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Evaluating Novel Vector Control Strategies

Modeling the impact of gene editing for malaria elimination in the Democratic Republic of Congo

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Abstract

The tremendous burden of malaria has led to renewed efforts focusing on malaria elimination in the high burden countries. However, to achieve elimination, novel tools including driving-Y gene drive mosquitoes may be necessary in these settings. Gene drives offer a pathway to propagate transgenes and their associated phenotypes to future generations more efficiently than the natural 50% probability, and driving-Y has been proposed as a gene drive mechanism for population suppression by ensuring offspring are predominantly male. This research systematically explores the potential impact of integrating driving-Y gene drive mosquitoes in malaria elimination strategies in the Democratic Republic of the Congo (DRC) using a stochastic, spatially explicit, agent-based, mathematical model. In simulations of various intervention mixes in study locations across the country, releases of gene drive mosquitoes are capable of eliminating malaria and are the most cost-effective intervention overall with certain ranges of driving-Y parameters, specifically with high X-shredding rate. Our model results show that tailoring the frequency of releases and the number of gene drive mosquitoes to be released can make malaria elimination achievable within 5 years after a single release of gene drive mosquitoes under certain conditions, including but not limited to no importation of vectors or infections into the study areas. The cost of intervention in scenarios with and without gene drives suggest that the cost of gene drives affects the marginal costs of other malaria control methods. Gene drive is thus worth considering as a supplement to commonly used malaria interventions as long as the drive is sufficiently powerful and cost-effective. Broader discussion of gene drives has spanned from the feasibility and economic viability of the gene drive technology to concerns on environmental, and touching base on societal and ethical impacts of the technology. This research offers a framework to effectively plan gene drive strategies in malaria control in other high burden countries where parasite transmission intensity varies, identifies key aspects of both gene drive technology and its implementation that are fundamental for the technology to be a cost-effective component of a malaria control program. This helps advance the understanding of gene drives and how this or other novel tools can ultimately contribute to the elimination of malaria even in high-burden countries like the DRC.

Zusammenfassung

Die enorme Belastung durch Malaria hat zu erneuten Anstrengungen geführt, die sich auf die Beseitigung der Malaria in den Ländern mit hoher Belastung konzentrieren. Um eine Eliminierung zu erreichen, können für diese Einstellungen jedoch neuartige Werkzeuge erforderlich sein, einschließlich Mücken, die Driving-Y-Gen antreiben. Gen-Drive bieten einen Weg, um Transgene und die damit verbundenen Phänotypen für zukünftige Generationen effizienter als mit der natürlichen Wahrscheinlichkeit von 50% zu vermehren, und Driving-Y wurde als Gen-Drive-Mechanismus für die Unterdrückung der Population vorgeschlagen, indem sichergestellt wird, dass die Nachkommen überwiegend männlich sind. Diese Studie untersucht systematisch die möglichen Auswirkungen der Integration von Mücken mit Y-Gen-Drive in Strategien zur Beseitigung von Malaria in die Demokratischen Republik Kongo (DRK) unter Verwendung eines stochastischen, räumlich expliziten, agentenbasierten mathematischen Modells. In Simulationen verschiedener Interventionsmischungen an Studienorten im ganzen Land können Freisetzungen von Gen-Drive-Mücken Malaria beseitigen und sind insgesamt die kostengünstigste Intervention mit bestimmten Bereichen von Driving-Y-Parametern, insbesondere mit hoher X-Shredder-Rate . Unsere Modellergebnisse zeigen, dass eine Anpassung der Freisetzungshäufigkeit und der Anzahl der freizugebenden Gen-Drive-Mücken die Eliminierung von Malaria innerhalb von 5 Jahren nach einer einzelnen Freisetzung von Gen-Drive-Mücken unter bestimmten Bedingungen erreichen kann, einschließlich, aber nicht beschränkt auf keinen Import von Vektoren oder Infektionen. Die Kosten für Interventionen in Szenarien mit und ohne Gen-Drive legen nahe, dass die Kosten für Gen-Drive die Grenzkosten anderer Malariakontrollmethoden beeinflussen. Der Gen-Drive ist daher als Ergänzung zu häufig verwendeten Malaria-Interventionen in Betracht zu ziehen, solange der Drive ausreichend leistungsfähig und kostengünstig ist. Die breitere Diskussion der Studie über Gen-Drive reichte von der Machbarkeit und Wirtschaftlichkeit der Gen-Drive-Technologie bis hin zu Bedenken hinsichtlich der Umwelt und der berührenden Grundlage der gesellschaftlichen und ethischen Auswirkungen der Technologie. Diese Forschung bietet einen Rahmen für die effektive Planung von Gen-Drive Strategien bei der Malariakontrolle in anderen Ländern mit hohem Befallsdruck, in denen die Intensität der Parasitenübertragung variiert, und identifiziert Schlüsselaspekte sowohl der Gen-Drive-Technologie als auch ihrer Implementierung, die für die Technologie von grundlegender Bedeutung sind, um eine kostengünstige Komponente eines Malariakontrollprogrammes zu sein. Dies trägt dazu bei, das Verständnis der Gen-Drive zu verbessern und zu zeigen, wie dieses oder andere neuartige Instrumente letztendlich zur Beseitigung von Malaria beitragen können, selbst in Ländern mit hoher Belastung wie die DRK.

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Abbreviation

ACT: Treatment of symptomatic cases with Artemisinin-based Combination Therapy. This research applied the combination of Artemether and Lumefantrine.

Afr-E: Africa-E is one of WHO country groupings for global assessment according to WHO subregions. Afr-E includes Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, the Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania Zambia, Zimbabwe.

AU: The African Union

C50: Concentration at which drug killing rates are half of the maximum

Cmax: Maximum drug concentration

CSP: Circumsporozoite protein

CEA: Cost-effectiveness analysis

CER: Cost-effectiveness ratios

COVID-19: Coronavirus disease 2019

CRISPR-Case system: Clustered Regularly Interspaced Short Palindromic Repeats-Cas, CRISPR-associated proteins, system

DALY: Disability-adjusted life year

Drives, Gene drives: gene drive mosquitoes developed by a genetic technique that is a novel method that includes 'driving' targeted traits from one generation to the next. This process aims to defeat Mendelian inheritance, by which genes have a 50% chance of being inherited by the progeny, and instead gives specific genes a substantially higher or lower probability of inheritance and thereby alters the frequency of such genes in the population. If given a gene that could alter fertility or survival of the target species, this could alter its population size over a few generations.

DRC: The Democratic Republic of the Congo

DHS: Demographic and health survey

DW: Disability weight

EMOD: Epidemiological modeling software

GDP: Gross domestic product

GIS: Geographic information system

GTS: Global technical strategy

ICER: Incremental cost-effectiveness ratio

IDM: Institute for Disease Modeling

ITNs: Insecticide-treated nets

IRS: Indoor residual spraying

IRBC: Infected red blood cell

International Dollar ($int): a hypothetical unit of currency that has the same purchasing power as that of the US$ in the United States at a given point in time.

MAP: Malaria Atlas Project

MSP: Merozoite surface protein

NTDs: Neglected tropical diseases

NEPAD: The New Partnership for Africa's Development

$PfPR_{2-10}$: *Plasmodium falciparum* parasite rate in 2-10 years old

PD: Pharmacodynamics

PK: Pharmacokinetics

PfEMP: *Plasmodium falciparum* erythrocyte membrane protein 1

RDTs: Rapid diagnostic tests

RBCs: Red blood cells

RNA: Ribonucleic acid

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

SDGs: Sustainable development goals

SSA: Sub-Saharan Africa

TB: Tuberculosis

USGS: United States Geological Survey

VCAP: Vectorial capacity

Vd: Volume of distribution

vs.: versus

WHO: World Health Organization

YLD: Years lost due to disability

YLL: Years of life lost due to premature mortality

Chapter 1

1. Introduction and context of the study

1.1. Introduction

Female *Anopheles* spp. (Dipt.: Culicidae) mosquitoes can transmit *Plasmodium* parasites that cause malaria, a life-threatening infectious disease. The disease could have dated back to over millennia and, in the 20th century alone, claimed roughly 300 million lives worldwide (Arrow KJ, Panosian C, 2004). The most commonly used vector control methods to prevent mosquito bites are sleeping under insecticide-treated mosquito nets (ITNs) and spraying the inside walls of a house with an insecticide, termed indoor residual spraying (IRS). In both IRS and ITNs, synthetic pyrethroids are most often the insecticide class of compounds of choice. Also, the management of symptomatic malaria cases with artemisinin-based combination therapy (ACT) is widely used to counter the disease. Presently, vector control (ITNs and IRS) and ACT are the two main anti-malaria strategies.

Nevertheless, despite being preventable and treatable and considerable control successes during the last 20 years (WHO, 2019c), malaria still has devastating impacts on people's health and livelihoods around the world. The World Health Organization (WHO) estimates that around 3.7 billion people were at risk of the disease in 97 predominantly tropical countries, even though billions of dollars are spent annually on malaria control and elimination. Most malaria cases occur in sub-Saharan Africa (SSA), accounting for 93% of total malaria cases worldwide. With 12% of all cases in SSA, the Democratic Republic of the Congo (DRC) is the second highest-burden country on the continent. Nearly all of the DRC's population live in high malaria transmission zones. Consequently, the disease remains the country's most serious public health problem and is the number one cause of death (IHME, 2018; WHO, 2018a, 2019c; Vector Link, 2019).

WHO's Global Technical Strategy for 2016-2030 highlights the economic value, outcomes, and impacts of malaria interventions as success indicators of malaria programs that need to be monitored in order to achieve malaria control and elimination (WHO/TDR and FNIH, 2014). Moreover, indicator 3.3 of the Sustainable Development Goal (SDG), Good Health and Well Being is quoted "By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, waterborne diseases and other communicable diseases". The achievement of malaria control is then set at a high global priority (WHO, 2016b).

With the continuous global effort to fight malaria, the incidence rate of malaria has been reduced by one half within the past decade (WHO, 2019c). However, the rate of change has been stagnant in the past five years, necessitating a radical change to

reach the global 2030 targets for malaria morbidity (WHO, 2019c). Present malaria control activities are limited to an extremely narrow range of control measures, principally synthetic pyrethroids for ITNs and IRS and artemisinin-based combination therapy. However, emerging resistance to pyrethroids, artemisinin, and ACT partner drugs (CDC, 2018) threaten the previous gains and render achieving malaria elimination in the near future elusive. Thus, novel alternatives are highly necessary (CDC, 2018). With very few alternative insecticides and curative malaria drugs available (WHO, 2014b; Mnzava *et al.*, 2015; Bhagavathula, Elnour, and Shehab, 2016; Protopopoff *et al.*, 2018), gene drives are a promising new strategy to maintain and have the potential to accelerate and achieve lasting gains in malaria control.

1.2. Malaria elimination vs. eradication

This study focuses on malaria elimination by looking at the reduction to zero of the prevalence of *An. gambiae*, main vector species in SSA, in study areas in the DRC, once the malaria intervention and combination were deployed to interrupt the local transmission of the disease. Malaria elimination differs from malaria eradication as elimination requires continued measures to prevent re-establishment of transmission in one vector species in specific areas. In contrast, eradication is the permanent reduction to zero of the worldwide incidence of malaria caused by all vector species of human malaria parasites. It thus requires no further intervention measures once achieved (WHO, 2019b).

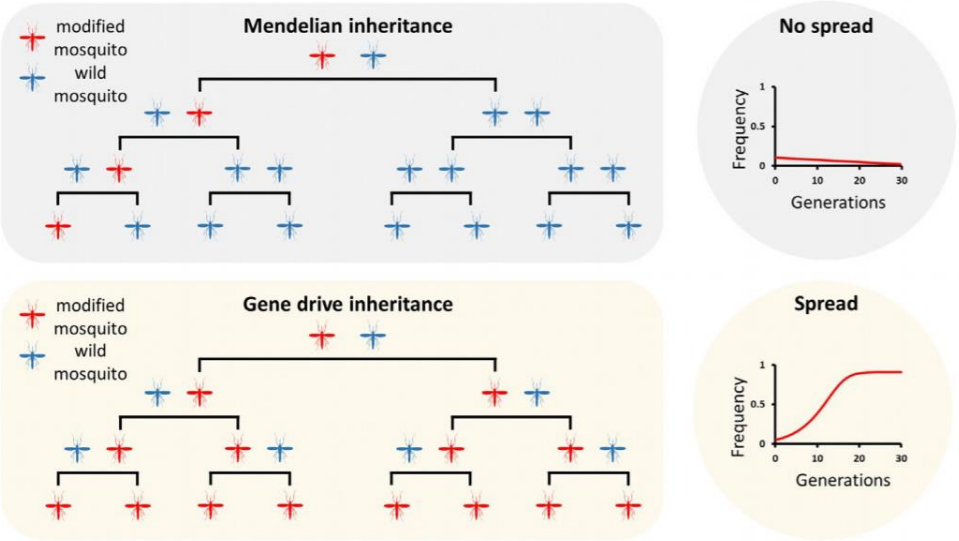
1.3. CRISPR/Cas Gene Drives: The end game?

Biomedical research has advanced and spanned from reading genomes of most organismal diversity and many disease states to ultimately engineering the genomes (Jennifer Doudna, 2016). The most recent advancement is the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-Cas (CRISPR-associated proteins) system – a promising approach to defeat parasitic genome invaders including prokaryotes – tackling Ribonucleic acid (RNA)-directed, nucleic acid selecting adaptive restriction machineries, a major mechanism of many bacteria and most archaea. The CRISPR/Cas system opened possibilities for researchers to develop a wide range of applications to address genetic-related questions, including controlling and altering organisms that transmit diseases to humans such as mosquitoes. The technique is contributing to the advancement of developing novel methods for malaria control and elimination (Heidrich *et al.*, 2015; Committee on Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct; Board on Life Sciences; Division on Earth and Life Studies; National Academies of Sciences Engineering and Medicine, 2016; Egelie *et al.*, 2016; Jennifer Doudna, 2016; Ratner, Sampson and Weiss, 2016).

Transgenic mosquitoes carrying gene drives have recently been successfully developed in the laboratory (Committee on Gene Drive Research in Non-Human

Organisms: Recommendations for Responsible Conduct; Board on Life Sciences; Division on Earth and Life Studies; National Academies of Sciences Engineering and Medicine, 2016). Gene drive is a novel method that includes 'driving' the targeted traits from one generation to the next. This process aims to defeat Mendelian inheritance (Figure 1: Upper panel), by which genes have a 50% chance of being inherited by the progeny, and instead gives specific genes a substantially higher or lower probability of inheritance and thereby alters the frequency of such genes in the population. If a given gene could alter fertility or survival of the target species, this process could alter its population size over a few generations (Figure 1: Lower panel) (Burt and Deredec, 2018; North, Burt, and Godfray, 2019a).

Figure 1 Mendelian vs. gene drive inheritance (Hammond and Galizi, 2017)



Recently, the proof-of-concepts using CRISPR/Cas9 to create gene drives to spread anti-*Plasmodium* genes in *An. stephensi* (Gantz *et al.*, 2015) and a gene drive that alters the fitness of female *An. gambiae* mosquitoes (Hammond *et al.*, 2016) were accomplished (Table 1). Nonetheless, the former failed to transmit the drive constructed at Mendelian frequencies in some instances (WHO/TDR and FNIH, 2014). As multiple gene drive approaches have recently shown promising outcomes in laboratory settings, gene drive mosquitoes might hold high potentials to help eliminate malaria under real-life conditions (Committee on Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct; Board on Life Sciences; Division on Earth and Life Studies; National Academies of Sciences Engineering and Medicine, 2016). Each genome-related system proposed to introduce disease refractory genes into a population may lead to different mosquito fitness costs, e.g. female fecundity, mating competitiveness, effectiveness to spread the gene that would inform the necessary release numbers etc. (Alphey, Koukidou and Morrison, 2014). Such crucially important biological and ecological factors like fitness costs/ gains, conversion rate, population structure,

gene flow, and ecological interactions will strongly influence the outcome of any field releases of gene drive modified mosquitoes. Various techniques of mathematical modeling can simulate and evaluate realistic field settings to determine such constraints on construct parameters and release strategies for the use of gene drive approaches (Eckhoff *et al.*, 2016).

Table 1 CRISPR/Cas-based gene drives for malaria control

Strategy	Approach
Mosquito population suppression in *Anopheles gambiae* mosquitoes (Hammond *et al.*, 2016)	• The modification reduces the number of progenies • Strong gene drive possession • Intention to spread the modification indefinitely or until the mosquito population is eliminated
Mosquito population replacement in *Anopheles stephensi* (Gantz *et al.*, 2015)	• Modification limits pathogen replication, thereby reducing transmission • Strong gene drive possession • Intention to spread the modification through the population indefinitely

(Adapted from Table 1.1 GMM technologies currently under development (WHO/TDR and FNIH, 2014)).

In the context of malaria, three approaches are considered and developed for using gene drives.

Mosquito population replacement:

- Moving an anti-parasite transgene through the mosquito population, rendering it refractory to *Plasmodium* infection or ineffective at transmission.

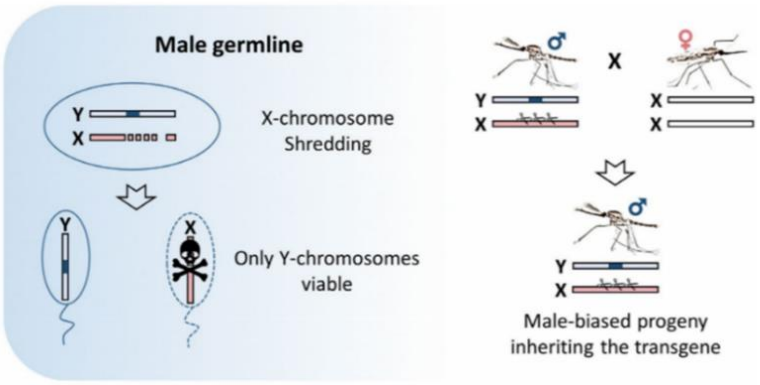
Mosquito population suppression:

- Selected fertility genes in mosquitoes lead to population suppression or collapse.
- Driving-Y system: Y chromosome in the modified male mosquito damages ('shreds') the X chromosomes in the germline, resulting in gametes that predominantly carry a Y chromosome and a distorted sex ratio in viable offspring.

In the driving-Y system, the X-shredding process results in male-biased progeny as the Y-chromosome can still be carried through unaffected sperm to be driven to the next generation (Hammond and Galizi, 2017). The system leads to fecundity reduction, the reduction of the potential to produce offspring, that reduces the egg batch size and has implications for the success of the driving system (Figure 2) (Bradshaw and McMahon, 2008; Moro *et al.*, 2018).

In *Aedes* and *Culex* mosquitoes, there is a naturally occurring driving-Y chromosome that, in some crosses, is transmitted to >90% of a male's progeny. A strong bias toward Y chromosome-carrying spermatozoa could also be developed in the laboratory (Windbichler, Papathanos, and Crisanti, 2008). These results demonstrated the achievability of synthetic sex distortion mechanisms. Both mathematical modeling and studies of naturally occurring sex distorters in some insect species predicted that, if linked to the Y chromosome, such distorters would represent extremely powerful tools to knock down a selected population in a relatively short time (Burt and Deredec, 2018).

Figure 2 Driving-Y system (Hammond and Galizi, 2017)



Parameters that determine the potential success of a driving-Y system are X-shredding rate and fecundity reduction. X-shredding rate is the rate of the X chromosome, which favors the unaffected Y-bearing sperm and results in the production of a male-biased progeny. The X-shredding rate needs to be high enough to prevent wild-type female offspring from being born in each egg batch because sufficient numbers of wild-type females will sustain the local population and stave off collapse. Fecundity reduction is the reduction of the potential to produce offspring. Fecundity reduction affects the egg batch size, while the X-shredding rate affects the number of driving-Y offspring in each egg batch. If the fecundity reduction is too high, female mosquitoes mated with driving-Y males produce much smaller egg batch size even though the X-shredding is 100%. Fewer driving-Y males will subsequently emerge for such an egg batch compared with wild-type males in a wild-type-mated egg batch. Thus, the driving-Y construct will disappear and not sustain (Eckhoff *et al.*, 2016).

The release of previously developed genetically engineered insects into the environment poses two immense risks. One is the possible environmental risk associated with the introduction of large numbers of mass-reared insects; the other entails specific risks associated with the process of genetic modification (Mumford, 2012). Hence, WHO recommended that experiments and modeling be conducted before transgenic mosquito field testing to determine in which seasons and ecological contexts the transgenic mosquitoes have a reasonable chance of affecting both environmental and epidemiological outcomes (WHO/TDR and FNIH, 2014). Genetically modified mosquito

technology was primarily developed to address health problems, mainly present in low- to middle-income countries. However, challenges remain in identifying a viable model for technology. WHO also suggested that genetically modified mosquitoes might be combined with existing vector control such as ITNs, IRS, or environmental management because the methods may be complementary and synergistic effects could possibly be anticipated. Ultimately, genetically modified mosquitoes may even be considered as a substitute for conventional vector control if there is evidence that such a modification is more cost-effective or more environmentally favorable relative to existing control measures (WHO/TDR and FNIH, 2014). Therefore, it is useful to apply quantitative and computational methods to gauge the probabilities of success and possible outcomes of drives that are strictly laboratory-contained or intended for field release. The estimates of gene drive impacts in more extensive and more genetically variable populations will also help the scientific community, public, and policymakers get a better understanding of possible risks and benefits of the technology even before its implementation (Alphey, Koukidou, and Morrison, 2014; WHO/TDR and FNIH, 2014; Committee on Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct; Board on Life Sciences; Division on Earth and Life Studies; National Academies of Sciences Engineering and Medicine, 2016).

Critical environmental and ethical concerns have overshadowed possible releases of gene drive mosquitoes (Fisher, 2018; Meghani and Kuzma, 2018; Thompson, 2018). Even though gene drive has yet to pass the research and development stage and only lead, candidates are now in confined cage trials (ENSSER, 2019a), public voice concerns over releasing previously developed genetically modified organisms. For instance, a genetically modified version of *Aedes aegypti* (OX513A) for control of mosquito-transmitted arboviral diseases like Zika, which led to extensive discussions on whether the technology is suitable for a large-scale implementation (Paes de Andrade *et al.*, 2016). At the same time, its proof of efficacy has been questioned. Therefore, informed decision-making on gene drive releases into the wild will require additional information about potential effectiveness (GeneWatch UK, 2018). However, for informed decision making on whether to release gene drives in the wild, in addition to possible environmental and ethical outcomes, their potential effectiveness needs to be assessed as well (Committee on Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct; Board on Life Sciences; Division on Earth and Life Studies; National Academies of Sciences Engineering and Medicine, 2016). Apart from small-scale laboratory experiments (Gabrieli, Smidler and Catteruccia, 2014; Hammond and Galizi, 2017), little has been done to gather evidence on the potential efficacy of gene drives, especially under more realistic settings.

Gene drives have the potentials to produce profound changes in both social and economic environments (Council of Europe, 2020). Therefore, challenges related to decisions on gene drive research and development include the fact that existing governance mechanisms may be inadequate, especially in many low- and middle-income countries (Committee on Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct; Board on Life Sciences; Division on Earth

and Life Studies; National Academies of Sciences Engineering and Medicine, 2016). We are mindful of the significance of our work and aware of the importance of much broader sense of risks and potential impacts of the technology that needs to be addressed beyond the extent of our work in this research. These broader aspects included encompassing societal impacts, public perception, and acceptance, biosafety and biosecurity issue, as well as how regulation and other forms of governance might manage the risks and communicate the benefits (The Royal Society, 2018). Thus, this research underscores the importance of working with communities where gene drives are proposed to be used to ensure concerns are addressed, and mutual agreements are reached before deployment.

