergence of mosquitos before they become a threat through four different approaches: habitat modification, habitat elimination, larviciding, or biological control (WHO, 2013). Habitat modification and elimination include, for example, drainages or filling of small puddles and removal of human-made breeding sites. Larviciding is the application of different active ingredients which kill larvae to the surface of water bodies and biological control entails the use of predators, such as larvae-eating fish (WHO, 2013). The recommended areas for LSM are decided based on feasibility and cost-effectiveness, as the required frequent application is resource intensive. The WHO guidelines suggest that LSM would be most efficient in areas where breeding sites are “fixed, few and findable” and at low transmission intensity (Choi et al., 2019; Tusting et al., 2013).

1.2.4 Risk factors

As malaria involves human, parasites and mosquitoes, numerous factors influence malaria transmission and morbidity. Immunity, insecticide resistance and outdoor transmission have already been briefly described in the previous sections while many more risk factors exist, broadly classified into biological, environmental, and human-related factors (Protopopoff et al., 2009). There are too many risk factors associated with each of the categories to be described all and only the most relevant ones are described. Climate substantially influences the mosquito population dynamics. For example, low temperature extends the life cycle of mosquitoes, and the larval time can take twice and the pupae time four times as long as under ideal conditions (Service, 2012). Rainfall creates additional breeding sites and increasing mosquito abundance leads to a peak in malaria transmission shortly after the rainy season (Kaindoa et al., 2017), while excessive rain can wash mosquito eggs out of breeding sites, leading to reduced emergence of adult mosquitoes. The survival of adult mosquitoes depends on temperature and humidity (Lindblade et al., 2000), and some species aestivate during the dry season (Jawara et al., 2008). An understanding of these factors and their influence on mosquito abundance and behaviour is critical for effective vector control.

The effectiveness of the interventions often relies on human behaviour, whether sleeping under a bed net, agreeing to have the house sprayed or adhering to the prescribed treatment regimen. It is natural that humans behave differently, and not always as public health specialists would like them

to. In malaria, this can have significant consequences for the community, as some interventions reach the highest effectiveness only after achieving high coverage, while other interventions such as larval source management often rely on active community participation. Hence, an understanding of such human-related factors is critical for the design and delivery of interventions but also for the evaluation of intervention programs.

Although not a risk factor for malaria transmission per se, funding is an important factor, as it regulates global and national malaria control efforts. The target area or population and coverage of intervention deployment are confined by the costs. Similarly, the total available budget puts a constraint on the number of interventions to combine, although they are often complementary or synergistic in their effectiveness. An area of increasing concern is also the scale down of already implemented interventions either because of decreasing funding or supposedly achieved elimination or both. In fact, many of the resurgences in malaria observed in the past occurred after funding, and consequentially interventions were decreased in the conjecture of achieved elimination (Cohen et al., 2012).

1.3 Malaria surveillance, monitoring and risk stratification

Knowing the extent of the malaria burden and transmission risk in the population geographically is essential for effective targeting of interventions and for monitoring of low transmission areas, often subject to more relaxed intervention coverage. Various measures exist to define malaria risk, and burden and specific indicators have been established to monitor and evaluate treatment and prevention efforts. As the malaria transmission and burden changes over time as well as spatially, continuous data collection is vital to be able to appropriately and timely adapt the deployment of the interventions to the current situation and avoid a waste of resources more urgently needed or more effective elsewhere.

1.3.1 Malaria burden and risk measures

Malaria burden is commonly expressed using the number of cases, and the number of malaria-related deaths. The risk of malaria transmission is approximated with measures in humans or mosquitoes. The number of malaria infections in humans allows to calculate the incidence, defined as the number of new infections within a time period in the total population at risk, often expressed as rate per 1000 population. It also allows to calculate the prevalence, defined as number of infections present in the population at risk at a particular time point, often expressed as a proportion. Other transmission measures exist, such as the parasite density or seroprevalence. In mosquitoes, an important measure of malaria infections is the number of mosquitoes with detected

sporozoites out of all mosquitoes tested (sporozoites rates). Further transmission relevant measures include the vector species occurrence, biting and resting behaviour, vector density, resistance, human blood index, and human biting rate, with the latter one defined as the average number of bites per human per night. When multiplying the sporozoites rate with the human biting rate, one obtains the number of infectious bites per person (per year), which is the most accurate measure of transmission intensity (Shaukat et al., 2010). Notably, the entomological measures are incredibly laborious to collect in the field and highly variable over time and geographically (Hay et al., 2000).

1.3.2 Health system performance and intervention indicators

Health facilities routinely record multiple indicators of case management performance and service delivery, such as the total number of cases, the test positivity rate, the malaria test rate, the annual blood examination rate, and the number of direct and indirect malaria deaths. Measures to assess the service delivery performance of health facilities include the availability of drugs, diagnostics and number of tests or treatments performed. In addition, antenatal care facilities provide routine estimates of malaria infections in pregnant women. Typical intervention indicators are the coverage of the target population, the number of commodities or items delivered, and the duration of the campaign. For example, during IRS campaigns, the number of households sprayed are monitored, and the coverage is calculated by dividing this number by all households targeted (PMI, Africa IRS (AIRS) Project, 2016). Other indicators, such as the number of sprayers, number of spraying equipment, and duration of the campaign, are relevant for operational planning and budget calculations. Another example is the planning of ITN campaigns, which involves estimation of the longevity of bed nets, the average number of people per household sleeping under the same bed net, and the number of bed nets required to achieve universal coverage.

1.3.3 Data sources

In most malaria-endemic countries, the only available nationwide data sources are often routine data collection in health facilities (Dehnavieh et al., 2019) and population household surveys. Sub-nationally, data may also be collected in sentinel surveillance, research study, and intervention implementation sites. Additionally, population censuses, meteorological observations, and remote sensing images of the environment, among others, can provide valuable additional information on the determinants and risk factors of malaria transmission.

The health information system is a routine surveillance system that captures symptomatic malaria cases that seek care. Health facilities submit monthly reports that are integrated into the so-called demographic health information system (DHIS2) in many countries. Population household surveys

include demographic surveys and malaria indicator surveys and are usually conducted every three to five years and representative at the regional level (ICF International, 2019). Some countries also conduct school surveys that complement household surveys (Ashton et al., 2011; Gitonga et al., 2010a; Mathanga et al., 2015; Nankabirwa et al., 2013; Ndyomugyenyi and Kroeger, 2007; Okebe et al., 2014; Sarpong et al., 2015; Takem et al., 2013; Walldorf et al., 2015; Houngbedji et al., 2015). The existing infrastructure provides a practical platform for health education programmes or health interventions (Anderson et al., 2013) as well as data collection on a large number of children in relatively short timeframes (Brooker et al., 2009). Malaria surveys commonly include a standardised questionnaire and testing for malaria infections in children using mRDTs. Based on the survey questionnaire information on the health-seeking behaviour and intervention use among household members are obtained, such as the proportion of the population with access to and usage of an ITN among others, while malaria testing allows calculating prevalence.

1.3.4 Malaria risk maps and stratification

The geographical context of malaria and related measures is critical for efficient targeting of control interventions (Cohen et al., 2017). Spatial analysis and mapping allow identifying trends and patterns and are useful to assess the relationships between spatially correlated factors. Regardless of the quantity of sampled locations, there are always unsampled areas, and data from one data source alone are often limited in the accuracy. Model-based geostatistics (MBG) is a widely used method to extrapolate unknown locations from sampled areas. This methodology has been applied for example to estimate the burden, describe the transmission risk globally (Hay et al., 2009), obtain sub-regional risk estimates from MIS surveys within a country (Gosoniu et al., 2010), identify the under-or over allocation of ITNs (Macharia et al., 2017), calculate the distance to health facilities (Battle et al., 2016), or mapping the distribution of malaria vectors (Sinka et al., 2012). A combination of all these factors is crucial for the appropriate geographical targeting of malaria interventions within countries, defined as stratification[7]. At which administrative level a country should be a) sampled or b) stratified is as much a financial and operational question as it is epidemiological and will be different for each country.

[7] Classification of geographical areas or localities according to epidemiological, ecological, social and economic determinants to guide malaria interventions (WHO, 2016).

1.4 Mathematical modelling of malaria

In infectious disease modelling, dynamical transmission models[8] simulate the spread of infections taken into account relevant determinants of transmission (Mishra et al., 2011). These models can produce generalised estimates beyond the epidemiological studies they rely on, hence are an affordable tool to provide estimates for various hypothetical scenarios and for a wide range of settings, which would be impossible to test in the field (Chubb and Jacobsen, 2010). Up to today, various modelling tools have been developed for a wide range of diseases (Andrews and Basu, 2011; Bowman et al., 2005; Cassels et al., 2008; Houben et al., 2016; Páez Chávez et al., 2017), particularly for malaria (Mandal et al., 2011; Smith et al., 2018).

Modelling of malaria started around 1911 with for describing the relationship between mosquitoes and malaria incidence (Ross, 1911; D. L. Smith et al., 2012). Since then, the application of modelling has been broadened, and models are applied not only to understand biological phenomena for research but also in the design of effective control strategies and a better understanding of the impact, among many other applications as summarised by the *malEra Research Agenda* (The malERA Refresh Consultative Panel on Combination Interventions and Modelling, 2017). Geographical and temporal predictions are especially useful for decision-making processes at country level or global level (e.g. WHO) (WHO, 2015a; RBM, 2010; WHO, 2014) and have been used to inform WHO treatment and prevention recommendations as well as to set global goals and timeframes (Feachem et al., 2019; WHO, 2015a).

1.4.1 Modelling methods and terminology

Mathematical models differ in their formal classification, complexity, and purpose. The simplest models are based on populations moving between disease-specific compartments (e.g. susceptible, infected, and infectious) at an assumed average rate. Although the compartmental structure can be extended to include demography and behavioural factors such as age-specific risks or treatment adherence, they cannot efficiently capture heterogeneity in the human population. Individual-based models include probabilities of change for each simulated individual; hence can capture combinations of individual risk and protection measures more accurately. The rate of change can be expressed with differential or stochastic questions. While deterministic models are useful and often similar to the average of stochastic equations, accounting for random variation is especially

[8] While weather driven models for outbreak forecast and geospatial decision-support-tools include mathematical aspects, this thesis focuses on agent-based dynamic transmission and their use for predicting (long-term) impact of disease prevention and treatment.

important for low transmission scenarios, where events are rare, and for estimating the probability of an event of interest (Mishra et al., 2011).

To obtain meaningful and valid predictions, models need to be parameterised and calibrated to data. More specifically, the transmission and intervention effect parameters are fitted to data[9] and in the process, unknown parameters estimated using statistical methods, such as least squares, maximum likelihood, or Bayesian methods. Simulations can be computational extensive and the more complex, the longer the processing time. Complex models are not always the best and simple models are not necessarily inferior; the selection of the right balance between the two depends mainly on the purpose and the end-user, but also on the technical expertise and available time (McKenzie, 2000; White et al., 2009). While the basic principles can be applied across various infectious diseases, models are more specific for vector-borne diseases, particularly malaria.

1.4.2 OpenMalaria

OpenMalaria is a model of the transmission dynamics of malaria and its pathogenesis[10] developed at the Swiss Tropical and Public Health (Swiss TPH) institute and collaborators around 2006 (Smith et al., 2006a, 2008). The human population is simulated using a stochastic individual-based model and the vectors using a deterministic population-based model (Chitnis et al., 2012). Both have been fitted to field datasets. The models include parameter to define the human population and demography, vector bionomics, transmission dynamics and seasonality, the health system, as well as varying drug-based and vector control interventions. The human model simulates infections, acquisition of immunity, disease, and treatment at an individual level. The different stages can be broadly separated into susceptible, infected, asymptomatic, symptomatic (uncomplicated and severe), care-seeking and treatment (health facilities or hospitalisations). After treatment, partial or successful clearance of parasites occurs, and the individual moves either back to the infected or susceptible-uninfected stage. Progression to severe symptoms and deaths despite treatment are also possible. The transition between stages depends on defined probabilities, the age and immunity and parameters defining the case management (care-seeking, treatment, case fatality rate). The health system, as part of the model, had been described in detail by Tediosi et al. (Tediosi et al., 2006), and the relationship between cases and progression to severe by Ross et al. (Ross et al., 2006). The vector model includes combined larval stages and detailed host-feeding cycle and can be defined for multiple vectors species (Chitnis et al., 2012, 2008b). The adult stages include non-infected, infected,

[9] Mostly clinical trials or randomised controlled trials to avoid bias and can be generalised across areas.
[10] For *Plasmodium falciparum* infections only.

and infectious host-feeding mosquitoes. The mosquito emergence is estimated based on the defined EIR with the larvae progressing to host-seeking adults at a constant rate.

OpenMalaria is an open-source platform and can be freely downloaded and detailed instructions on how to run the model are provided in the related online wiki (Swiss TPH, 2020). OpenMalaria is written in C++ and uses *eXtensible Markup Language* (XML) files as input. Although an interface exists, mainly for teaching purposes, one needs to work with the XML files to use the full potential of the model. A single experiment easily reaches thousands of scenarios, and high-performance computing systems allow many simulations to run in parallel and relatively fast.

1.4.3 Country specific modelling applications

Many models are developed in specific country settings, and various examples exist, where mathematical modelling was used to simulate the impact of interventions in specific countries at different resolutions (Gerardin et al., 2017; Hamilton et al., 2017; Nikolov et al., 2016; Scott et al., 2017; Walker et al., 2016; Winskill et al., 2017). Although the application in geographical contexts, with modelling informed by local data, provides a powerful decision-making tool for national malaria control programs in countries (Kramer et al., 2009; Maude et al., 2010; White et al., 2009; WHO, 2014), they are rarely applied to address country needs and even less have an impact on national policy.

1.5 National malaria control programmes

At the country level, national malaria control programs (NMCPs) plan and coordinate malaria surveillance and control activities. The NMCPs adopt the WHO recommendations to the local levels at which interventions will be implemented. The choice of an intervention depends on multiple context-specific factors: 1) geographical heterogeneity in transmission and intervention impact (e.g. due to resistance); 2) differences in operational feasibility depending on the environment, infrastructure, and local capacities; 3) influence of cultural, behavioural and political contexts on utilisation of interventions; and 4) varying budgets and funders interests.

1.5.1 Development of national malaria strategic plans

When planning malaria control intervention, the type, combination, active ingredient, timing, coverage, target population, distribution scheme and geographical allocation are amongst the critical determinants of successful interventions. Inaccurate planning and deployment is not only an inefficient use of valuable resources (Gerardin et al., 2016) but may also prevent the success of future interventions by triggering community fatigue or enhancing resistance development in the

malaria parasites and vectors (Gerardin et al., 2015; Newby et al., 2015). National control strategies need to be based on evidence, obtained from local data to ensure efficient use of resources. For developing evidence-based and effective strategies, data from various sources is collated and analysed, i.e. through geographical mapping, time-series analysis and potentially complemented with geospatial and mathematical modelling (Massoud Moussavi et al., 2017).

Use of modelling in strategic planning

In the development process of a strategic plan, geographical and temporal predictions for different intervention combinations and deployment determinants (e.g. active ingredient, frequency, duration, and coverage) are useful information. It is important to emphasise that modelling is not competing with the existing data and tools; it instead makes the best use of what is already available to strengthen the evidence and the decision making for improved strategic planning (Fig. 1.2).

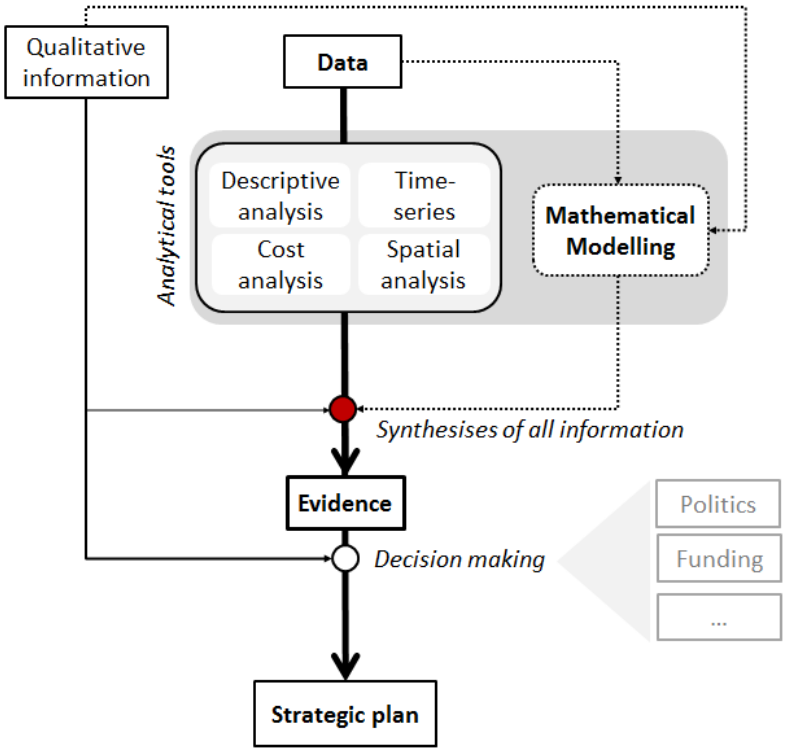


Fig.1.2: Conceptual visualisation of modelling in the development of national malaria strategies.
The thick solid lines schematically indicate the analytical flow from data to a strategic plan. The dashed lines indicate the role of modelling as an additional tool that integrates all available quantitative as well as qualitative information into one coherent model. The simulated impact of interventions adds to the existing evidence for improved decision-making in the process of selecting interventions to deploy in the next strategic planning cycle. The components shown are indicative only and not exhaustive.

1.6 Supporting strategic planning of malaria control in Tanzania

The United Republic of Tanzania is formed by the sovereign states Zanzibar and Mainland Tanzania[11]. Tanzania is among the countries with the poorest economy, and almost 70% of the population is living below the poverty line (Central Intelligence Agency (CIA), 2015). Around 50 million people live in the country, about 45% are under the age of 15 years and >30% live in urban areas (NMCP et al., 2013). Until 2016, the mainland was divided into 25 regions and 166 districts, which changed into 26 regions and 184 councils in 2018.

1.6.1 Malaria situation and rationale for modelling

In 2017, Tanzania contributed 15% to the malaria burden in East and South African countries (WHO, 2017a). Malaria is very heterogeneously distributed in the country, with areas at low prevalence eligible for pre-elimination and regions with high prevalence, and the national prevalence decreased from 14% in 2012 to 9% in 2016 (MoHCDGEC et al. 2016). The NMCP manages malaria control at the central level, and since 1997, four strategic plans have been developed (MoHCDGEC, 1997; MoHCDGEC, 2002, 2008; NMCP, 2010; MoHCDGEC, 2014). The latest NMSP 2015-2020 recognises heterogeneity and defines different strata, whereas the operational unit remained at the regional level. The NMSP includes case management, IPTp/i, universal ITN distributions and targeted IRS. A scale-up of larviciding in the whole country is also included despite the limited evidence on its effectiveness in various settings (Choi et al., 2019; Tusting et al., 2013). The strategy aims to reduce the malaria prevalence from 10% in 2012 to 5% in 2015 and 1% in 2020 (MoHCDGEC, 2014). In 2015, an observed prevalence of 14% (MoHCDGEC et al. 2016) questioned whether it would technically be feasible to reach the targets by 2020. This called for a revision of the strategy with councils as new operational unit for better targeting of interventions.

However, the transmission intensity at council level was mostly unknown, as prevalence estimates from MIS surveys, for children below five years, are only at the regional level representative for the population. The epidemiological profile provides a high-resolution map, based on household cluster prevalence estimates and epidemiological studies, but has not been updated since 2012 (NMCP et al., 2013). The health information system provides malaria burden estimates at the health facility level, but only captures symptomatic cases seeking care. School surveys might be practical as well, as school enrolment rates are very high (PMO-RALG, 2014). School surveys would also allow collecting more data on school children, a potentially neglected subgroup, which might need to be specifically targeted in future control interventions (Griffin et al., 2014; Walldorf et al., 2015). This approach can

[11] In the following referred to Tanzania only for the mainland.

be strengthened by using geospatial risk mapping methods, combining the school survey data with MIS and routine data, to provide smoothed annual trends in malaria risk at higher resolution and accuracy.

The projection of future impact to assess the feasibility of the strategic plan target and expected impact of new strategies requires a sophisticated approach given the non-linear relationships in transmission and long-term effects such as immunity in the population. Mathematical modelling can be used for such purposes, and the high availability of data in Tanzania provides a solid basis for the simulations at sub-national level. While the strategic plan and WHO recommendations for the core vector control interventions are relatively clear for informing the model to provide meaningful predictions, considerable uncertainty remains in the deployment and effectiveness for larviciding. In Tanzania, larviciding was applied in Dar es salaam during the Urban Malaria Control Program between 2006 and 2009 (Castro et al., 2004; Fillinger et al., 2008; Geissbühler et al., 2009; Maheu-Giroux and Castro, 2014, 2013), and also in a rural area in 2015 (Rahman et al., 2016). Although shown effective in many studies (Tusting et al., 2013), few examples also exist where larviciding did not have an impact (Majambere et al., 2010; Zhou et al., 2013), and not much is known about the deployment factors and influence on malaria in different settings, whereas interventions that also target outdoor biting vectors are urgently needed.

Objectives and outline

This dissertation aims to contribute to a stronger basis for the rational development of malaria strategies for maximum progress towards control and elimination targets in Tanzania. The methods are developed using the country context of Tanzania, and the developed methodology is meant to be applicable for most malaria-endemic countries in Sub-Saharan Africa.

The objectives were:

- to describe the malaria prevalence at council level and to perform a regression analysis to assess protective and risk factors of prevalence among school children, using data from the School Malaria Parasitaemia Survey;
- to develop a model calibration workflow using the OpenMalaria transmission model with setting parameter informed by local data and over time for council-specific impact predictions of future interventions;
- to use the developed model workflow to assist the program in strategic planning by
    - predicting the impact of interventions included in the NMSP, to determine the most impactful and the most cost-effective intervention allocations, and by

  - predicting the impact of alternative intervention scenarios defined by the program in the revision of the NMSP;
- to evaluate the influence of variations in larviciding deployment (timing, duration, frequency, interval length, coverage) on the impact on entomological and epidemiological outcomes in different transmission and seasonality settings to inform operational planning.

The second chapter presents data from the first nationwide school malaria parasitaemia survey in Tanzania, representative at council level. The SMPS is a cross-sectional survey conducted in primary schools and using rapid diagnostic tests and questionnaires to collect information on malaria parasitaemia, bed net coverage and care-seeking behaviour among school children.

The third chapter describes the development of a workflow to obtain intervention impact predictions for each council using the dynamic transmission model OpenMalaria to assess whether the current National Malaria Strategic Plan would technically be feasible to achieve the national malaria target. Setting specific parameters were informed with data and estimates obtained from various long-term and cross-sectional surveys between 2000 and 2016.

The fourth chapter demonstrates the usefulness of modelling in the strategic planning process by using the developed workflow guided by the NMCP to aid in the revision of the strategic plan. The revision was initiated based on the results of a midterm review of the current strategy in 2017, which were supported by the previous modelling results.

The fifth chapter shows the application of modelling to investigate different larviciding deployment options by simulating parameter ranges for the coverage, duration, frequency and seasonal timing of larviciding applications in generic settings with different transmission intensities and seasonality patterns.

The sixth chapter critically reflects the process of using modelling for malaria strategic planning in collaboration with the NMCP in Tanzania and describes challenges and strengths, leading to key components for a successful modelling process.

The final chapter provides a comprehensive discussion of the previous chapters and their role to achieve the overall aim of the PhD. The chapter starts with the use of schools for malaria surveillance and improved risk stratification for better targeting of interventions, the development and use of mathematical modelling to provide an additional layer of evidence for the selection and allocation of interventions, which also includes a comparison of the different intervention stratifications from an epidemiological perspective, followed by a broader reflection of modelling as part of the strategic planning process. After outlining the limitations, challenges and suggestions for future directions, the chapter closes with the contribution of the PhD towards achieving its aim in the context of the latest developments in global malaria policy.

2 Nationwide school malaria parasitaemia survey in public primary schools, the United Republic of Tanzania

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2.1 Abstract

Background: A nationwide, school, malaria survey was implemented to assess the risk factors of malaria prevalence and bed net use among primary school children in mainland Tanzania. This allowed the mapping of malaria prevalence at council level and assessment of malaria risk factors among school children.

Methods: A cross-sectional, school, malaria parasitaemia survey was conducted in 25 regions, 166 councils and 357 schools in three phases: (1) August to September 2014; (2) May 2015; and (3) October 2015. Children were tested for malaria parasites using rapid diagnostic tests and were interviewed about household information, parents' education, bed net indicators as well as recent history of fever. Multilevel mixed-effects logistic regression models were fitted to estimate odds ratios of risk factors for malaria infection and bed net use while adjusting for school effect.

Results: In total, 49,113 children were interviewed and tested for malaria infection. The overall prevalence of malaria was 21.6%, ranging from < 0.1 to 53% among regions and from 0 to 76.4% among councils. The malaria prevalence was below 5% in 62 of the 166 councils and above 50% in 18 councils and between 5 and 50% in the other councils. The variation of malaria prevalence between schools was greatest in regions with a high mean prevalence, while the variation was marked by a few outlying schools in regions with a low mean prevalence. Overall, 70% of the children reported using mosquito nets, with the highest percentage observed among educated parents (80.7%), low land areas (82.7%) and those living in urban areas (82.2%).

Conclusions: The observed prevalence among school children showed marked variation at regional and sub-regional levels across the country. Findings of this survey are useful for updating the malaria epidemiological profile and for stratification of malaria transmission by region, council and age groups, which is essential for guiding resource allocation, evaluation and prioritisation of malaria interventions.

2.2 Background

Tanzania is currently under epidemiological transition from meso-endemic to hypo-endemic levels characterized by marked heterogeneity across and within regions and/or councils (NMCP et al., 2013). This calls for an accurate and timely estimate of the spatial-temporal distribution of malaria transmission; malaria burden; and the impact of deployed control interventions. Since 2000 it has been estimated that the malaria burden has shown a marked declined in Sub-Saharan Africa, due to a large scale up of control interventions (Bhatt et al., 2015b; WHO, 2015e). Malaria prevalence among school-aged children in Tanzania is under-researched and not well understood. To date, few data have been collected in older children in small-scale studies which have shown an increasing

proportion of the malaria burden in adolescents despite transmission falls in the general population (Mazigo et al., 2017; Nzobo et al., 2015). In addition, the observed high heterogeneity of malaria transmission calls for the timely identification of populations and areas at greatest need for additional interventions (Hemingway et al., 2016; Tanner et al., 2015; WHO, 2015f). The major sources for malaria data are Health Management Information Systems (HMIS) and large household surveys, such as the Malaria Indicator Surveys (MIS) and the Tanzania Demographic and Health Surveys (TDHS). However, the HMIS only captures malaria cases for those seek care at health facilities, while household surveys which are conducted every four to five years have been a useful tool to inform on the prevalence of malaria situation in the country. Household surveys are logistically complex, expensive, time-consuming and have limited scope of sample size whereby in Tanzania it focuses only on children below than five years old (Brooker et al., 2009). Additionally, unsteady funding and weak health systems hinder the timely and reliable data collection of malaria cases (Hemingway et al., 2016). In this context, school surveys have gained increased attention for national surveillance, complementing household surveys (Gitonga et al., 2010b; Stevenson et al., 2013; Swana et al., 2018). Schools are often well organized and easily accessible and provide the possibility of collecting malariometric and control data from many children in a short period of time and at a low cost compared to TDHS/MIS which are too costly for routine surveillance. The importance of school survey data for the planning of targeted interventions was demonstrated by school surveys conducted in other African countries, such as Kenya, Ethiopia, Uganda, Malawi, Côte d'Ivoire, DRC and The Gambia (Ashton et al., 2016; Gitonga et al., 2010b; Houngbedji et al., 2016; Mathanga et al., 2015; Nankabirwa et al., 2013; Ndyomugyenyi and Kroeger, 2007; Okebe et al., 2014; Sarpong et al., 2015; Stevenson et al., 2013; Swana et al., 2018; Takem et al., 2013; Walldorf et al., 2015) summarised by Brooker et.al. (Brooker et al., 2009).

A national school malaria parasitaemia survey (SMPS) was conducted to close that data gap by increasing the scope from children under-five years to children 5-16 years old and increase and complement the power of the population surveys through increased sites and sample size. The SMPS was designed to allow estimates of malaria prevalence and determine spatial and temporal risks *of P. falciparum* transmission among public primary school age pupils in Mainland Tanzania. The objectives were (1) to determine the prevalence of malaria among public primary school enrolled pupils, (2) to establish the spatial and temporal risks of *P. falciparum* transmission across malaria-endemic councils and (3) to determine the access and use of insecticide-treated bed nets among school-age children.

2.3 Methods

2.3.1 Context of Tanzania

Malaria in Tanzania

Around 95% of the population is at risk of malaria (MoHCDGEC, 2014). Malaria transmission has been described as unstable, seasonal in the arid central plateau, as stable seasonal in the southern part (unimodal) and northern and western parts (bimodal), and stable throughout the year in the coastal fringe, southern lowlands and in the Lake Zone (NMCP et al., 2013). In the past decade, there was an overall decrease in the malaria prevalence among children under the age of five years from 18.9% to 9.5% between 2008 and 2012 (TACAIDS et al., 2013, 2008). However, the decline was not everywhere and even increased in some parts of the country, leading to an overall prevalence of 14% in 2016 observed in the 2015-2016 TDHS-MIS survey (MoHCDGEC et al., 2016).

Geography and Population

Tanzania is among the Eastern African countries, with a total area of 945,000 km^2. The Mainland Tanzania is divided into regions, councils, wards, and villages. Tanzania is mostly rural, with around 28% of the population living in urban councils, while ten percent of the population lives in Tanzania's largest city Dar es Salaam. According to the 2012 population census, Tanzania has almost 45 million inhabitants with half of the population younger than seventeen years (National Bureau of Statistics (NBS), Tanzania and Office of Chief Government Statistician (OCGS), Zanzibar, 2013a).

Climate and Seasonality

The climate in Tanzania is tropical with temperatures between 25°C and 31°C during the hottest period (November to February) and temperatures between 15°C and 20°C in the cooler period (May to August). In most parts of the country, the temperature rarely falls below 20°C, while in highland areas the temperature ranges from 10°C to 20°C throughout the year. There are two different rainfall seasons in Tanzania: (1) from December to April in Southern, South-Western, Central and Western parts of Tanzania, and (2) from October to December and March to May in Northern and Northern coastal parts of Tanzania (Government Portal Content Committee, 2013).

Education system and schools

In Tanzania, in the year 2002 primary education had been made compulsory to all eligible children (MoEVT, 2014). According to the Ministry of Education and Vocational Training (MoEVT) data in 2015, there were 16,960 registered primary schools in Mainland Tanzania, whereas 928 (5.5%) of those were non-governmental (MoEVT, 2015). The school enrolment is described through intake and

enrolment ratios, whereas the National Intake Ratio (NIR) is the percentage of new enrolments of children of official school entrance age over all children of official school entrance age (PMO-RALG, 2014). In 2014 it was estimated that the net enrolment ratio ranged from 73% in Katavi region to nearly 100% in Iringa region (PMO-RALG, 2014).

2.3.2 School Malaria Parasitaemia Survey (SMPS)

Survey design, procedures, and study tools

A cross-sectional school malaria parasitaemia survey was conducted in three phases; namely, phase one which was considered as a pilot phase, included 113 schools in five regions between August and September 2014; the second phase included 217 schools in eleven regions in May 2015; the third phase included 207 schools in nine regions in October 2015 (Fig. 1). The sample was calculated and selected using a multistage stratified proportional probability sampling method. In each council, the number of children to be tested was calculated based on the known population figures (National Bureau of Statistics (NBS), Tanzania and Office of Chief Government Statistician (OCGS), Zanzibar, 2013a) and estimated mean population-weighted parasite prevalence rate adjusted for children aged two to ten years ($PfPR_{2\text{-}10}$) for 2010 (NMCP et al., 2013). The number of children to be tested was then used to determine the number of schools included in the survey in each council, assuming an average of 100 children per school. As a next step, the list of wards in each council was confirmed and updated during a national orientation meeting by local expert teams from health and education sectors. The councils were stratified according to the altitude, population density, demographic characteristics, and any other features available such as urban/rural. The number of strata was equal to the pre-defined number of schools, aiming to select one school within each stratum. The stratification was done to ensure that the study design captured the heterogeneity of malaria transmission at sub-council level. In each stratum one ward and subsequently one village were randomly selected, using a list of the administrative units obtained from the National Bureau of Statistics Tanzania (NBS Tanzania, 2017). Thus, the probability of a school to be selected was dependent on the number of wards within the strata and the number of villages within the selected ward. In case there was more than one school located in a village, the school was randomly selected. Proportionate stratification was used to obtain the actual number of children to be tested at each school. In each school, all seven primary school classes were included with an equal number of children in each class, balancing the sample for sex groups. In phase III, only classes one to six were included, due to the near end of the school term for children in class seven. The selection of children in each class was done separately for boys and girls, using a systematic sampling procedure from a class register. A detailed flowchart of the sampling design can be found in SI-1.

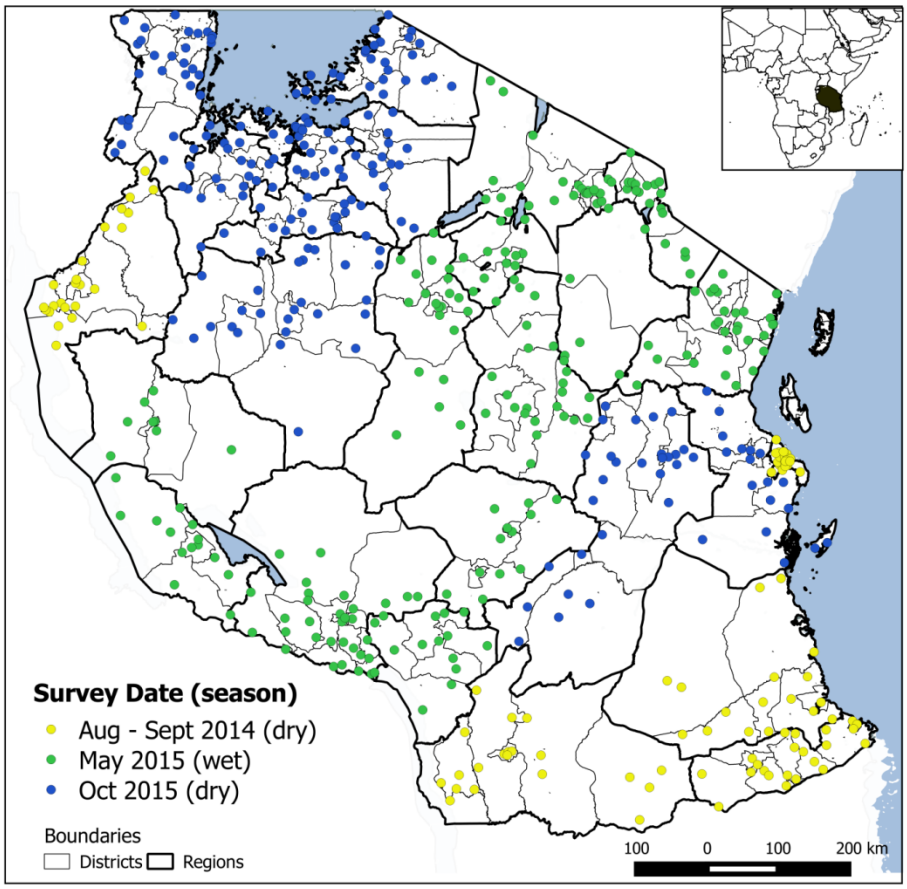

Fig. 2. 1: Locations of sampled schools (N = 537) coloured by survey date.

An average of 8 days was used for data collection per region, ranging from 4 – 15days. Within councils the data collection took on average 4 days, ranging from 1 to 11 days (Fig. SI-2). In each surveyed school, a total of two days was used; one day was used for planning, sampling and consenting and second day for interviewing and testing. Each council was given one additional day for data management and reporting. To test the children for malaria parasites, the "SD BIOLINE Malaria Ag *P.f/Pan*" rapid malaria tests were used (Standard Diagnostics Inc., Republic of Korea). The individual test results were recorded in the designated mRDT register and in the respective individual children's questionnaire. Furthermore, the questionnaire captured information on household size, bednet ownership and use, school absenteeism and fevers during the last two weeks prior the survey and, for phase II and III, education level of one parent. Children with a positive test result were treated with Artemether-Lumefantrine (ALu), as recommended in the National Malaria Diagnosis and Treatment Guidelines (National Malaria Control Programme, Tanzania, 2014) and referred to the nearest health facility when necessary. To confirm the consistency of recording of the malaria test results, 20% of the used rapid diagnostic tests were reviewed by quality assurance team and the results were compared with the recorded test results on the paper forms. For wrongly recorded test

results, the amendment was handled at the study site by drawing a single line through an incorrect value and dated.

Survey staff and training

Data collection was done by council teams, including the malaria focal person, two laboratory technicians, one education officer, and one teacher from each surveyed school. Regional teams, including the regional malaria focal person and a national supervisor from the National Malaria Control Programme (NMCP), National Institute for Medical Research (NIMR) or Ifakara Health Institute (IHI), supervised the data collection at regional level and visited one council team per day to assess the performance of malaria testing, assess data quality issues and individuals' interview. All teams participated in a national three day-training, directly before the start of the data collection.

Ethical considerations

Ethical clearance was given by the National Health Research Ethics Committee of the National Institute for Medical Research (NIMR). Informed consent for the survey was based on a passive, opt-out method of parental permission. Schools were instructed to inform the students and parents concerning the exercise. It was assumed that parents who did not express their disapproval for the survey, approved children's participation.

Data entry

Paper forms and mRDT kits were transported to the head office of the NMCP in Dar es Salaam for data entry and storage. Data was single entered by a group of trained data entry clerks, using EpiData (EpiData Association, Denmark) templates in phase I and phase III, and Microsoft Excel (Microsoft Corporation, Seattle, USA) in phase II under supervision of study investigators and a statistician. Entered data into Epi-data were exported into excel for daily simple quality checks. Daily quality checks were performed through comparing entered data per data entry clerk for data entry errors using the filter function in excel. After data entry, twenty percent (20%) of the data from each data entry clerk were validated by comparing entered data with paper forms. The whole dataset was screened for suspicious data entries such as invalid values, out of range or missing values following a checklist for each variable. Suspicious entries were recorded, and hardcopies revisited to diagnose the entries as erroneous with correction, or as invalid.

2.3.3 Data analysis

The data were analysed in STATA version 14 (StataCorp LP, 2013) and maps were created using QGIS (QGIS Development Team, 2016). Descriptive statistics were done for all variables. Prevalence and

proportions together with their 95% confidence intervals were calculated adjusted for clustering effect of children between schools. Chi-square tests were used to compare characteristics of children and schools with the outcome variables “malaria infection” and “bed-net use”.

Variable definitions and sources

The age range was categorized into three groups: five years to less than nine years, nine to twelve years, and older than twelve years. Councils were classified as urban or rural based on the type of council. Municipals, township authorities, and city councils were classified as urban, remaining councils were classified as rural. Transmission zones were classified according to the categories used in the most recent epidemiological profile and based on the predicted mean $PfPR_{2\text{-}10}$ from 2010, adjusted for the ages two to ten years (NMCP et al., 2013). The following categories were created: low stable ($PfPR_{2\text{-}10}$ < 1%), hypoendemic 1 ($PfPR_{2\text{-}10}$ 1 - < 5%), hypoendemic 2 ($PfPR_{2\text{-}10}$ 5 - < 10%), mesoendemic ($PfPR_{2\text{-}10}$ 10 - < 50%), and hyper-holo-endemic ($PfPR_{2\text{-}10}$ ≥ 50%). Bed-net ownership was defined as having at least one mosquito bed-net in a household. Values presented on malaria infection type (*e.g. P.falciparum*, other *Plasmodium* species or Pf and pan infection (when control and other two lines appear)), were based on the mRDT designated register dataset (N = 49,169), which included slightly more children than the questionnaire dataset (N = 49,113). The altitude was extracted for the geo-location of the schools, using data from Shuttle Radar Topography Mission (“U.S. Releases Enhanced Shuttle Land Elevation Data,” n.d.), downloaded from WorldClim (“WorldClim - Global Climate Data | Free climate data for ecological modeling and GIS,” n.d.; Hijmans et al., 2005). The altitude was categorized into: below 750 meters, 750 to 1,250 meters, 1,250 to 1,750 meters, and above 1,750 meters. Further environmental variables added were: ecozone and temperature suitability index (TSI). The ecozones were classified by the Food and Agriculture Organisation (FAO) as tropical rain forest, tropical moist deciduous forest, tropical dry forest, tropical shrubland and tropical mountain system (Food and Agriculture Organisation (FAO), n.d.). The temperature suitability index is a relative measure of the impact of the temperature on vectorial capacity (number of infectious mosquitoes), ranging from 0 to 1 (Gething et al., 2011). The TSI raster file for 2015 was downloaded from the Malaria Atlas Project at the University of Oxford (MAP, 2016) and mean values were extracted per council using R version 3.3.1 (R Core Team, 2020).

Population data were obtained from the national population census 2012, available from the National Bureau of Statistics (NBS) Tanzania (NBS Tanzania, 2017), and gridded population densities from WorldPop (Tatem, 2017). Bed-net use for a child was defined as a binary variable stated as “yes” if a child reported general use of net regardless of bednet ownership and “no” otherwise. Malaria infection was defined as “yes” for a positive mRDT case regardless of the malaria infection type and “no” if no infection was detected.

Multilevel mixed-effects logistic regression analysis

To assess the influence of risk factors for malaria infection and bednet use, multilevel mixed-effects logistic regression models were fitted for each outcome separately. Data were assumed to be clustered at council and schools; hence these were included in the model as random effects. Variable selection was based on available environmental, socio-economic and individual covariates, which were previously associated with malaria, such as annual rainfall, temperature and vegetation index, TSI, altitude, type of council, reported education of parents, gender, age, fever in the 2 weeks prior to survey. In addition, log-likelihood ratio tests of bivariate models, with a cut-off at a significance level of 0.01 were used. In the model with outcome "malaria infection" the following interaction terms were assessed: sex and bed net use, age, and bed-net use, reported parental education level and bed-net use, reported parental education level and urban area. Interaction terms were included at a significance level of 0.05. The final set of selected variables, which was used in both models included: sex, age, bed-net use or mRDT result, reported parental education, type of council, school-point altitude, geographical zone, and school-point TSI. Due to limited available variables in phase I, two multivariable models were calculated: model I included data from all regions but had fewer covariates (n = 47,157; 96%), whereas model II excluded data from phase I regions but more covariates (n = 30,715; 62.5%) (Table 2.1).

Table 2.1: Multivariable regression models used in the present analysis.

	Model I	**Model II**
Regions	All	Excluding Phase I data: Kigoma, Mtwara, Lindi, Ruvuma, Dar es Salaam
Number of observations	47,157 (96%)	30,715 (62.5%)
Variables		
included	sex, age, bed-net use or mRDT result, type of council, altitude, geographic zone, TSI	sex, age, reported parental education, bed-net use or mRDT result, type of council, altitude, eco-zone, geographic zone, TSI
excluded	Reported parental education, eco-zone	
Random effects	council, school	council, school

2.4 Results

Overall, 49,113 children in 357 schools were tested for malaria and interviewed. On average 91 children were sampled in each school, ranging from 44 to 199 children. Regarding the transmission zones, 7,606 (15.5%) children were sampled in councils classified as low stable, 11,845 (24.1%) in

hypoendemic 1, 8,188 (16.7%) in hypoendemic 2, 21,208 (43.3%) in mesoendemic and 146 (0.3%) in hyper-holoendemic (Table 2.2).

Table 2.2: Number of included councils, schools and children, by transmission area.

	Councils				Schools				Children		Total pop. (2010) *
	N	Children per council			N	Children per school			N	%	
		mean	min	max		mean	min	max			%
Transmission zone*											
Low stable	30	253.5	111	546	88	86.4	44	166	7,606	15.5	25.4
Hypoendemic 1	40	296.1	64	501	130	91.1	42	157	11,845	24.1	20.4
Hypoendemic 2	27	303.3	97	653	91	90	44	199	8,188	16.7	13.3
Mesoendemic	67	316.5	89	1,109	224	94.7	44	165	21,208	43.2	38.4
Hyper-Holoendemic	1	146	146	146	2	73	73	73	146	0.3	2.3
Missing**	1	120	120	120	2	60	60	60	120	0.2	-
Total	**166**	**295.9**	**64**	**1,109**	**537**	**91.5**	**42**	**199**	**49,113**	**100**	**100**

***** Source: (NMCP et al., 2013)
** no data for Mafia council in Pwani Region

2.4.1 Characteristics of sample

Malaria test results were available for 49,102 (99.9%) children and bed-net use information was available for 47,800 children (97.3%). Majority of the children were sampled in rural councils (80%). The mean altitude was 1,016 meters (inter-quartile-range 615 to 1,351 meters) and the mean TSI was 0.4 (inter-quartile-range 0.22 to 0.57). The sample included as many boys as girls (boys 49.2%), and the children were on average 11 years old (range: 4-20; inter-quartile-range: 9 to 13 years) (Fig. SI-3). Girls were found to be on average one year younger than the boys. Majority of the children reported to have parents with primary school education (n = 23,445; 72%), while around ten percent of the children reported to have parents who had never been to school (n = 3,736; 11.6%). In the two weeks prior to the survey, 17,272 (35.7%) children were absent due to sickness and 15,709 (32.7%) had fever; of those, 8,383 (53.4%) children went to a health facility for treatment seeking and reported to be diagnosed with malaria. Almost all the children diagnosed with malaria had received treatment (n = 8,155, 97.7%), while 1,421 (14.8%) children received treatment but were not diagnosed with malaria. In total, 41,914 (89.5%) children reported to have at least one bednet at home, while the bed-net use was 69.6%. In urban councils significantly, more children reported to sleep under a bed-net than in rural councils (82.20%, 95%CI, 78.7-85.2% versus 66.50%, 95%CI, 64.1-68.8%) (Table 2.3).

Table 2.3: Sample characteristics and risk factors for malaria infection and bed-net use in school children in Tanzania.

	Total Children		Malaria (N = 49,102)			Bed-net Use (N = 47,800)		
			Children tested positive			Children sleeping under bednet		
	N	%	n	%	95%CI	n	%	95%CI
Total	49,113	100	10,62	22	(19.6-23.9)	33,284	70	(67.6-71.6)
Sex								
Male	24,205	49.3	5,606	23.2	(21.0-25.5)	16,077	68.3	(66.1-70.3)
Female	24,681	50.3	4,940	20.0	(18.0-22.2)	17,078	71.0	(68.9-73)
Missing	227	0.5	81	35.7	-	129	63.9	-
Age								
<9	9,075	18.5	1,651	18.2	(16.1-20.5)	5,974	68.8	(66.3-71.2)
9-12	18,892	38.5	4,045	21.4	(19.2-23.8)	13,106	71.2	(69.2-73.3)
>12	20,730	42.2	4,847	23.4	(21.2-25.7)	13,957	68.6	(66.3-70.8)
Missing	416	0.9	84	20.2	-	247	62.7	-
Parental education								
No school	3,736	7.6	1,074	28.8	(24.4-33.5)	1,930	54.7	(50.2-59.1)
Primary	23,445	47.7	5,163	22.0	(19.4-24.8)	14,968	65.8	(63.1-68.3)
Secondary	4,547	9.3	808	17.8	(15.1-20.9)	3,430	77.5	(74.8-80)
Diploma or higher	525	1.1	52	9.9	(7.0-13.9)	415	80.7	(76.1-84.7)
Missing	5,424	11.0	970	17.9	-	3,617	69.7	-
Not interviewed*	11,436	23.3	2,560	22.4	-	8,924	78.4	-
Bednet use								
No	14,516	29.6	2,943	20.3	(17.8-23.0)	-	-	-
Yes	33,284	67.8	7,270	21.9	(19.6-24.2)	-	-	-
Missing	1,313	2.7	414	31.5	-	-	-	-
Zone								
Eastern	6,967	14.2	1,269	18.2	(13.3-24.4)	5,819	86.6	(83.4-89.3)
Western	4,805	9.8	1,449	30.2	(25.5-35.2)	3,221	68.8	(64-73.2)
Southern	4,002	8.1	1,344	33.6	(27.2-40.8)	3,255	81.6	(76.8-85.6)
Southern Highlands	4,116	8.4	495	12.0	(7.2-19.4)	2,350	58.7	(52.4-64.7)
Southwest	4,867	9.9	846	17.4	(11.6-25.2)	2,946	61.6	(55.3-67.5)
Central	5,653	11.5	156	2.8	(1.6-4.6)	3,077	55.1	(49.6-60.5)
Northern	6,191	12.6	317	5.1	(3.1-8.4)	3,360	55.6	(49.4-61.7)
Lake	12,512	25.5	4,751	38.0	(33.6-42.5)	9,256	77.2	(73.1-80.8)
Missing	0	0.0	0	0.0	-	0	0.0	-
Area								
Urban	9,708	19.8	588	6.1	(4.0-9.1)	7,866	82.2	(78.7-85.2)
Rural	39,405	80.2	10,03	25.5	(23.1-28.0)	25,418	66.5	(64.1-68.8)
Missing	0	0.0	0	0.0	-	0	0.0	-
Eco-zone (tropical)								
Dry forest	7,124	19.0	2,247	31.5	(25.9-37.8)	5,417	79.4	(74.7-83.4)
Moist decid. forest	5,819	15.5	1,816	31.2	(25.1-38)	3,786	67.8	(62-73.1)
Mountain system	6,053	16.1	723	11.9	(7.9-17.6)	3,329	57.0	(50.3-63.5)
Rainforest	3,331	8.9	1,272	38.2	(28.6-48.7)	2,664	82.8	(76.3-87.8)
Scrubland	15,216	40.5	2,009	13.2	(10.3-16.7)	9,078	61.2	(57.4-64.9)
Missing	11,570	23.6	2,560	22.2	-	9,010	77.9	-
Altitude								
<750	13,228	26.9	3,248	24.6	(20.7-28.9)	10,697	82.7	(80.1-85)
750-1250	18,901	38.5	5,040	26.7	(23.3-30.4)	13,284	72.0	(68.8-75)
1250-1750	14,581	29.7	2,335	16.0	(12.6-20.1)	8,434	59.8	(56-63.4)
>1750	2,403	4.9	4	0.2	(0.1-0.5)	869	37.8	(30.5-45.7)
Missing	0	0.0	0	0.0	-	0	0.0	-

*no data for children sampled in phase I

Malaria infections

In total, 10,627 children (21.6%) tested positive for malaria (95%CI, 19.5-23.9) (Table 3). Out of those, 6,840 children (65%) had a mono-infection with *Plasmodium falciparum*, 3,582 children (34.1%) had a malaria infection with *Plasmodium falciparum* and a non-*falciparum* parasite (*P. vivax, P. ovale, or P. malariae*) infection and 93 children (0.9%) were only infected with a non-*falciparum* parasite. Furthermore, from the positive tested children, 2,316 children (21.8%) reported to have been diagnosed with malaria in the past two weeks preceding the survey, and 2,153 children (20.3%) received treatment. Slightly more boys than girls were tested positive (n = 5,606 (23%, 95%CI, 21-25.5%) versus n = 4,940 (20%, 95%CI, 18-22.2%)). The malaria prevalence was 18.2% in children 5 to < 9 years (95%CI, 16.1-20.5%), 21.4% in children aged 9 to 12 years (95%CI, 19.2-23.8%) and 23.3% in children older than 12 years (95%CI, 21.2-25.7%). The malaria prevalence was highest in children reported parents with no school education (28.8%, 95%CI, 24.4-33.5%), compared to children with reported parents with primary (22.0%, 95%CI, 19.4-24.8%), reported parents with secondary (17.8%, 95%CI, 15.1-20.9%) and reported parents to have higher education (9.9%, 95%CI, 7.0-13.9%). In mesoendemic, and hyper-holo-endemic almost one third of the children were tested malaria positive (31.4%, 95%CI 28.1-34.9%, and 29.9%, 95%CI, 25.1-35.3%, respectively), in hypoendemic councils only ten percent were tested positive (10.9%,95%CI, 8.3-14.1%), and in low stable endemic councils fewer than 2% were tested positive (1.4%, 95%CI, 0.5-3.7%) (Fig.2.2). The malaria prevalence slightly increased by age in all transmission zones (SI-4: Fig.4). The malaria prevalence was highest at altitudes below 750 and between 750 to 1,250 meters above sea level (24.6% and 26.7%) and lowest in areas with 1,750 meters above sea level (0.2%), (16.0% at 1,250 to 1,750 meters). In rural councils, the malaria prevalence was four times higher than in urban councils (25.5%, 95%CI, 23.1-28.0% versus 6.1%, 95%CI, 4.0-9.1%) (Table 2.3). Exceptions were the urban councils of Geita TC, Handeni TC, Kigoma MC and Masasi TC, with prevalence higher than the national average.

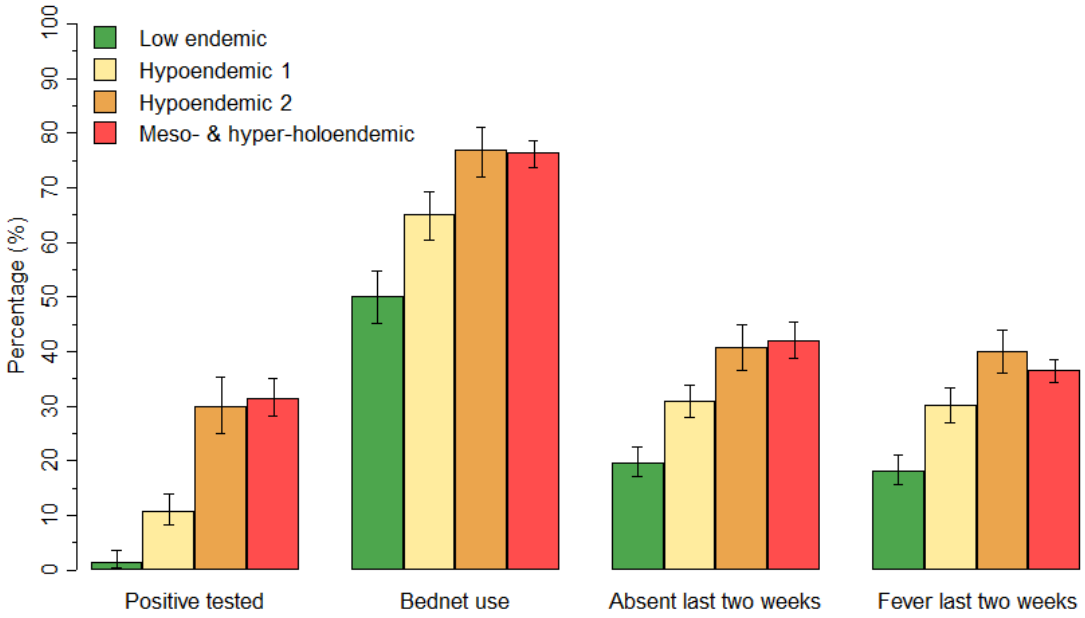

Fig. 2.2: Malaria prevalence, bed net use, school absenteeism, and recent fever of school children compared by transmission zone.
Error bars indicate 95% CI adjusted for school clustering

Fig. 2.3 shows the main indicators among school children by age. Bed-net use was high and close to the mean for all ages until it declined at age fourteen. The percentage of children who reported to be absent from school due to sickness in the two weeks preceding the survey was higher in younger children and decreased after the age of eleven years. The percentage of children who reported to have had a fever, went to a health facility, and were diagnosed with malaria was higher in younger children and started to decline after the age of ten years. With increasing age fewer children were diagnosed with malaria at a health facility in the two weeks before the survey, while the percentage of children tested positive for malaria at the day of the survey showed an increasing trend with age.

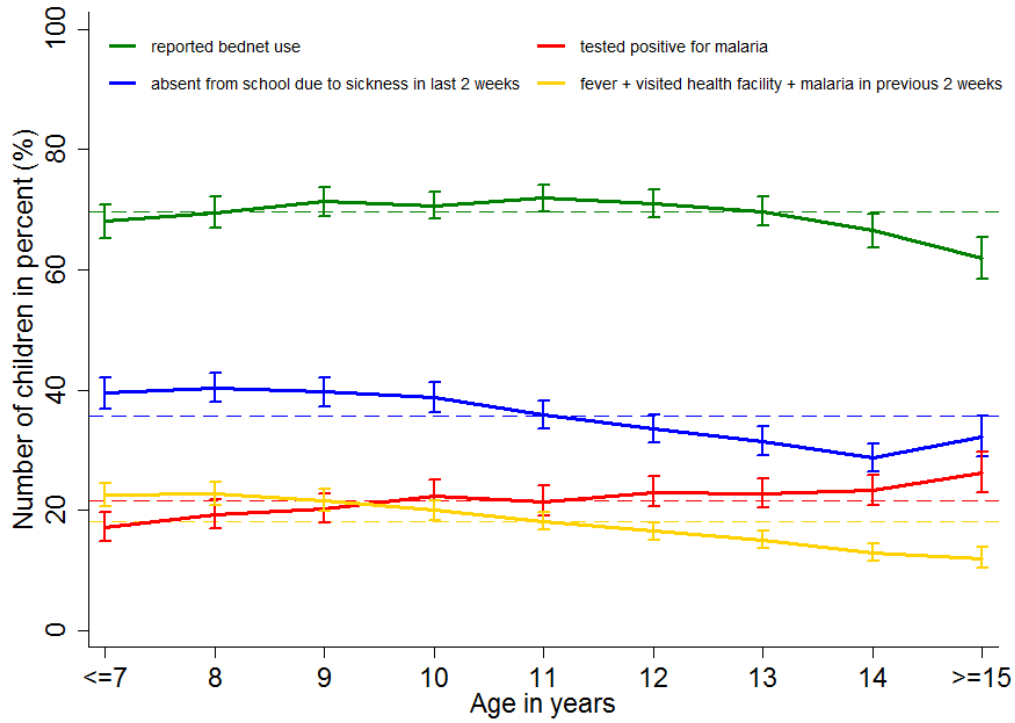

Fig. 2.3: Bed net use, measured malaria prevalence, school absenteeism, and history of sickness in previous 2 weeks, by age.
The error bars present the 95% CI adjusted for school clustering and the dashed line presents the mean for all ages

Malaria infection, bed-net use, and associated risk factors

In the multivariable analysis[12] girls had lower odds of malaria infection than boys (OR: 0.74; 95%CI, 0.69-0.79) and higher odds of sleeping under a bed-net (OR: 1.21; 95%CI, 1.14-1.28). The association between malaria infection and age was not significant, (children 9 to 12 years OR: 1.03; 95%CI, 0.92-1.15, and children older than 12 years OR: 1.05; 95%CI, 0.95-1.17 compared to children 5 to 9 years). The association between age and bed-net use was significant, but the difference in the odds ratio was only marginal (OR: 1.10 versus OR: 1.12). Children who reported to sleep under a bednet were less likely to have malaria (OR: 0.81; 95%CI, 0.74-0.88) (Table 2.4).

[12] If not otherwise stated, the described results refer to the multivariable regression analysis model II. The results from the regression model I can be obtained from Table 2.4.

Table 2.4: Multivariable analysis of the risk factors for malaria and bed net use in primary school children in Tanzania

Outcome/ Covariates	**Univariable**		**Model I (N = 47,157)**		**Model II (N = 30,715)**			
	Malaria		**Malaria**		**Malaria**		**Bednet use**	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-
Gender								
Male vs. female	0.75 (0.71-0.79)	<0.0	0.77 (0.72-0.81)	<0.01	0.74 (0.69-0.79)	<0.01	1.21 (1.14-1.28)	<0.01
Age (years)								
< 9 vs. 10-12	1.06 (0.98-1.15)	0.11	1.05 (0.96-1.14)	0.36	1.03 (0.92-1.15)	0.55	1.1 (1.01-1.20)	0.02
< 9 vs. > 12	1.09 (1.01-1.18)		1.06 (0.98-1.15)		1.05 (0.95-1.17)		1.12 (1.03-1.22)	
Parental education								
Primary vs. no school	1.18 (1.06-1.31)	<0.0	-		1.18 (1.06-1.32)	<0.01	0.69 (0.63-0.76)	<0.01
Primary vs. secondary or	0.74 (0.67-0.82)		-		0.75 (0.67-0.83)		1.48 (1.35-1.61)	
Bednet use								
No vs. yes	0.76 (0.71-0.81)	<0.0	0.76 (0.71-0.82)	<0.01	0.81 (0.74-0.88)	<0.01	-	
Malaria								
Negative vs. positive	-		-		-		0.81 (0.74-0.88)	<0.01
Area								
Rural vs. urban	0.14 (0.05-0.38)	<0.0	0.12 (0.066-0.21)	<0.01	0.15 (0.072-0.29)	<0.01	1.92 (1.25-2.94)	<0.01
Altitude (meter)								
< 750 vs. 750-1250	0.25 (0.12-0.48)	<0.0	0.18 (0.081-0.39)	<0.01	0.26 (0.11-0.62)	0.02	0.43 (0.25-0.74)	0.01
< 750 vs. 1250-1750	0.07 (0.04-0.15)		0.12 (0.045-0.31)		0.25 (0.088-0.72)		0.27 (0.14-0.53)	
< 750 vs. > 1750	0.002 (0.00-0.02)		0.02 (0.003-0.14)		0.07 (0.0093-0.47)		0.12 (0.049-	
Temperature suitability index								
TSI (2er intervals)	3.51 (2.80-4.39)	<0.0	-	<0.01	2.2 (1.56-3.09)	<0.01	1 (0.81-1.24)	0.98
Zone								
Central vs. Eastern	28.15 (7.68-103.20)	<0.0	1.86 (0.60-5.72)	<0.01	2.11 (0.63-7.01)	<0.01	2.13 (0.96-4.71)	<0.01
Central vs. Western	59.21 (15.40-		31.13 (11.6-83.4)		11.21 (3.23-39.0)		2.18 (0.91-5.19)	
Central vs. Southern	72.58 (17.70-		2.79 (0.83-9.33)					
Central vs. Southern Highlands	2.13 (0.53-8.53)		2.64 (0.91-7.67)		0.41 (0.092-1.85)		0.71 (0.33-1.52)	
Central vs. Southwest	10.33 (2.82-37.80)		6.7 (2.52-17.9)		3.19 (1.06-9.60)		1.57 (0.78-3.15)	
Central vs. Northern	1.05 (0.29-3.77)		0.47 (0.17-1.31)		0.43 (0.15-1.19)		0.72 (0.40-1.30)	
Central vs. Lake	69.76 (23.0-211.9)		40.97 (18.0-93.4)		24.43 (10.4-57.1)		3.54 (2.03-6.18)	
Eco-zone (tropical)								
Scrubland vs. Dry forest	4.92 (2.44-9.94)	<0.0	-		2.06 (1.14-3.72)	0.22	0.93 (0.61-1.41)	0.81
Scrubland vs. Moist deci.	4.98 (2.31-10.73)		-		2.36 (1.21-4.60)		0.89 (0.57-1.38)	
Scrubland vs. Mountain	0.56 (0.23-1.34)		-		1.51 (0.68-3.38)		1.01 (0.64-1.60)	
Scrubland vs. Rainforest	7.63 (2.90-20.08)		-		3.01 (1.41-6.40)		1.33 (0.76-2.31)	

Reported education of parents

The reported education of the parents was strongly associated with both malaria infection and bed-net use, with lower odds of malaria infection and higher odds of bednet use in children associated with higher educated parents. For malaria infection, the odds ratio in children with parents with no school education was 1.18 (95%CI, 1.06-1.32), and in children with parents with secondary or higher education 0.75 (95%CI, 0.67-0.83), compared to children with parents with primary education. The odds ratios of bed-net use increased with increasing education of the parents. Children with non-educated parents had an odds ratio of 0.69 (95%CI, 0.63-0.76), with secondary or higher education was 1.48 (95%CI, 1.35-1.61), compared to children reported to have parents with primary education.

Geographical zone and altitude

In comparison to children living in the Central Zone, children living in Northern and Southern Highlands had lower odds of malaria infection, and children living in the other zones had higher odds of malaria infection. For instance, children living in the Lake Zone had 24.4 times higher odds of malaria infection compared to children living in the Central Zone (95%CI, 10.4-57.1). Children living in Southern Highlands and Northern zones, were less likely to sleep under a bed-net (OR: 1.57; 95%CI, 0.78-3.15, and OR: 0.72; 95%CI, 0.40-1.30), while higher odds ratios were found in children living in the Lake Zone (OR: 3.54; 95%CI, 2.03-6.18), compared to children living in the Central Zone. The odds of malaria infection significantly decreased at higher altitudes, with an odds ratio of 0.26 at 750 to 1250 meters (95%CI, 0.11-0.62), an odds ratio of 0.25 at 1250-1750 meters (95%CI, 0.09-0.72) and an odds ratio of 0.07 at altitudes higher than 1750 meters (95%CI, 0.01-0.47), compared to areas below 750 meters. The odds for children to sleep under a bed-net decreased significantly with increasing altitude (OR: 0.43; 95%CI, 0.25-0.74 at 750 to 1250 meters, OR: 0.27; 95%CI, 0.14-0.53 at 1250 to 1750 meters, and OR: 0.12; 95%CI, 0.05-0.31 at 1750 meters and higher, compared to 750 meters and lower).

Council type

Living in urban councils was significantly associated with lower odds of malaria infection, compared to living in rural councils (OR: 0.15, 95%CI, 0.08-0.29). Children living in urban councils were two times more likely to sleep under a bed-net than children living in rural councils (OR: 1.92; 95%CI, 1.25-2.94).

Eco-zone

For the risk of malaria infection as well as bed-net use, it made no significant difference in which eco-zone the children were living, the chance of malaria infection was higher in dry forest (OR: 2.06,

95%CI, 1.42-3.72), moist deciduous forest areas (OR: 2.36, 95%CI, 1.21-4.60), mountain system (OR: 1.51, 95%CI, 0.68-3.38), and three times higher in rainforest areas (OR: 3.01, 95%CI, 1.41-6.40) compared to scrubland areas. Regarding bed-net use, children in tropical rainforest areas were more likely to use a bed-net (OR: 1.33; 95%CI, 0.76-2.31), while children in moist deciduous forest were least likely to use a bed-net (OR: 0.89; 95%CI, 0.57-1.38), in comparison to tropical scrubland areas (Table 2.4).