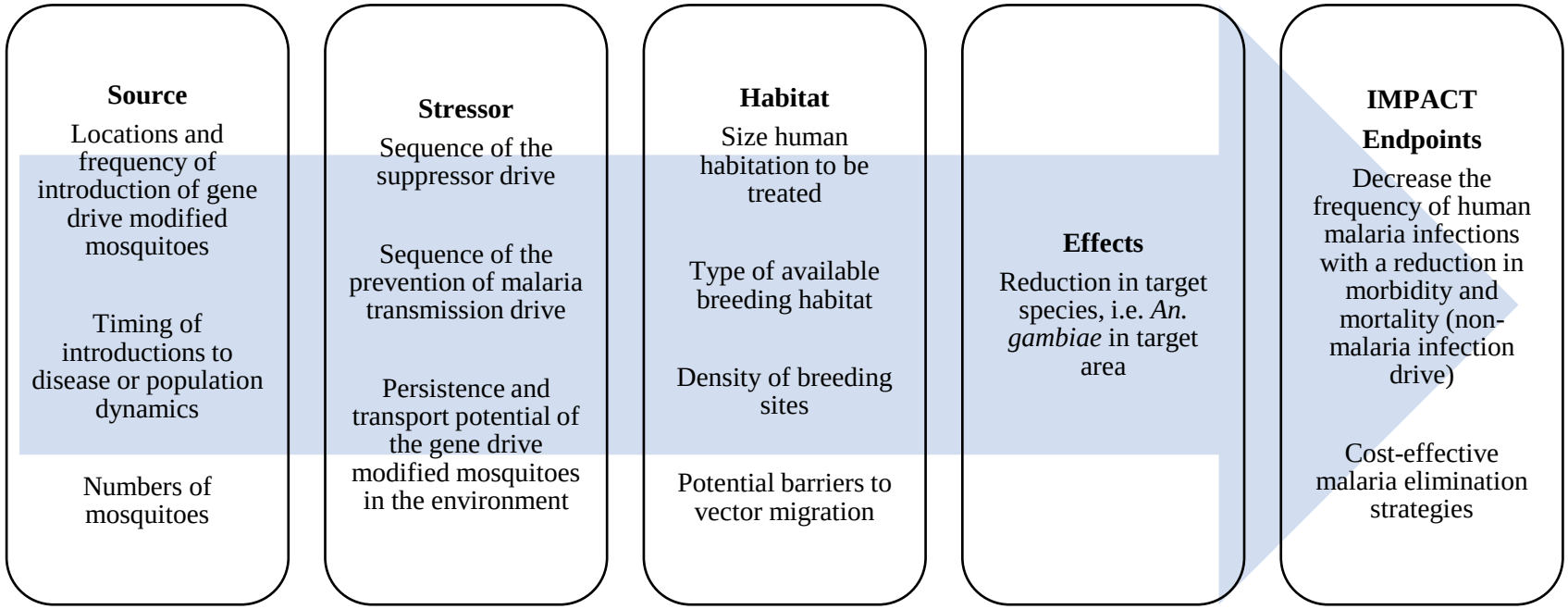
1.4. Research objectives

- Primary objective: To assess gene drives as a vector control method in malaria control and elimination for developing countries.
- Secondary objectives: To perform an economic assessment of gene drives in order to jointly assess the following aspects of the method by comparing and performing impact evaluation, i.e., cost-effectiveness of gene drives with existing vector control methods in malaria control.

1.5. Conceptual framework

This study focuses on impact assessment of gene drives as a malaria intervention as single and combination to existing malaria control methods, i.e., ITNs, and treatment of symptomatic cases with ACT. Diagram 1 shows the conceptual framework of the study starting from the modeling work that includes source, stressor, and habitat to assess the effects of gene drives and ultimately evaluate the impacts of the method both in disease and economic perspectives.

Diagram 1 Conceptual model for the release of gene drive modified mosquitoes



Adapted from generalized conceptual model for the release of a gene drive modified organism (Committee on Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct; Board on Life Sciences; Division on Earth and Life Studies; National Academies of Sciences Engineering and Medicine, 2016).

1.6. Study areas in the DRC

Despite sustained malaria control strategies, among high-burden countries, the DRC had the highest increase in incidence from 2015-2018, and more than 40% of children who fell ill because of malaria were not brought to care (President's Malaria Initiative, 2018; WHO, 2019c). Mainly, health system weaknesses and financial and programmatic factors caused significant gaps in the coverage of core interventions (ITNs, IRS and ACT), which have been deemed responsible for the recent rise in cases (Malaria Policy Advisory Committee Meeting, 2018). Especially the difficulties in providing continued access to vector control have been prominent in this complex operating environment, compounded by domestic political conflicts and insufficient funding for malaria control. These challenges emphasize the urgent necessity of developing new strategies for malaria control and elimination for the DRC and beyond (Roll Back Malaria Partnership, 2017; Malaria Policy Advisory Committee Meeting, 2018; President's Malaria Initiative, 2019; WHO, 2019c).

The DRC (Figure 3) is the second highest-burden country in Africa, accounting for 11% of all cases of malaria in SSA (WHO, 2018b). Given that the country is around two thirds the size of Western Europe (December and Gowan, 2013) and nearly all of the DRC's population lives in high malaria transmission zones, malaria remains the most serious public health problem that causes the most deaths in the country (WHO, 2018b; IHME, 2019). Since the First Congo War (1996–1997), the DRC has been struggling with a series of violence and political unrest (Human Rights Watch, 2018). Despite sustained malaria control strategies, in 2017, the country reported an increase of more than half a million cases compared with 2016, the highest increase in malaria cases among high malaria burden countries (President's Malaria Initiative, 2018; WHO, 2018b; Vector Link, 2019). For example, in its North Kivu province, 0.5 million people live in an isolated, difficult to access region with few functional health facilities.

Moreover, the area is highly volatile with armed groups putting an additional risk to people seeking healthcare, and who are often forced to move and seek refuge in temporary shelters. These reduce further the practicality of ITNs and IRS. Finally, many abandoned ponds have become major breeding habitats for mosquitoes, exacerbating the disease burden (Roll Back Malaria Vector Control Working Group, 2017). This emphasizes the urgent necessity of developing new and more focused malaria control and elimination strategies for the DRC (WHO, 2015a; Roll Back Malaria Partnership, 2017; Malaria Policy Advisory Committee Meeting, 2018; President's Malaria Initiative, 2019).

Figure 3 Geographical location of DRC

1.7.Outline of the study

This work explored the possibilities of applying gene drives as an intervention for malaria control in SSA using modeling approaches based on existing databases. The models were set up in eight provinces of the DRC with transmission intensity calibrated to open data sources, including Malaria Atlas Project prevalence estimates. The gene drive release strategies were firstly explored in a non-spatial simulation framework and later in a spatial simulation framework combined with commonly used vector control methods. By fitting larval habitat parameters into the models, the potential number and pattern of gene drives were determined. Testing intervention packages in the spatial simulation framework gave an idea of how gene drives could fit into the current intervention strategies. Interventions and combinations that could eliminate malaria in the selected locations were identified and evaluated. The economic evaluation was performed to elucidate the cost-effectiveness of the interventions and combinations.

Chapter 2

2. Mathematical and computational transmission disease modeling

2.1. Introduction

Mathematical disease modeling

Infectious diseases cause deaths and burdens physically, psychologically, and economically to patients, their families, and communities. Throughout history, we have been fighting the transmission of diseases from flu to plague to HIV/AIDS (Brauer, 2017). Now, the world is faced with the outbreak of the Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is spreading rapidly and continues taking away lives (WHO, 2020b). The unpredictable nature of disease transmission has promoted fear, and worldwide panic at the precept of their emergence as the feeling of dread intensifies fueled by the unknowns (Choisy, Guégan and Rohani, 2007).

The epidemic modeling aims to synthesize existing information about a disease to systematically investigate hypotheses to identify control measures that are likely to have the most significant impact (Brauer, 2017). Since the pioneering work of Ross in malaria modeling became the backbone of the epidemic modeling field, mathematical modeling has played a critical role in malaria research and policy (Choisy, Guégan and Rohani, 2007; The malERA Consultative Group on Modeling, 2011; The malERA Refresh Consultative Panel on Combination Interventions and Modelling, 2017). Mathematical models have been developed to characterize diseases, determine efficacious intervention strategies, and inform health policy decisions (Foppa, 2016). In recent years, increases in available computational power have enabled ever more realistic models of disease spread, making disease modeling a more critical aspect of infectious disease response than ever before (Lengauer, 2013). This study advanced and applied malaria disease modeling to expand the understanding of gene drives as a novel vector control method.

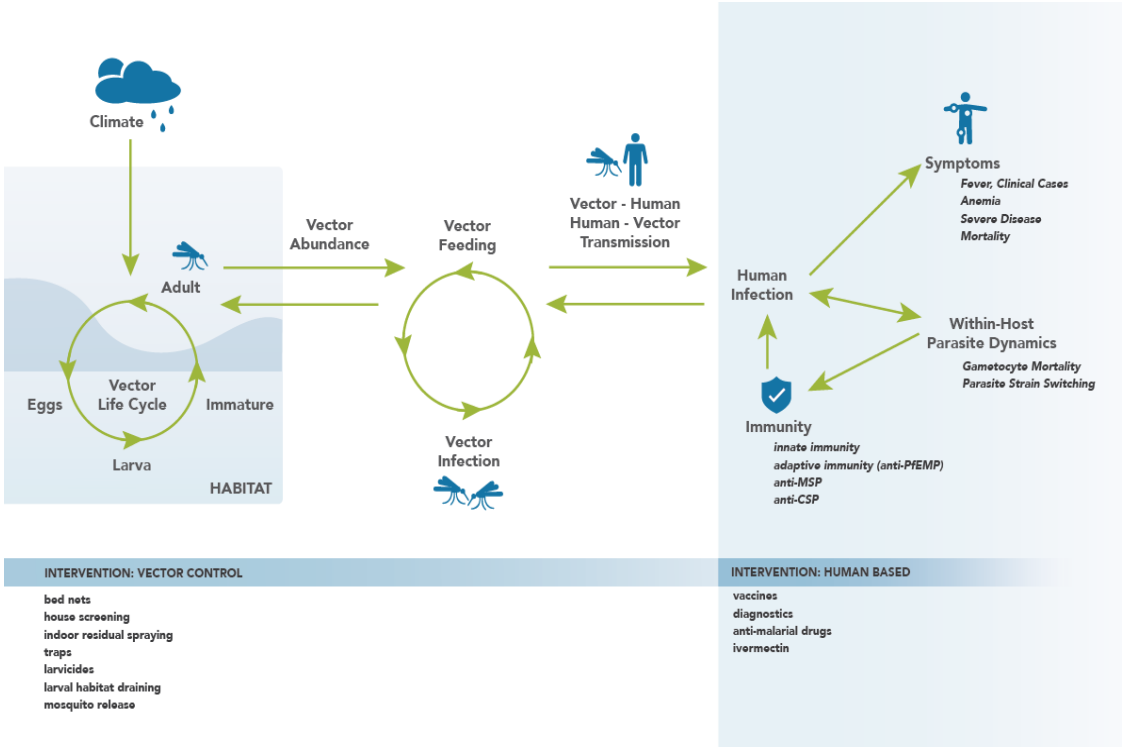
Mathematical and computational simulations of malaria for the DRC

Epidemiological MODeling software (EMOD) is an agent-based, stochastic, discrete-time, Monte Carlo simulator initially developed by the Institute for Disease Modeling (IDM). The software can be used to model a variety of diseases that are generic Susceptible-Exposed-Infectious-Recovered (SEIRS) bases, including vector-borne diseases such as malaria (IDM, 2019).

For malaria modeling in this study, mechanisms to implement gene drives are added to the primary EMOD model applying genetic variables. To simulate malaria transmission, the model dynamically combines a detailed vector population, human

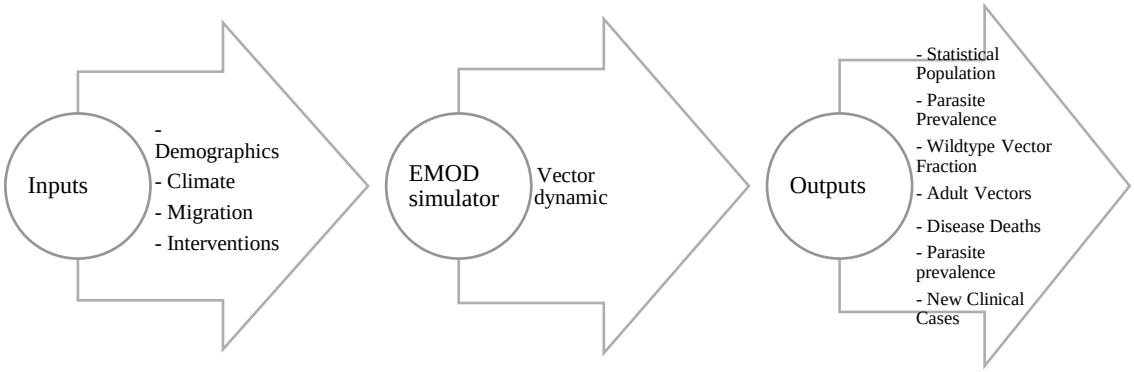
population, human immunity, within-host parasite dynamics, effects of antimalarial drugs, and other aspects of malaria biology (Diagram 2). The model uses modified cohort simulations with explicit mosquito ages.

Diagram 2 Network diagram illustrating the malaria model and its constituent components (IDM, 2019b)



In this research, EMOD software version 2.18 was calibrated to the DRC selected locations, and the model's functionality was modified to simulate gene drive intervention. The model's modular framework includes the climate and demographics spatial data, larval habitat, vector transmission model, malaria infection including symptoms and diagnosis, and immunity model (Diagram 3).

Diagram 3 Simplified EMOD malaria model structural components of the environmental inputs (left), the vector model (middle), and the human model (right)



In order to model the host dynamics of malaria disease, this study applied the following EMOD simulator components within-host dynamics for malaria simulations.

Input data:

Demographic

In the non-spatial simulation framework, a single node (i.e., a 5 x 5 km^2 grid) at the center of each selected area represents each province.

In the spatial simulation framework, 25 nodes in a 25 x 25 km^2 grid node per province were applied. The initial number of individuals was set to 1,000 people per node.

Migration

In the spatial simulation framework, vector migration input was generated, followed the approach in (IDM, 2019c) to include local vector migration. Vectors moved to a randomly selected adjacent node at a rate of 0.15 per day or, on average, around 7 days until migration. The rate parameterizes an exponential distribution, which is used to draw duration until the vectors migrate. Humans moved between nodes less than 10 km apart with a rate proportional to their distance.

Climate (includes rainfall, temperature, and humidity): the model used climate data

Climate is a crucial determinant of geographic distribution and seasonality of malaria since it directly influences the availability of larval habitats, determines mosquito development and its survival rates, as well as impacts human behavior leading to contact with infectious mosquitoes. Climate parameters include rainfall, air temperature, and humidity. The model's climate inputs are as follows.

- *Rainfall* - this was set to be stochastic by reading climate-related information of daily rainfalls drawn from an exponential distribution, which preserved approximate monthly total with the same daily mean but produced a more realistic rainfall pattern for the simulations.
- *Air temperature* - air temperature values were measured two meters above the ground. The standard deviation of 2°C was applied for a normally distributed noise to the daily air temperature values.
- *Humidity* - humidity values were also measured two meters above the ground. The relative humidity values were multiplied by the scale factor of 1. The standard deviation of 0.05% was applied for a normally distributed noise to the daily relative humidity values assuming no air migration.

Weather station and readings by National Oceanic and Atmospheric Administration (NOAA) Global Surface Summary of the Day (GSOD layer) were used for generating temperature and dewpoint anomalies. Baseline monthly averages were generated using WorldClim 1.4 raster files in a grid format, 2.5 arc minutes, and 30 arcseconds from WorldClim 1.4 (Hijmans *et al.*, 2005). Rainfall files were generated by downscaling RFE 2.0 Rainfall Estimates from NOAA's Climate Prediction Center (NOAA, 2006).

Mosquito populations not only depend on habitat availability, which is the primary driver, but also on larval development and the mortality rates. A variety of factors such as climate and densities of other larvae could affect them. The effects of climate on a larval habitat can be intense. The magnitude, however, depends on the mosquito species and their particular habitat preference. A given climatic region can have several types of larval habitats; therefore, the climate was configured separately from habitat type in the model.

Anopheles gambiae mosquitoes breed primarily in temporary puddles replenished by rainfall and drained through evaporation and infiltration (Sinka *et al.*, 2010). In the present model, the larval population of *An. gambiae* was estimated using a simple numeric scale factor. The following series of equations are for larval carrying capacity, which evaporation rates are scaled in a functional form. Thus, when the weather is hot and dry, evaporation and infiltration are higher. Temporary habitats increase with rainfall and decay with a rate proportional to the evaporation rate driven by temperature and humidity (Equation 1). For temporary habitats, the factor of 0.05 was used to convert the raw evaporation rate, excluding boundary layer effects, to the daily rate of larval habitat loss. Clausius-Clayperon (as in Equation 2) is frequently used in meteorology and climatology to describe the behavior of water vapor. In Equation 2, Clausius-Clayperon relation provides a method to find a relationship between temperature and pressure along phase boundaries.

Equation 1:

$$\mathrm{H_{temp+}} = \mathrm{P_{rain}}\,\mathrm{K_{temp}}\,\mathrm{D_{cell}^2} - \mathrm{H_{temp}}\left(\frac{\Delta \mathrm{t}}{\mathrm{T_{temp}}}\right)$$

Equation 2:

$$\frac{1}{\mathrm{T}_{temp}} = (5.1 \times 10^{11} Pa)\, e^{-\frac{5628.1K}{\mathrm{T}_K}} k_{tempdecay} \sqrt{\frac{0.018 kg/mol}{2\pi T T_k}} (1 - RH)$$

where:

$\mathrm{H_{temp}}$ = temporary habitat

$\mathrm{P_{rain}}$ = rainfall

$\mathrm{K_{temp}}$ = habitat scalars

$\mathrm{D_{cell}^2}$ = a grid of diameter $\mathrm{D_{cell}}$

$\mathrm{T_{temp}}$ = decay rate

$k_{tempdecay}$ = a factor to relate mass evaporation per unit area to habitat loss
T = temperature in kelvin
RH = humidity

Larval density was set to be constant at 80,000,000 larvae per a 1x1 degree area (D^2_{cell}) throughout the year and did not depend on the weather. However, a seasonal signal in adult population levels or mosquito abundance was detectable due to the effects of temperature upon aquatic development rates. For a given carrying capacity, a faster development time allowed a local habitat to have a higher larval through-put with corresponding impacts on the adult population. The temporary rainfall habitat was set to 800,000,000 larvae per a 1x1 degree area (D^2_{cell}).

In the EMOD framework, the vector transmission was comprised of the following components (Eckhoff, 2011):

1) Vector tracking and mosquito lifecycle

The present model counted the number of identical vectors of each state that existed at a location. It provided a compartment for every possible entry in state space (Diagram 4) and tracked the number of vectors in each compartment. This successfully accounted for each vector but did not distinguish between vectors that had identical states.

Diagram 4 Mosquito lifecycle as a malarial vector in EMOD

Vector life cycle

Egg: Larval density did not affect egg hatching while the habitats were set to be filled to capacity. The model discarded excess eggs that were saturated at oviposition. Egg hatching happened simultaneously after oviposition with no delays.

Larva: The daily rate of fractional progression of mosquito aquatic development or egg-hatching through emergence was parameterized using the Arrhenius equation, $a_1^{-a_2/T}$, with T in degrees Kelvin. The duration of development was, therefore, a decreasing function of temperature. a_1 was set to 84,200,000,000. a_2 was set at 8,328.

Immature: The mosquito development rate had an inverse relationship with the number of days, which was set at 2 days in the model.

Adult: The development from immature to adult did not depend on temperature. Adult vectors entered a cycle of host-seeking, feeding, and egg-laying that continued until their death with a 3-day constant gap between each successful blood meal with no effect from temperature. The feeding rate of 1/3, approximately 0.33, was then used to determine the probability that one of each feeding modes occurred.

Various feeding cycle outcomes were calculated from branching trees of conditional probabilities, while individual interventions modulated the probability of choosing between branches. Feeding cycle outcomes included death (before, during, or after feeding), host unavailable, successful human feed. The allocation of mosquitoes to feeding-cycle outcomes was based on end-state probabilities that had been aggregated over the individual humans in the simulation. The deterrent and toxic effects of multiple interventions were represented simultaneously by selecting various branches in the vector feeding tree.

Then each successful blood-fed adult female mosquito laid 100 female eggs and 100 male eggs. The risk of people being bitten rose linearly from 7% to 23% for the first two years of their lives. The biting risk continued to rise with a shallower linear slope to the age of 20.

Infected:

The model parameterized the daily rate of fractional progression of infected mosquitoes to the infectious state using the Arrhenius equation. The duration of sporogony was then a decreasing function of temperature given that a_1 equals 117,000,000,000, and a_2 was 8,336.

Infectious: The dimensionless factor of 0.8 was set in the model to account for reduced mosquito egg bach size due to increasing fertility effects from infection.

Mortality reduced the vector population at every stage of its development and every timestep. The vector mortality is determined by the Adult_Life_Expectancy parameter, which was set at 20 days in the model. The mortality could be parameterized as follows:

Egg-larva-immature: 0.1 aquatic base mortality per day was uniformly applied to all larvae when the population exceeded the specified carrying capacity for the habitat (overpopulation) before adjusting for the effects of drying out of aquatic habitat. No larvae died due to rainfall.

Immature-adult-infected-infectious: An adult mosquito was set to survive for 10 days. The daily adult mortality rate was then 1/10, meaning 0.1 of mosquitoes died while feeding on humans.

Infected-infectious: The model modified the death rate of mosquitoes when feeding on humans with a dimensionless factor of 1.5 due to

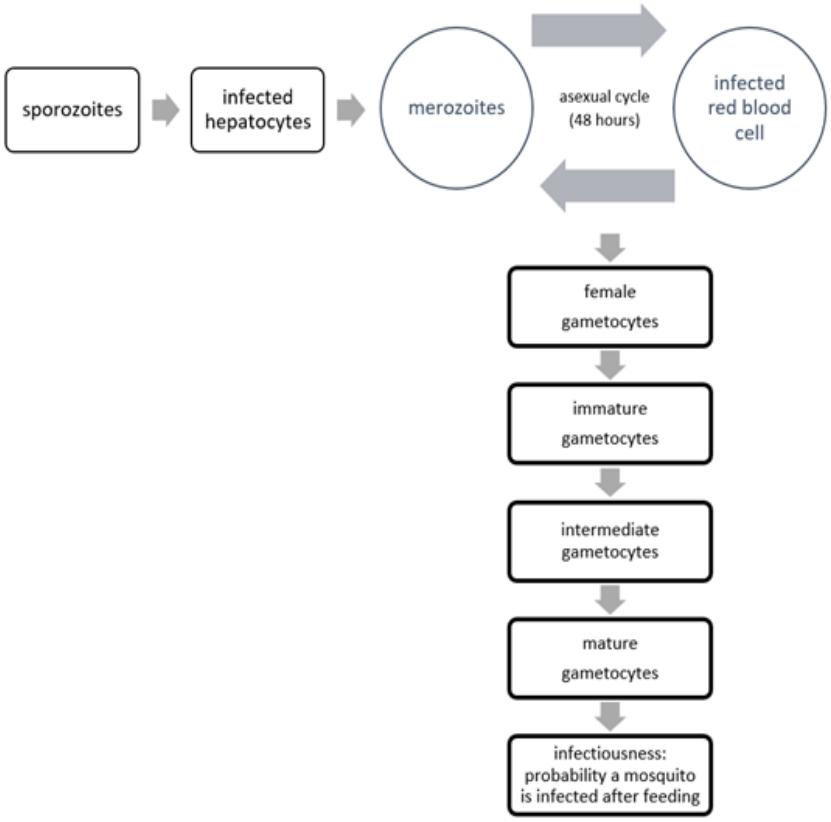
the higher mortality rate that infected mosquitoes experience during human feeds compared to uninfected ones.

2) Within-host parasite dynamic

The model could simulate the measured prevalence over time of various diagnostics, including slide microscopy and Rapid Diagnostic Tests (RDTs), by tracking a detailed parasite count of each infected individual over time. The tracking included gametocyte production and decay to study the human infectious reservoir.

Each new infection began with a hepatic latency or hepatocyte of 7-day fixed duration, which proceeded to a 2-day fixed duration of the asexual cycle and to gametocyte production that took 10 days (Diagram 5). The model traced several antigenic components presented in either innate or adaptive immunity which were the merozoite surface protein (MSP) variant, the *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) presented on the surface of the infected red blood cell (IRBC), and less immunogenic minor surface epitopes (nonspecific epitopes).