Geographical distribution of observed malaria prevalence

The malaria prevalence was highest in the Lake Zone (38%, 95%CI, 33.5-42.4), Southern Zone (33%, 95%CI, 26.8-40.5%), as well as Western Zone (30%, 95%CI, 25.3-35%), and lowest in Central (2.8%, 95%CI, 1.4-4.2%), and Northern zones (5.1%, 95%CI, 2.5-7.7%). At council level, the malaria prevalence ranged from zero to 76.4%. In 62 of the 166 councils, the malaria prevalence was below 5%, in 27 between 5% and 10%, in 25 between 10% and 25%, in 51 between 25% and 50%, and in 18 councils above 50%. Highest malaria prevalence was found in Geita, Pwani, Mwanza, and Katavi (>= 40%); lowest prevalence in Arusha, Kilimanjaro, Manyara and Iringa (<1%) (Fig.2.4).

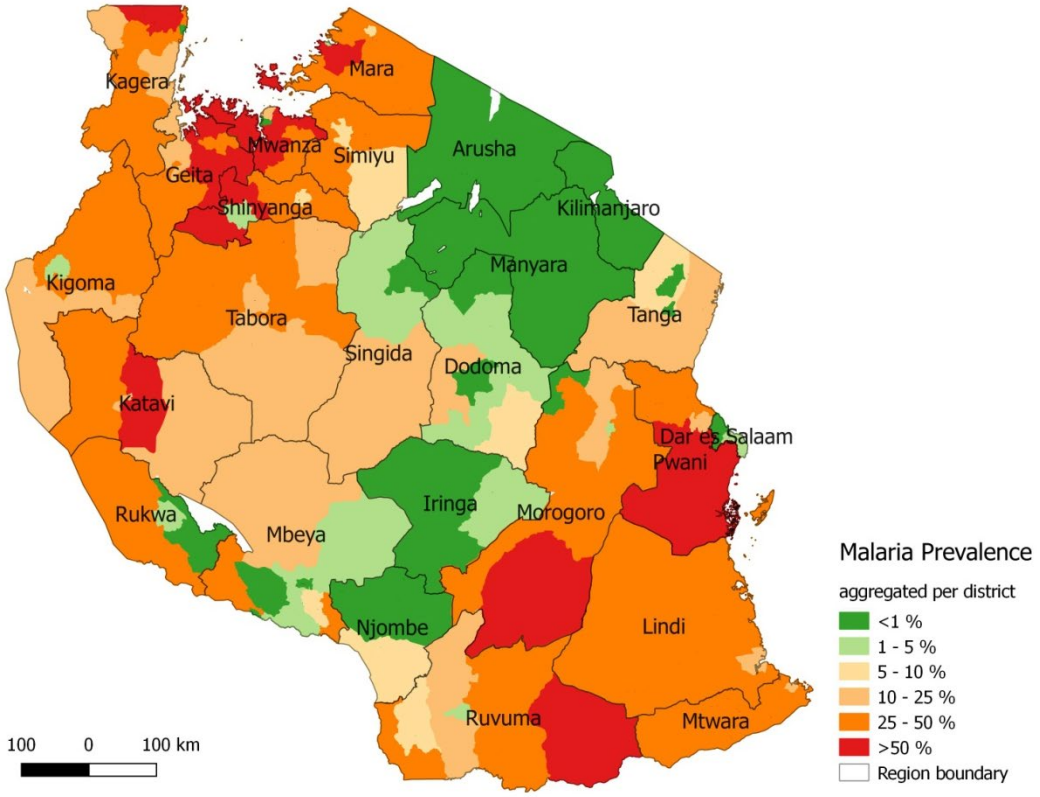

Fig.2.4: Geographical distribution of the observed mean malaria prevalence among school children per council.

The prevalence shown is the unadjusted observed prevalence, measured in different times of the year.

Between schools, the variation of the malaria prevalence was greatest in regions with a high mean prevalence, while the variation was marked by only a few outlying schools in regions with a low mean prevalence (Fig. 2.5). The geographical pattern of the malaria prevalence aggregated by districts and the heterogeneity among prevalence in schools within regions separated by survey phase is shown in the supplement (Fig. SI-5).

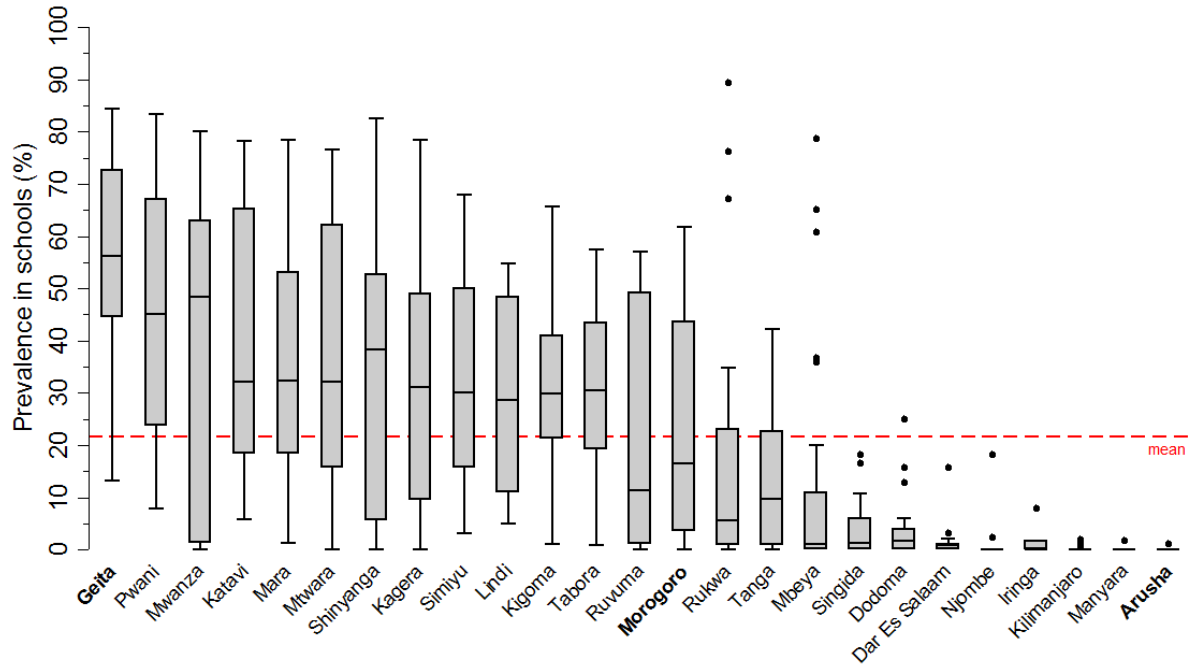

Fig. 2.5: Distribution of malaria prevalence in schools by region.
The regions are sorted by regional mean malaria prevalence. Geita had the highest prevalence (53.7%) and Arusha the lowest prevalence (< 0.1%). The grey box visualizes the interquartile range (25–75%) of the school prevalence within each region. The horizontal line within the grey box is the median of the school prevalence distribution. The spikes mark the lowest and highest quartile. The points present outlying schools with prevalence higher or lower most of the rest of the prevalence (1.5 times the interquartile range above the upper quartile/below the lower quartile)

2.5 Discussion

Almost 50,000 children from 537 public primary schools across all transmission zones in Tanzania were interviewed and tested for malaria infection. The nationwide malaria prevalence was 21.6%, marked by high variation across transmission zones, and administrative borders. The malaria prevalence in Tanzania was low in the “middle corridor”, ranging from Arusha and Kilimanjaro in the north-east to Njombe and Rukwa in the southwest of Tanzania, and high in the northwest (mainly Lake Zone) and in the southeast lowlands of Tanzania. The geographical pattern was similar to the previously described geographical pattern of malaria prevalence and vulnerability (Gosoniu et al., 2012; Hagenlocher and Castro, 2015; NMCP et al., 2013). Compared to the TDHS-MIS 2015-16, the national and regional malaria prevalence among school children, was higher than the prevalence

among children under the age of five years (21.6% versus 14%) (MoHCDGEC et al., 2016). Although the trend across the regions was similar, the especially high prevalence in the Lake Zone was surprising. One possible explanation could be the "El Ninõ Southern Oscillation (ENSO) unstable climate conditions", which had caused "dramatic malaria outbreaks" before (NMCP et al., 2013).

Bed-net ownership and use

The percentage of reported bed net ownership in the children's household was much higher than the reported percentages in the TDHS-MIS (89% vs 65%). However, the trend among regions was similar, with lower percentages in the middle part of Tanzania and higher percentages in regions in the Lake Zone and Southern Zone of Tanzania. The high reported bed net ownership among school children could likely be influenced by recall, reporting or interviewer bias, leading to overestimated values, although it was found that school children give reliable answers about bed net coverage in their community (Ndyomugyenyi and Kroeger, 2007). The percentage of children generally sleeping under a bed net was higher than the percentage for children under the age of 5 years, who slept under a bed net the previous night (69.9 vs 54.5%) (MoHCDGEC et al., 2016). This is different from previous findings that school children were less likely to sleep under a bed net than other age groups (Nankabirwa et al., 2014a). The disparity may be explained by the differences in the terms used, whereas "general" bed net use is much broader than bed net uses the previous night, leading to an overestimation of bed net use among school children. While on the other hand, bed net use among children under the age of five decreased since the previous MIS survey in 2011–2012 (MoHCDGEC et al., 2016; TACAIDS et al., 2013) which is attributed to variations in distribution campaigns. Bed net use was higher in urban than in rural councils, which is similar to the findings in the TDHS-MIS. Moreover, bed net ownership and use were higher among children with higher educated parents, which is concordant with the TDHS-MIS findings (MoHCDGEC et al., 2016; TACAIDS et al., 2013), assuming parental education and socio-economic status of the household to be the same indicator as with findings from a survey in Uganda (Pullan et al., 2010).

Malaria and its risk factors

The small increase in the malaria prevalence by age at all transmission zones, as well as the lack of significant association between age and malaria, might be surprising. Whilst the proportion of children with malaria slightly increased by age in all transmission zones, it would have been expected that younger children have a higher prevalence in high transmission areas and that older children would have a higher prevalence in low transmission zones (Carneiro et al., 2010). A significant association between age and malaria was found in Ghana (Gitonga et al., 2012a) and for a high transmission zone in Kenya (Kepha et al., 2016), whereas no association was found in a school survey

in Ethiopia and Côte d'Ivoire (Ashton et al., 2011). However, the association between malaria and age highly depends on the transmission intensity among many other factors (Carneiro et al., 2010; Doolan et al., 2009). The lack of association in the univariable model could be due to the fact that it was not distinguished between low and high transmission zones.

2.5.2 Limitations

Statistical Analysis

Considering the variety of putative risk factors for malaria and bed-net use, our regression models were not fully adjusted and in future analysis, it would be interesting to include risk factors such as distance to nearest health facility, distance to nearest water body, population density, housing conditions and/or socioeconomic status. Also, the model included TSI and altitude, which were correlated but remained significant in the multivariable log-likelihood ratio test. Children, excluded in model I, adjusted for education and ecozone had significantly higher reported bed-net use and were on average younger than the children included in the model. One possible reason for the higher percentage of bed-net use in the excluded children would be the school net distribution campaign in Southern Tanzania (Lindi, Mtwara and Ruvuma) in 2013 (Roll Back Malaria, n.d.). This would be supported by the reported higher percentages of obtained bed-net through schools in Lindi and Mtwara region in the TDHS-MIS (MoHCDGEC et al., 2016). Further analysis could use stratification by region or transmission zone, geo-spatial analysis or geographically weighted logistic regression, to assess the spatial correlation and its association with risk factors of malaria or bed-net use.

Malaria testing

Malaria rapid diagnostic tests were used to test children for malaria, which may have led to an overestimation in high transmission areas since the mRDT were found to be limited in their ability to distinguish between "active and resolved infections" (Gitonga et al., 2012b). Also, although not further investigated in the present analysis, the number of positive tested children may be biased by the proportion of children who had taken antimalarial treatment recently before the day of testing. In future, this information could be of use for evaluation of the performance of malaria diagnosis and treatment at sub-regional level among school children. In low transmission areas, the use of mRDT's may underestimate the true prevalence, since very low parasitaemia, which lies below the detection level of the rapid tests, were missed (Bousema et al., 2014; Gitonga et al., 2012b). It has been recommended to use molecular detection tools in low transmission areas (Bousema et al., 2014). This would enable school surveys to track down remaining human parasite reservoirs, which further would contribute to an improved evaluation of the progress of malaria elimination in low transmission zones (Hay et al., 2008). Moreover, it would be of interest to evaluate the use of schools

in addition to health facilities for active case detection in the community, in order to identify remaining parasite reservoirs in low transmission zones and to identify hotspots within the catchment area of the schools.

Validity of children interviews

Self-reported values are likely to differ from the truth, depending on interviewer and respondent characteristics, and face-to-face interviews are more likely to lead to answers influenced by social expectations (Bowling, 2005; Coughlin, 1990). Since interviews were not standardised, interviewer bias might have varying influence on the results. However, considering the large scale and sample size, it is less likely that this had an impact on the results at council level.

Representativeness of sample

The data were analysed without adding sampling weights to account for the varying probability of selection at sub-council level. Nevertheless, with respect to representativeness, the study design included a population-weighted selection of council and stratum. In addition, the lack of available data at sub-council level to determine sampling weights would have provided limited additional accuracy to the results. Another limitation of the representativeness would be school absenteeism at day of the survey, drop out, and enrolment rates in schools. According to a national educational survey conducted in 2013, the enrolment rates were lowest in Kigoma, Katavi and Manyara regions (72.9%, 73,6% and 79.8% respectively), and otherwise mostly above 90% (PMO-RALG, 2014). School absenteeism caused by malaria infection could have introduced a “healthy child effect”. This would lead to an underestimation of the malaria prevalence, especially in low transmission areas, where children would be more likely to show symptoms and stay at home when infected (Gitonga et al., 2010b; Stevenson et al., 2013). In Tanzania, there is not much known about how well the school prevalence reflects the community prevalence, although a study in Kenya found that data obtained in schools may reflect the community (Kapesa et al., 2018; Stevenson et al., 2013). Moreover, the use of school survey data for sentinel surveillance at community level could be validated in further research.

Seasonality

The SMPS, as all cross-sectional surveys, captures the malaria infection prevalence only at a certain time point and seasonal variations are inevitable. In the middle corridor, with low malaria prevalence, the survey was conducted during the end of wet season in most of the councils, while around the Lake Zone and in the Southern parts of the country, with high malaria prevalence, the survey was conducted during the beginning of the short rains and dry seasons. The authors

acknowledge that there is no quantifiable way to adequately and entirely adjust for differences in timing of the survey with expected PR, and this is a challenge even in most sophisticated mapping models or malaria prevalence. However, most of school children (5-16 years), including those in this study, carry asymptomatic infections (Walldorf et al., 2015), which are less likely to be treated; thus, it has been documented that school children tend to harbour such infection for long period, over five months (Males et al., 2008; Buchwald et al., 2018), potentially reducing the influence of seasonality on malaria infections in this age group. Future alternative sampling methods might include surveys at the beginning of every term, or more frequently surveys throughout the year, similar to the approach of rolling malaria indicator surveys.

Advantages of SMPS compared to MIS

This SMPS, which is powered with adequate sample size to provide malaria prevalence estimates at council and sub-council levels, provides a complementary approach to malaria surveillance and parasitological monitoring in a short period of time alongside with other national representative surveys, such as Tanzania DHS and MIS. The nationwide school survey is the first survey in Tanzania describing the malaria risk among school children and the geographical trend. This is of importance for malaria control and elimination, as malaria infections in school children are often asymptomatic, contributing to malaria transmission in the community as 'hidden' parasite reservoirs (Walldorf et al., 2015). The SMPS costs US$10 per test performed compared to MIS, which costs an average of US$410 per test performed. However, apart from malaria testing, MIS also captures household information such as coverage indicators including ownership and use of bed net, use of intermittent preventive treatment (Sulfadoxine Pyrimethamine) during pregnancy, and social and behaviour change communication (NBS Tanzania, 2013).

2.6 Conclusion

The observed overall malaria prevalence of 21.6% ranging from <0.01 (Arusha & Manyara) to 53.6% (Geita) among regions indicate similar malaria heterogeneity and patterns as reported in the national surveys (TDHS/MIS). Findings of this survey are useful for updating the malaria epidemiological profile and for stratification of the malaria transmission by region, council and age groups which is essential for guiding resource allocation and prioritising future malaria interventions.

2.7 Declarations

Acknowledgments

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Author contributions

FC, RM, SFR, PC and FM were responsible for study design, survey tools and fieldwork supervision. FC, SFR, PC, FM, PM and MR participated in the data collection. FC, PM, PC and SR supervised data collection. FC provided logistic guidance. FC, RM, and AM provided administrative guidance. MR and PM cleaned the data. MR analysed the data and wrote the draft manuscript. FC, MR, SFR, and PM supervised data entry processes and interpretation of findings. FM, CL, EP, FC, PM, SFR contributed to the interpretation of findings. FM, CL and EP provided technical advice to data analysis. FC, PM, SFR, EP, FM, AM, JJM, RWS and CL provided technical inputs to the manuscript. EP, SFR, FM, RWS and CL provided scientific expertise. All authors read and approved the final manuscript.

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2.8 Supplementary information

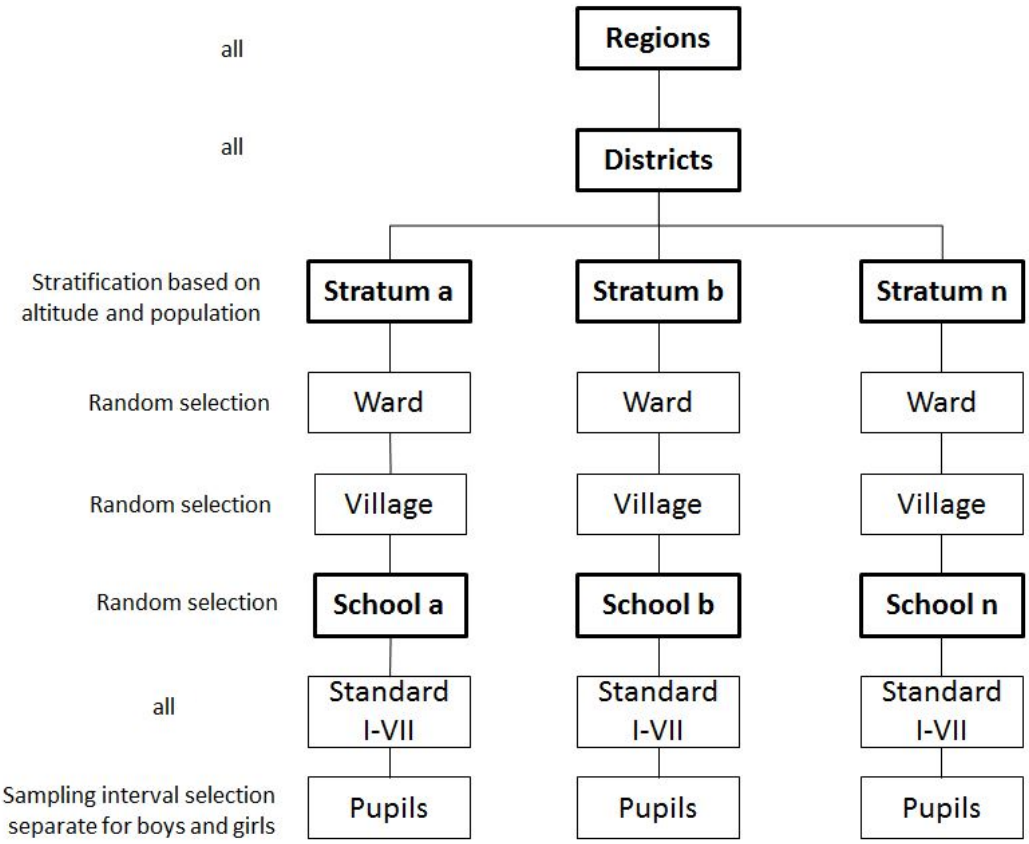

Fig. SI-1: Flow chart of sampling design

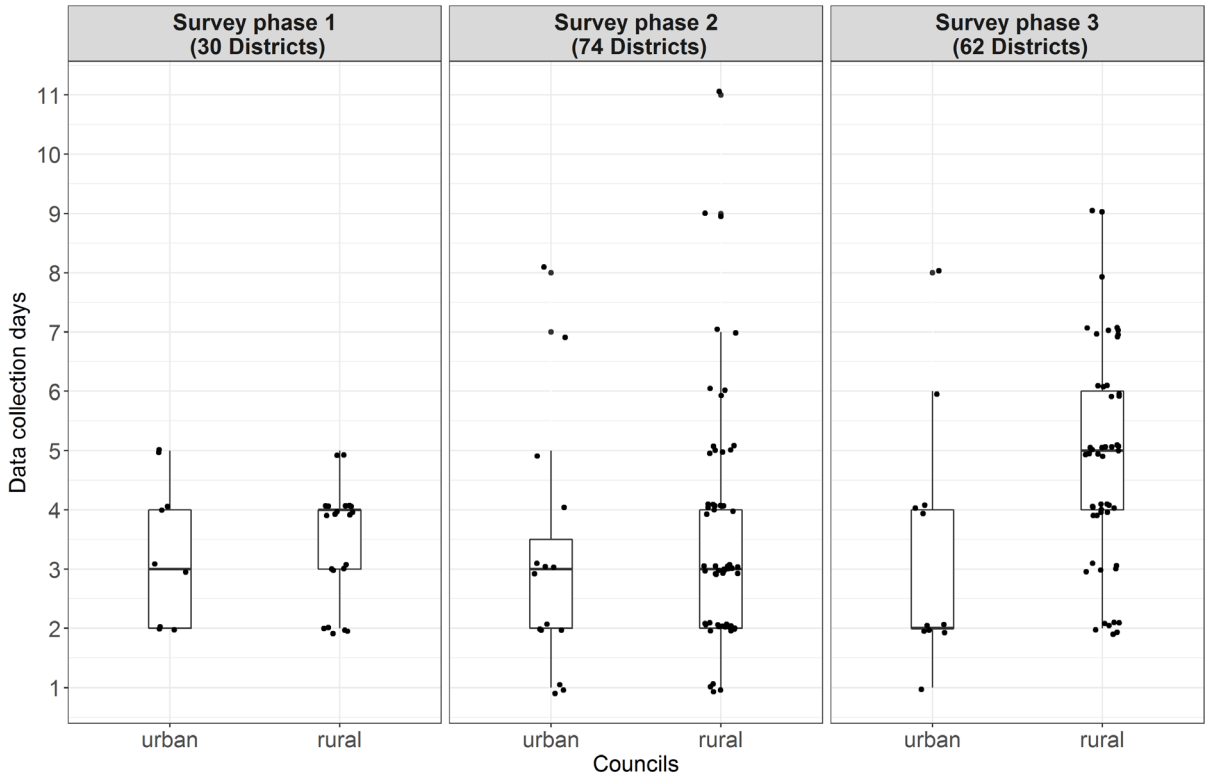

Fig. SI-2: Duration of data collection in days per survey phase and district

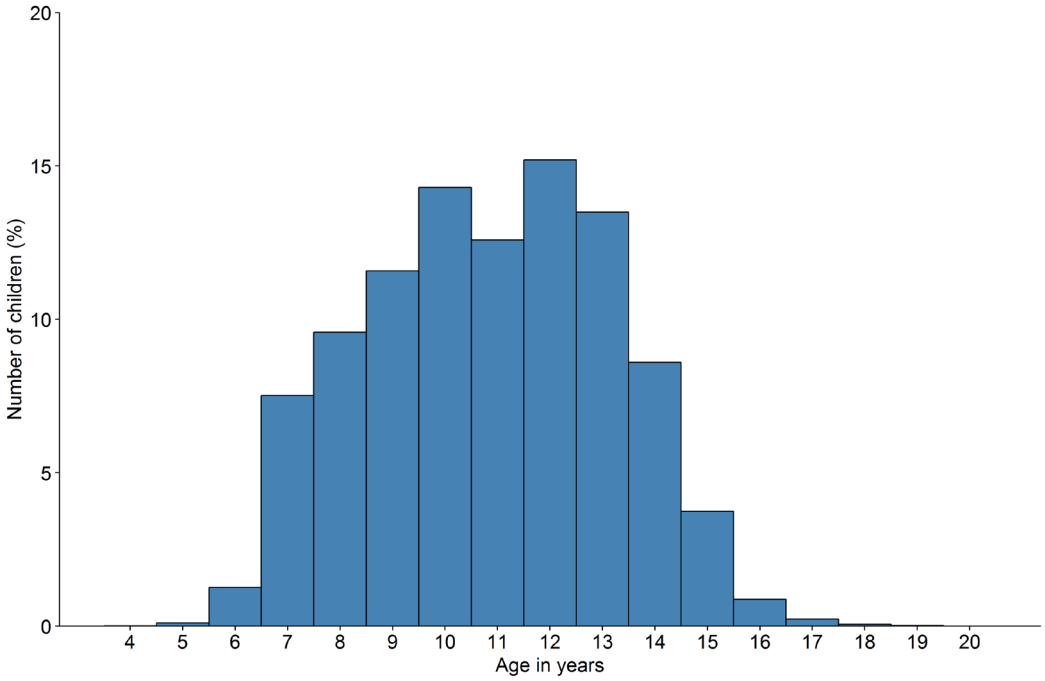

Fig. SI-3: Age histogram

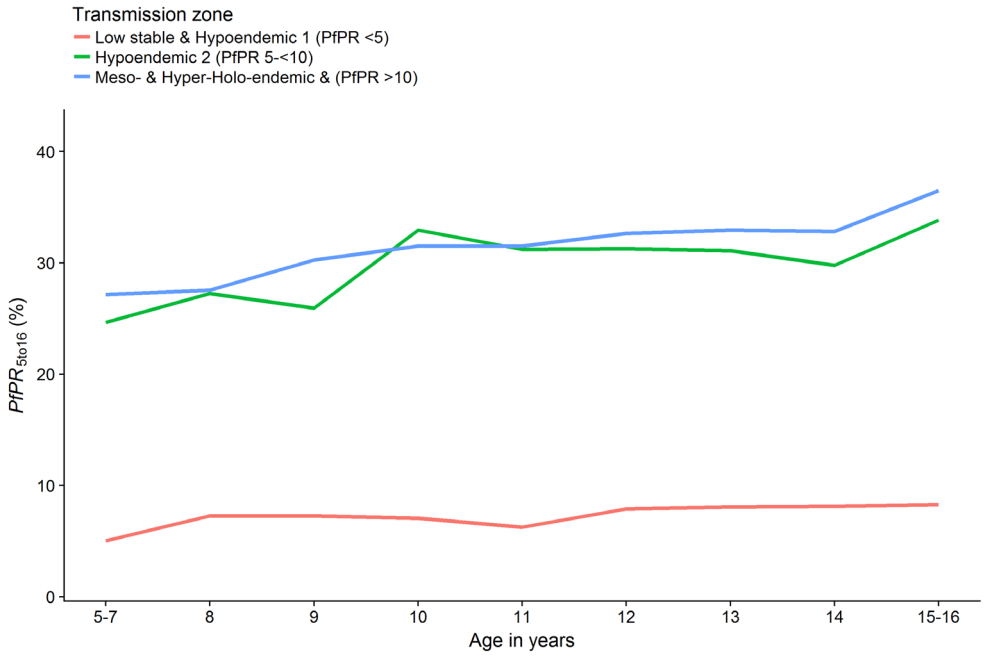

Fig. SI-4: Malaria prevalence per age by transmission zone

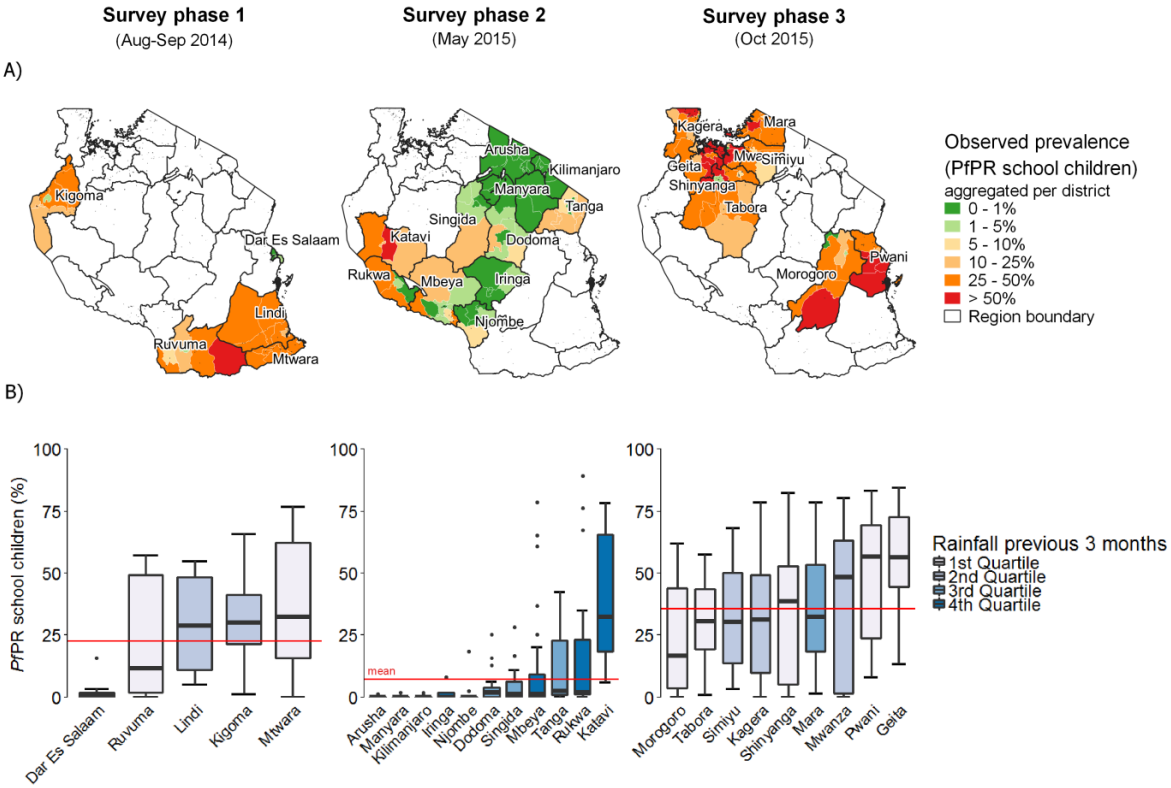

Fig. SI-5: A Map of the observed prevalence among schools aggregated per council, separated by survey phase. B Boxplot showing the distribution of observed prevalence among schools per region sorted by amount of rainfall in the 3 months preceding the survey and separated by survey phase.

3 Simulating the council-specific impact of antimalaria interventions: A tool to support malaria strategic planning in Tanzania

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3.1 Abstract

Introduction: The decision-making process for malaria control and elimination strategies has become more challenging. Interventions need to be targeted at council level to allow for changing malaria epidemiology and an increase in the number of possible interventions. Models of malaria dynamics can support this process by simulating potential impacts of multiple interventions in different settings and determining appropriate packages of interventions for meeting specific expected targets.

Methods: The OpenMalaria model of malaria dynamics was calibrated for all 184 councils in mainland Tanzania using data from malaria indicator surveys, school parasitaemia surveys, entomological surveillance, and vector control deployment data. The simulations were run for different transmission intensities per region and five interventions, currently or potentially included in the National Malaria Strategic Plan, individually and in combination. The simulated prevalences were fitted to council specific prevalences derived from geostatistical models to obtain council specific predictions of the prevalence and number of cases between 2017 and 2020. The predictions were used to evaluate in silico the feasibility of the national target of reaching a prevalence of below 1% by 2020, and to suggest alternative intervention stratifications for the country.

Results: The historical prevalence trend was fitted for each council with an agreement of 87% in 2016 (95%CI: 0.84–0.90) and an agreement of 90% for the historical trend (2003–2016) (95%CI: 0.87–0.93) The current national malaria strategy was expected to reduce the malaria prevalence between 2016 and 2020 on average by 23.8% (95% CI: 19.7%-27.9%) if current case management levels were maintained, and by 52.1% (95% CI: 48.8%-55.3%) if the case management were improved. Insecticide treated nets and case management were the most cost-effective interventions, expected to reduce the prevalence by 25.0% (95% CI: 19.7%-30.2) and to avert 37 million cases between 2017 and 2020. Mass drug administration was included in most councils in the stratification selected for meeting the national target at minimal costs, expected to reduce the prevalence by 77.5% (95%CI: 70.5%-84.5%) and to avert 102 million cases, with almost twice higher costs than those of the current national strategy. In summary, the model suggested that current interventions are not sufficient to reach the national aim of a prevalence of less than 1% by 2020 and a revised strategic plan needs to consider additional, more effective interventions, especially in high transmission areas and that the targets need to be revisited.

Conclusion: The methodology reported here is based on intensive interactions with the NMCP and provides a helpful tool for assessing the feasibility of country specific targets and for determining which intervention stratifications at sub-national level will have most impact. This country-led application could support strategic planning of malaria control in many other malaria endemic countries.

3.2 Introduction

In the last decade, the malaria burden has substantially decreased globally. However, in recent years the decline in malaria burden has stagnated, with 435,000 estimated deaths due to malaria in 2017, compared to 451,000 in 2016, and only marginal improvements in insecticide treated bed net (ITN) coverage since 2015 (WHO, 2018). Mosquito resistance to insecticides used for vector control, parasite resistance against antimalarials, weak case management systems as well as waning immunity and insufficient funding are current challenges for achieving more ambitious malaria control and elimination goals (WHO, 2018, 2015a). Intensified efforts are needed, especially in high burden countries in Sub-Saharan Africa, and national malaria control strategies need to be adapted to local settings and challenges (WHO, 2018, 2015a). At the same time, the decision-making process for selecting appropriate malaria control and elimination strategies has become more challenging because of changing malaria epidemiology. As risk levels have decreased significantly in many areas but not in others, there is now a need to target interventions at sub-national level, in order to prioritise and efficiently allocate resources (Patouillard et al., 2017). At the same time, there is a need to consider new interventions, and more generally, the cost and impact of all interventions as well as their combinations (Nkumama et al., 2017; WHO, 2015a). The combination of available empirical data with mathematical models is a powerful approach for providing and additional layer of information for strategic planning by predicting the impact of interventions given local knowledge (The malERA Consultative Group on Modeling, 2011).

3.2.1 Malaria in Tanzania

Tanzania is one of the highest malaria burden countries in the world (WHO and RBM Partnership to End Malaria, 2019), but transmission intensity (predominantly of *Plasmodium falciparum*) is very heterogeneous, with areas of low prevalence in the middle part of the country, from north-east to south-west, and areas with high prevalence around the Lake Zone and in the South-East. The main malaria vectors are *An. funestus s.l.*, *An. gambiae s.s* and *An. arabiensis* (Kabula et al., 2011). Scale-up of malaria control interventions after 2000 started relatively early in Tanzania, as described in the national epidemiological profile (NMCP et al., 2013). In brief, the Tanzanian National Long-Lasting Insecticide Nets Voucher Scheme (TNVS) was introduced in 2004 (Kramer et al., 2017), artemisinin combination therapy (ACT) became first-line antimalarial therapy in 2006, and indoor residual spraying (IRS) was introduced in 2007 in selected councils in the Lake Zone (NMCP et al., 2013). ITNs were distributed in three mass campaigns in the whole country between 2009 and 2011 (NMCP et al., 2013; Renggli et al., 2013; WHO et al., 2012) and again in 2016, while in 2013 ITN distribution in schools started in selected regions (Mtwara, Ruvuma, Lindi) (Lalji et al., 2016; “The Johns Hopkins Center for Communication Programs’ VectorWorks,” 2014). These campaigns were recently scaled

up to include Geita and Kagera Regions. According to recent Demographic Health and Malaria Indicator Surveys, the national malaria prevalence in children less than five years had been reduced from 18% in 2008 to 10% in 2012, it then increased to 14% in 2016 before decreasing to 5% in 2017 (TACAIDS et al., 2008, 2013; MoHCDGEC et al., 2016, 2017a). The achievement of the past years are challenged by insufficient coverage rates in all interventions, resistance against pyrethroids and by changing vector occurrence and their contribution to transmission (Govella et al., 2013; Kabula et al., 2014; Kisinza et al., 2017; Lwetoijera et al., 2014a). These factors require an intensified approach to control, with higher intensity of implementation, new products to deal with resistance, and finally also new interventions to deal with residual transmission. Since available resources are unlikely to increase, it is now more important than ever to define appropriate mixes of interventions according to the epidemiological situation, as mentioned above (WHO, 2018).

3.2.2 National Malaria Strategic Plan 2015-2020

The National Malaria Strategic Plan 2015-2020 ('current NMSP') envisages ITN distribution in all councils, IRS in some councils around the Lake Zone, strategies to improve case management (CM) everywhere (MoHCDGEC, 2014) and larval source management (LSM), in particular, larviciding in urban areas. The current NMSP aimed at halving the malaria prevalence from 10% in 2012 to 5% in 2015 to less than 1% in 2020 and to achieve at least 85% access to ITNs. In line with World Health Organisation (WHO) recommendations, Tanzania is poised to define ways to maximise the future disease impact, reduce inefficiencies and create, for the first time, a platform to sub-nationally target resources and monitor progress (WHO and RBM Partnership to End Malaria, 2019).

3.2.3 Modelling to support strategic planning

Many malaria models exist, and a detailed description of existing models and classifications has been published elsewhere (Arifin et al., 2016; Mandal et al., 2011; Smith et al., 2018). Mathematical modelling is used to simulate the impact of interventions to explore and assess relationships among malaria transmission parameters (Brady et al., 2017, 2016; Chitnis et al., 2012) or simulate the impact of interventions for defined geographical areas at different spatial resolutions (Gerardin et al., 2017; Hamilton et al., 2017; Nikolov et al., 2016; Scott et al., 2017; Walker et al., 2016; Winskill et al., 2017). Geographical and temporal predictions are useful for decision-making processes at country level or global level (e.g. WHO) (WHO, 2015a, 2014; RBM, 2010). Mathematical models have been applied in various studies at high resolution in all sub-Saharan African (SSA) countries (Galactionova et al., 2017; Goodman et al., 1999; Walker et al., 2016; Winskill et al., 2017), or more local levels, for example in Kenya (Gu et al., 2003; Kramer et al., 2009; Otieno et al., 2016; Stuckey et al., 2014b), Nigeria (Dietz et al., 1974; Hamilton et al., 2017; Scott et al., 2017), South Africa (Okosun et al., 2013;

Silal et al., 2015), Ghana (Kramer et al., 2009; Oduro et al., 2012, 2015), Uganda (Kramer et al., 2009), Mozambique (Lee et al., 2017), and Tanzania (Kramer et al., 2009), and modelling is also being done in Asia (Celhay et al., 2019; Maude et al., 2012; Silal et al., 2019). Previous country specific model predictions were either generalised based on archetypical settings at regional level (admin 1) (Hamilton et al., 2017), at 5x5 km^2 level (Walker et al., 2016), or applied for a specific sub-area of the country (Gerardin et al., 2017; Griffin et al., 2010; Molineaux et al., 1978; Stuckey et al., 2012). But this process has never been applied for a whole country at an administrative level useful for sub-national strategic planning or for resource allocation (e.g. council for financing) and based on country specific data as well as the history of malaria in each setting.

The NMCP in Tanzania is in the process of re-evaluating its national malaria strategic plan, moving towards interventions targeted at council level. Modelling has been used previously as part of the strategic planning for the NMCP (Kramer et al., 2009), but not for all councils. This paper describes the developed modelling calibration and analysis workflow for all 184 councils in Tanzania (NBS Tanzania, 2019). The objectives were: (1) to present how this methodology can simulate the current epidemiology of malaria in each council, (2) to present the council-specific predicted impact of different anti-malaria interventions, (3) to assess *in silico* whether the 2015-2020 NMSP objectives to reduce malaria prevalence below 1% by 2020 is feasible with currently available interventions assuming malaria situation is known until 2016, and (4) to suggest an allocation of interventions per council optimised for cost-effectiveness or one that would reach the 2015-2020 NMSP target at minimised costs.

3.3 Methods

3.3.1 Data collation

An assemblage of malaria prevalence data built up from the Mapping Malaria Risk in Africa (MARA) project database (Snow et al., 1996) and updated in 2013 and 2018, provided a national geo-coded repository of malaria survey data on mainland Tanzania (Snow et al., 2017). These data have been used within a model based geo-statistical framework to provide properties of malaria risk, as measured by the parasite rate in children aged 2-10 years ($Pf PR_{2-10}$), across the entire country for every year between 1990-2017. The geostatistical model did not include covariates, following the same approach as applied in Somalia (Giorgi et al., 2018b), Kenya (Macharia et al., 2018) and Malawi (Chipeta et al., 2019) (methods provided in the S1 File)). The high-resolution prevalence estimates were aggregated at council level for the years 2003 to 2016. Intervention coverage estimates were obtained from malaria indicator surveys (MoHCDGEC et al., 2016; NBS Tanzania and ICF Macro, 2011; TACAIDS et al., 2013), and in addition, average insecticide treated net coverage estimates were obtained from the Malaria Atlas Project (MAP) (Bhatt et al., 2015b; MAP, 2016). MAP uses geo-

spatial modelling to generate high-resolution predictions for different malaria outcomes using household survey data, surveillance, and research data. Information on vector occurrence and sporozoites rates were obtained from national entomological surveillance surveys carried out in 2016, entomological research studies conducted in Tanzania, previous model parameterisations (Chitnis et al., 2012, 2008a; Smith et al., 2006b), as well as expert discussion with local entomologists. Commodities data for net distributions and indoor residual spraying coverage per council per months were also extracted from NMCP records. The ITN distribution data was compared to reported coverage from Malaria Indicator Surveys (MIS) and model-predicted estimates from MAP (S2 File, Fig. S2.4). Population estimates were obtained per council from the national census in 2012 with forward projections based on an assumed constant growth rate per council (National Bureau of Statistics (NBS), Tanzania and Office of Chief Government Statistician (OCGS), Zanzibar, 2013b). The collated data was combined into a comprehensive database including regional and council estimates if available.

3.3.2 Simulation models

The OpenMalaria modelling platform was used to simulate the impact of different intervention strategies at council level. OpenMalaria is a stochastic simulator of malaria epidemiology and control developed at the Swiss Tropical and Public Health Institute (Swiss TPH) (Smith et al., 2008). It includes individual-based models of the dynamics of malaria in humans combined with a population model of malaria vectors. Biological parameter and intervention efficacy were calibrated to field data and not changed. Country specific were obtained from the collated data, including intervention deployment and coverage, case management levels, as well as vector composition, resistance and biting behaviour. Details on OpenMalaria development and parameterisations are available in previous literature (Briët et al., 2013; Chitnis et al., 2012, 2008a; Smith et al., 2008; Stuckey et al., 2013) and online ("SwissTPH/openmalaria," 2016). A comprehensive comparison of the model with other models was published by Smith et al. (Smith et al., 2018).

3.3.3 Simulation design

OpenMalaria version 32, model variant *R0068* (T. Smith et al., 2012) was used. The simulations ran for a population of 10,000 individuals, assuming an importation rate of five infections per 1,000 population per year (Le Menach et al., 2011; Tatem et al., 2009). The parasite detection limit was set to 200 parasites per microliter (p/μL), corresponding to the detection limit for standard microscopy procedures as well as rapid diagnostic tests (WHO, 2011). Both diagnostics were used in generating data underlying the study but the differences between model estimates based on the different diagnostics would be small in relation to the size of effects needed to change the conclusions of this

study. The simulations were run per region and fitted to prevalence per councils after the simulations. The assumption of similar parameters among councils within regions was shown in the available data for seasonality and historical ITN coverage (S2 File, Fig. S2.2, Fig. S2.5), and necessary for parameters for which only sparse data (i.e. vector bionomics), or no representative data was available at council level (i.e. case management). This substantially reduced the number of simulations to run.

Separate model parameterisations were used for each of the 184 councils and 26 regions of Tanzania (Fig 3.1a). Each simulation was initiated at an approximate endemic steady state determined by vector bionomics parameters (Table 3.1). Simulations then ran for a further pre-intervention phase of 46 years at this steady state; a historical intervention phase of 13 years starting in 2003 (simulation time), and a future intervention phase from 2017 to 2020.

During the historical intervention phase, simulated levels of coverage of both vector control and effective case management (Table 3.1) changed annually based on values obtained by averaging the local field data given for each region. A full factorial experiment of simulations was run with ranges of values for varying pre-intervention EIR values in 2003 and effective ITN coverage between 2012 and 2016 per region (Table 3.2). Council-specific simulations were obtained by estimating the levels of those two parameters council by assigning weights based on simulated and geospatial model predicted prevalence as reference for the historical trend 2003 to 2016. The methodology to assign an estimated weight for each simulation in order to fit council-specific data is described in S2 File.

The future intervention phase considered five interventions simulated individually and in combination, leading to a total of 36 scenarios for future strategies for the 2017-2020 period. These, combined with factors representing the historical intervention phase led to a total of 900 simulations per region (Table 3.2). The future interventions considered were: effective treatment coverage (improved case management - CM), long-lasting insecticidal nets (ITNs), wither as mass campaign (ITN MRC), or annual distribution targeting schoolchildren (“ITN continuous”), indoor residual spraying (IRS), larviciding (larval source management - LSM), and mass drug administration (MDA). The interventions were selected based on the core interventions (CM, ITN, and IRS) included in the national malaria strategic plan in Tanzania and potential additional interventions (MDA, LSM). Details on the simulated intervention effectiveness and deployment are provided in the S2 File.

Table 3.1: List of parameters assigned at regional level for 2003-2016

Category	Parameters
Vector bionomics	Mosquito population characterised by biting and resting behaviours Contribution of each mosquito population to transmission Proportion of vectors affected by indoor intervention Seasonality
Case management	Proportion of symptomatic cases effectively treated
Insecticide treated bed nets	Coverage (assumption: coverage = effective usage) Deployment scheme Frequency
Indoor residual spraying	Coverage Timing Frequency

Table 3.2: Description of the full factorial simulation experiment for each region.*)

Region parameters	**Council parameters to fit historical prevalence trend**			**Future intervention scenarios and coverages**			
		ITN coverage* **					
Region	**EIR**	**ITN decay 2011 (k,L)**	**ITN distribution coverage 2012-2016**	**CM**	**ITN**	**IRS**	**Additional**
Arusha	0	0.5, 3.5	0	Region specific	0	0	None
Daressalaam	4	2.1, 6.1	0.2	0.85	MRC (0.8)	0.85	LSM (0.6)
Dodoma	16	5.7, 3.5	0.5		Continuous (0.7)		MDA (0.8)
Geita	54	6, 5.3	0.8				
…. [26 regions]	120 550**	5449, 749	0.95				

*) In total 23940 scenarios were simulated, including, 36 future scenarios for all 26 regions and 25 levels for the council parameters baseline EIR and ITN coverage in 23 regions with 30 levels in the other 3 regions.

**) The regions receiving nets through schools (SNP) had higher prevalence estimates in 2003 and six instead of five pre-intervention EIR levels were simulated.

***) ITN coverage for regions receiving nets through schools between 2012-2016 (Mtwara, Lindi and Ruvuma) and ITN decay for regions that had a mass campaign in 2012 and no large scale ITN distribution until 2015/16.

3.3.4 Fitting and future projections per council

The OpenMalaria simulations resulted in a large database with predicted malaria prevalences and number of cases for the years 2003 to 2020 per region, per future intervention scenario, for five different levels of pre-intervention EIR until intervention scale-up starting from 2003, and for five ITN coverage levels determining the population protected by ITNs between 2012 and 2016 (Table 3.2). The varying ITN coverage levels at council level between the mass campaigns in 2011 and 2016 were obtained by applying a standard model for net attrition to the coverage achieved by the net distribution in 2011 for 23 regions. In the three other regions (Mtwara, Lindi, and Ruvuma) nets were distributed yearly via a school net program, and the annual ITN coverage level was varied between

2012 and 2016 (Lalji et al., 2016). Each council was treated as a weighted average of the 25 simulations per region, based on varying council parameter (5 EIR levels x 5 ITN coverage levels). The weights were estimated using a Bayesian MCMC model that compared the weighted average prevalence with the values extracted from the geostatistical model (S1 File). This provided weighted averages of simulation outcomes per council over time (Fig 3.1c). The simulation outcomes were processed and fitted using R and JAGS software (R Core Team, 2020; Plummer, 2003). The median estimates of the posterior distribution resulting from the model calibration were used for the analysis. Lin's concordance correlation coefficients (CCC) were calculated to assess fitting performance between geospatial model predicted and mathematical predicted prevalence estimates (Lin, 1989).

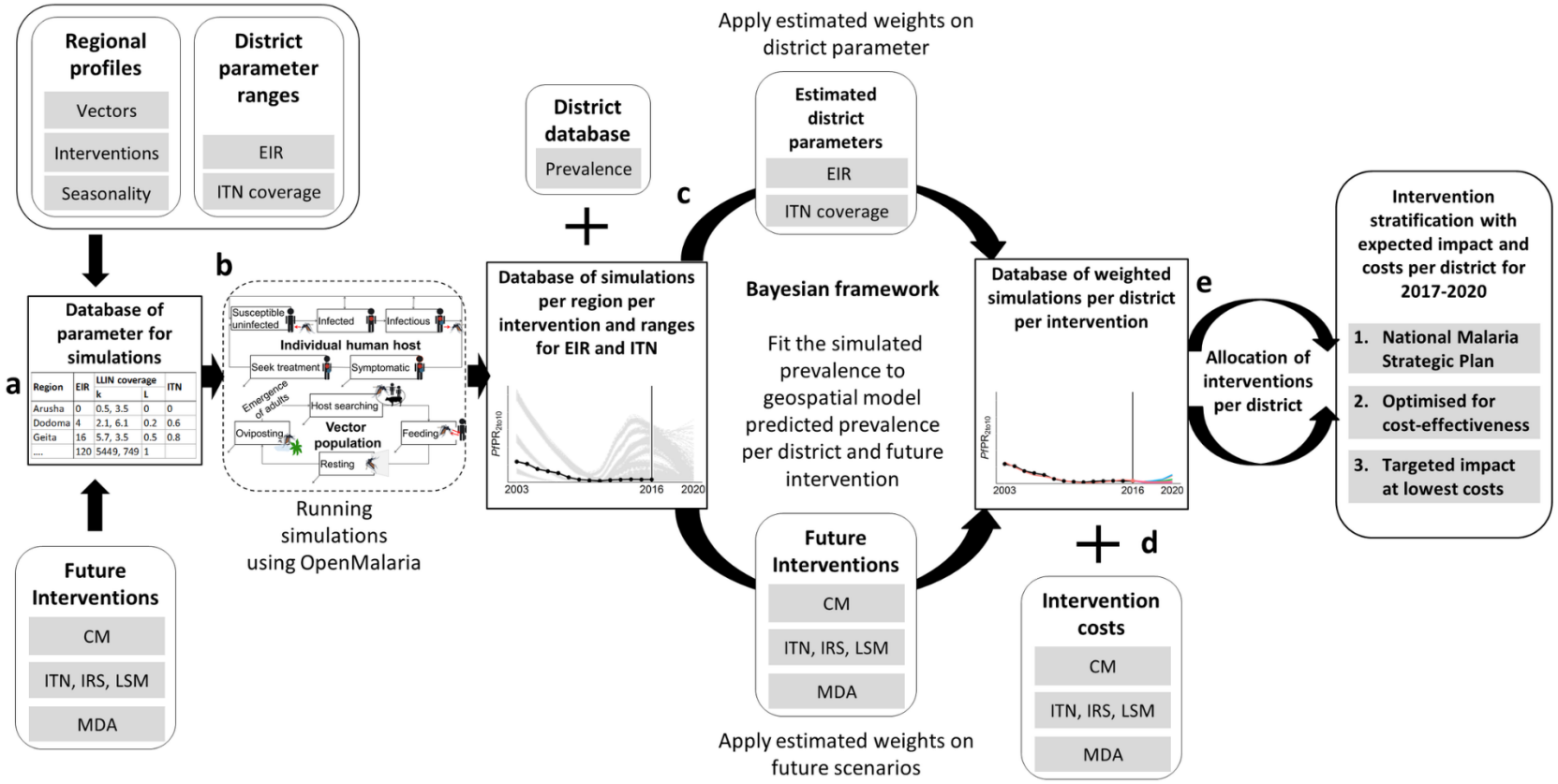

Fig. 3.1: Schematic visualisation of the calibration and analysis methodology.

a) Illustrates model parameterisation, including selection of parameters derived from data per region, base transmission parameter previously determined from field data, and future intervention scenarios. **b**) The regional transmission models were run using OpenMalaria resulting in a database of simulation outcomes. **c**) The simulated prevalence per region, including several levels of pre-intervention EIR and ITN coverage and future intervention scenarios, were fitted to the to geospatial model-predicted prevalence per council, using a Bayesian framework. In this process weights were generated for each simulated historical scenario and each council and applied on the future intervention scenarios, resulting in a reduced database of weighted simulations per council per intervention. **d**) Intervention unit costs from literature were attached to the database, and the costs for every single intervention per council were calculated. **e**) Allocation of intervention combinations per council according to the current NMSP or by either optimising for cost-effectiveness or by conditioning the simulated prevalence to meet the national target (*Pf*PR <1% by 2020).

3.3.5 Approximation of costs

For each intervention, assumptions on unit costs in USD per population were extracted from the literature and agreed upon based on local expert knowledge on intervention deployments in Tanzania. Total costs were calculated for the years 2017 to 2020, for each intervention and their combinations for the total population per council (Fig 3.1d). A full description of the process is provided in the supplement (S3 File).

3.3.6 Intervention stratification

The council-specific simulation database included predicted yearly prevalence and cases and was combined with the cost for each intervention in order to explore impact and cost of three alternative intervention allocations per council (referred to as 'strategies') (Fig 3.1e).

Strategy 1: Allocation of interventions according to the NMSP 2015-2020

The current NMSP 2015-2020 described intervention packages at the regional level. The whole country is expected to receive ITNs distributed through different channels and combined with IRS in selected councils in the Lake Zone. Additionally, LSM is expected to be implemented in urban councils (city councils and municipalities). The current NMSP was simulated with considering vector control only or in combination with improved case management in all councils.

Strategy 2: Allocation of interventions optimised for cost-effectiveness

The interventions were optimised for cost-effectiveness at council level, by iteratively minimising the incremental cost-effectiveness ratio (ICER) among 'admissible' interventions (interventions that remain after removing interventions that are more expensive but less effective than the least costly intervention (Laska et al., 1999)). Impact was defined by the cumulative cases averted compared to the counterfactual scenario, and costs defined as the total costs per capita from 2017 to 2020 per council. The ICER calculation followed the approach used by Otieno *et al*. (Otieno et al., 2016) based on Okosun *et al.* (Okosun et al., 2011).

Strategy 3: Allocation of interventions according to the selection of cost-minimised interventions that lead to the NSMP target (National prevalence below 1% in 2020)

The second algorithm for intervention allocation per council based on simulated impact and costs consisted of selecting the intervention scenario with the minimum cost and expected prevalence of less than 1% per council by 2020.

3.3.7 Presentation of results

The prevalence was categorised into six groups (*Pf*PR_{2-10} <1%, 1-5%, 5-10%, 10-25%, 25-50% and >50%) according to the adapted traditional endemicity classes as described in the epidemiological profile of Tanzania (NMCP et al., 2013). The simulated total number of cases included both, the total number of uncomplicated and severe cases, with the incidence calculated as total cases per 1000 population. Two scenarios were defined as a comparator for the calculation of relative reductions per future intervention scenario: 1) the situation in 2016 before deployment of future interventions, referred to as "baseline", and 2) the future scenario with discontinuation of vector control referred to as "counterfactual". The relative prevalence reductions were calculated by comparing each future intervention to the baseline scenario, and the number of cases averted was calculated in comparison to the counterfactual. At national level, an un-weighted mean of the council estimates was calculated with confidence intervals based on the variation between councils. Maps were generated using QGIS (QGIS Development Team, 2016) and R (R Core Team, 2020).

3.4 Results

3.4.1 Historical trend of malaria – geostatistical model predictions

The national prediction from the geostatistical model for malaria prevalence in 2003 was 29.9%, ranging from 0.96% to 71.5% among councils and in 2016 15.7%, ranging from 0.006% to 52.9% among councils. The average decline in prevalence between those years was 56.6%, ranging from -51.6% to 99.4% among councils.

3.4.2 Fitting performance

The typical geographical pattern of malaria prevalence in Tanzania, with the highest prevalence around the Lake Zone as well as in the South-Eastern Zone and low prevalence in the "middle corridor", was well reproduced with OpenMalaria simulations. The concordance correlation coefficient for the whole historical trend between geostatistical model predictions and OpenMalaria predictions was on average 0.83 (95%CI: 0.82, 0.84), 0.91 (95%CI: 0.89, 0.93) for the year 2003, and 0.93 (95%CI: 0.91, 0.94) for the year 2016. The mean deviance between observed and simulated prevalence in 2003 was 5.8%, and in 2016–0. 8% (Fig 2). In the baseline year 2016, the fitting was best in twelve regions (CCC > 0.80), moderate in nine regions (CCC > = 0.6), poor in four regions (CCC < 0.6), and very poor in Geita region (CCC < 0) (S4 File). Very low or very high prevalence was not fitting the historical trends as well.

3.4.3 Council specific parameter estimates

The estimated mean pre-intervention EIR (2003) was 94 infectious bites per person per annum (ibpa) (95%CI: 76–111 ibpa), ranging from 0.7, in Siha Council (Kilimanjaro Region) to 507 ibpa in Tandahimba (Mtwara Region) (IQR: 26–96 ibpa). The estimated pre-intervention EIRs are shown in the S4 File. The geographical pattern of the estimated pre-intervention EIR corresponds to the frequently described pattern of malaria in Tanzania, with low malaria transmission in the dry and hot 'middle corridor' and higher transmission around the Lake Zone and the South-Eastern areas. The estimated mean ITN coverage between 2012 and 2016 for councils in the school net program was 56% (95%CI: 49% - 65%), ranging from 16% in Namtumbo (Ruvuma Region) to 79% in Nachingwea (Lindi Region) (IQR: 41% - 73%).

3.4.4 Historical trend of malaria – mathematical model predictions

The simulated national prevalence was 30.8% (95%CI: 28.6% - 33.1%) in 2003 and 14.7% (95%CI: 13.1% - 16.2%) in 2016, dropping by 59.9% (95%CI: 57.1% - 62.8%). In 2003, the simulated national incidence was 752 cases per 1000 population (95%CI: 727 - 779) with a reduction of 25.6% (95%CI: 20.3% - 30.1%) between 2003 and 2016.

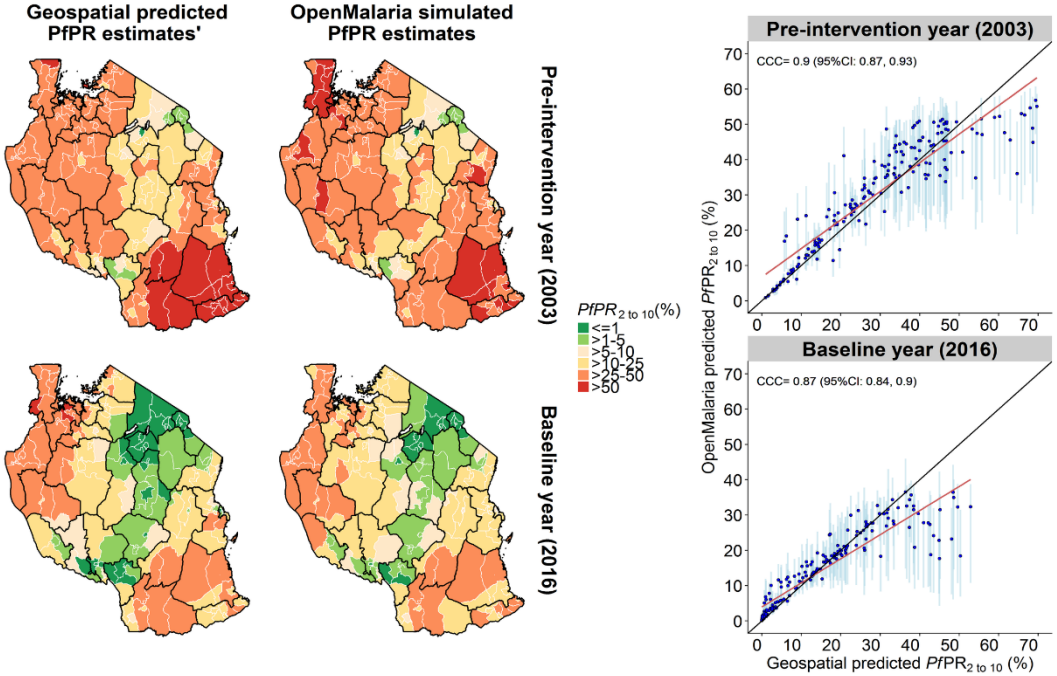

Fig. 3.2: Fitting performance for simulated prevalence per council.
The figure shows the predicted prevalence (median) and the geo-statistical model prevalence (mean). The pre-intervention (2003) and baseline year (2016) are the most relevant historical time points since the prevalence before the deployment of interventions determines the level of possible rebound, and the prevalence in the baseline year is used as a comparator for assessing the relative impact of future interventions. The scatter plots (right) shows the respective prevalence estimates (points), with the regression line (blue line), and perfect correspondence line (black line). CCC = Lin's concordance correlation coefficients (Lin, 1989).

3.4.5 Predicted impact in 2020 of single interventions and combinations

Without additional interventions (counterfactual scenario), the national prevalence was expected to increase by 65.7% (95%CI: 58.0% - 73.6%) in 2020 compared to the baseline in 2016. A scenario with an improvement in case management, assuming 85% of the cases would be effectively treated, and discontinued vector control predicted an increase in prevalence by 12.0% (95%CI: 7.3% - 16.7%, median = 4.5%), but the increase was expected to be lower than the increase of the counterfactual scenario (31.0% increase, 95%CI: 29.3% - 32.7%). The simulated ITN mass campaign in 2019, with 80% coverage, was simulated with a national prevalence reduction of 25.0% (95%CI: 21.1% - 28.8%). ITN distributed annually, maintaining 70% coverage, were expected to lead to a prevalence reduction of 16.7% (95%CI: 13.6% - 19.8%). When IRS was implemented, the simulated national prevalence was roughly maintained (95%CI: -3.9 – 3.6). The single deployment of larviciding at 60% for three months during the dry season was on average not expected to decrease the prevalence in the absence of other interventions (60.0% increase, 95%CI: 51.8% - 67.9%). MDA was expected to result in the highest impact with a prevalence reduction of 79.0% (95%CI: 75.1%-83.0%). The combination of improved case management and a ITN mass campaign resulted in an expected prevalence reduction of 53.4% (95%CI: 50.4% - 56.5%), additional IRS deployment led to a further reduction of 65.5% (95%CI: 63.0% - 68.1%), while additional MDA deployment let to an even further reduction of 99.3% (95%CI: 99.1%-99.5%). Overall, the higher the prevalence reduction, the higher the number of cases averted, whereas the costs were highest for interventions including MDA, IRS and LSM (blanket intervention for four years, not considering treatment savings) (Fig. 3.3).

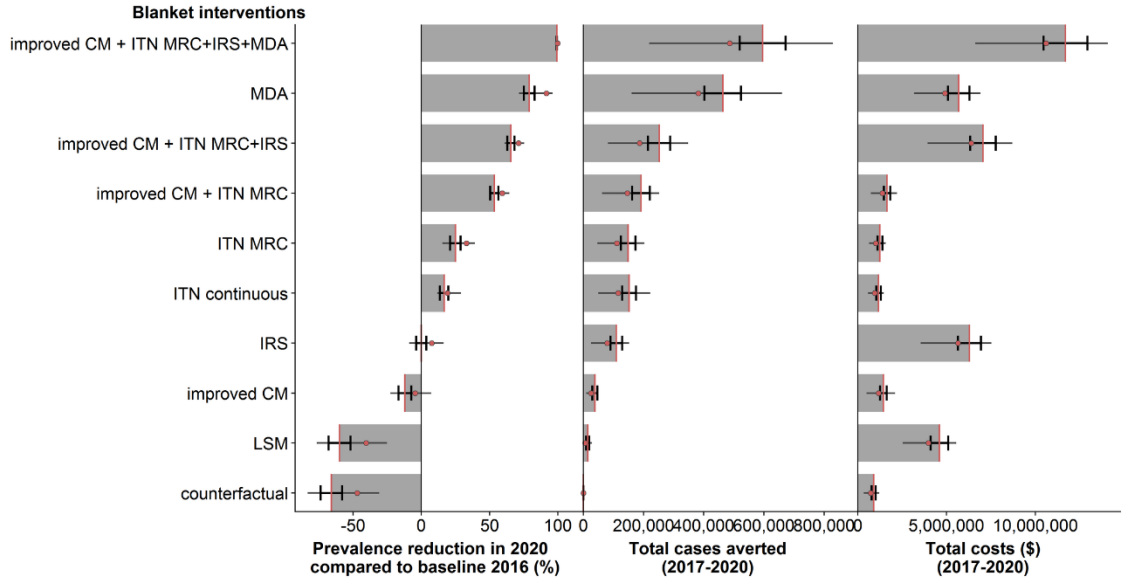

Fig. 3.3: Simulated prevalence, cases averted and costs for single and incremental intervention scenarios from 2017-2020.

The interventions scenarios shown visualise blanket distributions, with the same intervention scenario for all councils. The vertical lines indicate the confidence interval around the mean (red line), the red point the median, and the horizontal lines the 50% interquartile range between councils.

The simulated outcomes showed high heterogeneity between councils, as shown for the prevalence per single intervention in Fig. 3.4.

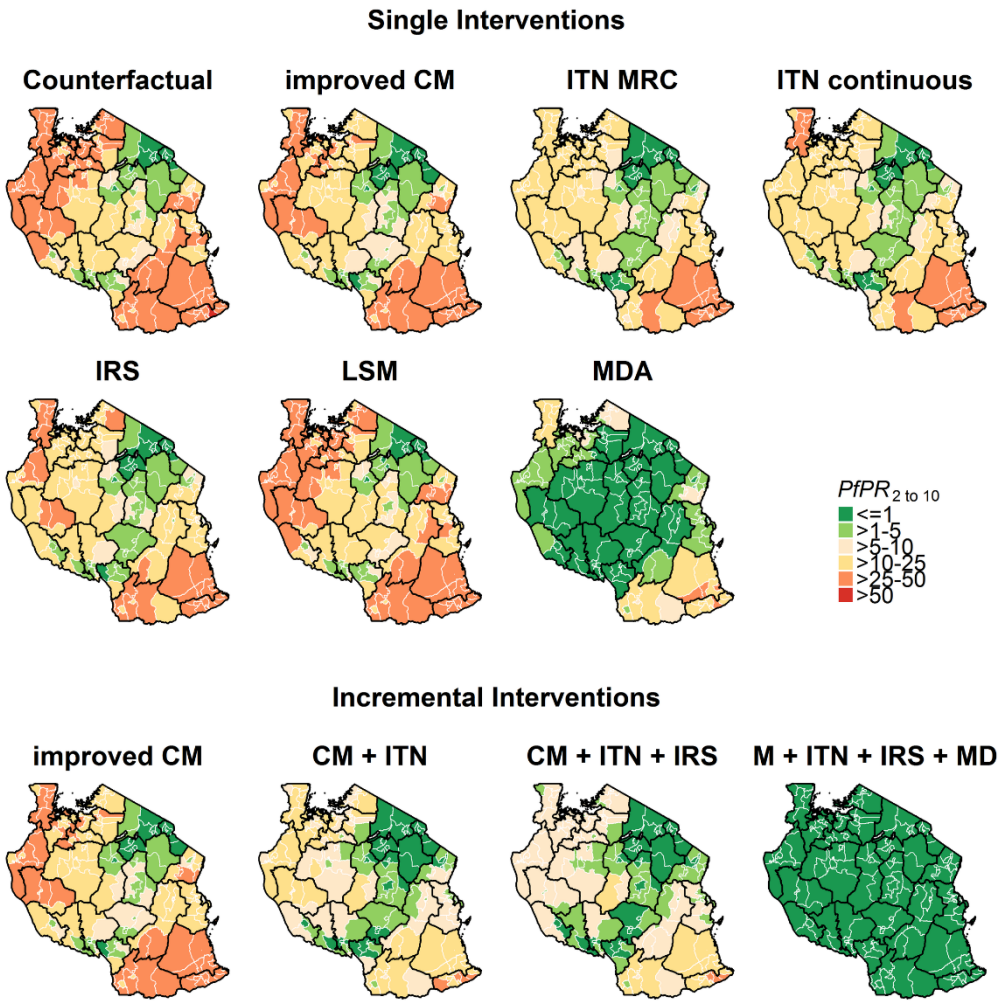

Fig. 3.4: Simulated prevalence in 2020 for single and incremental intervention scenarios between 2017 and 2020.

Each map shows the 2020 council-specific predicted prevalence for the age-group 2-10 years, resulting from the scale-up of every single intervention, or selected combinations of interventions. The intervention scenarios shown visualise blanket distributions, with the same intervention scenario for all councils.

Strategy 1: Allocation of interventions according to the NMSP 2015-2020

The NMSP envisaged ITN mass campaigns in 79 councils, ITN continuous distribution through schools in 105 councils, IRS in 24 councils and LSM in 25 councils (Fig 3.4). The simulated malaria prevalence in 2020 was 7.4% (95%CI: 6.4% - 8.4%), with improved case management levels, and 11.2% (95%CI: 9.9% - 12.6%) with maintained case management levels (Fig 3.5). This corresponds to a reduction of

23.8% (95% CI: 19.7%-27.9%) between 2016 and 2020 if current case management levels were maintained, and of 52.1% (95% CI: 48.8%-55.3%) if the case management were improved. The strategy was further expected to avert around 39-46 million cases between 2017 and 2020 while saving around $42-101 millions in treatment costs, with the ranges depending on improvement in case management. The total costs for this strategy (ITNs, treatments, IRS and LSM) were estimated at around $536-606 Mio for 2017-2020 ($16.7-15.2 per case averted, $412 Mio excluding treatment costs). While this impact is impressive, these results suggest that the current plan would not be sufficient to achieve the stated target to obtain a national prevalence of less than 1% by 2020.

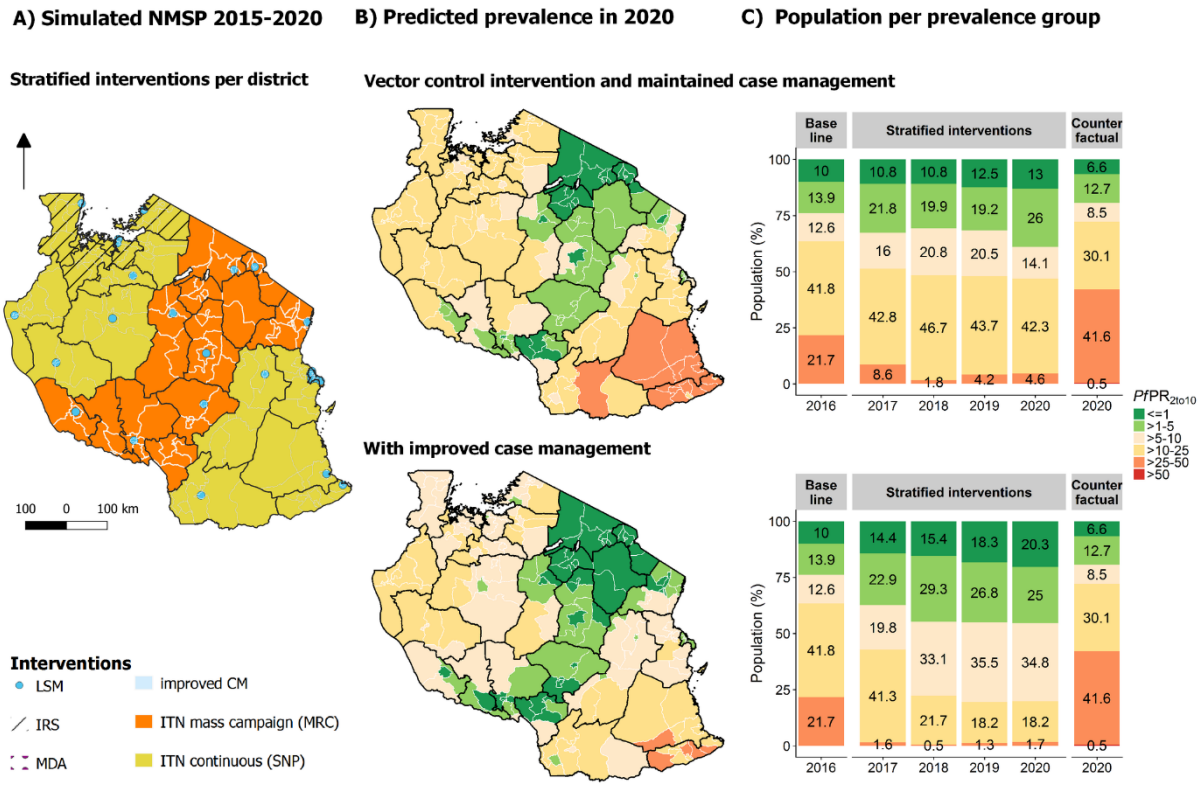

Fig. 3.5: Strategy based on the NMSP 2015-2020 and simulated impact (Strategy 1).
(A) Allocation of interventions per council, showing vector control interventions only. (B) Predicted prevalence per council in 2020 shown in the map and number of councils per simulated endemic group by year for 2017-2020 shown in the bar charts.

Strategy 2: Allocation of interventions optimised for cost-effectiveness

In most councils, the distribution of ITNs (mainly continuous), which is assumed to lead to a high level of use, would be the most cost-effective intervention. The intervention allocation optimised for cost-effectiveness entailed distribution of ITNs in all but very few councils (149 councils), together with an increase in case management coverage (50 councils) and a mass drug campaign (13 councils). The optimal intervention allocation per councils, its expected impact on prevalence and resulting

percentage of population living per endemic category is shown in Fig 6. It was simulated that the national malaria prevalence in 2020 would be 10.5% (95%CI: 9.1% - 11.9%), corresponding to a prevalence reduction of 25.0% (95% CI: 19.7%-30.2). This strategy was further predicted to avert around 37 million cases between 2017 and 2020 while saving around $54 million in treatment costs. The total costs for this strategy were estimated at around $254 Mio ($6.90 per case averted), and $131 million excluding treatment costs for 2017-2020. MDA was selected in 23 councils (12.5%), yet contributed 50% of the estimated costs.

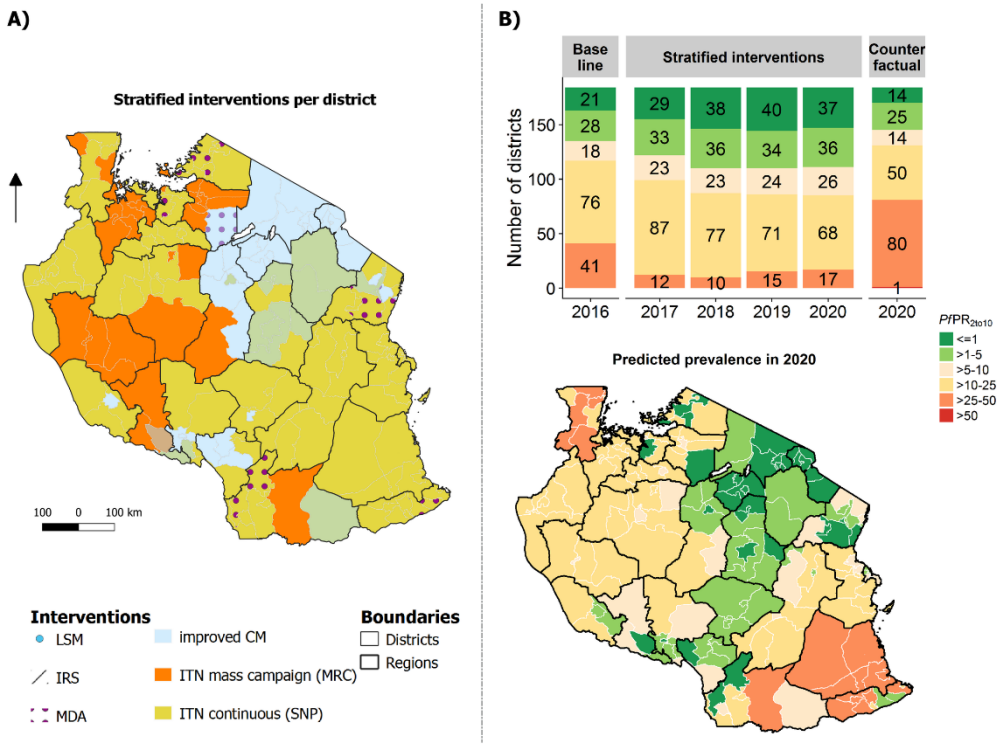

Fig. 3.6: Strategy optimised for cost-effectiveness and simulated impact (Strategy 2).
(A) Allocation of interventions per council. (B) Predicted prevalence per council in 2020 shown in the map and number of councils per simulated endemic group for 2017-2020 shown in the bar chart.

Strategy 3: Allocation of interventions according to the selection of cost-minimised interventions that lead to the NSMP target

The intervention stratification and intervention allocation that maximize impact on prevalence for a minimum cost are shown in Fig 7. The model predicted that the overall malaria prevalence in 2020 would be 0.43% (95%CI: 0.38% - 0.47%), corresponding to a prevalence reduction of 77.5% (95%CI: 70.5%-84.5%) between 2016 and 2020. This strategy was predicted to avert 102 million cases between 2017 and 2020 while saving around $153 million in treatment costs. The total costs for this strategy were estimated at around $891 million for 2017-2020 ($8.70 per case averted, $845 million excluding treatment costs).

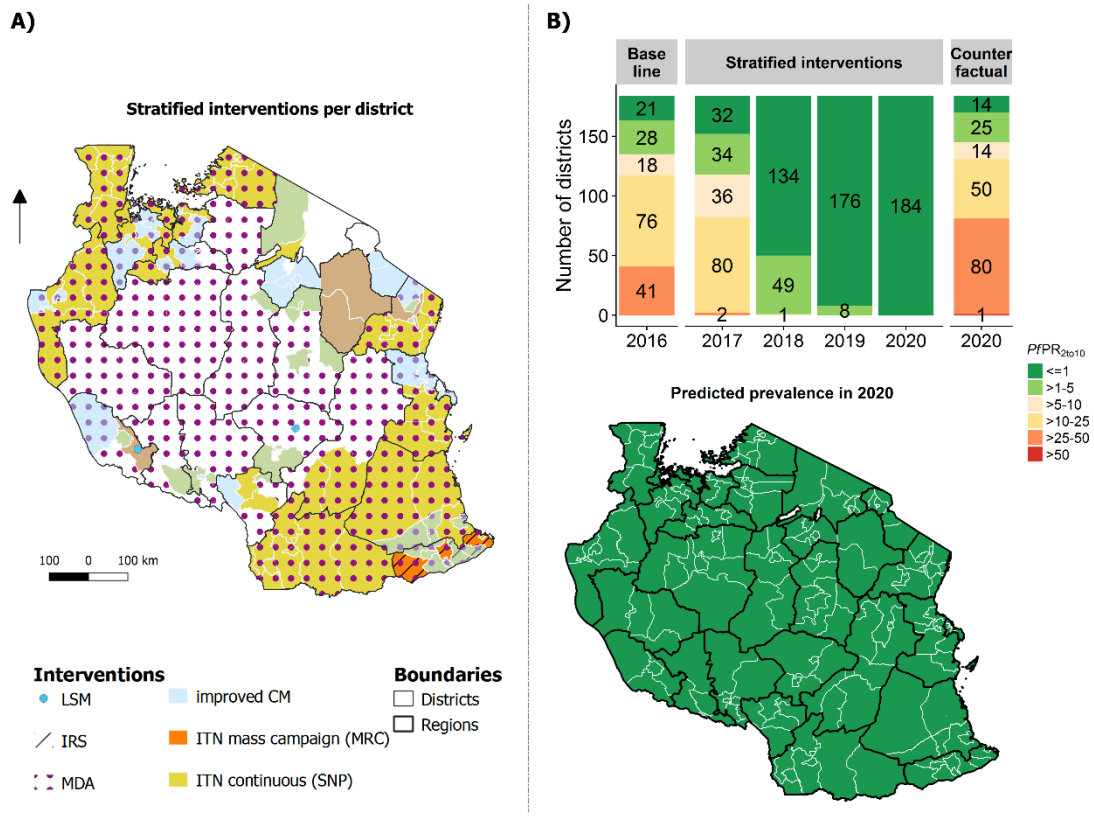

Fig. 3.7: Strategy according to the selection of cost-minimized interventions that lead to the NSMP target (Strategy 3).
(A) Allocation of interventions per council. (B) Predicted prevalence per council in 2020 shown in the map and number of councils per simulated endemic group for 2017-2020 shown in the bar chart.

3.4.6 Comparison of intervention allocations per council

At national level, the predicted impact over time was very similar between the simulated NMSP and the most cost-effective strategy, whereas the NMSP with an additional increase in case management led to a substantially lower prevalence – without reaching the national targeted prevalence of less than 1% (Fig 3.8), and timelines per region and impact cases are shown in S4 File, Fig. S4.6-8. For 44 councils the interventions as allocated in the simulated NMSP were also the most cost-effective interventions and for one council the intervention achieving the national target at lowest costs. The intervention combinations achieving the national target at lowest costs were also the most cost-effective strategy for 22 councils.

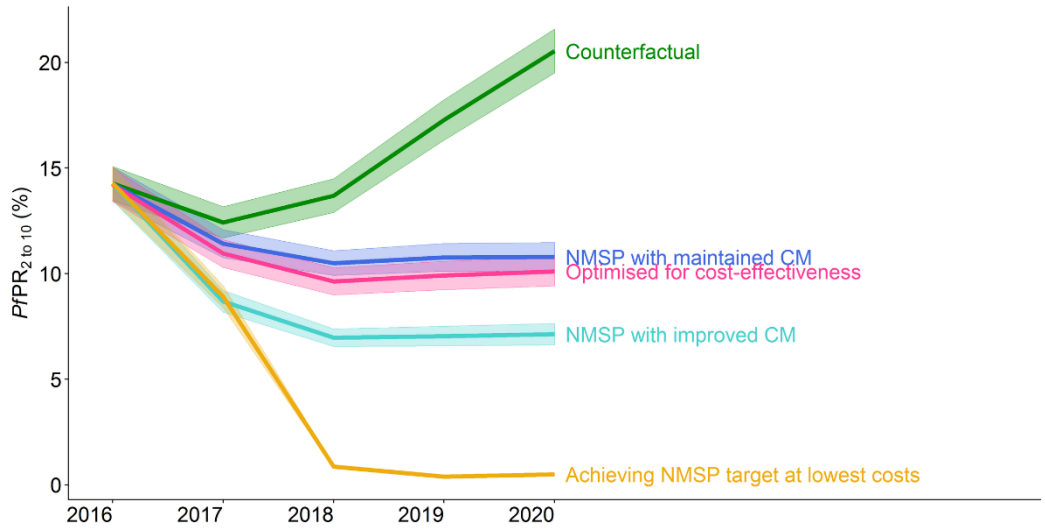

Fig. 3.8: Predicted prevalence per strategy over time.
The solid line shows the aggregated mean and the shaded area the 95% confidence interval based on heterogeneity among councils. The NMSP with maintained case management as well as the NMSP with improved case management refers to strategy 1, the most cost-effective intervention package to strategy 2, and the intervention package achieving the NMSP target to strategy 3. The counterfactual shows the simulated scenario with maintained case management levels and the discontinuation of vector control interventions.

3.5 Discussion

Tanzania was formerly one of the world's most highly endemic countries for *P. falciparum.* The NMCP has made a concerted effort to assemble all available data on malaria prevalance, vector compositions and resistance and intervention coverage at units of delivery deemed essential for a pragmatic, decentralised stratified future repsonse. Tanzania has demonstrated an impressive reduction in incidence and prevalence with scale-up of interventions over the last decade. Given the sub-national heterogenity of the malaria ecology in 2016, any future control demands a more nuanced selection of interventions at council levels. Exploring future projected impacts demands mathematical modelling to take into account all these factors, since the health impacts are not directly proportional to coverage and can take several years to emerge.

Simulation modelling was used to predict the impact of specific malaria interventions in 184 councils in mainland Tanzania. Council level transmission potential and the impact of past interventions were estimated by fitting the simulated prevalence to high-resolution prevalence estimates at council level. Core interventions included in the current NMSP supplemented or not by MDA were simulated when deployed alone or in combination. The impact of the intervention allocation according to the current NMSP was compared between vector control interventions alone or in combination with an increase of case management coverage. Three main strategies of interventions assigned at council level defined packages of interventions either chosen to minimise the incremental cost-effectiveness

ratio or to meet the national target of reducing prevalence to less than 1% nationally by 2020 at minimal cost.

The requirements of the NMSP constrained the geographical units and timeframe for the analysis, the list of interventions, the target coverages (Table 3.2) and the measures that were optimised subject to these constraints. Administrative councils represent the operational units of the Tanzanian NMCP, and the geographical heterogeneities mean that the most appropriate intervention strategies are different by council, so a stratification and intervention allocation at this level is essential. In contrast, sub-council spatial heterogeneity was not considered, even though there is important smaller-area variation in intervention usage, components of vectorial capacity (Beier et al., 1999; Drakeley et al., 2003) and malaria endemicity (Baidjoe et al., 2016; Cohen et al., 2017). While the EIR can be estimated based on only a few key parameters (Killeen et al., 2000; Penny et al., 2015), the available mosquito bionomic data are inadequate for detailed parameterisations at council level or lower, and the workflow did not make use of the uncertainty or sub-council variation in the predictions from the geostatistical models.

The transmission potential and the starting point for the future interventions are important determinants of impact, and a very good fit to the prevalence for 2003 and 2016 was generally obtained by representing each council as a weighted average of settings varying in ITN historical coverage and pre-intervention EIR. Exceptions to the good fit to pre-intervention data were found in the Southern Zone, where the observed and geospatial model predicted prevalence sometimes exceeded the maximum in the simulated prevalence. The councils included in the school net program were estimated to have particularly high pre-intervention EIR, and it is unclear whether this is because they were indeed higher transmission areas, or if the differences arise because of over-estimation of the average impact of nets. This could have arisen because of reliance on the standard OpenMalaria parameterisations on data from experimental huts and field trials, where ITNs are unusually well implemented. OpenMalaria analyses of vaccine impacts suggest that the temporal trend in intermediate years is less important in determining future impacts (Brooks et al., 2012), and the modelled time trends did not consider factors like housing, climate change and urbanisation (Jones et al., 2007; Reynolds et al., 2017) that are beyond the control of the NMCP. In general, the model fitted the time trends only moderately well and with considerable uncertainty, especially for 2012-2015 (which lacked both ITN coverage and prevalence data). This was especially true for councils with high ITN coverage, where estimates of prevalence and coverage were highly correlated. Moreover, the assumption of standard patterns of attrition and decay in effectiveness of ITNs

imposed a maximum on the fitted rate of decline in prevalence, which in particular affected the estimates for councils without the school net program which made use of the ITN decay model.

The need for a limited number of intervention strata with standard fixed coverage targets meant that there was only one (high) target coverage for each intervention. This took into account technical, but not operational or financial feasibility (WHO, 2014), although variations in access, provider adherence, population compliance and other operational challenges (Chaki et al., 2009; Newby et al., 2015; Theiss-Nyland et al., 2016) will generally lower effective coverage, especially for prompt and effective curative care (Galactionova et al., 2015). An improvement in future stratification and intervention allocation exercises would be to define stratum-specific targets in terms of increments in coverage, rather than uniform target levels.

The methods used by the program to maintain coverage of the primary interventions (behaviour change communication campaigns to keep up use of ITNs, surveillance of clinical cases to keep up treatment rates) (MoHCDGEC, 2014), were not analysed (thus avoiding double-counting of effects). Interventions not expected to affect prevalence in children and transmission in the community (*e.g.* intermittent preventive treatment for pregnant women) were also excluded, as were or others that the NMCP are not yet considering, such as vaccines (Penny et al., 2016), pyrethroid and piperonyl butoxide (PBO) treated nets (Protopopoff et al., 2018; WHO, 2017b), or other novel vector control tools (Killeen et al., 2017b). Among interventions included, modelling larviciding is a particular challenge. Models of vector control, in general, are sensitive to local variations in mosquito ecology, but the feasibility and effectiveness and costs of larviciding are particularly challenging to predict because the achievable coverage depends critically on local larval ecology (Mwangangi et al., 2010).

As a single intervention, ITN deployments were simulated to have the highest impact, irrespective of the distribution scheme. This is in agreement with other studies indicating that ITNs alone will only very gradually shift high prevalence areas (*Pf*PR >40%) to very low transmission and are unlikely to interrupt it (Cibulskis et al., 2016; Cotter et al., 2013; Moonen et al., 2010). In agreement with previous analyses using OpenMalaria the ITN effects synergised with increases in effective coverage of case management (Briët and Penny, 2013). The simulations predicted high impact despite the assumed high resistance against pyrethroids, due to the physical barrier, while in practice this also depends on the vector population, biting behaviour and physical state of the net (Lindblade et al., 2015; Ochomo et al., 2013).

With no improvement in the effective coverage of case management, the simulated NMSP was predicted to only slightly reduce the baseline prevalence from 2016 until 2020, while an

improvement in effective coverage could have a substantial effect. There may be some marginal benefits in optimising timing and effectiveness duration of larviciding, as there is limited evidence on large scale deployment of larviciding (Tusting et al., 2013). It could be that the reduction of emerging adult mosquitoes lasted not long enough to have a lasting impact on the coming transmission season (Fillinger et al., 2009a). Therefore, the deployment of larviciding needs careful consideration, especially as larviciding is planned to be scaled up despite reported limitations in the impact depending on ingredient and conductor (Msellemu et al., 2016). Overall, the predicted impact was very heterogeneous between councils with the impact depending on current and historical levels of transmission as extensively described previously (Cohen et al., 2012; Hay et al., 2008; Yukich and Chitnis, 2017). This should encourage the use of council-level malaria control targets as in Ethiopia, where the transition of councils into the next lower prevalence endemicity class is one of the targets (PMI, 2018a).

Only strategies including MDA in most councils appeared to be technically capable of achieving the original ambitious target of 1% national prevalence in 2020. Deployment of MDA at 80% coverage would be expected to bring the prevalence in most councils beneath this threshold (Fig 4). Though very high coverage of MDA has been achieved in Zanzibar (Ali et al., 2017), this would be extremely difficult to achieve and sustain across so many councils. Historically MDA programs have rarely achieved the coverage needed to meet such targets (Newby et al., 2015; Poirot et al., 2013), and we concur with the WHO Global Malaria Program Global Technical Strategy (WHO, 2015a) and other modelling studies (Walker et al., 2016) concluding that additional innovative tools are needed to achieve elimination. The strategy including MDA is clearly unaffordable with drug costs alone averaging $195 million per annum and the impact of such MDA would, in any case, be transient (Brady et al., 2017; Gerardin et al., 2017; Okell et al., 2011; Pemberton-Ross et al., 2017), especially as many areas in Tanzania still have high transmission potentially leading to high importation rates to areas with lower transmission and impeding sustainability of elimination efforts.

The intervention stratification that was most cost-effective conditional on these constraints comprised mostly ITNs, case management, with MDA in just a few councils. This is broadly in agreement with a previous intervention stratification proposed for Tanzania (Walker et al., 2016). Previous modelling and cost-effectiveness studies found that IRS with CM were the most cost-effective combination if high coverage could be achieved and otherwise the combination of ITN and CM (Okosun et al., 2013; Otieno et al., 2016). In our findings IRS was not included in any council, due to low impact and high costs. The costs of $30 per household sprayed correspond to the very high costs of targeted IRS, as shown in Tanzania for 2015 (Stelmach et al., 2016), and other distribution

schemes may have lower costs and IRS might be cost-effective in specific areas (Stelmach et al., 2018; Yukich et al., 2008). In many low transmission settings, ITNs alone were the most cost-effective strategy, which agrees with Hansen *et al.* (Hansen et al., 2012); however, in practice, case-management might be prioritised over ITNs. The strategy optimised for cost-effectiveness suggested only an improvement in case management few very low transmission councils, whereas in practice discontinuation of vector control might not always be possible and certainly not recommendable without further evidence and in-depth analysis (Crowell et al., 2012; Yukich and Chitnis, 2017). Moreover, resistance, although accounted for in this analysis, was not analysed in-depths and assumed to be homogeneous across the country with remained high effectiveness. In reality, the resistance varies per setting and species. To address high resistance, the WHO recommends deployment of PBO treated bed nets (WHO, 2019b), which would influence the cost-effectiveness estimates of ITNs deployments.

The costing is from a provider perspective and is only indicative, including only consumable costs. It ignores salaries and infrastructure costs (much of which fall outside the NMCP budget), and economies of scale or scope (which would be particularly relevant for full costing of improved case management). The analysis does capture returns to scale (Elbasha and Messonnier, 2004), in terms of health impacts of varying coverage. The annual budget of the program was between $100 Mio and $150 Mio from 2010 until 2017 (MoHCDGEC et al., 2017b). The most cost-effective simulated strategy was estimated to fit into this envelope, with simulated costs of $64 Mio per annum over four years, while the simulations of the current NMSP estimated its costs (including treatment costs) at $137 Mio. As the interactions between the modelling and NMCP evolve, it will become feasible to make more nuanced use of the data and to broaden the scope of the optimisation, while propagating uncertainties throughout the analysis. For instance, council level targets, varying target coverages (Korenromp et al., 2016; Winskill et al., 2019) and sequential introduction of interventions (Winskill et al., 2017) might be considered. The economic analysis could include additional costs, economies of scale and scope, optimisation within defined budgets, or extended time horizons with discounting.

3.6 Conclusion

The developed modelling workflow generated information to understand the predicted impact of three main strategies, and allowed an *in silico* assessment of the targets included in the National Malaria Strategic Plan 2015-2020. This work has been used to suggest optimal stratification under the given operational and financial constraints. Results suggest that current interventions are not enough to reach the national aim of a prevalence lower than 1% by 2020 and that a revised strategic plan needs to consider additional interventions, especially in high transmission areas. The

OpenMalaria model together with the calibration methodology developed here provides a helpful tool for assessing the feasibility of country specific targets and for determining alternative more impactful intervention combinations at sub-national level. Hence, the application of modelling can support strategic planning of malaria control, if based on realistic assumptions and done in close collaboration with the national malaria control programme.

3.7 Declarations

Author Contributions

MR collated information on country specific model parameter, ran the simulations, performed the analysis, and drafted the manuscript. RWS, PM, EG performed the geo-statistical analysis. AM, RM, ST, FM facilitated data collation. EP designed the Bayesian model for fitting and supervised simulations and analysis. TAS, EP contributed to design of the setting specific models and interpretation. EP, TAS, CL, RWS and FM provided detailed feedback on the manuscript. AM, RM, FM critically reviewed interpretation and implications of the modelling results. All authors read and approved the final manuscript.

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3.8 Supplementary information

SI-1: Developing a time-series risk map for Tanzania 1990-2017 based on empirical survey data

1. Assembly o*f Plasmodium falciparum* prevalence surveys

Details of parasite prevalence survey data assembly, cleaning and geo-coding are provided elsewhere (Snow et al., 2017). Important national household surveys of malaria infection prevalence included those undertaken in 2007/2008 (TACAIDS et al., 2008), 198 clusters sampled as part of national scale-up of ITN programme in 2008 [NMCP, unpublished data], 2012 (TACAIDS et al., 2013), 2015 (MoHCDGEC et al., 2016) and 2017 (MoHCDGEC et al., 2017a). In addition, national school-based surveys were undertaken in 2014-15 (Chacky et al., 2018) and 2017 [NMCP, unpublished data].

5772 surveys undertaken at 4146 unique locations between August 1980 and May 2018 were included in the modelling of infection prevalence. The majority of the surveys were undertaken after 2010 (3464, 60%), Rapid Diagnostic Tests (RDTs) were used to detect malaria infection in 4040 (70%) surveys, microscopy in 1692 surveys (29%) and RDTs confirmed with microscopy in 40 (1%) of surveys. The spatial distribution of the data repository used in subsequent analysis is shown in Fig. S1.1.

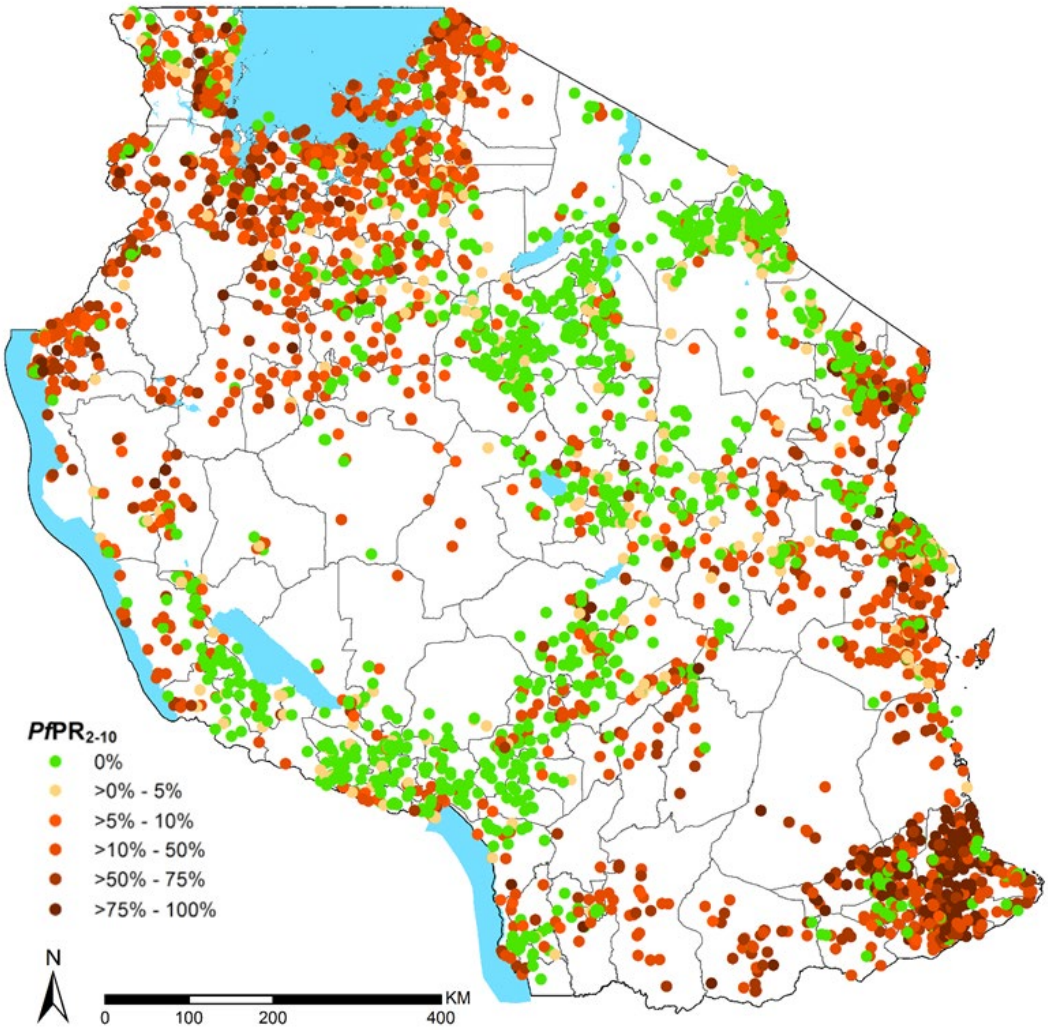

Fig. S1.1: Distribution of 5772 malaria prevalence surveys undertaken at 4146 locations between August 1980 and May 2018.

Surveys documented malaria prevalence across different age groups and were standardized to the 2 to 10 years age group (*Pf*$PR_{2\text{-}10}$) (Smith et al., 2007; Snow et al., 2017).

2. Geostatistical analysis

Model Based Geostatistics (MBG) (Diggle et al., 1998; Diggle and Giorgi, 2019) is a likelihood-based approach that allows a prediction of a health outcome of interest using sparsely sampled data. This modelling framework has also been extended to interpolate both the spatial and temporal variation of disease prevalence through the analysis of repeated cross-sectional data (Giorgi et al., 2018b)

To model changes in *Pf*PR_{2-10} by borrowing strength of information across time and space, an MBG model was used. In order to avoid estimates of prevalence resulting from misspecified regression relationships, a decision was made not to include covariates during the modelling exercise The inclusion of covariates in geostatistical models was examined by Weiss et al (Weiss et al., 2015) and applied in Malawi and Tanzania (Bennett et al., 2013; Gosoniu et al., 2012) among others, whereas the specification of covariates was outside the scope of the presented work., following the approach

of previous national malaria risk mapping efforts in Somalia (Giorgi et al., 2018a), Kenya (Macharia et al., 2018) and Malawi (Chipeta et al., 2019). Let *x* be the location of a surveyed community in year *t*. Define a spatio-temporal Gaussian process, *S*(*x, t*), and unstructured random effects, *Z*(*x, t*), to account for the unexplained variation between and within communities, respectively. Conditionally on *S*(*x, t*) and *Z*(*x, t*), the counts of positive tests for *P. falciparum* were assumed to follow mutually independent binomial distributions with number of trials *N*, corresponding to number of sampled individuals, and probability of a positive outcome *p*(*x, t*) at location *x* (n=surveyed locations) and year *t* (1990 – 2017) given by

$$log\left\{\frac{p(x,t)}{1-p(x,t)}\right\} = \alpha + \beta mA + \gamma MA + S(x,t) + Z(x,t). \qquad (1)$$

where *mA* and *MA* are the minimum and maximum age among the sampled individuals at a location *x* and time *t*. In carrying the spatio-temporal predictions, *mA* and *MA* were set to 2 and 10 respectively to standardise to the age group 2-10 years. A stationary and isotropic Gaussian process for the spatio-temporal random effects is assumed *S*(*x, t*), with an exponential correlation function given as

$$cor\{S(x,t), S(x',t')\} = e^{\{-||u||/\varphi\}} e^{\{-|v|/\psi\}} \qquad (2)$$

where φ and ψ are scale parameters which regulate the rate of decay of the spatial and temporal correlation for the increasing distance and time separation, respectively; $u = ||x - x'||$ is the distance in space between the location of any two communities, one at *x* and the other at x'; $v = |t - t'|$ is the time separation in years between any two surveys.

The model parameters were estimated via Monte Carlo maximum likelihood in the R statistical software environment using the PrevMap package (Giorgi and Diggle, 2017). The targets for predictions were *Pf*PR_{2-10} over the 1×1 km regular grid covering the whole of mainland Tanzania. Maps of malaria risk were generated for every year from1990 to 2017 using ArcMap 10.5 (ESRI Inc., Redlands, CA, USA) (Fig. SI 2).

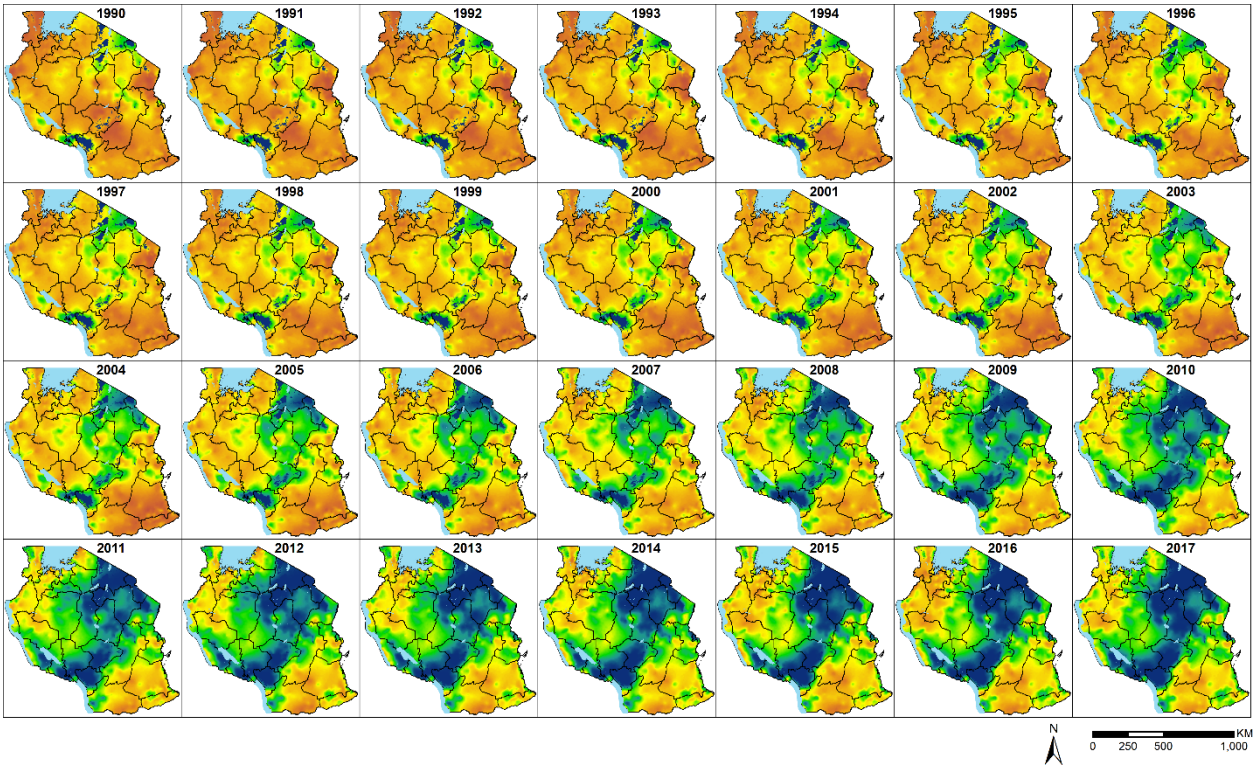

Fig. S1.2: **Annual predicted posterior mean community *Plasmodium falciparum* parasite rate standardized to the age group 2–10 years (*Pf*PR$_{2–10}$) at 1 × 1 km spatial resolution from 1990 to 2017 ranging from zero (dark blue) to 94% (dark orange in Tanzania).**

Note all pixels are treated as zero *Pf*PR$_{2-10}$ if they are represented by a temperature suitability index (TSI) of zero (Gething et al., 2011), these areas, located at high-altitude, have ambient temperatures that cannot support a period long enough for sporogony in the local dominant vectors and are therefore intrinsically climatically refractory to local malaria transmission.

3. Model validation

The model was validated using two methods: first by testing evidence against the residual spatio-temporal correlation in the data through the following variogram- based validation algorithm (Giorgi et al., 2018b): 1) Generate a point estimate $Z(x_i, t_i)$ i.e. $\tilde{Z}(x_i, t_i)$ from a non-spatio-temporal model, for each observed location x_i and time t_i. ; 2) Permute the order of the data, including $\tilde{Z}(x_i, t_i)$, while holding (x_i, t_i) fixed; 3) Compute the empirical semi-variogram for $\tilde{Z}(x_i, t_i)$; 4) Repeat steps (1) and (2) a large number of times, say *B;* 4) Using the resulting *B* empirical variograms to generate 95% confidence intervals at each of the pre-defined distance bins. To conclude that there is no evidence against the adopted spatio-temporal model correlation the empirical semi-variogram from the original data must fall within the generated 95% confidence intervals (Fig. S1.3). Secondly, validation statistics based on a 10% hold-out dataset (577 survey data points) for correlation against observed and predicted estimates of *Pf*PR$_{2-10}$, bias and mean absolute error (Fig. S1.4).

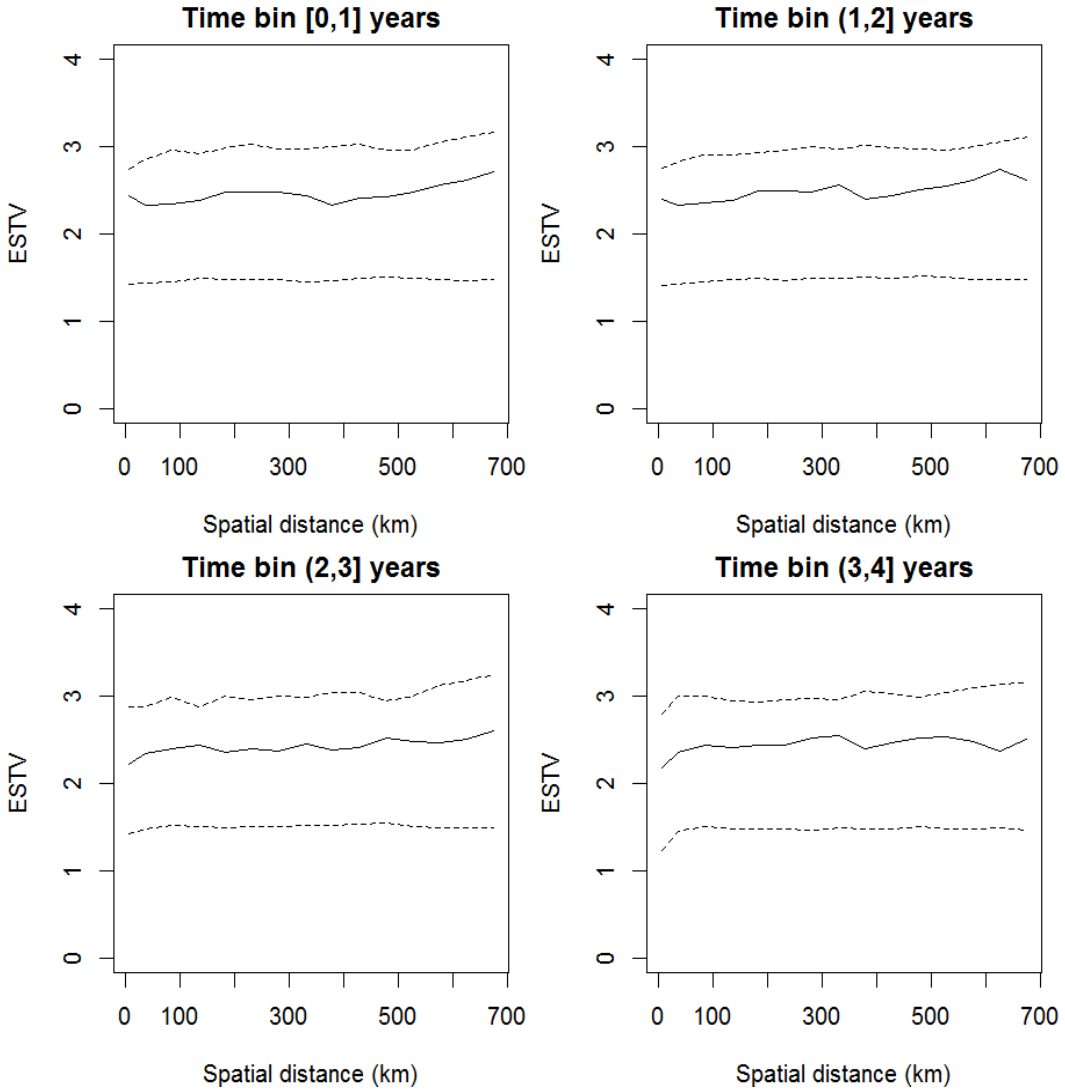

Fig. S1.3: The solid line in each panel show the empirical spatial spatio-temporal variogram (ESTV), at four different time lags.

The dashed lines represent the 95% confidence intervals generated under the hypothesis that the fitted spatio-temporal covariance function correspond to the true covariance function that generated the data. At any of the four time lags, the ESTV falls within the 95% bandwidth, which is evidence that the adopted covariance function is compatible with the data.

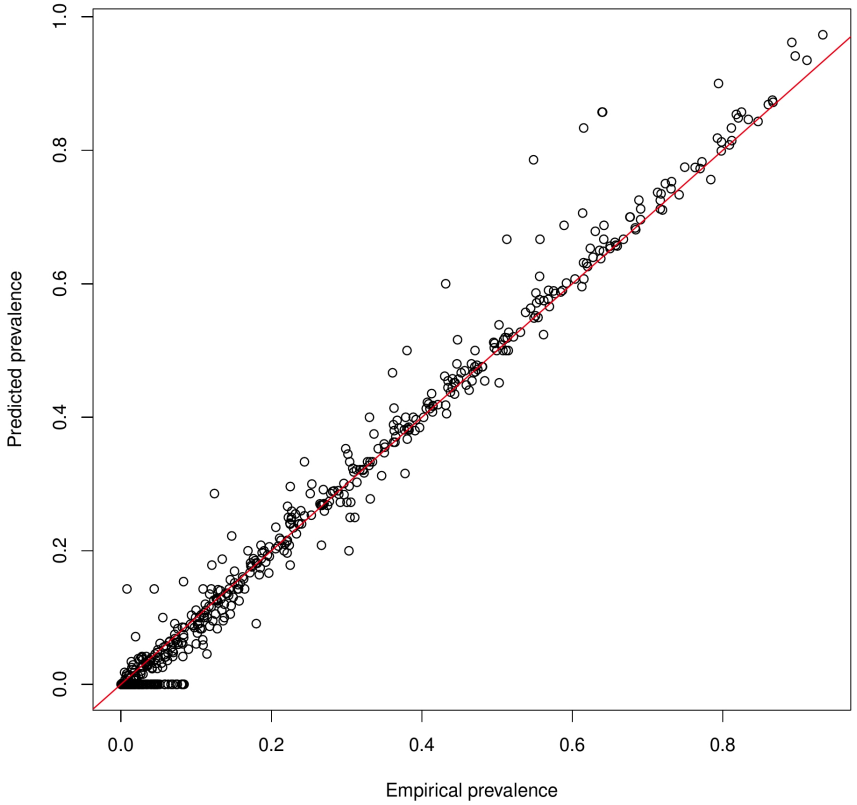

Fig. S1.4: Scatter plot of the predicted prevalence from the geostatistical model (y-axis) against the empirical prevalence (x-axis).

The predictive performance of the model was assessed on a test sample of 577 hold-out data points, resulting in a MAE of 0.7% and a bias of 0.4%.

4. Acknowledgements

The many scientists, archivists, institutions, and national control programmes, who have helped assemble malaria data from across Tanzania over the last 22 years include the following:
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SI-2: Data sources, model parameterisation, calibration method, and future intervention deployment and effectiveness

Content

Data and information sources

Table S2.1: Data and information sources used for parameterising OpenMalaria models and analysing outputs.

Indicator	Definition	Use	Resolution	Age group	Years	Source
Population and administrative units						
Administrative boundaries	Geographical areas that are defined by boundaries for administrative and operational purposes	To define the number of distinct models to run	NA	NA	2018	NMCP (unpublished data)
Population	Population estimates at high resolution	To extract population-weighted averages from high resolution ITN usage raster files	5 × 5 km^2 pixel raster	All	2012	WorldPop http://www.worldpop.org.uk/
	Total number of people per council	To calculate costs of interventions targeting a certain proportion of the population within councils	Council	All	2012	NBS (NBS Tanzania 2013) https://www.nbs.go.tz/
Population per household	Number of people living in the same household	To determine the number of total household per council as denominator for IRS coverage calculation	Council	All	2012	NBS (NBS Tanzania 2013) https://www.nbs.go.tz/
Vector bionomics						
Vector occurrence and sporozoites rates	Counts of mosquito species per area and proportion of mosquitoes found with sporozoites per species	To determine the relative contribution per vector species to malaria transmission	Council	NA	2016	Entomological surveillance data [NMCP, unpublished data]
Vector occurrence	Presence or absence of mosquito species at different locations and times	To determine the relative contribution per vector species to malaria transmission	Study sites	NA	NA	Personal communication, assembled literature database from the Ifakara Health Institute
Indoor/ outdoor biting	% of vectors affected by indoor interventions	To inform vector bionomics parameter	Study site	NA	2016	(Ngowo et al., 2017)
Resistance	Assumed resistance against pyrethroids (% mortality)	To inform assumptions about insecticide resistance	Council	NA	2014, 2015	NIMR, resistance reports (Kisinza W et al., 2015, 2014)
Transmission and seasonality						
Pre-intervention Transmission intensity	Infectious bites per person per year before large scale up of control interventions	No data available for all councils and parameter was estimated				
*Pf*PR	% of children who were tested positive using an mRDT, out of all children tested with mRDT	To compare with other prevalence sources and the simulated prevalence	Region	0-5 years	2008, 2012, 2016	MIS (MoHCDGEC et al., 2016; NBS Tanzania and ICF Macro, 2011; TACAIDS et al., 2013, 2008) https://www.statcompiler.com/
	Model predicted prevalence ($PfPR_{2to10}$)	To fit to simulated prevalence to obtain weighted predictions	5 × 5 sq km pixel raster	2-10 years	1990 - 2017	Described in S1 file

Seasonality	Monthly climate suitability for malaria transmission	To define the seasonal trend of transmission	Council	All	1983-2010	TMA (Grover-Kopec et al., 2006) http://maproom.meteo.go.tz/maproom/index.html
Case management and control interventions						
CM	% of febrile children who were taken to any health facility at any time during the last two weeks out of all febrile children	To approximate the effective treatment coverage between 2003 and 2016	Region	0-5 years	2008, 2012, 2016	MIS (MoHCDGEC et al., 2016; NBS Tanzania and ICF Macro, 2011; TACAIDS et al., 2013, 2008) https://www.statcompiler.com/
ITNs distributed	1) total number of nets distributed 2) number of nets distributed per population	To inform the timing of ITN deployment To distinguish between mass campaign and cumulative distribution	Council	Mixed	2004-2016	Commodity data [NMCP, unpublished data]
ITN decay	% of nets remaining over time	To determine functions for attrition of nets 1) for calculating the ITN usage at the time of the last campaign, and 2) for use as fitting parameter	*)			VectorWorks (NetCALC) https://www.vector-works.org/resources/netcalc-planning-tool/ (Koenker et al., 2013); (Briët et al., 2012)
ITN coverage (effective usage)	% of the total population who slept under an ITN the night previous to survey	To calculate the ITN usage at the time of the last campaign in 2012 and 2016	Region	0-5 years	2008, 2010, 2012, 2016	MIS, DHS (MoHCDGEC et al., 2016; NBS Tanzania and ICF Macro, 2011; TACAIDS et al., 2013, 2008) https://www.statcompiler.com/
		To inform annual ITN coverage between 2003 and 2011	5 × 5 sq km pixel raster	All	2003 - 2010	MAP (Bhatt et al., 2015b) https://map.ox.ac.uk
IRS coverage	% of population protected by IRS	To calculate historical IRS coverage	Council	All	2007-2016	Commodity data [NMCP, unpublished data], IRS spraying reports (PMI, Africa IRS (AIRS) Project, 2016)

NA = Not applicable

*) Decay functions have been modelled based on multiple field observations as described in the references.

Model parameterisation

The setting-specific model parameterisation is separated into four sections 1) vector bionomics, 2) transmission intensity and seasonality, and 3) historical interventions. Each section describes the processes applied to derive model parameters from the available data and information, or the assumptions made in case of insufficient data.

Vector bionomics

The vector bionomics refers to multiple characteristics attributable to the malaria vector, including the species, the human blood index, gonotrophic cycle, susceptibility to indoor interventions, resistance against insecticides, and contribution to transmission. Below it is briefly summarised for each of the attributes how the parameters were derived, and the actual parameters are shown in Table S2.2.

Mosquito species

The main malaria vectors in Tanzania are *An. funestus*, *An. gambiae s.s* and *An. arabiensis*. The parameterisations for the different mosquito species were already realised elsewhere (Chitnis et al., 2010b, 2008b), and only their contribution to transmission and proportion being affected by indoor interventions were adjusted for the setting specific models. In regions with no information about the vector populations and infectiousness fixed relative contributions were assumed with 80% *An. funestus*, 10% *An. gambiae s.s* and 10% *An. arabiensis*.

Human blood index

The tendency of mosquitoes to bite on humans vs animals also influences the malaria transmission as well as the impact of interventions. The parameterisation of the human blood index for each species was extracted from the literature (Chitnis et al., 2010b, 2008b), assuming *An. arabiensis* to be more zoophilic than *An. funestus* and *An. gambiae s.s.*

Gonotrophic cycle

The proportion of mosquitoes host seeking on the same day as ovipositing is also species specific and will influence the timing of the transmission cycle and therefore the impact of the interventions. The values for its parameterisation were selected according to an available parameterisation by Chitnis et al., based on literature (Chitnis et al., 2010b, 2008b).

Susceptibility to indoor interventions

The susceptibility of a mosquito to indoor interventions depends on its biting pattern and level of endophily. The assumptions made in the model were based on knowledge from local experts and published literature (Kabula et al., 2011; Lwetoijera et al., 2014b). *An. funestus* and *An. gambiae s.s* are mostly indoor biting while *An. arabiensis* mostly feeds outdoors (Kabula et al., 2011; Lwetoijera et al., 2014b). Hence, it was assumed that indoor interventions would affect 90% of *An. funestus,* 80%, of *An. gambiae s.s,* and 30% of *An. arabiensis* mosquitoes.

Insecticide resistance

Until 2010 all vectors were assumed to be susceptible against pyrethroids, after that the assumed pyrethroid resistance was 80%. The resistance level was assumed to be the same in all regions and for all vectors (Kisinza W et al., 2015; Kisinza et al., 2017). All species were assumed to be susceptible for insecticides used for IRS.

Contribution of vectors to malaria transmission

In Tanzania, entomological surveys were conducted in selected sentinel sites since mainly by the National Institute for Medical Research (NIMR), for insecticide resistance monitoring. In August 2016, the NMCP started entomological surveillance throughout the country [NMCP, personal communication]. The mosquitoes were caught with light traps. At the time of the analysis, in November 2016, 874 mosquitoes were processed from thirteen councils, and the number of mosquitoes with infectious sporozoites was reported per council, but no information was available on the total number of mosquitoes caught (NMCP, unpublished data). For those, four mosquito species were listed, namely *An. gambiae s.s., An. arabiensis*, *An. funestus s.s*., and *An. leesoni*. The latter two were combined into one category '*An. funestus'*, due to low numbers for *An. leesoni*. Reports on insecticide resistance were accessed from NIMR (Kisinza W et al., 2015) to complete the collation of information on occurrence and vector composition for each council in Tanzania, which also included a comprehensive extraction of entomological data from the literature (Dr Fredros Okumu, Ifakara health Institute, personal communication) (Biro, 1987; Charlwood et al., 1998; Huho et al., 2013; Kabula et al., 2012, 2011; Kaindoa et al., 2017; Killeen et al., 2007; Kisinza W et al., 2015; Kisinza et al., 2017; Mwanziva et al., 2011; Ngowo et al., 2017; Smith et al., 1993; Temu et al., 1998).

When available, the entomological surveillance data were used to estimate the contribution to transmission per vector species. The relative contribution of a vector species to the annual EIR was defined as the product of the relative infectiousness and occurrence of a mosquito species. For that, the relative occurrence of each vector species was assumed to be reflected by the relative frequency

of the analysed mosquitoes included in the preliminary results report. Moreover, the same mosquito-specific infectiousness was assumed across all councils and calculated as the proportion of infectious mosquitoes per species (Table S2.2). In the absence of available entomological surveillance data, the collated database was screened for the occurrence of vector species. If all three vectors were known to be present, their contribution to EIR was distributed as 45% for *An. funestus,* 45% for *An. gambiae s.s*. and 10% for *An. arabiensis,* otherwise 80% for *An. funestus*, 10% for *An. gambiae s.s.* and 10% for *An. arabiensis* (Fig. S2.1).

Table S2.2: Malaria vector characteristics.

Species specific parameter	***An. funestus s.l***	***An. gambiae s.s.***	***An. arabiensis***
Seasonality	Same for all species following council specific climate suitability trends		
Pyrethroid resistance	before 2011: 0% after 2011: 80%		
Affected by indoor intervention	90%	80%	30%
Human blood index	0.980	0.939	0.871
Proportion of mosquitoes host seeking on same day as ovipositing	0.616	0.313	0.313
Sporozoites rate	0.694	0.264	0.042
Contribution to EIR **(assumed in the absence of data)** If no information on vector occurence If presence of all three vectors	 80% 45%	 10% 45%	 10% 10%
Previously determined base parameters as described by Chitnis et al. (Chitnis et al., 2012) **with values, accessible on the OpenMalaria wiki** (Chitnis et al., 2010b)**.**			
Duration of resting stage "Time required for a mosquito that has encountered a host to return to host-seeking"	3	3	3
Extrinsic incubation period "The time required for sporozoites to develop in the mosquito"	11	11	11
Proportion of eggs laid same day "Proportion of host-seeking parous mosquitoes that have laid eggs that day."	0.616	0.313	0.313
Duration of host seeking "Maximum length of time that a mosquito searches for a host in one day if it is unsuccessful."	0.33	0.33	0.33
Parous rate "Proportion of host-seeking mosquitoes that have laid eggs at least once."	0.611	0.623	0.623
Availability variance "Total availability rate of all nonhuman hosts"	0	0	0
Biting probability "Probability that a mosquito bites a human after encountering one."	0.95	0.95	0.95

Probability finding resting site "Probability that a mosquito finds a resting place after biting a human."	0.95	0.95	0.95
Probability of surviving resting stage "Probability that a mosquito survives the resting phase after biting a human."	0.99	0.99	0.99
Ovipositing probability "Probability that a mosquito lays eggs and returns to host-seeking after biting a human"	0.88	0.88	0.88

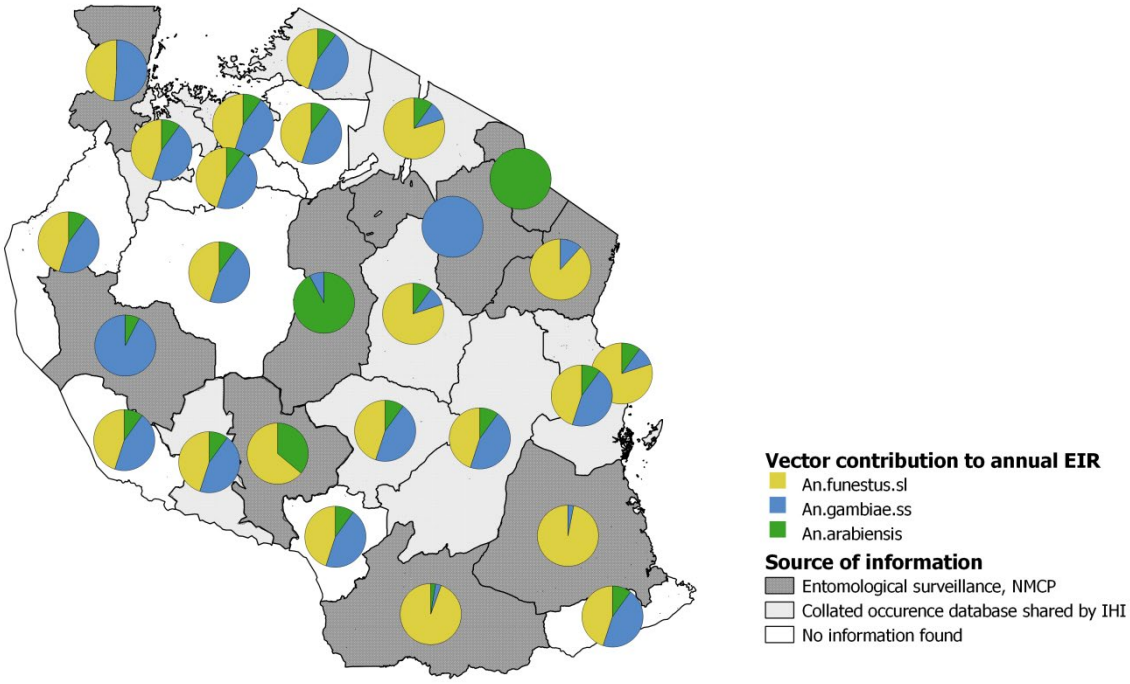

Fig. S2.1: Assumed geographic distribution of the contribution to malaria transmission per vector species. Dark grey areas show estimated contribution of different vectors to EIR, based on preliminary entomological data send by NMCP (NMCP unpublished data). Light grey areas show estimates derived based on a collated occurrence database. White areas show assumed vector contributions to EIR, based on a defined default distribution after discussions with experts, for those regions with missing data.

Transmission intensity and seasonality

Pre-intervention transmission intensity

The entomological inoculation rate (EIR) determines the prevalence and intervention impact and resurgence, and historically EIRs from less than zero up to 500 (Lengeler et al., 1998) or 1000 (Beier et al., 1999) were reported. The relationship between prevalence and EIR is log-linear, starting to saturate at an EIR around 100 and is mediated depending on case management, seasonality and other factors (Beier et al., 1999; Penny et al., 2015; Stuckey et al., 2013). Therefore, six EIR levels were selected, ranging from 0 to 550 (0, 4, 16, 54, 120, 550).

Seasonality

The vector abundance was assumed to follow the same trend as the monthly climate suitability for malaria transmission (Grover-Kopec et al., 2006; TMA, n.d.) and to be the same for all mosquito species included in the model. The climate suitability indicator combines temperature (mean temperature between 18°C and 32°C), rainfall ("precipitation accumulation > 80 mm") and humidity (> 60%) per month (Grover-Kopec et al., 2006; TMA, n.d.) (Fig. S2.2).

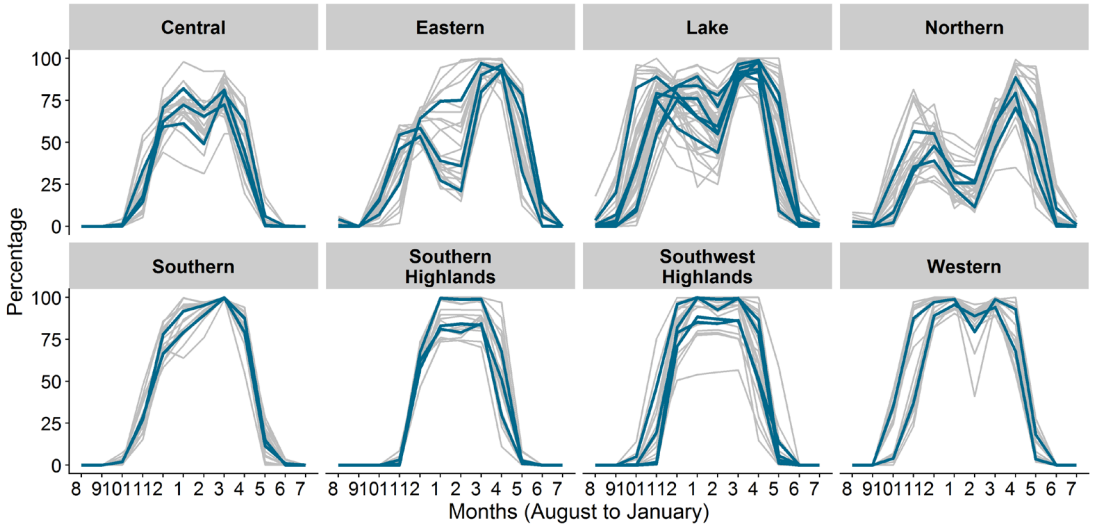

Fig. S2.2: Monthly climate suitability for malaria transmission grouped by geographical zones.
The grey lines show the councils and the blue line aggregated mean per region. Data source: Tanzania Meteorological Agency (Grover-Kopec et al., 2006; TMA, n.d.).

Case management and control interventions

Case management

According to the national MIS survey results from 2016, around 66% of febrile children under the age of five years sought treatment (Fig. S2.3), 36% were tested for malaria, and 43.4% received any antimalarial, of which 85% were ACTs (MoHCDGEC et al., 2016). For simplicity only the care-seeking estimates was used, assuming that out of all febrile children accessing care 59.7% are effectively treated, based on a previous study assessing effective treatment in Sub Saharan Africa (Galactionova et al., 2015). Hence, the effective treatment coverage was calculated by multiplying the proportion of children accessing care per region with the scaling factor of 0.6, estimated at national level for Tanzania (Galactionova et al., 2015).

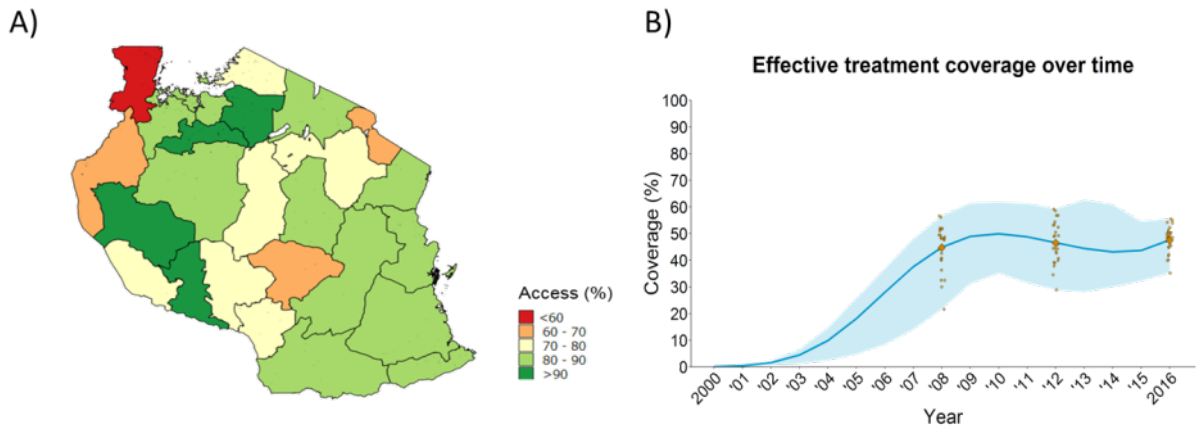

Fig. S2.3: Historical case management.
A) Geographic distribution of the proportion of children accessing any health facility within two weeks prior survey as estimated in the TDHS-MIS 2015/16. **B)** National temporal trend of the estimated proportion of individuals effectively being cured when they have a fever (effective treatment coverage). The orange dots correspond to regional estimates for care seeking behaviour from malaria indicator surveys (MoHCDGEC et al., 2016; TACAIDS et al., 2013, 2008), scaled with the estimate for effective treatment (Galactionova et al., 2015). The solid blue line corresponds to a fitted line for effective treatment based on the survey data with the assumption of no effective treatment before 2003. The light blue area corresponds to the minimum and maximum of the fitted lines.