Diagram 5 Within-host parasite dynamic



At the start of infection, a single infected hepatocyte could cause 15,000 IRBCs. If treated, the treatment could cause a maximum (4.8) log reduction in

IRBCs per day. Each infected hepatocyte went through only one cycle of asexual reproduction that produced gametocytes. 4.4% IRBCs produced gametocytes, of which 80% were female. The female gametocytes advanced through five developmental stages, which had different drug susceptibilities. A fraction of the gametocytes died at each stage. Gametocytes reached maturity after ten days and remained in the bloodstream with a 2.5-day half-life. An average fraction of 0.002 mature gametocytes in a blood meal could successfully infect mosquito without other modulating effects such as fever.

Immune response to infection

The model includes two types of immune responses to parasite infection: innate and adaptive immune responses.

The innate immune response was modeled to depend on a temporary contribution from a rupturing schizont at the end of each asexual cycle and the concentration of IRBC surface antigens to which an antibody response had not yet been developed. The immune response to infection was characterized by innate inflammatory and specific antibody components that limited maximum parasite density and worked to clear the infection. When the level of bloodstream infection reached half of its maximum value, the asexual parasite density reached the level to trigger cytokine production. The innate response suppressed by the presence of specific antibodies was responsible for driving febrile symptoms and broad-spectrum parasite suppression. As fever increased above 38.5 °C, the kill rate became successively higher along a sigmoidal curve approaching the maximum kill rate of IRBC at 1.4. The model, however, did not include variation in innate immune between individuals.

Through the sequential variation of highly polymorphic antigens, consisting of an immunodominant molecule PfEMP1 and a second family known as rifins, inserted by *P. falciparum* into the surface of the infected erythrocyte, a specific agglutinating antibody response, a major function in naturally acquired protective immunity, target each variant. Each antigenic variant comprises of unique major epitope and elicits a long-lived immune response and several minor epitopes elicit transient immune responses that are not unique to the variant (Recker *et al.*, 2004). After the antibody response appeares, continued antigenic stimulation drives up the adapted response until that antigenic variant is cleared. Then, both the antibody levels and the capacity to respond would decay over time. The larger the antigenic population, the more infections, and thus more time it takes to acquire broad parasitological immunity. The capacity to generate specific antibodies grows in response to the concentration of each novel antigen. The initial rate of increase in antibody capacity depends on antigen concentration, a minimum level of antibody stimulation to novel antigen, a maximum daily rate of antibody capacity increase, and adjusted antibody growth rate for minor epitopes.

Since adaptive immune responses to PfEMP1 and minor epitopes, the minimum level of antibody simulation (0.05) to the novel antigen set the low-range asymptote for antibody capacity growth and antigen density, in the presence of any non-zero antigen level. In the 30 IRBC/μl antigen concentration, antibody capacity grew against the antigen increased at half the maximum rate specified. The antibody concentration began to increase when antibody capacity was above 0.3. The model used the factor of 0.5 to adjust the concentration of an antigen, measured in IRBC/μl at which growth in antibody capacity against the antigen increased at half the maximum rate specified at 0.09 for less immunogenic surface proteins, i.e., minor epitopes. Above a capacity threshold level, antibodies were produced in increasing concentration (with the scale factor of 1.596 multiplied by antibody level to produce the rate of clearance of the IRBC population) until the corresponding antigenic variant was cleared. The adaptive immune also responded to MSP antigens. During each asexual cycle, 43% of merozoites were inhibited from invading new erythrocytes, and MSP1 antibody capacity could reach the maximum increase at 0.045. At the threshold value of the circumsporozoite protein (CSP) antibody concentration of 20, the adaptive immune started to kill sporozoite.

The antibody capacity gradually decayed to the level of 0.34 after the infection was apparent. The decay rate in antibody capacity was set so that hyperimmune would be lost within 4 months, and capacity continued to decay to this level. At this time, the capacity would decay to a non-zero memory level. The antibody memory level was relevant for year-scale dynamics, but not for long-term (10-20 years) dynamics. The mechanism by which the antibody capacity evolved captures the time delay of specific antibody response on re-infection (Eckhoff, 2012).

Malaria symptoms and diagnostics

Symptoms indicated the presence of disease. The symptoms included in the model were clinical symptoms such as fever, anemia, and the end result (death). They were modeled in terms of the spectrum of disease severity, which related to past infection and immune response. Therefore, symptoms could help further to inform the transmission dynamics of the selected population.

Fever:

Fever was triggered by cytokine production through the innate immune response. The level of body temperature above normal body temperature of 37°C corresponds to detectable fever. A clinical case began when fever surpassed a certain threshold (1.5 °C above normal), and the clinical incident continued until the fever subsided below another threshold (0.5 °C). The model simulated the fever subsided below the low-threshold for at least 14 days before a new incident could start when fever again exceeded the high-threshold.

Anemia:

Rupture of IRBCs destroyed nearby red blood cells (RBCs) and led to anemia. 3.29% of total RBCs were destroyed per infected rupturing schizont. In order to increase the rate of RBC production, erythropoiesis was stimulated in anemic individuals at an exponential rate of 3.5.

Severe disease and mortality:

Excessive fever, anemia, or parasite counts could all lead to severe disease and mortality. Anemia, fever as a pro-inflammatory correlating with cerebral malaria, and total parasite density cause severe or fatal malaria. Severe or fatal malaria probability was calculated and configure with two parameters of a sigmoidal function.

Severity was calculated from the inverse width relative to the threshold value of mortality turn-on around the threshold for fever. The inverse width of severity was 30.323 for fever, 100 for anemia, and 7.931 for the parasite. The inverse width of mortality was 1,000 for fever, 150 for anemia, and 100 for the parasite. The severe threshold for fever indicating severe disease was 3.8719 °C above normal body temperature (defined as 37 °C), and the mortality threshold was 10 °C above normal body temperature. The parasite density threshold level that results in the severe disease was 317,351, and the mortality threshold for simulation was 3,000,000. The severe disease threshold level for anemia was 5 g/dL, and the mortality turn-on around the threshold for hemoglobin count was 1 g/dL, at which 50% of individuals died per day.

Diagnostics:

Malaria diagnostics tested for the presence of asexual parasites in an individual's blood. A parasite count was drawn from a Poisson distribution centered around the true asexual parasite count. The model used 0.1 microliters of blood tested to find single parasite in a traditional smear, and 0.05 microliters of blood tested to find single parasites in a new diagnostic corresponded to inverse parasites/microliters sensitivity.

Interventions

The following interventions were added to the model as single and mixed interventions. By specifying the demographic coverage, the model set the value of probability that each individual in the selected population would receive the intervention. However, this did not guarantee that the exact fraction of the selected population set to re-

ceive the intervention. The interventions were distributed simultaneously to the same individual independently, even when the person had already received another intervention.

Insecticide-treated nets (ITNs)

Insecticide-treated nets are bednets that are usually made of a polyethylene or polyester mesh that is impregnated with a slowly releasing pyrethroid insecticide to repel and kill mosquitoes that land on them. For ITNs used in the model, the initial strength of the blocking effect on indoor mosquito fed on an individual with an ITN was 0.9, and the blocking decayed at an exponential rate in 730 days. The initial strength of the killing effect was 0.6, conditionally on a successfully blocked feeding event. The killing effect decayed at an exponential rate in 1,460 days. The model assumed an individual who received an ITN had 0.65 probability of using it on any given night, and ITNs were redistributed every 3 years. Since the ITN coverage was varied, the fraction of individuals in the selected demographics that received ITNs varied.

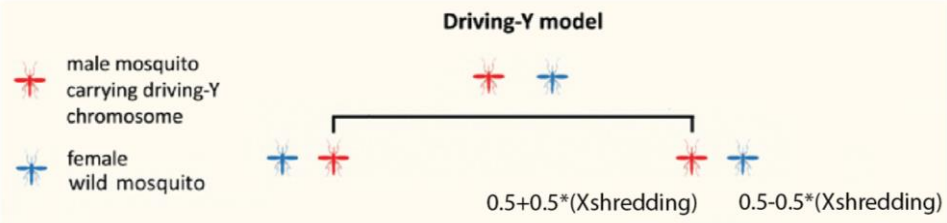
Driving-Y gene drive mosquito release

The CRISPR/Cas9 system has been applied in the inoculative concept of control for gene drives based on self-sustaining populations intended to spread and persist, with the expectation that they will interact with other organisms in a beneficial manner, either reducing a selected population of a different species or replacing a wild population of the same species with a new gene drive-based one with more desirable attributes. There are substantial differences between self-sustaining transgenic insects and classical biological control. Classical biological control uses a different organism related to invasive pest through predation or parasitism; meanwhile, a self-sustaining transgenic agent is using the same species as the selected pest. In the case of malaria control, transgenic insect release is related to *Anopheles* mosquitoes that are vectors of malaria. Gene drives could potentially be used as part of 'integrated vector management' (IVM) to control mosquitoes that transmit malaria in combination with several methods such as ITNs, IRS, and eliminating breeding habitats.

The mechanisms to implement gene drives were added to the primary malaria model. A new genetic variable was added for the gene drive construct (Figure 4). In driving-Y, all females are considered wildtype, while modified males carry a driving-Y chromosome. Females that mate with a male carrying the driving-Y will have offspring wildtype females and males carrying the driving-Y. The fraction of offspring that are driving-Y males is then **0.5+0.5*(Xshredding)**, and the fraction of offspring that are wildtype females is

0.5-0.5*(Xshredding). The total egg batch size is reduced by the parameter fecundity reduction for each female that mates with a modified male. Only females that mate with a driving-Y male have their fertility reduced.

Figure 4 Mechanisms to implement gene drive were added to the primary EMOD model



Case Management (artemisinin-based combination therapy; ACT)

Case management refers to the first-line antimalarial drug (in this case, ACT) administered to symptomatic patients presenting at outpatient clinics. The model assumed that a patient given an antimalarial drug does indeed have malaria, thus benefiting from receiving the drug. One health center visit per case was assumed.

Antimalarial drugs are considered a powerful tool for malaria control and elimination. Based on high-quality evidence, WHO guidelines for the treatment of malaria strongly recommends treating children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with ACT and that the ACT regimens should provide 3 days' treatment with an artemisinin derivative. ACT regimen used in the model is Artemether + Lumefantrine (AL), as it is the most commonly used ACT regimen across Africa (Sinka *et al.*, 2010).

Pharmacokinetics (PK) and Pharmacodynamics (PD) of Artemether and Lumefantrine were considered independently from each other for both PK and PD. The parameters used in the model for modeling AL are elaborated in Table 2 (Gerardin, Eckhoff, and Wenger, 2015).

Table 2 Antimalarial drug parameters applied in EMOD model for this study

Parameter	Artemether	Lumefantrine
Power of bodyweight	1	0.35
Drug adherence rate	1	1
Cmax	114	1017
The primary drug decay rate	0.12	1.3

The secondary drug decay rate	0.12	2
Dose interval	0.5	0.5
Full treatment dose	6	6
Log reduction per day in early-stage gametocytes	2.5	2.4
Log reduction per day in late-stage gametocytes	1.5	0
Log reduction per day in mature gametocyte numbers at saturated drug concentrations	0.7	0
Log reduction in hepatocyte numbers per day	0	0
C_{50}	0.6	280
Vd	1	1.2
Maximum log reduction in IRBCs per day due to treatment	8.9	4.8

Notes for Table 2:

Cmax: maximum drug concentration
C_{50}: concentration at which drug killing rates are half of the maximum
Vd: volume of distribution
IRBCs: infected red blood cells

Pharmacokinetics (PK) of antimalarial drugs can be modeled with a double exponential decay. The model uses 1-compartment PK for Artemether and 2-compartment PK for Lumefantrine.

For PD, the concentration at which drug killing rates are half of the maximum (C_{50}) determines the drug concentrations where parasite killing is effective (drug concentration > C_{50}) and ineffective (drug concentration < C_{50}). The model sets the shape of the parasite killing curve based on the parasite kill rate and C_{50}. The maximum drug concentration (Cmax), primary and secondary drug decay rate, the volume of distribution (Vd), and C_{50} together determine when the drug is effectively killing parasites. Changing each of these parameters will affect how long the parasites are exposed to a strong killing effect. Adding additional doses will also increase the duration of the parasite-killing window.

Children can be dosed with a fraction of the adult dose according to the fractional dose by age, where each dose fraction is paired with the maximum age of children receiving that dose. Depending on the specific PK characteristic of each drug, body weight may affect the rate of drug clearance. In the double exponential PK model, bodyweight is directly determined by age, and Cmax is multiplied by the inverse of the body weight raised to the specified power. Bodyweight affects Cmax in an individual patient since Cmax is divided by patient

body weight raised to the power of 1 to account for the influence of body size on the volume of distribution. The fraction of adult drug doses given to children below the age of 3, 6, and 10 years old are 0.25, 0.5, and 0.75 of adult drug doses accordingly (Eckhoff, 2012).

2.2. Simulation frameworks

Simulations were carried out with Epidemiological MODeling software (EMOD) v2.18 (IDM, 2019a), an agent-based, discrete-time, Monte Carlo simulator of malaria transmission with a vector life cycle (Eckhoff, 2011) and within-host parasite and immune dynamics (Eckhoff, 2012, 2013). The simulations in this study were executed in both non-spatial and spatial simulation frameworks. The main difference between both frameworks is that spatial framework includes vector and human migration while non-spatial does not. Non-spatial data are not related to a specific, precisely defined location and are independent of all geometric considerations. Meanwhile, spatial data includes location, shape, size, and orientation relating to a specific location and are linked in the Geographic Information System (GIS) (Sharma, 2019). The following is an overview of the modeling method.

1. **Selecting previously identified study provinces** that span the range of transmission intensities across the whole DRC.
2. **Calibrating larval habitat calibration in non-spatial simulation framework** in eight selected DRC provinces based on stratification to replicate Malaria Atlas Project (MAP) estimates of malaria prevalence data.
3. **Setting up modeling architecture for both non-spatial and spatial simulation frameworks.**
   3.1. Generating inputs.
   3.2. Adding pre-existing interventions in the run-in period.
   3.3. Calibrating seasonality and larval multipliers to vectorial capacity data.
   3.4. Simulating baseline scenarios and adding interventions.
4. **Planning gene drive mosquito release strategy in non-spatial simulation framework:**
   4.1. Determining potential mosquito release patterns: single release versus multiple releases (small batches, same total number).
   4.2. Assessing the X-shredding rate and fecundity reduction, applying the mosquito release strategy from the previous step (4.1).
5. **Modeling malaria control strategies in the selected provinces using spatial simulation framework:**
   5.1. Evaluating interventions.

2.2.1. Selecting previously identified study provinces

To ensure that selected locations spanned the range of transmission intensities across the whole DRC, eight provinces (Table 3; Figure 5) were chosen to represent each stratum of the provincial stratification which is based on malaria parasite prevalence from DRC-DHS 2013-14 and the main geographical determinants (President's Malaria Initiative, 2019). For this basis, the original stratification table presented in the most recent President's Malaria Initiative showed that the stratum I included only Nord Kivu while the stratum IV had only Kinshasa.

The simulations were based on parasite prevalence data of each specific location within a 625 square kilometer grid of each province. An individual 625 square kilometer grid contained 25 simulation points (nodes), which were 5 kilometers apart from each other. This resulted in 25 simulation units of 25 square kilometer grids.

2.2.2. Calibrating larval habitat in the non-spatial simulation framework

MAP prevalence estimates ($PfPR_{2-10}$) of each selected location (Figure 5) were used in the model to calibrate baseline transmission intensity. The Driving-Y model was applied to estimate both the selected number of *An. gambiae* gene drive mosquitoes that would be released in the environment and the level of X-shredding rate and fecundity reduction. Additional epidemiological data for setting up the model baseline were obtained from Malaria Operational Plan FY2019 of DRC President's Malaria Initiative (President's Malaria Initiative, 2019) and DRC-Demographic and Health Survey (DSH) II 2013-14, malaria supplement report (Meshnick *et al.*, 2014).

2.2.3. Planning a mosquito release strategy in the non-spatial simulation framework

2.2.3.1. Determining potential mosquito release patterns: single release versus multiple releases (small batches, same total number).

The driving-Y model applied for gene drive mosquitoes in this study is based on the fertility disruption of the mosquito population in the release area. The X-distorter was placed to intervene in the transferring of X chromosome to offspring; thereby, more male offspring will be produced than female offspring. This results in a male-biased population suppressing the total mosquito population and eventually collapses the mosquito population (Beaghton, Beaghton, and Burt, 2017).

In planning a release strategy, both the number and frequency of mosquitoes released were explored. The number of mosquitoes released tested to identify an appropriate number of transgenic mosquitoes released were 100, 200, and 300. The frequency of releases was also tested for the gene drive scenarios. Single and multiple releases of gene drive mosquitoes were simulated to pro-

vide estimates of how different release frequencies with the same total number of mosquitoes released (300 mosquitoes in this case) would affect the outputs in the selected DRC provinces. Eight provinces from different provincial strata based on the level of reported parasite prevalence were chosen to represent each provincial stratum.

2.2.3.2. Assessing the X-shredding rate and fecundity reduction, applying the mosquito release strategy from the previous step (2.2.3.1).

The number of mosquitoes released in the setting for each province was increased to identify the appropriate sets of X-shredding rate and fecundity reduction for gene drives that had enough potency to eliminate malaria in the selected provinces.

The number of mosquitoes released was 100, 200, and 300 in each selected province. The sets of X-shredding rate and fecundity reduction that could reduce the parasite prevalence in the selected province to zero would be selected to be later applied in the spatial simulation framework.

2.2.4. Testing interventions in the spatial simulation framework

2.2.4.1. Generating modeling inputs

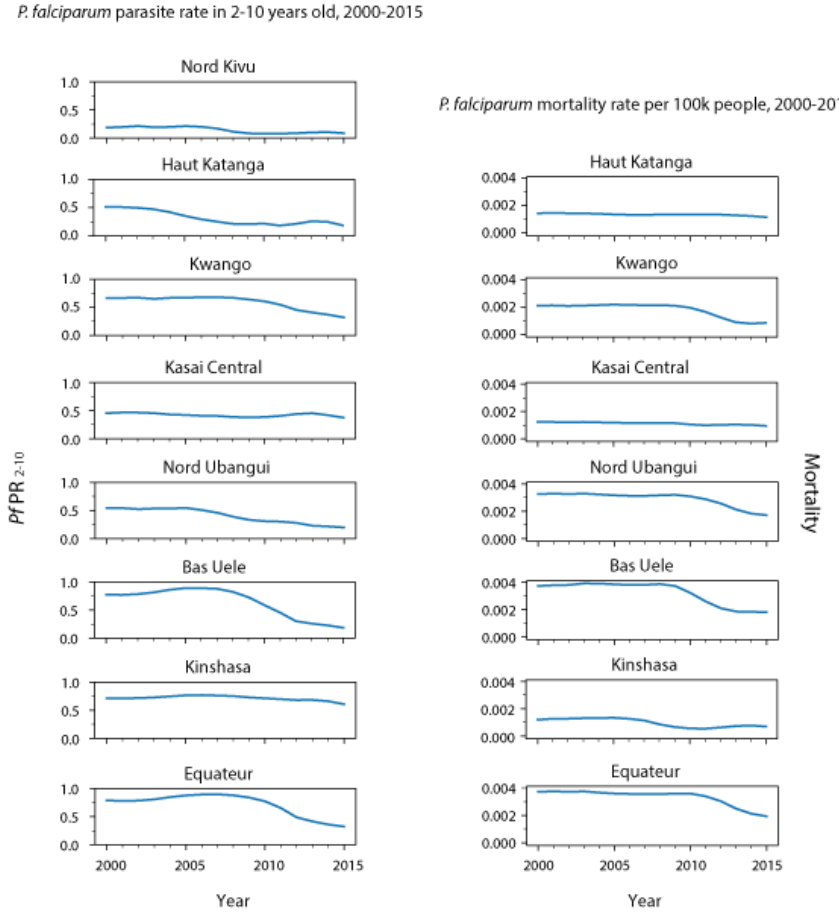
The annual means of estimated parasite rate in children between the ages of two and ten ($PfPR_{2-10}$) of all nodes (25 nodes per province) were retrieved from MAP rasters from the year 2000 to 2015 (The Malaria Atlas Project, 2018).

The central nodes (one central node per province; Figure 6; Table 3) were selected based on the coordinates available from the MAP prevalence estimates source to ensure the selected locations were populated. The coordinates were then checked in the Quantum GIS (QGIS) map using QGIS 3.6.0 'Noosa' to ensure all the 25 nodes (5km*5km pixel resulting in 25km*25km grid) were in the geographical boundary of each selected province.

Table 3 Profiles of selected central nodes

Strata	Parasite prevalence (%)	Main determinant	Provinces	Latitude of center	Longitude of center	Area (urban or rural)
I	≤5	Mountain facies, hypoendemic zone	Nord Kivu	-1.2419	28.8887	Rural
II	6 to 30	Equatorial and tropical facies, mesoendemic zone	Kwango	-6.9811	17.3894	Rural
			Equateur	0.1691	19.8866	Rural
			Haut Katanga	-10.1523	28.0999	Rural
III	>30	Tropical facies, hyperendemic	Nord Ubangui	3.6575	22.572	Rural
			Kasai Central	-7.5587	22.5536	Rural
			Bas Uele	2.746	23.7858	Urban
IV	18.3	Urban context, with variations from the city center to the periphery	Kinshasa	-4.459	15.276	Urban

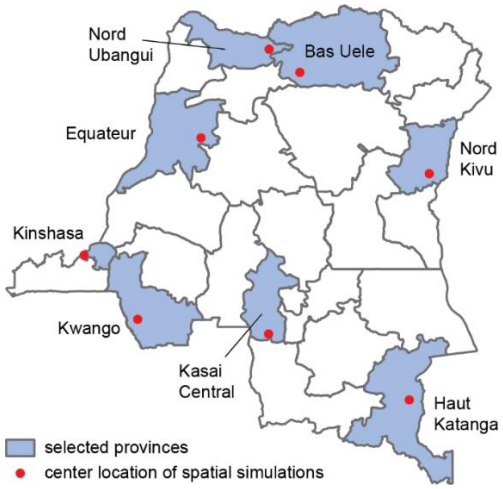
Figure 5 MAP *P. falciparum* parasite rate in 2-10 years old (Bhatt *et al.*, 2015) and mortality rate per 100,000 population (100k people) (Weiss *et al.*, 2019) at central node by selected DRC province from year 2000 to 2015



Notes for Figure 5:

P.falicparum: *Plasmodium falciparum*
MAP: Malaria Atlast Project
PfPR: *Plasmodium falciparum* parasite rate
The source did not report mortality rate of the selected Nord Kivu site.

Figure 6 Central nodes of eight selected provinces



The prevalence of each year from 2000 to 2015 were then mapped with the provincial locations. Demographics, climate, and vector migration inputs for every node (25 nodes per province) were then generated, followed an approach used in a previous modeling study (Chabot-Couture, Nigmatulina, and Eckhoff, 2014).

2.2.4.2.Adding pre-existing interventions

The following pre-existing interventions data reported in the Malaria Operational Plan FY2019 of DRC President's Malaria Initiative (President's Malaria Initiative, 2019) were added into the model.

Insecticide Treated Nets (ITNs): the pre-existing ITNs were based on % of the number of children under five years old who slept under an ITN the previous night (of the total population), which were 6% in 2007, 38% in 2010, and 56% in 2013.

Case management with ACT: Treatment-seeking for febrile cases in children under five years of age with treatment with an ACT at 19% of the total population in 2013.

Indoor Residual Spraying (IRS) was not included as less than 1% of the DRC population was protected by IRS between 2007 and 2018 (WHO, 2010, 2019c).

2.2.4.3.Calibrating seasonality and larval habitat multipliers to vectorial capacity data

In both non-spatial and spatial simulation frameworks, seasonality was enforced in the models by setting the seasonality of larval habitat abundance such that monthly vectorial capacity matched the average monthly vectorial capacity between 2000 to 2015 in two public datasets (v200906 and Sheffield) (IRI/LDEO, 2019). Daily temperature series was generated for each node as in Chabot-Couture, Nigmatulina, and Eckhoff (2014).