Insecticide-treated bed nets

In Tanzania, three large ITN mass campaigns were conducted: the universal coverage campaign (UCC) from 2009 to 2010, the keep up campaign from 2010 to 2011, and the mass replacement campaign from 2016 to 2017. In addition, continuous deployments mechanisms exist and the most relevant one at the community level is the school net program implemented since 2013 in three regions. The reported ITN usage from MIS surveys roughly as well as the estimated ITN usage from MAP roughly follow the trend in number of nets distributed, but did not capture the differences between the deployment schemes since 2013 (Fig. S2.4).

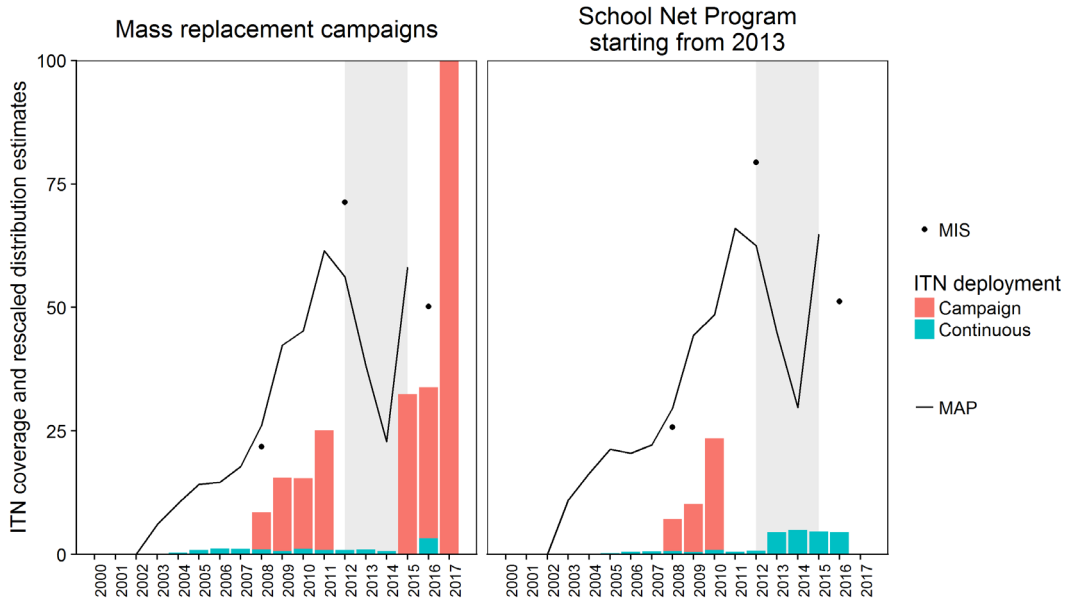

Fig. S2.4: Historical ITN coverage and distribution 2000-2016/17.
Average estimates of ITN usage from household surveys (MIS) and the Malaria Atlas Project (MAP) between regions receiving ITNs mostly through mass campaigns after 2012 (n=23) and between regions receiving ITNs mostly through school net distributions after 2012 (n=3). The grey area shows the time between 2012 and 2015 with no available data on ITN usage from household surveys and no mass deployment campaigns of ITNs.

The estimated ITN coverage trends from MAP were similar among councils within regions (Fig. S2.5).

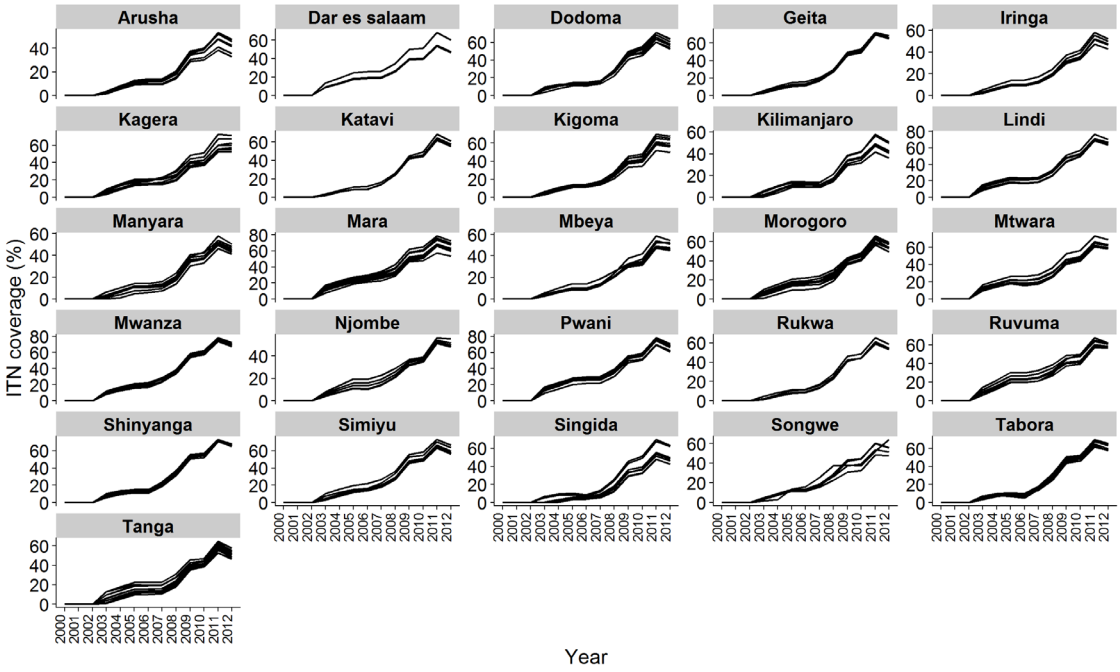

Fig. S2.5: Historical ITN usage per council and region between 2000 and 2012.
Estimates obtained from MAP mean raster files.

Simulated ITN deployments and coverage

The model, does not distinguish between ITN coverage and usage, using the terms interchangeably, referring to the proportion of the people protected by a net from all indoor bites. The figure below (Fig. S2.6) shows the assumed ITN use in 2016 per region and the national aggregated trend over time with range per regions used in the simulations (for each region separate trends).

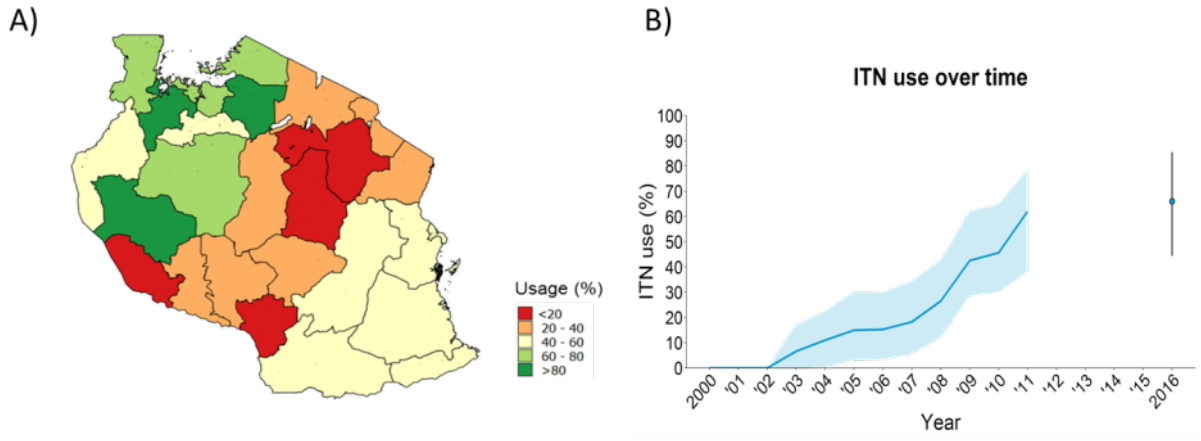

Fig. S2.6: Historical ITN use.

A) Geographic distribution of the proportion of the population who slept under any ITN the night prior the survey in 2016; **B)** National temporal trend of the estimated proportion of the population who use their bed between 2000 and 2011. The map shows reported ITN usage obtained from the THDS-MIS 2016 (MoHCDGEC et al., 2016). The solid blue line corresponds to population weighted median ITN usage extracted from ITN usage raster files downloaded from the MAP website (MAP, 2016) and population estimates from WorldPop (Tatem, 2017). The light blue area corresponds to minimum and maximum estimates among regions. The blue dot and error bar in 2016 correspond to the estimates of the proportion of the population who slept under any ITN the night before the survey (mean and range among regions) (MoHCDGEC et al., 2016).

Between the years 2003 and 2011, ITN distribution data (nets delivered per person), per region, showed a very similar trend as the trend of the ITN usage estimated by the Malaria Atlas Project (MAP) (MAP, 2016). Hence, the estimates of the population-weighted mean ITN usage were extracted for each region and used to define the historical ITN coverage. A step function of one year effectiveness was assumed to exactly match the estimated annual estimates.

Between 2008 and 2011, the “catch up” (2008-2010) and “keep up” (2010-2011) campaigns were considered as one with universal deployment in January 2011. The regional estimates of the proportion of the population using their nets the night before the survey was used as a proxy for bed net usage among all age groups and was extracted from the MIS 2012 survey data. The presumed effective use of nets during the 2011 campaign was back-calculated using the date of the distribution and the net use from 2012, assuming exponential attrition of nets with a half-life of three years (NBS Tanzania and ICF Macro, 2011; TACAIDS et al., 2013).

Between 2012 and 2016, nets were distributed to school children annually in three regions, namely Lindi, Mtwara, and Ruvuma (Lalji et al., 2016), while no large scale net distribution took place in other regions. For councils without ITN deployments between those years, the decay of nets distributed in 2011 was estimated during the model calibration, whereas, for councils included in the school net program, the annual ITN coverage between 2013 and 2016 was estimated. This allowed to reproduce the reported increase in prevalence between the MIS surveys in 2012 and 2016 (MoHCDGEC et al., 2016; TACAIDS et al., 2013) in some councils. ITN decay curves were estimated from the data and compared with the assumed ITN decay used in NetCALC (Koenker et al., 2013) (NetCalc 3.2 background document available from https://www.vector-works.org/resources/netcalc-planning-tool/).

In 2016, a mass distribution of ITNs was conducted at the same time than the TDHS-MIS 2015-16 surveys. The coverage of ITN distribution was therefore adjusted to account for the difference of timing between campaign and survey. For the adjustment, the regions were divided into three groups: 1) regions in which the net distribution took place before the survey, 2) regions in which the net distribution took place after the survey 3) regions in which there are no mass campaigns but only continuous (annual) school net distribution. For the regions, surveyed before the mass campaign in 2016, a scaling factor was derived from those regions surveyed before and after the mass campaign in 2016, using ITN usage estimates from the MIS surveys in 2010, 2012 and 2016. The scaling factor was derived by estimating the relative increase in coverage after mass campaign depending on the coverage before the mass campaign (Fig. S2.7). The ITN groups and ITN usage estimates per region are shown in Table S2.3. The adjusted ITN use among the whole population in 2016 was estimated to be on average 66% ranging from 44.4% to 85% across the regions (Fig. S2.7). The parameterisation of ITN efficacy is described elsewhere (Briët et al., 2012).

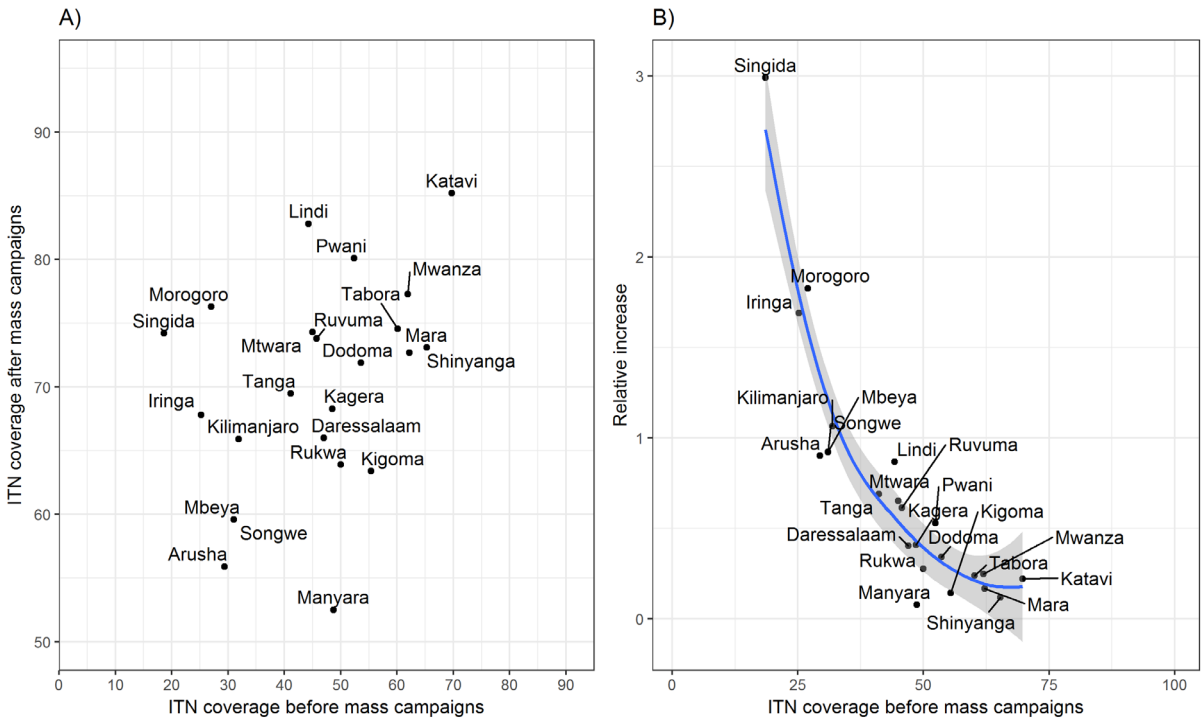

Fig. S2.7: Relation between reported ITN use before and after mass distribution campaign.
A) Mean ITN usage estimates from MIS 2010 and 2012 for before mass campaigns, and MIS 2012 and 2015/16 for after mass campaigns (deployments in 2011 and 2015) per region. **B)** Mean ITN usage before mass campaign and relative increase in coverage per region with fitted loess function. Note: in both plots, only regions are shown which had the MIS survey before the ITN mass campaign in either 2012 or 2016 (n= 23, missing= 3).

The timing of the ITN deployments was assumed to be the same across all regions, but accounting for differences in deployments i.e. school net distributions in Mtwara, Lindi and Ruvuma (Table S2.3).

Table S2.3: ITN deployment coverage per region in 2016.

Campaign	Adjustment method	Region	Mass campaign	MIS	MIS	Adjusted
Campaign before survey	Attrition of nets function to get the usage at deployment. Since the change was < 1%, the original value was kept	Geita	01.10.2015	07.01.2016	85.5	
		Kagera	01.08.2015	20.01.2016	67.5	
		Katavi	01.07.2015	12.01.2016	85.2	
		Kigoma	01.08.2015	28.10.2015	54.3	
		Mara	01.10.2015	24.10.2015	66.7	
		Mwanza	01.08.2015	16.10.2015	68	
		Shinyanga	01.09.2015	10.10.2015	46.8	
		Simiyu	01.11.2015	09.01.2016	83.5	
		Tabora	01.07.2015	20.01.2016	75.6	
Campaign after survey	Scaled by increase ratio before/after campaign (The scaling ratio was obtained from	Arusha	01.02.2016	24.09.2015	29.2	67.4
		Daressalaam	24.12.2016	20.09.2015	54.4	75.6
		Dodoma	01.05.2016	28.11.2015	16.7	70.8
		Iringa	01.02.2016	26.11.2015	28	68.1
		Kilimanjaro	01.03.2016	15.09.2015	36.1	64.5
		Manyara	01.01.2016	28.11.2015	12.6	65.9

	reported ITN usage from the DHS and MIS surveys in 2010 and 2012, in comparison to the ITN campaigns in 2009-2011)	Mbeya	22.11.2016	19.11.2015	26.4	69.0
		Morogoro	07.06.2016	01.12.2015	47.5	68.7
		Njombe	01.11.2015	20.10.2015	16.9	70.9
		Pwani	01.05.2016	08.01.2016	48.1	69.3
		Rukwa	01.12.2016	20.10.2015	15.1	69.5
		Singida	01.01.2016	20.01.2016	29.7	67.1
		Songwe	01.12.2016	03.11.2015	26.4	69.0
		Tanga	12.05.2016	30.11.2015	33.3	65.3
SNP before survey	Estimated in model calibration process when fitting to prevalence	Lindi		30.12.2015	48.2	-
		Mtwara		06.11.2015	44.4	-
		Ruvuma		11.01.2016	47.8	-

Attrition of nets

For nets distributed in 2012 various decay curves were simulated for councils that did not receive nets through schools. For nets distributed in 2016 and in future, a half-life of three years (Kilian et al., 2008; WHO, 2017c), following an exponential decay function as defined by Briët et al. (Briët et al., 2012) was assumed (line 4 in Fig. S2.8).

BOX 1: Smooth-compact decay function:

$$y = \exp \frac{k - k}{(1 - \left(\frac{t}{L}\right)^2)}$$

$t = time,$

$k = shape\ parameter\ (no\ dimension),$

$L = \ rate\ of\ decay, either\ the\ time\ until\ half\ \ decay\ or\ the\ time\ until\ full\ decay$

Note: for $t < L$, otherwise 0

Source: https://github.com/SwissTPH/openmalaria/wiki/ModelDecayFunctions

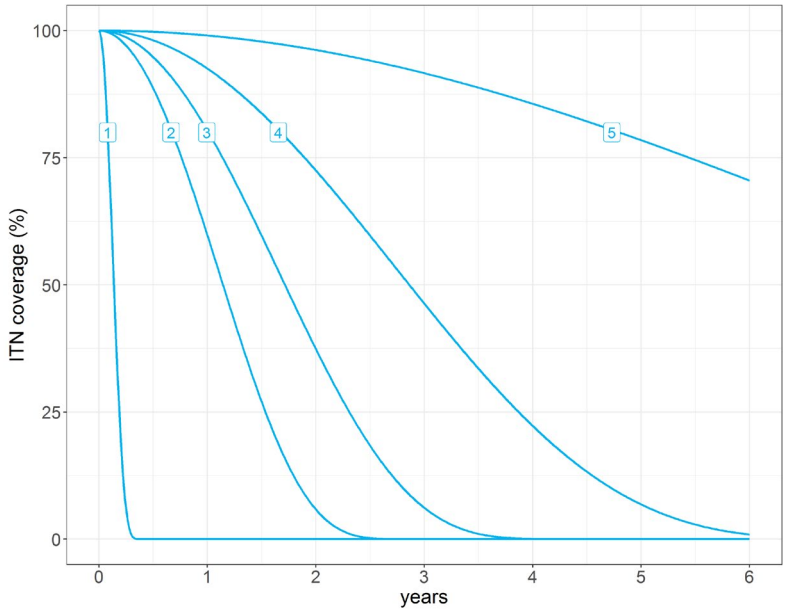

Fig. S2.8: ITN decay curves.

Indoor residual spraying

IRS implementation started in Mainland Tanzania in 2006/7 in the Lake Zone, targeting high prevalence areas, prone to malaria epidemics (RTI International, 2012). The coverage was calculated by dividing the targeted population by the total population of the council and start date of the IRS campaign used as deployment date. The maximum coverage and average timing were used for defining IRS deployments at regional level for Geita, Mara, Mwanza and Shinyanga (Fig. S2.9). The IRS coverage and timing were aggregated per region, assuming the whole region had IRS.

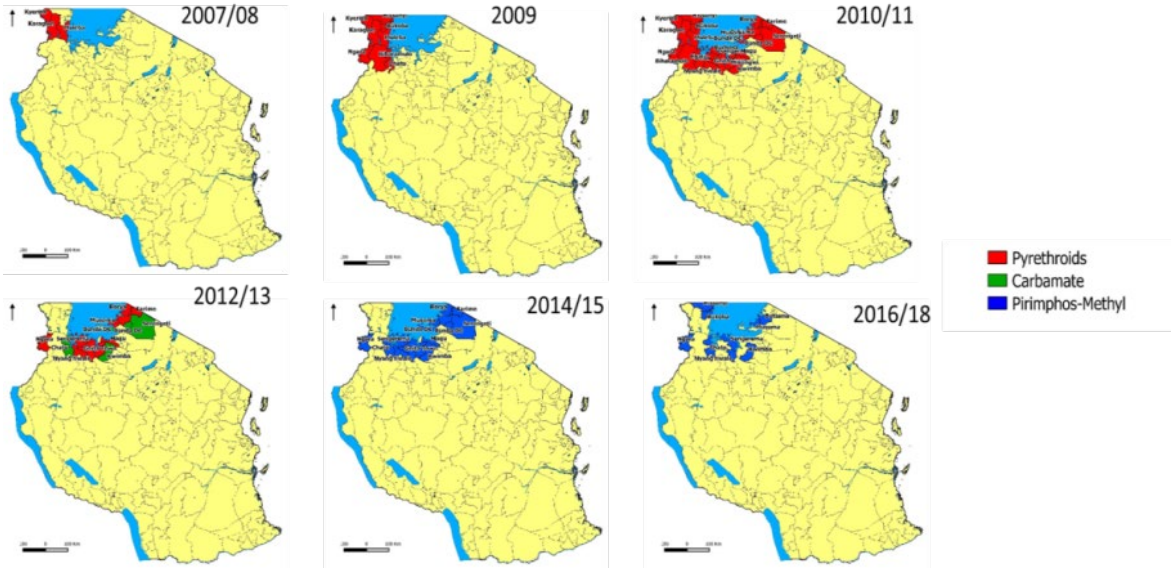

Fig. S2.9: Geographical distribution of IRS campaigns with various type of active ingredient between 2007 and 2018.

Source: NMCP, reproduced with permission.

Model calibration

The model was calibrated by fitting the simulated prevalence to the geospatial model predicted prevalence using MCMC methods and Gibbs sampler for likelihood estimation, estimating the pre-intervention EIR in 2003 and ITN usage parameter in 2012 per council. The Bayesian model was run separately for each council, with an adaptation phase of 100 iterations for one chain. The JAGS model was updated with 10'000 further iterations, and 10'000 samples were drawn from the posterior distribution, with a thinning interval of 10. Model priors were the geospatial prevalence predictions, and the likelihood functions the simulated prevalence, and the weighting parameter was estimated and applied to the estimated output parameter within the JAGS model. The outputs provided weights for each simulation which allowed reconstructing the historical trend of malaria transmission for each council. Since the predicted impact depends on the pre-intervention EIR (2003), and on the year before the deployment of future interventions in 2016 (baseline), the years 2003 and 2016 were weighted more than the years in between.

Simulated future scenarios 2017-2020

In total six interventions were simulated as described below:

- Case management was simulated assuming an immediate increase in the effective treatment coverage to 85% via improvements in case management in 2017 with constant effectiveness.
- ITNs were simulated assuming nets treated with pyrethroids and with two different types of deployment: 1) mass replacement campaign (MRC) in January 2019, 2) continuous distributions every year, e.g. via schools net programs (SNP). The ITN coverage was set equal to the usage, assuming that all individuals who have a net are using the net (Kilian et al., 2008). The ITN parameterisation is described elsewhere (Briët et al., 2012).
- IRS was simulated assuming annual deployments in September, corresponding to the end of the dry season in most regions. The active ingredients organophosphate (Actellic 50EC) and carbamates (Bendiocarb) were rotated, starting with Bendiocarb in 2017. The effect duration was assumed to six and three months, respectively for Bendiocarb and Actellic.
- Larval source management (LSM) was simulated assuming larviciding rounds every two weeks for three months during the dry season. The effect was simulated with a constant reduction of 60% in the emergence rate of adult mosquitoes for fourteen days after deployment, irrespective of vector species.
- Mass drug administration (MDA) was simulated assuming deployment of three rounds per year for the years 2017 to 2020. The deployment rounds were in June, August and October. The effectiveness, not parameterised to field data, was simulated with immediate blood-

stage clearance without protective effect. A previous MDA modelling study concluding that coverage needs to be very high for MDA to be effective (Pemberton-Ross et al., 2017). However, not all in the population are eligible for MDA deployment or can be reached, and a moderate to target coverage of 80% was used.

SI-3: Outcome and cost calculations

The model predicted outcomes were further processed, calculating outcome measures, such as prevalence or cases averted and attaching costs to the simulated intervention scenarios per council (Table S3.1).

Table S3.1: Parameter and abbreviations used.

Symbol	Name	Unit /description
t	Time	Years
j	Setting	Councils
k	Age group	0-5 years; 2-10 years, 0-99 years (total population)
l	Intervention scenario	Future interventions (single or combined)
Abbreviations	**Full name**	**Description**
c	Counterfactual	Discontinuation of all interventions apart from case management running at current levels, as in 2016
b	Baseline	Baseline year 2016
U	Uncomplicated	Uncomplicated malaria cases
S	Severe	Severe malaria cases
$PopPerNet$	Population per net	Number of people sleeping under the same net.
$Pop.perHH$	Population per household	Number of people living in the same household.
OpenMalaria output*	**Description**	
$nPatent$	The number of human hosts whose total (blood-stage) parasite density is above the detection threshold.	
$nHost$	Total number of humans.	
$nUncomplicated$	Number of episodes (uncomplicated). An episode of uncomplicated malaria is a period during which an individual has symptoms caused by malaria parasites present at the time of illness, where the symptoms do not qualify as severe malaria.	
$nSevere$	Number of episodes (severe). An episode of severe malaria is a period during which an individual has symptoms, qualifying as severe malaria, caused by malaria parasites present at the time of illness.	

*) https://github.com/SwissTPH/openmalaria/wiki/XmlMonitoring

Table S3.2: Calculated outcome measures from OpenMalaria monitoring measures

Outcome	Description	Calculation
Prevalence	Percentage of patent infections above the detection limit (200 parasites/ul blood) out of the total population	$Pf\mathrm{PR}_{jklt} = \left(\frac{nPatent_{jklt}}{nHost_{jklt}}\right)$
Incidence	The number of all symptomatic malaria infections per 1000 population, regardless of health seeking behaviour.	$Incidence_{jklt} = \left(\frac{nUncomplicated_{jklt} + nSevere_{jklt}}{nHost_k}\right) * 1000$
Malaria cases	The number of all symptomatic malaria infections per council population, regardless of health seeking behaviour.	$Cases.U_{jklt} = \left(\frac{nUncomplicated_{jklt}}{nHost_k}\right) * Population_{2016}$ $Cases.S_{jklt} = \left(\frac{nSevere_{jklt}}{nHost_k}\right) * Population_{2016}$ $Cases_{jklt} = \left(\frac{nUncomplicated_{jklt} + nSevere_{jklt}}{nHost_k}\right) * Population_{2016}$
Malaria cases averted	The number of malaria cases averted by intervention compared to the counterfactual.	$Cases.Averted.U_{jklt} = Cases.U_{jkct} - Cases.U_{jklt}$ $Cases.Averted.S_{jklt} = Cases.S_{jkct} - Cases.S_{jklt}$ $Cases.Averted_{jklt} = Cases_{jkct} - Cases_{jklt}$
Relative reduction in malaria cases	The number of malaria cases averted by intervention compared to the counterfactual	$Cases.red.perc_{jklt} = \left(\frac{(Cases_{jkct} - Cases_{jklt})}{Cases_{tjkc}}\right) * 100$

Cost estimates

All intervention costs were costs per person in USD. The numbers of rounds of an intervention were per year and had the values "0" for no intervention deployment and "1" for intervention deployment. The cost calculation for school net distribution took into account that with time more nets need to be distributed to maintain a certain coverage level in the population. The annual total costs were calculated per council, considering the council population of 2016. The costs of each scenario were summed over the years 2017-2020 and interventions in that strategy. Three types of cost were generated per scenario: total net costs, total costs, and total intervention costs (excluding CM). The treatment savings (treatment costs from cases averted) were subtracted from the total net cost (Table S3.3).

Table S3.3: Unit costs per intervention.

	Cost	Unit	Source
CM	\$2.1 (Uncomp) \$49.4 (Severe)	Per episode	(Galactionova et al., 2017)
MRC	\$4.00	Per net,	Personal communication with NMCP
SNP	\$3.11	(~ 2 people per net)	
IRS	\$30	Per structure (~5 people per hh*)	(PMI, Africa IRS (AIRS) Project, 2016)
MDA	\$5.95	Cost per drug (= cost per person)	(Scott et al., 2017; Walker et al., 2016)
LSM	\$4.32	Per population per year (3 rounds a year)	(Rahman et al., 2016) and personal communication

*) Council specific based on data from the population census (NBS Tanzania, 2013).

Table S3.4: Cost calculations

Type	Calculation
Case management	$CMcost.U_{jlt} = \left(Cases.U_{jlt} * TreatmentCoverage_{jlt}\right) * Treatment.cost.U$ $CMcost.S_{jlt} = \left(Cases.S_{jlt} * TreatmentCoverage_{jlt}\right) * Treatment.cost.S$ $CMcost_{jlt} = CMcost.U_{jlt} + CMcost.S_{jlt}$
Treatment savings	$TreatmentSavings.U_{jlt} = \left(CasesAverted.U_{jlt} * TreatmentCoverage_{jlt}\right) * Treatment.cost.U$ $TreatmentSavings.S_{jlt} = \left(CasesAverted.S_{jlt} * TreatmentCoverage_{jlt}\right) * Treatment.cost.S$ $TreatmentSavings_{jlt} = TreatmentSavings.U_{jlt} + TreatmentSavings.S_{jlt}$
ITN	$ITNcost.MRC_{jlt} = \left(\left(\frac{Population_{2016}}{PopPerNet}\right) * ITNcov.MRC_{jlt} * MRCrounds_{jlt}\right) * ITN.cost.MRC$ $ITNcost.SNP_{jlt} = \left(\left(\left(\frac{Population_{2016}}{PopPerNet}\right) * attrition_k * ITNcov.SNP_{jlt}\right) * SNProunds_{jlt}\right) * ITN.cost.SNP$ $ITNcost_{jlt} = ITNcost.MRC_{jlt} + ITNcost.SNP_{jlt}$
IRS	$IRScosts_{jlt} = \left(\left(\frac{Population_{2016} * IRScoverage_{jlt}}{Pop.perHH}\right) * IRSrounds_{jlt}\right) * IRScost$
LSM	$LSMcosts_{jlt} = \left(\left(Population_{2016} * LSMcoverage_{jlt}\right) * LSMrounds_{jlt}\right) * LSMcost$
Total costs	$Total\ costs_{jlt} = CMcosts_{jlt} + ITNcosts_{jlt} + IRScosts_{jlt} + LSMcosts_{jlt} + MDAcosts_{jlt}$
Total net costs	$Total\ net\ costs_{jlt} = Total\ costs_{jlt} - TreatmentSavings_{jlt}$
Intervention costs	$Intervention\ costs_{jlt} = Total\ costs_{jlt} - CMcosts_{jlt}$

SI-4: Additional results

Contents

Estimated pre-intervention EIR

The estimated council-specific pre-intervention EIR reflects the trend in geospatial predicted prevalence used for fitting, shown in the main manuscript Fig 2 and in Fig. S1.2. The geographical pattern is similar to previously published prevalence risk maps (Chacky et al., 2018; Gosoniu et al., 2012; Hagenlocher and Castro, 2015), and climate factors (NMCP et al., 2013) (Fig. S4.1).

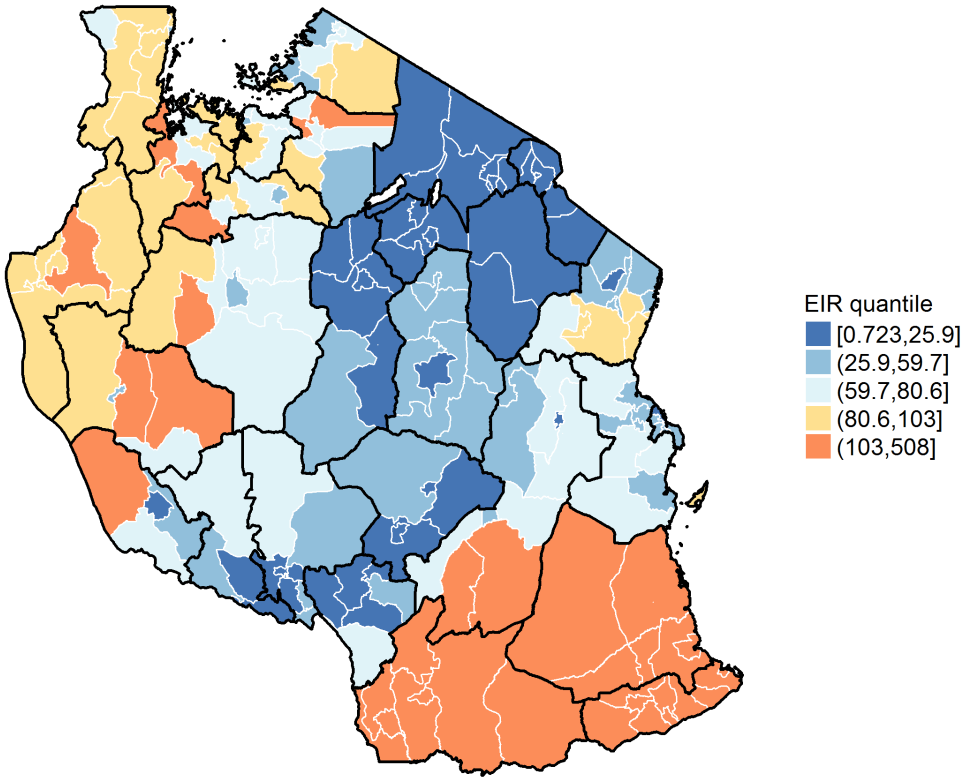

Fig. S4.1. Map of the estimated pre-intervention EIR per council.

Comparison of estimated and observed pre-intervention EIRs

The validation of estimates of EIR is challenging due to high variations in entomological outcomes, which highly depend on the local environment, often seasonality and vector species. A previously literature review on entomological studies in Tanzania was used to extract annual EIR values between 1990 and 2005 (Dr Fredros Okomu personal communication). The identified studies were compared with the database from Massey et al. (Massey et al., 2016), to ensure most relevant studies were captured, and 15 unique studies were identified, reporting EIR estimates for 53 study sites in 14 councils from four regions (Table S3.1). Most of the study sites were located in Kilombero and Ulanga (17 and 12 study sites respectively), while in 6 councils only one study site was included. Some studies reported the EIR per vector species (Huho et al., 2012); in that case, the total annual

EIR was calculated by summing the annual EIR per species, and some studies sites reported daily EIR, in which case annual EIRs were projected, as in (Curtis et al., 1998). The limited available data did not permit a proper validation, and a simple comparison of the reported EIR with the model-estimated EIR was done. The single annual EIR estimates for all species were compared with the mean, median and credible intervals of the estimated EIR. Overall, the comparison showed high variability in both estimated and reported values (Fig. S3.2). Possible reasons for large discrepancies could be ecological factors of the study sites since heterogeneity within councils was not accounted for in the modelling. For example, in Bagamoyo, Shiff et al. conducted a study to assess the relationship between transmission and altitude (Shiff et al., 1995); hence the EIR values show high variation due to different elevation of the study sites included. The EIR estimation for rural Moshi was extremely far from the observed values, which could be due to differences in study sites of the prevalence studies used for the geospatial model used to estimate the EIR, and the sites included in the study from Ijumba et al., which was all located in different agro-ecosystems (Ijumba et al., 2002). The comparison between reported annual EIR and the estimated EIR, based on the geo-spatial prevalence predictions (S1 file), is also limited, as the relationship between prevalence and EIR is not linear (Beier et al., 1999). For high levels of EIR, prevalence is expected to have little variations. In OpenMalaria the simulations are plateauing around a prevalence of 80% prevalence and an EIR of 100 ibpa (Penny et al., 2015), and for high transmission the trends rather than the actual EIR need to correspond to each other, as in Tanga, estimated EIRs of >80 correspond to reported EIRs of > 200 ibpa and above.

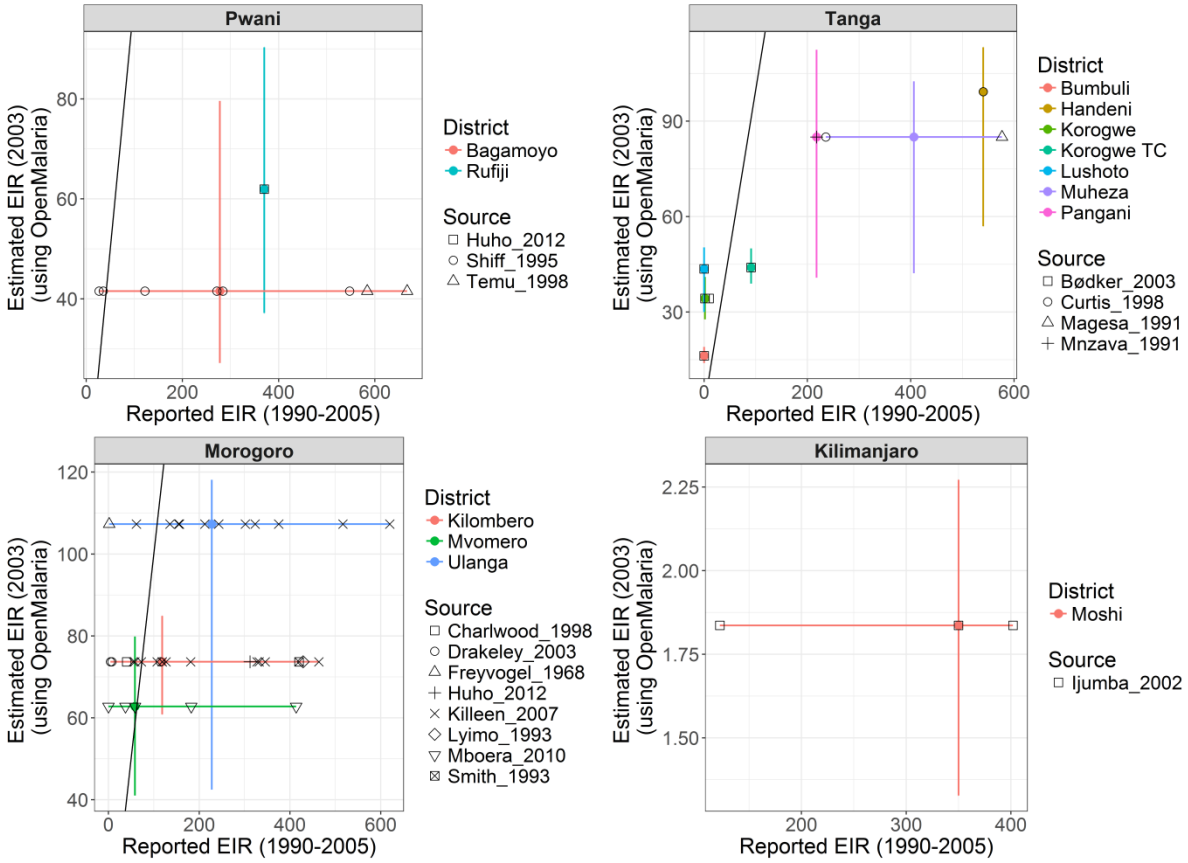

Fig. S4.2: Comparison of estimated and observed pre-intervention EIR around the year 2000 (1990-2005).
N=11 councils. Points show EIR values reported per study site per council and source[13]. Vertical error bars credible intervals, and horizontal error bars represent minimum and maximum values aggregated per council (no horizontal error bars if there was only one study site per council). The black line shows perfect correspondence.

[13] EIR estimates were collated from literature and shared by Dr Fredros Okumu, Ifakara Health Institute and each reference was individually reviewed if accessible.

Table S4.1: Comparison of estimated and observed pre-intervention EIR around the year 2000 (1990-2005)

Region	Council	Estimated annual EIR based on model predictions*				Reported annual EIR	Study site	Source
		mean	median	q2.5	q97.5			
Kilimanjaro	Moshi	1.83	1.84	1.33	2.27	122	Chekereni	(Ijumba et al., 2002)
Kilimanjaro	Moshi	1.83	1.84	1.33	2.27	350	Kisangasangeni	(Ijumba et al., 2002)
Kilimanjaro	Moshi	1.83	1.84	1.33	2.27	402	Mvuleni	(Ijumba et al., 2002)
Morogoro	Kilombero	73.53	73.68	60.83	84.88	40.2	Idete	(Charlwood et al., 1998)
Morogoro	Kilombero	73.53	73.68	60.83	84.88	4.4	Ifakara	(Drakeley et al., 2003)
Morogoro	Kilombero	73.53	73.68	60.83	84.88	114.4	Ifakara	(Drakeley et al., 2003)
Morogoro	Kilombero	73.53	73.68	60.83	84.88	7.6	Ifakara	(Drakeley et al., 2003)
Morogoro	Kilombero	73.53	73.68	60.83	84.88	312	Ulanga/ Kilombero	(Huho et al., 2012)
Morogoro	Kilombero	73.53	73.68	60.83	84.88	54.65-463.74	11 villages	(Killeen et al., 2007)*
Morogoro	Kilombero	73.53	73.68	60.83	84.88	126.85	Itongoa A	(Killeen et al., 2007)
Morogoro	Kilombero	73.53	73.68	60.83	84.88	428.8	Michenga	(Smith et al., 1993)
Morogoro	Kilombero	73.53	73.68	60.83	84.88	420	Namawala	(Smith et al., 1993)
Morogoro	Ulanga	100.1	107.3	42.48	118.12	1.51	Matanila-Chindwangi	(Freyvogel and Kihaule, 1968)
Morogoro	Ulanga	100.1	107.3	42.48	118.12	61.68 - 620.02	11 villages	(Killeen et al., 2007)*
Morogoro	Mvomero	62.16	62.77	41.03	79.86	58.4	Mkindo	(Mboera et al., 2010)
Morogoro	Mvomero	62.16	62.77	41.03	79.86	182.5	Mkindo	(Mboera et al., 2010)
Morogoro	Mvomero	62.16	62.77	41.03	79.86	37.5	Luhindo	(Mboera et al., 2010)
Morogoro	Mvomero	62.16	62.77	41.03	79.86	0	Dakawa	(Mboera et al., 2010)
Morogoro	Mvomero	62.16	62.77	41.03	79.86	413.5	Mtibwa	(Mboera et al., 2010)
Pwani	Rufiji	61.73	61.94	37.15	90.32	370	Rufiji	(Huho et al., 2012)
Pwani	Bagamoyo	45.34	41.56	27.15	79.59	284	Matimbwa	(Shiff et al., 1995)
Pwani	Bagamoyo	45.34	41.56	27.15	79.59	26.7	Chasimba	(Shiff et al., 1995)
Pwani	Bagamoyo	45.34	41.56	27.15	79.59	547.5	Zinga	(Shiff et al., 1995)
Pwani	Bagamoyo	45.34	41.56	27.15	79.59	271.6	Mapinga	(Shiff et al., 1995)
Pwani	Bagamoyo	45.34	41.56	27.15	79.59	122.1	Yombo	(Shiff et al., 1995)
Pwani	Bagamoyo	45.34	41.56	27.15	79.59	35.5	Kongo	(Shiff et al., 1995)
Pwani	Bagamoyo	45.34	41.56	27.15	79.59	584	Kongo	(Temu et al., 1998)
Pwani	Bagamoyo	45.34	41.56	27.15	79.59	667	Matimbwa	(Temu et al., 1998)
Tanga	Bumbuli	16.31	16.24	13.93	19	0.08	Balangai	(Bødker et al., 2003)
Tanga	Korogwe	34.33	34.25	27.68	41	9.7	Magundi	(Bødker et al., 2003)
Tanga	Korogwe	34.33	34.25	27.68	41	1.7	Kwamhanya	(Bødker et al., 2003)
Tanga	Korogwe	34.33	34.25	27.68	41	1.8	Bagamoyo	(Bødker et al., 2003)
Tanga	Korogwe TC	44.09	43.99	38.93	49.98	91	Kwameta	(Bødker et al., 2003)
Tanga	Lushoto	42.45	43.56	30	50.31	0.03	Milungui	(Bødker et al., 2003)
Tanga	Handeni	95.29	99.25	56.95	113.22	540.2	Hale	(Curtis et al., 1998)
Tanga	Muheza	81.24	85.02	42.18	102.52	235.6	Temgini and Enzi	(Curtis et al., 1998)
Tanga	Muheza	81.24	85.02	42.18	102.52	576.7	Kumbamtoni	(Magesa et al., 1991)
Tanga	Pangani	82.7	85.03	40.76	112.45	217.7	Kikwazu	(Mnzava, 1991)

*) Unpublished data and EIR values per village not shown.

Fitting performance at sub-national level

The calibration of the model at council level used as much as possible local data and complementary information at a lower resolution when needed. Only two parameters were fitted to ensure adequation with historical malaria trends between 2003 and 2016. The figures below show the fitting of the baseline prevalence in 2003 and in 2016 per council grouped by region (Fig. S4.3 and Fig. S4.4) and, and the historical prevalence over time by region (Fig. S4.5).

Pre-intervention prevalence 2003

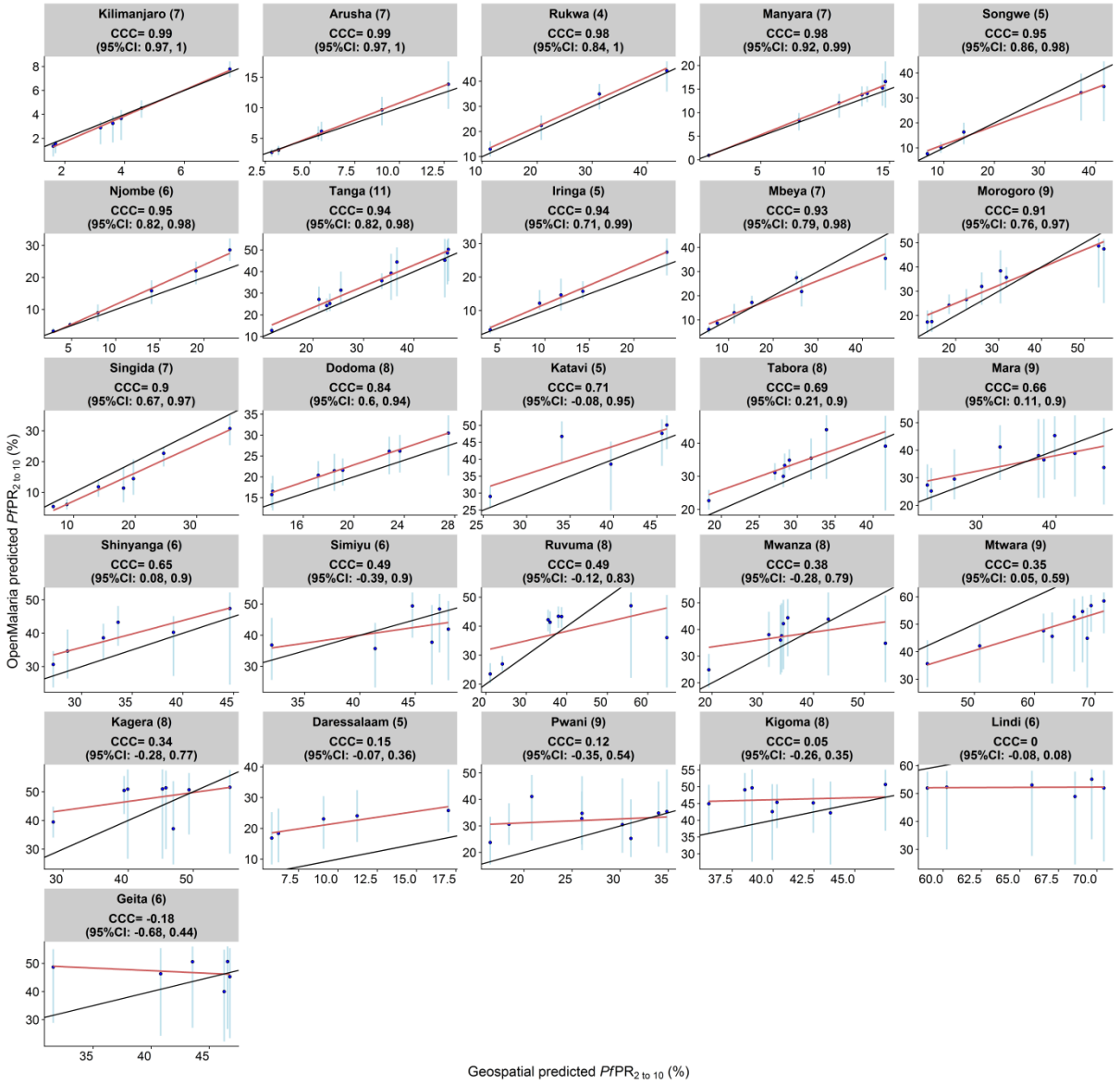

Fig. S4.3: Fitting per 2003 prevalence per council, grouped by region.
The facets show each region with the number of councils in the brackets. Each point represents one council within the region. The scatter plots (right) shows the respective prevalence estimates (points), with the regression line (blue line), and perfect correspondence line (black line). CCC = Lin's concordance correlation coefficients (Lin, 1989).

Baseline prevalence in 2016

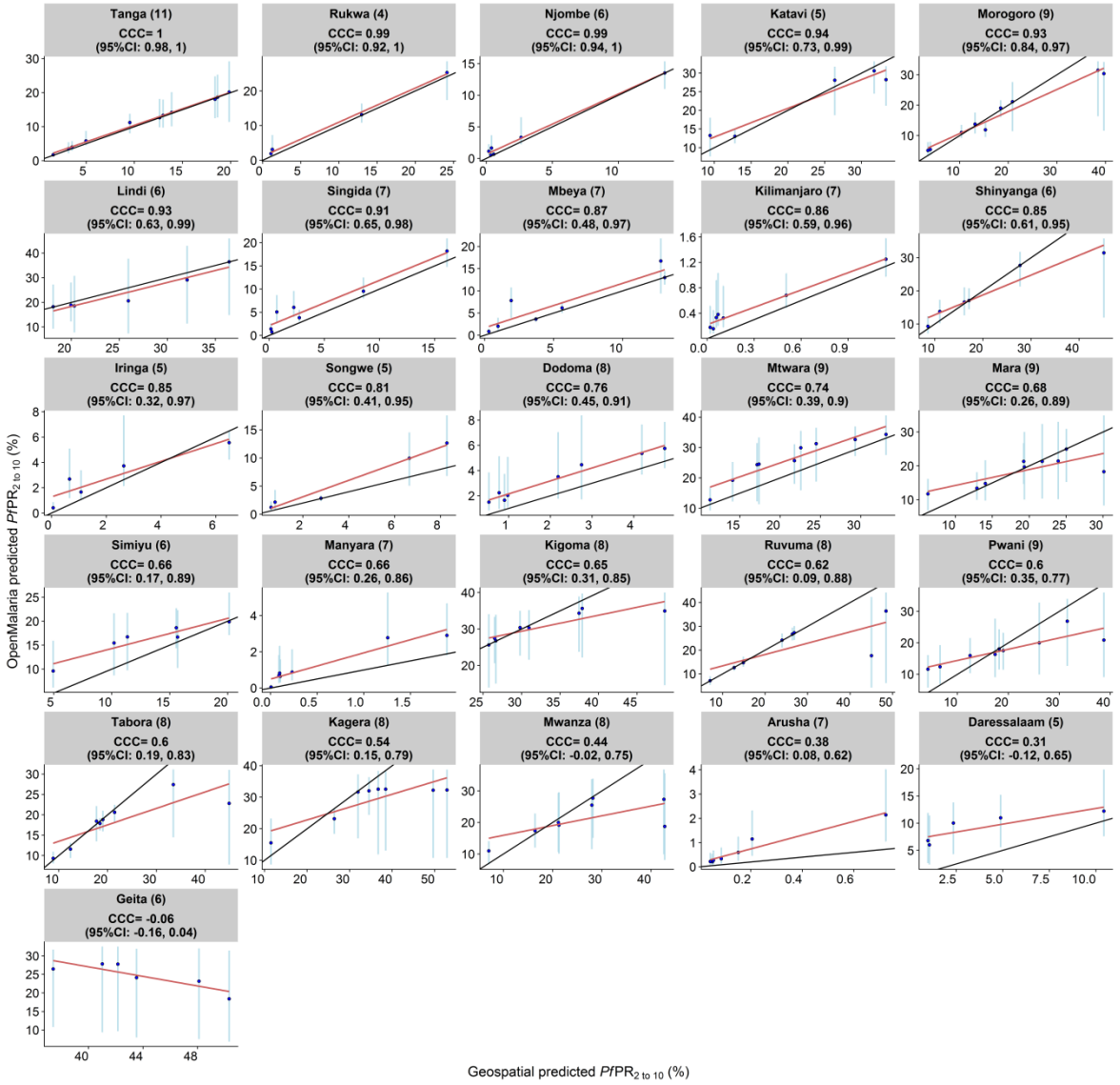

Fig. S4.4: Fitting per 2016 prevalence per council, grouped by region.

The facets show each region with the number of councils in the brackets. Each point represents one council within the region. The scatter plots (right) show the respective prevalence estimates (points), with the regression line (blue line), and perfect correspondence line (black line). CCC = Lin's concordance correlation coefficients (Lin, 1989).

Historical trend

The ITN coverage was assumed to be known and therefore fixed (see S2 File), and in some regions and councils, the reduction in prevalence did not correspond to the increase in coverage over time. It was assumed that the pre-intervention EIR and the baseline year before future intervention deployment would be the most relevant time points for the model to reproduce.

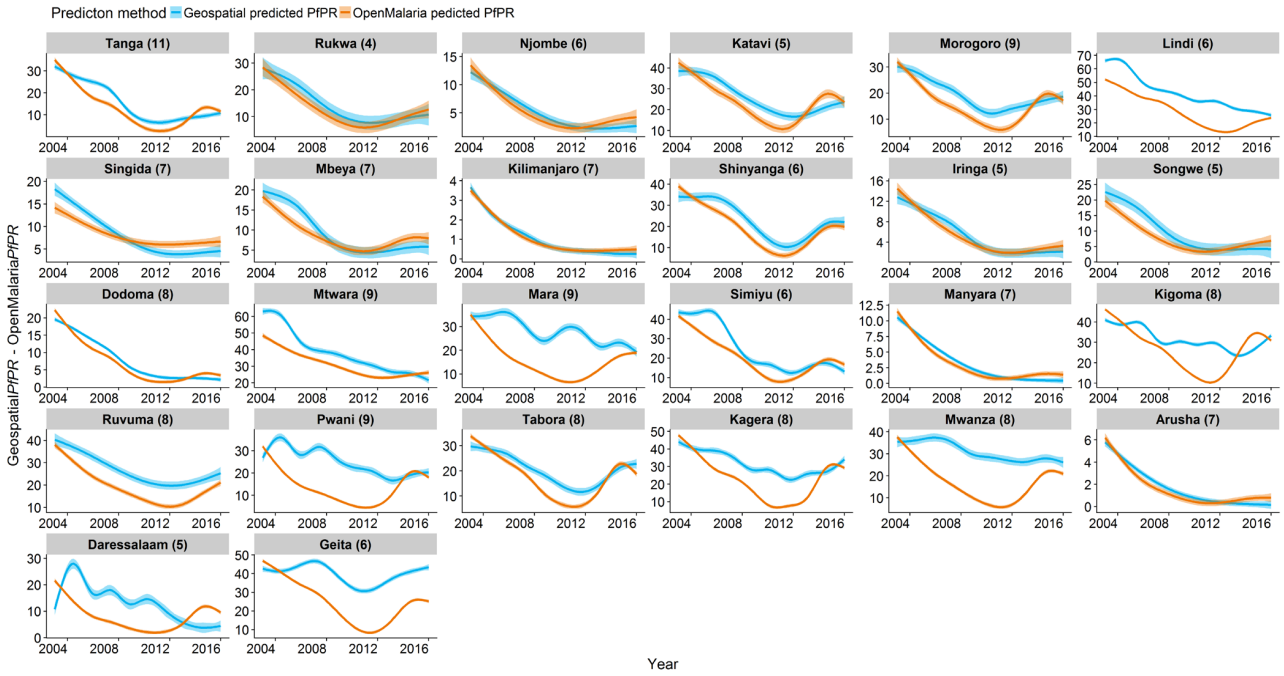

Fig. S4.5: Reproduced historical trend aggregated per region.
The prevalence estimates per council (n=184) were aggregated per region (n=26). The number in brackets shows the number of councils within a region and the facets was sorted by the fitting performance, as shown in Fig. S4.4.

Comparison of impact per intervention strategies per region

Three strategies were used for stratification and the choice of interventions. For each council, the choice of the interventions was defined as (1) the interventions that comply with the current NMSP a) without or b) with an improvement of the case management, (2) the interventions that form the most cost-effective strategy or (3) the interventions that lead to the national target with the smallest resources. These strategies were compared to the counterfactual scenario, which was defined as the discontinuation of vector control and with maintained case management at current levels in 2016 (see main manuscript).

The predictions of the 184 councils were aggregated per region for simplicity and visualisation of sub-national heterogeneity. The regional mean predictions for prevalence as well as for cases averted are shown in Fig. S4.6-8. Overall, the counterfactual scenario led to an increase in prevalence everywhere, but at different speed and to different levels. The rebound depends on the pre-intervention transmission intensity and effectiveness of historical interventions (not shown). The most cost-effective strategy lies between both the current NMSP, with and without improved case management and the strategy leading to the national target was the most impactful strategy in terms of prevalence and cases averted. The order of the strategies varied substantially in very low regions, namely in Arusha, Kilimanjaro, and Manyara, most likely due to stochastic and model uncertainty at such low transmission levels. The most cost-effective strategy was predicted to avert more cases and to reach lower prevalences than both the NMSP strategies in some regions but not in others and the differences between the two current NMSPs, with maintained and with improved case management, varied among the regions.

Those variations were likely due to differences in setting specific increase in case management levels, varying from 40% to 21% increase among the regions. Furthermore, region-specific differences may arise when interventions, which were part of the current NMSP, were discontinued in the other strategies. For instance, IRS was part of the current NMSP in the Lake Zone but was predicted not to be cost-effective and discontinued. Comparing the current NMSP with the most cost-effective strategy in those regions is different from the other regions which did not have IRS in the past. Another example would be the discontinuation of ITNs in low transmission regions, in Arusha, Kilimanjaro and Manyara (main manuscript Fig 6). The sub-national comparison highlights the heterogeneity and the importance to consider the historical trends, differences in seasonality and entomology when predicting likely impact of future intervention scenarios at local level and the importance to select proper outcome measures depending on transmission intensity.

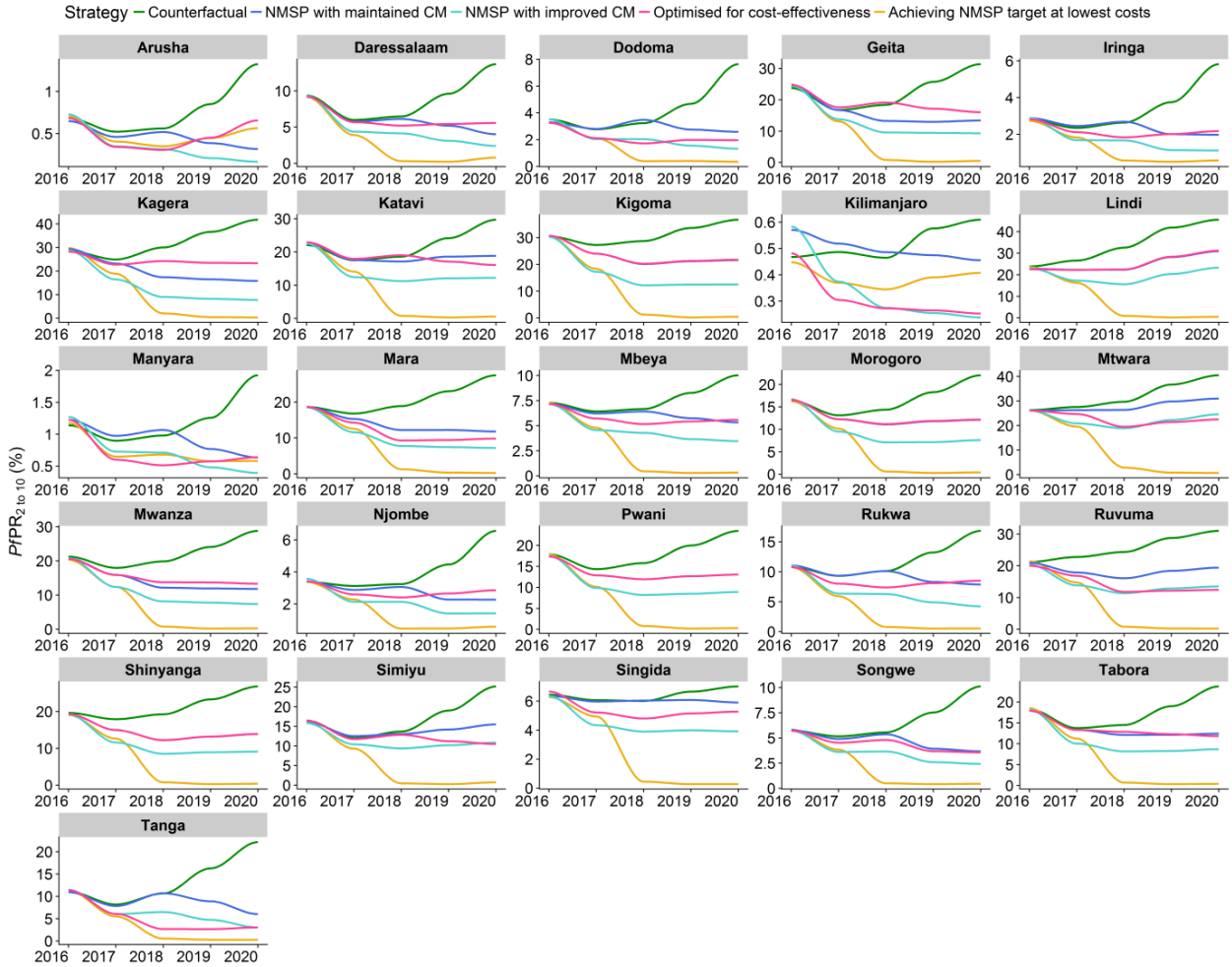

Fig. S4.6: Predicted prevalence over time per strategy and region.

Solid lines show the aggregated mean of council predictions. Confidence intervals showed high overlap and were removed.

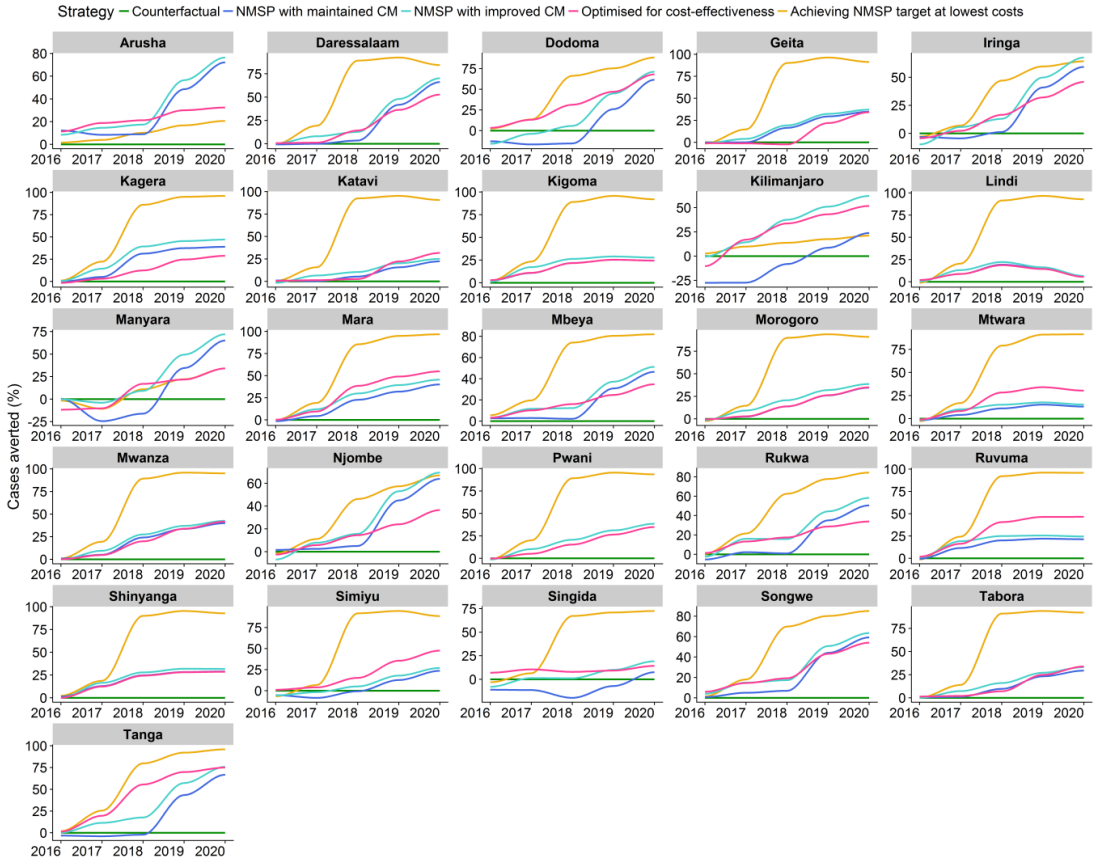

Fig. S4.6: Reduction in cases (%) over time per strategy and region.
Solid lines show the aggregated mean of council predictions. The confidence intervals showed high overlap and were removed.

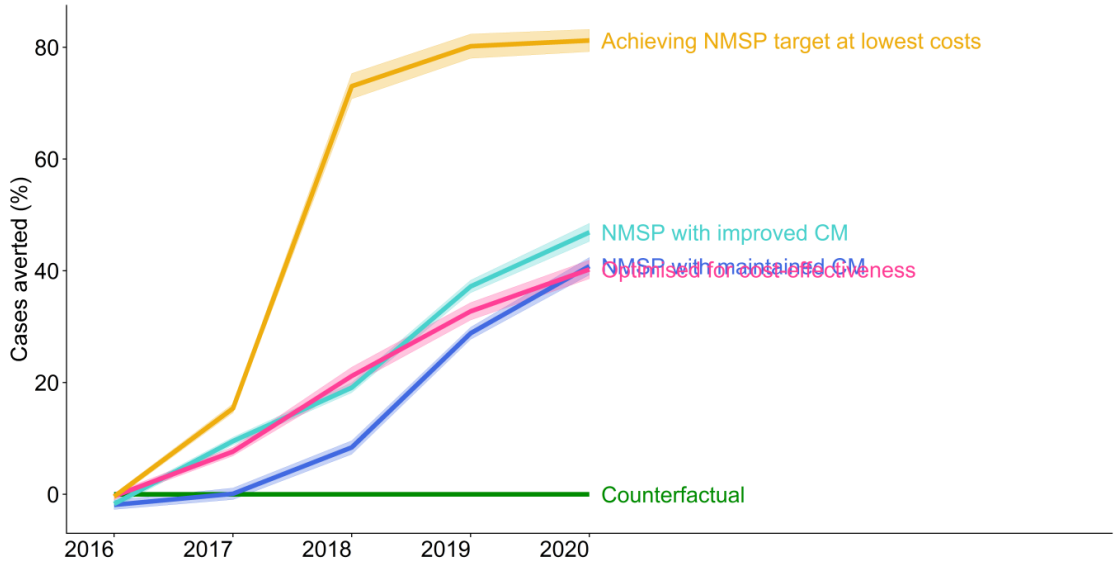

Fig. S4.7: Reduction in cases (%) over time per strategy.

The solid line shows the aggregated mean and the shaded area the 95% confidence interval based on heterogeneity among councils. The NMSP with maintained case management as well as the NMSP with improved case management refers to strategy 1, the most cost-effective intervention package to strategy 2, and the intervention package achieving the NMSP target to strategy 3. The counterfactual shows the simulated scenario with maintained case management levels and the discontinuation of vector control interventions.

Population weighed and unweighted mean prevalence

The presented predicted prevalences, aggregated at country level, were unweighted averages of the prevalence among the councils. The table below (Table S4.2) shows the averages weighted by the council population to obtain population-weighted mean predictions at national level. The two estimates, unweighted and weighted, were compared per strategy for three prevalence outcomes. The three prevalence outcomes were the predicted prevalence in 2020, the relative prevalence reduction compared to the baseline in 2016 ($Pf\text{PR}_{2020}$ – $Pf\text{PR}_{2016}$/$Pf\text{PR}_{2016}$), and the relative reduction in prevalence compared to the counterfactual in 2020 ($Pf\text{PR}_{strategy}$ – $Pf\text{PR}_{counterfactual}$/$Pf\text{PR}_{counterfactual}$). The weighted prevalence was very similar to the unweighted prevalence for all strategies for the prevalence, and the prevalence reduction compared to counterfactual, and showed higher differences in the prevalence reductions compared to the baseline in 2016 (Table S3.2).

Table S4.2: Comparison of population-weighted and unweighted predicted mean prevalences per strategy at national level for 2020.

Strategy	$Pf\text{PR}_{2to10}$ (%)		$Pf\text{PR}_{2to10}$ reduction compared to baseline in 2016 (%)		$Pf\text{PR}_{2to10}$ reduction compared to counterfactual (%)	
	unweighted	weighted	unweighted	weighted	unweighted	weighted
Counterfactual	21.5	20.8	-65.8	-60.2	0.0	0.0
NMSP	11.2	10.1	23.8	30.2	51.0	54.2
NMSP with improved case	7.4	6.5	52.1	56.9	69.0	71.5
Optimised for cost-effectiveness	10.5	10.0	25.0	29.1	53.0	54.2
Achieving NMSP target at lowest costs	0.4	0.5	77.5	79.6	87.4	88.1

4 Sub-national tailoring of malaria interventions in Mainland Tanzania: simulation of the impact of strata-specific intervention mixes using modelling

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This manuscript is a working paper

4.1 Abstract

Background: In the past few years significant progress has been made in mainland Tanzania to reduce malaria prevalence. In 2017, following the mid-term review of the 2015-2020 national malaria strategic plan (NMSP), it was recognised that a strategic reorientation of resources at the sub-national level was needed to sustain the progress made. This paper describes how mathematical modelling was used to support the strategic revision by assessing the council-level impact of various intervention combinations per malaria risk strata.

Methods: Intervention mixes, selected by the NMCP were simulated for each malaria risk strata at council level. Interventions included insecticide treated bed nets (ITN), indoor residual spraying, larval source management, and preventive therapies (seasonal chemoprevention and intermittent preventive therapies for school children (IPTsc). Two levels of effective treatment of clinical cases were considered: one based on estimates from the malaria indicator survey in 2016 and one corresponding to a hypothetical target of 85% effective treatment. A mathematical model in OpenMalaria, previously calibrated to all councils in Tanzania, was and used to compare trends in intervention impact predictions for prevalence and incidence between 2016 and 2020 or 2022.

Results: For each malaria risk stratum four to ten intervention mixes were simulated between 2017 and 2020. The resulting impact of various scenarios of intervention mixes were explored in the different transmission settings. In the low-risk and urban strata, no ITN mass campaign (scheduled for 2019), predicted moderate to high increase in prevalence by 2020 and 2022, while in the very-low strata a prevalence of less than 1% could be maintained by 2020 when the pre-intervention annual EIRs was less than 3 under the assumption of high case management and constant small importations. In the moderate and high strata, introduction of IPTsc predicted to reduce the incidence by an additional 15% and prevalence by 22.3% respectively. In the high-risk strata, improved case management with ITN mass campaigns were predicted to reduce malaria prevalence by an average of 50% and any additional intervention had only marginal impact, reaching a maximum reduction of 76%. The simulation of the 2018-2020 NMSP was predicted to achieve a slightly lower prevalence in 2020 compared to the simulation of the 2015-2020 NMSP (5.9%, [5.1-6.8%] vs 7.2%, [6.2-8.2%]), assuming high case management in both strategies.

Conclusion: Modelling was used to support the choice of intervention per malaria risk strata by simulating the expected impact of selected intervention mixes in each council. This approach complemented the epidemiological risk stratification developed for Tanzania. The use of a council-calibrated model, that reproduces local malaria trends, represents a useful tool for compiling available evidence into a single analytical platform, that complement other evidence, to aid National Programs with decision-making processes.

4.2 Introduction

Since 2000, increased funding towards the universal scale-up of malaria control prevention mainly through insecticide-treated bed nets (ITNs), and treatment with artemether-combination therapies (ACTs), substantially reduced the malaria transmission and burden in Africa (Snow et al., 2017; WHO, 2019c). However, in recent years, progress has stalled, and many countries are not on track to achieving national and global targets for 2020 and 2025 as defined in the WHO Global Technical Strategy (WHO, 2015a). Mainland Tanzania, together with nine other countries in Africa contribute to 66% of the global malaria burden, and this has instigated a more targeted 'high burden to high impact' (HBHI) approach for the allocation of limited resources in malaria strategic planning (WHO and RBM Partnership to End Malaria, 2019). This approach encourages national malaria control programs (NMCPs) in high malaria burden countries to include sub-national stratification of malaria risk with targeted interventions, thereby allowing to intensify control efforts in high transmission areas while maintaining the gains achieved in low transmission areas. In this context, a rigorous approach for sub-national tailoring of interventions that consist in appropriately selecting intervention mixes for specific risk areas remains a challenge and requires a good understanding of the local context. This can be informed with the use of mathematical modelling to predict the impact that different strategies might have.

Data from epidemiological, clinical, and operational studies along with routine health information systems represent a valuable data source for informing on malaria trends and retrospective intervention impact. However, they can be limited in predicting the impact of interventions over time in specific geographies and for specific combinations of interventions (Chubb and Jacobsen, 2010). Mathematical models represent a powerful tool for simulating setting specific malaria transmission dynamics and quantify, with some level of uncertainty, the impact of interventions and their combination in such settings. Mathematical modelling has been used to inform global and national strategies (Hamilton et al., 2017; Otieno et al., 2016; Scott et al., 2017; Walker et al., 2016), develop target product profiles for new interventions, investigate potential intervention combinations and alternatives (e.g. vector control (Chitnis et al., 2010a), or vector control and chemoprevention (Selvaraj et al., 2018)), predict the impact of new interventions such as vaccines (Penny et al., 2016), and to understand the potential role of surveillance-response (RBM, 2010), among other. The application of mathematical modelling at country level with simulations of suggested intervention mixes for specific geographies has a strong potential to aid decision-making and facilitate a better strategic approach in the selection of interventions.

In mainland Tanzania, the overall malaria prevalence decreased from 18% in 2008 (TACAIDS et al., 2008) to 7.3% in 2017 (MoHCDGEC et al., 2017a). As prevalence declines, the heterogeneity in malaria transmission has increased, with 40% of the population living in areas of low or very low malaria risk, 23% living in moderate risk areas, and 37% in high-risk areas that are predominantly located in the North-west and South-east of the country (Thawer et al., 2020). The 2015-2020 National Malaria Strategic Plan (NMSP) defines intervention packages at the regional level with ITNs distributed through mass campaigns or school net programs (SNP), indoor residual spraying (IRS) in the Lake Zone and larval source management (LSM) in some urban councils with a national target prevalence of less than 1% by 2020 (MoHCDGEC, 2014). In 2017, modelling approaches were applied to assess technical feasibility of reaching the NMSP target and to determine which intervention mixes would maximise impact to meet the target and within the constraint of cost-effectiveness (Runge et al., 2020b). In alignment with the modelling results, the mid-term strategic review of the NMSP in 2017, concluded that national prevalence targets would not be achieved with the current strategy (MoHCDGEC et al., 2017b).

In response to this, the NMCP developed an innovative approach to stratify the epidemiological risk of the country using combinations of routine and school survey data (Thawer et al., 2020). The resulting risk map divided the county into four epidemiological strata: very low, low, moderate, and high, and one operational strata, urban. The selection of appropriate interventions for each of these strata (subnational tailoring of interventions) was then performed in partnership with mathematical modellers who provided simulated evidence to compare the impact of various pre-determined intervention combinations, including interventions not yet implemented in countries and/or for which World Health Organisation (WHO) guidance was lacking. In 2018, recommendations from a consultative meeting (MoHCDGEC, 2018b) with a group of national and international malaria experts, selected a series of intervention mixes to be simulated for each strata (see complete list in Additional file 1). Three questions were of particular interest: (a) what would be the impact of stopping ITN mass distribution campaigns in the very-low, low, and urban strata? (b) what would be the additional benefit of intermittent preventive therapy in school-aged children (IPTsc) when ITNs (and/or IRS) are already deployed in moderate and high-risk strata? and (c) what combination of interventions would be required to substantially reduce malaria in the high risk-stratum? This paper presents the modelling approach that was used to provide some evidence that could support the answer these specific programmatic questions. The results of the present analysis, conducted in 2018, provided additional information for the NMCP to update their national strategic plan for the period 2018-2020 (MoHCDGEC, 2019).

4.3 Methods

Update of the National Malaria Strategic Plan

Following the mid-term strategic review in 2017, the NMCP decided to update their NMSP and introduce a malaria risk stratification in mainland Tanzania (MoHCDGEC, 2019; Thawer et al., 2020). The selection of appropriate interventions in each stratum was discussed in consultative meetings held in 2018 (MoHCDGEC, 2018b) with various stakeholders including local researchers, funders, implementers, interregional collaborators, and international partners. A 'Strength, Weakness, Opportunity and Threat' (SWOT) analysis was conducted to help in the selection of potential intervention packages for each of the strata and to suggest various potential intervention mixes. Mathematical modelling was then used to simulate the impact of these suggested intervention packages per council in order to support the final version of the strategy (Fig. 4.1 and Table 1) (MoHCDGEC, 2019).

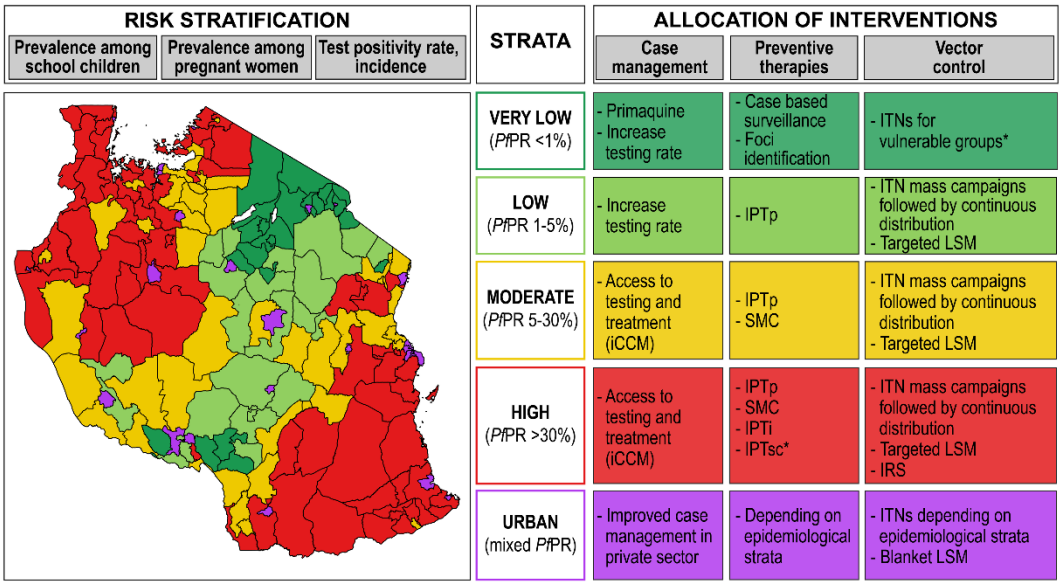

Fig. 4.1: Overview of malaria risk stratification and selected interventions per strata in Mainland Tanzania
This figure is a simplified version, adapted from the supplementary malaria midterm strategic plan (2018-2020 NMSP) (MoHCDGEC, 2019), that includes details on the stratification method (Thawer et al., 2020), intervention deployment and antimalarial drugs used. **Additional intervention allocation constraints and sub-groups:** IRS regions were Kagera, Geita, Mara, Mwanza, and Kigoma. Councils eligible for seasonal malaria chemoprevention (SMC) included Nachingwea DC, Bahi DC, Itigi DC, Nanyumbu DC, Masasi DC, and Manyoni DC. Continuous ITN distribution through schools (ITN-SNP) was operational in fourteen regions (Katavi, Kagera, Mara, Mwanza, Simiyu, Shinyanga, Geita, Lindi, Mtwara, Ruvuma, Morogoro, Tabora, Kigoma, Pwani), and in those areas no ITN-MRC was planned for 2019. **Abbreviations**: iCCM= integrated Community Case Management; ITN=Insecticide Treated Nets; IPT=Intermittent preventive therapy in (p) Pregnancy, (i) infants, (sc) school children; IRS: Indoor Residual Spraying. LSM= Larval Source Management. SMC: Seasonal Malaria Chemoprevention.
***)** Interventions not included in the WHO recommendations in 2018. In the very low strata, ITNs were considered for vulnerable groups only while universal coverage is recommended for ITNs in all malaria endemic areas (WHO, 2019b).

Model parameterisation and calibration

The microsimulation platform OpenMalaria (Swiss TPH, 2020) was used to simulate the dynamics of malaria and the impact of interventions in each council. This malaria transmission model represents the dynamics of malaria in humans with an individual-based model, and includes a population model simulating the vector dynamics (Briët et al., 2013; Chitnis et al., 2012, 2008a; Penny et al., 2015; Smith et al., 2008; T. Smith et al., 2012; Stuckey et al., 2013, 2012) as well as the effect size of interventions (Briët et al., 2013; Camponovo et al., 2019; Chitnis et al., 2010a; Reiker et al., 2019; Ross et al., 2008). The within-host component of the model had been previously calibrated to historical studies (Chitnis et al., 2008a; Smith et al., 2008). Transmission seasonality and intensity, historical intervention coverage and vector bionomics are key parameters that characterize a council and were informed by country specific data. Data sources included national-level household surveys and malaria indicator surveys, as well as entomological surveillance reports and intervention distribution information available from the NMCP. Details about the model parameterisation and calibration have been described elsewhere (Runge et al., 2019). In brief, assumptions for historical ITN usage were extracted from estimates by the Malaria Atlas Project (MAP) (Bhatt et al., 2015a). Assumptions on treatment seeking behaviour were informed by estimates from the national-level household survey data. Estimates of effective treatment given access to health services were extracted from Galactionova et al. for Tanzania (Galactionova et al., 2015). Geospatial predictions of *Plasmodium falciparum* prevalence among children aged 2 to 10 years ($Pf\text{PR}_{2\text{to}10}$) were derived for each council between 1990 and 2017, based on various community surveys conducted in Tanzania [2,32]. Using a Bayesian framework, the model was fitted to these predictions to represent historic trends of malaria transmission in each council [29,19]. Population estimates were obtained from the national census in 2012, assuming linear growth between 2012 and 2016 (NBS Tanzania 2013). A constant importation rate of 5 cases per 1000 population per year was used, corresponding to the estimated range of importations with Zanzibar (Tatem et al., 2009). The model was calibrated for each council and fitted to the model-based prevalence estimates per year between 2003 and 2016. The total simulation time spanned from 2003 to 2022, capturing historical trends until 2016 and projected impact of intervention combinations of interest from 2017 to 2022. In the model, no explicit distinction between urban and rural councils was made. Details on fitting are provided in Additional file 2.

Characteristics of interventions

Seven different interventions were simulated either alone or in combinations. The detailed coverage and deployment times are summarised in Table 1. In the simulations, “effective treatment rates” also

referred to as “case management” (CM) were defined as the proportion of symptomatic malaria cases effectively cured after treatment with an antimalarial.

Coverage of ITNs was defined as the ratio of the population protected by bed nets amongst the total population at risk. The ITN distributions were simulated so that coverage levels (proportion of population protected by a net) increased either at once, representing mass replacement campaigns (ITN-MRC), or coverage were maintained at constant levels, representing continuous distribution mechanisms (Lalji et al., 2016). In Tanzania, these continuous delivery mechanisms include school net programs (SNP) and distribution through reproductive and child health clinics (RCH). In the model the effect of both continuous ITN distribution mechanisms were assumed to be the same and the intervention abbreviated using ITN-SNP for simplicity. The ITNs were assumed to have a half-life of 3 years, inferring that only 50% of these would still be used after three years (Kilian et al., 2008) and for conservative purposes, it was assumed that high insecticide resistance to pyrethroids was established throughout the country for all vectors.

The simulations for IRS assumed the insecticide had organophosphate (Actellic 50EC) or carbamate (Bendiocarb) as active ingredients. The effect size parameterization was already established previously, with Actellic 50EC parameterized based on an experimental hut study In Côte d’Ivoire (Tchicaya et al., 2014) and Bendiocarb based on a study in Benin (Agossa et al., 2014) (Briët et al personal communication). Annual rotation between these insecticides was assumed starting with Bendiocarb in September 2017.

Although mass drug administration (MDA) had not been implemented in the country, the intervention was explored in the simulations, assuming an immediate clearance of blood-stage parasites without any lasting prophylactic effect after administration and targeting the whole population.

LSM, specifically with larviciding, was simulated with an effective coverage defined as the proportion of larvae killed (when compared to the number that should have emerged).

For intermittent preventive treatment in school-aged children (IPTsc), targeting children aged 5 to 16 years it was assumed that the drug would lead to immediate parasite clearance and have a prophylactic effect of fourteen days. Seasonal malaria chemoprevention (SMC) was considered for only six eligible councils was not specifically simulated, although roughly approximated with IPTsc in the strategic plan simulations. Intermittent preventative treatment in pregnant women (IPTp) is included in the national strategy but not in the simulations as its impact on transmission is limited (Ross et al., 2008). Similarly, behaviour change communication was not explicitly modelled as its direct impact is difficult to quantify. For all simulated interventions it was assumed that the coverage and the effectiveness would be homogeneous within each council.

Table 4.1: Simulated interventions and number of councils per intervention

	Deployment		Efficacy		Number of councils (N=184)	
	Coverage	**Timing**	**Efficacy mechanism / resistance**	**Duration**	**2015-2020 NMSP**	**2018-2020 NMSP**
CM	As in MIS 2016 (MoHCDGEC et al., 2016) or 85%	Jan 2017	No treatment resistance	Constant	all	all
ITN-MRC	80%	Jan 2019	80% pyrethroid resistance	50% effectively used after 3 years	105	76*
ITN-SNP**	40%, 70%	Jan Yearly between 2017 & 2020	80% pyrethroid resistance	50% effectively used after 3 years	79	76* +80
IRS	85%	Sep Yearly between 2017 & 2020***	No insecticide resistance	3 months (Actellic 50EC) 6 months (Bendiocarb)	27****	27****
LSM	60%	Setting specific, covering peak in transmission Yearly between 2017 & 2020	Reduction of emerging adult mosquitoes	4 months of constant effectiveness	25	25
IPTsc	80% 5-16 years	Jun, Oct Yearly between 2017 & 2020	Immediate clearance of blood-stage parasites	2 weeks prophylactic effect	0	73 (6)
MDA	80%	Jun, Aug, Oct Yearly between 2017 & 2020	Immediate clearance of blood-stage parasites	No prophylactic effect	(0 - for exploration only)	

* ITN-MRC followed by ITN-SNP in 76 councils.

** ITN-SNP was simulated with 40% or 70% coverage to either reflect school net distributions when deployed in moderate to high transmission strata (assumed higher coverage), or cumulative coverage of other routine distributions schemes in health facilities and through the commercial sector when deployed the low-malaria risk strata and in urban councils (assumed lower coverage).

*** Applying in rotation Bendiocarb and Actellic 50EC, starting with Bendiocarb in 2017

**** Different councils between the two NMSPs.

Analysis of simulation results

The full factorial combination of interventions including ITNs (distributed through MRC and/or SNP), IRS, IPTsc, MDA and strengthened CM were simulated for all councils. The model outputs are summarized with prevalence rates among children aged between two and ten years ($Pf\text{PR}_{2\text{to}10}$) and incidence in the whole population, defined as the total number of new cases (i.e. uncomplicated and severe malaria episodes) within a year per 1000 population. Model estimates for council predictions

are summarized with median and credible intervals from the posterior distribution from the model calibration. In addition, estimates per strata and at national level were summarized with population-weighted means and 95% confidence intervals (shown in squared brackets) of the council median estimates.

Relative reduction between 2016 and 2020 was calculated as $(x_{2016}-x_{2020}/ x_{2016})*100$, with x being either prevalence or incidence per council or strata.

The impact of discontinuation of ITNs mass campaigns (very low-risk, low-risk, and urban strata) was estimated by comparing a scenario in each stratum with strengthened CM only (discontinued vector control interventions starting in 2017) to a scenario with ITNs deployed as a mass campaign (ITN-MRC in 2019).

The impact of IPTsc (moderate and high risk-strata) was estimated by calculating the relative reduction in prevalence and incidence compared to no IPTsc, using predictions for 2020. The impact of strengthened CM was assessed in the same way using current CM levels as the counterfactual scenario.

The incremental benefit of adding interventions in the high-risk strata was described using the relative reduction for each intervention mix between 2016 and 2020. The intervention scenarios were: (1) no intervention other than strengthened CM; (2) ITN-MRC; (3) ITN-MRC in combination with IPTsc; (4) ITN-MRC in combination with IRS; (5) ITN-MRC in combination with ITN-SNP; (6) ITN-MRC in combination with ITN-SNP and IPTsc; (7) ITN-MRC in combination with ITN-SNP and IRS; and (8) ITN-MRC in combination with ITN-SNP, IRS and IPTsc. All eight scenarios were simulated assuming strengthened CM.

To compare the impact of the intervention strategies in the 2015-2018 NMSP and in the 2018-2020 NMSP, the difference in predictions ($X_{2015\text{-}2020\_NMSP}$ - $X_{2018\text{-}2020\_NMSP}$, with X being either prevalence or incidence in 2020) was computed for each council and then aggregated per strata (and nationally) using unweighted and population weighted means. All analyses were performed using R and RStudio (R Core Team, 2020).

4.4 Results

1) Impact of strata-specific intervention combinations for 2017-2020

Four to eleven intervention scenarios and two levels of CM were compared per strata, with fewest scenarios in the moderate risk and most scenarios in the urban stratum (Fig 4.2).

In the **very low-risk stratum**, the predicted prevalence for 2020 ranged from <0.1% to 1.5% across the simulated interventions and for both CM levels. Maintaining current CM level without additional interventions (counterfactual) was the least effective and implementing MDA was found to be the most effective intervention. The intervention scenario selected for the 2018-2020 NMSP was the

strengthening of case management and showed a prevalence close to the 2016 baseline prevalence as highlighted in green on Fig 4.2.

In the **low-risk stratum**, the predicted prevalence for 2020 ranged from 0.7% to 4.7% across the simulated intervention mixes. In this stratum, the coverage of ITNs and delivery mechanisms were drivers of impact. Prevalence in 2020 had comparable low levels either when mass campaigns were implemented or if the coverage was at least of 70% when distributed continuously. Amongst the suggested strategies, the ITN mass campaign combined with implementation of LSM had the most impact with predicted prevalence of 0.7% [0.5-0.9%] in 2020. On the contrary, a continuous distribution of nets with low coverage (40%) showed the lowest impact, especially with low CM levels (4.6% [4.0-5.4%]). All scenarios had lower prevalence compared to the 2016 baseline level (3.5%), except for ITN continuous distribution with 40% coverage and current CM.

In the **moderate-risk stratum**, all four simulated scenarios resulted in lower prevalence in 2020 than in 2016 (12.5%), that was further reduced when assuming strengthened CM, with prevalence ranging from 5.0% to 10.8%. The implementation of both ITN delivery mechanisms simultaneously, as included in the 2018-2020 NMSP, and assuming 70% coverage, was predicted to have similar impact as an ITN mass campaign coupled with the implementation of IRS (5.1%, [4.6-5.6%] vs 5.0% [4.5-5.5%]).

In the **high-risk stratum**, the predicted prevalence for 2020 ranged between 4.5% and 16.2% across the suggested scenarios, all lower than the baseline prevalence of 20.1%. The simulations showed that the implementation of both ITN delivery mechanisms simultaneously demonstrated a lower prevalence compared to either one alone or in combination with other interventions (7.5% [7.0-8.1%] for ITN-MRC + ITN-SNP; 9.2% [8.5-9.8%] for ITN-MRC; 10.7% [10.1-11.5%] for ITN-SNP). The most impactful intervention mix corresponded, as expected, to the scenario with the most interventions (both ITN distribution mechanism, IPTsc and IRS) and was expected to lower the prevalence down to 4.5% [4.0-5.0%] in 2020. The intervention mixes simulated for the 2018-2020 NMSP were ITN-SNP, IPTsc and IRS in some councils, the associated predicted prevalence for 2020 was 5.6% [5.2-6.2%] with IRS and 9.0% [8.4-9.7%] without IRS.

The **urban stratum** included a broad mix of intervention scenarios, ranging from single interventions such as strengthened CM, LSM, or MDA to combinations of those in addition to either ITN mass or continuous campaigns, depending on the epidemiological strata. The predicted prevalence of the simulated interventions ranged between 0.6% and 7.7%. All intervention combinations were predicted to reduce the prevalence compared to the baseline, except LSM with current CM. In this stratum, four intervention combinations were suggested for the 2018-2020 NMSP depending on the epidemiological risk-strata.

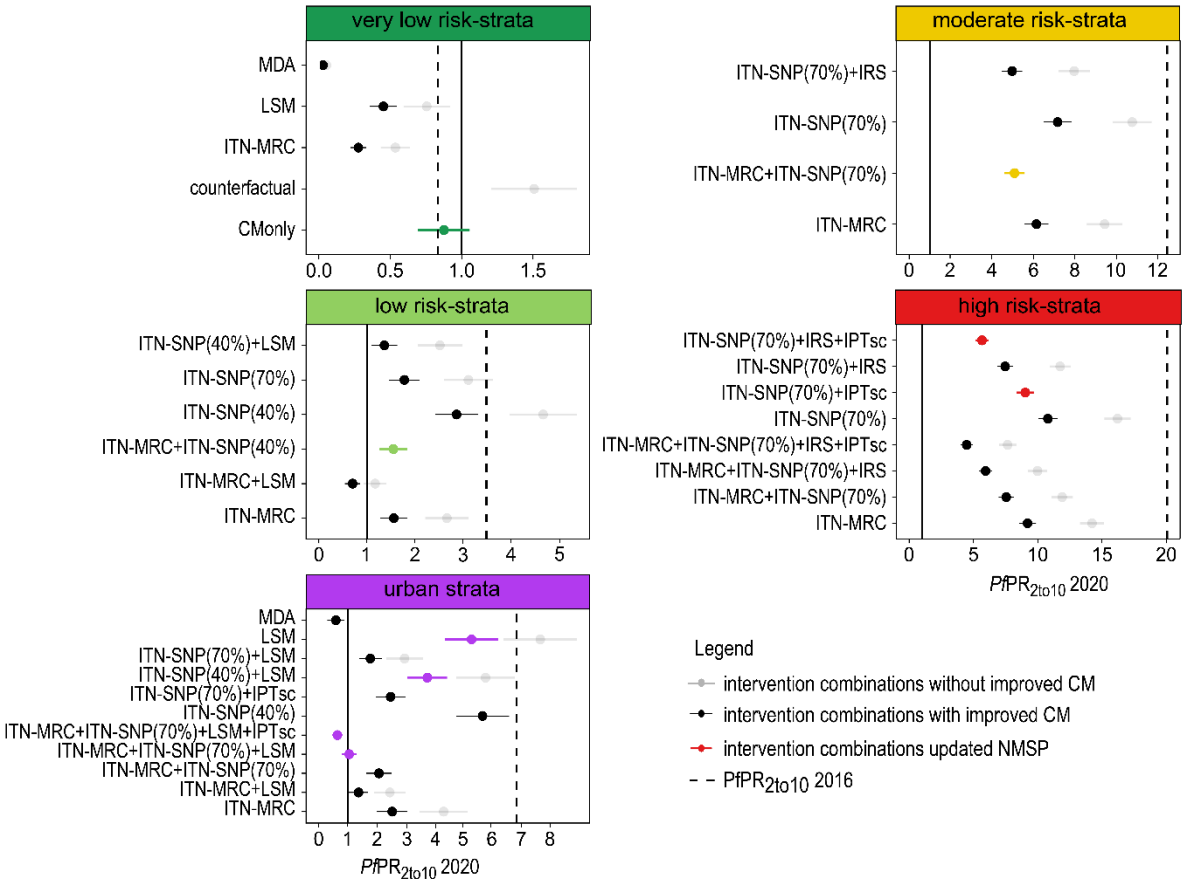

Fig. 4.2: Predicted prevalence for intervention mixes per strata for 2020.
The error bars show the mean and 95% confidence intervals based on heterogeneity among councils. The black and highlighted error bars correspond to current CM level simulations and the grey error bars to strengthened CM. The highlighted error bars show the intervention combinations selected for the 2018-2020 NMSP. The vertical solid line indicates a prevalence of 1% and the dashed line shows the simulated prevalence for 2016.

2a) Impact of discontinuation of ITN mass campaigns in very low, low, and urban strata

Without an ITN mass campaign in 2019, an increase in prevalence was predicted in all the three strata with moderate increase by 2020 and considerable increase by 2022. For 2020, the absolute increase was marginal in the very low-risk strata (0.58% [0.35-0.81%]), slightly higher in the low-risk strata (1.96% [1.49-2.44%]), and almost 4 percent points in the urban strata (3.94% [2.79-5.09%]) (Fig. 4.3**Error! Reference source not found.**A). The magnitude in increase differed depending on the pre-intervention transmission intensity. In councils in the very low-risk strata with pre-intervention entomologic inoculation rate (EIR) lower than 3 infectious bites per person per annum (ibpa), the prevalence remained below the 1% threshold until at least 2022. When the pre-intervention transmission level was between 3 and 8 ibpa, the prevalence exceeded 1% by 2022, and at pre-intervention transmission levels above 8 ibpa, a prevalence below or at 1% could not be maintained or reached in 2020 and increased further by 2022 (Fig 4.3B).

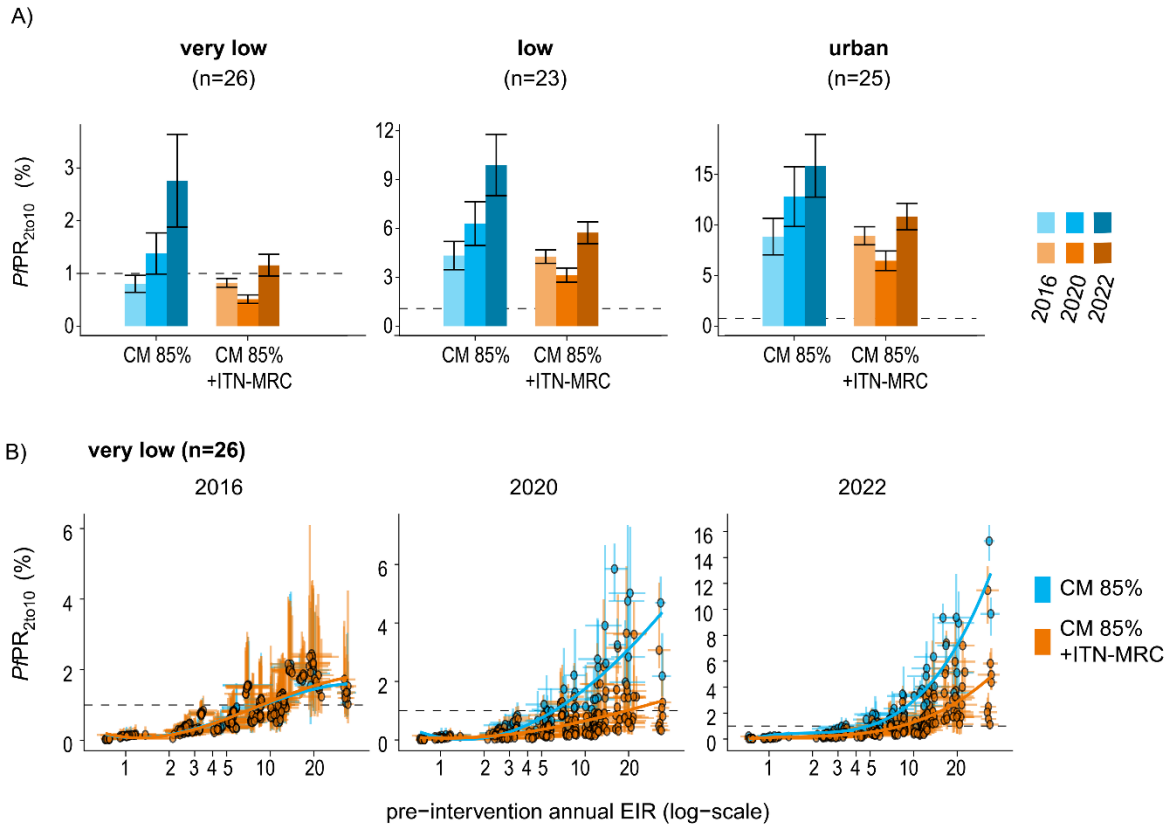

Fig. 4.3: Predicted impact on prevalence for discontinuation of ITN mass campaigns in the very low, low, and urban strata.

A) The bar charts show the mean and confidence interval of council prevalence aggregated per strata comparing improved CM without ITN-MRC distribution in 2019 (blue) to improved CM with ITN-MRC distribution in 2019 (orange). **B)** Prevalence per pre-intervention transmission intensity per council in the very low-risk stratum compared for the two scenarios with or without additional ITNs for the years 2016, 2020 and 2022. The points indicate the posterior median, the error bars and the credible intervals resulting from the model calibration. The dashed line highlights a prevalence of one percent.

2b) Potential benefit of adding IPTsc in the high and moderate-risk strata combined

IPTsc reduced the predicted prevalence for 2020 on average by 22.3% [21.8-22.8%] and the incidence by 15.2% [14.7-15.6%], when combined with vector control intervention mixes (ITN-MRC, ITN-SNP, IRS). In comparison to IPTsc, strengthening CM was less effective in reducing incidence in all ages (8.2%, [7.8-8.5%], while more effective in reducing prevalence in children between 2 and 10 years (38%, [38.0-38.8%]) (Fig 4.4).

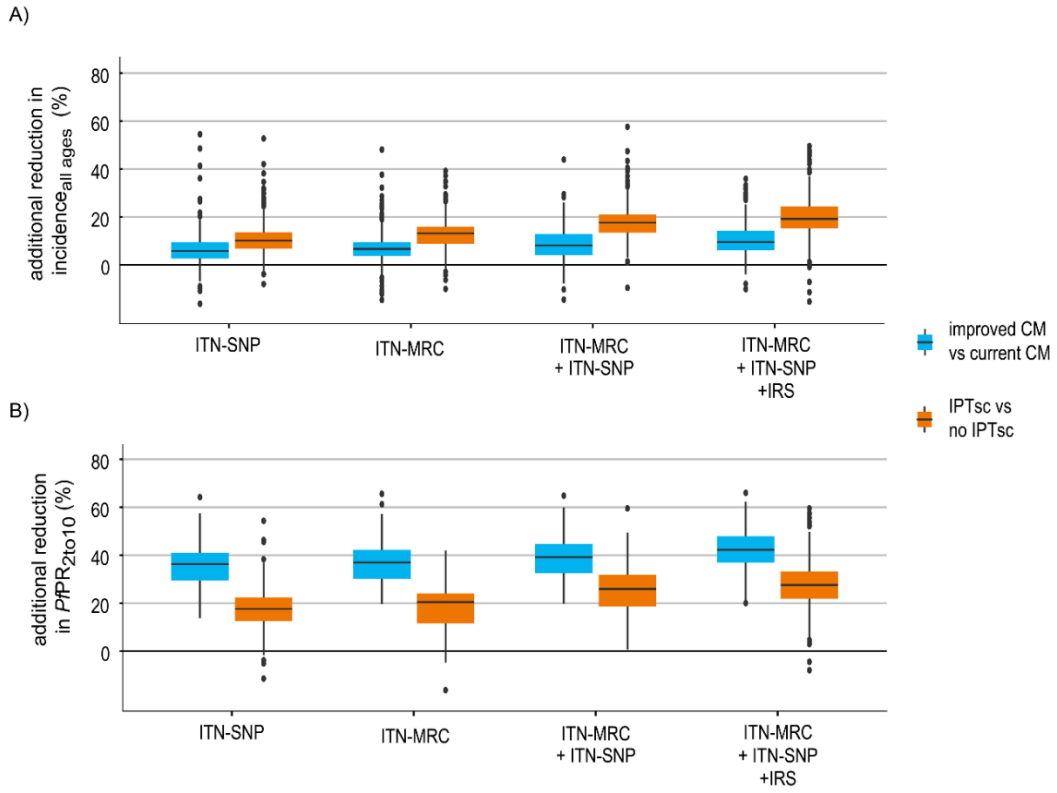

Fig. 4.4: Predicted impact of IPTsc and CM in the moderate and high-risk strata combined.
Panel **A)** shows the impact on incidence in the total population for 2020 and panel **B)** on *Pf*PR_{2to10} for 2020. The impact of IPTsc was evaluated when deployed on top of vector control interventions and the impact of strengthened CM was plotted as reference. The boxplots show the distribution among councils in the moderate- and high-risk strata combined. The x-axis presents the different combinations of vector control interventions.

2c) Incremental benefit of interventions in the high-risk stratum

The choice of the intervention mixes considered in the high-risk stratum were made to understand the incrementable benefit of each additional interventions. The simulated scenario that corresponded to a maximum number of interventions (both ITN delivery mechanism, strengthened CM, IRS and IPTsc) predicted an average reduction in prevalence by 72.8% [68.1-77.6%] between 2016 and 2020. Of that reduction, approximately 70% was attributed to strengthened CM and ITN-MRC (mean reduction 47.5%, [41.7-53.3%]. The other interventions were predicted to reduce the prevalence by an additional 8% to 25%. The relative reduction in prevalence of additional IRS was comparable to that of additional IPTsc or ITN-SNP (relative reduction in *Pf*PR_{2to10} 58.7% for IRS, 56.3% for IPTsc, 56.9% for ITN-SNP when administered in addition to strengthened CM and ITN-MRC) (Fig. 4.5A). Strengthened CM and ITN-MRC were predicted to reduce the prevalence by at least 50% in most councils (n = 52 out of 73 districts in high strata). However, in at least 13 councils, even the implementation of all interventions would not be sufficient to reduce prevalence by more than 50% (Fig 4.5B).

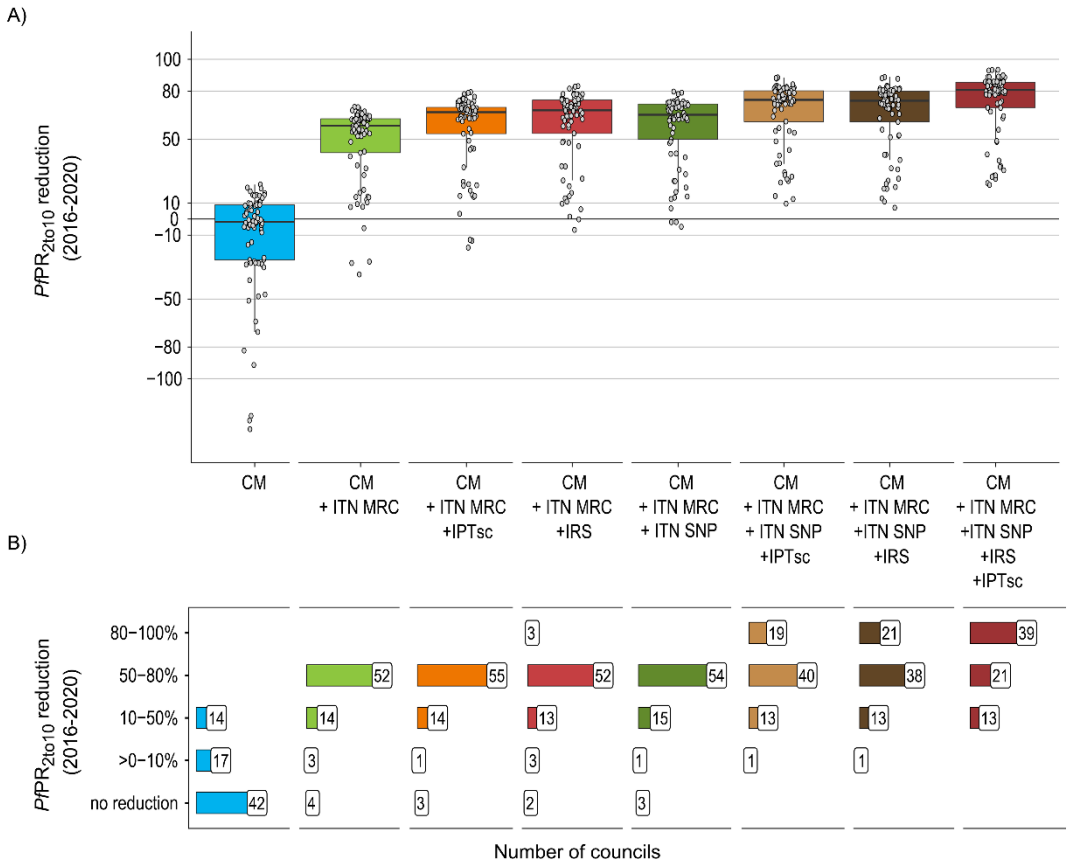

Fig. 4.5: Predicted reduction in prevalence in 2020 compared to 2016 per intervention combinations for councils in malaria high-risk strata.

A) Predicted prevalence reduction between 2016 and 2020 per incremental intervention mix, each point represents a council (n=73, including four urban councils). The solid line in the boxplot shows the median and the dashed line the mean. **B)** Number of councils per incremental intervention mix grouped by prevalence reduction.

3) Predicted impact of the simulated 2015-2020 NMSP and 2018-2020 NMSP

In the simulation of the 2018-2020 NMSP, the prevalence reductions between 2016 and 2020 were highest in the high and moderate-risk strata (mean *Pf*PR$_{2to10}$ reduction 63.5%, [57.8-69.2%] and 58.9%, [55.6-62.2%] respectively), followed by the low- and urban risk strata (57.8%, [53.3-62.4%] and 60.1%, [52.8-67.3%] respectively) and the lowest in the very low-risk strata (1.5%, [13.1-16.1%]). Figure 4.6 shows the ratio of the predicted prevalence and incidence for 2020 between of both simulated NMSPs. Compared to the simulated 2015-2020 NMSP scenario, the simulated 2018-2020 NMSP scenario projected lower prevalence and incidence values for most of the councils in the moderate and high-risk strata (with mean ratio of for both strata respectively). In the low-risk strata the simulated 2015-2020 NMSP performed better, while the impact was heterogeneous in the low-risk and in the urban strata. In all, except the urban, strata did the mean across councils correspond to the population weighted mean across councils (Fig 4.6). In the simulation of the 2018-2020 NMSP,

the proportion of the population that would live at a high malaria risk (*Pf*PR$_{2to10}$ greater than 10%) in 2020 would be around 10% less than in the simulation of the 2015-2020 NMSP (Table S2.1).

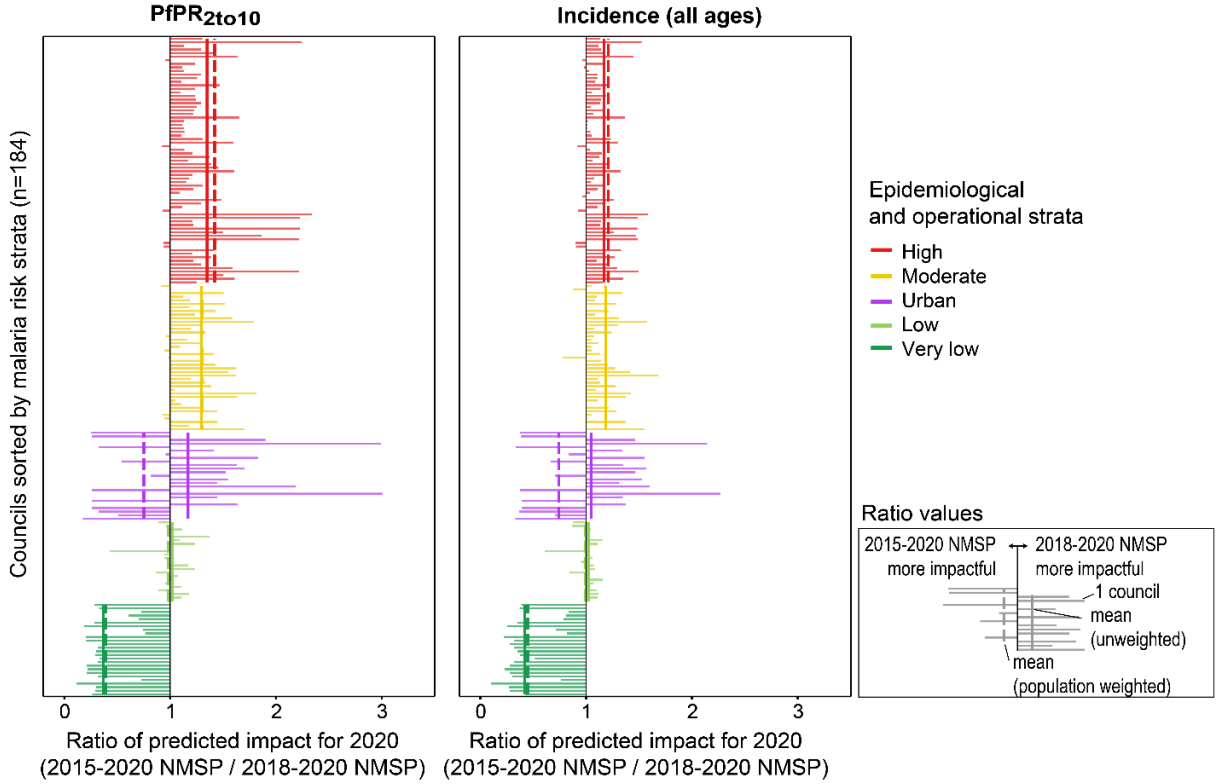

Fig. 4.6: Comparison of predicted impact of the simulated 2015-2020 NMSP and 2018-2020 NMSP per council for 2020.

Ratio in predicted prevalence (left panel) and incidence (right panel) for 2020 between both simulated NMSPs. Each horizontal line represents one council. The vertical lines show the mean ratio per strata with solid line for unweighted mean and dot-dashed line for population-weighted mean.

4.5 Discussion

In this work, mathematical modelling was used to simulate a set of selected intervention mixes, tailored to the malaria risk strata at council level in mainland Tanzania, followed by predicting the impact of relevant interventions between 2016 and 2022. The simulated strata-specific intervention mixes were selected to (i) represent the 2015-2020 (MoHCDGEC, 2014) and the 2018-2020 NMSP (MoHCDGEC, 2019); (ii) and to address specific questions relevant to the NMCP. These questions were: (a) what would be the impact of stopping ITN mass distribution campaigns in the very-low, low, and urban strata; (b) what would be the additional benefit of IPTsc when ITNs (and/or IRS) are already deployed in moderate and high-risk strata; and (c) what intervention mix would be required to substantially reduce malaria in the high risk-stratum. The simulations and main analyses were conducted during the strategic planning process in 2018 (Runge et al., 2020a) that accompanied the

development of the initial malaria risk stratification (Thawer et al., 2020). This work utilizes a previously parameterized model, calibrated to each council in mainland Tanzania, to provide timely model predictions interactively discussed with the NMCP, as described in (Runge et al., 2020a). A table for each of the simulated intervention scenario per strata and the corresponding strategic response was included in the 2018-2020 NMSP (MoHCDGEC, 2019) (Additional file 3).

Overall, both simulated NMSPs had similar impact predictions at national level, but highly varying predictions among risk strata. For instance, in the high- and moderate-risk strata the 2018-2020 NMSP was predicted to achieve higher reductions than the 2015-2020 NMSP, which in turn performed slightly better in the very low-risk stratum. Impact predictions for the low-risk and urban strata were mixed and did not show a clear tendency for either strategy above the other. Although, the model predicted substantial reductions in prevalence for all strategies at national level between 2017 and 2020, they were not high enough to reach the 2015-2020 NMSP target prevalence of less than 1% by 2020. Notably, in both simulated NMSPs the impact on prevalence, with strengthened CM in addition to vector control, was higher than the impact gained through the reallocation of vector control or additional IPTsc for the time frame in consideration. A high effect from strengthened CM in combination with vector control was also observed in other countries (Farooqui et al., 2012; Hamilton et al., 2017).

In mainland Tanzania, most of the councils in the very low-risk stratum have low receptivity due to unsuitable climate and environmental conditions (NMCP et al., 2013), hence a sub-analysis of the simulations assessed the scenario of discontinuing large scale ITN mass campaigns in the very-low and low risk strata as well as urban strata. The results showed clear increasing trends by 2020 in the low-risk and urban strata for the scenario without an ITN-MRC in 2019 and an even higher increase by 2022, whereas predictions were not homogeneous among councils. In the very low-risk strata, the increase by 2020 was on average low but highly varied depending on the pre-intervention EIR. At low pre-intervention EIR, the prevalence predicted for 2020 was not substantially higher than with a ITN mass campaign in 2019, whereas at higher pre-intervention EIR, high CM alone was not enough to keep prevalence low, which aligns with previous modelling studies (Crowell et al., 2012; Yukich and Chitnis, 2017). While the results could suggest that universal coverage and large-scale deployment of nets might not be required to maintain baseline levels in low-risk settings with persistent low transmission, the results should be interpreted with caution as local contextual factors, especially surveillance and monitoring capacities, were not captured in the model, and as model stochasticity is high for simulations with low transmission.

To the best of our knowledge, only very few areas in malaria-endemic countries discontinued ITNs. For instance, in Kenya, ITNs that were previously deployed countrywide (Noor et al., 2010), are now deployed in the low-risk zone in only 50% of counties via routine ITN distributions (PMI, 2019a). Zambia is moving from universal ITN to more targeted campaigns (PMI, 2019b), whilst in Namibia, ITNs are mostly recommended for personal protection or in transmission foci in malaria risk free or low transmission areas (National Vector-borne Diseases Control Programme, 2010), and in Zimbabwe nets are not distributed in the highland areas that are at very low risk of malaria (PMI, 2018b). Recent analysis on cancellation of ITN mass campaign due to the COVID-19 pandemic in 2020, in low as well as high transmission areas across Sub-Saharan Africa predicted potential substantial increase in cases and deaths, varying across countries (Weiss et al., 2020). In practice discontinuation of interventions in persistently low transmission areas should only be considered when having a strong surveillance system in place (Yukich and Chitnis, 2017), as well as strategies for foci detection and protection of the vulnerable population as included in the 2018-2020 NMSP (MoHCDGEC, 2019).

In mainland Tanzania as well as other countries, school children were found to be a large reservoir for malaria parasites (Chacky et al., 2018; Coalson et al., 2016; Gitonga et al., 2012a), with malaria prevalence as high as 76% in some councils (Chacky et al., 2018). A randomised control trial conducted in Ugandan schoolchildren demonstrated high efficacy of preventive therapies in these groups as well as community-wide effect (Nankabirwa et al., 2014b; Staedke et al., 2018). Results of a recent systematic review showed beneficial impact of preventive treatment in low and high transmission areas (Cohee et al., 2020) and highlights the importance targeting school children in malaria control. IPTsc, simulated in the moderate and high-risk strata, showed an additional benefit on prevalence and incidence independent of the underlying vector control interventions. These results are lower than estimated effectiveness between 66% to 83% combined across field studies (Cohee et al., 2020). However, a direct comparison is not possible as the in the present analysis IPTsc was simulated on top of strong vector control interventions, and the effectiveness was calculated compared to counterfactual after three years of deployment. Interestingly, IPTsc showed a higher impact on incidence (all ages) but lower impact on prevalence when compared to the impact of strengthened CM. This could be explained by the differences in target population between the two strategies. Simulated IPTsc targeted 5 to 16-years-old, one of the most vulnerable group that gets highly infected and symptomatic during the transmission season, whereas CM affects the whole population that might have built disease immunity despite high prevalence. Hence, effectively treating infections might reduce transmission in children and adults but affect the burden, especially for the whole population, less. A simplified IPTsc parameterisation was used assuming immediate parasite clearance and prophylactic effect of two weeks with four deployment rounds during the

transmission season. In practice, the post-treatment prophylactic effect was found to range between 14 to 35 days and the deployment schedule differed across trials (Cohee et al., 2020). whereas the optimal deployment of IPTsc across different settings is unclear (Matangila et al., 2017). In practice, concerns also exist about development of resistance in the parasite against the antimalarials used for IPTsc (O'Meara et al., 2005), and further in-depth analysis with varying antimalarials and deployment schemes would be useful for more accurate IPTsc impact predictions.

In the third sub-analysis of the presented work, it was assessed what it would take to substantially reduce malaria in the high-risk strata by comparing the incremental impact of additional interventions. In the analysis, a high CM coverage was assumed since strengthening the health care system is a priority independent from vector control and other malaria interventions. The model predictions showed a reduction of around 50% for high coverage levels in CM and ITN-MRCs, and a maximum reduction of around 70% when ITN-SNP, IPTsc and IRS were added. In some councils however, additional interventions of one or more of ITN-SNP, IRS, or IPTisc would be needed to achieve at least a 50% reduction in prevalence. While these findings with greatest impact for CM and ITN align with expectations based on previous published studies (Bhatt et al., 2015a), the high impact predicted for ITNs is to some extent surprising, as high pyrethroid resistance was assumed for all vectors in all areas. This could be due to the high coverage of at least 80% immediately after the mass campaign simulated in 2019 and the continued protection provided by the physical net barrier (Lindblade et al., 2015; Ochomo et al., 2013). The evidence on reduced net effectiveness at different resistance intensities is limited (Pryce et al., 2018) and varies between modelling studies (Briët et al., 2013; Churcher et al., 2016). In addition, the simulated IRS deployments in 2018 and 2020 used the more short-lived Actellic 50EC (Fuseini et al, 2011; Aïkpon et al 2014) instead of Actellic 300CS (Haji et al 2015; Mashauri et al., 2017), which likely underestimates predicted impact of IRS. An important additional in-depths analysis in mainland Tanzania would be using vector and location specific resistance parameters and including new insecticides for ITNs (Protopopoff et al., 2018) and IRS (Agossa et al., 2018).

Utilizing a previously calibrated model to address questions that are relevant to the current situation in the country, enabled delivering timely results to meet the needs of the NMCP during the funding application and strategic planning cycle, as it provided an additional layer of information for the selection process of targeted interventions per malaria risk strata. While it provides an impactful approach, the modelling analysis has several limitations that affect the accuracy of the results.

First, the simulated NMSPs are a simplified version of the actual NMSPs (MoHCDGEC, 2014, 2019), as not all interventions were simulated. For instance, IPTp and IPTi were excluded as they were assumed not to have a major impact on malaria transmission in the community (Ross et al., 2008). Piperonyl butoxide treated nets were not simulated as, at the time of analysis, planned in only two councils (Muleba and Kagera) (PMI, 2019c). Similarly, SMC, planned in six councils, was approximated with IPTsc. In the model larviciding did not distinguish between targeted or blanket deployment and due to large uncertainties around feasible larviciding coverages and related effectiveness (Runge et al., 2021) simulation outputs were excluded from results presented to the NMCP. Improved CM was simulated with a target coverage of 85% effective treatment, whereas health system strengthening and improvement in CM will likely differ across councils as they depend on baseline performance and strategies to improve CM in respect to the local contexts.

Second, the specific questions addressed would benefit from further in-depth analyses at a more granular level and including more sources of uncertainty, i.e. uncertainty in intervention parameters and model structure, stochasticity and increased population sizes especially in councils with small populations and low transmission intensities. With strata and intervention specific characteristics requiring additional parameters, one large simulation-model becomes inefficient and insufficient to address all programmatic questions. However, to allow for a constant re-evaluation and adjustments in interventions, a fast and flexible modelling approach using a parsimonious model that can be easily updated would be an advantage.

Third, while the results include heterogeneity within strata, the model results are likely less accurate at council level because seasonality, entomology as well as historical intervention parameters were assumed to be homogeneous for councils within a region. Sub-region as well as sub-council heterogeneity will be increasingly relevant and feasible to account for in future models as data continues to improve and country malaria risk stratifications being developed at higher resolution, and intervention being deployed at finer spatial scale. Similarly, urban and rural councils only differed in their transmission intensity and setting specific parameters for seasonality and intervention coverage, whereas socio-demographic factors (Smith et al., 2021), population density (Kabaria et al., 2017), local environment and infrastructure (Kabaria et al., 2016), as well as human mobility malaria case importation rates (Lowa et al., 2018; Wesolowski et al., 2012) among other factors that are important considerations for intervention implementation.

Finally, the applied model primarily addresses the technical feasibility, not the operational or financial feasibility (The malERA Consultative Group on Modeling, 2011), hence model predictions are likely overestimated and should be interpreted in relative terms. The model predictions obtained in this analysis were designed for comparing intervention impact predictions at the time of the analysis rather than making predictions about the future impact of the strategy. This distinction is

especially important since long-term temporal effects might bias the intervention impact predictions. Examples for long-term temporal effects include inter-annual variations in climate, that might lead to local malaria epidemics (Bangs and Subianto, 1999; Kilian et al., 1999; Lindsay et al., 2000; Mabaso et al., 2007), or public health emergencies, such as the COVID-19 pandemic in 2020 (Dawood et al., 2020) that caused service delivery interruptions and delays in several countries and was predicted to potentially substantially increase malaria burden and deaths (Aborode et al., 2020; Heuschen et al., 2021; Sherrard-Smith et al., 2020; Weiss et al., 2020).

In mainland Tanzania, the IRS campaign in few councils got delayed by around six months due to COVID-19, while the ITN campaign initially planned for 2019, was rescheduled to 2020 due to reasons not related to COVID-19. DHIS-2 trends indicate a reduction in outpatient health care seeking and testing whereas test positivity ratio and incidence remained relatively constant. The next round of DHS has not been completed at the time of writing the manuscript and a validation of modelling results was not possible and would have been challenging due to the reasons outlined above. It is however critical to update and recalibrate these models as a dynamic process as new data becomes available to maintain an up-to date country specific model.

The results of this work extend previous work where modelling was applied to assess the technical feasibility of reaching the 2015-2020 NMSP target prevalence of less than 1% by 2020 and to explore alternative intervention allocations at council level that would lead to most impact on prevalence or be most cost-effective in reducing incidence (Runge et al., 2019). In contrast to these previous objectives where modelling was used to obtain a new council stratification based on modelled impact, this work used modelling to obtain a comparison for selected interventions for a fixed council stratification based on malaria risk (MoHCDGEC, 2019; Thawer et al., 2020). Both use cases demonstrate the potential value of modelling to support the development of malaria strategic plans, which under the HBHI initiative (WHO and RBM Partnership to End Malaria, 2019) finds increasing application in other high burden countries (WHO, 2020).

In Tanzania, the shift from almost fully unconstrained mathematical modelling analysis (free combination of interventions and allocation to councils (Runge et al., 2019)) to a modelling analysis under meaningful constraints set by the NMCP (present analysis) demonstrates two distinct yet related use cases for applying modelling to inform a national malaria control strategy. Although risk stratification should be based on local data, geographical patterns in intervention impact predictions could play a supportive role for sub-national tailoring of interventions to guide intervention allocation for each strata.

The process will become more reliable and dynamic with the use of increasing high-quality routine data as basis for stratification and modelling. The increased use of mathematical modelling outputs in consultation with National Malaria Control Programs will result in strengthened strategic and operational planning that will lead towards burden reduction and ultimately elimination.

4.6 Conclusion

A modelling approach was presented for predicting the impact of intervention mixes targeted to malaria risk strata in mainland Tanzania as defined by the NMCP during the strategic planning process. By using a previously calibrated model, the model could readily address emerging questions and provided a powerful analytical insight into likely trends of intervention impacts on malaria prevalence and incidence across and within malaria risk strata. The application of modelling for exploring alternative intervention scenarios is likely to increase confidence in the selection of intervention mixes when developing a new national malaria control strategy. Continuous model updates and improvements in the approach will be crucial when scaling up the application of modelling for strategic planning processes in countries.

4.7 Declarations

Author contribution

MR performed the analysis and wrote the draft manuscript. ST, FM, FC, RM, AM, SM supported interpretation of modelling results during the strategic planning workshop and contributed to the discussions of the selection of scenarios to simulate. RWS, CL and EP provided overall guidance in the project and in the preparation of the draft. All authors read and approved the final manuscript.

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4.8 Supplementary information

SI-1: Strategic planning questions for modelling in Mainland Tanzania

Explanation of past impact

1. How could the increase in malaria prevalence since the Tanzania HIV/AIDS and Malaria Indicator Survey (THMIS) 2012 (SMPS data) be explained/be predicted?

Assessment of the feasibility of targets

2. Will the proposed strategies in the Malaria Strategic Plan 2015 -2020 result in the target of less than 1% prevalence by 2020 in all parts of the country?

Comparison of strategies

3. What are the differences in impact and costs of current and revised NMSP?

Comparison of intervention combinations by setting

6. What is the additional impact of IRS in combination to ITN in settings where there is pyrethroid resistance?
7. Understanding the additional benefit of using PBO nets.
8. What is the additional impact of MDA in very low transmission districts (in low strata)
9. What is the impact of increased surveillance and active case detection system to target efforts for focal and reactive MDA

Effectiveness of single interventions

10. What is the difference in the impact of using ACT versus primaquine for MDA?
11. How sustainable is MDA, and what are the influencing factors?
12. What is the potential role of larviciding in urban areas and low transmission settings?
13. Does changing insecticide used for IRS to SumiShield lead to higher impact?

Targeting of interventions

14. What is the effect of adding PBO-nets through continuous distribution channels in regions with high insecticide resistance?
15. Should urban areas be handled differently when targeting interventions? (e.g. discontinuing mass ITN distribution campaigns?)
16. Are ITNs still needed at persistent very low transmission?
17. Is CM enough to maintain low prevalence at persistent very low transmission?
18. Additional impact and costs of IPTsc (which is a not yet WHO recommended intervention) in high strata, only in high strata or also in moderate strata?

Deployment and operational considerations

19. What is the effect of alternative health care delivery modes for hard-to-reach populations?
20. What is the effect of scaling up diagnostics in the informal health sector (ADDO) and increasing access to affordable quality-assured ACT in the private sector?
21. What is the optimal deployment regimen for larviciding?
22. How to sequentially best deploy PBO nets? At which rate and how many districts to include?

Technical questions

23. How far to go back in time to produce accurate future predictions?
24. Which parameters to fit and which to fix?
25. How detailed do the historical interventions be included? (e.g. only considering ITN coverage, or also IRS and LSM?)
26. How detailed do the simulations need to be for district predictions? Generic simulations, simulations confined to administrative boundaries?