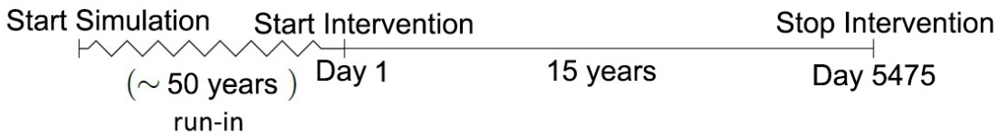
The overall larval habitat abundance was then calibrated by scaling the previously fitted seasonality profile such that the model's parasite prevalence was consistent with the mean 2015 annual parasite prevalence of the location from MAP estimates (Bhatt *et al.*, 2015). The annual means of estimated parasite rates in children between the ages of two and ten ($PfPR_{2-10}$) from the year 2000 to 2015 were retrieved from MAP rasters (Bhatt *et al.*, 2015) for all simulation nodes. For Haut Katanga, the larval habitat multiplier was calibrated so that the average modeled parasite prevalence for years 2013-2015 was close to the MAP estimates for the same period. This adjustment was made due to the site's very low parasite prevalence. Each node's population was set to 1,000 individuals and set birth and mortality

rates to 36.3 per 1,000 people per year. The simulation was run for 50 years to initialize population immunity.

2.2.4.4.Simulating baseline scenarios and adding interventions

In order to portrait the reality of vector control management in the area, ITNs with 50% coverage and ACT with 19% coverage were applied in baseline scenarios, which were used as the main comparator against other scenarios. Baseline scenarios and scenarios with added interventions were simulated for 15 years after the 50-year run-in to build up the immunity of the human population in the simulations (Figure 7). Vector migration was present throughout the modeling, including in the run-in period.

Figure 7 Schematic of the scenario description for EMOD simulations conducted for this study



2.2.5. Evaluating interventions

The transgenic mosquitoes were evaluated as one of the preventive interventions. Commonly used interventions for vector control and gene drive mosquitoes were analyzed as individual and combinations or packages that could be undertaken together. Model input parameters for commonly used interventions are provided in Table 4. It should be, however, noted that the list of common intervention is not exhaustive, and excluding an intervention does not imply its cost ineffectiveness.

Table 4 Model input parameters for commonly used intervention options

Intervention	Parameter	Value
ITN	Adherence	65%
	Probability of success when not fully compliant	0%
ACT (Artemether + Lumefantrine)	Parameters and values used in the model followed (Gerardin, Eckhoff, and Wenger, 2015).	

Interventions evaluated:

- ITNs
- Case management with an artemisinin-based combination treatment of symptomatic cases with Artemisinin-based Combination Therapy (ACTs): Artemether + Lumefantrine
- Gene drive mosquitoes (fertility suppression, driving-Y chromosomes)

Each intervention, ITNs, ACT, and the combination of ITNs and ACT, was analyzed at three standard levels of coverage: 50%, 80%, and 95%. A rationale for the coverage selection was based on the prior work of WHO (President's Malaria Initiative, 2019; Evans *et al.*, 2005).

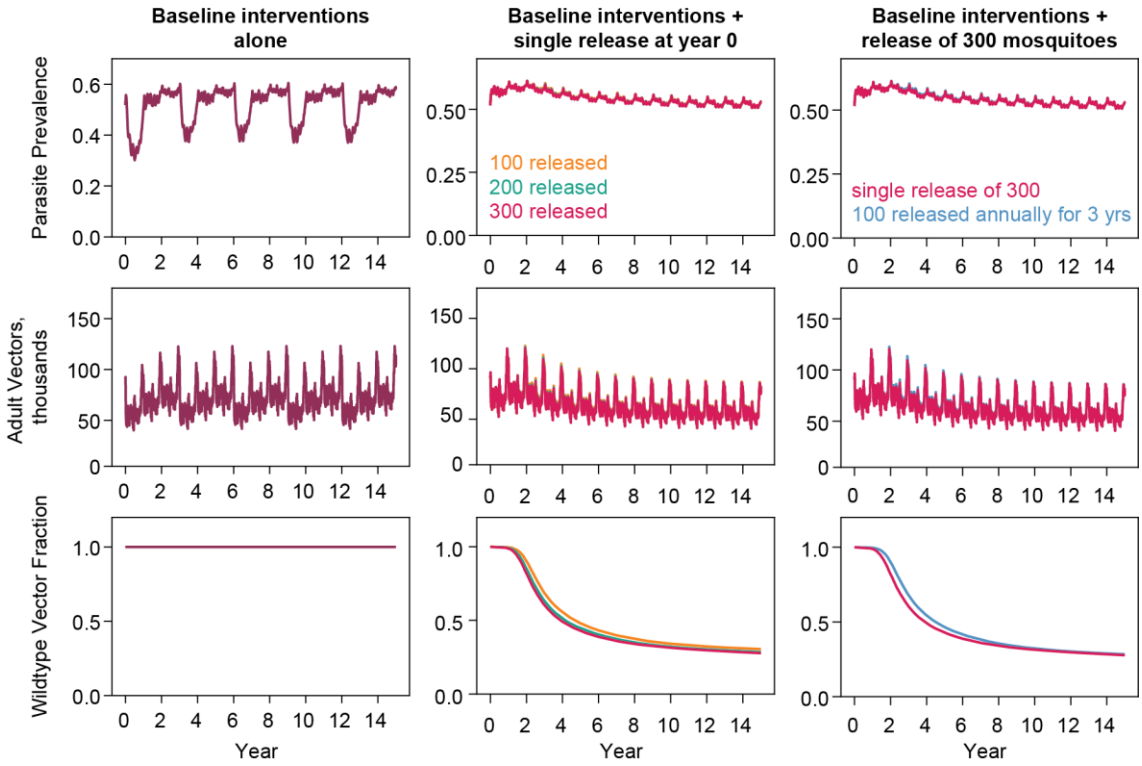
All interventions and combinations were assessed, assuming they were implemented for 15 years, starting in 2015 to match the WHO strategic plan 2016-2030 (WHO, 2015a). Gene drives were then added when the individual intervention or combinations could not achieve elimination within the initial 15-year timeframe.

2.3. Results and discussion

2.3.1. Mosquito release strategy

In most locations, multiple releases of a smaller number of 100 gene drive mosquitoes per release – resulting in the same 300 gene drive mosquitoes in total – have a similar delay time between decreases in wildtype vector fraction and decrease in simulated parasite prevalence, compared to the single release of 300 gene drive mosquitoes. Figure 8 shows the modeling outputs of gene drive mosquito release in the selected location in Equateur province as a sample site. The modeling outputs of all selected locations are included in Appendix 1.1 Modeling outputs of mosquito release planning within a nonspatial framework in selected locations in DRC. 300 gene drive mosquitoes were selected to apply in the spatial simulation framework to increase the elimination possibility and slightly faster wildtype fraction reduction (Figure 8, middle panel).

Figure 8 Modeling outputs of mosquito release planning in Equateur province in the non-spatial simulation framework



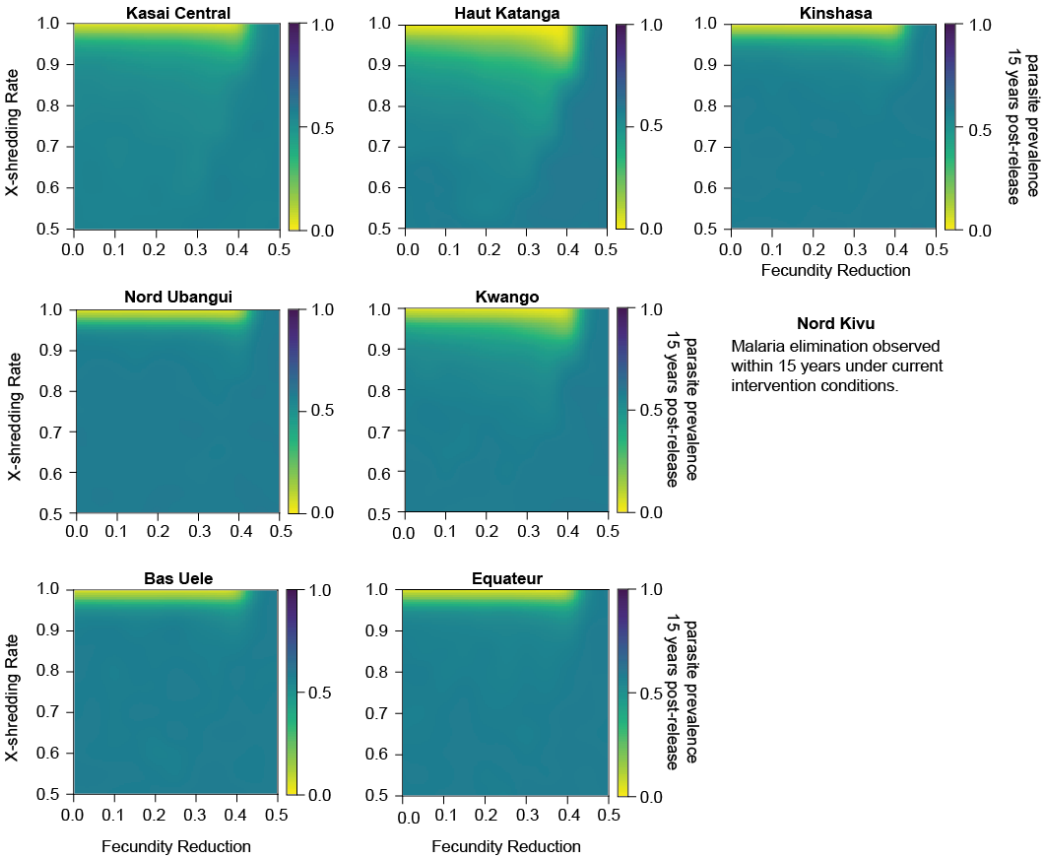
The combination of driving-Y parameters, fecundity reduction, and X-shredding rate, is the main factor for the sustainability of driving-Y mosquitoes in the environment (Alcalay *et al.*, 2019). Once the driving-Y mosquito population sustains in the environment, the possibility of malaria transmission decreases and, in some scenarios, could result in malaria elimination in the area. In Figure 9, the color bar indicates % parasite prevalence in humans from 0 (yellow) to 1 (dark blue). Fecundity reduction negatively affects the egg batch size, while the X-shredding rate reduces the number of driving-Y offspring in each egg batch. If the fecundity reduction is too high, females mated with driving-Y males produce much smaller egg batch size (even though the X-shredding is 100%). Fewer driving-Y males will then be produced in an egg batch compared with wild-type males in a wild-type-mated egg batch. Thus, the driving-Y construct cannot sustain and will disappear.

Meanwhile, the X-shredding rate needs to be high enough to prevent wild-type female offspring from being born in each egg batch because enough wild-type females will sustain the local population and stave off population collapse. For these reasons, to sustain the drives, the upper limit of fecundity reduction = 0.15 and the lower limit of the X-shredding rate = 0.9 were selected. The

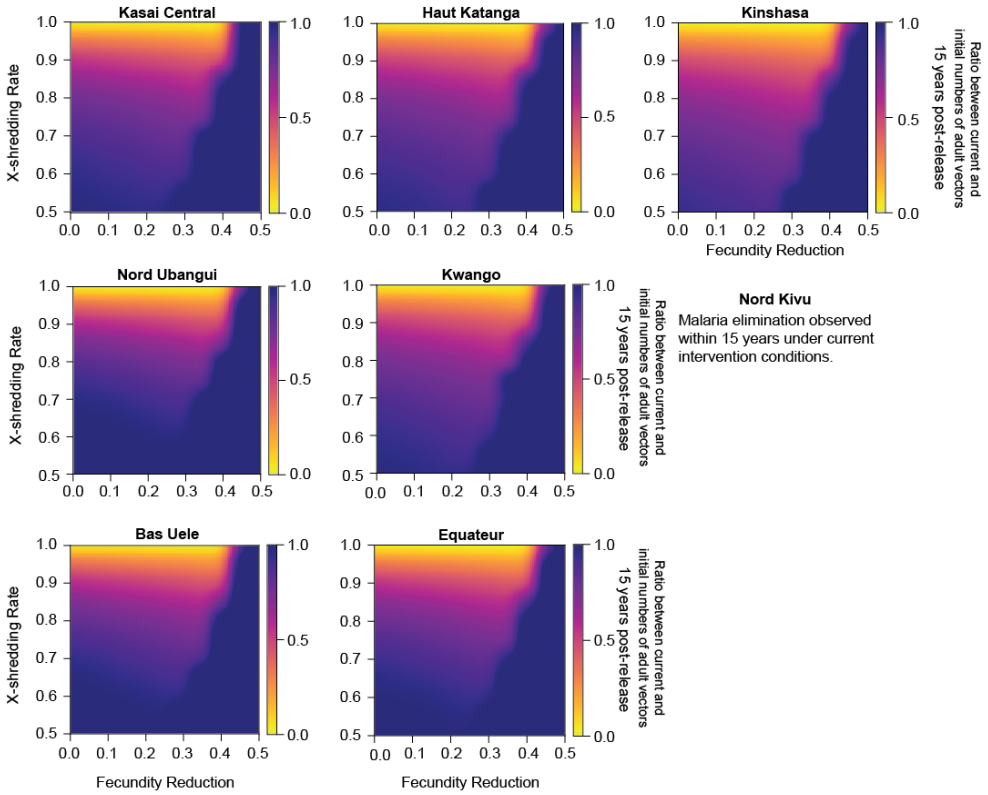
modeling outputs of all selected locations are included in Appendix 1.2 Simulation outputs after a single release of 100, 200, and 300 gene drive mosquitoes within a non-spatial framework in eight study locations at 5, 10, and 15-year post-release.

Figure 9 Simulation outputs of releasing 300 gene drive mosquitoes in non-spatial framework of eight study locations at the end of 15-year timeframe

a) Parasite prevalence, 15 year post-release



b) Ratio between current and initial numbers of adult vector, 15 years post-release



The following gene drive setting to be implemented in the spatial simulation framework was then developed from the non-spatial experiments previously described:

- The single release of 300 gene drive mosquitoes
- Driving-Y parameters of transgenic mosquitoes that were later applied in spatial simulation framework:
    - Fecundity limiting: 0.05, 0.1, 0.15
    - X-shredding rate: 0.9, 0.95, 1.0

2.3.2. Adding interventions to achieve malaria elimination

In the spatial simulation framework, once adding the interventions and combinations, only 95% coverage of the ITNs and ACT combination could result in malaria elimination in most locations (Table 5).

Releasing 300 driving-Y mosquitoes with an X-shredding rate of 1.0 with fecundity reduction 0.05 or 0.10 or 0.15 at the center of each location as a single intervention could eliminate malaria in each selected location within a 15-year timeframe (Table 6). In the scenarios where gene drives were applied, the simulations were carried out to see if the gene drives with more variable X-shredding rates could eliminate malaria in selected locations. The gene drives with less variable X-shredding rates were then tested

when the higher variable X-shredding rates failed to achieve malaria elimination. 300 gene drives of shredding rate 1.0 were also assessed as a single intervention.

The modeling outputs suggest that, between the two gene drive parameters, the X-shredding rate had a more considerable influence on the success of 300 gene drive mosquitoes released as a malaria intervention than the fecundity limiting. Regarding the malaria elimination timeline, the modeling outputs indicated that, in scenarios that achieved disease elimination, malaria elimination could be achieved within 7 years, and in many of these scenarios, disease elimination could already be achieved within 4 years. Details of simulation outputs for all sites can be found in Appendix 2: Simulation outputs – spatial framework.

Table 5 shows the results of adding interventions. Color code green indicates that the % parasite prevalence in the human population in the selected area decreased to 0 (achieve malaria elimination), while color code red indicates that the interventions failed to eliminate malaria in the human population in the selected area.

Table 5 EMOD simulation outcomes when adding commonly used interventions within a 15-year timeframe

Province	**The minimal intervention(s) that could achieve elimination**								
Intervention	**ITN**			**ACT**			**ITN+ACT**		
Coverage	50%	80%	95%	50%	80%	95%	50%	80%	95%
Haut Katanga	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Succeed	Succeed
Kwango	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Succeed
Kasai Central	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Succeed
Nord Ubangui	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Succeed
Bas Uele	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail
Kinshasa	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail
Equateur	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail

Notes for Table 5:

1) The elimination is possible with pre-existing interventions in study location in Nord Kivu province. Thus, the site was excluded from this table.
2) Color codes:

Succeed means the scenario achieved malaria elimination

Fail means the scenario failed to eliminate malaria

Table 6 shows the minimum intervention or combination that could achieve malaria elimination in each target location within 15 years after adding driving-Y mosquitoes into the scenarios. In the scenarios that gene drives were applied, the simulations were carried out to see if the gene drives with highly varied X-shredding rates, which are 0.9, 0.95, and 1.0, could eliminate malaria in study locations. The X-shredding rate indicates in the table is the minimum X-shredding rates that could result in malaria

elimination. For example, 0.9 means gene drives with X-shredding rates 0.9 is the lowest X-shredding rate that could eliminate malaria. Gene drives with a higher X-shredding rate of 0.95, and 1.0 could individually eliminate malaria in the scenario as well.

Table 6 EMOD simulation outcomes when adding 300 gene drive mosquitoes to scenarios that previously failed to achieve malaria elimination within the 15-year timeframe

Province	**The minimal intervention(s) that could achieve malaria elimination**								
Intervention	**ITNs**			**ACT**			**ITNs+ACT**		
Coverage	50%	80%	95%	50%	80%	95%	50%	80%	95%
Haut Katanga	1.0	0.95	0.95	1.0	1.0	0.95	0.95	NA	NA
Kwango	1.0	1.0	0.95	1.0	1.0	1.0	1.0	0.95	NA
Kasai Central	1.0	1.0	0.95	1.0	1.0	1.0	1.0	0.95	NA
Nord Ubangui	1.0	1.0	0.95	1.0	1.0	1.0	1.0	0.95	NA
Bas Uele	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.95	0.9
Kinshasa	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.95	0.9
Equateur	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.95	0.9

Notes for Table 6:

Orange fields: malaria elimination without gene drives Blue fields: malaria elimination with gene drives 1.0: gene drives with X-shredding rate = 1.0 0.95: gene drives with X-shredding rates = 0.95 and 1.0 0.9: gene drives with X-shredding rates = 0.9, 0.95 and 1.0	ITNs: insecticide-treated nets ACT: case management with artemisinin-based combination treatment (Artemether + Lumefantrine)
NA: not applicable, gene drives were not applied in the scenarios because the scenarios could achieve malaria elimination with the indicated intervention or combination without gene drives.	

2.4.Conclusion

This study is the first study that modeled the impact of gene drive mosquitoes on malaria elimination using existing databases. This study used the DRC's data to systematically compare malaria control strategies using interventions that have been implemented in the country, which are ITNs and ACT, and explored the possibility of using gene drive mosquitoes to eliminate malaria in various transmission contexts. Estimates were made for the full range of *P. falciparum* parasite prevalence settings in the DRC. The analysis indicated that gene drives provided potentially highly effective malaria control across the transmission spectrum in the DRC. This modeling work provides insights that could inform efforts to tailor gene drive mosquitoes to best suit the malaria transmission environment of the selected areas, maximizing their effect.

The study found that the potential success of a driving-Y system in malaria elimination highly depended on the X-shredding rate. Between the two driving-Y parameters, the X-shredding rate has narrower values of parameter adjustment than the fecundity reduction. Malaria elimination was achievable without gene drive mosquitoes by

combining high coverage of both ITNs and ACT in Haut Katanga (80% coverage of both). In contrast, elimination was not achievable in Kwango, Nord Ubangui, and Kasai Central at these coverage levels, showing the need for new tools and echoing conclusions of the Lancet Commission on Malaria Eradication (Feachem *et al.*, 2019) and WHO's Strategic Advisory Group on Malaria Eradication (WHO, 2020c). For all remaining selected areas with moderate to high parasite prevalence (18.6%, 32.6%, and 60.7% in Bas Uele, Equateur, and Kinshasa provinces accordingly) a single release of single species 300 driving-Y mosquitoes with an X-shredding rate of 1.0 and fecundity reduction between 0.05 and 0.15 eliminated malaria within 15 years (Table 2). In the simulations, we assumed all *Plasmodium falciparum* parasites exclusively transmitted by *Anopheles gambiae* as this single species dominates transmission in the DRC. However, results are generalizable to other species or multi-species systems if multiple species-specific drives are released.

The results suggest that gene drives could potentially be applied as an intervention to control or eliminate malaria, either alone or in combination with other methods. As demonstrated in this study, tailoring the frequency of release and the number of gene drive mosquitoes to be released could make malaria elimination achievable with much fewer gene drive mosquitoes released compared to other previously developed genetic control methods, e.g., sterile insect technique (Feldmann *et al.*, 2005; Capinera, 2008).

Chapter 3

3. Economic evaluation

3.1. Introduction

The achievement of malaria control is interpreted by WHO as the attainment of the Global Technical Strategy (GTS) for Malaria 2016-2030, as part of the Sustainable Development Goals (SDGs), to end the epidemics of AIDS, tuberculosis (TB), malaria, and (other) neglected tropical diseases (NTDs) by 2030 (Gueye *et al.*, 2016). Appropriate malaria control contributes to other health-related goals of the SDGs, such as SDG 3 of ensuring healthy lives and promoting well-being for populations of all ages (WHO, 2016b). Gene drive is a promising new vector control method that potentially helps the global community achieve these ambitious goals. The future of gene drives itself also depends on the economic aspect of the technology compared with existing or future alternatives (ENSSER, 2019b). The GTS for malaria control highlights the economic value, outcomes, and impacts as part of indicators to measure how well a malaria strategy does in disease control and elimination (WHO, 2015a). This study estimated Disability-Adjusted Life Years (DALYs), DALYs averted, and cost-effectiveness of vector control methods in the DRC.

3.2. Theory of the cost-effectiveness model

An economic evaluation of interventions involves a comparison of costs and benefits of different interventions (Goodman, Coleman and Mills, 2000). Cost-effectiveness analysis (CEA) applied in this study is an evaluation of the costs and health effects of specific interventions. Health outcomes, both premature death, and mortality, of disability, can be measured using DALYs (Goodman, Coleman and Mills, 2000). Population health can be summarized using DALY, which combines information on mortality and non-fatal health outcomes into a single measure. DALYs are the sum of years of life lost due to premature mortality (YLL) in the population and the equivalent healthy years lost due to non-fatal health conditions (YLD) (WHO, 2020e). One DALY can be thought of as a representation of one lost year of “healthy” life (Equation 1).

Equation 1:

$$DALY = YLL + YLD$$

By multiplying the number of deaths with the standard life expectancy at the age at which death occurred, YLL was calculated for each age group. The YLL was then added up to obtain the total YLL for each scenario. The basic formula for YLL excluding other social preferences is the following (Equation 2) for a given cause, age, and sex.

Equation 2:

$$YLL = N \times L$$

where:

N = number of deaths

L = standard life expectancy at the age of death in years

YLD of a particular cause in a particular period was estimated by multiplying the number of incident cases in that period with an average duration of the disease and a disability weight factor, which reflects the severity of the disease on a scale ranging from 0, perfect health, to 1, dead. The formula for YLD is the following, again with no social preferences:

Equation 3:

$$YLD = I \times DW \times L$$

where:

I = number of incident cases

DW = disability weight

L = average duration of the case until remission or death (years)

The effectiveness of each intervention can be estimated by calculating DALYs averted for each intervention, following the method used in the WHO guide to cost-effectiveness analysis (WHO, 2003). The number of DALYs averted by the intervention, a standard measure of the effectiveness of health interventions, provides estimates of the cost-effectiveness of health interventions, which is a critical input to strategic decision making in healthcare (Longfield *et al.*, 2013). To estimate the burden of disease, CEA focuses on health benefits, i.e., the gain in health due to an intervention applying DALYs averted as many health interventions yield benefits beyond the immediate improvement of health status (The World Bank, 2006). The valuations of DW used in CEA calculations are a range of 1, the full health, to 0, death (WHO, 2003). CEA applies cost-effectiveness ratios (CER), which use monetary value to compare a new intervention to a known comparator (other interventions or no intervention at all). The study uses the following formula to calculate cost per DALY averted:

Equation 4:

$$\text{CE Ratio} = \frac{\text{Cost}_{\text{intervention}} - \text{Cost}_{\text{Comparator}}}{\text{DALY Averted}_{\text{intervention}} - \text{DALY Averted}_{\text{comparator}}}$$

An intervention is considered dominated by other interventions or combinations if other interventions have more favorable cost-effectiveness identified by the incremental cost-effectiveness ratio (ICER), additional costs required to avert each additional DALY by moving from the lower-cost to the higher-cost intervention (WHO, 2003).

Methods for economic evaluation

The DALYs and DALYs averted were calculated using cases and deaths from the model simulations and employing a generalized cost-effectiveness analysis to determine the cost-effectiveness of selected malaria control interventions in the context of the WHO 2030 malaria elimination goals. The cost-effectiveness of each scenario was calculated in the year 2000, using international dollars ($int). $int is a hypothetical unit of currency. The unit has the same purchasing power to that of the US$ in the United States at a given point in time (WHO, 2003). Effects were assessed as DALYs averted by a 15-year implementation program. All analyses were restricted to the DRC.

3.2.1. DALY calculations

Definitions and selected interventions:

In this study, CEA was applied to derive ranges for the cost per DALY averted by malaria interventions from disease transmission modeling outcomes. This research focuses on interventions concerning vector control by selecting the mosquitoes capable of transmitting malaria parasites. The term intervention is defined to include preventive vector control techniques like insecticide-treated bed nets (ITNs), which is a core malaria vector control according to WHO (WHO, 2015). However, indoor residual spraying (IRS), another widely practiced vector control practice, was not included in the analysis because it is not part in the DRC's national malaria control strategy and has not been widely used in DRC, reflecting in less than 1% coverage of IRS in the country reported in WHO's World Malaria Report 2018 (WHO, 2018). For a complete view of analysis, case management using artemisinin-based combination therapy (ACT) was included in this analysis.

The uniqueness of the analysis performed in this study includes gene drive mosquitoes as one of the preventive interventions. Commonly used interventions for vector control and gene drive mosquitoes were analyzed as individual and combinations or packages that could be undertaken together, taking into account interactions in costs and effectiveness. It should be, however, noted that the list of interventions is not exhaustive, and excluding an intervention in this analysis here does not imply its cost ineffectiveness in any way.

Interventions evaluated:

- Insecticide-treated bed nets (ITNs)
- Case management with artemisinin-based combination treatment (ACT): Artemether + Lumefantrine

• Gene drive mosquitoes (fertility suppression, driving-Y chromosomes)

Each of the individual ITNs and ACT and the following intervention mixes was analyzed at three standard levels of coverage: 50%, 80%, and 95% of the population (Evans *et al.*, 2005).

All interventions and combinations were assessed, assuming they were implemented for 15 years, starting in 2015 to match WHO's strategic plan (WHO, 2015). Gene drives were then added when the individual intervention or combinations could not achieve elimination (indicated by driving parasite prevalence to 0) within the 15-year timeframe.

In the scenarios where gene drives were applied, the simulations were carried out to see if the gene drives with more variable X-shredding rates could eliminate malaria in selected locations. The gene drives with less variable X-shredding rates were then tested once the more variable rates failed to achieve malaria elimination. Three hundred (300) gene drives of shredding rate 1.0 were also assessed as a single intervention. Applying 300 gene drives of shredding rate 1.0 as a single intervention could eliminate malaria in all selected locations. The minimum intervention or combination that could achieve malaria elimination in selected locations within 15 years is presented in Table 7. It shows the minimum intervention or combination that could achieve malaria elimination in each target location within 15 years after adding driving-Y mosquitoes into the scenarios. In the scenarios where gene drives had been applied, the simulations were carried out to see if the gene drives with more variable X-shredding rates could eliminate malaria in target locations. The gene drives with lower variable rates were then tested when the higher variable rates failed to achieve malaria elimination. Three hundred gene drives of shredding rate 1.0 were also assessed as a single intervention in all selected locations.

Table 7 EMOD simulation outcomes when adding 300 gene drive mosquitoes to scenarios that previously failed to achieve malaria elimination within the 15-year timeframe

Province	**The minimal intervention(s) that could achieve malaria elimination**								
Intervention	**ITNs**			**ACT**			**ITNs+ACT**		
Coverage	50%	80%	95%	50%	80%	95%	50%	80%	95%
Haut Katanga	1.0	0.95	0.95	1.0	1.0	0.95	0.95	NA	NA
Kwango	1.0	1.0	0.95	1.0	1.0	1.0	1.0	0.95	NA
Kasai Central	1.0	1.0	0.95	1.0	1.0	1.0	1.0	0.95	NA
Nord Ubangui	1.0	1.0	0.95	1.0	1.0	1.0	1.0	0.95	NA
Bas Uele	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.95	0.9
Kinshasa	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.95	0.9
Equateur	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.95	0.9

Notes for Table 7:

Orange color: malaria elimination without gene drives Blue color: malaria elimination with gene drives 1.0: gene drives with X-shredding rate = 1.0 0.95,1.0: gene drives with X-shredding rates = 0.95 and 1.0 0.9,0.95,1.0: gene drives with X-shredding rates = 0.9, 0.95 and 1.0	ITNs: insecticide-treated nets ACT: case management with artemisinin-based combination treatment (Artemether + Lumefantrine)
NA: not applicable, gene drives were not applied in the scenarios because the scenarios could achieve malaria elimination with the indicated intervention or combination without gene drives.	

Case calculation: this study estimated the following case elements in DALY calculation.

- The number of populations per age group: these are proportions of the modeled population, not absolute population.
- The number of uncomplicated malaria clinical cases and the number of severe malaria (discounted cases that received ACT)
- The number of deaths by malaria

The number of populations per age group

The population proportion per age group, severe cases proportion by age and clinical cases proportion by age were extracted from the Epidemiological MODeling software (EMOD) model. The following age groups, which were grouped according to the years of age followed WHO national tools (Mathers *et al*., 2001) of both males and females, were then calculated assuming a 50-50 split in the simulations (see Appendix 3.1: Case calculation, Table 17).

Age groups in year unit: 0, 1-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and 85+

The number of malaria cases was calculated as follows (see Appendix 3.1: Case calculation, Table 18).

The number of uncomplicated malaria clinical cases and the number of severe malaria cases (discounted cases that received ACT)

The number of uncomplicated malaria clinical cases and the number of severe malaria cases used in YLD calculation were untreated cases. Therefore, in scenarios in which ACTs were applied, the number of treated uncomplicated clinical cases and treated severe malaria cases were subtracted from the total number of uncomplicated clinical cases and severe cases accordingly (see Appendix 3.1: Case calculation, Table 19-22).

The number of deaths caused by malaria

The number of deaths (D_t) in Equation 5 was calculated applying modeling outputs performed in this study and country-c values obtained from the previous incidence and admission rates study (Camponovo *et al.*, 2017) (see Appendix 3.1: Case calculation, Table 23-24).

Equation 5:

$$D_t = \mu Q_h S_t + (1 - \mu) Q_c S_t$$

where:

- D_t = the overall incidence of malaria deaths
- μ = the deaths-adjusted estimate proportion of severe cases receiving in-patient care = 0.67
- Q_h = the in-patient case fatality for DRC = 0.03
- S_t = the total incidence rate of severe clinical malaria from modeling
- Q_c = the community case fatality rate for DRC = 0.15

DALYs of scenarios of each selected location were calculated following the WHO definition of DALYs (WHO, 2019a). The DALY calculation templates were modified from WHO templates (see Appendix 3.2 Templates used for DALY calculation). The DALYs averted were then calculated by averaging DALYs averted from the scenarios from selected areas where a similar level of intervention(s) had been applied.

The standard life expectancy at the age of death in years and DRC's country lifetable were applied in YLL calculations (WHO, 2016a). YLDs were calculated from the incident cases of uncomplicated and severe cases (not dead) using DW according to severity level. DW used in determining YLDs according to the severity level is presented in Table 8.

Table 8 Severity level, lay description, and disability weigh

Severity level	Lay description	Disability weight (DW) (95% CI)	Cases that DW was applied in DALY calculation for this study
Mild	The patient has a low fever and mild discomfort but no difficulty with daily activities.	0.006 (0.002-0.012)	None
Moderate	The patient has a fever and aches and feels weak, which causes some difficulty with daily activities.	0.051 (0.032-0.074)	Uncomplicated
Severe	The patient has a high fever and pain and feels very weak, which causes great difficulty with daily activities.	0.133 (0.088-0.19)	Severe, not dead

(Adapted from Table 1. Severity level, lay description, and DW (GBD 2017 Causes of Death Collaborators, 2017)*)*

A continuum from asymptomatic malaria to uncomplicated illness through to severe and lethal malaria is acknowledged from a clinical perspective. When *Plasmodium* parasite inoculates in the human body, a variety of clinical effects may follow, within the following sequence (WHO, 2014a): Infection → asymptomatic parasitemia → uncomplicated illness → severe malaria → death.

Determining severe malaria syndrome also depends on clinical manifestations and laboratory indices in prognostic value and frequency. Severe malaria, by definition, is associated with high mortality. Excessive fever, anemia, or parasite counts can all lead to severe disease and mortality (WHO, 2014a). The average duration of a case until remission or deaths for YLD calculation were 7 days (0.02 year) for uncomplicated cases (Kumar *et al.*, 2007; Gunda, Chimbari and Mukaratirwa, 2016) and 30 days (0.08 year) for severe cases (Stevens and Jeffries, 2011).

3.2.2. Cost calculation

Using the number of DALYs averted, we calculated costs using the simulation outputs combined with data from previous WHO's studies (Evans *et al.*, 2005; Morel, Lauer, and Evans, 2005). Estimated costs measure and the value of resources needed to provide the intervention are expressed in international dollars ($int).

Costs per year per one million population of applying ITNs, ACT, and ITNs + ACT at coverage levels of 50%, 80%, and 95% were from the WHO-CHOICE database (Table 9) (Morel, Lauer and Evans, 2005). For scenarios that included gene drive mosquito releases (Table 9), the costs per person were obtained from previous studies. The lower bound cost was estimated from the cost presented in a previous study on *Wolbachia* infected mosquitoes, which estimated that the deployment cost could be US$1 per person in 2016 (O'Neill *et al.*, 2018). The upper bound cost was estimated from the cost presented in a previous study on Oxitec Ltd. Genetically Engineer (GE) mosquito, which indicated that the Oxitec GE mosquito was projected to cost 10 US$ per person in 2016 (Meghani and Boëte, 2018). The study applied costs per person since the focus is to measure effectiveness. The monetary cost data were then standardized to 2000 US$ for the estimates to be comparable to the WHO's estimates of other malaria interventions (Morel, Lauer and Evans, 2005). Applying the US government consumer price index (CPI) (U.S. Bureau of Labor Statistics, 2019) to adjust for inflation and calculate the cumulative inflation rate to year 2000 values, the lower bound and upper bound costs of gene drives applied in this study were 0.72 $int and 7.17 $int per person accordingly. If gene drive mosquitoes were applied in combination with other interventions or combinations, the gene drive costs were added to the costs of such intervention or combinations.

This study selected costs based on field release studies applying genetic control methods in other transmission diseases, e.g., dengue and zika. As the cost data of genetic controls are scarce, the study considered the best available cost evidence, which could help estimate the potential cost of gene drive technology. The rationale to apply the unit cost per person is to be conservative in approaching the cost estimation since other cost data are likely to be favorable of gene drive technology given that gene drive is self-sustaining which would yield a lower cost to deploy as fewer mosquitoes are required in theory (Alphey *et al.*, 2013). The range of costs applied in the study reflects the reality in the field as the genetic control methods are varied in cost components even though the methods were developed to tackle the same disease under a similar genetic control strategy (Alphey, Alphey and Bonsall, 2011). Costs were calculated using the 2000 base year to reduce uncertainty in the value conversion when compared with the WHO's estimates and did not include discount rates.

Table 9 Estimates of costs per year per one million population for interventions applied in the study.

	Interventions	Coverage (%)	Cost per year ($int, millions) per one million population [i.e. cost per capita] using 2000 base year	
Scenarios without gene drives	Insecticide-treated bed nets (ITNs)	50	0.47	
	Insecticide-treated bed nets (ITNs)	80	0.63	
	Insecticide-treated bed nets (ITNs)	95	0.71	
	Case management with artemisinin-based combination therapy (ACT)	50	0.19	
	Case management with artemisinin-based combination therapy (ACT)	80	0.20	
	Case management with artemisinin-based combination therapy (ACT)	95	0.21	
	Combination of ITNs and ACT	50	0.68	
	Combination of ITNs and ACT	80	0.82	
	Combination of ITNs and ACT	95	0.74	
			Lower bound	**Upper bound**
Scenarios with gene drives	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	NA	0.72	7.17
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	80	1.35	7.80
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	95	1.43	7.88
	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	95	0.93	7.38
	ITNs+ACT plus gene drives with X-shredding rates = 0.95 and 1.0	50	1.40	7.85
	ITNs+ACT plus gene drives with X-shredding rates = 0.95 and 1.0	80	1.54	7.99
	ITNs+ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0	95	1.46	7.91

3.2.3. Cost-effectiveness calculation

The interventions were compared by measuring the cost of each intervention as related to the number of DALYs averted (see Appendix 3.3 Template used for cost per DALY averted calculation). Cost-effectiveness was then calculated using for each 5-year interval beginning in 2015 by dividing average yearly costs in $int by average yearly effectiveness in DALYs averted (WHO, 2003). More cost-effective interventions were identified by drawing a graph of an expansion path through incremental cost-effectiveness ratio (ICER), which use monetary value to compare the interventions (WHO, 2003), and selecting interventions that have more favorable cost-effectiveness.

Average cost-effectiveness ($int per DALY averted) of each scenario was calculated by applying Equation 6 using the yearly effectiveness (DALYs averted) derived from the modeling outputs.

Equation 6:

$$\text{Average cost effectiveness (\$int/DALY averted)} = \frac{\text{Average yearly costs (\$int)}}{\text{Average yearly effectiveness (DALYs averted)}}$$

The interventions were compared by measuring the cost of each intervention as related to the number of DALYs averted. The CER and ICER of interventions were also calculated as well as the graphical depiction of cost-effectiveness showing interventions at three assumed coverage levels and gene drives, and expansion paths in all 5-year intervals over the period of 15 years.

3.3.Results and discussion

3.3.1. DALYs

This study projected the impact of intervention scenarios in terms of DALYs. The DALYs per one million population of all age groups were calculated at the end of year 5, 10, and 15 (Table 10). For most scenarios, the commonly used interventions – ITNs, ACT, and their combination – could not eliminate malaria as the DALYs sustain at a similar level throughout the 15-year period. Only when the coverage of ITNs and ACT was increased from the baseline scenario of 50% ITNs, and 19% ACT, to at least 80% ITNs and 80% ACT the DALYs of the selected area in Haut Katanga, which has the lowest transmission intensity in the studied provinces of DRC, reduced to 0. At 95% coverage of the combination of ITNs and ACT, the impact of the interventions increased to reduce DALYs in higher transmission intensity areas further. However, the combination could not help reducing the DALYs in the high transmission intensity area. Once gene drives were released in the areas, gene drives could increase the impact on DALY reduction in all areas as a single intervention as well as in combination with ITNs and/or ACT at lower coverage levels and even at the lowest coverage level studied of 50% of ITNs and ACT combined.

Table 10 Model's estimates of DALYs (thousand) per one million population of all age groups by the site at year 5, year 10, and year 15

			Baseline	Intervention(s)														
				ITNs			ACT			The combination of ITNs and ACT			Scenarios with gene drives					
				Coverage (%)														
Parasite prevalence at the end of the 50-year run-in (%)	Province	Interval	50%ITNs and 19%ACT	50	80	95	50	80	95	50	80	95	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	95%ITNs plus drives 2X ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0
7.27	Haut Katanga	Year 5	332	385	189	52	445	325	208	211	1	1	433	271	140	132	136		
		Year 10	416	426	451	262	394	360	329	405	0	0	0	8	139	1	1		
		Year 15	404	416	430	261	355	321	312	383	0	0	0	9	0	0	0		
20.81	Kwango	Year 5	455	495	394	318	495	411	333	383	85	4	466		230			62	
		Year 10	423	428	430	446	406	363	337	393	354	0	0		6			0	
		Year 15	438	447	466	472	384	345	317	411	393	0	0		0			0	
29.65	Kasai Central	Year 5	458	492	396	319	491	363	332	383	88	6	457		234			69	
		Year 10	414	426	425	434	398	363	336	391	353	0	0		7			0	

			Baseline	Intervention(s)														
				ITNs			ACT			The combination of ITNs and ACT			Scenarios with gene drives					
				Coverage (%)														
Parasite prevalence at the end of the 50-year run-in (%)	Province	Interval	50%ITNs and 19%ACT	50	80	95	50	80	95	50	80	95	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	95%ITNs plus drives 2X ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0
		Year 15	433	443	463	475	384	342	315	408	399	0	0		0			0	
45.03	Nord Ubangui	Year 5	456	492	396	339	491	405	322	385	94	8	411		227			63	
		Year 10	409	423	413	426	401	362	336	385	347	0	0		1			0	
		Year 15	440	445	473	483	383	341	320	414	398	0	0		0			0	
51.64	Bas Uele	Year 5	468	497	416	347	495	414	335	397	124	89	413					87	11
		Year 10	411	425	417	423	404	365	341	388	388	9	0					0	0
		Year 15	438	450	477	487	387	345	321	420	401	22	0					0	0
52.33	Kinshasa	Year 5	449	472	419	380	460	396	329	399	205	63	402					140	41
		Year 10	407	421	414	408	398	356	323	388	348	249	0					0	0

			Baseline	Intervention(s)														
				ITNs			ACT			The combination of ITNs and ACT			Scenarios with gene drives					
				Coverage (%)														
Parasite prevalence at the end of the 50-year run-in (%)	Province	Interval	50%ITNs and 19%ACT	50	80	95	50	80	95	50	80	95	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	95%ITNs plus drives 2X ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0
		Year 15	440	449	466	477	389	343	313	417	391	339	0					0	0
54.33	Equateur	Year 5	458	481	417	370	469	399	333	394	355	39	392					125	23
		Year 10	409	422	409	414	401	362	330	385	355	215	0					0	0
		Year 15	434	443	476	482	387	351	318	413	399	313	1					0	0

Note for Table 10: Scenarios that could achieve malaria elimination within 15 years were highlighted in green.

3.3.2. DALYs averted

The average DALYs averted per year per one million population were calculated for each 5-year interval (Table 11). In the case of commonly used interventions (ITNs, ACT, and the combination of ITNs and ACT), DALYs averted of all selected areas were included regardless of the success of malaria elimination in the area. The average DALYs averted in the case of gene drives were calculated from the scenarios that could reach malaria elimination when gene drives were applied, as shown in Table 7. The average DALYs averted from the study were then compared to the WHO's estimates for the WHO's subregional country groupings for the global assessment of disease burden, Afr E, as the best available comparator since there are no DRC national data available at the time of analysis and DRC is part of the Afr E. The Afr E includes Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, DRC, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, and Zimbabwe (WHO, 2001). WHO has not yet estimated DALYs averted in the case of gene drive mosquitoes. The negative results of average DALYs averted in some scenarios is due to the chosen baseline scenario, which included presently existing in-country malaria control measures, 50% coverage of ITNs, and 19% coverage of ACT. Therefore, the baseline scenario could have a higher impact than scenarios that have lower coverage of ITNs and ACT.

DALYs averted estimated from the model's outputs were compared with those previously estimated by WHO (Table 11). A similar trend can be seen; however, the estimates differ since WHO's estimates are at the regional grouping and comparing scenarios with interventions to null or do-nothing scenario over 10 years. In our study, scenarios with intervention mixes were compared to the baseline scenario, in which 50% ITNs and 19% ACT coverage were applied. Therefore, negative DALYs averted could be observed in some intervention scenarios less effective than baseline (Table 11). Scenarios with combined interventions (ITNs and ACT) had higher DALYs averted than those with single ones, and areas with similar disease transmission patterns had similar levels of DALYs averted once the same interventions were applied. Higher ACT coverage levels resulted in lower parasite prevalence, but a higher number of clinical cases. This can likely be explained by decreased exposure to malaria decreasing the level of immune protection in children, such that given infection, they are more likely to develop clinical symptoms. However, despite an increased number of clinical cases, scenarios with higher ACT coverage averted more DALYs due to fewer severe cases and deaths. Gene drives with specified X-shredding rate range (Table 5) and the same fecundity reduction range of 0.05-0.15 could help convert more DALYs since it could help eliminate malaria in the areas. The average DALYs averted per year are depicted in Figure 10.

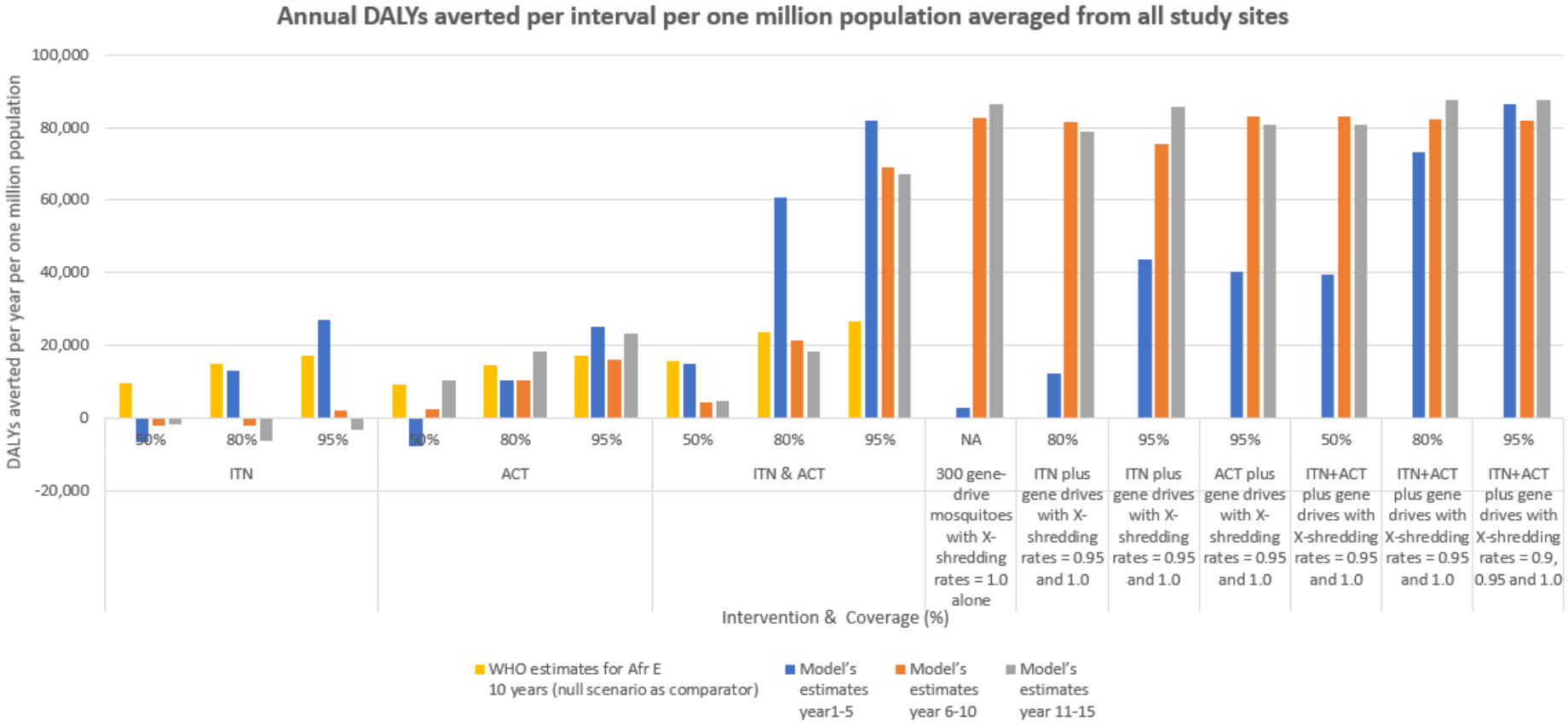
Table 11 Average DALYs averted per year per one million population across all locations estimated from model's outputs in spatial simulation framework. Estimates of each scenario were compared with the baseline scenario, which 50% ITNs and 19% ACT coverage were applied. For scenarios that included gene drives, only the estimates from scenarios that resulted in malaria elimination were included.