SI-2: Fitting performance and additional result figures and tables

Historical trend in prevalence

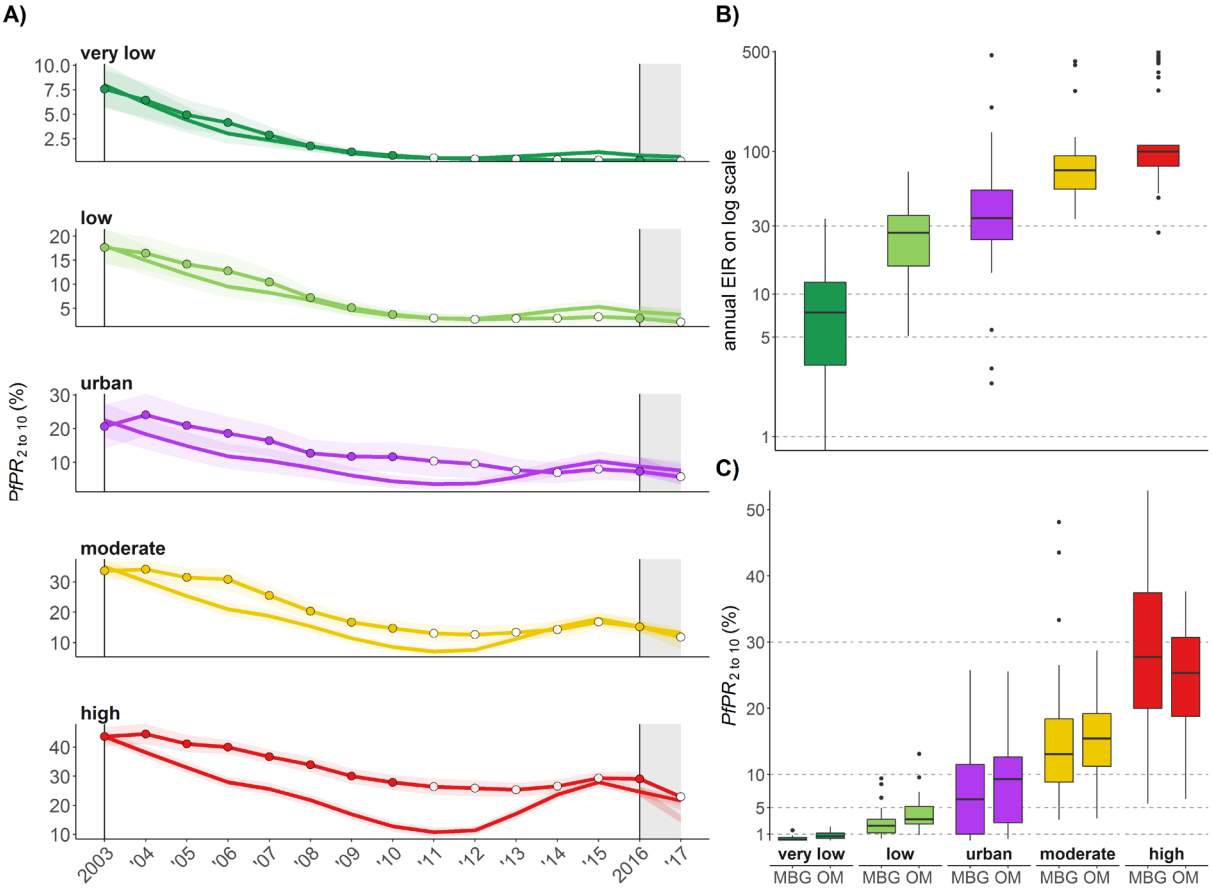

Fig. S2.1: Model-predicted and simulated malaria prevalence and estimated transmission intensity

A) The lines without points show the prevalence simulated from the mathematical model and the line with annual points shows the geospatial predicted prevalence. The filled points indicate the estimates included and the white points the estimates not included in the fitting. The shaded area shows the confidence interval based on geographical heterogeneity between the councils. The vertical dashed lines show the baseline year and the grey shaded area the time between 2016 and 2017. **B)** Estimated pre-intervention EIR. **C)** Average-weighted simulated prevalence (OpenMalaria) in comparison to model-based geostatistical (MBG)-predicted prevalence for 2016.

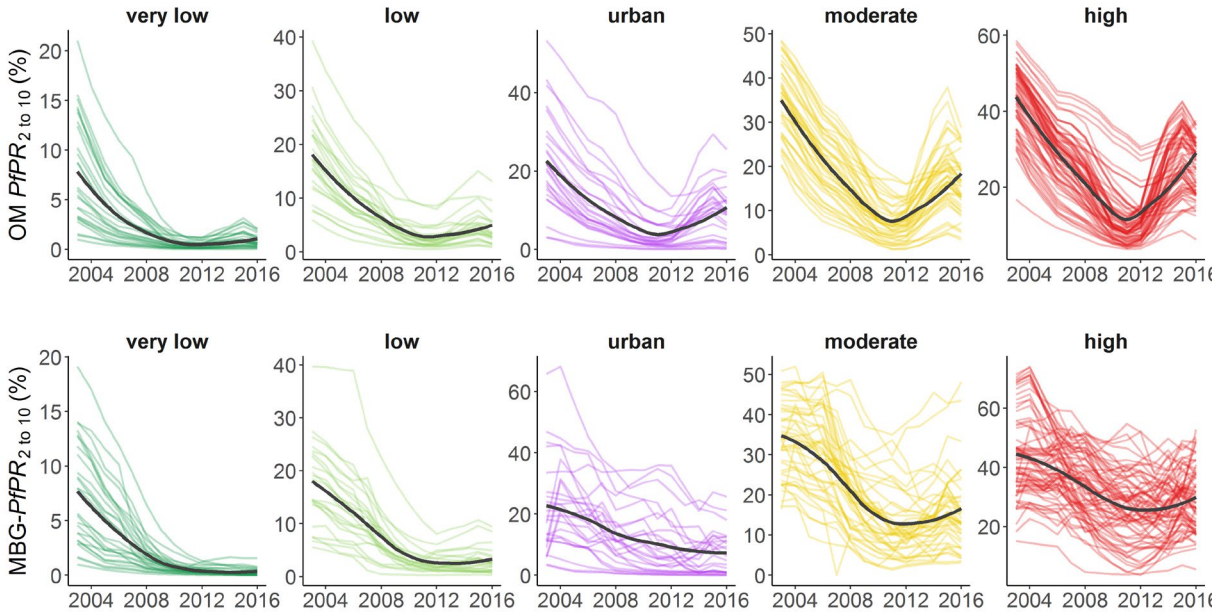

Fig. S2.2: Heterogeneity in malaria prevalence per council, grouped by strata, 2003-2016

The historical trend in simulated prevalence (top row) and geospatial predicted prevalence (bottom row). Each line corresponds to one council, and the black line shows the average per strata.

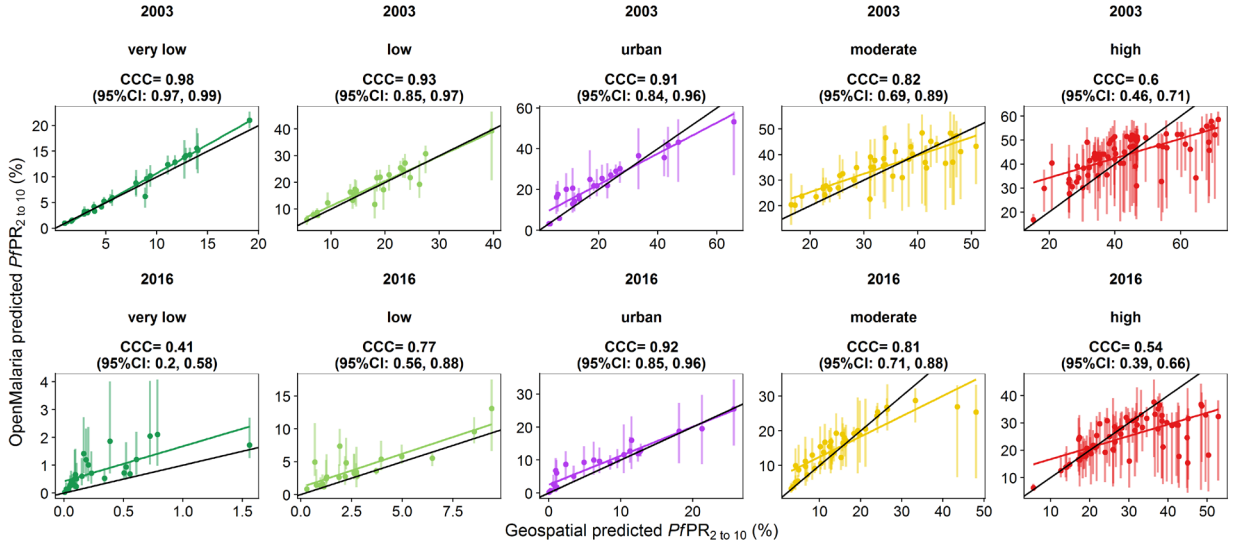

Fig. S2.3: Fitting performance for simulated prevalence per council grouped by strata

The figure shows the predicted prevalence and the geo-statistical model prevalence. The pre-intervention (2003) and baseline year (2016) are the most relevant historical time points since the prevalence before the deployment of interventions determines the level of possible rebound, and the prevalence in the baseline year is used as a comparator for assessing the relative impact of future interventions. The scatter plots show the respective prevalence estimates with the regression line (coloured line) and perfect correspondence line (black line) grouped by strata. CCC = Lin's concordance correlation coefficients.

Intervention predictions

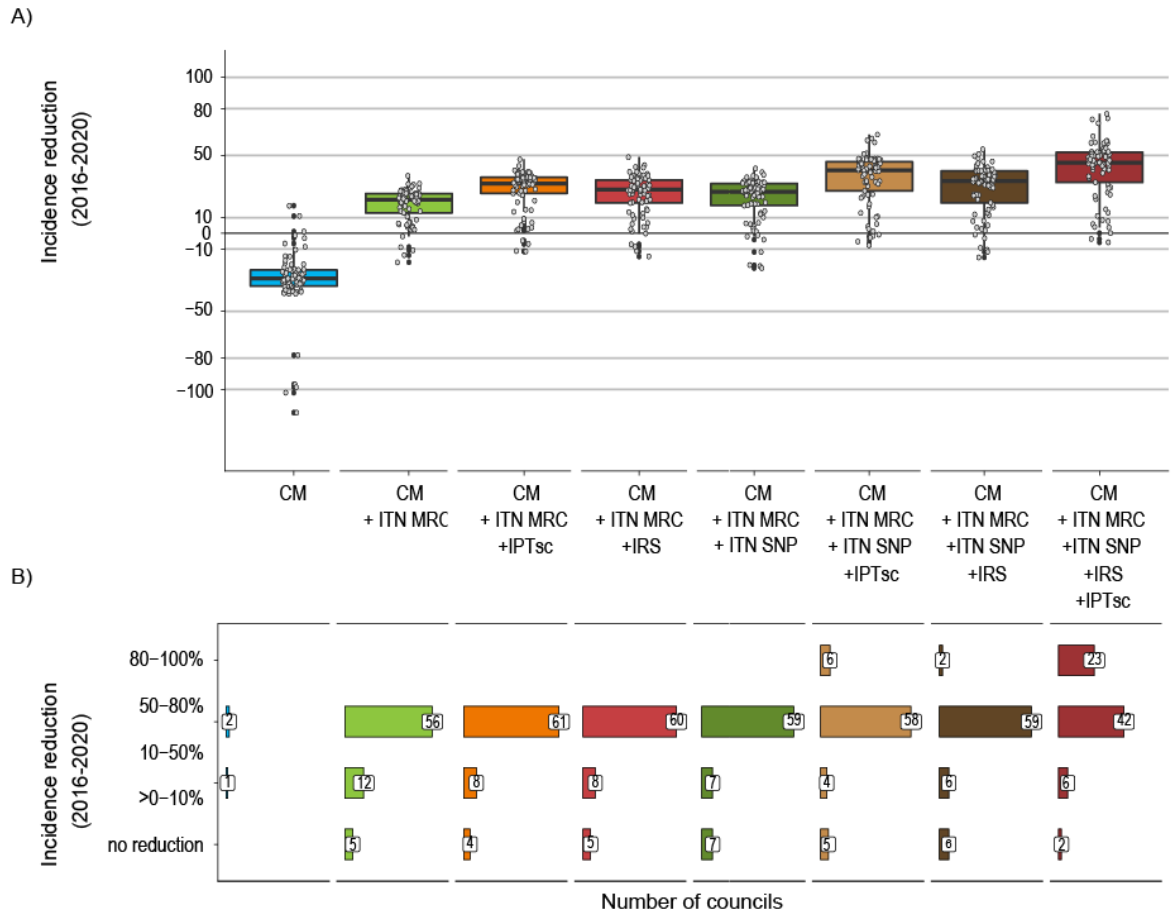

Figure S2.4: Predicted reduction in incidence in 2020 compared to 2016 per intervention combinations for councils in malaria high-risk strata.

A) Predicted incidence reduction per intervention mix on the x axis, each dot represents a single council (n=73, including 4 urban councils). **B)** Number of districts per intervention mix grouped by incidence reduction.

Table S2.1: Proportion of the population at risk compared between the two national strategies

Endemic prevalence categories (%)	Proportion of the population (%)		Proportion of the population, cumulative (%)	
	2015-2020 NMSP	2018-2020 NMSP	2015-2020 NMSP	2018-2020 NMSP
<=1	24.7	13.4	24.7	13.4
>1-5	23.6	29.5	48.3	42.9
>5-10	31.1	47.5	79.4	90.4
>10-25	19	8.7	98.4	99.1
>25-50	1.7	1.0	100	100
Total	100	100	100	100

SI-3: Results table as included in the revised strategic plan*

Stratum	Modelling Results	Strategic response and mitigation
Very low	• Without ITN replacements but with high effective treatment rate, the prevalence was predicted to be maintained until 2020. • Depending on the pre-intervention EIR, a slight increase in prevalence was predicted after the effect of the last MRC (2016) decayed, while prevalence in 2020 remained lower as the baseline prevalence in 2016. • MDA was predicted to rapidly interrupt transmission, although the impact was predicted to not last for more than two years after stopping MDA in councils with low transmission intensity assuming improved case management.	• Establishment of improved surveillance and response, including case-based surveillance with reactive case detection; Foci investigation and response with reactive vector control interventions; Epidemic detection and response
Low	• ITNs were assumed to be maintained at least 40% coverage in the population (e.g. through continuous distributions) with improved CM at least 80% and results predicted to maintain the baseline prevalence in 2016 until 2020. • In the scenario without additional implementation of ITNs, the prevalence was predicted to increase in 2020.	• Establishment of ITN coverage surveillance for optimizing ITN distribution mechanisms. • Improved malaria surveillance and response including epidemic detection and response
Moderate	• ITN mass campaign followed by continuous ITN distributions (e.g. SNP), was predicted to result in a large decrease in prevalence until 2020 if no other control measure was in place.	• Establishment of ITN coverage surveillance for optimizing ITN distribution mechanisms.
High	• The combination of annual ITN distributions, maintaining an ITN coverage of at least 70%, additional IRS campaigns in districts in the Lake Zone and Kigoma, and IPTsc in all districts was predicted to result in high reductions in prevalence until 2020, which reached the same predicted prevalence as in the moderate strata. • Implementation of IPTsc showed some additional impact and the deployment would need to be assessed at the council level. • The combination of mass campaign and annual ITN distributions led to additional marginal reductions.	• Establishment of ITN coverage surveillance for optimizing ITN distribution mechanisms. • IRS to be deployed according to optimized resource allocation.
Urban	• The baseline prevalence in 2016 was highly heterogeneous, and discontinuation of ITN distributions in all urban areas was predicted to result in a rebound in prevalence. • Therefore, ITN distributions in urban areas should follow epidemiological strata. • In practice, LSM, e.g. larviciding, might have an additional impact but was not included in the simulations.	• ITN distribution mechanisms to be deployed according to the underlying epidemiological stratum. • Optimal CM coverage to be reached with private sector quality improvement schemes.

*) edited format and shortened from the SMMSP [14]

[14] National Malaria Control Program, 2019. Supplementary malaria midterm strategic plan 2018 - 2020, National Malaria Strategic Plan. Ministry of Health Community Development Gender Elderly & Children, Dar Es Salaam, Tanzania.

5 Applied mathematical modelling to inform national malaria policies, strategies and operations in Tanzania

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5.1 Abstract

Background: More than ever, it is crucial to make the best use of existing country data, and analytical tools for developing malaria control strategies as the heterogeneity in malaria risk within countries is increasing, and the available malaria control tools are expanding while large funding gaps exist. Global and local policymakers, as well as funders, increasingly recognize the value of mathematical modelling as a strategic tool to support decision making. This case study article describes the long-term use of modelling in close collaboration with the National Malaria Control Programme (NMCP) in Tanzania, the challenges encountered and lessons learned.

Case description: In Tanzania, a recent rebound in prevalence led to the revision of the national malaria strategic plan with interventions targeted to the malaria risk at the sub-regional level. As part of the revision, a mathematical malaria modelling framework for setting specific predictions was developed and used between 2016 and 2019 to (1) reproduce setting specific historical malaria trends, and (2) to simulate in silico the impact of future interventions. Throughout the project, multiple stakeholder workshops were attended and the use of mathematical modelling interactively discussed.

Evaluation: In Tanzania, the model application created an interdisciplinary and multisectoral dialogue platform between modellers, NMCP and partners and contributed to the revision of the national malaria strategic plan by simulating strategies suggested by the NMCP. The uptake of the modelling outputs and sustained interest by the NMCP were critically associated with following factors: (1) effective sensitization to the NMCP, (2) regular and intense communication, (3) invitation for the modellers to participate in the strategic plan process, and (4) model application tailored to the local context.

Conclusion: Empirical data analysis and its use for strategic thinking remain the cornerstone for evidence-based decision-making. Mathematical impact modelling can support the process both by unifying all stakeholders in one strategic process and by adding new key evidence required for optimized decision-making. However, without a long-standing partnership, it will be much more challenging to sensibilize programmes to the usefulness and sustained use of modelling and local resources within the programme or collaborating research institutions need to be mobilized.

5.2 Background

5.2.1 Why using modelling for strategic planning?

The concept of using mathematical modelling for strategic planning of infectious disease control is not new (Garnett et al., 2011; Maude et al., 2010; RBM, 2010). Multiple examples exist for a wide range of infectious diseases (Fung, 2014; Grassly and Fraser, 2008; Habbema et al., 1992; Njeuhmeli et al., 2019; Van Kerkhove and Ferguson, 2012) and specifically for malaria (Brady et al., 2017; Maude et al., 2010; Penny et al., 2016; The malERA Refresh Consultative Panel on Combination Interventions and Modelling, 2017; White et al., 2009). Mathematical modelling uses available information to generate data-driven simulations of transmission dynamics and control for specified settings (Kramer et al., 2009; Maude et al., 2010; White et al., 2009; WHO, 2014). The model predictions can quantify with some uncertainty the expectations of the impact of interventions for different areas. The exploration of alternative scenarios aids in decision-making and facilitates a more strategic approach in the selection of interventions (Hamilton et al., 2017; Otieno et al., 2016; Scott et al., 2017; Walker et al., 2016). More than ever, it is crucial to make the best use of existing country data and analytical tools (WHO, 2015a) because: (1) there is an increasing complexity with the expanding available malaria control tools as a result of effective research and development, (2) the local epidemiology is becoming more heterogeneous as a result of massive ongoing control efforts, and (3) resources, especially funding, are not increasing. Hence, global and local policymakers, as well as funders, increasingly recognize the value of mathematical modelling as a strategic tool to support decision-making (RBM, 2010; The malERA Refresh Consultative Panel on Combination Interventions and Modelling, 2017) (Table 5.1). In addition, growing stakeholder coordination and the need to use evidence will lead to more strategic questions about priorities and combination of interventions. In parallel, more and better quality data become available in endemic settings, enhancing the value of modelling (Maude et al., 2010).

These developments clearly call for a more sustainable and in-depth relationship between modellers, NMCP managers and donors. Given the historical difficulty of linking modelling and strategic planning, intensified technical support, closer interactions, and capacity building within-country NMCPs are required. This case study presents such close collaboration between modellers, donors and the NMCP managers, providing a unique and effective example of modelling for strategic planning.

Table 5.1: Value of modelling for strategic planning of malaria control interventions

Additional layer of information collating all available evidence to disentangle key determinants, predict expected impact and identify knowledge or data gaps.
Generation of hypotheses and guidance of decisions by comparing scenarios that might not necessarily have been evaluated on the ground.
Establishment of an interdisciplinary platform for structured discussions on strategies.
Assessment of technical feasibility to achieve specific goals that can be useful in the context of strategic plan updates, funding applications, prioritization of interventions, and operational planning.

5.2.2 Geographic specific malaria modelling

Mathematical models have been applied for various countries at varying resolutions, examples include sub-Saharan African (SSA) countries (Korenromp et al., 2016; Walker et al., 2016; Winskill et al., 2019, 2017), Ghana (Awine et al., 2017; Oduro et al., 2012), Kenya (Stuckey et al., 2014b, 2012), Mozambique (Lee et al., 2017; Silal et al., 2015), Nigeria (Hamilton et al., 2017; Molineaux et al., 1980; Scott et al., 2017), Uganda (Tompkins et al., 2019), South Africa (Silal et al., 2014), Zambia (Gerardin et al., 2017; Nikolov et al., 2016; Slater, 2017; Stuckey et al., 2016), and the Asia-Pacific Region (Celhay et al., 2019; Silal et al., 2019). In those examples, modelling was used to investigate relevant transmission dynamics, intervention effectiveness or for stratification. While sometimes useful for global policy writing, there have been fewer examples where mathematical modelling has been applied in a country at the required operational unit and accompanied with a national policy dialogue. Exceptions are Zambia (Slater, 2017), Ghana (Awine et al., 2017), South Africa (Silal et al., 2014), Cambodia and Thailand (Mahidol Oxford Research Unit (MORU)), Mozambique, Sri Lanka, Philippines, Benin (Swiss TPH). In Kenya, Tanzania and Uganda, a decision support tool has been developed in communication with local stakeholders, to link research and policy for “guiding the selection of more effective, evidence-based control strategies” (Brown et al., 2012; Kramer et al., 2009); however, no country-wide application could be found.

5.3 Country application Mainland Tanzania

In 2016, a team of modellers from Swiss TPH were invited by the Global Fund to Fight AIDS Tuberculosis and Malaria (GFATM) to provide support to the Tanzanian NMCP for preparing the upcoming funding request (The Global Fund, 2013). After this initial undertaking ended in early 2017, the NMCP and the Swiss TPH team suggested to continue modelling which then could be made an intrinsic part of the on-going planning processes of the NMCP. The sections below describe the non-technical process of applying mathematical modelling, its added value, challenges and lessons

learned. The development of the modelling approach is described in (Runge et al., 2019) and the results of modelling application are included in the Supplementary Midterm Malaria Strategic Plan 2018-2020 (MoHCDGEC, 2019).

5.3.1 Partnerships and collaborations

The Swiss TPH has a long-established relationship with the NMCP in Tanzania. In 2002, the Swiss Agency for Development and Cooperation (SDC) launched the NETCELL project to provide technical and strategic support to the NMCP, with the Swiss TPH as implementing partner (Duncan, 2019). Since its launch, NETCELL contributed to the strengthening of the NMCPs capacities to plan, coordinate, and implement malaria control interventions, in particular insecticide-treated bed nets (ITNs) (Alliance for Case Studies for Global Health, 2009; Renggli et al., 2013). The NETCELL team collaborates with the Ministry of Health, Community Development, Gender, Elderly and Children (MoHCDGEC), the President's Office, Regional Administration and Local Government (PO-RALG), UK Department for International Development (DfID), United States Agency for International Development (USAID), Worldbank, GFATM, among others (Duncan, 2019). The Swiss TPH modelling team closely worked with the NETCELL team, which in turn facilitated the interactions between the modellers and the NMCP programme members. The NETCELL project has recently been renewed under the financing of the SDC and has many more years to provide continuous support to the MoHCDGEC. Another important regional partner was the KEMRI-Wellcome Trust Programme, who managed DFID funded projects (INFORM and LINK) (KEMRI - Wellcome Trust Research Programme, n.d.) to provide spatial epidemiological analytical support using nationally available malaria data for subnational decision making in Tanzania and other NMCPs across Africa (NMCP et al., 2013; Snow and Noor, 2015).

5.3.2 National malaria strategic planning

Strategic planning in Tanzania is based on a strong malaria monitoring and surveillance system, including high-quality district health information system (DHIS2) data (Lungo, 2008), entomological surveillance (Kabula et al., 2011), resistance monitoring (Kisinza W et al., 2015), demographic and health surveys, and malaria indicator surveys (MoHCDGEC et al., 2017a, 2016; TACAIDS et al., 2013, 2008; NBS Tanzania and ORC Macro, 2005). Since 2014, nationwide annual school malaria parasitaemia surveys also bring high-quality and high-resolution cross-sectional data to the NMCP database (Chacky et al., 2018). The Tanzanian epidemiological data show nowadays a highly heterogeneous malaria transmission and burden throughout the country (MoHCDGEC et al., 2017a, 2016; TACAIDS et al., 2013, 2008; NBS Tanzania and ORC Macro, 2005; Chacky et al., 2018). The National Malaria Strategic Plan (NMSP) for 2015-2020 acknowledged that diversity of malaria

transmission and disease burden within the borders of Mainland Tanzania, but largely adopted a uniform approach to disease management and prevention nationwide (MoHCDGEC, 2014). An increase in national average prevalence from 9.5% to 14.8% between 2012 and 2015-16 (MoHCDGEC et al., 2016; TACAIDS et al., 2013), led to the questions of whether the current NMSP would technically be feasible to achieve the national target, of a prevalence of less than one per cent in 2020. In line with this question arose the issue of optimizing intervention mixes according to endemicity and key epidemiological parameters. As a result, a decision was made by the NMCP to work on a supplementary malaria midterm strategic plan aiming at optimal intervention mixes in different epidemiological strata to ensure optimal impact for available resources (MoHCDGEC, 2019). A timeline describing the events leading to the supplementary malaria midterm strategic plan is shown in Fig. 5.1.

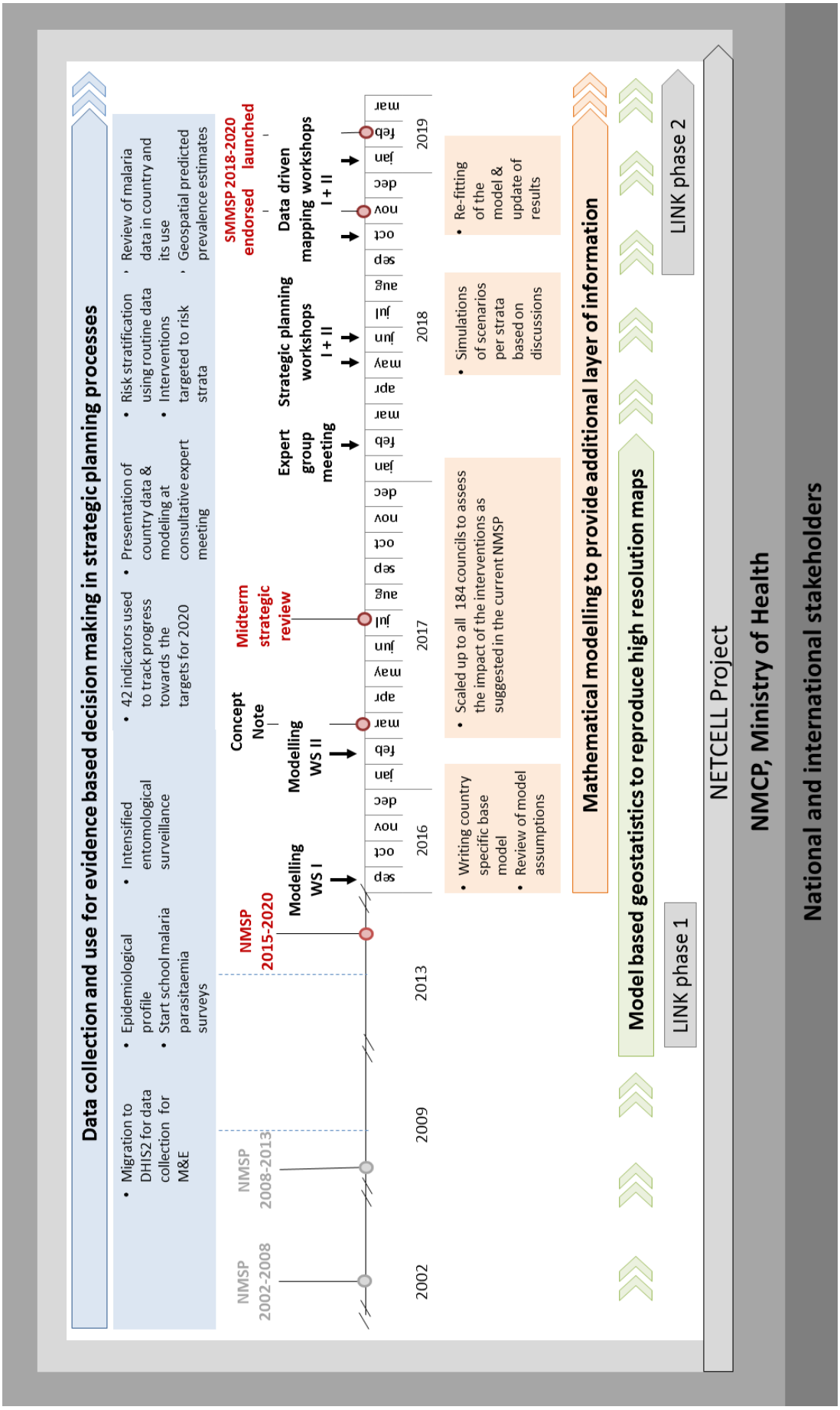

Fig. 5.1: Timeline of events leading to the supplementary malaria midterm strategic plan 2018-2020.
A summary of the attended meetings including modelling is provided in the supplement (SI-1).

In 2016, two workshops were held in Dar es Salaam to introduce the concepts of modelling, to assess available data sources and data owners, and to discuss input parameters and model assumptions. Following these two workshops, an extended phase was used for the model calibration. In 2017, the results of the initial models were fed into a midterm-review of the strategy, which concluded that the national prevalence target of less than one per cent by 2020 would not be achievable. Indeed, the modelling results suggested that the current NMSP objective could not be achieved unless a much more aggressive intervention mix was put in place. Unfortunately, that was neither operationally feasible nor financially doable. At a malaria expert meeting held in February 2018, with national and international stakeholders, the modelling results were presented alongside with the empirical view of the NMCP on the country context. At that meeting, it was decided to (1) gather all available data for risk stratification at council level, and (2) put together a more detailed plan for improved targeting of interventions at council level.

In May 2018, the modelling team was invited alongside NMCP staff and the NETCELL team to join a strategic planning workshop. During that meeting, the NMCP and stakeholders stratified the councils according to malaria risk (Thawer et al. pers. commun.) and discussed the allocation of appropriate interventions targeted to the strata. The previously calibrated transmission model (using OpenMalaria) was then used interactively during the work session by simulating requested alternative scenarios and directly answering questions from the country programme. Finally, selected outputs of the model were included as an additional set of evidence in the revision of the strategic plan launched in February 2019 (MoHCDGEC, 2019).

5.3.3 Added value

Mathematical modelling allowed primarily a technical assessment of the national malaria targets. Once calibrated, predictions of the likely impact of current and potential future interventions at council level could be provided. Beyond the simulation results, the process in itself was useful to inform policy. Modelling did not only use and process quantitative data, but also expert opinions, programme experiences, and local knowledge. Together, these created a platform for an in-depth interdisciplinary dialogue. Presenting model assumptions and the comparisons of the predicted *versus* expected impact triggered controversial as well as constructive comments. Controversial or unexpected predictions led to a critical review of the data, model structure, assumptions made, as well as the planned intervention scenarios. The ongoing engagement between modellers and practitioners enabled knowledge transfer and established a long-term interest in modelling. The former one was demonstrated by a developed critical but more appreciative view which replaced an

initial misconception about modelling (i.e. "*why to use modelling when you have data"* changed to *"why is the model different from the data, and how would the predictions change if…*"). The interaction and close collaboration were also of great benefit to the modellers, as the local knowledge and data were invaluable for model improvements leading to more context-specific modelling.

Moreover, statistical modelling and traditional descriptive analyses were performed to describe temporal and spatial trends based on empirical data and not on dynamics of malaria transmission as the mathematical model used has. Indeed, dynamic transmission model use available data to inform parameters to simulate malaria transmission and burden based on an understanding of the transmission dynamics, while statistical models only infer relationships based on collected data, without necessarily understanding the system. Discussions with partners on data for input parameters and major model assumptions were highly relevant to understand and inform the main drivers of malaria transmission. As a direct illustration, the prevalence predictions from the geospatial model provided by KEMRI-WT were discussed between partners including the NMCP and decided to be used to calibrate the transmission model for council prevalence.

5.3.4 Challenges

A number of challenges affected the accuracy of the modelling outputs and timeliness of the project. First, there was no previous experience for country modelling available at that level of detail that could have guided the process and the type of required outputs. Second, methodological challenges led to extended times for model calibration and complicated uncertainty estimates around the predictions (Runge et al., 2019). Uncertainty resides in model predictions. This uncertainty can be due to data quality and accuracy for model parameters, or due to model structure and random variability. The advantage of a simulation model would be to assess the impact of this uncertainty on the predictions. However, given the fact that this framework is representing each council of the entire country, the computational power becomes challenging. As a result, assessment of uncertainty was kept to its minimal, only accounting for random variability by using multiple runs for the historical simulation period, and accounting for uncertainty in transmission intensity by fitting a range of transmission intensities to prevalence estimates. Third, gaps in communication and understanding slowed down the process, requiring much more frequent and in-depth engagement between the modelling team and NMCP staff than had been anticipated. Fourth, challenges also included the busy schedule of the NMCP staff, as well as tight deadlines expected by external donors. Moreover, building capacity within the NMCP without a dedicated modelling person within the

NMCP or at least within a local institution was challenging and the NETCELL advisory team was invaluable to bridge that gap. However, in order to sustain the modelling support on the long term, the analytical capacities within the NMCP need further strengthening i.e. through additional personnel with quantitative skills, training and increasing experience as the modelling application continues. The first phase of the project has been to set up a framework and ensure engagement with and usefulness for the programme, the second phase will be to transfer knowledge by training in-country modellers. Lastly, it took time to build trust between all partners, to be able to understand the strengths and limitations of the models. The main key challenges and their implications are summarised in Table 5.2.

Table 5.2: Challenges and their potential implications for a productive interaction between modelling teams and NMCP staff

CHALLENGES	IMPLICATIONS
No previous experience with country modelling at that level of detail, hence need to create process Short timelines especially by external donors Insufficient time of NMCP staff for required activities Delays by NMCP in data sharing Delays by modellers in getting a clear understanding of the available data in order to increase accuracy of model parameters based on the available data Use of a complex transmission model and long processing time of simulations	Need for NMCP to invest required time in interactions – depending critical on NMCP understanding value of modelling and the process of interactions Prolonged time for model set up and calibration Delays in modelling deliverables and missed opportunities to inform key decisions Additional resources needed to extend the project period in order to adequately improve technical aspect and standardize processes to provide timely deliverables
Low spatial resolution for most indicators and temporal data gaps Use of most of the available data to inform the model while reducing the number of assumptions made Inclusion of model complexities and uncertainties while simplifying the model to shorten simulation time	Increased uncertainty in model parameters and predictions and impossibility to use model predictions at a higher resolution Undermining of model usefulness and credibility and potential reluctance towards future modelling applications
Maintaining communication between in-country visits between modelling team and NMCP Need to use a simplified language without leaving out relevant technical details Transparency on model limitations and uncertainty without undermining perceived modelling value Negative perception towards modelling by some stakeholders Misunderstanding the role of modelling as a replacement instead of an addition to data	Loss of interest in modelling process that could potentially lead to a negative perception of its use. Constant need to highlight the practical contribution made by models and the process of interaction with NMCP
Conflicting deadlines for activities at the NMCP level Difficulty to find in-country personnel to train for taking over the methodology Project funding with a focus on short term deliverables rather than long-term support	Dependency on external modeller and temporary project funds that prevent sustained effort and gains of the initiative Missed opportunity for improvements and refinements to shape the model into a truly setting specific tool and use of its maximum potential

5.3.5 Key components for successful modelling use in strategic planning

Once modelling activities were understood and adopted by the NMCP (and not perceived only as an academic exercise), the modelling process was used systematically as a way to think about the data. Furthermore, model strengths and limitations became better understood by the NMCP and partners, making the entire effort more productive. Ultimately, the whole process fed into the strategic planning process through interactive presentations and discussions. This exchange allowed for an additional layer of thoughts and interpretation and was found to be essential for the model to be meaningful and appropriate at the end (SI-2). To achieve this, multiple interactions, workshops and demonstration of the model were required. The NETCELL team made up of technical experts understanding both programme constraints, and the basics of modelling facilitated the communication by 'translating' between technical language to programmatic language. The NETCELL team also ensured continuity in the process, especially in-between visits by the modelling team. Their country-specific knowledge and resources were invaluable for many aspects of the modelling. A summary of the critical elements for success identified throughout the process is provided in Table 5.3.

Table 5.3: Key components for successful modelling use in strategic planning at country level

	COMPONENT	RECOMMENDATION	RELEVANCE
CONTEXT	Ownership	The modelling should be led by the Ministry of Health through the NMCP while including all other key stakeholders.	Coordination of partners and activities centred around country needs and country-specific questions.
	Aim & purpose	The aim of the modelling application should be clear to all stakeholders involved with defined deliverables.	Establishment of transparent and shared expectations of modelling output and impact.
	Data sharing & accessibility	Relevant data from local research or governmental institutions should be made available to programme managers and modelling team.	Reinforcement of country-ownership and enhanced use of data.
	Data quantity & quality	Data quality and suitability to inform the models need to be assessed, and if necessary, proper adjustments should be made, in consultation with the programme.	Improvement of model accuracy and usefulness of predictions.
PROCESS	Timeliness	Timelines need to be set by the programme and need to be sufficient for completion of programmatic as well as modelling tasks.	Feasibility of timely deliverables for a successful and efficient strategic planning process.
	Consistency	A systematic workflow should be developed and consistently be used throughout the project.	Reproducibility of modelling results facilitates potential evaluation of applied modelling.

	COMPONENT	RECOMMENDATION	RELEVANCE
	Integration	The outputs from programme activities should feed into the modelling process, which in turn should inform the next programmatic activity.	Utilization of modelling results by the programme and prevention of unnecessary additional modelling iterations.
	Monitoring	The modelling outputs should be compared to the parallel activities at the NMCP.	Usefulness of modelling targeted to relevant and current country needs in consideration of latest available data.
COMMUNICATION	Dissemination & Discussion	Modelling process and results should be presented to relevant stakeholders and at the end, final reports and documentation should be made available.	Provision of a discussion platform for exchange and knowledge transfer between partners, essential for impactful application of modelling.
	Engagement, commitment & responsibility	All parties involved should actively participate in the discussions and maintain constant commitment.	Opportunity of achieving highest benefit for all partners involved.
	Understanding	Knowledge transfer (in all directions), and capacity building should be a fixed part of the modelling.	Growths of mutual understanding and capacity despite substantial differences in disciplines and technical level between stakeholders.
	Transparency	The strengths and limitations of modelling need to be transparent.	Consideration of modelling as a thinking tool with sensible interpretation of results.
MODELLING	Parameterization & calibration	Available data should be used to identify and inform setting specific model parameter and the calibration methodology should account for the historical trends in malaria.	Simulation of data-driven impact predictions specific to local settings.
	Validation	The predictions need to be compared with data not included in the modelling, especially when developing or using new models and parameterizations	Alignment between modelled and observed data earns credibility, whereas discrepancies can be helpful for the identification of knowledge gaps or model improvements.
	Complexity	The model complexity should be appropriate for the questions asked (“as complex as necessary but as simple as possible”).	Reduction of computational efforts and simplified interpretation of modelling results.
	Flexibility	The modelling workflow needs to be flexible enough to be able to respond to current country needs and questions as they come up.	Prevention of unnecessary modelling iterations and strengthening the potential of modelling as a routine tool integrated into strategic planning processes.

5.4 Discussion

The Global Technical Strategy for malaria (WHO, 2015a) and its more recent adaptations under the High Burden High Impact (HBHI) initiative (WHO and RBM Partnership to End Malaria, 2019) emphasize the need to target control strategies. Ultimately, it aims to ensure that future policies are evidence-based and promote country-led and data-driven decision-making (WHO and RBM Partnership to End Malaria, 2019). This publication described a unique example of an iterative modelling process resulting from a close collaboration between the NMCP in Tanzania, a modelling team at the Swiss TPH and other stakeholders. Similar experiences and challenges were identified previously in health policy and decision-making research (Bowen et al., 2009; Kramer et al., 2009; Solter and Solter, 2013; White et al., 2018).

Close cooperation and on-going communication are crucial to prevent on the one hand the risk of overconfidence in model predictions (MacKenzie, 1998), or scepticism from control programme staff leading to a lack of uptake of model outputs. In the presented application, the comparison of alternative scenarios in multiple epidemiological settings provided qualitative guidance. Already described by MacKenzie in 1998, modelling should be used as a "thinking tool" rather than as a "future machine" (MacKenzie, 1998).

In modelling, there is a well-known trade-off between accuracy and simplification, and the acceptable level of the accuracy is defined by the purpose of the model (e.g. operational planning, high-level policy recommendation, advocacy and resource mobilization, or academic exercises). As the interactions between the modelling and NMCP evolve, it will become feasible to make more nuanced use of the data and to broaden the scope of the optimization, while propagating uncertainties throughout the analysis. For instance, council level targets, varying target coverages (Korenromp et al., 2016; Winskill et al., 2019) and sequential introduction of interventions (Winskill et al., 2017) might be considered and more seeds or model variants added to also account for uncertainties in model structure and random variation. The importance of uncertainty when using modelling for decision-making has been addressed in detail elsewhere (Bilcke et al., 2011; Briggs et al., 2012).

It is also essential to set realistic targets and expectations on what modelling can and cannot deliver (Van Kerkhove and Ferguson, 2012) in a given timeframe. The outputs of the process, described in (Runge et al., 2019), did ultimately not inform the 2017 concept note for the GFATM application as was initially foreseen. Neither the model outputs nor the NMCP were ready for that exercise because

of tight deadlines and additional time required for the model calibration. Had communication been stopped, it could have led to suboptimal utilization of modelling. The long-term process, however, was only possible with the dedication of all participants and the steady country support. Without a long-standing partnership, it will be much more challenging to sensibilize programmes to the usefulness and sustained use of modelling, local resources within the programme or collaborating research institutions need to be mobilized.

Modelling received appreciation when it was used for impact predictions of the intervention stratification selected by the programme. This emphasizes the necessity to establish shared ownership of all processes despite knowledge asymmetry, to facilitate the country-led use of modelling. In our application, a country-led use of modelling was achieved with open discussions on data and model uncertainties, with constant raising of questions for the model to answer. Through this first phase of engaging with the Tanzanian NMCP the modellers have raised awareness not only to the NMCP and partners in country themselves but also to a broader community, promoting the need for review of data and benefit of modelling to predict impact of intervention and support decision making processes.

The varying understanding of modelling usefulness by the NMCP and partners and the inability to know what decisions would have been taken in absence of modelling, highlight the difficulty to evaluate impact of modelling in the decision-making process.

Modelling guidelines for country application have been recently published for tuberculosis (TB MAC and WHO, 2018), but no such guidelines exist yet for malaria. The malERA consultative group provides a modelling research agenda (The malERA Consultative Group on Modeling, 2011; The malERA Refresh Consultative Panel on Combination Interventions and Modelling, 2017), and the use of modelling for malaria control and elimination strategies has been described by WHO and partners (RBM, 2010). However, they do not include practical guidance on how to use modelling collaboratively to make best use of local data for strategic planning at country level. Such guidelines would also facilitate the comparison of multiple models applied for the same questions within and between countries. The example presented here provides valuable challenges and lessons learned and reinforces the urgency of such guidelines in malaria.

5.5 Conclusions

Modelling provides a platform unifying empirical and simulated outputs, where policymakers, technical experts and other stakeholders can discuss and then agree on what constitutes an optimal national malaria control plan. Such discussions need to consider many parameters and priorities and hence must result from constant interactions between programme managers and modellers. In addition, all other national stakeholders including donors, academics and technical/implementation agencies are encouraged to participate in this process. Empirical data analysis and its use for strategic thinking remain the cornerstone for evidence-based decision making. Mathematical impact modelling can then support the process both by unifying all stakeholders in one strategic process and by adding new key evidence required for optimized decision-making. Given that most malaria-endemic countries (1) have now a high level of epidemiological heterogeneity (WHO, 2018) and (2) that all countries are facing a rapidly increasing number of technical and strategic options, it follows that many could benefit from process similar to the one described here. To support this, minimal essential guidelines for country modelling are now urgently needed for improved evidence-based national and local malaria control planning, implementation and evaluation. Local consortia made up by NMCPs, donors and research institutions need then to be established to carry out strategic planning processes. Not only will this allow for faster progress in malaria control impact at a given level of funding, but it represents an essential step for coming close to the goal of finally eliminating malaria.

5.6 Declarations

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Author contribution

EP and MR developed the study concept. MR wrote the draft manuscript. EP, CHL and RWS provided substantial feedback to the manuscript. AM, EP, FM and CL provided critical support throughout the project. AM, RM, FM, MR, EP, RWS participated in relevant workshops in Tanzania. AM, RM, FM, MR participated in the strategic planning workshop in 2018. All authors have read and approved the final manuscript.

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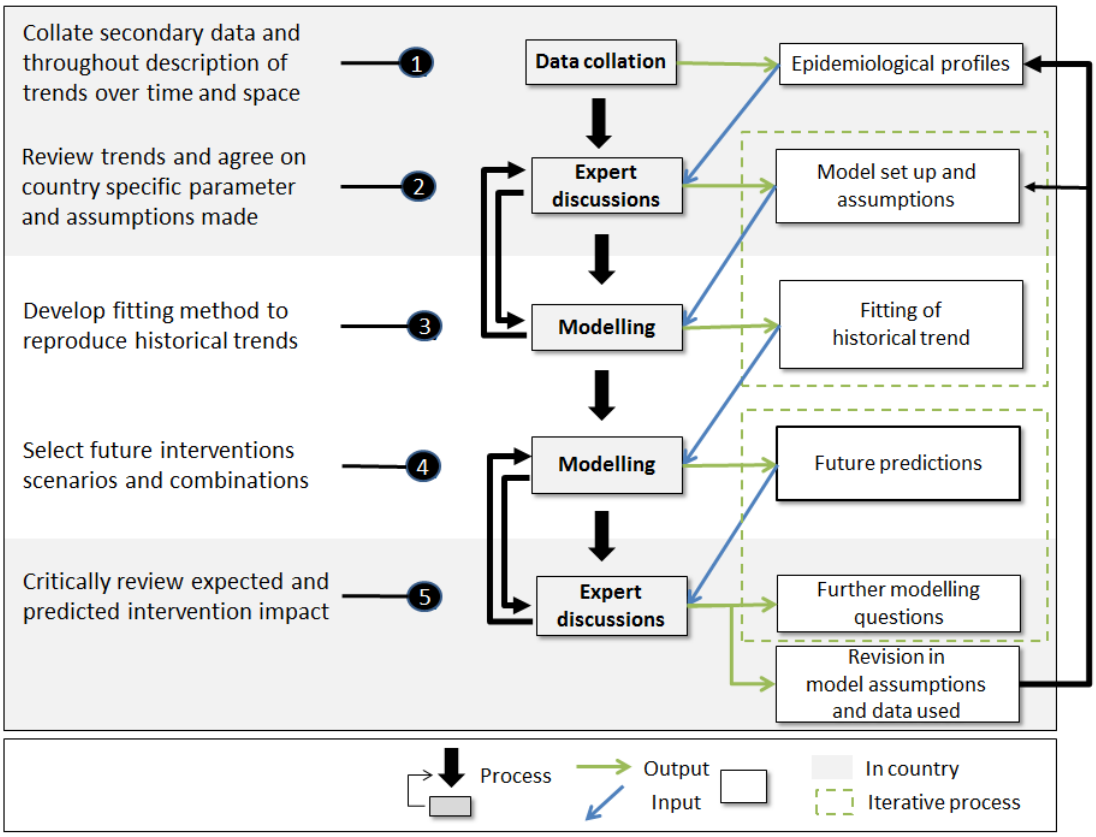
5.7 Supplementary information

SI-1: Details of the main interactive activities between 2016 and 2018

	Modelling Workshop (#1)	**Modelling Workshop (#2)**	**Consultative Experts Malaria meeting**	**Malaria Strategic Plan Review 1+2 workshops**	**Tanzania M&E Mapping workshop I + II**
Organiser	Swiss TPH and GFTAM	Swiss TPH and GFTAM	NMCP	NMCP	NMCP+ KEMRI Nairobi
Date	27 - 28 Oct. 2016	22 Mar. 2017	26 -27 Feb. 2018	14-19 May 28-2 Jun. 2018	3 -7 Sep. 2018
Participants	~30 (Day 1) ~15 (Day 2)	~20	~30	~20-30	~15
Institutions	NMCP, NIMR, IHI, NBS, UDSM, WHO , PMI, PATH, PSI, RTI, VectorWorks, LSTM, GFATM, CHAI, Swiss TPH	NMCP, NIMR, IHI, VectorWorks, CHAI, Swiss TPH	MoHCDGEC (CMO), NMCP, NIMR, IHI, PMI, Global lFund, WHO, WHO Afro, VectorWorks, Swiss TPH, KEMRI WT	NMCP, NIMR, IHI, MoHCDGEC, WHO, GFATM, PMI, ALMA, CHAI, Swiss TPH	NMCP, NIMR, IHI, NBS, TMA, UDSM, PMI, KEMRI WT, Swiss TPH
Objectives	▪ To introduce modelling concepts to key stakeholders, ▪ To identify key questions to be addressed by the model application, ▪ To discuss expected outcomes ▪ To identify data to be collated & data owner.	▪ To present preliminary results on calibration and impact of interventions in 8 districts, ▪ To discuss feedback and agree on next steps.	▪ To critically review, analyse and discuss the elimination agenda in Tanzania, ▪ To deliberate on effective approaches that will help Tanzania to achieve malaria elimination, ▪ To formulate recommendations and experts resolutions.	▪ To realign the NMSP 2015 - 2020 to current epidemiological and implementation achievements, ▪ To develop and define a pragmatic stratification, ▪ To identify appropriate and tailored intervention packages according to needs, ▪ To model impact and costs, ▪ To redefine the strategic outline and the implementation framework.	▪ To generate a new prevalence risk map to improve malaria stratification and plan and implement targeted malaria control interventions, ▪ To update modelling results after fitting to new prevalence estimates per district.
Modelling outputs	▪ Preparation of modelling, ▪ List of available and data sourced and contacts, ▪ Refinement of modelling questions, ▪ Selection of eight pilot districts for testing methodology.	▪ Impact of interventions in eight pilot districts, ▪ Comparison of predicted and observed prevalence in 2016, ▪ Workflow to reproduce historical trend and future predictions Collated database.	▪ Impact of interventions in all districts in Tanzania, ▪ Impact of current NMSP strategies, ▪ Evaluation of NMSP target and suggestion of aggressive intervention to reach such optimistic target.	▪ Impact of potential strategies, ▪ Predicted costs per strata per intervention of the strategies in the revised NMSP, ▪ Differences in impact and in costs of current and revised NMSP.	▪ Historical trend and baseline prevalence fitted to estimates from new prevalence risk map, ▪ Updated predicted impact and costs of interventions and comparison to previous outcomes.

ALMA= The African Leaders Malaria Alliance, CHAI = Clinton Health Access Initiative, IHI= Ifakara Health Institute, MoHCDGEC = Ministry of Health, Community Development, Gender, Elderly and Children; NIMR= National Institute for Medical Research, NBS = National Bureau of Statistics, MUHAS= Muhimbili University of Health and Allied Sciences, PMI = President Malaria Initiative, TMA = Tanzania Meteorological Agency, UDSM= University of Dar es Salaam, Swiss TPH = Swiss Tropical and Public Health Institute, RTI = Research Triangle Institute, WHO = World Health Organisation

SI-2: Iterative process between modelling and discussions



6 Evaluation of different deployment strategies for larviciding to control malaria: a simulation study

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6.1 Abstract

Background: Larviciding against malaria vectors in Africa has been limited compared to indoor residual spraying and insecticide-treated nets, but is increasingly being considered by some countries as a complementary strategy. However, despite progress towards improved larvicides and new tools for mapping or treating mosquito-breeding sites, little is known about the optimal deployment strategies for larviciding in different transmission and seasonality settings.

Methods: A malaria transmission model, OpenMalaria, was used to simulate varying larviciding strategies and their impact on host-seeking mosquito densities, entomological inoculation rate (EIR) and malaria prevalence. Variations in coverage, duration, frequency, and timing of larviciding were simulated for three transmission intensities and four transmission seasonality profiles. Malaria transmission was assumed to follow rainfall with a lag of one month. Theoretical sub-Saharan African settings with *Anopheles gambiae* as the dominant vector were chosen to explore impact. Relative reduction compared to no larviciding was predicted for each indicator during the simulated larviciding period.

Results: Larviciding immediately reduced the predicted host-seeking mosquito densities and EIRs to a maximum that approached or exceeded the simulated coverage. Reduction in prevalence was delayed by approximately one month. The relative reduction in prevalence was up to four times higher at low than high transmission. Reducing larviciding frequency (i.e., from every 5 to 10 days) resulted in substantial loss in effectiveness (54, 45 and 53% loss of impact for host-seeking mosquito densities, EIR and prevalence, respectively). In seasonal settings the most effective timing of larviciding was during or at the beginning of the rainy season and least impactful during the dry season, assuming larviciding deployment for four months.

Conclusion: The results highlight the critical role of deployment strategies on the impact of larviciding. Overall, larviciding would be more effective in settings with low and seasonal transmission, and at the beginning and during the peak densities of the target species populations. For maximum impact, implementers should consider the practical ranges of coverage, duration, frequency, and timing of larviciding in their respective contexts. More operational data and improved calibration would enable models to become a practical tool to support malaria control programmes in developing larviciding strategies that account for the diversity of contexts.

6.2 Introduction

Larviciding is the application of biological or chemical insecticides that kill the larvae of mosquitoes, and one of the approaches of larval source management (LSM), along with habitat modification, habitat manipulation and biological control (WHO, 2013). The World Health Organisation (WHO) recommends larviciding as a supplementary intervention against malaria in addition to the core vector control interventions of insecticide-treated bed nets (ITNs) and indoor residual spraying (IRS) (WHO, 2019b). Larviciding is recommended in areas where the intervention is feasible and cost-effective, mostly in urban areas and during the dry season where breeding sites are "fixed, few and findable" (WHO, 2019b, 2013). Biolarvicides, *Bacillus thuringiensis israelensis* and *Bacillus sphaericus*, are currently the most prominent larvicides as they are environmentally safe (Lacey, 2007). However, under most environmental conditions, they have short residual effectiveness (*B. thuringiensis israelensis* lasts for only 1–2 weeks (Fillinger et al., 2003; Kroeger et al., 1995) and *B. sphaericus* for 2-3 weeks (Fillinger and Lindsay, 2006; Shililu et al., 2003b). Frequent applications have been widely recognized as a challenge for effective large-scale implementation (Chaki et al., 2009; Dambach et al., 2016b; Fillinger et al., 2008, 2004; Tusting et al., 2013).

Larviciding was widely used in the first half of the 20th Century, most successfully outside sub-Saharan Africa, but fell out of favour after the introduction of IRS with DDT (Fillinger and Lindsay, 2011; Killeen et al., 2002a, 2002b; Kitron and Spielman, 1989; WHO, 2013). In the last decade, LSM, especially larviciding, has been reconsidered within an integrated vector management approach, especially as longer-lasting agents (Afrane et al., 2016; Derua et al., 2018; Kahindi et al., 2018), or novel deployment strategies and breeding site identification, i.e., using drones (Carrasco-Escobar et al., 2019; Hardy et al., 2017) might become increasingly available (Derua et al., 2019). Post-2000, pilot programs of larviciding have been conducted in urban and in rural areas in multiple countries of Africa (Afrane et al., 2016; Chanda et al., 2016; Dambach et al., 2014b; Djènontin et al., 2014; Fillinger et al., 2009a; Geissbühler et al., 2009; Ingabire et al., 2017; Kandyata et al., 2012; Magesa et al., 2009; Majambere et al., 2010, 2007; Martinez et al., 2015; Mazigo et al., 2019b; Nartey et al., 2013; Nyarango et al., 2006; Obopile et al., 2018; Rahman et al., 2016; Shililu et al., 2003b; Tchicaya et al., 2009; Worrall and Fillinger, 2011; Yapabandara and Curtis, 2002; Zhou et al., 2016). For example, the Urban Malaria Program in Dar es Salaam, Tanzania, demonstrated operational feasibility and effectiveness of larviciding on larvae reduction and epidemiological outcomes in urban areas (Fillinger et al., 2008; Geissbühler et al., 2009). In Burkina Faso, a trial in 84 rural villages with *B. sphaericus* applications during the main transmission season showed larviciding to be feasible and cost-effective when targeted to the most productive breeding sites (Dambach et al., 2016a, 2014b).

Pilot implementations have previously been included in national malaria strategic plans in Eritrea (Nyarango et al., 2006; Shililu et al., 2003; Shililu et al., 2007; Shililu et al., 2003), Zambia (Chanda et al., 2008; Martinez et al., 2015; Chanda, 2012), and Nigeria (NMEP Nigeria et al, 2013). Despite the long history of larviciding, its impact on malaria prevalence in humans (Choi et al., 2019; Tusting et al., 2013) in different settings, and the influence of variations in its application, particularly frequency and timing of the year as well as duration (Afrane et al., 2016; Fillinger and Lindsay, 2006; Majambere et al., 2010) remain insufficiently understood. For example, the application during the rainy season was described as impractical and less effective in study sites in Tanzania and The Gambia (Geissbühler et al., 2009; Majambere et al., 2010), but as feasible in the study in Burkina Faso whereas its effectiveness during the dry season, as currently recommended, is still being debated (Kitron and Spielman, 1989; WHO, 2013).

Mathematical models have been used to simulate mosquito population dynamics and the relationship between larval stages and adult mosquitoes (Alam et al., 2017; Arifin et al., 2013; Barbosa et al., 2018; Brady et al., 2016; Eckhoff, 2011; Gu and Novak, 2005; Magombedze et al., 2018; Menach et al., 2005; Smith et al., 2013; White et al., 2011b; Yakob and Yan, 2010). However, most models consider only a small sub-set of the highly variable larviciding deployment scenarios. The models also include implicit assumptions about optimal deployment in relation to seasonality, (i.e., deployments either throughout the year, during rainy season or during dry seasons) and duration of larviciding effectiveness (i.e., constant or interrupted) without regard to re-treatment intervals and duration of product efficacy. While models have been used to simulate variations in the deployment strategies for other malaria control interventions, such as IRS (Griffin et al., 2010; Ratti et al., 2018; Selvaraj et al., 2018; Worrall et al., 2007) and drugs (Brady et al., 2017; Cairns et al., 2015; Gao et al., 2020; Griffin et al., 2010), larviciding strategies have not been investigated as much. In this study the impact of larviciding applications was simulated to assess the influence of different deployment strategies on expected entomological outcomes and malaria infections in human for different seasonality and transmission settings.

6.3 Methods

6.3.1 Larviciding and influencing factors

The application and effectiveness of larviciding is highly dependent on aquatic habitat characteristics and mosquito species (WHO, 2013). Identification and accessibility of these habitats throughout the year is problematic yet essential (Chaki et al., 2009; Dambach et al., 2016b; Fillinger et al., 2008). Larviciding can reduce the number of emerging mosquitoes with a lag of two to three weeks

between larviciding and reduction in adult mosquito density (Kroeger et al., 1995). The number of infected host-seeking mosquitoes determines the entomological inoculation rate (EIR), which is related to the number of new infections in humans and the proportion of humans carrying malaria parasites. An overview of the most relevant influencing factors on larviciding application and effectiveness is shown in Fig 6.1.

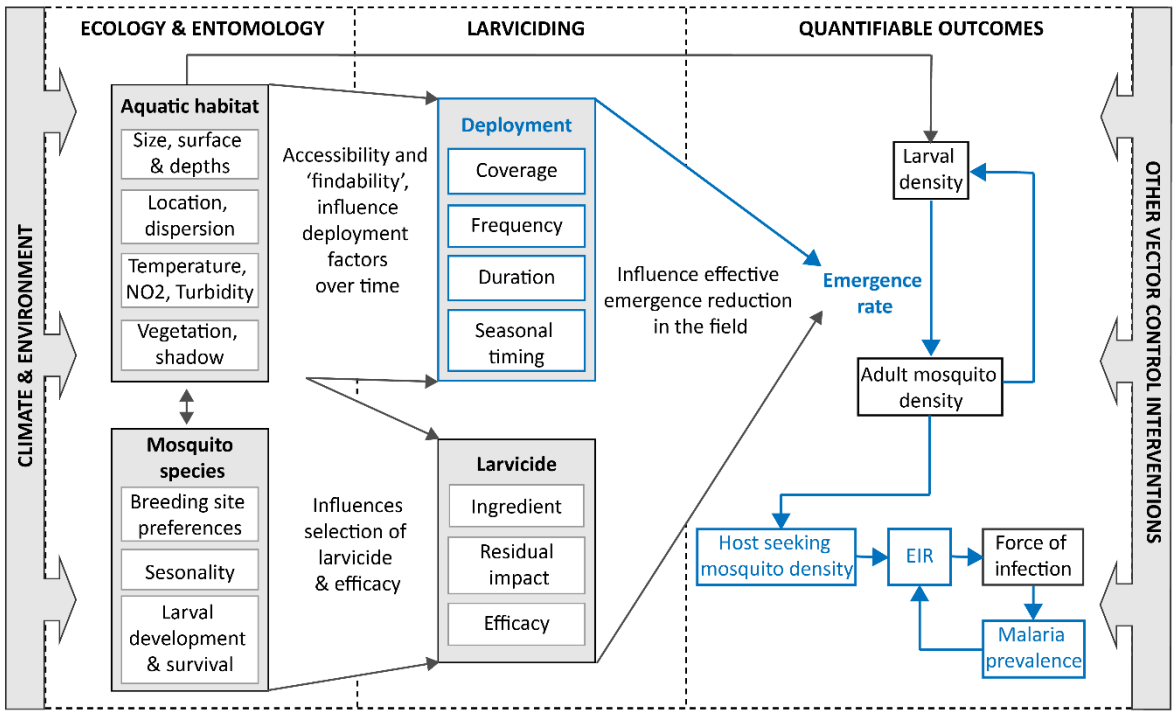

Fig. 6.1: Flowchart of factors influencing larviciding effectiveness and malaria transmission outcomes.
The flowchart reads from left to right, with climate and environmental factors influencing the whole system and relationships inside. This study focuses on the deployment factors and their impact on the quantifiable outcomes as highlighted in blue. All other factors were considered standard and non-varying.

6.3.2 Mosquito dynamics

A deterministic discrete-time model of overlapping generations of mosquitoes with a time step of one day was used (Chitnis et al., 2012, 2008a, 2008b). This was extended to include density-dependent larval dynamics using a Beverton-Holt formulation (Beverton and Holt, 1957; Bohner and Warth, 2007). This model includes a single juvenile stage of mosquitoes arising at a rate proportional to the time-lagged number of eggs laid, with the larval population regulated by periodically varying larval-carrying capacity and the larvae progressing to host-seeking adults at a constant rate. The assumed lag times between rainfall was 10 days for mosquito emergence, 20 days for host-seeking mosquitoes and 30 days to actual transmission events (measured as EIR). The models and derived parameters are described in Additional file 1. The entomological model was connected to a stochastic individual-based model for malaria in humans (Smith et al., 2008) within the OpenMalaria

platform (Briët et al., 2013; Chitnis et al., 2012, 2008a; Smith et al., 2008; Stuckey et al., 2013), for which the source code is available online (Swiss TPH, 2020). The parasite densities per simulated infection vary by 5-day timesteps.

6.3.3 Model parameterization

Malaria transmission intensity was defined as annual pre-larviciding EIR and simulated with three intensity levels: 3 infectious bites per person per annum (ibpa) for low transmission, 10 ibpa for moderate transmission and 90 ibpa for high transmission. Seasonality was characterized as high or medium seasonal with either one or two peaks and reproduced from another modelling study (Stuckey et al., 2014a). The seasonality in transmission was assumed to follow the same pattern as the rainfall with a lag of one month, and lag time between key indicators are shown in Additional file 2, Fig. S2.1. The characteristics of the setting, including resistance, host preferences and biting behaviour were held constant over time. Differences between species were not considered, and a previously determined parameterization for *Anopheles gambiae sensu stricto (s.s.)*, predominantly indoor biting and anthrophilic, was used. To explore sensitivity to highly uncertain mosquito population density-dependency parameters, the survival probability of larvae, the development duration and the number of female eggs per gonotrophic cycle were varied.

Simulated parameters of larviciding included the coverage, deployment duration, application frequency, and seasonal deployment. The coverage was defined as the reduction in emerging mosquitoes as a result of treated breeding sites (operational coverage) and larvicide efficacy (Additional file 3). It was assumed that important aquatic habitats had been pre-identified and characterized, and that they were accessible and evenly distributed. Larviciding deployment duration was simulated for 120 and 356 days, allowing for irregular applications, but with fixed efficacy duration of the minimum time step (5 days). The seasonal deployment was described in terms of the number of months during which larviciding was applied per year (beginning, during or end of the rainy season, during the dry season or throughout the year) (Fig. 6.2).

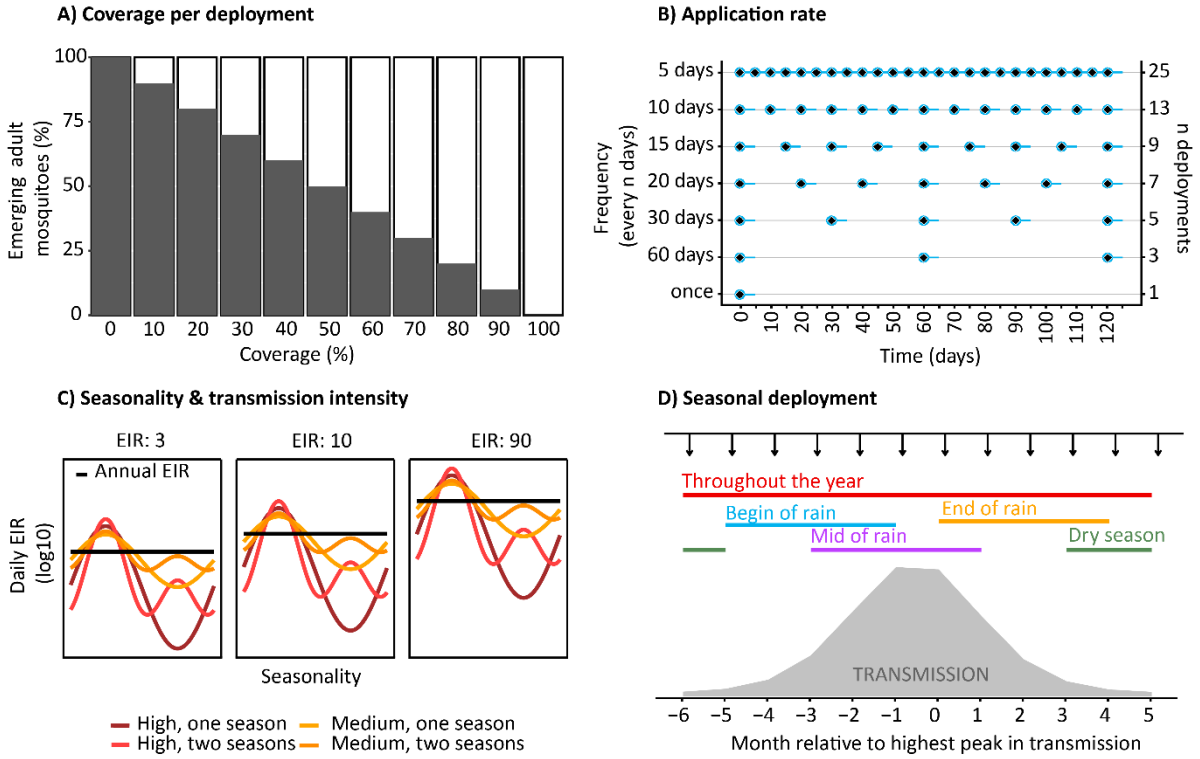

Fig. 6.2: Illustration of setting and deployment specific parameter.
A) Larviciding coverage, held constant for all deployments. **B)** Deployment frequency during one deployment period of 120 days. The deployment frequency is characterized by the number of deployments per unit of time (rectangles on the right) and characterize the lengths of gaps in effective coverage between single deployments. The blue lines correspond to the duration of time that the larvicide is active, assumed to be five days. The emergence rate is unaffected outside of these blue lines. **C)** Transmission seasonality patterns reproduced from (Stuckey et al., 2014a). **D)** Seasonal deployment times with larviciding starting at different months (twelve independent scenarios) assuming a constant efficacy of 120 days, or 365 days in case of deployment 'throughout the year', included for comparison.

6.3.4 Simulation scenarios

The larviciding parameters were explored with three distinct simulation experiments. Larviciding was simulated: 1) for 365 days at maximum application rate throughout the year and constant transmission (no seasonality); 2) for 120 days at varying application rates and coverage at constant transmission throughout the year; and, 3) for 120 days at maximum application rate starting in different months during the year considering four different seasonality profiles. Simulations 1 and 2 were run with 11 coverage levels, three transmission intensities, 18 unique mosquito density dependency parameter combinations, and three stochastic representations, whereas the coverage levels and density parameters were reduced for Simulation 3 to limit simulation size. Simulations were run for a host population of 10,000 people, with a 'warm-up' period equivalent to 60 years before the implementation of larviciding. The 'warm-up' period led to the defined level of transmission assumed to result from previous interventions not explicitly simulated (Table 6.1).

Table 6. 1: Summary of simulation experiments and varied model parameter

	Simulation 1	**Simulation 2**	**Simulation 3**
Setting			
Transmission intensity (ibpa)	3, 10, 90	3, 10, 90	3, 10, 90
Transmission seasonality	-	-	None, medium, high, one peak, two peaks (based on (Stuckey et al., 2014a))
Intervention deployment			
Coverage	0-1, interval of 0.1	0-1, interval of 0.1	0-1, interval of 0.2
Duration (days)	30, 60, 90, 120, 365, 730, 1095	120	120
Frequency (interval in days)	5**	5, 10, 15, 20, 25, 30, 60, 90	5**
Decay* (days)	5	5	120
Seasonal deployment (month larviciding started)	-	-	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
Mosquito density dependency parameters* **			
Female eggs laid	99, 50,200	99, 50,200	99
Development survival	0.6, 0,1, 0.9	0.6, 0,1, 0.9	0.6
Development duration (days)	11, 5	11, 5	11

* A step function with constant effectiveness for the specific number of days.

** Minimum timestep size in OpenMalaria

*** Based on OpenMalaria default parameters with upper and lower value for female eggs laid based on (Service, 2012) and assumed maximum range for survival probability of larvae.

6.3.5 Analysis of simulation outputs

The outputs of the simulations included the number of larvae emerging and surviving to first feeding cycle (mosquito emergence), the number of host-searching mosquitoes, the EIR, and the *Plasmodium falciparum* parasite rate (*Pf*PR) in the human population, assessed during the intervention period, at the end of the intervention period or one year after the intervention period. The impact of larviciding was assessed by comparing the scenarios with larviciding to those without larviciding, defined as the counterfactual. The relative reduction (RR) compared to no larviciding, was calculated per five-day time step paired by deployment parameters. The mean of the relative reductions per time step was calculated for the entire duration (meanRR). The equations are shown below, where t denotes the timestep and n the total number of timesteps, either at the end of the larviciding intervention or after 12 months after intervention start, in the results specified in the figure captions.

$$RR_t = (X[Counterfactual_t] - X[larviciding_t])/X[Counterfactual_t]$$

$$meanRR = \frac{1}{n}\sum_{t=0}^{n} RR_t$$

Where

$$X[.]\ denotes\ the\ model\ outputs\ (EIR, vector\ density\ or\ prevalence)\ for\ either\ the\ counterfactual\ scenario\ or\ with\ larviciding\ intervention$$

The loss in the effectiveness was defined as 1- meanRR calculated at the end of the evaluation period, either after larviciding was stopped or one year after larviciding started. For the prevalence and EIR, the predicted value at the timepoint (at the end of the evaluation period) was taken, whereas for the vector outcomes the average was taken. The three seeds were averaged and the simulated range among the mosquito population density-dependency parameters was used to obtain uncertainty intervals. Linear regression models were run to quantify the relationship between deployment frequency or coverage and reduction on prevalence.

6.3.6 Simulation to represent a study site

Additional simulations were run to compare the predicted with the reported impact of larviciding and to establish the relationship between effective coverage and reported operational coverage based on a field study conducted before other vector control interventions were scaled up (Fillinger and Lindsay, 2006). In that study, larviciding was applied in Mbita, a rural village in western Kenya, between June 2002 and September 2004 using Bti and Bs. The number of treated breeding sites per deployment ranged from 65 to 219 among the 50 applications during the study period. Simulation scenarios intended to represent the study site and informed parameters as reported for the annual baseline transmission intensity, the seasonality, vector species, time of the larviciding applications and the larvicide, only varying the coverage. A detailed description of the study is available in the publication by Fillinger et al. (Fillinger and Lindsay, 2006), and the simulations setup is included in Additional file 4.

6.4 Results

6.4.1 Impact of effective coverage and duration of larviciding (Simulation 1)

The impact of larviciding coverage and duration is shown in Fig. 6.3. After one year of larviciding at 60% coverage, the number of host-seeking mosquitoes was reduced by 62% (range 60-70%), the EIR by 81% (range 78-86%), and the prevalence by 48% (range 45-55%), assuming moderate transmission and no seasonality (Fig. 6.3A). The number of host-seeking mosquitoes and EIR appeared to reach equilibrium ahead of malaria prevalence rates. The effects on host-seeking mosquitoes started immediately after larviciding but EIR started to decrease after around 10 days and faster than for host-seeking mosquitoes. Malaria parasite prevalence was predicted to decrease around two months after larviciding and had the lowest relative reductions compared to the other outcomes.

The relationship between effective coverage and reduction in prevalence highly depended on the pre-intervention transmission intensities, with the greatest relative reductions being in low-transmission settings. Overall, we consider effective coverage above 60% as high, since it refers to

the reduction in all emerging adult mosquitoes, whereas in practice not all breeding sites might be identified, and treatment might not affect all premature stages within a breeding site equally (Additional File 3). Taking 60% effective coverage as an example, the relative reduction in prevalence at low EIR was around four times higher than at high EIR (meanRR$_{EIR-3}$=66% vs. meanRR$_{EIR-90}$=17%) (Fig. 6.3B), while at 20% coverage the relative reduction was almost ten times higher (meanRR$_{EIR-3}$=25% vs. meanRR$_{EIR-90}$=2.5%). The population density dependency parameters did not substantially influence these relationships, nor the immediate effect of larviciding, however extreme values considerably delayed repopulation after high reductions in the mosquito population (Fig. S2.2 and A2.3). Coverage of larviciding strongly influenced the overall impact of the intervention, except at high transmission intensities (EIR >90 ibpa) where larviciding was predicted to not have much impact, showing the higher the transmission intensity the lower the impact of the intervention.

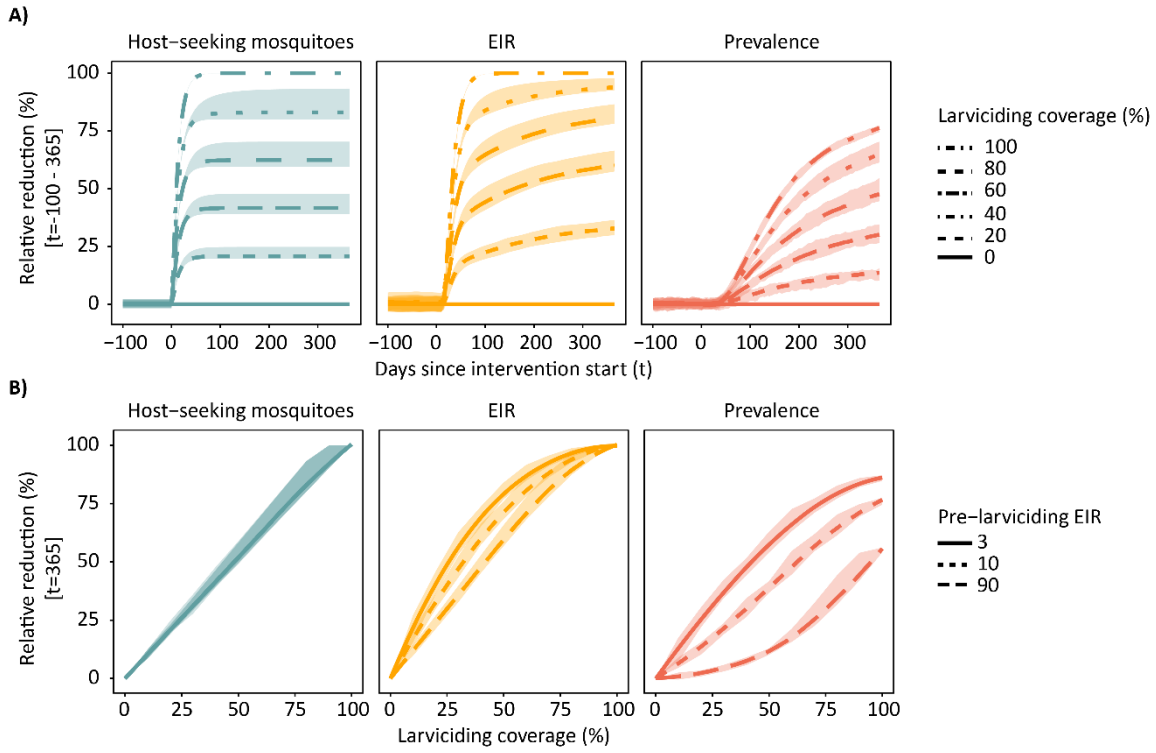

Fig. 6.3: Simulated relative reduction in host-seeking mosquitoes, EIR and prevalence after one year of larviciding.

A) Relative reduction for different coverage levels over time at moderate transmission (EIR=10 ibpa). **B)** Relative reduction by coverage at different transmission intensities after one year. The shaded area indicates the minimum and maximum range among variation in the mosquito density-dependence parameters. The *t* denotes the time in days after intervention start.

6.4.2 Impact of deployment frequency of larviciding (Simulation 2)

The highest impact at any larviciding coverage was achieved at maximum duration of the intervention period (assumed to be 120 days for this specific simulation) (Fig. 6.4). In practice, this

could be achieved through frequent deployments with short-lived larvicides or fewer deployments when using larvicides that have longer residual efficacy. Interrupting the effective coverage by deployment every 10 instead of every 5 days resulted in a loss of effectiveness by 54% (51-56%) for mean host-seeking mosquito density, by 45% (39-49%) in EIR, and by 53% (45-70%) in prevalence. This had assumed coverage of 80%, averaged over the three transmission intensities. For host-seeking mosquitoes, there was high interaction between frequency and coverage with higher loss in impact at high than at low coverage (Fig. 6.4B). For EIR and prevalence (Fig. 6.4C), the levels of pre-larviciding transmission intensity influenced the impact of deployment frequency on prevalence but not on EIR. For instance, for a deployment of larviciding at 80% every 10 days (when assuming a short-lived larvicide effective for 5 days), the resulting RR in EIR was predicted at 49% (46-56%) for a pre-intervention EIR of 3 ibpa, 47% (45-53%) for a EIR of 10 ibpa, 44% (41-50%) for a EIR of 90 ibpa. The corresponding RRs in prevalence were 17% (14-21%), 12% (9-13%) and 4% (3-5%) for EIR of 3, 10, and 90 ibpa, respectively.

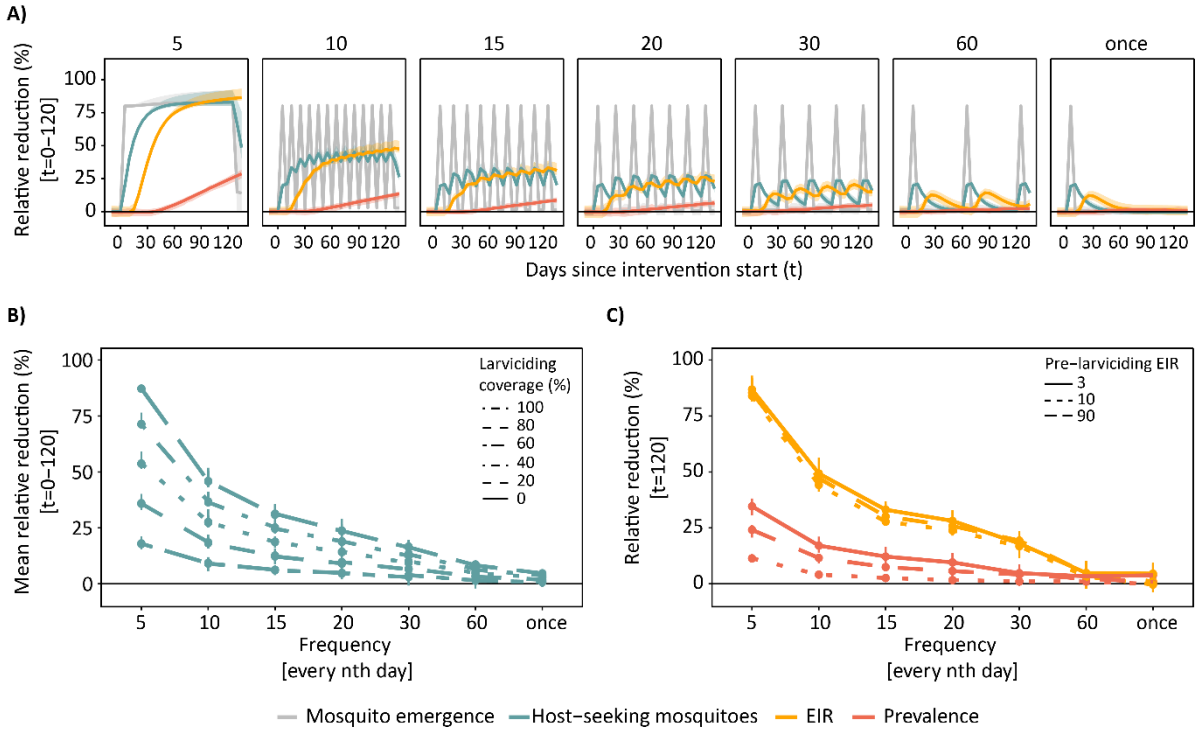

Fig. 6.4: Relative reduction in outcome measures resulting from varying deployment frequencies.
A) Impact of larviciding on the different outcomes measured over time and per deployment frequency (panels) for 80% coverage and in moderate transmission intensity (EIR=10 ibpa). **B)** Mean relative reduction in mosquito emergence during the intervention period by frequency and larviciding coverage irrespective of transmission intensity (averaged for EIR values of 3, 10 and 90 ibpa). **C)** Relative reduction in EIR and prevalence at the end of the larviciding deployment period with larviciding at 80% coverage and varying frequency. The *t* denotes the time in days after intervention start. The figure shows simulation results for a deployment period of 120 days (no seasonality).

An increase of 1% in coverage would lead to an average increase of the impact in prevalence by 0.10%, while an additional lag of five day between deployments would decrease the relative reduction in prevalence by 2.32% (Fig 6.4). To achieve and maintain high impact of larviciding with a short efficacy, the frequency of deployments was more important than the coverage. For instance, an increase in the coverage from 40% to 80% for deployment every five days increased the relative reduction in prevalence from 18% to 36%, whereas not even 100% coverage could compromise fewer deployments, that leave gaps in effective coverage, to achieve the same reduction (Fig. A2.4).

6.4.3 Impact of timing on effectiveness of larviciding (Simulation 3)

The timing of larviciding relative to the transmission season substantially influenced the impact on the prevalence. Regardless of seasonality, transmission intensity or coverage, larviciding in the rainy season was most impactful in reducing EIR and prevalence, followed by deployment during the beginning of the rainy season, followed by deployment at the end of the rainy season. For highly seasonal settings, larviciding during the rainy season (for 120 days) was predicted to have a similar impact as deployment all year round, whereas larviciding at the end of the rainy season or during the dry season (for 120 days) had a very low impact. In moderate endemicity setting (EIR=10 ibpa), larviciding at 80% coverage was predicted to reduce the prevalence after one year by 58% when deployed all year round, by 57% when implemented during the middle of the rain season, by 40% when implemented at the beginning of the rainy season, by 9% at the end of the rainy season and no reduction when deployed at the dry season. The relative reduction in prevalence were on average across the deployment timing 10% higher at lower transmission (EIR=3 ibpa) and 20% lower at higher transmission (EIR=90) compared to the reduction simulated for the moderate transmission level (Fig. A2.9).

The optimal deployment timing for highest impact on prevalence was found to be three months before the peak in transmission, assuming lasting effectiveness until one month after the peak. When coverage of larviciding during the rainy season was reduced to 20% (intended to represent operational challenges to cover all breeding sites during the rainy season), the impact of larviciding, although substantially lower (19% difference in peak meanRR), remained higher as when deployed during the dry season, especially at high seasonality with one transmission season. At medium seasonality and two transmission seasons, the optimal deployment timing became less distinct (Fig. 6.5B). The model predictions therefore suggest that timing the larviciding deployment to the rainy season would be more impactful, even at lower coverage, than achieving high coverage during the other seasons, even when the effective coverage would drop to until a coverage of 20%, given the

transmission and seasonality scenarios considered in this analysis. Additional seasonal plots are provided in the Additional File 2, Fig. S2.7-10.

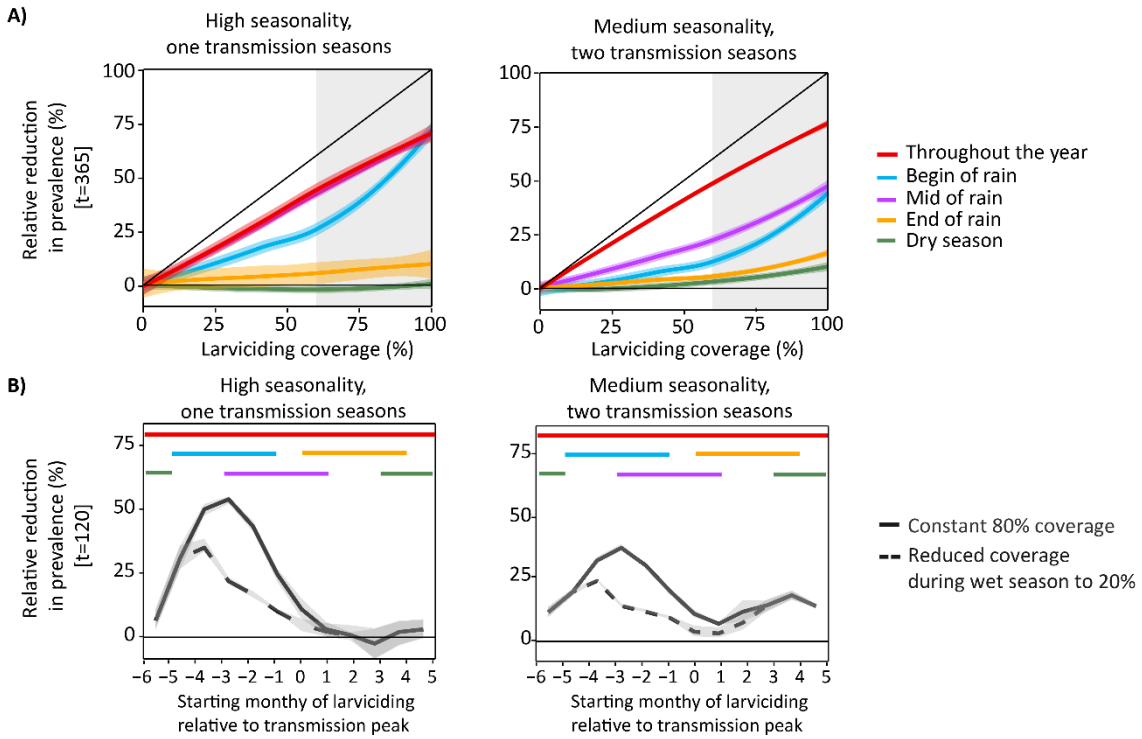

Fig. 6.5: Relative reduction in prevalence due to larviciding compared by seasonal timing at moderate transmission intensity (EIR=10).
A) Reduction in prevalence after 1 year with larviciding deployed for 1 year compared to 120 days at varying seasons. The x-axis shows the effective larviciding coverage, with a coverage above 60% shadowed in grey as these coverage levels might be difficult to achieve in practice (Alam et al., 2017; Arifin et al., 2013). The diagonal black line indicates a 1-to-1 relationship. **B)** Relative reduction in prevalence at the end of the deployment period (120 days) at moderate transmission for varying deployment starts, relative to the peak in transmission. The t denotes the time in days after intervention start. Mosquito density-dependence parameters were fixed, and uncertainty intervals are not shown.

Comparison of deployment factors and post-larviciding resurgence (Simulation 2)

After the end of an assumed intervention period of 120 days. the number of host-seeking mosquitoes resurged immediately to pre-larviciding levels whereas the EIR, after an initial drop, resurged at a slower rate, and the prevalence resurged at the slowest rate after a delay of 25-30 days (Fig. A2.5). A year after the end of the intervention period, the EIR and prevalence did not return fully to pre-larviciding levels, depending on the deployment factors and achieved impact. The higher the maximum reduction during the intervention period (as a product between coverage and frequency) the slower the resurgence to initial levels (Fig. 6.6). The reduction in EIR and prevalence that remained after the intervention period also varied depending on when larviciding was applied as well as the seasonal pattern (Fig. S2.6).

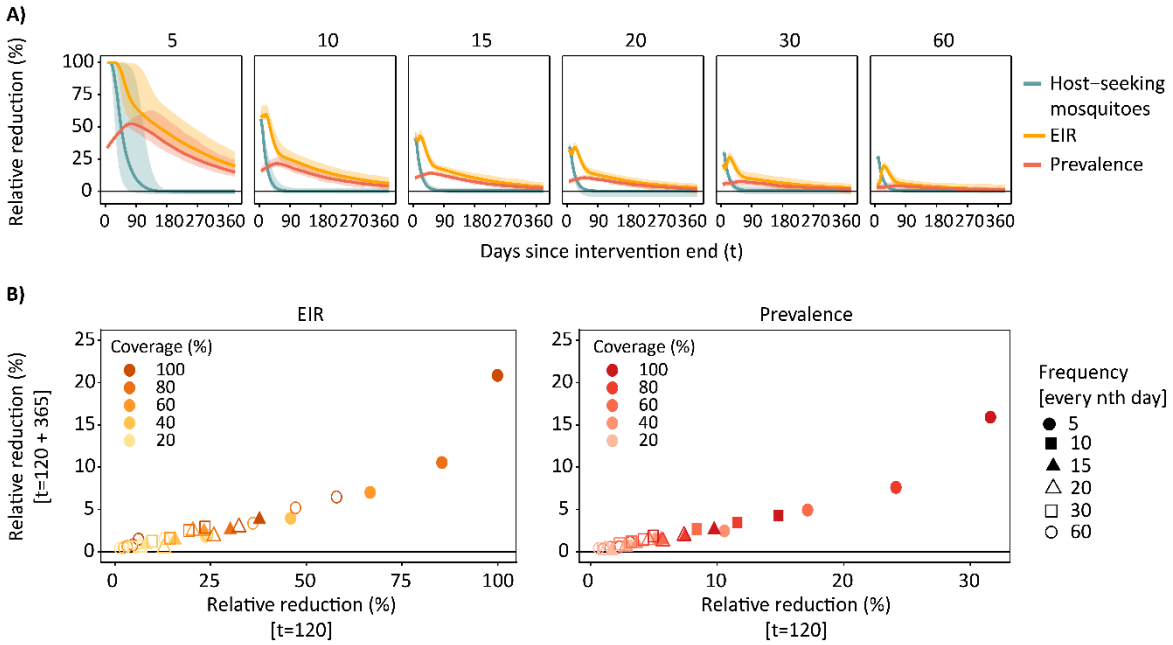

Fig. 6.6: Residual impact in outcome measures by deployment frequencies.
A) Decay of achieved impact on the different outcomes measured over time after stopping larviciding per deployment frequency (panels) for a demonstrative 100% coverage at moderate transmission intensity (EIR=10 ibpa). **B)** Remaining relative reduction in EIR and prevalence by coverage and frequency after one year of intervention stop compared to at the end of the intervention period. Note, the relative reduction in prevalence is selected at the specified timesteps while the prevalence reaches a maximum around 30-60 days after the intervention period of 120 days (Fig. S2.6). Results shown for a deployment period of 120 days (no seasonality) and moderate transmission intensity, with uncertainty intervals and errorbars corresponding to simulated range of mosquito density-dependence parameters.

6.4.4 Re-simulated larviciding study

In the selected field study in Mbita, western Kenya, larviciding was reported to reduce the larval density by 95%, the adult density by 92%, and the EIR from 9 to 0.8 ibpa during the two-year intervention period compared to the pre-and post-intervention period (Fillinger and Lindsay, 2006). Larviciding was simulated with the same number of deployments as reported (on average every 11 days when using *Bacillus thuringiensis israelensis*, every 22 days when using *Bacillus sphaericus* (Table A4.1)) with a range of larviciding coverage between zero and 100%, using an input EIR of 10 ibpa. At an assumed effective coverage of >90%, the maximum reduction in larval density was around 77%, in adult density 67%, and in EIR 40%. The reported high reductions in adult density and EIR of >90% could only be simulated with assumed constant effectiveness and unrealistically high coverage (predicted to reduce the larval density by 94%, the adult density by 93% and the EIR from 10 to 1.37). The results are shown in Additional file 4.

6.5 Discussion

This modelling study investigated the impact of larviciding deployment strategies varying by coverage, duration, application frequency, and seasonal timing, for three transmission intensities (3, 10 or 90 ibpa), and five seasonality patterns, assuming homogeneous vector population similar to *An. gambiae*. Overall, larviciding impacted the prevalence at a slower rate than the number of host-seeking mosquitoes and transmission intensity, while reduction in prevalence remained beyond the intervention period. The effective coverage during the intervention period, as a result of the efficacy duration of the larvicide, frequency and emergence reduction (effective coverage per single application), highly influenced the impact of larviciding. To ensure high impact, the product of the deployment factors need to be high, with regular deployments, tailored at the efficacy duration of the larvicide being more important than the effective coverage (number of emerging mosquitoes killed at each single round of larviciding) even at high coverage, when assuming short-lived larvicides. In highly seasonal settings, the deployment during the rainy season was predicted to have the highest impact on EIR and prevalence even at much lower coverage than during the dry season, and dry season larviciding had negligible impact. Larviciding at lower compared to high transmission intensity was further predicted to have a higher epidemiological impact with greater and longer lasting RR in the prevalence. This difference could be attributable to the differences in mosquito densities and faster rate of re-establishment at high transmission after larvicide decay to be effective (Fig. S.2.5).

Field observations (Kroeger et al., 1995; Tusting et al., 2013) and simulations agree that larviciding reduces the number of emerging mosquitoes for the duration of the killing effect and that the vector population re-establishes immediately afterwards (Dambach et al., 2014a; Kroeger et al., 1995; Tchicaya et al., 2009). In field studies, the time to reduce numbers of host-seeking mosquitoes varies between immediate impact and to lag times of two to three weeks (Dambach et al., 2014a; Kroeger et al., 1995; Tchicaya et al., 2009), with reductions in host-seeking mosquitoes ranging from very low to almost as high as the reduction in observed larval density (Dambach et al., 2014a; Kroeger et al., 1995; Tchicaya et al., 2009), with reductions in host-seeking mosquitoes ranging from very low to almost as high as the reduction in observed larval density (Afrane et al., 2016; Fillinger and Lindsay, 2006; Majambere et al., 2010). The simulations showed that prevalence is affected at a slower rate than the mosquitoes and transmission intensity and did not reach an equilibrium after one year of constant larviciding. This relates to the important role of duration of infection and parasite reservoirs in humans. It requires more time to clear infections in the human population by only reducing the mosquito population, whereas the reduction will also depend on malaria case management, which

was not included in the simulations. However, this finding indicates that longer follow-up times would be required in field studies to capture impact of larviciding on prevalence with follow-up times varying depending on the seasonality.

Shorter intervals between deployments to reduce gaps in effective coverage over time were predicted to increase the average impact and reduce fluctuations in outcomes, as observed in two studies in Kenya (Fillinger and Lindsay, 2006; Mwangangi et al., 2011). In practice, the required deployment frequency depends on the emergence rate of new breeding sites and the persistence of the specific active agent (Afrane et al., 2016; Fillinger et al., 2003; Karch et al., 1992; Magesa et al., 2009; Shililu et al., 2003b). Notably, some programmes focus on treating only productive breeding sites (Fillinger et al., 2004; Gu and Novak, 2005), a strategy considered cost-effective in a rural district in Burkina Faso (Dambach et al., 2014b). Concentrating efforts on peri-domiciliary breeding sites has also been advocated (Smith and McKenzie, 2004). The appropriate deployment strategy to achieve high coverage of larviciding, or LSM in general, will further depend on dispersal of breeding sites and total land area to cover, surface area and quantity of breeding sites as well as their proximity to houses.

Larviciding is currently recommended by the WHO to be deployed in areas or seasons where breeding sites are fixed, few and findable, commonly associated with the dry season or urban areas (WHO, 2019b, 2013), however, the simulation results suggest that larviciding in the dry season would have limited impact in seasonal settings (WHO, 2019b, 2013). The results further suggest that the additional benefit of larviciding throughout the year would be marginal in highly seasonal settings. The greatest impact on prevalence was predicted when implementation preceded the peak in transmission, hence averting seasonal increases in host-seeking mosquito density. However, rainy season larviciding is more challenging, in particular because of proliferation of breeding sites and dilution of larvicide (Afrane et al., 2016; Majambere et al., 2007; Mwangangi et al., 2011; Obopile et al., 2018), while on the other hand emergence rates might be reduced when larvae are flushed away by very high rainfall (Imbahale et al., 2011; Kahindi et al., 2018; Mwangangi et al., 2011). The trade-off between achieving high coverage (often described as more feasible in the dry season or arid areas (Kweka et al., 2012; WHO, 2013)) and the epidemiological impact associated with a given coverage (in simulation estimated higher in the rainy season) must play out differently in diverse environments and might well account for some of the variation in seasonal patterns of impact observed in the field.

In this modelling study, the operational challenge was attempted to reflect lowering the coverage during the rainy season while keeping the coverage during the dry season high, which did not change

the recommended timing for larviciding unless coverage dropped to less than 20% of emerging mosquitoes killed. Alternative approaches to adjust for operational challenges would include simulating shorter effectiveness (Majambere et al., 2007) or more frequent deployments (Mwangangi et al., 2011) in the rainy season, presumably with similar implications. The results apply for settings with low vector densities and little to no transmission during the dry season, and where peak in transmission follows with one month lag after peak in rainfall.

The model results suggest that the relative impact would be greater at low than at high transmission in which high coverage would be needed. Nevertheless, larviciding has been successfully deployed in moderate to high transmission areas in several studies (Dambach et al., 2019; Rahman et al., 2016; Tchicaya et al., 2009). One study in particular showed that larviciding could be implemented at high transmission in highly seasonal areas with findable breeding sites (Dambach et al., 2019). Reduction in prevalence has rarely been studied in larviciding field studies (Tusting et al., 2013) although one study reported a reduction of more than 70% (Geissbühler et al., 2009). Based on the simulations, such high reductions would only be achievable at very high coverage and long duration of effective larviciding, either with more frequent deployments or longer residual activity (e.g. longer than 120 days), and seems unlikely to be achieved with larviciding alone as reported in the study.

In most instances, larviciding, recommended as a supplementary intervention (WHO, 2013), will be deployed alongside ITNs or IRS, to reduce transmission and create a context where larviciding is more effective. While interactions were not explicitly modelled, implicitly synergistic effects with these interventions were assumed by simulating low pre-larviciding transmission intensity. This assumption is supported by the higher impact at low transmission seen in the predictions. For the same reason, synergies with chemotherapeutic interventions can also be anticipated (Briët and Penny, 2013). Further synergies are likely where there is insecticide or drug resistance because larvicides have different biochemistry and act independently of host-seeking and resting behaviour of adult mosquitoes (Killeen et al., 2002b), and they can address transmission that is refractory to the core interventions. In practice, larviciding might also be combined with other LSM approaches (Imbahale et al., 2012; van den Berg et al., 2018; WHO, 2013) that together reduce the adult mosquito emergence in an area.

Although the measurement of coverage is critical for predicting the impact of a larviciding programme, there is no standardization of operational coverage measures. These have been variously defined as the number of treated breeding sites out of the total identified, the proportion of the surface area of water bodies that are treated, or even the proportion of larvae covered by

larvicide out of all larvae within a breeding site (Additional file 3). Targeting specific areas (or selection of sub-sets of breeding sites or other criteria) reduce the denominators in such calculations. All these measures of coverage are challenging to estimate (Chaki et al., 2009; Dambach et al., 2016b; Fillinger et al., 2009b; Fillinger and Lindsay, 2011), especially since the proportion of breeding sites identified varies in each setting and over time. Regardless of the suitability of the local settings, the effectiveness also depends on the performance of field staff, community engagement and supervision (Chaki et al., 2014, 2011).

The simulations of larviciding in Mbita, western Kenya, attempted to calibrate the model to allow for these factors. The results emphasize the difficulty of correctly reproducing the impact of larviciding, and on estimating coverage levels that would be feasible, despite accounting for details of deployment. In the simulations, the vector population immediately increased between the larvicide applications, whereas in the field measurements adult densities remained relatively low (Fillinger and Lindsay, 2006). Hence, the low levels in host-seeking mosquito density maintained throughout the intervention period of two years could only be reproduced with constant high effective coverage. It could be that the sampling under-represented the true adult mosquito density in the community or that the simulated re-treatment intervals underestimated the effectiveness in practice. Another reason could be additional use of ITNs, or other factors not accounted for in the simulations that lowered the transmission throughout the study period.

In contrast to the homogeneous vector populations in the simulations, multiple vector species are usually present in the field, and some of this variation in outcomes result from environmental and ecological factors that cannot be captured in the model. For instance, larviciding of rice fields has been found to be impractical in The Gambia, due to low accessibility (Majambere et al., 2010), but was feasible in Tanzania and Rwanda (Ingabire et al., 2017; Mazigo et al., 2019a). One study in Kenya found positive effects of dry season implementation on mosquito density and clinical malaria using long-lasting larvicides (Afrane et al., 2016). Another study in western Kenya reported higher effectiveness during the rainy season, using short-lived larvicides (Zhou et al., 2013). For instance, while a high number of breeding sites existed throughout the dry season in an urban setting (Dar es Salaam) (Fillinger et al., 2008) they substantially varied by season in the rural village setting in Mbita, western Kenya (Fillinger and Lindsay, 2006). Hence, field operations should always consider local climate, breeding site permanence based on water sources and characteristics, dominant vector species, available resources, and engagement of the community (Hardy et al., 2013). The diversity of operational implementation and outcomes highlights the need for more setting-specific guidelines for larviciding to differentiate between strategies for different localities. For instance, in Tanzania,

the national malaria strategic plan includes larviciding the whole country (MoHCDGEC, 2014), but heterogeneities in malaria epidemiology and environmental factors represent a huge challenge for planning appropriate large-scale strategies (Chacky et al., 2018; Grover-Kopec et al., 2006) and implementation will require a thorough assessment of the context at local level.

6.6 Conclusion

In seasonal transmission settings, larviciding was predicted to be most impactful if done before and during the peak in vector density; in many settings this corresponded to the rainy season instead of during the dry season as currently recommended by WHO. Some deployment parameters, including coverage, are difficult to determine accurately in reality versus in a model. Field studies find substantial variation in outcomes that appears to stem from diversity in eco-environmental settings, vector biology and in operational strategies, and are often difficult to relate to model predictions. To make model-based impact predictions that can be compared between areas, the different deployment strategies and coverage should be calibrated against effects on densities of host-seeking vectors and prevalence in humans. Such calibration would enable models to become a practical tool to support malaria control programmes in developing operational strategies for larviciding that account for diversity of context.

6.7 Declarations

Author contribution

FO, SM, EP, MR developed the research idea. MR reviewed the literature, performed the analysis, and wrote the draft manuscript. NC developed and extended the vector model. TS, EP and FO provided substantial feedback to early and final versions of the manuscript. TS, NC, FO, EP provided technical advice. All authors have read and contributed to the final manuscript.

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Data and code sharing

The analysis code is available on GitHub at https://github.com/ManuelaRunge/om_larviciding_tza. The simulation output is available from Zenodo at https://doi.org/10.5281/zenodo.5033187.

6.8 Supplementary information

Additional file 1: A simple periodically forced difference equation model for mosquito population dynamics

VectorModel[15]

The previous developed model for malaria in mosquitoes did not include the dependence of the emergence rate of new mosquitoes on the number of eggs laid (Otero et al., 2006). Hence, it did not include the nonlinear effects of adultcides on reducing the population size. To include this effect and, also, to better model the effects of larval control a model for mosquito population dynamics was developed. Most models of mosquito population dynamics have focussed on Aedes mosquitoes and have used ordinary differential equations (ODEs) (Otero et al., 2006), delay differential equations (DDEs) (Cooke et al., 1999; Dye, 1984; Hancock and Godfray, 2007), or stochastic individual based models (Ahumada et al., 2004; Depinay et al., 2004; Focks et al., 1993). Dye (Dye, 1984) and Yakob et al. (Yakob et al., 2008) developed difference equation models but only for successive generations. However, to link with the existing mosquito model in OpenMalaria, a model for population dynamics with overlapping generations and a discrete time step of one day is needed. It is assumed that the dynamics of the population are regulated by a periodically-varying larval carrying capacity. Further, a simple model where only one juvenile stage is simulated is assumed.

Table SI-1.1: Model parameters

Parameter	Description
T_p	Period of the system. This period is usually set to 365 days when using a daily timestep. Dimension: Time. $T_p \in \mathbb{N}$ (Otero et al., 2006)
τ	Duration of resting period of mosquitoes. Dimension: Time. $\tau \in \mathbb{N}$ (Otero et al., 2006)
θ_j	Duration of the juvenile stage. Dimension: Time. $\theta_j \in \mathbb{N}$
b	Number of female eggs laid by one female mosquito per ovipost. Dimensionless. $b > 1$
ρ	Survival probability of a mosquito from egg to emergence in the absence of density dependent mortality.
$\gamma(t)$	Resource availability at time t. Dimension 1/Animals. $\gamma(t) > 0.\ \gamma(t + T_p) = \gamma(t)\ \forall t \in \mathbb{N}$

[15] This report is also available online at https://github.com/SwissTPH/openmalaria/wiki/ModelMosqPopDynamics

In the model of malaria mosquitoes, (Otero et al., 2006), the population of adult host-seeking mosquitoes was determined by,

$$x(t) = g(x(t-1), x(t-\tau), t) + \mathrm{E}(t) \qquad (1)$$

Table SI-1.2: Derived parameters

Parameter	Description
P_{df}	Probability of finding a host and surviving the feeding cycle. Dimensionless. $0 < \mathrm{P}_{df} < 1$ (Otero et al., 2006)
$\mathrm{E(t)}$	Emergence rate of adult mosquitoes at time t. Dimension: Animals. $\mathrm{E}(t) > 0. \mathrm{E}(t + T_p) = \mathrm{E}(t)\ \forall t \in \mathbb{N}$

Where $x(t)$ is the population of adult host-seeking mosquitoes at time t, $\mathrm{E(t)}$ is a fixed periodic sequence of emerging mosquitoes, and $g(x(t-1), x(t-\tau), t)$ determines the survival of adult mosquitoes. Here, we extend (1) to allow the emergence rate to depend on the adult population using a Beverton-Holt model,

$$x(t) = g(x(t-1), x(t-\tau), t) + \frac{\rho y(t-\theta_j)}{1+\gamma(t-\theta_j)y(t-\theta_j)}, \qquad (2a)$$

$$y(t) = b\mathrm{P}_{df}x(t-\tau) \qquad (2b)$$

Where $y(t)$ is the population of juvenile stages at time t. To initialize the system, we assume that the system (2) has a locally asymptotically stable periodic orbit that is has reached. In that case the estimated periodic emergence rate is

$$\mathrm{E(t)} = \frac{\rho y(t-\theta_j)}{1+\gamma(t-\theta_j)y(t-\theta_j)} \qquad (3)$$

$$= \frac{\rho b\mathrm{P}_{df}x(t-\theta_j-\tau)}{1+\gamma(t-\theta_j)b\mathrm{P}_{df}x(t-\theta_j-\tau)} \qquad (4)$$

Solving (4) for $\gamma(t)$ provides[16],

$$\gamma(t-\theta_j) = \frac{\rho b\mathrm{P}_{df}x(t-\theta_j-\tau) - \mathrm{E(t)}}{\mathrm{E(t)}b\mathrm{P}_{df}x(t-\theta_j-\tau)} \qquad (5)$$

To simulate larviciding, we can use

$$x(t) = g(x(t-1), x(t-\tau), t) + (1-c)\frac{\rho y(t-\theta_j)}{1+\gamma(t-\theta_j)y(t-\theta_j)} \qquad (6a)$$

$$y(t) = b\mathrm{P}_{df}x(t-\tau) \qquad (6b)$$

Where c is the proportional coverage of breeding sites treated with larvicides with $0 < c < 1$.

[16] We again need to ensure that (t) > 0: I assume this will always be the case but there should be a check for it. Also, since (t), x(t), and E(t) are periodic sequences, it is OK to solve both forwards and backwards in time.

Additional file 2: Additional result figures

Relationship among outcome measures in absence of larviciding

The lag time between peak density of emerging mosquitoes and peak density in host-seeking mosquito was 10 days, followed by 40 days until peak in EIR and 55 days until peak in prevalence. Relative to peak in density of emerging mosquitoes, the peak in EIR followed after 50 days (1.6 months) and the peak in prevalence after 105 days (3.5 months) (Fig. S2.1A). The incidence (number of new cases) showed the same trend and peak as the simulated EIR (Fig. S2.1B). The average prevalence is 23% for an annual EIR of 3 ibpa, 40% for an annual EIR of 10 ibpa, and 50% for an annual EIR of 90 ibpa, the seasonal variation is shown in Fig. A2.1C. More information available in the OpenMalaria wiki[17].

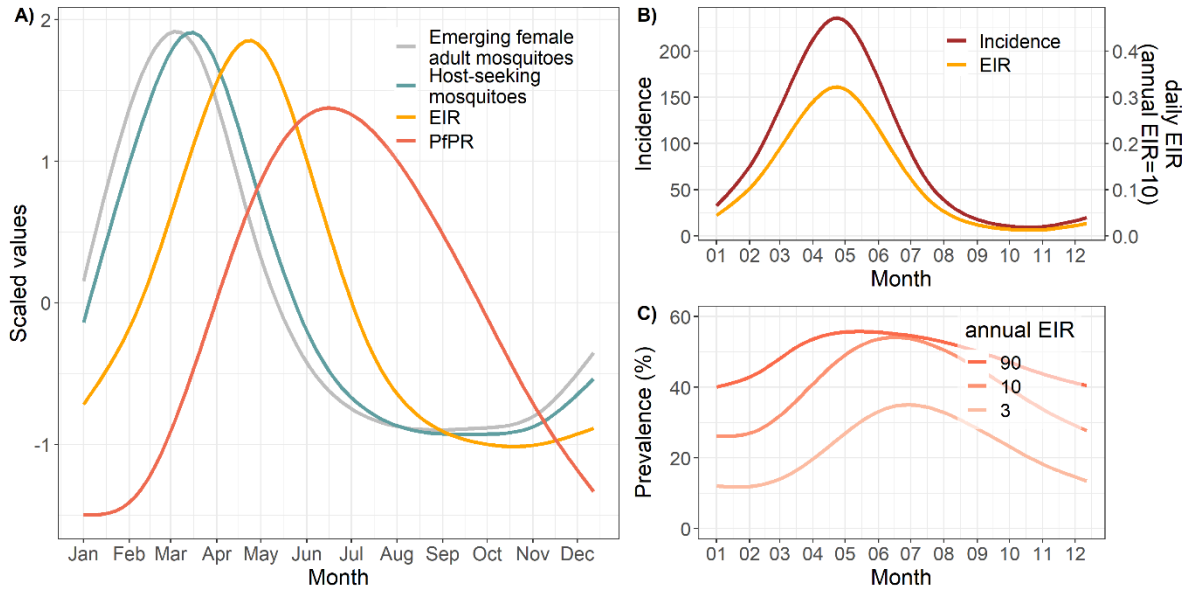


Fig. S2.1: Simulated outcome measures for one year in absence of larviciding for a high seasonality setting. **A)** Comparison of seasonality and delay between mosquito emergence, host seeking mosquito density, EIR and prevalence (values on relative scale). **B)** Comparison of incidence and EIR over time for an annual EIR of 10. **C)** Predicted prevalence over time by annual EIR.

[17] https://github.com/SwissTPH/openmalaria/wiki/ScenarioTransmission

Larviciding in absence of seasonality

Influence of mosquito population density-dependency parameters

Larviciding was simulated at fours coverage levels (20%, 40%, 80%,100%) that stayed constant for 60 days. In addition, three parameters that describe the mosquito density-dependence were varied, the survival probability, the number of eggs laid and the development duration. The range for the survival probability were selected to explore the whole range regardless of biological feasibility whereas for the other two parameters the values were selected based on biological reported development durations for *Anopheles* mosquitoes[18]. The model operates on a five-day timestep.

On average, the reduction in emerging adult mosquitoes per population over time corresponded to the larviciding coverage, with small variations depending on the mosquito density-dependence parameters. At low coverages (<40%), the initial reduction in emergence was lower for specific mosquito density-dependence parameter combinations, while the emergence reduction increased over time at high coverage (>80%). At high coverage, some combinations of the mosquito density-dependence parameters prolonged the reestablishment of the vector population over time. The parameters affected the rate at which the mosquito population reestablished especially when the population was completely depleted (100% coverage), whith slower reestablishment when the survival probability and numbers of female eggs laid per oviposting were low.The level to which the mosquito population re-established was similar to the pre-larviciding levelwith few exceptions when the re-establishment rate was slower (Fig. S2.2).

The survival probability was predicted to have the strongest impact on the reestablishment rate and the development durations was predicted to have the lowest impact on the reestablishment rate. When assessing each parameter separately, they did not change the mean predictions substantially, except for the very low survival probability of 0.1%, with wide ranges in the predictions suggesting high interaction among the parameters (Fig. S2.3).

[18] Service MW. Medical entomology for students. 5th ed. Cambridge: Cambridge University Press; 2012.

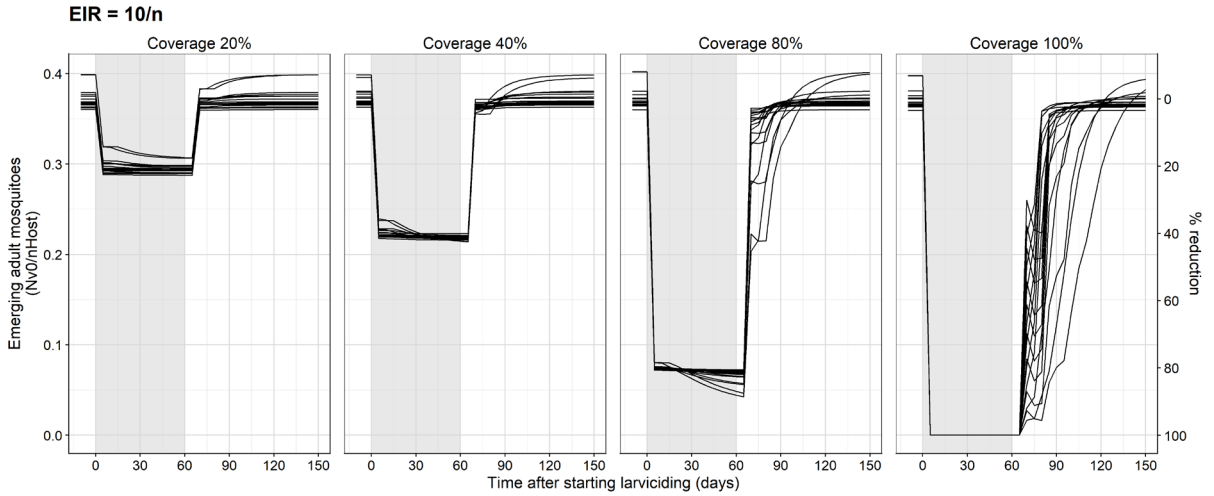


Fig. S2.2: Simulated impact of constant larviciding for 60 days at four different coverage levels on vector density.

Each line corresponds to a unique set of mosquito density-dependence parameters as shown in Fig. S2.3. The figure was identical across the simulated transmission intensities (EIR 3, 10 and 90 ibpa) and this figure shows the predictions at moderate transmission intensity (EIR=10 ibpa). The corresponding emerging adult mosquito to host ratios were 0.15 per 10000 humans at 3 ibpa, 0.37 at 10 ibpa, and 2.7 at 90 ibpa. The model operates at minimum timesteps of 5 days.

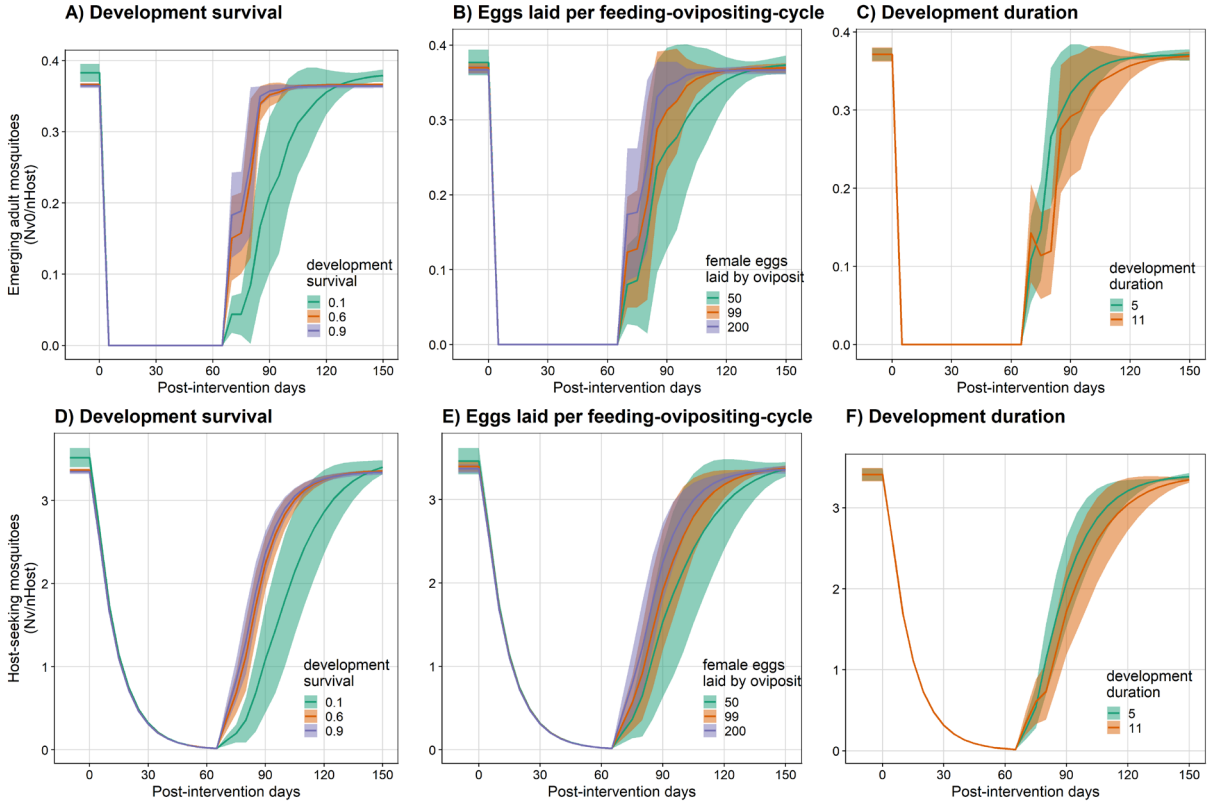


Fig. S2.3: Influence of population density parameters vector populations with constant larviciding for 60 days at 100% coverage.

A-C) Emerging adult mosquitoes. **D-F)** Host-seeking mosquitoes. Each panel in a row shows one of the mosquito density-dependence parameter values (colors) while the other two mosquito density-dependence parameters are averaged

Larviciding frequency versus coverage

The relative reduction in prevalence depending on larviciding coverage and deployment frequency was assessed at the end of the intervention period (120 days) and by transmission intensity as well as for two different decay functions (step decay versus exponential decay). When the deployment frequency or the coverage were reduced by half (e.g. deployments every five to every ten days, coverage from 80 to 40%), the predicted effectiveness was approximately reduced by half as well, assuming a step decay after five days. Overall, fewer deployments led to higher loss in effectiveness than lower coverage. With longer breaks between deployments, the decay rate of the larvicide was predicted to have less influence on the impact. The predicted relationship between frequency and coverage was the same for the three transmission intensities included in the analysis, whereas the maximum reduction was 2.5 times lower at high transmission compared to low transmission (Fig. S2.4).

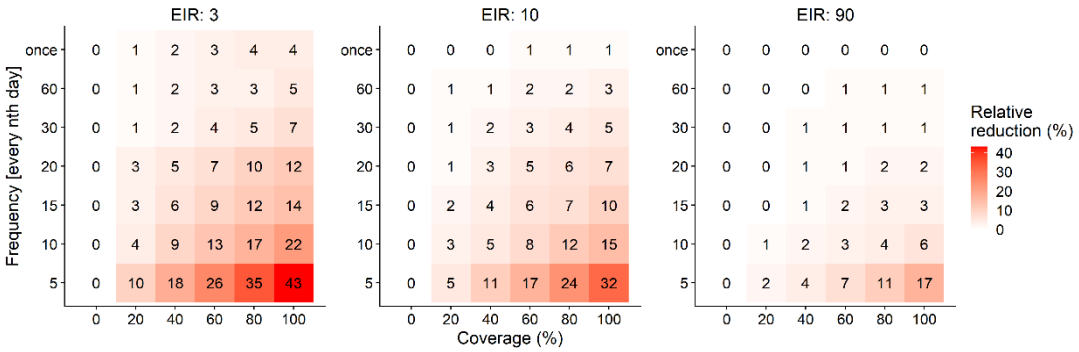


Fig. S2.4: Relative reduction in prevalence by frequency versus coverage at the end of the intervention period (120 days).

The plot shows the relative reduction for an effectiveness decay of 100% for 5 days (1 timestep in OpenMalaria) and reaching 0% directly after (timestep 2).

Post-larviciding resurgence in predicted outcome measures

The re-surgence in the outcome measures after stopping larviciding depending on the deployment frequency during the intervention period is shown in Fig. S2.5. The predicted rebound was similar for all deployment scenarios but very different for the three outcome measures included in the analysis. The reduction in prevalence reached a peak that was much lower as for EIR and adult mosquito density, and the resurgence to pre-larviciding levels was predicted to also take much longer (Fig. S2.5). For prevalence, the resurgence was slower at low compared to high transmission intensity (Fig. S2.6.).

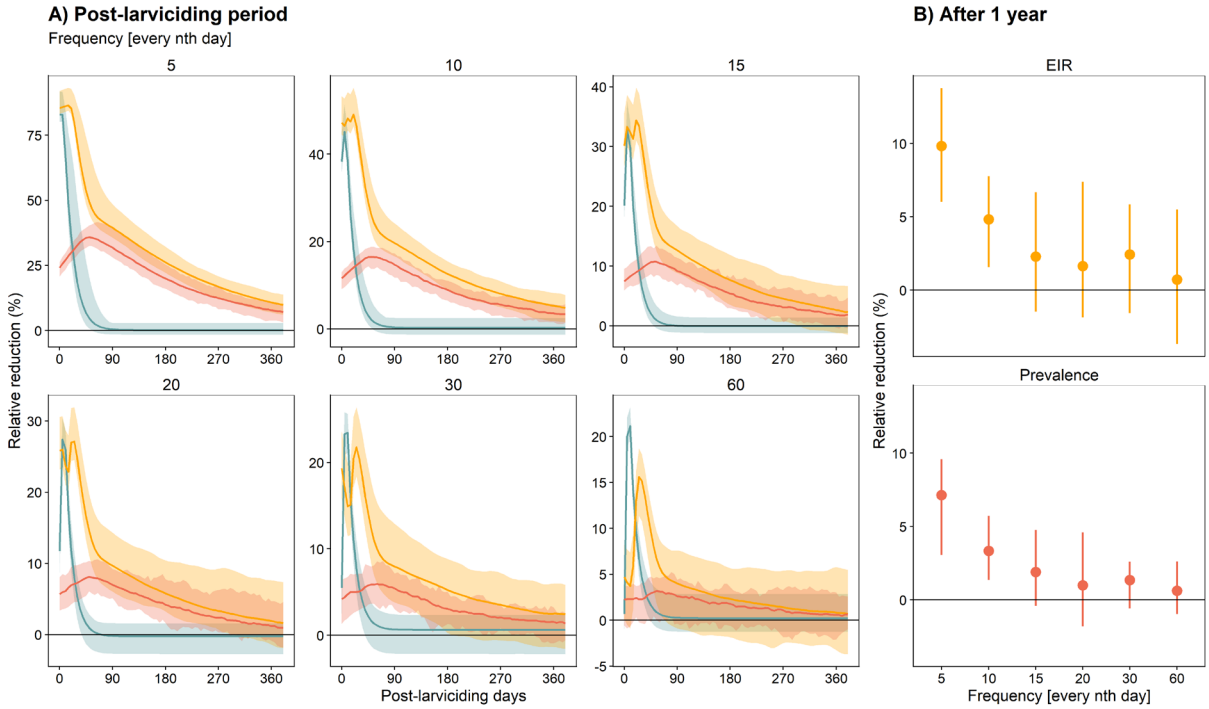


Fig. S2.5: Varying larviciding deployment and impact on vector density, EIR and prevalence over time with 80% coverage at moderate transmission intensity (EIR = 10 ibpa).

A) Predicted relative reduction compared to no larviciding during the post-larviciding period. **B)** Predicted relative reduction after one year. The uncertainty interval and the errorbars show the range around the mosquito density-dependence parameters (development survival, number of female eggs laid per ovipositing, development duration).

The relative reduction in prevalence showed a lag time of 25-30 days after start of larviciding and 30-60 days after end of larviciding, depending on coverage (Fig. S2.6).

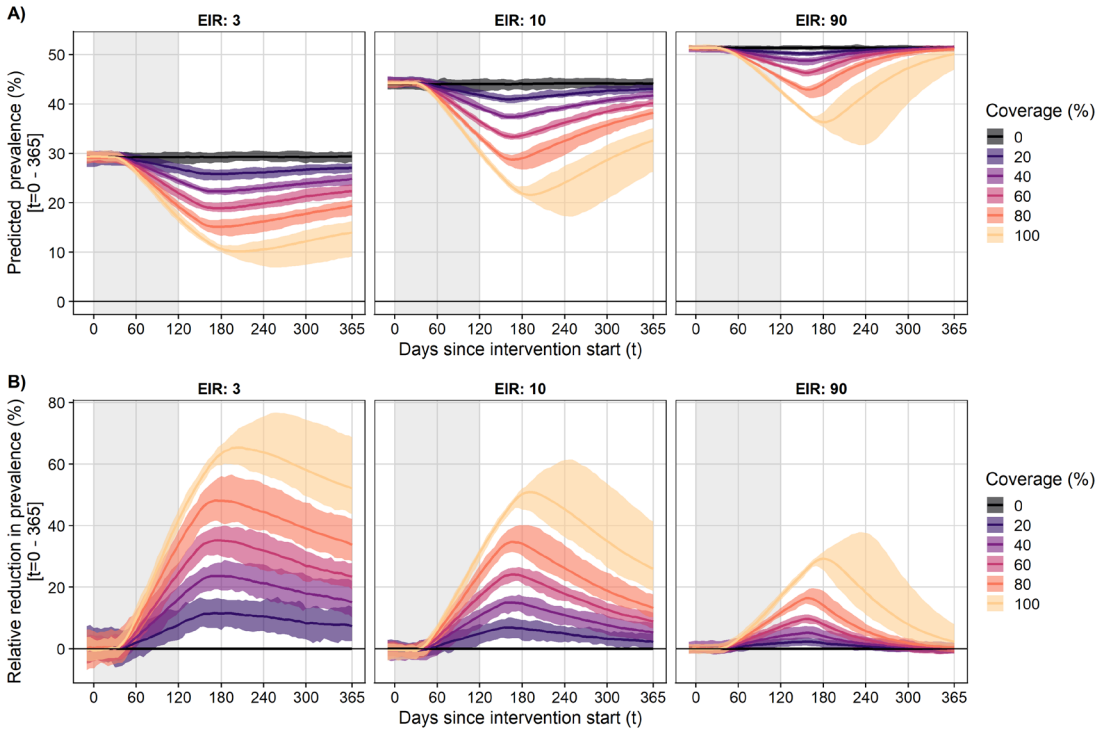


Fig. S2.6: Impact on prevalence over time with constant larviciding deployment for 120 days at different coverage levels and varying transmission intensity.

A) Predicted prevalence over time. **B)** Relative reduction compared to no larviciding. The grey shaded area indicates the time larviciding was deployed assuming constant effectiveness. The uncertainty intervals show the range around the mosquito density-dependence parameters (development survival, number of female eggs laid per ovipositing, development duration).

Larviciding and seasonality

Seasonality and timing of larviciding

The highest reduction was predicted for larviciding starting around three months before the peak in transmission with the assumption of a fixed effectiveness duration of 120 days, lasting until one months after the peak. (Fig. S2.7). Regardless of seasonality, transmission intensity or larviciding coverage, deployment of larviciding in the wet season was the most impactful timing, followed by deployment during the beginning of the rain, then the end of the rainy season. For high seasonal settings, deployment of larviciding during the rainy season only or throughout the whole year would have a similar expected impact. During the dry season, the relative impact of larviciding was equally low across all transmission intensities. The modelling results further suggest that at very high transmission intensity with perennial transmission (no seasonality) larviciding would not have any impact on the malaria prevalence in human (Fig. S2.8).

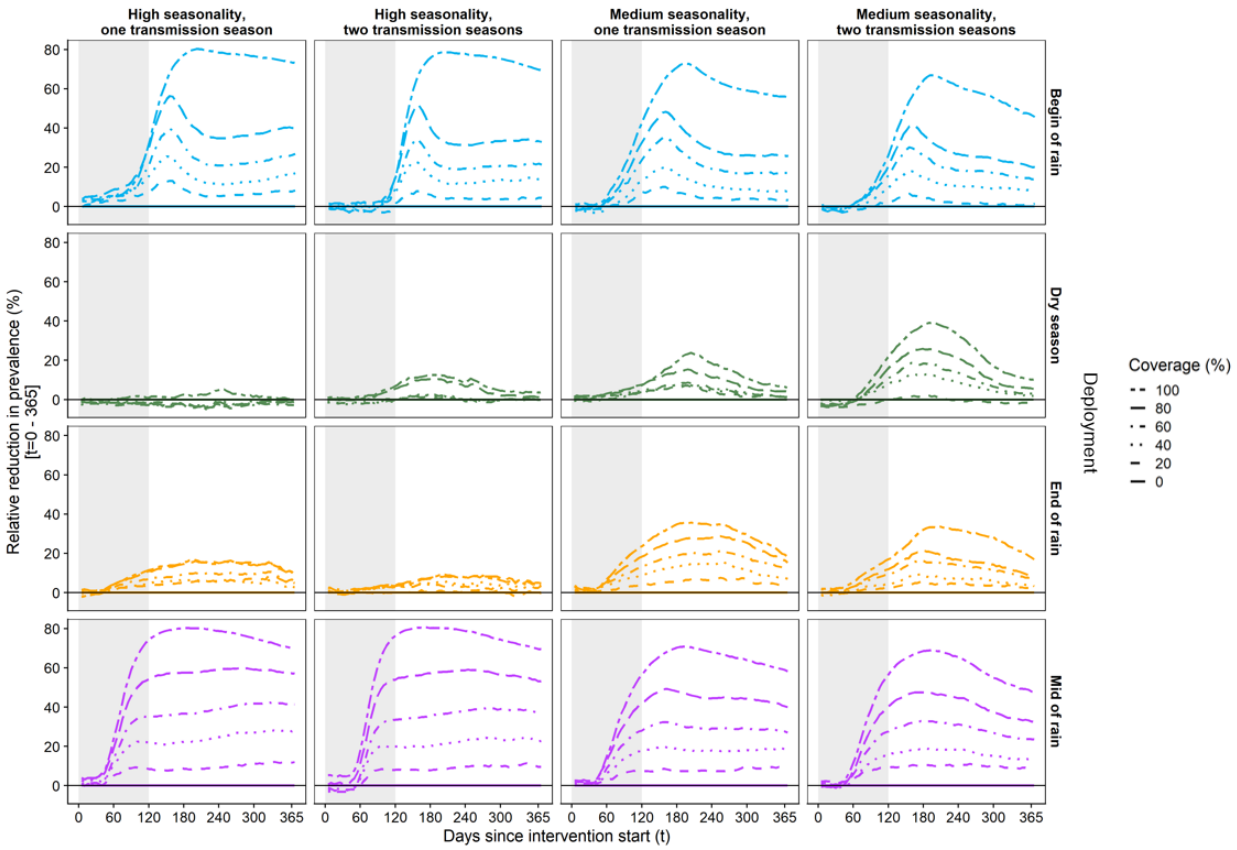


Fig. S2.7: Relative reduction in prevalence over time for varying starting months of larviciding and varying coverages at moderate transmission intensity (EIR=10 ibpa).

The grey shaded area indicates the time larviciding was deployed assuming constant effectiveness. The colored lines show the starting months as selected for the defined seasonal deployment of larviciding.