			Average DALYs averted per year per one million population				
			WHO's estimates for Afr E (Morel, Lauer and Evans, 2005)	**Model's estimates**			
	Intervention	**Coverage**	**10-year period**	**Average over 15 years**	**The first interval: year 1-5**	**The second interval: year 6-10**	**The last interval: year 11-15**
Scenarios without gene drives	ITNs	50%	9,589	-3,696	-6,818	-2,361	-1,910
		80%	14,925	1,482	12,827	-1,990	-6,390
		95%	17,101	8,727	27,165	2,158	-3,143
	ACT	50%	9,112	1,680	-7,733	2,506	10,266
		80%	14,632	12,962	10,390	10,212	18,283
		95%	17,037	21,437	25,261	15,883	23,169
	ITNs & ACT	50%	15,691	8,004	14,973	4,432	4,606
		80%	23,551	33,477	60,693	21,288	18,451
		95%	26,450	72,706	81,875	69,014	67,230
Scenarios with gene drives	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	NA	NA	57,298	2,888	82,542	86,464
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	80	NA	57,561	12,201	81,580	78,904
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	95	NA	68,222	43,505	75,420	85,741
	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	95	NA	68,006	40,162	83,090	80,766
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	50	NA	67,740	39,311	83,142	80,766
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	80	NA	81,029	73,234	82,414	87,441
	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0	95	NA	85,307	86,609	81,819	87,492

Notes for Table 11:

1) NA: Not applicable
2) Green highlight: the scenario achieved malaria elimination
3) It is possible that the DALY averted results turned out to be negative figures in some modeling scenarios since the combination of ITNs at 50% coverage and ACT at 19% coverage was applied in the baseline scenarios (comparator) to include presently existing in-country malaria control measures. Negative DALYs averted are in red.
4) WHO estimated the DALYs averted using null (do nothing) scenario as a comparator.
5) Afr E is one of WHO's sub-regional country groupings for the global assessment of disease burden that includes Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, DRC, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, and Zimbabwe (WHO, 2001).

Figure 10 Annual DALYs averted per interval per one million population averaged from all study sites



The areas with similar transmission patterns had similar DALYs averted outcomes once the same interventions were applied at the same coverage levels (Table 12). The patterns could be grouped into three transmission patterns: low (Haut Katanga), medium (Kwango, Kasai Central, Nord Ubangui), and high (Bas Uele, Kinshasa, Equateur) transmission based on % parasite prevalence in human populations in the area.

The assessment of the modeling outputs indicated that the lower transmission areas required a lower level of % coverage of intervention(s), meanwhile, a single commonly used intervention at the lower level of % coverage could lead to malaria elimination once combined with gene drives. The DALYs averted suggested the higher effectiveness of interventions at a lower level of % coverage in areas with lower % parasite prevalence. Gene drives as a single intervention and as a combination with ITNs and/or ACT could result in effective malaria elimination.

Table 12 Model's estimates of yearly DALYs averted per one million population of three intervals by site

			Scenarios without gene drives									Scenarios with gene drives						
			Intervention(s)															
			ITNs			ACT			The combination of ITNs and ACT			300 gene drive mosquitoes with X-shredding rates = 1.0 alone	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0
			Coverage (%)															
Parasite prevalence at the end of the 50-year run-in (%)	**Coverage (%)**	**Interval**	**50**	**80**	**95**	**50**	**80**	**95**	**50**	**80**	**95**	**NA**	**80**	**95**	**95**	**50**	**80**	**95**
7.27	**Haut Katanga**	**Year 1-5**	-10,571	28,710	56,001	-22,558	1,503	24,859	24,322	66,197	66,276	-20,133	12,201	38,455	40,162	39,311		
		Year 6-10	-1,994	-6,877	30,839	4,500	11,243	17,466	2,296	83,262	83,262	83,262	81,580	55,510	83,090	83,142		

			Scenarios without gene drives									Scenarios with gene drives						
			Intervention(s)															
			ITNs			ACT			The combination of ITNs and ACT			300 gene drive mosquitoes with X-shredding rates = 1.0 alone	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0
			Coverage (%)															
Parasite prevalence at the end of the 50-year run-in (%)	**Coverage (%)**	**Interval**	**50**	**80**	**95**	**50**	**80**	**95**	**50**	**80**	**95**	**NA**	**80**	**95**	**95**	**50**	**80**	**95**
		Year 11-15	-2,395	-5,184	28,542	9,807	16,551	18,369	4,083	80,766	80,766	80,766	78,904	80,766	80,766	80,766		
20.81	**Kwango**	**Year 1-5**	-7,876	12,248	27,482	-8,003	8,881	24,495	14,393	74,131	90,211	-2,138		45,068			78,748	
		Year 6-10	-1,129	-1,411	-4,576	3,459	11,889	17,165	5,941	13,758	84,566	84,566		83,280			84,563	
		Year 11-15	-1,833	-5,477	-6,727	10,765	18,718	24,169	5,512	8,990	87,637	87,637		87,637			87,637	
29.65	**Kasai Central**	**Year 1-5**	-6,874	12,271	27,705	-6,718	18,980	25,126	14,845	73,859	90,333	120		44,737			77,788	
		Year 6-10	-2,566	-2,353	-4,129	3,058	10,173	15,473	4,566	12,178	82,711	82,711		81,271			82,708	
		Year 11-15	-1,961	-5,946	-8,382	9,928	18,204	23,714	4,980	6,903	86,653	86,653		86,653			86,653	
45.03		**Year**	-7,311	11,906	23,404	-6,994	10,209	26,710	14,130	72,363	89,496	8,822		45,758			78,431	

			Scenarios without gene drives									Scenarios with gene drives						
			Intervention(s)															
			ITNs			ACT			The combination of ITNs and ACT			300 gene drive mosquitoes with X-shredding rates = 1.0 alone	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0
			Coverage (%)															
Parasite prevalence at the end of the 50-year run-in (%)	**Coverage (%)**	**Interval**	**50**	**80**	**95**	**50**	**80**	**95**	**50**	**80**	**95**	**NA**	**80**	**95**	**95**	**50**	**80**	**95**
	Nord Ubangui	**1-5**																
		Year 6-10	-2,747	-713	-3,401	1,517	9,374	14,572	4,853	12,337	81,790	81,790		81,620			81,790	
		Year 11-15	-1,134	-6,673	-8,680	11,362	19,715	23,829	5,058	8,284	87,910	87,910		87,910			87,910	
51.64	**Bas Uele**	**Year 0-5**	-5,928	10,220	24,115	-5,473	10,685	26,553	14,091	68,752	75,745	10,990					76,112	91,214
		Year 6-10	-2,635	-1,056	-2,286	1,596	9,264	14,071	4,781	4,781	80,476	82,298					82,297	82,298
		Year 11-15	-2,318	-7,784	-9,764	10,333	18,732	23,488	3,739	7,405	83,313	87,688					87,688	87,688
52.33	**Kinshasa**	**Year 1-5**	-4,583	6,148	13,837	-2,106	10,710	24,011	10,136	48,871	77,303	9,409					61,793	81,557
		Year 6-10	-2,776	-1,548	-330	1,850	10,128	16,658	3,824	11,824	31,505	81,350					81,316	81,343

			Scenarios without gene drives									Scenarios with gene drives						
			Intervention(s)															
			ITNs			ACT			The combination of ITNs and ACT			300 gene drive mosquitoes with X-shredding rates = 1.0 alone	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0
			Coverage (%)															
Parasite prevalence at the end of the 50-year run-in (%)	**Coverage (%)**	**Interval**	**50**	**80**	**95**	**50**	**80**	**95**	**50**	**80**	**95**	**NA**	**80**	**95**	**95**	**50**	**80**	**95**
		Year 11-15	-1,834	-5,259	-7,282	10,308	19,496	25,379	4,713	9,823	20,167	88,022					88,022	88,022
54.33	**Equateur**	**Year 1-5**	-4,579	8,284	17,609	-2,274	11,766	25,070	12,891	20,678	83,764	13,143					66,531	87,055
		Year 6-10	-2,678	26	-1,011	1,562	9,412	15,775	4,763	10,876	38,789	81,816					81,808	81,816
		Year 11-15	-1,892	-8,409	-9,706	9,360	16,562	23,234	4,160	6,988	24,163	86,573					86,736	86,767

Notes for Table 12: 1) It is possible that the DALY averted results turned out to be negative figures in some scenarios (marked in red) since the combination of ITN at 50% coverage and ACT at 19% coverage was applied in the baseline scenarios (comparator) to include presently existing in-country malaria control measures.
2) Scenarios that could achieve malaria elimination were highlighted in green.

3.3.3. Cost

Population-level cost-effectiveness estimates for individual and combined interventions as costs per DALY averted in comparison with the baseline scenario indicated that DALY averted is the main factor determining cost-effectiveness (Table 12). In scenarios that include gene drives which resulted in malaria elimination, the costs per DALYs averted are lower in the areas where the transmission intensity is initially higher than other selected locations. The costs decrease over time as DALYs continue to be averted throughout the study period in comparison with the baseline comparator (Table 13). On the contrary, the scenarios with gene drives yielded higher costs during the first interval (year 1-5) then noticeably decreased afterward. In the context of the DRC's economy, almost 80% of the population is living in extreme poverty on less than $1.90 a day (The World Bank, 2019) and the total expenditure of health per capita is only 32 $int (WHO, 2020d), the cost figures in Table 13 emphasize the need for complementary strategies with high effectiveness. From the analysis, gene drives could help complement the existing malaria control strategies, especially when its own cost is at the lower bound. If we had calculated the financial cost of applying gene drive assuming the cost per gene drive pupae (ranging from 0.9 to 1.2 US$ per 1,000 insects) (Singh, K R P; Patterson, R S; Labrecque, G C; Razdan, 1975; Asman, McDonald and Prout, 1981; Alfaro-Murillo *et al.*, 2016; Khamis *et al.*, 2018) being similar to transgenic mosquitoes previously developed by other genetic control techniques, e.g., sterile insect technique (SIT), genetically engineered mosquitoes (Oxitec®), *Wolbachia* infected mosquitoes, the financial cost of gene drives as a malaria intervention would have been negligible since we only released once 300 gene drive mosquitoes per scenario.

Table 13 Average cost per DALY averted of interventions and combinations applied estimated from model's outputs.

				Scenarios without gene drives									Scenarios with gene drives							
				Intervention(s)																
				ITNs			ACT			The combination of ITNs and ACT			Bound price	300 gene drive mosqui-toes with X-shred-ding rates = 1.0 alone	ITNs plus gene drives with X-shred-ding rates = 0.95 and 1.0	ITNs plus gene drives with X-shred-ding rates = 0.95 and 1.0	ACT plus gene drives with X-shred-ding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shred-ding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shred-ding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shred-ding rates = 0.9, 0.95 and 1.0
				Coverage (%)																
	Parasite prevalence at the end of the 50-year run-in (%)	Coverage (%)	Inter-val	50	80	95	50	80	95	50	80	95	NA	NA	80	95	95	50	80	95
	WHO's estimates for Afr E (4)			49	42	41	21	14	12	43	35	28	NA	NA	NA	NA	NA	NA	NA	NA
Estimates from model' s outputs	7.27	Haut Ka-tanga	Year 1-5	-45	22	13	-9	143	9	28	12	11	Lower bound	-36	111	37	23	36	NA	NA
													Upper bound	-355	641	205	184	200	NA	NA
			Year 6-10	-238	-91	23	43	18	12	303	10	9	Lower bound	9	17	26	11	17	NA	NA
													Upper bound	96	142	89	95	96	NA	NA
			Year 11-15	-207	-121	25	20	12	11	169	10	9	Lower bound	9	17	18	12	17	NA	NA
													Upper bound	99	98	91	97	99	NA	NA

				Scenarios without gene drives									Scenarios with gene drives							
				Intervention(s)																
				ITNs			ACT			The combination of ITNs and ACT			Bound price	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0
				Coverage (%)																
	Parasite prevalence at the end of the 50-year run-in (%)	Coverage (%)	Inter-val	50	80	95	50	80	95	50	80	95	NA	NA	80	95	95	50	80	95
	20.81	Kwango	Year 1-5	-60	51	26	-24	23	9	47	11	8	Lower bound	-340	NA	32	NA	NA	20	NA
													Upper bound	-3,382	NA	175	NA	NA	101	NA
			Year 6-10	-427	-494	-156	55	17	12	112	59	9	Lower bound	9	NA	17	NA	NA	18	NA
													Upper bound	85	NA	95	NA	NA	94	NA
			Year 11-15	-275	-117	-106	18	11	9	120	89	8	Lower bound	8	NA	16	NA	NA	18	NA
													Upper bound	82	NA	90	NA	NA	91	NA
	29.65	Kasai Central	Year 1-5	-69	51	26	-29	11	8	46	11	8	Lower bound	11,661	NA	32	NA	NA	20	NA
													Upper bound	116,124	NA	176	NA	NA	103	NA

				Scenarios without gene drives									Scenarios with gene drives							
				Intervention(s)																
				ITNs			ACT			The combination of ITNs and ACT			Bound price	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0
				Coverage (%)																
	Parasite prevalence at the end of the 50-year run-in (%)	Coverage (%)	Inter-val	50	80	95	50	80	95	50	80	95	NA	NA	80	95	95	50	80	95
			Year 6-10	-175	-245	-161	64	20	14	157	68	9	Lower bound	9	NA	18	NA	NA	19	NA
													Upper bound	87	NA	97	NA	NA	97	NA
			Year 11-15	-220	-102	-81	20	11	9	142	121	9	Lower bound	8	NA	16	NA	NA	18	NA
													Upper bound	83	NA	91	NA	NA	92	NA
	45.03	Nord Ubangui	Year 1-5	-64	53	30	-27	20	8	48	11	8	Lower bound	82	NA	31	NA	NA	20	NA
													Upper bound	816	NA	172	NA	NA	102	NA
			Year 6-10	-168	-925	-206	125	22	15	138	66	9	Lower bound	9	NA	17	NA	NA	19	NA
													Upper bound	88	NA	96	NA	NA	98	NA

				Scenarios without gene drives									Scenarios with gene drives							
				Intervention(s)																
				ITNs			ACT			The combination of ITNs and ACT			Bound price	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0
				Coverage (%)																
	Parasite prevalence at the end of the 50-year run-in (%)	Coverage (%)	Inter-val	50	80	95	50	80	95	50	80	95	NA	NA	80	95	95	50	80	95
			Year 11-15	-419	-96	-82	17	10	9	129	98	8	Lower bound	8	NA	16	NA	NA	17	NA
													Upper bound	82	NA	89	NA	NA	91	NA
	51.64	Bas Uele	Year 0-5	-81	61	29	-36	19	8	48	12	10	Lower bound	65	NA	NA	NA	NA	20	16
													Upper bound	645	NA	NA	NA	NA	105	87
			Year 6-10	-181	-606	-322	117	22	15	140	170	9	Lower bound	9	NA	NA	NA	NA	19	18
													Upper bound	87	NA	NA	NA	NA	97	96
			Year 11-15	-204	-81	-73	19	11	9	180	111	9	Lower bound	8	NA	NA	NA	NA	18	17
													Upper bound	82	NA	NA	NA	NA	91	90

				Scenarios without gene drives									Scenarios with gene drives							
				Intervention(s)																
				ITNs			ACT			The combination of ITNs and ACT			Bound price	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0
				Coverage (%)																
	Parasite prevalence at the end of the 50-year run-in (%)	Coverage (%)	Inter-val	50	80	95	50	80	95	50	80	95	NA	NA	80	95	95	50	80	95
	52.33	Kinshasa	Year 1-5	-103	104	51	-89	19	9	67	17	10	Lower bound	77	NA	NA	NA	NA	25	18
													Upper bound	765	NA	NA	NA	NA	129	97
			Year 6-10	-170	-366	-1,602	110	20	13	181	69	23	Lower bound	9	NA	NA	NA	NA	19	18
													Upper bound	88	NA	NA	NA	NA	98	97
			Year 11-15	-271	-118	-98	18	10	8	143	82	36	Lower bound	8	NA	NA	NA	NA	17	17
													Upper bound	81	NA	NA	NA	NA	91	90
	54.33	Equateur	Year 1-5	-104	76	40	-86	17	8	53	40	9	Lower bound	55	NA	NA	NA	NA	23	17
													Upper bound	547	NA	NA	NA	NA	120	91

				Scenarios without gene drives									Scenarios with gene drives							
				Intervention(s)																
				ITNs			ACT			The combination of ITNs and ACT			Bound price	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0
				Coverage (%)																
	Parasite prevalence at the end of the 50-year run-in (%)	Coverage (%)	Inter-val	50	80	95	50	80	95	50	80	95	NA	NA	80	95	95	50	80	95
			Year 6-10	-180	5,457	-706	115	21	13	143	75	19	Lower bound	9	NA	NA	NA	NA	19	18
													Upper bound	88	NA	NA	NA	NA	98	97
			Year 11-15	-252	-75	-74	20	12	9	164	115	31	Lower bound	8	NA	NA	NA	NA	18	17
													Upper bound	83	NA	NA	NA	NA	92	91

Notes for Table 13:
1) NA: Not applicable
2) The scenarios that could achieve malaria elimination when adding gene drives were highlighted in green.
3) $int: International Dollars
4) upper bound: upper bound price, lower bound: lower bound price
5) Negative costs per DALY averted (marked in red) reflect the negative DALY averted, not negative cost.

3.4.4. Cost-effectiveness

The expansion paths of all sites show the order in which interventions would be selected at different levels of resources available based on ICER, which indicates additional costs required to avert each additional DALY by moving from the lower-cost to the higher-cost intervention (WHO, 2003) and calculated using average yearly costs and yearly effectiveness (Figure 11). Notable differences exist between the first and the following two intervals. For the first interval (Table 14 and Figure 11), ACT case management at 95% coverage is the most cost-effective intervention overall and would be the first choice where resources are limited. The second intervention on the path represented a similar level of artemisinin-based combination treatment in combination with ITNs at 95% coverage level, followed by a lower coverage level of ACT and ITNs combined (Table 14). In the following years (second and third intervals Table 14), the unit cost of gene drive mosquitoes affects the priority of the strategies on the expansion path (Table 14 and Figure 11). Using the lower bound price for the cost of gene-edited mosquitoes, gene drive as a single intervention is the most cost-effective intervention overall as gene drive mosquitoes with X-shredding = 1.0 could eliminate malaria in all contexts and would be the first choice where resources are limited. The second interventions on the paths are the combination of gene drives and ACT, and gene drives, ITNs, and ACT at 95% coverage in the second and third intervals accordingly. Details on site-specific cost-effectiveness are summarized in Appendix 3.4 Expansion paths by study site.

The average yearly cost per one million population in the scenarios with and without gene drives and the parasite prevalence reduction of all 5-year intervals over the period of 15 years (Table 15) suggest that the cost of gene drives affects the marginal costs of the malaria control methods with gene drives that potentially have a high impact on disease elimination in the study locations. Average yearly upper bound costs, 7.17-7.99 $int, per one million population in the scenarios that gene drives were applied are still well comparable to 7.91 $int per 20-minute visit health center cost, excluding costs of drugs and diagnostics, for the DRC population (WHO, 2020a). Therefore, the benefits of increased labor productivity of more cost-effective strategies are foreseeable as the country’s per capita gross domestic product (GDP) growth has been driven by productivity and rising labor force (The World Bank, 2017).

Table 14 Incremental cost-effectiveness ratio of all 5-year intervals calculated from average $int and average DALYs averted of scenarios that same intervention(s) or combinations were applied

					ICER ($int per DALY averted)					
					The first interval: year 1-5		The second interval: year 6-10		The last interval: year 11-15	
	Intervention	Cover-age	Malaria elimination	Label	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound
Scenarios without gene drives	ITNs	50%	No	A	dominated	dominated	negative	dominated	negative	dominated
		80%	No	B	dominated	dominated	negative	dominated	negative	dominated
		95%	No	C	6.52	6.52	negative	dominated	negative	dominated
	ACT	50%	No	D	negative	negative	negative	negative	negative	negative
		80%	No	E	negative	negative	negative	negative	negative	negative
		95%	No	F	**First point**	**First point**	negative	**First point**	negative	**First point**
	ITNs & ACT	50%	No	G	dominated	dominated	negative	dominated	negative	dominated
		80%	No	H	0.43	0.43	dominated	2.82	dominated	dominated
		95%	No	I	0.23	0.23	dominated	0.25	dominated	0.30
Scenarios with gene drives	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	NA	Yes	J	dominated	dominated	**First point**	2.62	**First point**	2.76
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	K	dominated	dominated	dominated	2.90	dominated	3.42
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	L	1.67	10.56	dominated	3.23	dominated	3.07
	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	M	1.22	12.10	9.74	2.68	dominated	3.12
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	50	Yes	N	2.12	13.66	28.36	2.85	dominated	3.33
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	O	0.69	4.06	dominated	2.93	20.99	3.03
	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0	95	Yes	P	0.51	3.14	dominated	2.92	17.93	2.99

Keys for Table 14:

- ICER: Incremental cost-effectiveness ratio
- Negative: the incremental cost and the incremental effect are negative
- Dominated: the incremental cost is positive, and the incremental effect is negative
- Vector control strategies that could reach malaria elimination were highlighted in green. The first, second, third points of each expansion path were highlighted in red, orange, and yellow.

Figure 11 Cost-effectiveness plane showing 16 analyzed interventions (10 individual and combination interventions at three assumed coverage levels) and expansion path for year 1-5, year 6-10, and year 11-15

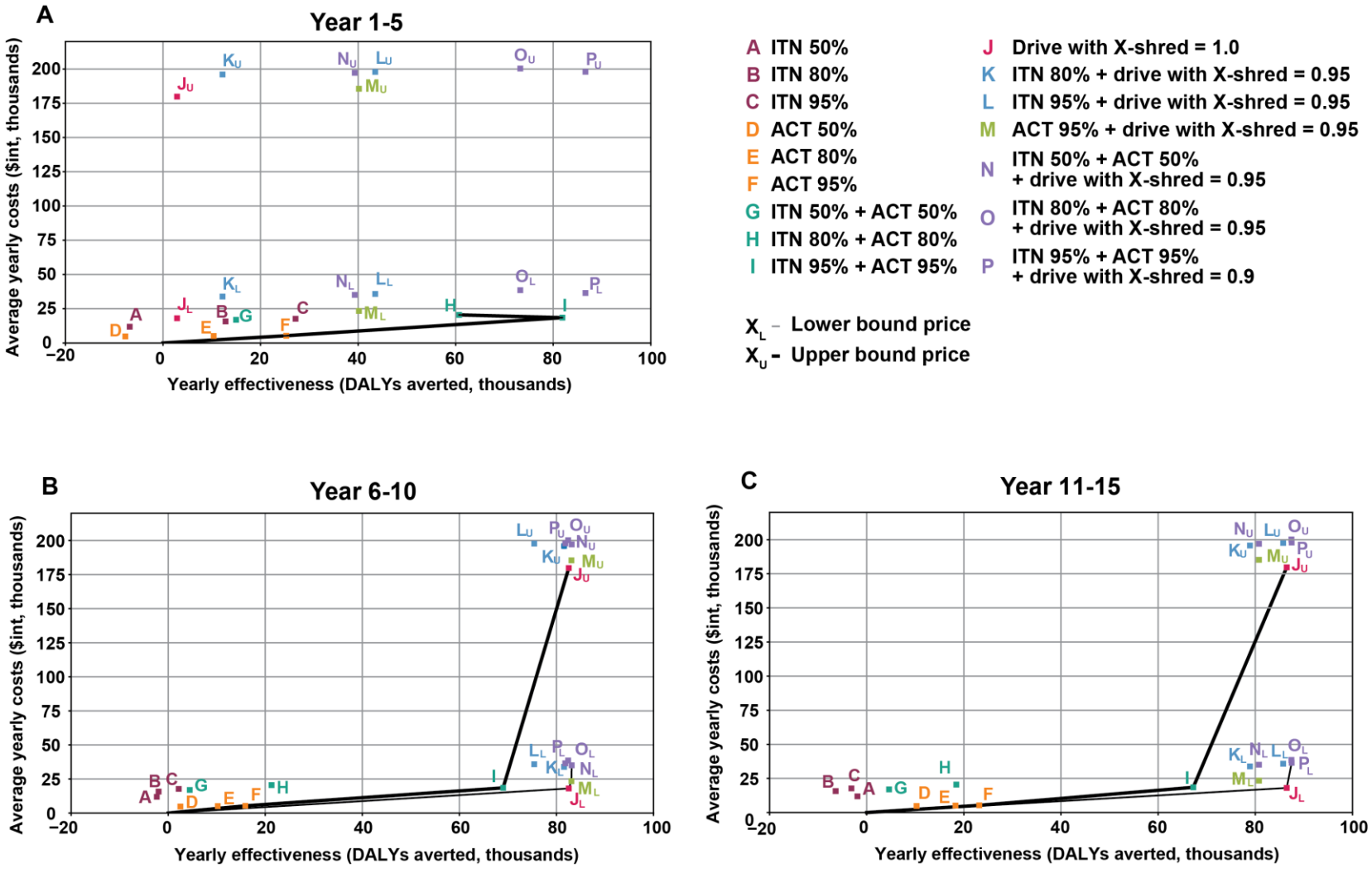


Table 15 Average yearly cost per one million population using 2000 base year and mean parasite prevalence reduction from baseline of interventions and combinations applied in the study

	Intervention	Coverage	WHO's	Estimates from model's outputs							
			Average yearly costs per one million population ($int, million)		Mean parasite prevalence reduction from baseline over 15 years (%)	The first interval: year 1-5		The second interval: year 6-10		The last interval: year 11-15		Transmission intensity
						Yearly cost ($int, million) per million population	Mean parasite prevalence reduction from baseline (%)	Yearly cost ($int, million) per million population	Mean parasite prevalence reduction from baseline (%)	Yearly cost ($int, million) per million population	Mean parasite prevalence reduction from baseline (%)	
Scenarios without gene drives	ITNs	50%	0.47	0.48	-0.03	0.47	-0.05	0.48	-0.03	0.50	-0.03	Low
				0.47	-0.03	0.47	-0.03	0.46	-0.02	0.47	-0.02	Medium
				0.48	-0.02	0.48	-0.03	0.48	-0.02	0.48	-0.02	High
		80%	0.63	0.63	0.08	0.63	0.13	0.62	0.06	0.63	0.05	Low
				0.63	0.06	0.63	0.10	0.64	0.06	0.63	0.03	Medium
				0.57	0.05	0.63	0.08	0.45	0.05	0.63	0.02	High
		95%	0.71	0.71	0.23	0.71	0.23	0.71	0.23	0.71	0.23	Low
				0.70	0.11	0.71	0.15	0.69	0.10	0.7	0.07	Medium
				0.69	0.10	0.71	0.15	0.66	0.09	0.71	0.05	High
	ACT	50%	0.19	0.19	-0.08	0.19	-0.14	0.19	-0.06	0.19	-0.04	Low
				0.19	-0.04	0.19	-0.06	0.19	-0.04	0.19	-0.01	Medium
				0.19	-0.02	0.19	-0.04	0.19	-0.03	0.19	0.00	High
		80%	0.2	0.21	0.01	0.22	-0.02	0.21	0.03	0.21	0.04	Low
				0.20	0.02	0.20	0.01	0.20	0.02	0.20	0.04	Medium
				0.20	0.03	0.20	0.03	0.20	0.03	0.20	0.05	High
		95%	0.21	0.21	0.11	0.21	0.08	0.21	0.13	0.21	0.12	Low
				0.21	0.10	0.21	0.12	0.21	0.09	0.21	0.10	Medium
				0.21	0.09	0.21	0.09	0.21	0.09	0.21	0.09	High

	Intervention	Coverage	WHO's	Estimates from model's outputs										
			Average yearly costs per one million population ($int, million)		Mean parasite prevalence reduction from baseline over 15 years (%)	The first interval: year 1-5		The second interval: year 6-10		The last interval: year 11-15			
						Yearly cost ($int, million) per million population	Mean parasite prevalence reduction from baseline (%)	Yearly cost ($int, million) per million population	Mean parasite prevalence reduction from baseline (%)	Yearly cost ($int, million) per million population	Mean parasite prevalence reduction from baseline (%)	Transmission intensity
	ITNs & ACT	50%	0.68	0.69	0.07	0.68	0.10	0.70	0.07	0.69	0.06	Low
				0.68	0.06	0.68	0.08	0.68	0.05	0.67	0.04	Medium
				0.68	0.05	0.68	0.06	0.68	0.05	0.68	0.04	High
		80%	0.82	0.82	0.36	0.82	0.26	0.82	0.40	0.82	0.42	Low
				0.82	0.28	0.82	0.36	0.82	0.25	0.81	0.23	Medium
				0.82	0.23	0.82	0.27	0.82	0.22	0.81	0.18	High
		95%	0.74	0.74	0.36	0.74	0.27	0.74	0.40	0.74	0.42	Low
				0.74	0.48	0.74	0.43	0.74	0.49	0.74	0.51	Medium
				0.74	0.42	0.74	0.43	0.74	0.41	0.74	0.40	High
Cost calculation range				**Lower bound**	**Upper bound**		**Lower bound**	**Upper bound**		**Lower bound**	**Upper bound**		**Lower bound**	**Upper bound**		
Scenarios with gene drives	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	NA	NA	0.72	7.17	0.23	0.72	7.15	-0.13	0.72	7.18	0.40	0.72	7.18	0.42	Low
				0.80	7.94	0.36	0.95	9.47	0.08	0.72	7.17	0.48	0.72	7.17	0.51	Medium
				0.72	7.17	0.36	0.72	7.16	0.04	0.72	7.17	0.51	0.72	7.17	0.53	High
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	80	NA	1.35	7.81	0.28	1.35	7.83	0.04	1.35	7.81	0.39	1.35	7.8	0.41	Low
				NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Medium
				NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	High

Intervention	Coverage	WHO's	Estimates from model's outputs												
		Average yearly costs per one million population ($int, million)			Mean parasite prevalence reduction from baseline over 15 years (%)	The first interval: year 1-5			The second interval: year 6-10			The last interval: year 11-15			Transmission intensity
						Yearly cost ($int, million) per million population		Mean parasite prevalence reduction from baseline (%)	Yearly cost ($int, million) per million population		Mean parasite prevalence reduction from baseline (%)	Yearly cost ($int, million) per million population		Mean parasite prevalence reduction from baseline (%)	
ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	95	NA	1.43	7.89	0.33	1.43	7.89	0.16	1.43	7.89	0.40	1.43	7.88	0.42	Low
			1.43	7.88	0.42	1.43	7.88	0.26	1.43	7.88	0.48	1.43	7.88	0.51	Medium
			NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	High
ACT plus gene drives with X-shredding rates = 0.95 and 1.0	95	NA	0.93	7.39	0.32	0.93	7.39	0.14	0.93	7.39	0.40	0.93	7.39	0.42	Low
			NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Medium
			NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	High
ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	50	NA	1.40	7.86	0.32	1.4	7.86	0.16	1.4	7.86	0.40	1.4	7.85	0.42	Low
			NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Medium
			NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	High
ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	80	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Low
			1.54	7.99	0.46	1.54	7.99	0.38	1.54	7.99	0.49	1.54	7.99	0.51	Medium
			1.54	7.99	0.47	1.54	7.99	0.36	1.54	7.99	0.51	1.54	7.98	0.53	High
ITNs & ACT plus	95	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Low
			NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Medium

Intervention	Coverage	WHO's	Estimates from model's outputs												
		Average yearly costs per one million population ($int, million)			Mean parasite prevalence reduction from baseline over 15 years (%)	The first interval: year 1-5			The second interval: year 6-10			The last interval: year 11-15			
						Yearly cost ($int, million) per million population		Mean parasite prevalence reduction from baseline (%)	Yearly cost ($int, million) per million population		Mean parasite prevalence reduction from baseline (%)	Yearly cost ($int, million) per million population		Mean parasite prevalence reduction from baseline (%)	Transmission intensity
gene drives with X-shredding rates = 0.9, 0.95 and 1.0			1.46	7.91	0.49	1.46	7.9	0.44	1.46	7.91	0.51	1.46	7.93	0.53	High

Notes for Table 15: 1) It is possible that the DALY averted results turned out to be negative figures in some scenarios since the combination of ITNs at 50% coverage and ACT at 19% coverage was applied in the baseline scenarios (comparator) to reflect reality. For example, a 50% ITNs scenario means only ITNs were applied as a single intervention in the scenario; thus, the lower efficacy of 50% ITNs alone could be observed once compared to the comparator, which the combination of 50% ITNs and 19% ACT was applied.

2) Scenarios that could achieve malaria elimination are in green.

3) Transmission intensity in study areas:

Low: Haut Katanga

Medium: Kwango, Kasai Central, Nord Ubangui

High: Bas Uele, Kinshasa, Equateur

3.5. Conclusion

The study results suggest that gene drives could potentially be applied as an intervention to control or eliminate malaria, either alone or in combination with other methods. As demonstrated in this study, tailoring the frequency of release and the number of gene drive mosquitoes to be released could make malaria elimination achievable. Gene drives would result in better cost-effectiveness in comparison with the other tested vector control strategy, i.e., the use of ITNs, because gene drives could result in malaria elimination even in high transmission areas where the elimination effect could not be achieved by applying ITNs alone. The results of the tested non-gene drive scenarios show that both vector control (in this study ITNs) and case management (ACT) are necessary but, in most cases, are insufficient to eliminate malaria, confirming results from previous modeling research (Nikolov *et al.*, 2016). Our economic evaluation of malaria interventions differs from previous studies (Gunda and Chimbari, 2017) since we assessed the cost-effectiveness from the outputs once interventions and combinations were applied simultaneously, rather than assuming costs and effects sum when interventions are used concurrently. Other studies that assume costs and effects of concurrent interventions are purely additive might not provide decision-makers the necessary information needed for malaria management and can be misleading (Morel, Lauer and Evans, 2005). Furthermore, compared to previously developed genetic control methods, gene drives require a significantly lower number of gene drive mosquitoes released compared to an overwhelming number of gene-edited mosquitoes developed for other genetic control methods and self-limiting mosquitoes. For example, to control malaria in an area of similar size, millions of (male) mosquitoes would need to be produced and released when using the SIT (Feldmann *et al.*, 2005; Capinera, 2008).

The economic analysis of this study shows that gene drives could be the most cost-effective malaria control strategy for malaria elimination. The financial cost of malaria elimination per person per year (0.77-7.72 US$) for gene drives as a single intervention is comparable to the financial costs of protecting one person for one year applying other commonly used interventions including ITNs (0.71- 7.66 US$) and IRS (1.78-10.31 US$) (White *et al.*, 2011). Notably, drive strategies were more cost-effective than non-drive strategies in the second and third 5-year periods, in some cases eliminating malaria. This is indicative of gene drive strategies having a long-term benefit at a short-term cost and stresses the importance of long-term strategic planning to eliminate malaria. If decisions are made using a short time horizon for cost-effectiveness, gene drive mosquitoes release is unlikely to be the most effective strategy, but with an expanded time horizon, it becomes a more effective and economically sound option.

This study demonstrated a modeling approach applied to *An. gambiae*, the principal malaria vector in Africa (Miles *et al.*, 2017). This modeling approach, in principle, can be generalized to tackle other malaria-transmitting mosquito species (Eckhoff *et al.*, 2016). Amid uncertainty about vector abundance and its behavior (Guerra *et al.*, 2014),

the study offers a framework to effectively plan gene drive strategies in malaria control in other high burden countries where parasite transmission intensity varied. The study identified key aspects of both gene drive technology and its implementation that are fundamental for the technology to be a cost-effective component of a malaria control program. This helps advance the understanding of gene drives and how this or other novel tools can ultimately contribute to the elimination of malaria even in high-burden countries like the DRC.

Chapter 4

4. Discussion

This study uses mathematical modeling to describe the potential role of driving-Y gene drive mosquitoes in malaria control across the transmission spectrum in the DRC, an area where achieving effective control has historically been challenging. The study results, from evaluating the efficacy, compatibility, and cost-effectiveness of gene drive for malaria vector control, suggest that gene drive may be an effective strategy for malaria elimination in a high burden country like the DRC, either as a single intervention or in combination with other interventions (i.e., ITNs and ACT). To the best of our knowledge, this is the first study that has modeled the epidemiological impact and cost-effectiveness of gene drive mosquitoes for malaria elimination. The study advances understanding of how gene drives could be incorporated into the existing malaria control strategies. Previous studies involving gene drives for malaria control are limited in scope to laboratory experiments (Curtis, 1968; Akbari *et al.*, 2014; Galizi *et al.*, 2016; Pike *et al.*, 2017), and to the development and parameterization of mathematical models (Godfray, North, and Burt, 2017; Heffel and Finnigan, 2019; Noble *et al.*, 2019; North, Burt and Godfray, 2019b). By extending previous modeling work (Eckhoff *et al.*, 2016) to estimate the cost-effectiveness of gene drive in realistic settings, our work helps fill the evidence gap about the programmatic implementation of gene drive in the context of limited resources. This work also helps gauge the probabilities of success and possible outcomes of gene drives that are strictly laboratory-contained or in the transition from the laboratory-based research to future field-based research.

By using disease modeling to identify crucial factors determining the outcome for gene drives in malaria elimination, the study indicates that the success of driving-Y gene drives in all areas regardless of vector density highly depends on the ability of gene drives to shred the X chromosome. This furthers the understanding of the driving-Y system, which occurs naturally and has been successfully synthesized in the laboratory (Windbichler, Papathanos, and Crisanti, 2008; Burt and Deredec, 2018). The adoption of this strategy could, however, be very challenging because it may be challenging to achieve a perfect X-shredding rate at every development stage and during implementation while overcoming the challenge of meiotic sex chromosome inactivation (Aljunid *et al.*, 2012). Moreover, possible resistant mutants that could convert wildtype genes

and spread resistance, especially in *An. gambiae* that cleavage resistant alleles have already been observed (Galizi *et al.*, 2014).

As observed in this study, the success of these gene drives relies on mosquito population size and enough time for the drives to propagate in the mosquito population. Hence, understanding interactions between existing vector control methods such as ITNs, IRS, and sterile insect technique (SIT) that temporarily reduce the mosquito population (Alphey *et al.*, 2010; WHO, 2015b) and gene drives will be essential given the methods tamper with the mosquito population. The study demonstrates that existing interventions, even with remarkably high coverages and in the absence of insecticide and drug resistance, could only lead to malaria elimination in areas of the DRC where malaria transmission is low. Achieving such high coverages of existing measures is not only extremely difficult but also come with high implementation and logistics costs (Zelman *et al.*, 2014; Shretta *et al.*, 2017). It may take much more investment in logistics and systems to achieve 95% coverage of both ITNs and ACT than WHO's estimates applied in the study (Haakenstad *et al.*, 2019). Even if theoretically achievable, it is highly improbable to sustain necessary coverage levels in the complex operational environment of high disease burden countries like the DRC (WHO, 2005; Carrel *et al.*, 2015).

The model results show that gene drives could be applied as an intervention to control or eliminate malaria, either alone or in combination with other methods. Tailoring the frequency of releases and the number of gene drive mosquitoes to be released can make malaria elimination achievable within 5 years after a single release of gene drive mosquitoes under certain conditions, including but not limited to no importation of vectors or infections into the study areas. The study modeled compatibility of gene drive mosquitoes with existing malaria control measures, i.e., ITNs and ACTs, and found that driving-Y effectively reduces transmission both individually and in combination with other control interventions. Further work is necessary to include importation of vectors and infections to address the feasibility of release, as well as specify release schedule that is operationally practical and technically necessary for intended deployment areas.

From the cost-effectiveness analysis, gene drives would result in better cost-effectiveness once implemented in comparison to other genetically engineered mosquitoes. The self-propagating and self-sustaining property (Hammond and Galizi, 2017) of gene drives make the method less reliant on human adherence and compliance, unlike other interventions such as ITNs (Willey *et al.*, 2012) and ACTs (Banek *et al.*, 2014). The study based our cost-effectiveness analysis on the unit costs of OX513A (Alphey, Alphey, and Bonsall, 2018) and *Wolbachia* infected mosquitoes (Meghani and Boëte, 2018) considering the limited cost data of other genetic control methods. The rationale to apply the unit cost per person is to be conservative in approaching the cost estimation given the low number of gene drive mosquitoes released in the models in this study. The range of costs applied in our study partially reflects the reality in the field as the genetic control methods are varied in cost components even though the methods were developed to tackle mosquito-transmitted infectious diseases under a similar control strategy

(Alphey, Alphey, and Bonsall, 2011). Future research could explore the cost components of gene drives, especially development and environmental costs, that may affect the cost-effectiveness of the method.

4.1.Differences from other studies

This study estimates the impact of the transgenic mosquitoes (CRISPR/Cas gene drives) and its cost-effectiveness in populations for malaria control using mathematical models. This is also the first modeling study to use existing open data and estimates from the DRC to systematically compare the malaria control methods, including transgenic mosquitoes. Predictions are made for the full range of *P. falciparum* parasite prevalence settings across multiple regions of the country. This analysis differs from previous studies in that this study has specifically assessed combinations of interventions, rather than assuming that costs and effects sum up when interventions are used concurrently. Previous studies that assumed costs and effects summation when interventions are used concurrently can be misleading and lack the necessary information about suitable combination(s) (Morel *et al.*, 2013).

4.2.Implications of the study

With the availability of high computing performance, a re-evaluation of existing and potential strategies, as demonstrated in this study is appropriate. Adequate attention should be given to disease modeling work that would help improve disease management strategies and strengthen capacity building and knowledge transfer to local healthcare staff who will determine the long-term viability of vector control strategies. From the analyses combining computational work and cost-effectiveness, this study suggests that gene drives could be applied as a vector control strategy in a high malaria burden country like the DRC. This study aligns with WHO's recommendation on emphasizing the urgency of acquiring an innovative method for malaria control and prevention as the existing interventions alone are not sufficient for malaria elimination in high burden areas (WHO, 2018a).

The study sheds light on questions on gene drive technology and provides a framework on how to evaluate and perform a cost analysis of the technology. The study offers a framework to effectively plan gene drive strategies for malaria control in high burden countries where transmission intensity varies and identifies key aspects of both gene drive technology and its implementation that are fundamental for the technology to be a cost-effective component of a malaria control program. In addition to integrating precautionary measures into research processes, the evaluation framework provided in this study would make an important contribution once integrated into public policy guidelines that may constrain researches on gene drives or releases of gene drive modified organisms to help balance potential conflicts.

Significant potential benefits of gene drives for basic and applied research justify proceeding with laboratory research and highly-controlled field trials (Committee on Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct; Board on Life Sciences; Division on Earth and Life Studies; National Academies of Sciences Engineering and Medicine, 2016). By quantifying the probability of outcomes, simulated cause-and-effect pathways, identified and incorporated sources of uncertainty, comparing cost-effectiveness with alternative strategies, this study significantly helps to advance the knowledge of risks that might come with the gene drive approach in malaria control. The evaluation in this study, which includes the simulated ecosystem, fills considerable gaps in knowledge, particularly concerning ecological and environmental considerations if the technology is implemented. This knowledge can be further extended in additional steps in public engagement and governance, as there are increased efforts to coordinate and collaborate in recent years (James *et al.*, 2018). Recognition on the issue prompted The African Union (AU) and The New Partnership for Africa's Development (NEPAD) to develop the recommendations for gene drives for malaria control and elimination in the African region (AUDA-NEPAD, 2019), which is the study area of this research. For high malaria burden countries like the DRC, the challenges remain in lack of policies for collaborating not only with other countries but also with different systems of governance (Innovation to Impact, 2019). A gene drive modified organism is intended to spread after release (Committee on Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct; Board on Life Sciences; Division on Earth and Life Studies; National Academies of Sciences Engineering and Medicine, 2016), which poses a challenge to governance of gene drives as it knows no political boundaries, and as the current regulation of genetically modified organisms under the Cartagena and Nagoya Protocols is predicated on containment (UN-the Secretariat of the Convention on Biological Diversity, 2011).

Even though this research is a significant step forward to provide scientific and economic considerations regarding gene drive application, it is by no means a definite end to the pursuit of gene drive technology. Further research may help reduce uncertainties and characterize potential risks and benefits that involve crucial ethical and social challenges (Committee on Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct; Board on Life Sciences; Division on Earth and Life Studies; National Academies of Sciences Engineering and Medicine, 2016; The Royal Society, 2018). Given their ability to spread and persist in the receiving environment, if released into the wild, it is undeniable that gene drives will have environmental implications, including potential risks of gene drive organisms to the environment and challenges for the environmental risk assessment and monitoring (Umweltbundesamt, 2020). These implications should be discussed and addressed at an early stage of development. Precedents of international efforts in this regard could be

seen from both WHO and European Food Safety Authority whose guidance and regulatory frameworks for genetically modified organisms recommend a tiered approach to underpin step-wise environmental risk assessment which, at each step, assured that scientific evaluation is accompanied by risk assessment, risk management and risk communication (Mathematical Ecology Research Group, 2017).

Nonetheless, many countries have insufficient resources to individually follow these recommendations and to enforce legislation required under the Cartagena Protocol (Kingiri and Hall, 2012). As a result, further development in capacity building and public awareness activities, combining lessons learned from another context, especially in countries that have limited resources, are needed to stimulate public discussion regarding ethical, legal, environmental, and social aspects of the technology. For example, more constructive open public discussions on the topic should be encouraged, as seen in the project on public discourse on genome editing, which is a cooperation between Wissenschaft im Dialog (WiD) and the German National Academy of Sciences – Leopoldina (Council of Europe, 2020).

4.3.Further research

Further research on potential uses of gene drives in case of insecticide and antimalarial drug resistance could be explored as the higher baseline transmission or higher dry season transmission make it easier for gene drives to succeed. This because the approach has a higher potential in suppressing mosquito populations under such conditions. More work on tailoring gene drive release strategies before implementation, including adjusting the timing of gene drive mosquito release in response to seasonality patterns of the geographic locations, could result in more effective gene drive mosquito release strategies.

Further research would extend the knowledge of vector migration that was included in this study to address the uncertainty surrounding vector dispersion and its frequency and include human migration into the model. Adding human migration will be useful to address the issue of malaria reintroduction in previously cleared areas because of the movement of the infected population. The uncertainty about vector abundance and behavior limits the extent to which this study's findings may be representative of the actual impact of gene drive should it be implemented. Another source of uncertainty that should be further explored involves mosquito movement patterns, which result in their dispersal through the environment and affect disease transmission and genetic mixing (Guerra *et al.*, 2014).

The transboundary nature of living modified organisms present challenges and externalities. As demonstrated in this study, gene drive could potentially reduce the use of insecticides, thereby reduce negative externalities substantively (Florax, Travisi, and

Nijkamp, 2005). Further research could help address concerns on environmental and social costs because deploying areas or countries may not internalize risks or benefits spilling over to neighboring areas or countries. Opinions are shared that gene drive deployments would very likely provide public goods and create various positive and negative externalities and divergences between private incentives and social payoffs (Champ, Boyle and Brown, 2003; Mitchell, Brown, and Mcroberts, 2017). Further research to carefully look at these externalities and how they interact in addition to the economic evaluation provided in this study would be especially useful.

In addition to the technical perspective provided in this study, further work is necessary, including on the ethical perspective, i.e., standard research ethics, procedural ethics, and democratizing the technology (Thompson, 2018), as a critical component to implement this technology in wild mosquito populations (Wedell, Price and Lindholm, 2019).

Data sets grow exponentially partially because of the data are increasingly gathered by many low-cost information-sensing internets of things devices. Thus, future research would benefit from taking advantage of accelerating technology even further from which demonstrated in this study both in data collection and data analysis. For example, optimization in modeling could be used to identify the most effective mosquito release strategies and expedite the time spent for developing vector control strategies. All efforts to keep relevant data up to date are needed as the technology could better assist the virtual collaboration both locally and internationally. The efforts would lead to better strategies to tackle malaria and, hopefully, eventually eradicate the disease worldwide.

References

Akbari, O. S. *et al.* (2014) 'Novel synthetic medea selfish genetic elements drive population replacement in drosophila; A theoretical exploration of medea -dependent population suppression', *ACS Synthetic Biology*. American Chemical Society, 3(12), pp. 915–928. doi: 10.1021/sb300079h.

Alcalay, Y. *et al.* (2019) 'The potential for a released autosomal X-shredder becoming a driving-Y chromosome and invasively suppressing wild populations of malaria mosquitoes', *bioRxiv*. Cold Spring Harbor Laboratory, p. 860551. doi: 10.1101/860551.

Alfaro-Murillo, J. A. *et al.* (2016) 'A Cost-Effectiveness Tool for Informing Policies on Zika Virus Control', *PLoS Neglected Tropical Diseases*, 10(5), pp. 1–14. doi: 10.1371/journal.pntd.0004743.

Aljunid, S. M. *et al.* (2012) 'Health-care data collecting, sharing, and using in Thailand, China Mainland, South Korea, Taiwan, Japan, and Malaysia', in *Value in Health*. Elsevier, pp. S132–S138. doi: 10.1016/j.jval.2011.11.004.

Alphey, L. *et al.* (2010) 'Sterile-insect methods for control of mosquito-borne diseases: An analysis', *Vector-Borne and Zoonotic Diseases*. Mary Ann Liebert, Inc., pp. 295–311. doi: 10.1089/vbz.2009.0014.

Alphey, L. *et al.* (2013) 'Genetic control of Aedes mosquitoes', *Pathogens and Global Health*. Taylor & Francis, pp. 170–179. doi: 10.1179/2047773213Y.0000000095.