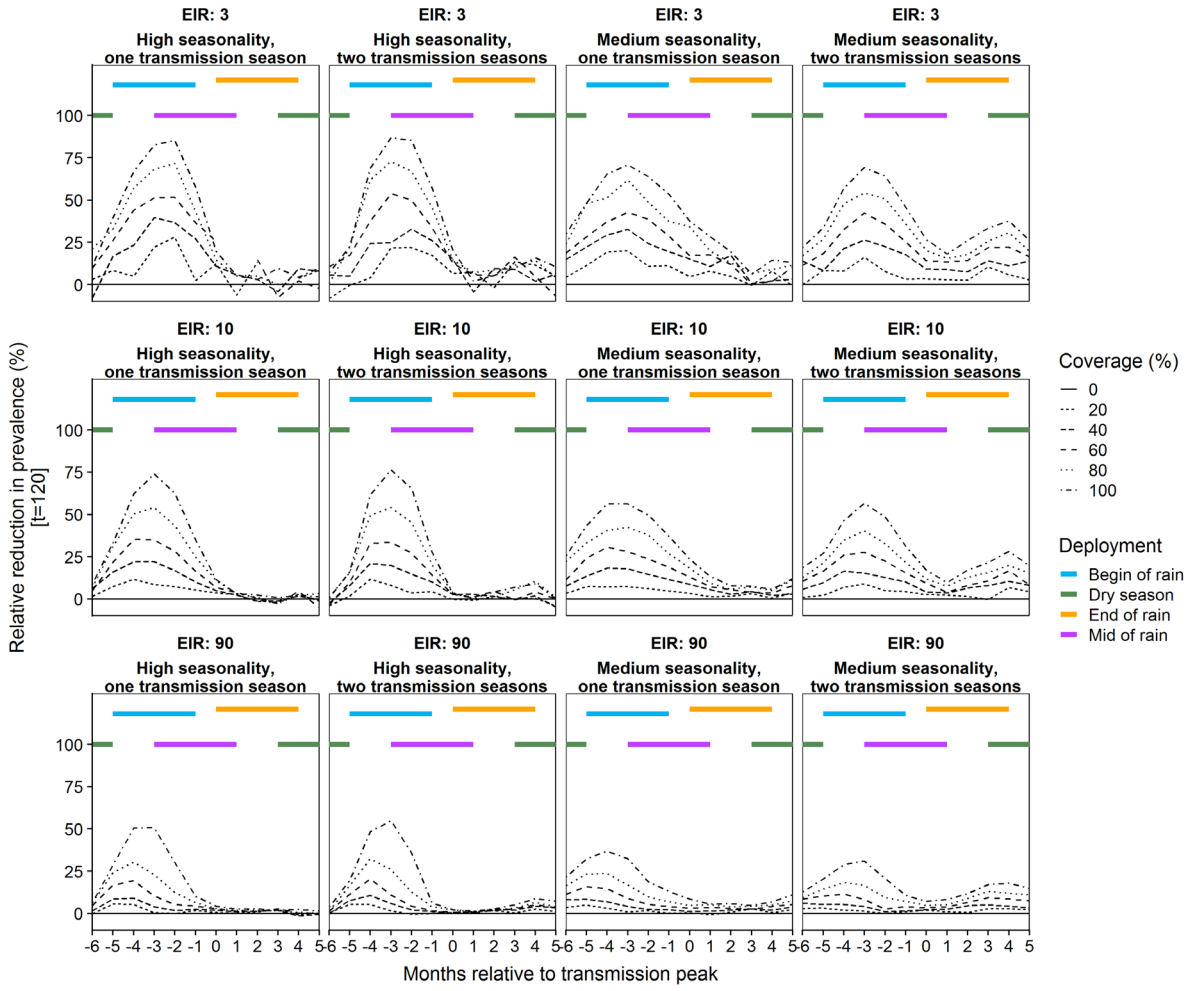


Fig. S2.8: Monthly shift in deployment and relative reduction in prevalence with varying coverage and transmission intensity.

The colored lines indicate the seasonal timing explored (begin of rain = -6 to -4, dry season = 3 to 5, end of rain=0 to 2, and mid of rain=-3 to -1 months before the peak in transmission).

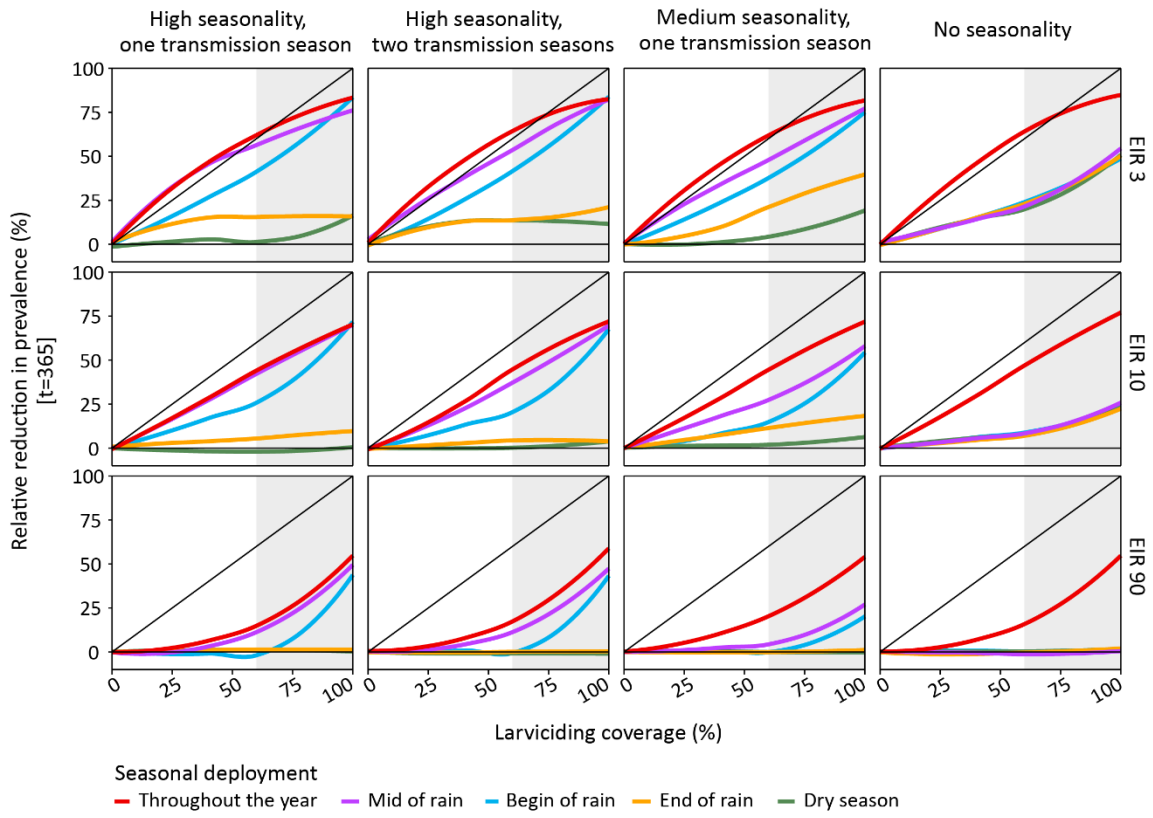


Fig. S2.9: Simulated relative reduction in prevalence, after one year of larviciding deployment, by coverage and timing of deployment for different seasonality and intensity of transmission.
The x-axis shows the effective larviciding coverage. The grey area shows effective larviciding coverage above 60%, which might be difficult to achieve in practice. The coloured shaded areas represent the 95% confidence interval for the relative reduction for different timing of deployment, assuming a fixed deployment period of one year (throughout the year) or 120 days (seasonal deployment).

Coverage thresholds and seasonal timing

At the end of the intervention period, the maximum relative prevalence reduction of larviciding during the wet season ranged between 69.8% and 47.8% depending on seasonality with higher reductions at high seasonality and one peak. In this setting (high seasonality and one peak) the prevalence reduction ranged from 0.5% for larviciding applied at maximum coverage during the dry season to 73.2% during the beginning of the wet season. The difference depending on timing was lowest in settings with medium seasonality and two peaks ($RR_{dry\ season}$=10.4%, $RR_{wet\ season}$=47.8%). The maximum reduction in perennial settings (constant transmission) would be 26.5% for 120 days and 76.8% for 365 days of effective larviciding (Table S2.1).

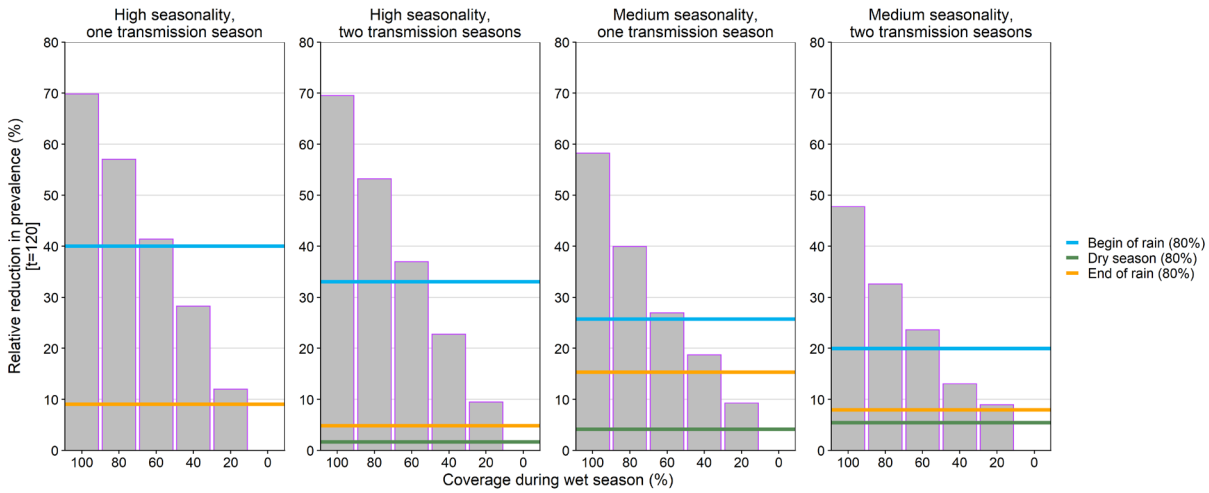
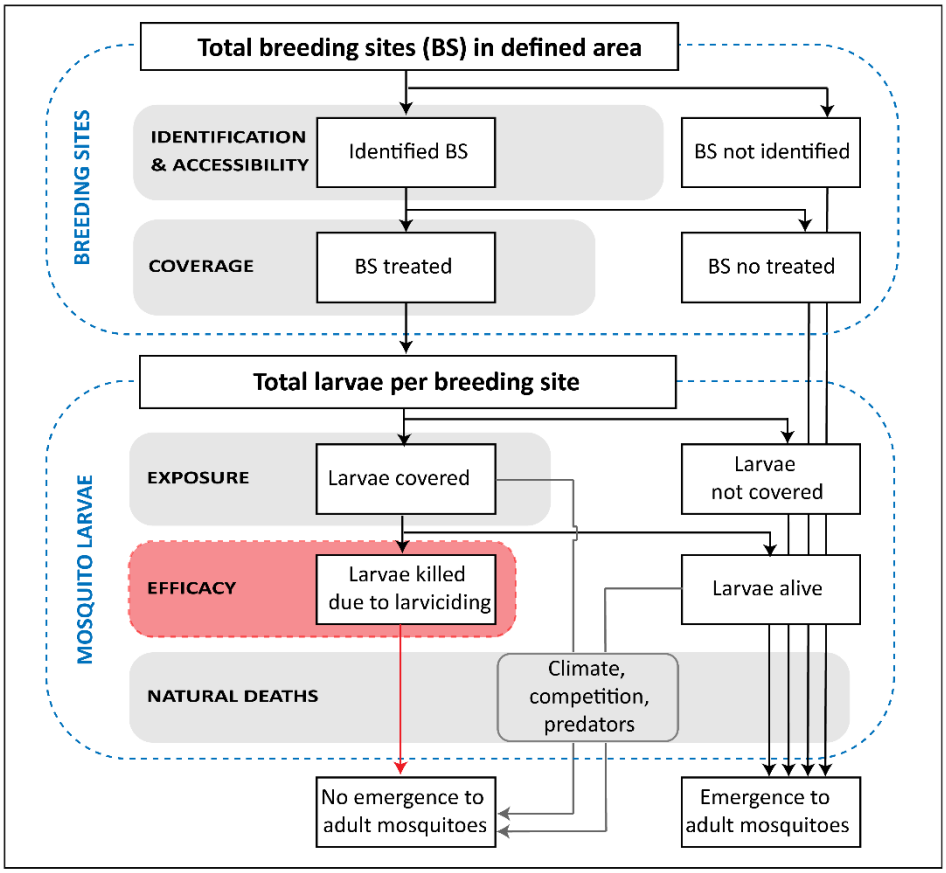


Fig. S2.10: Threshold for larviciding coverage during the wet season compared to an arbitrary effective target coverage of 80% during the other seasons after larviciding with constant effectiveness throughout deployment period of 120 days at moderate transmission (EIR= 10 ibpa).

Table S2.1: Relative mean reduction in prevalence at moderate transmission (EIR=10 ibpa) with varying seasonality and deployment times after 120 days effective larviciding.

			Start of larviciding, effective for four months				Throughout the year
Seasonality	**Peaks**	**Coverage**	**Begin of rain**	**Dry season**	**End of rain**	**Wet season**	
None		20	2.5	4.2	3.1	2.6	13.1
Medium	one	20	3.3	1.6	4.2	9.3	13.7
Medium	two	20	1.5	-1.6	2.3	8.9	16.5
High	one	20	8.3	-1.5	4.9	12.0	12.0
High	two	20	4.4	0.0	-0.2	9.5	9.4
None		40	6.4	5.7	4.4	5.7	30.0
Medium	one	40	7.4	1.8	7.0	18.7	27.9
Medium	two	40	7.6	1.9	3.3	13.0	33.0
High	one	40	17.1	-1.1	2.6	28.2	29.0
High	two	40	14.5	0.1	4.1	22.7	26.5
None		60	9.4	8.0	7.2	8.9	46.8
Medium	one	60	17.0	1.2	11.6	27.0	44.7
Medium	two	60	14.1	2.9	6.7	23.6	48.9
High	one	60	26.9	-2.8	5.5	41.4	44.2
High	two	60	21.4	-0.1	3.6	37.0	44.9
None		80	12.6	11.8	12.2	13.1	63.2
Medium	one	80	25.7	4.1	15.4	39.9	59.9
Medium	two	80	20.0	5.4	7.9	32.6	62.9
High	one	80	40.0	-1.1	9.1	57.0	57.6
High	two	80	33.0	1.7	4.8	53.2	60.5
None		100	24.8	23.5	22.7	26.5	76.8
Medium	one	100	55.8	6.1	18.2	58.2	71.5
Medium	two	100	45.6	10.4	17.0	47.8	76.6
High	one	100	73.2	0.5	9.2	69.8	70.4
High	two	100	69.4	3.7	3.8	69.5	71.7

Additional file 3: Flowchart from operational to effective larviciding coverage



The figure reads from top to bottom, capturing coverage factors between identification of a breeding site and effective emergence reduction. **IDENTIFICATION & ACCESSIBILITY**: Out of all productive breeding sites, only a subset of such is identified and accessible, depending on the performance of larviciding staff as well as environmental conditions. **COVERAGE**: Out of the identified and accessible breeding sites either all or only a subset might be treated, due to factors related to either staff performance, or study design, as some studies only treat breeding sites in which larvae were found to be present. This coverage is referred to operational coverage and the only measurable coverage (number of breeding sites treated out of all (identified) breeding sites. **EXPOSURE**: Within breeding sites, it might be that the larvicide is not applied evenly on the breeding site surface, due to either staff performance or environmental conditions, leading to the possibility that not all larvae within a breeding site get exposed to the larvicide. **EFFICACY**: The efficacy describes the effect rate of the larvicide on exposed larvae, and some larvae might survive despite being exposed, due to environmental factors or decay of the larvicide, this refers also to the effective coverage as used in the modelling. **EMERGENCE REDUCTION**: the proportion of larvae killed due to being exposed to the larvicide; it is a combination of the effective coverage and the larvicide efficacy.

Additional file 4: Re-simulated larviciding study

Study summary

Between 2002 and 2005 Fillinger and colleagues conducted a larviciding field study in a rural village in Kenya (Mbita). At that time, ITNs and IRS had not been scaled up (Fillinger and Lindsay, 2006). Malaria transmission in Mbita was described as perennial, with two rainy seasons: long rains from March to June and shorter rains from October to December. Larviciding was applied throughout the year between June 2002 and September 2004 using *Bacillus sphaericus* (*Bs*) and *Bacillus thuringiensis var. israelensis* (*Bti*). In total, 419 breeding sites were reported, with around half of those containing *Anopheles* larvae, and 65-219 breeding sites treated per larviciding deployment (n=50 deployments) (varying habitat availability per deployment) (Fillinger and Lindsay, 2006).

Table S4.1: Number of deployments separated by larvicide used. Reproduced from (Fillinger and Lindsay, 2006).

Bs.				***Bti.***			
No	**Date**	**Breeding habitats treated**	**Days between treatments**	**No**	**Date**	**Breeding habitats treated**	**Days between treatments**
1	13.06.2002	101	–	8	07.11.2002	165	22
2	24.06.2002	88	10	14	30.01.2003	94	22
3	09.07.2002	67	16	16	02.04.2003	185	58
4	23.07.2002	78	14	17	09.04.2003	120	7
5	12.08.2002	76	20	18	16.04.2003	219	7
6	03.09.2002	66	22	19	23.04.2003	180	7
7	16.10.2002	108	43	20	01.05.2003	155	8
9	13.11.2002	189	6	21	07.05.2003	178	6
10	26.11.2002	153	13	22	14.05.2003	194	7
11	18.12.2002	144	22	23	21.05.2003	192	7
12	22.12.2002	206	4	24	28.05.2003	126	7
13	08.01.2003	145	17	28	10.12.2003	172	25
15	05.02.2003	73	6	29	17.12.2003	110	7
25	04.06.2003	123	7	30	24.12.2003	120	7
26	01.07.2003	132	27	31	31.12.2003	83	7
27	15.10.2003	72	105	32	07.01.2004	75	7
34	21.01.2004	93	7	33	14.01.2004	145	7
35	11.02.2004	68	21	37	31.03.2004	156	27
36	04.03.2004	82	22	38	07.04.2004	191	7
47	09.06.2004	79	7	39	14.04.2004	198	7
48	15.07.2004	68	36	40	21.04.2004	200	7
49	03.09.2004	65	50	41	28.04.2004	202	7
50	15.09.2004	135	12	42	05.05.2004	166	7
				43	12.05.2004	139	7
				44	20.05.2004	102	8
				45	26.05.2004	85	6
				46	02.06.2004	76	5

Simulations and analysis

Simulations in OpenMalaria were run to compare the predicted effect of larviciding to outcomes of the larviciding study conducted in Mbita (Fillinger and Lindsay, 2006). In the simulations, the annual baseline transmission intensity, the seasonality, vector species, time of the larviciding applications and the larvicide used were selected as reported in the study and the coverage was varied. The assumed effectiveness decay was twenty days for *Bs* and ten days for *Bti* using step function for simplicity. The simulations were run with three seeds for a population of 10000 people without importation of infections. A "warm-up" period of 60 years before the implementation of larviciding was run to reflect on-going transmission intensity. The predictions were aggregated per months and relative reductions calculated as described in the main document.

Table S4.2: Specified setting and deployment parameters

	Simulation 1	**Simulation 2**
Simulation setup		
Scenarios	363	393
Population	10000	10000
Seeds	3	3
Setting		
Transmission intensity (annual EIR)	10	10
Vector species	*An. gambie s.s*	*An. gambie s.s*
Monthly seasonality (approximated by rainfall)	238, 100, 283, 500, 471, 240, 131, 126, 164, 145, 316, 319	238, 100, 283, 500, 471, 240, 131, 126, 164, 145, 316, 319
Importation	None	None
Larviciding		
Deployment time	As reported (see Table A4.1)	Fixed (constant during intervention period)
Decay of larvicides	Specific to *Bs* or *Bti* as reported (see Table 2)	No distinction between larvicide Fixed to be identical to the deployment time
Larviciding coverage	Varied, separately per larvicide *Bti* = 0-100% *Bs* = 0-100%	Varied, for both larvicide combined, but varied per season *Dry* = 0-100% *Wet* = 0-100% All year round = 0-100%

Result figures

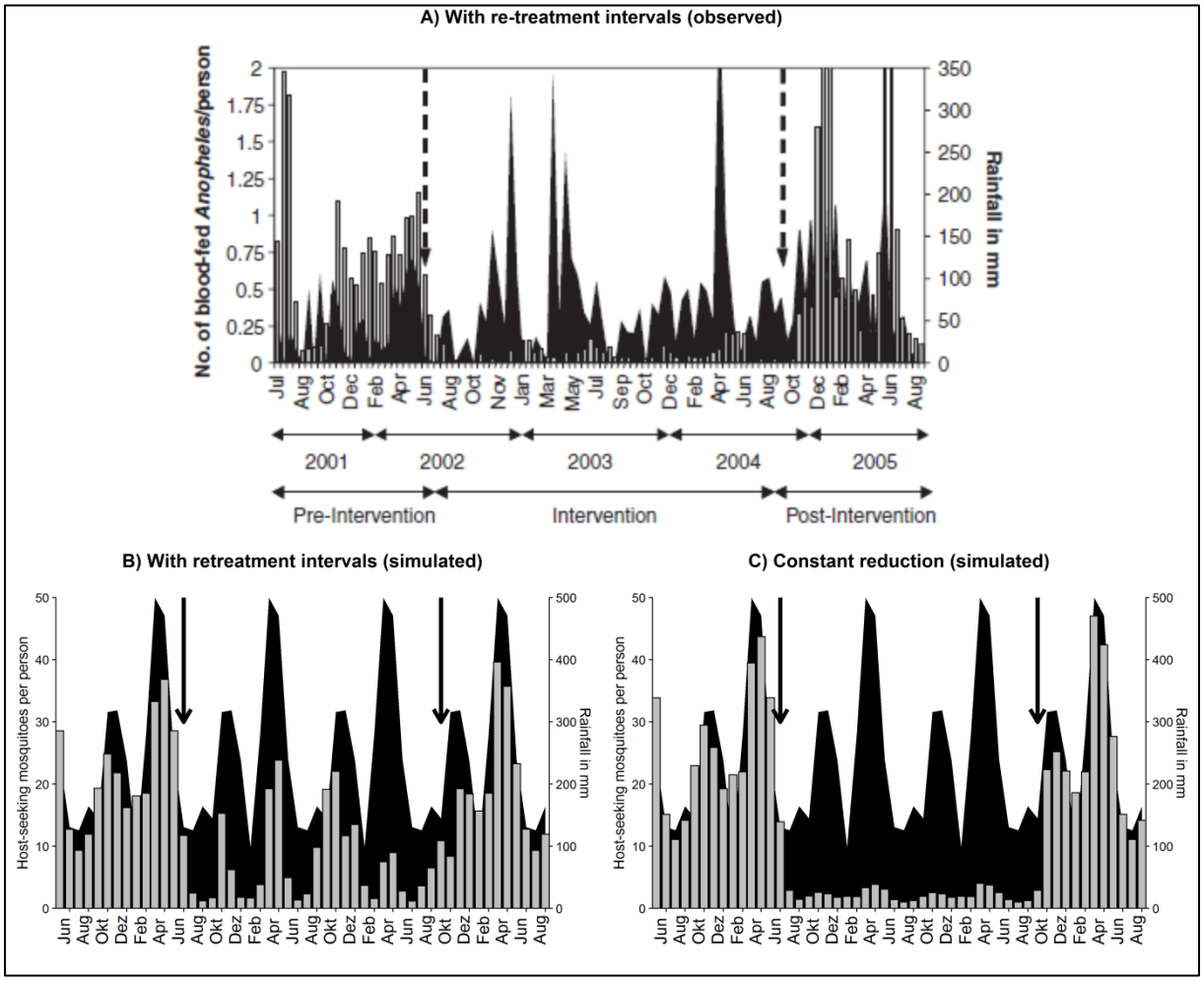


Fig. S4.1: Visualised observed and simulated reduction in adult mosquitoes due to larviciding.
A) Reprinted results from **(Fillinger and Lindsay, 2006)** with larviciding impact on blood fed mosquitoes caught indoors. The black area indicates the seasonality and the bars the larvae density, the colour of the bars type of mosquito. **B-C)** Simulated impact of larviciding with 90% coverage on mosquito emergence per population with **B)** exact decay and deployment as reported in the study and **C)** constant effectiveness throughout the intervention period. The scales need to be interpreted in relative terms, as the caught number of mosquitoes was much lower than the number of simulated mosquitoes per person for an EIR of 10 infectious bites per person.

7 Discussion

The overall aim of this thesis was to contribute to a stronger basis for the rational development of malaria strategies for maximum progress towards control and elimination targets in Tanzania. The aim was achieved through a combination of data analysis and mathematical modelling applied in close collaboration with the Tanzanian NMCP. This discussion starts with malaria surveillance in schools, then addresses the development of the country-specific model calibration approach and its use including a comparison of the different intervention stratifications from an epidemiological perspective, which is followed by a critical view on the overall process of the application of modelling to support the NMCP. Relevant limitations and challenges of all previous sections are outlined, and after depicting policy and contextual recommendations for improved malaria strategies, the chapter closes with the contribution of the PhD towards achieving its aim in the context of latest developments in global malaria policy.

7.1 Malaria surveillance in schools

The analysis of the national school malaria survey in Tanzania, presented in Chapter 2, investigates the malaria transmission and burden at council level and among school children. The methods include geographical mapping of malaria indicators aggregated per council and multivariate hierarchical regression analysis to describe malaria risk factors in this age group. The results show a high percentage of asymptomatic infections among school children and high heterogeneity in prevalence within regions. The prevalence risk map provides a basis for better targeting of interventions at a sub-regional level. The obtained council prevalence estimates, together with other malaria risk indicators from health facilities were used for a new risk stratification as presented in Thawer et al (Thawer et al., 2020). The school survey data also fed into a geospatial model which updated the previous risk map from the epidemiological profile in 2012 (NMCP et al., 2013). The results of the children questionnaire describe malaria risk factors among school children, who were found to be less likely to sleep under bed nets or to seek care despite having a fever. These results confirm the need for specific interventions in this age group (Nankabirwa et al., 2014a). While school surveys were also conducted in other countries in Sub-Saharan Africa (Gitonga et al., 2010b; Ndyomugyenyi and Kroeger, 2007; Okebe et al., 2014; Swana et al., 2018), none were, to our knowledge at the time of writing, nationwide. Hence, this survey is among the first to demonstrate the feasibility and practicality of schools as a sentinel group for improved malaria surveillance for a whole country.

7.2 Country specific modelling and use for national strategic planning

The updated malaria prevalence risk map at council level based on data from the school malaria survey and model-based geostatistics formed the basis for assessing the impact of the current strategy (NMSP 2015-2020) and the targeting of potential future interventions. Mathematical modelling was used to aid in the assessment of the current and planning of the new strategy, after it was calibrated to the historical prevalence trend per council.

7.2.1 Development of parameterisation and calibration workflow

Chapter 3 describes a unique approach for modelling malaria in countries with consideration of long timeframes at a sub-regional level for a whole country informed by local data and developed in collaboration with the NMCP. A standardised calibration- and parameterisation-workflow was designed to produce sub-regional predictions of malaria interventions, based on OpenMalaria simulations. The model parameters were informed by setting specific data for 2003 to 2016, using statistical models to interpolate between years. The simulated prevalence was fitted to geo-spatial estimated prevalence to produce 1) weighted council-specific predictions and 2) to determine unknown parameters including the pre-intervention transmission intensity for all 184 councils in Tanzania. Previous workflows had been developed for optimal intervention allocation and to facilitate decision- making (Brown et al., 2012; Hamilton et al., 2017; Silal et al., 2019). However, for predictions tailored to the country context, a tool was needed that could be readily parameterised with local data, reproduce different historical time trends, and that would allow to simulate custom intervention packages at the relevant operational level. Moreover, in anticipation of constant re-evaluation, adjustments in intervention prioritisation and evolving targets, a modelling workflow was required that could be easily updated. A workflow tailored explicitly to the country needs, is likely to be too time-consuming and data-intensive to be suitable for global modelling, whereas, at national level, it has several strengths, since the use of local data enforces country-ownership and complies with the call for more strategic use of country data (WHO and RBM Partnership to End Malaria, 2019).

Few aspects of the developed workflow were particularly challenging and different from other approaches, particularly the fitting of the council-specific historical trend in prevalence, and the choice of the parameters to fit.

The selection of the historical time frame is critical as, mathematically, the rebound in transmission after stopping interventions will always be as high (or temporarily higher) as the pre-intervention transmission equilibrium, which is also influenced by the immunity in the population. To re-produce

the observed malaria prevalence in the past, it was assumed that the disease transmission and intervention coverage parameters would sufficiently explain the observed prevalence. However, due to high heterogeneity, especially at sub-regional level, the past trends might include significant changes in risk, not reflected in the coverage trends, requiring additional parameters to fit. In our analysis, the historical trend spanned from 2003, just before the start of large-scale distributions of bed nets (Bhatt et al., 2015b), until 2016, the last year in which malaria indicator survey data was available at the time of the analysis (MoHCDGEC et al., 2016). The pre-intervention transmission intensity defined the initial prevalence for 2003, while the fitted ITN coverage between 2012 and 2016 allowed to match varying change in prevalence between the survey years 2012 and 2016 in the absence of data between these years.

The calibration workflow combines historical trend and future predictions in the same simulation. Initially, it was attempted to reproduce the historical malaria trends for each council, estimating parameters specifically for each council, to then, in a second step, simulate future predictions. However, this was not possible with multiple fitting parameters, as the weighted simulation outputs did not equal the simulation outputs of weighted prevalence due to non-linearity between the parameters that affect transmission intensity as well as intervention impact. Assuming a constant state in transmission before simulating the deployment of future interventions is a much faster approach, but it neglects setting specific risks of rebounds in transmission. Another method would be to simulate different “profiles” of seasonality, transmission intensity, and historical interventions, to randomly sample from the parameter space, and to match the predictions to the profiles at a targeted resolution in a country, similar to the approach applied by Walker et al. (Walker et al., 2016). However, considering different combinations of EIR, historical intervention coverage and seasonality for all settings would quickly lead to more simulations required as the regional models used in our approach, which are already a defined and meaningful subset of the parameter space. The time spent on 1) translating data into parameters, and 2) ensuring that the predictions fit the data are the two most time-intensive and critical steps in the simulation and analysis process. The quantification of how sensitive future predictions are to changes in the historical timespan, and differences in historical trends, could be subject of further studies that assess how far back the historical timespan should go and at what geographical level the historical trend should be simulated without major loss in accuracy.

7.2.2 Results and use of model outputs

The council-specific predictions confirm the result of the strategic midterm review in 2017 that it will be unlikely to achieve the national target for prevalence with the NMSP 2015-2020 (MoHCDGEC et al., 2017b). In response, the NMCP revised the strategic plan and generated risk stratification for the deployment of interventions according to risk at council level, as recommended by the global technical strategy (WHO, 2015a). In Tanzania, with the exception of IRS in the Lake zone regions (PMI, Africa IRS (AIRS) Project, 2016), it is the first time that the interventions are allocated nationwide per council.

Chapter 3 and 4 illustrate two distinctive approaches of how modelling can support the allocation of interventions within a country. In the first approach, modelling was used to suggest a strategy based on predicted impact and required to meet specific goals. Additionally, alternative council stratifications were suggested based on impact, cost-effectiveness or to meet the national target at lowest cost possible. In the second approach, modelling was used to predict the impact of varying intervention combinations for each stratum as suggested by the NMCP for a revised strategy (NMSP 2018-2020). The strategies derived from the model in the first approach did not directly feed into the NMSP 2018-2020, while the modelling results as simulated in the second approach proved useful for decision making by providing an additional layer of evidence to the proposed plan. The additional evidence from the modelling was also valuable, as some of the interventions considered were, at the time of the analysis, not included in WHO recommendations, which is relevant in funding applications. Although many of the questions asked by the country were addressed in previous research (i.e. Yukich et al. predicted impact of discontinuation of vector control (Yukich and Chitnis, 2017), Brady et al. conducted a consensus modelling study on predicted impact and sustainability of MDA (Brady et al., 2017), and results from Korenromp et al. relate to the question on the incremental impact of interventions (Korenromp et al., 2016)), the results were often too generic, too specific, or not accessible to the country program to be of use in the revision process.

7.2.3 Stratification of interventions and epidemiological considerations

The strategy selected based on cost-effectiveness (Strategy 2), with an allocation of interventions at council level, suggested a higher impact than the strategy simulated to represent the NMSP 2015-2020 (Strategy 1), at similar estimated costs. Two major differences to the NMSP 2015-2020 were MDA suggested for a few areas, and improvement of case management but discontinuation of ITNs in the low transmission areas. Overall, the stratification results align with other research showing that case management and ITN distributions are the most cost-effective interventions (White et al.,

2011a), while the need for ITN mass campaigns in low transmission areas is currently highly being debated considering the need to efficiently allocate resources. The stratification required to lead to the NMSP target, i.e. a prevalence lower than one percent by 2020 at minimum cost (Strategy 3) was entirely different than the other strategies. Indeed, it suggested MDA almost throughout the entire country, often as a single intervention. The simulated revised NMSP (NMSP 2018-2020) could be seen as an improvement of Strategy 2 without necessarily meeting the objectives for Strategy 3; with interventions similar to those for Strategy 2, that were the most cost-effective interventions in low and moderate transmission areas, and with interventions that lead to more impact in the high transmission areas following the principle of the results of Strategy 3.

The differences in the allocation of interventions, suggested in simulation-derived strategies, versus the choices made for the NMSP 2018-2020 are interesting. For the NMSP 2018-2020 it was discussed to deploy IPTsc in high transmission areas, while the simulation results suggested MDA, which for apparent reasons mentioned in the discussion of Chapter 3 (costs, sustainability of impact, operational feasibility), would not have been possible. The decision to discontinue large-scale ITN mass campaigns in specific low transmission areas was already considered before the modelling results confirmed limited additional impact when case management levels are high. Indeed, the very low transmission strata included councils with low malaria risk over the past three years, and it was proposed that large-scale ITN campaigns would not be necessary in those councils while maintaining continuous distribution schemes to pregnant women, increasing surveillance and prompt and effective case management. The implementation of IRS, although not cost-effective in the modelling results, was proposed to be continued in donor-funded areas around the Lake Zone and extended to Kigoma region. Moreover, the NMCP plans an improvement in case management everywhere while the model-derived stratification based on cost-effectiveness would suggest case management only in some areas, treating case management as an additional intervention instead of a public health priority beyond malaria control. Some of these results might be due to the fact that the model-derived stratifications did not distinguish between core and additional interventions, which would imply a logical order, for example to increase coverage of core interventions first, before adding additional interventions such as larviciding or MDA.

Several other methods exist that aim for optimised intervention allocation based on predicted cases and costs, either combined with mathematical transmission models (Otieno et al., 2016; Scott et al., 2017; Stuart et al., 2017; Winskill et al., 2019) or as separate analyses (Drake et al., 2017, 2015; Faye et al., 2018). For example, Walker et al. (Walker et al., 2016) used an annealing algorithm to obtain an optimal intervention allocation that achieves a specific target (i.e. either reducing burden, or reducing transmission), at minimal costs. Optimisation algorithms ensure that the spending costs of

neighbouring areas are considered and search for a global optimum, whereas in our analysis each council was treated individually. An optimal intervention allocation also depends on the outcome measures, as further demonstrated by Scott et al, who conducted a modelling-cost-effectiveness analysis in Nigeria, optimising either to minimise mortality or incidence within a five-year time period (Scott et al., 2017). In that study, the authors found that in order to minimise mortality, an optimised allocation in the north-east of the country would entail for example to discontinue IRS, decrease ITNs, increase treatment coverage and adding SMC. In contrast, when aiming for minimising incidence, the optimal allocation would be discontinuing IRS and expanding behaviour change communication and ITNs (Scott et al., 2017).

The comparison of the model suggestions and NMCP plans for case management or MDA demonstrate a typical modelling fallacy of not including all relevant contextual factors. As for the example for case management which is in practice a health system priority independent of malaria campaigns, or for MDA, which is operationally challenging and uncertain in its sustainability. Funding and preferences of funders or program staff are other important contextual factors that for instance determine in Tanzania the deployment of IRS in 'donor-defined' high transmission areas. Hence, modelling only provides technical guidance and a "translation" from a technical to an operationally useful strategy is not always straight forward. To derive an optimised yet useful, hence "most appropriate", intervention stratification, modelling results need to be embedded into practical contexts. The combined results from Chapter 3 and 4 demonstrate the discrepancy between technical evidence and actual plans, as the actual planned intervention allocation differed from an allocation suggested from modelling outputs. This emphasises the importance of combining an optimisation method with relevant restrictions, prioritisations, and funding-related factors for a more systematic yet useful support in decision making. This concept is not new and has also been described by the malEra Consultative Panel (The malERA Refresh Consultative Panel on Combination Interventions and Modelling, 2017) which further emphasises the need for consensus modelling as an additional approach to provide more robust scientific evidence to inform policy.

7.2.4 Operational feasibility

Poor intervention deployment or utilisation (i.e. low ownership or usage) was mentioned as one of the challenges that contribute to the stagnating trends in malaria recorded in many countries since 2012 (Feachem et al., 2019). As previously mentioned, mathematical simulations generally assess the technical feasibility of interventions, assuming optimal timing and usage. Nevertheless, major gaps remain between target coverage and actual coverage in many malaria-endemic countries (Andrada et al., 2019), and the impact of poor implementation and the effectiveness of the intervention

themselves are often ill-defined. For example, variations in net use in seasonal low transmission areas have been observed, where people feel of less risk during the dry season (Koenker et al., 2019; MoHCDGEC et al., 2016). Hence, for any intervention, a potential loss in effectiveness might not always be related to deployment per se. Chapter 6 describes a use-case for modelling in the context of operational planning for larviciding. In this chapter the variability in larviciding deployment and related impact on malaria is evaluated through simulations. The scenarios include a wide range of varying deployment and population density parameters. The modelling results showed limited impact on prevalence for larviciding during the dry season, as it is the current WHO recommendation (WHO, 2013) and was also the simulated deployment strategy when assessing larviciding intervention combinations in Chapter 3 and 4. Higher impact was predicted for larviciding deployed before/during the wet season in seasonal settings, and when deployed without interruptions in the effectiveness duration, either due to frequent re-treatment intervals or longer residual effect of the larvicide. Operational difficulties can be described for all the interventions, which is out of the scope of the work presented in this thesis.

7.3 Process and contextual factors of modelling to support NMCPs

The process around the use of modelling was found to be at least as important as the outputs themselves, in the context of the collaboration with the Tanzanian NMCP. The following section critically reflects relevant aspects of the process and points out important considerations for an application in other malaria-endemic countries in Sub-Saharan Africa.

7.3.1 Application process and properties

In the initial modelling workshop in Dar es Salaam modelling concepts and methods were introduced and it was discussed how modelling could be of use to the NMCP. A secondary but essential objective of the workshop was also outlining the data requirements, available data sources and holders, as well as identifying necessary assumptions. It followed a period working remotely to setup and calibrate the model and to run simulations according to the process activities and deliverables. During that time continuous exchange with the country team was crucial to ensure that modelling outputs would be of use in time. The best outcome and value were achieved when simulations were performed promptly during the workshops to feed into on-going discussions and aid in rational decision making, as described in Chapter 4 and 5. To our knowledge, there seem to be no published records of similar interactive direct use of mathematical modelling in collaborations with NMCPs to date of the analysis, whereas a similar example exist for geospatial modelling as reported in Madagascar (Howes et al., 2019).

A long-term interest in the use of modelling in the country is crucial for the mobilisation of resources to sustain the modelling support beyond the initial project phase. Another modelling project took place in Tanzania, Kenya, and Uganda, which had similar intentions but stopped after the project funding ended. The project team anticipated in their report that "the extension […] beyond the project […would require…] *in-country lead with the interest and authority to engage*" (Kramer, 2009). A contributing factor to the discontinuation could have been that modelling was perceived solely as an external project with a focus on how to use the tool rather than *actually* using it. In the Tanzanian project, modelling was eventually used as a tool for the program purposes and did not remain a theoretical demonstration.

The time and resource-intense application of modelling could also be an additional burden as it may delay the development process of the new strategy. Chapter 3, 4 and 6 highlight the computationally demanding process and quickly increasing complexity of simulation scenarios. However, once the model has been originally calibrated for historic trends, the simulation of future interventions, and therefore subsequent modelling iterations, were faster. Chapter 4 demonstrates how the database of pre-simulated outputs can be re-used to respond to additional enquiries. The uptake of modelling could be facilitated with user-friendly communication interfaces, especially as NMCPs are often too overloaded with activities or lack personnel with sufficient analytical skills, or both, to understand all the details (Andrada et al., 2019). Indeed, many decision-support tools with user-friendly interfaces, that are based on modelling, have been developed for NMCPs and other decision-makers. Examples[19] include "*MDAST*" (Kramer, 2009), "*MalariaTools*" (Reynolds, 2014), "*METCAP*" (Silal et al., 2019), "*VCOM*" (Kiware et al., 2017), "*Optima Malaria"* (Optima Consortium for Decision Science, 2018), among others[20]. However, at the time of the analysis these were not used by NMCP staff, and it is unclear how and to what extent these tools would be used in practice. Interface-application are often limited in the complexity of simulations to run, and the underlying database of predictions is constrained in the questions to address as it can only include a pre-defined set of scenarios. Additionally, a minimum level of understanding and expertise in modelling is required, as users need to relate model and parameter assumptions, model functionalities and predictions to the real-world-contexts. It is therefore crucial to strengthen analytical skills in malaria control programs as well as the collaboration with local research institutions when including modelling as an additional tool in the routine planning processes. Importantly, efforts and resources to build modelling capacity should not compete with strengthening data analysis and statistical skills that remain the basis for data-driven decision making.

[19] Not including geospatial or whether driven decision support tools.
[20] Not all transmission models have a user-friendly interface.

7.3.2 Expectations and common misconceptions

Modelling is prone to misconceptions, especially among non-modellers. The most detrimental misconception is that modelling would provide a solution that replaces the thinking process and the need for data collection and thorough analysis. Predictions that only show what is already known might be perceived as trivial, whereas projections that conflict with prior beliefs might be perceived as wrong and undermines the validity of the model. In Tanzania that was not the case, as there was openness to constructively, yet critically, discuss the modelling outputs. For instance, during the malaria expert meeting in 2017, the predictions on MDA as sole option to achieve the target were rightly controversially debated. The critic circled around the feasibility of achieving targets but also touched on the validity of the model and methodology, hence identified areas in need of improvements or further clarification. This example on challenging feedback re-emphasises the critical role of a local facilitator with an understanding of modelling. Indeed, a comprehensive understanding was only reached after multiple country visits and numerous analysis iterations, as delineated in Chapter 5. An iterative process is, therefore, not only crucial to improve the methodology, but also for building trust and turning hidden misconceptions or neutral expectations into increased appreciation of the use of modelling – the latter a fundamental building stone for modelling capacity within the NMCP in the long-term perspective.

7.3.3 Evaluating the impact of modelling

The desired impact of modelling can be ambiguous and challenging to assess since there is no counterfactual of what decisions would have been in absence of modelling. When there is no change in the strategy or reconsideration based on modelling results the added benefit and impact of the modelling activity might not be obvious, although its validating empirical beliefs. When, in an opposite extreme all modelling suggestions are accepted it is likely demonstrating overconfidence in the model. In Tanzania, the successful uptake of the modelling was shown through the inclusion of modelling in the new strategic plan, and the application of modelling as an intrinsic component of the strategic planning process that is likely to continue. Overall, the uptake of modelling depends on the stakeholders involved and the other factors as described in Chapter 5 specific for the Tanzanian example, as well as in broader health policy research studies that assess determinants of policy change in low- and middle-income countries (Bennett et al., 2012). These factors differ between countries and systematic approaches with generalizable criteria to evaluate impact of modelling would be useful, especially at the early stages where many unknowns remain. The results of Chapter 5 could be formalised to inform urgently needed guidelines for malaria modelling at country-level, as available for country-modelling in tuberculosis (TB MAC and WHO, 2018). Such guidelines in malaria

would be helpful to standardise the process and define activities for all involved and would fit well to the WHO documents on strategic planning development (WHO, 2019d) and program reviews (WHO, 2019e).

7.3.4 Transferability of the process to other countries

In Tanzania, the amount of data, as well as data quality, is relatively high in comparison to other countries in Sub-Saharan Africa. In other countries, that for instance do not have nationwide school surveys, available data might be lacking sufficient sub-regional information as well as internal capacity or collaborations to generate geospatial modelling based on the local data. Another difference is the constellation of local partners of the NMCP, as well as the coordination of malaria control and the hierarchy of decision making. For example, in Nigeria, malaria control is coordinated at two levels, at national and at state level (NMEP Nigeria, 2013). An application to other countries was tested for Benin and Southern Mozambique, and indeed differences in data availability and quality as well as preferred indicators used were main contributors to the time required to generate useful predictions (Swiss TPH unpublished report).

7.4 Limitations and challenges

Different challenges were encountered across all research activities described in the previous chapters, including the analysis of the school survey data for malaria surveillance, parameterisation, and calibration of the OpenMalaria model, analysis and interpretation of predictions, approaches of intervention stratification, as well as in the overall process of providing analytical support to the NMCP. Since the process-related challenges were discussed in the text above, this section focuses on the technical and methodological aspects.

7.4.1 Survey sampling and representativeness

A common issue in cross-sectional surveys is the sampling time versus the seasonality in malaria transmission. In the school survey, some areas were sampled during the low transmission and others during the high transmission season. In anticipation of the high variation in the relationships between dry and wet season prevalence, an adjustment would only be a poor substitute for the lack of data. This problem also applies to malaria indicator surveys, and ‘rolling surveys’ (Roca-Feltrer et al., 2012) that collect data continuously might be a practical modification of the survey design to avoid the bias introduced through seasonal differences in sampling. However, such surveys would be difficult to sustain if not being operationalised as an intrinsic part of the surveillance system. Moreover, as transmission decreases, so does the benefit of population surveys, as larger sample

sizes will be required to obtain accurate estimates on the lower prevalence and costs increase. Another common issue in surveys are biases related to the questionnaire process, such as interviewer and recall or social desirability biases (Bowling, 2005; Coughlin, 1990), as discussed in Chapter 2. Although, responses from children were found to be reliable (Ndyomugyenyi and Kroeger, 2007), in the school survey, the quality of the filled questionnaire forms was noticeably reduced in very young compared to older children (MoHCDGEC, 2018a). Despite various quality measures and guidelines to minimise those biases, they cannot be completely avoided, and often not systematically adjusted for, which adds to the uncertainty in data.

7.4.2 Selection and use of data to inform model parameters and calibration

The quality of the input data has a large impact on the validity of the predicted outcomes from the model and proposed stratifications. Poor data quality often misrepresents the true picture. Related indicators from multiple sources could inform the same model parameters (i.e. programmatic net distribution data versus reported coverage in cross-sectional household surveys for the effective ITN coverage in the population) which can also be a great challenge especially when the trends of the indicators are diverging or contradictory to expectations. In the analysis presented in Chapter 3, this was addressed through a mix of approaches depending on the data availability and quality and assessed reliability per data source and indicator according to the NMCP. For example, to inform vector parameters, entomology surveillance data from the NMCP were used even though only available for a few sentinel sites, instead of globally produced estimates on vector occurrence per pixel, such as those presented by Massey et al. (Massey et al., 2016). For the effective treatment coverage parameters, regression lines were fitted to the data points obtained from malaria indicator surveys at regional level. For ITN coverage, MAP estimates were used until 2012 as they showed good agreement with ned distribution data and reported coverage from surveys, as described in the supplementary information (SI-2) in chapter 3.

Notably, many high-resolution maps for most relevant risk factors for malaria have been produced by different institutions globally. Although these are easier to access and generalizable between countries, trends should be compared with local data. In the selection to inform model parameters it is important to consider the need to enforce the use of local data and country-ownership. On the short term, this can be facilitated with interactive workshops and shared processes between researcher and the NMCP, as done in Tanzania, but also reported in Madagascar (Howes et al., 2019) as well as in other countries such as Mozambique or Benin (Swiss TPH personal communication).

Model calibration

Not all data, model or parameter uncertainties can be accounted for in the model. Despite the exploration of different fitting approaches unexplained discrepancies remained in the historical trend between the simulations and the data, and the effect of ITNs appeared to be overestimated. Possible reasons for the discrepancy could be residual transmission, outdoor biting, or overestimated ITN coverages or efficacy. Indeed, resistance and outdoor biting were increasingly reported in Tanzania around 2010 (NMCP et al., 2013). The triangulation of different malaria-related parameters during the model calibration is also affected by the measures used as delineated in the section above. The model calibration was based on prevalence, a frequently used and relatively robust measure of malaria transmission in the population. Not using incidence neglects a valuable source of information. The incidence could inform the seasonality or could also be used to validate the calibrated model by comparing observed with simulated incidence, or in the calibration instead or in addition to prevalence. However, the data quality is highly affected by health facility reporting rates and care-seeking behaviour and needs careful assessment and proper adjustment (Ashton et al., 2017). Including adjusted incidence estimates would be a valuable addition to the methodology, especially as low transmission areas are increasing, and as population surveys would be too costly to achieve the same geographical resolution as health facilities. A preliminary exploration of applying the developed modelling calibration workflow to Benin and Southern Mozambique using incidence estimates proved to be challenging and required further investigation. For instance, in-depths assessment of the relationship between prevalence and incidence stratified by age and transmission intensity in consideration of potential biases in incidence such as reporting rates, care seeking, non-malaria fevers, or potential biases in prevalence such as sampling method and months of data collection. While both measures could be used for fitting by combining the estimated weights for each one, the risk of not matching either of them would be high. An alternative approach to utilize both data sources would be to use incidence to inform seasonal trends within a year and the prevalence for the annual trends. An additional source of uncertainty is introduced when applying model based geostatistics to derive geospatial prevalence estimates at council level over time, also affecting the model predictions. In the end, the decision which data or metric are believed to best reflect the malaria situation in the country lies with the NMCP and the local malaria experts, ideally together with the modellers, since data quality, completeness and ‘model suitability’ are also important properties of the data to use.

OpenMalaria model

OpenMalaria was designed for moderate transmission and reaches saturation point at a prevalence of around 60% and an EIR of 100 ibpa after which an increase in EIR does only marginally increase prevalence (Penny et al., 2015; Smith et al., 2008) (Penny et al., 2015), which could explain the relatively poor fit in high transmission areas in the model calibration for Tanzania. For that reason, fitting to raw school survey data in 2016 with observed prevalence estimates up to 80% (see Chapter 1), would have been challenging with default basic model configurations (i.e. without changing model variants or diagnostic thresholds for RDTs). The simulated prevalence saturated at around 60% even at highest pre-intervention transmission intensities, which, when considering historical intervention trend, would only be possible to reach in 2016 when allowing the EIR to recover to pre-intervention levels through high importation, very low intervention coverage, or both. An intermediate stop in interventions after a decade of effective prevention might lead to higher pre-intervention levels, when assuming a decrease in immunity due to reduced exposure to malaria parasites However, asymptomatic infections were high even in areas with reported high intervention coverage. Although possible, the integration of inter-annual variations in transmission intensity in absence of interventions, is not easily integrated into OpenMalaria simulation and these variations in transmission intensity may in practice result from variations in climate conditions, i.e. El Niño-Southern Oscillation cycles (Mason and Goddard, 2001). Accounting for underlying change in transmission can be critical when assessing the impact of interventions as they may otherwise appear more or less effective. A generic intervention that regulates the mosquito emergence based on rainfall data could be used to incorporate inter-annual variations without changing the model structure but might as well interfere with the model calibration approach, and the estimation of the pre-intervention EIR hence requires further testing. Another technical limitation is that the model does not explicitly account for spatial connectivity. However, the most relevant aspect of the connectivity is the importation of malaria cases, especially from high to low transmission areas, less relevant in moderate to high transmission areas. In the simulations, fixed importation rates were assumed as data to inform council specific importation rates were not available. However, despite the heterogeneity, most councils in Tanzania have relatively high transmission, and the importations were not expected to have a relevant influence on the predicted impact of the national malaria strategic plan.

Larviciding parameterisation and impact

The data available for the analysis of larviciding deployment, presented in Chapter 6, was sparse. Estimating the effective coverage was challenging as most efficacy field studies only reported reduction in larvae, and for larviciding efficacy cannot easily be translated into effectiveness, due to

operational variability. For instance, a reduction in vector density does not translate proportionally to a reduction in prevalence, since the relationship is non-linear. Hence, larviciding effectiveness predictions are highly uncertain and were excluded in the analysis from Chapter 4. The challenge in simulating larviciding was addressed again in more detail in Chapter 6, explicitly accounting for uncertainty in deployment and vector population dynamics. However, the coverage could not be estimated with the identified research data. The analysis of the influence of larviciding deployment factors on malaria transmission in humans, might have benefitted from a more detailed vector model with different larval stages and spatial model taking into account habitat availability and dispersal. However, these parameters would be challenging if not impossible to define on large scale, while models with a more granular vector model exists (Kiware et al., 2017; Tompkins and Ermert, 2013; Wu et al., 2020), they often have a simplified version of the human model, and their use is specified to research questions on small or theoretical settings to focus on local vector behaviour and environmental or ecological influencing factors at fine scale. OpenMalaria was the model of choice as it was essential to understand how the deployment assumptions in OpenMalaria affect the predictions and interpretation of larviciding impact.

7.4.3 Developed workflow: complexity versus usability

The model parameterisation and fitting processes, using averaged estimates, ignored uncertainty and variability in data. Including more information about the distributions, i.e. interquartile range or even multiple samples, would increase the number of simulations tremendously and did not seem practical in the current set-up of the workflow. Future improvements would be prior distributions obtained from the geospatial model instead of selecting the mean only with very small standard deviations. The posterior distributions, representing heterogeneity in transmission per council, as well as uncertainty from the Bayesian model, were already extremely wide. In addition, the geographical heterogeneity was considerably large and aggregating estimates per strata or per country led to wide ranges in the predictions. Uncertainty and impact of heterogeneities have not been fully studied in this project. Also, the simulations took longer than potentially necessary, as fixed EIR ranges were run for all settings despite increased simulation time at higher EIRs (> 100 ibpa). In addition, the whole experiment needs to be re-simulated for every change (i.e. additional coverage levels or interventions). These computational challenges call for improvements in the efficiency of the modelling workflow. One possible improvement could be the use of known relationships between EIR and prevalence, such as presented in Penny et al. (Penny et al., 2015) to define a custom range of the EIR values per region which can make the simulations more efficient and more setting specific. The selection and number of parameters to fit and their ranges influences the fitting and hence the weighted predictions and remains subject of further testing. To give a

simplified example, high coverage in the historical trend and low prevalence would lead to higher estimated pre-intervention EIR as when assuming low intervention coverages which would result in lower estimated pre-intervention EIR for the same prevalence to fit to, and these relationship influences the predictions on future intervention impact and resurgence. It should also be noted that the use of simulations for inferring outputs, not originally accounted for during the design of the experiment, can be misleading, as the simulations were designed to answer specific questions for specific areas and not generic databases.

7.4.4 Intervention stratification and geographical heterogeneity in malaria risk

The results in Chapter 3 present simulation results for most cost-effective or most impactful intervention packages per council. The most-cost effective intervention stratification was derived based on minimising incremental cost-effectiveness ratios among full-factorial combinations of the future interventions per council, using total net costs and total cases averted between 2017 and 2020. This approach followed a similar methodology as described by (Okosun et al., 2013; Otieno et al., 2016). Although no budget constraint was added the analysis was useful to estimate the demand and, once the available budget will be known and translated to modelling budget, useful for estimating potential funding gaps. A second iteration would then be required that applies the limit for the stratification to be useful in more detailed planning, outside the scope of the presented work.

Even though the general pattern complied with the expectations based on the prevalence risk map, some intervention suggestions for individual councils were unexpected. For example, MDA was recommended as the most cost-effective intervention in addition to ITNs in one council in Mtwara (i.e. Nanyamba TC), but not in another (i.e. Newala TC). Both had the same historical trend in prevalence, ITN coverage and case management, similarly high EIR however, but different population sizes, the estimated costs and number of cases averted differed, resulting in a slightly different ranking of the 36 intervention combinations, hence leading to different comparisons of interventions compared in each iteration of the incremental cost-effectiveness algorithm. Similarly, the selection of the unit costs affects the intervention recommendation and incorporating cost distributions rather than using mean values into the cost-effectiveness analysis would be needed to increase the robustness of the intervention recommendations per council in future iterations, which has not been studied in greater detail in the presented work. The suggested interventions stratification will further be complicated when using council specific cost estimates that account for differences in scaling up interventions to the target coverage due to infrastructure, population density or other factors, but would also introduce a major source of uncertainty, hence not recommended for large-scale modelling.

In the simulations homogeneity within councils was assumed, a necessary simplification for planning at the central level for the whole country. In practice, some councils are more heterogeneous than others. Hence, simulations at a higher resolution that can assess cost-effectiveness and optimal allocation at the community level would be useful for operational planning and micro-stratification (given that the required data is available). The use of fine-scale modelling for operational planning has been demonstrated especially for reactive case detection in the Lake Zone in Zambia (Gerardin et al., 2017; Nikolov et al., 2016). A similar approach would be useful for whole Tanzania, or at least for a representative sample per epidemiological and operational strata.

7.5 Way forward

The role of modelling can change to address different questions at each step in the development process of the strategic plan. Chapter 3, 4, and 6 demonstrated the use of modelling for assessing the impact of the current strategy, and of alternative intervention stratifications based on impact and cost, for aiding in the selection of interventions per risk strata and for evaluating relevant operational deployment parameters. The use of modelling could be extended to support setting technically feasible targets at different operational or administrative units, to assess past intervention impact, and to provide estimates on the number of cases, required commodities and related costs to facilitate operational planning and funding acquisition. Technically, the efficiency of the modelling workflow needs to be improved to allow for proper uncertainty and sensitivity analysis and more robust predictions. At the same time, continuous data collection is fundamental for decision making as well as for validation of the transmission models used for intervention predictions.

Despite an increased interest in research to inform policy processes related to malaria control (Mutero et al., 2014), a barrier, that prevents making the best use of the evidence provided by research, is still apparent (Mwendera et al., 2016). To be useful for implementers as well as decision-makers, the outputs generated by research need to fit within the existing constraints at the country level. This can be best achieved when policymakers and researchers work in collaboration (Long and Brandeau, 2009). This work was conducted in the intersection between research and program support and the continuous communication between the modellers, local technical teams, the malaria control program managers, and partners proved invaluable. Chapter 5 emphasises the critical role of country ownership and leadership for a successful application of modelling in concordance with the HBHI approach (WHO and RBM Partnership to End Malaria, 2019).

Modelling provides a platform for dialogue among the stakeholders involved in national malaria policy and research. The different perspectives from the field and technical understanding facilitate a solution-oriented development of strategic policy. In this context, so-called "*Think Tanks*" that form a network of local experts to provide analytical support in the development of health policies are an interesting concept, that was applied for Tuberculosis and HIV policy (Bennett et al., 2012; White et al., 2018). However, given the high number of organisations already active in malaria, such "*Think Tanks*" would need to link existing organisation rather than creating an additional one. Collaboration among governmental sectors and streamlined health agendas could facilitate efficient allocation of government resources. A holistic approach would enable to tackle underlying risk factors for malaria, for instance, water management, housing, and poverty, as also recognised by WHO Strategic Advisory Group (WHO Strategic Advisory Group on Malaria Eradication, 2019). Indeed, such a multisectoral approach helped some NMCPs to achieve a higher quality of implementation (Smith Gueye et al., 2016).

Tanzania, as well as other malaria-endemic countries, are making great progress towards controlling the disease and preventing its adverse events, but still have a long way to go before elimination will be reachable. The Lancet Commission on malaria stated that eradication would be feasible by 2050 (Feachem et al., 2019), whereas the WHO distances themselves from setting a date for eradication to '*avoid a disappointment*' and donor-fatigue similar as after the failure of the GMEP to re-occur (WHO Strategic Advisory Group on Malaria Eradication, 2019). While having a date is useful for mobilising funding and global commitment, as demonstrated with the global technical strategy for malaria (WHO, 2015a), the action items to achieve a long term goal such as eradication likely would be similar if not the same regardless of a date. Both documents emphasise the need for strong political leadership and management, data-driven decision making and better coordination of stakeholders and partners, including the private sector, as well as strengthening of health systems and surveillance, all factors that were also identified as crucial factors in other infectious disease eradication programs, i.e. as described for smallpox (Cohen et al., 2019).

As long as extreme poverty, poor housing and sanitation are not tackled with the same passion and global attention as malaria, impairment in health and deaths due to malaria likely continue to occur. The continuous struggle to maintain the achieved gains in malaria, with considerable variations in the local effectiveness of current large-scale vector control, stress the fundamental role of strong health and surveillance systems. To respond to the need to approach malaria holistically, the tools presented in this thesis could progressively incorporate more factors. Relevant factors not covered in this thesis or methodology would be for example socio-demographic layers (i.e. hard to reach

populations), economic aspects (i.e. public-private partnerships), or novel tools for malaria prevention (i.e. vaccines) or delivery mechanisms (i.e. drones for larviciding application). Advances in technology with increasing utilisation of geospatial and mathematical modelling can facilitate rational decision making and efficient strategic planning despite increasing complexities and multiplicity of malaria transmission risk factors and control and prevention tools.

7.6 Conclusions

The presented work covered many of the steps critical in the planning of new national malaria control strategies. The outcomes did not only strengthen the basis for the rational decision making, but also the process. This provided a first step towards integrating modelling as a standard tool in national malaria policymaking, to ensure interventions are deployed where there are needed most and ultimately strives for maximum effectiveness and prevention of drawbacks in the efforts towards malaria control and elimination in Tanzania as well as other countries suffering from malaria. However, to make modelling an intrinsic part of the strategic planning process the critical role of capacity building, long-term collaboration and continued yet flexible funding need to be recognised and the immediate next steps will require strengthening of analytical skills and capacities in control programs.

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Curriculum vitae

EDUCATION

09/2016 – 12/2019 **PhD in Epidemiology** - Swiss Tropical and Public Health Institute, University of Basel, Switzerland.
Dissertation: Mathematical modelling of malaria control interventions to support strategic planning in Tanzania.

08/2014 – 02/2016 **MSc Epidemiology** - Swiss Tropical and Public Health Institute, University of Basel, Switzerland.
Thesis: The Use of Public Primary Schools for Malaria Surveillance in Tanzania

03/2011 – 02/2014 **BSc Health Sciences** - University of Applied Sciences Hamburg, Germany
Thesis: The influence of the menopausal hormone therapy on the overall mortality – survival analysis of the control group of the MARIE study.

WORK EXPERIENCE

01/2019 – 05/2019 **Consultant** – Swiss Tropical and Public Health Institute, (NETCELL project)
Main tasks: Extend the modeling work done in 2018 with a range of new interventions, following the request of the Tanzanian NMCP for further work in this area. Communicate the findings of the work carried out to a wider range of stakeholders in Tanzania and in neighboring countries.

01/2018 – 12/2018 **Consultant** – Swiss Tropical and Public Health Institute, (NETCELL project)
Main tasks: Data collation and cleaning in close collaboration with Tanzania medical staff. Risk mapping in pre-defined risk categories at district level. Stochastic modeling of a range of appropriate malaria control interventions in each epidemiological strata, to determine the most cost-effective mix of interventions. Interaction and exchange with relevant NMCP staff to align the processes and priorities and to provide knowledge transfer.

03/2016 – 08/2016 **Scientific Assistant** – Swiss Tropical Public Health Institute
Main tasks: data cleaning, writing of data management SOP's, data analysis and paper writing in collaboration with the NMCP in Tanzania and being based in Dar es Salaam.

03/2015 – 08/2015 **Student Intern** – Ministry of Health and Social Welfare Tanzania, National Malaria Control Programme
Main tasks: preparation of survey documents, supervision of fieldwork, data entry, cleaning and analysis, based in Dar es Salaam.

03/2014 – 07/2016 **Medical Data Manager** – University Medical Center Hamburg-Eppendorf, Department of Medical Biometry and Epidemiology
Main tasks: data cleaning and supervised statistical analysis.

03/2014 – 06/2014 **Assistant Lecturer** – University of Applied Sciences Hamburg, Germany
Main tasks: lectures and supervision of student group work in the "Surveillance and Health Reporting" seminar.

06/2013 – 09/2013 **Student Intern** – University Cancer Center, University Medical Center Hamburg-Eppendorf, Germany
Main tasks: data plausibility checks, data cleaning, merging of datasets, and survival analysis.

08/2010 – 02/2011 **Volunteer (nurse assistant)** – Marienhospital Stuttgart, Department of Internal Medicine and Pneumology, Germany

VOLUNTEERING

04/2018 **Correspondent** – Malaria Eradiation Alliance (MESA) and MalariaWorld. The volunteering position included daily reporting of selected scientific talks at the Malaria Initiative Meeting (MIM) in Dakar, Senegal.

01/2017 – 03/2018 **PhD student representative** – Swiss Tropical and Public Health Institute, University of Basel, Switzerland.

ADDITIONAL SKILLS

Software skills: R, Stata, SPSS (advanced), QGIS, ArcGIS (intermediate), Microsoft Office (Word, Excel, PowerPoint), LaTeX, Git (basics), Python (learning)

Languages: German (native speaker), Swahili (basics)

CONFERENCE PRESENTATIONS

2019 "Varying impact of malaria interventions at district level – implications of a mathematical model for strategic planning". European Conference for Tropical Medicine and Health (oral presentation)

2018 "Modelling the impact of different larviciding deployment regimens to inform strategic planning". American Society of Tropical Medicine 67th annual meeting (poster presentation)

2017 "Varying impact of malaria interventions at district level – implications of a mathematical model for strategic planning". American Society of Tropical Medicine 66th annual meeting (oral presentation)

2017 Varying impact of malaria interventions at district level: Implications of a mathematical model for strategic planning Joint annual meeting of the SSM, SSI, SSHH, SSTMP, and SSTTM (poster presentation)

2017 "A nationwide school malaria parasitaemia survey (SMPS) in Tanzania". European Conference for Tropical Medicine and Health (poster presentation).

2014 "The influence of the menopausal hormone therapy on the overall mortality: survival analysis of the control group of the MARIE Study" German Association for Epidemiology 8th annual meeting (oral presentation)

2013 "Measles in Northern Germany: is elimination by 2015 foreseeable?" German Association for Epidemiology 7th annual meeting (poster presentation)

REFEREES

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