Alphey, L., Koukidou, M. and Morrison, N. I. (2014) *Transgenic Insects, CABI Biotechnology Series*. Edited by M. Q. Benedict. Oxford, UK.

Alphey, N., Alphey, L. and Bonsall, M. B. (2011) 'A model framework to estimate impact and cost of genetics-based sterile insect methods for dengue vector control', *PLoS ONE*, 6(10). doi: 10.1371/journal.pone.0025384.

Alphey, N., Alphey, L. and Bonsall, M. B. (2018) 'A Model Framework to Estimate Impact and Cost of Genetics-Based Sterile Insect Methods for Dengue Vector Control Short title : Genetic Vector Control against Dengue', pp. 1–16.

Arrow KJ, Panosian C, and G. H. (ed.) (2004) 'A Brief History of Malaria - Saving Lives, Buying Time - NCBI Bookshelf', in *Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance*. Washington (DC): National Academies Press. Available at: https://www.ncbi.nlm.nih.gov/books/NBK215638/ (Accessed: 4 March 2020).

Asman, S. M., McDonald, P. T. and Prout, T. (1981) 'Field Studies of Genetic Control Systems for Mosquitoes', *Annual Review of Entomology*, 26(1), pp. 289–318. doi: 10.1146/annurev.en.26.010181.001445.

AUDA-NEPAD (2019) *Gene Drives for Malaria Control and Elimination in Africa*. Available at: https://www.nepad.org/publication/gene-drives-malaria-control-and-elimination-africa (Accessed: 2 April 2020).

Banek, K. *et al.* (2014) 'Adherence to artemisinin-based combination therapy for the treatment of malaria: A systematic review of the evidence', *Malaria Journal*. BioMed Central, 13(1), p. 7. doi: 10.1186/1475-2875-13-7.

Beaghton, A., Beaghton, P. J. and Burt, A. (2017) 'Vector control with driving y chromosomes: Modelling the evolution of resistance', *Malaria Journal*. BioMed Central, 16(1), pp. 1–14. doi: 10.1186/s12936-017-1932-7.

Bhagavathula, A. S., Elnour, A. A. and Shehab, A. (2016) 'Alternatives to currently used antimalarial drugs: In search of a magic bullet', *Infectious Diseases of Poverty*. BioMed Central Ltd. doi: 10.1186/s40249-016-0196-8.

Bhatt, S. *et al.* (2015) 'The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015.', *Nature*. England: Nature Publishing Group, 526(7572), pp. 207–211. doi: 10.1038/nature15535.

Bradshaw, C. J. A. and McMahon, C. R. (2008) 'Fecundity', in *Encyclopedia of Ecology, Five-Volume Set*. Elsevier Inc., pp. 1535–1543. doi: 10.1016/B978-008045405-4.00645-5.

Brauer, F. (2017) 'Mathematical epidemiology: Past, present, and future', *Infectious Disease Modelling*. KeAi Communications Co., pp. 113–127. doi: 10.1016/j.idm.2017.02.001.

Burt, A. and Deredec, A. (2018) 'Self-limiting population genetic control with sex-linked genome editors', *Proceedings of the Royal Society B: Biological Sciences*, 285(1883). doi: 10.1098/rspb.2018.0776.

Camponovo, F. *et al.* (2017) 'Incidence and admission rates for severe malaria and their impact on mortality in Africa', *Malaria Journal*. BioMed Central, 16(1), pp. 1–12. doi: 10.1186/s12936-016-1650-6.

Capinera, J. L. (2008) *Area-wide Control of Insect Pests: From Research to Field Implementation, Florida Entomologist*. doi: 10.1653/0015-4040(2008)91[349:awcoip]2.0.co;2.

Carrel, M. *et al.* (2015) 'The geography of malaria genetics in the Democratic Republic of Congo: A complex and fragmented landscape', *Social Science and Medicine*. Elsevier Ltd, 133, pp. 233–241. doi: 10.1016/j.socscimed.2014.10.037.

CDC (2018) *CDC - Malaria - Malaria Worldwide - How Can Malaria Cases and Deaths Be Reduced? - Drug resistance in the Malaria Endemic World*. Available at: https://www.cdc.gov/malaria/malaria_worldwide/reduction/drug_resistance.html (Accessed: 15 February 2020).

Chabot-Couture, G., Nigmatulina, K. and Eckhoff, P. (2014) 'An environmental data set for vector-borne disease modeling and epidemiology', *PLoS ONE*, 9(4). doi: 10.1371/journal.pone.0094741.

Champ, P. A., Boyle, K. J. and Brown, T. C. (eds) (2003) *A Primer on Nonmarket Valuation*. 1st edn. Kluwer Academic. doi: 10.1007/978-94-007-0826-6.

Choisy, M., Guégan, J.-F. and Rohani, P. (2007) *Mathemati cal Model i ng of Infecti ous Di seases Dynami cs*.

Committee on Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct; Board on Life Sciences; Division on Earth and Life Studies; National Academies of Sciences Engineering and Medicine (2016) *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*. National Academies Press. doi: 10.17226/23405.

Council of Europe (2020) *Committee on Bioethics (DH-BIO) Guide to Public Debate on Human Rights and Biomedicine*. Available at: https://rm.coe.int/guide-ee-final-e/16809ce642 (Accessed: 22 April 2020).

Curtis, C. F. (1968) 'Possible Use of Translocations to fix Desirable Genes in Insect Pest Populations', *Nature*, pp. 368–369. Available at: https://www.nature.com/articles/218368a0.pdf?origin=ppub (Accessed: 14 February 2020).

December, P. and Gowan, R. (2013) *How big is the Congo? Very big!* Available at: http://www.globaldashboard.org/2011/12/06/how-big-is-the-congo-very-big/.

Eckhoff, P. A. (2011) 'A malaria transmission-directed model of mosquito life cycle and ecology.', *Malaria journal*. England: BioMed Central, 10(1), p. 303. doi: 10.1186/1475-2875-10-303.

Eckhoff, P. A. (2012) 'Malaria parasite diversity and transmission intensity affect development of parasitological immunity in a mathematical model.', *Malaria Journal*, pp. 1–14.

Eckhoff, P. A. (2013) 'Mathematical models of within-host and transmission dynamics to determine effects of malaria interventions in a variety of transmission settings.', *The American Journal of Tropical Medicine and Hygiene*. United States, 88(5), pp. 817–827. doi: 10.4269/ajtmh.12-0007.

Eckhoff, P. A. *et al.* (2016) 'Impact of mosquito gene drive on malaria elimination in a computational model with explicit spatial and temporal dynamics', *Proceedings of the National Academy of Sciences*, 114(8), p. 201611064. doi: 10.1073/pnas.1611064114.

Egelie, K. J. *et al.* (2016) 'The emerging patent landscape of CRISPR–Cas gene editing technology', *Nature Biotechnology*. Nature Publishing Group, 34(10), pp. 1025–1031. doi: 10.1038/nbt.3692.

ENSSER (2019a) *GENE DRIVES A report on their science, applications, social aspects, ethics and regulations*. Bern. Available at: https://genedrives.ch/wp-content/uploads/2019/10/Gene-Drives-Book-WEB.pdf (Accessed: 15 February 2020).

ENSSER (2019b) *GENE DRIVES A report on their science, applications, social aspects, ethics and regulations*.

Evans, D. B. *et al.* (2005) 'Methods to assess the costs and health effects of interventions for improving health in developing countries', *The British Journal of Medicine*, 331(7525), pp. 1137–1140. doi: 10.1136/bmj.331.7525.1137.

Feachem, R. G. A. *et al.* (2019) 'Malaria eradication within a generation: ambitious, achievable, and necessary', *The Lancet*, 394(10203), pp. 1056–1112. doi: 10.1016/S0140-6736(19)31139-0.

Feldmann, U. *et al.* (2005) *Potential impact of tsetse fly control involving the sterile insect technique, Sterile Insect Technique: Principles and Practice in Area-Wide Integrated Pest Management*. doi: 10.1007/1-4020-4051-2_27.

Fisher, E. (2018) 'Gene drives and the expanding horizon of governance', *Journal of Responsible Innovation*. Routledge, pp. S1–S3. doi: 10.1080/23299460.2017.1422378.

Florax, R. J. G. M., Travisi, C. M. and Nijkamp, P. (2005) 'A meta-analysis of the willingness to pay for reductions in pesticide risk exposure', *European Review of Agricultural Economics*. Oxford Academic, 32(4), pp. 441–467. doi: 10.1093/erae/jbi025.

Foppa, I. M. (2016) *A historical introduction to mathematical modeling of infectious diseases : seminal papers in epidemiology*. Academic Press.

Gabrieli, P., Smidler, A. and Catteruccia, F. (2014) 'Engineering the control of mosquito-borne infectious diseases', *Genome biology*, p. 535. doi: 10.1186/s13059-014-0535-7.

Galizi, R. *et al.* (2014) 'A synthetic sex ratio distortion system for the control of the human malaria mosquito', *Nature Communications*. Nature Publishing Group, 5(1), pp. 1–8. doi: 10.1038/ncomms4977.

Galizi, R. *et al.* (2016) 'A CRISPR-Cas9 sex-ratio distortion system for genetic control', *Scientific Reports*. Nature Publishing Group, 6. doi: 10.1038/srep31139.

Gantz, V. M. *et al.* (2015) 'Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito Anopheles stephensi.', *Proceedings of the National Academy of Sciences of the United States of America*. United States, 112(49), pp. E6736-43. doi: 10.1073/pnas.1521077112.

GBD 2017 Causes of Death Collaborators (2017) 'Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016', *The Lancet*. Lancet Publishing Group, 390(10100), pp. 1211–1259. doi: 10.1016/S0140-6736(17)32154-2.

GeneWatch UK (2018) *Oxitec's GM insects: Failed in the Field?* Available at: http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/Failed_in_the_field_fin.pdf (Accessed: 15 February 2020).

Gerardin, J., Eckhoff, P. A. and Wenger, E. A. (2015) 'Mass campaigns with antimalarial drugs: A modelling comparison of artemether-lumefantrine and DHA-piperaquine with and without primaquine as tools for malaria control and elimination', *BioMed Central Infectious Diseases*, 15(1), pp. 1–14. doi: 10.1186/s12879-015-0887-y.

Godfray, H. C. J., North, A. and Burt, A. (2017) 'How driving endonuclease genes can be used to combat pests and disease vectors', *BioMed Central Biology*. BioMed Central Ltd., p. 81. doi: 10.1186/s12915-017-0420-4.

Goodman, C., Coleman, P. and Mills, A. (2000) *Economic Analysis of Malaria Control in Sub-Saharan Africa*. Available at: www.globalforumhealth.org (Accessed: 23 February 2020).

Guerra, C. A. *et al.* (2014) 'A global assembly of adult female mosquito mark-release-recapture data to inform the control of mosquito-borne pathogens', *Parasites and Vectors*, 7(1), pp. 1–15. doi: 10.1186/1756-3305-7-276.

Gueye, C. S. *et al.* (2016) 'Strategies and approaches to vector control in nine malaria-eliminating countries: a cross-case study analysis.', *Malaria journal*, 15.

Gunda, R. and Chimbari, M. J. (2017) 'Cost-effectiveness analysis of malaria interventions using disability adjusted life years: A systematic review', *Cost Effectiveness and Resource Allocation*. BioMed Central, 15(1). doi: 10.1186/s12962-017-0072-9.

Gunda, R., Chimbari, M. J. and Mukaratirwa, S. (2016) 'Assessment of burden of Malaria in Gwanda district, Zimbabwe, using the disability adjusted life years', *International Journal of Environmental Research and Public Health*. MDPI AG, 13(2). doi: 10.3390/ijerph13020244.

Haakenstad, A. *et al.* (2019) 'Tracking spending on malaria by source in 106 countries, 2000–16: an economic modelling study', *The Lancet Infectious Diseases*. Lancet Publishing Group, 19(7), pp. 703–716. doi: 10.1016/S1473-3099(19)30165-3.

Hammond, A. *et al.* (2016) 'A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae*', *Nature Biotechnology*, 34(1), pp. 78–83. doi: 10.1038/nbt.3439.

Hammond, A. M. and Galizi, R. (2017) 'Gene drives to fight malaria: current state and future directions', *Pathogens and Global Health*. Taylor & Francis, 111(8), pp. 412–423. doi: 10.1080/20477724.2018.1438880.

Heffel, M. G. and Finnigan, G. C. (2019) 'Mathematical modeling of self-contained CRISPR gene drive reversal systems', *Scientific Reports*. Nature Research, 9(1), pp. 1–10. doi: 10.1038/s41598-019-54805-8.

Heidrich, N. *et al.* (2015) *CRISPR Methods and Protocols*. Edited by M. Lundgren, E. Charpentier, and P. C. Fineran. Humana Press. doi: 10.1007/978-1-4939-1096-0.

Hijmans, R. J. *et al.* (2005) 'Very high resolution interpolated climate surfaces for global land areas', *International Journal of Climatology*, 25(15), pp. 1965–1978. doi: 10.1002/joc.1276.

Human Rights Watch (2018) 'Democratic Republic of Congo Events of 2018', *World Report 2019*, (March). Available at: https://www.hrw.org/world-report/2018/country-chapters/democratic-republic-congo.

IDM (2019a) *Epidemiological Modeling Software*. Available at: http://idmod.org/software (Accessed: 27 February 2019).

IDM (2019b) *Malaria model structure and framework — Malaria Model documentation*. Available at: http://idmod.org/docs/malaria/malaria-model-framework.html (Accessed: 16 February 2020).

IDM (2019c) *Migration files — Malaria Model documentation*. Available at: https://idmod.org/docs/malaria/software-migration.html?searchText=migration (Accessed: 17 March 2020).

IDM (2019d) *Welcome to EMOD malaria modeling — Malaria Model documentation*. Available at: https://idmod.org/docs/malaria/index.html (Accessed: 16 February 2020).

IHME (2018) 'Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017', *The Lancet. Global Health Metrics*, 392(10159), pp. 1736–1788. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32203-7/fulltext (Accessed: 4 February 2020).

IHME (2019) *Democratic Republic of the Congo, healthdata.org*. Available at: http://www.healthdata.org/democratic-republic-congo.

Innovation to Impact (2019) *Selected African Country Registration Processes for Vector Control Tools*.

IRI/LDEO (2019) *dataset: USGS VCAP eight-day*. Available at: https://iridl.ldeo.columbia.edu/SOURCES/.USGS/.VCAP/.eight-day/ (Accessed: 13 March 2019).

James, S. *et al.* (2018) 'Pathway to deployment of gene drive mosquitoes as a potential biocontrol tool for elimination of malaria in sub-Saharan Africa: Recommendations of a scientific working group', *American Journal of Tropical Medicine and Hygiene*. American Society of Tropical Medicine and Hygiene, pp. 1–49. doi: 10.4269/ajtmh.18-0083.

Jennifer Doudna (2016) *Crispr --Cas : A Laboratory Manual*. Edited by Jennifer Doudna and Prashant Mali. Cold Spring Harbor Laboratory Press.

Khamis, D. *et al.* (2018) 'Optimal control of malaria: Combining vector interventions and drug therapies', *Malaria Journal*. BioMed Central, 17(1), pp. 1–18. doi: 10.1186/s12936-018-2321-6.

Kingiri, A. N. and Hall, A. (2012) 'The Role of Policy Brokers: The Case of Biotechnology in Kenya', *Review of Policy Research*. John Wiley & Sons, Ltd, 29(4), pp. 492–522. doi: 10.1111/j.1541-1338.2012.00573.x.

Kumar, A. *et al.* (2007) *Burden of Malaria in India: Retrospective and Prospective View*.

Longfield, K. *et al.* (2013) 'Putting health metrics into practice: Using the disability-adjusted life year for strategic decision making', *BMC Public Health*. BioMed Central, 13(SUPPL 2), p. S2. doi: 10.1186/1471-2458-13-S2-S2.

Malaria Policy Advisory Committee Meeting (2018) *Universal access to core malaria interventions in high-burden countries*. Available at: http://www.who.int/malaria/mpac/mpac-april2018-universal-access-core-interventions-session8.pdf.

Mathematical Ecology Research Group (2017) *Ecological Risks of Gene Drive Technologies*. doi: 10.7554/eLife.03401.014.

Meghani, Z. and Boëte, C. (2018) 'Genetically engineered mosquitoes, Zika and other arboviruses, community engagement, costs, and patents: Ethical issues', *PLoS Neglected Tropical Diseases*, 12(7), pp. 1–7. doi: 10.1371/journal.pntd.0006501.

Meghani, Z. and Kuzma, J. (2018) 'Regulating animals with gene drive systems: lessons from the regulatory assessment of a genetically engineered mosquito', *Journal of Responsible Innovation*. Routledge, 5, pp. S203–S222. doi: 10.1080/23299460.2017.1407912.

Meshnick, S. *et al.* (2014) 'Demographic and health survey (DRC-DHSII) 2013-2014 Supplemental malaria report', pp. 1–4.

Miles, A. *et al.* (2017) 'Genetic diversity of the African malaria vector anopheles gambiae', *Nature*. Nature Publishing Group, 552(7683), pp. 96–100. doi: 10.1038/nature24995.

Mitchell, P. D., Brown, Z. and Mcroberts, N. (2017) 'Economic issues to consider for gene drives', *Journal of Responsible Innovation*. doi: 10.1080/23299460.2017.1407914.

Mnzava, A. P. *et al.* (2015) 'Implementation of the global plan for insecticide resistance management in malaria vectors: progress, challenges and the way forward', *Malaria Journal*. BioMed Central Ltd., 14(1), p. 173. doi: 10.1186/s12936-015-0693-4.

Morel, C. M. *et al.* (2013) 'Cost-effectiveness of long-lasting insecticide-treated hammocks in preventing malaria in South-central Vietnam.', *PloS one*. United States, 8(3), p. e58205. doi: 10.1371/journal.pone.0058205.

Morel, C. M., Lauer, J. A. and Evans, D. B. (2005) 'Cost effectiveness analysis of strategies to combat malaria in developing countries', *The British Medical Journal*. United Kingdom, 331(December), pp. 1–7. doi: 10.1136/bmj.38639.702384.AE.

Moro, D. *et al.* (2018) 'Identifying knowledge gaps for gene drive research to control invasive animal species: The next CRISPR step', *Global Ecology and Conservation*. Elsevier B.V., p. e00363. doi: 10.1016/j.gecco.2017.e00363.

Mumford, J. D. (2012) 'Science, regulation, and precedent for genetically modified insects', *PLoS Neglected Tropical Diseases*, 6(1), pp. 1–4. doi: 10.1371/journal.pntd.0001504.

Nikolov, M. *et al.* (2016) 'Malaria Elimination Campaigns in the Lake Kariba Region of Zambia: A Spatial Dynamical Model.', *PLoS computational biology*. United States, 12(11), p. e1005192. doi: 10.1371/journal.pcbi.1005192.

NOAA (2006) *The NOAA Climate Prediction Center African Rainfall Estimation Algorithm Version 2 .0*.

Noble, C. *et al.* (2019) 'Daisy-chain gene drives for the alteration of local populations', *Proceedings of the National Academy of Sciences of the United States of America*. National Academy of Sciences, 116(17), pp. 8275–8282. doi: 10.1073/pnas.1716358116.

North, A. R., Burt, A. and Godfray, H. C. J. (2019a) 'Modelling the potential of genetic control of malaria mosquitoes at national scale', *BMC Biology*. BMC Biology, 17(1), pp. 1–12. doi: 10.1186/s12915-019-0645-5.

North, A. R., Burt, A. and Godfray, H. C. J. (2019b) 'Modelling the potential of genetic control of malaria mosquitoes at national scale', *BMC Biology*. BioMed Central Ltd., 17(1), p. 26. doi: 10.1186/s12915-019-0645-5.

O'Neill, S. L. *et al.* (2018) 'Scaled deployment of Wolbachia to protect the community from dengue and other aedes transmitted arboviruses', *Gates Open Research*. F1000 Research Ltd, 2, p. 36. doi: 10.12688/gatesopenres.12844.3.

Paes de Andrade, P. *et al.* (2016) 'Use of transgenic Aedes aegypti in Brazil: risk perception and assessment', *Bull World Health Organ*. doi: 10.2471/BLT.16.173377.

Pike, A. *et al.* (2017) 'Changes in the microbiota cause genetically modified Anopheles to spread in a population', *Science*. American Association for the Advancement of Science, 357(6358), pp. 1396–1399. doi: 10.1126/science.aak9691.

President's Malaria Initiative (2018) *PMI Democratic Republic of the Congo*. Available at: https://www.pmi.gov/docs/default-source/default-document-library/country-profiles/drc_profile.pdf?sfvrsn=20.

President's Malaria Initiative (2019) 'FY 2019 Democratic Republic of Congo Abbreviated Malaria Operational Plan'. Available at: https://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy19/fy-2019-democratic-republic-of-the-congo-abbreviated-malaria-operational-plan.pdf?sfvrsn=5.

Protopopoff, N. *et al.* (2018) 'Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: a cluster, randomised controlled, two-by-two factorial design trial', *The Lancet*. Lancet Publishing Group, 391(10130), pp. 1577–1588. doi: 10.1016/S0140-6736(18)30427-6.

Ratner, H. K., Sampson, T. R. and Weiss, D. S. (2016) 'Overview of CRISPR–Cas9 Biology', *Cold Spring Harbor*

Protocols, (12), pp. 1023–1038. doi: 10.1101/pdb.top088849.

Recker, M. *et al.* (2004) 'Transient cross-reactive immune responses can orchestrate antigenic variation in malaria', *Nature*. Nature Publishing Group, 429(6991), pp. 555–558. doi: 10.1038/nature02486.

Roll Back Malaria Partnership (2017) 'RBM Partnership Strategic Plan 2017 – 2020', (February 2018).

Roll Back Malaria Vector Control Working Group (2017) *Vector Control in Humanitarian Emergencies*.

Sharma, V. (2019) *Spatial and Non Spatial Data*. Available at: https://www.up-4ever.com/9f5dwtnzdgej.

Shretta, R. *et al.* (2017) 'Tracking development assistance and government health expenditures for 35 malaria-eliminating countries: 1990-2017', *Malaria Journal*. BioMed Central Ltd., 16(1), p. 251. doi: 10.1186/s12936-017-1890-0.

Singh, K R P; Patterson, R S; Labrecque, G C; Razdan, R. K. (1975) 'Mass rearing of Culex pipiens fatigans Wied. Author(s)', *Journal of Communicable Diseases*, 7(1), pp. 31–53. doi: 10.2989/10220110509485863.

Sinka, M. E. *et al.* (2010) 'The dominant Anopheles vectors of human malaria in Africa, Europe and the Middle East: Occurrence data, distribution maps and bionomic précis', *Parasites and Vectors*. BioMed Central, 3(1), pp. 1–34. doi: 10.1186/1756-3305-3-117.

Stevens, W. and Jeffries, D. (2011) *PSI Malaria Health Impact Estimation Model*. Available at: http://www.psi.org/resources/publications (Accessed: 21 March 2020).

The Malaria Atlas Project (2018) *Explorer - Malaria Atlas Project*. Available at: https://malariaatlas.org/explorer/#/ (Accessed: 14 August 2018).

The malERA Consultative Group on Modeling (2011) 'A Research Agenda for Malaria Eradication: Modeling', *PLoS Medicine*. Public Library of Science, 8(1), p. e1000403. doi: 10.1371/journal.pmed.1000403.

The malERA Refresh Consultative Panel on Combination Interventions and Modelling (2017) 'malERA: An updated research agenda for combination interventions and modelling in malaria elimination and eradication', *PLoS Medicine*. Public Library of Science, p. e1002453. doi: 10.1371/journal.pmed.1002453.

The Royal Society (2018) *Gene drive research: why it matters*. Available at: https://royalsociety.org/~/media/policy/Publications/2018/08-11-18-gene-drive-statement.pdf (Accessed: 22 February 2020).

The World Bank (2006) 'Chapter 3Cost-Effectiveness Analysis', in *Priorities in Health*. Available at: https://www.ncbi.nlm.nih.gov/books/NBK10253/ (Accessed: 24 February 2020).

The World Bank (2017) *Jobs Diagnostic, Democratic Republic of Congo*. Washington DC, USA. Available at: http://documents.worldbank.org/curated/en/822881517551920780/pdf/123113-WP-P161849-1-2-2018-13-5-12-WBDRCJDWEB.pdf (Accessed: 16 April 2020).

The World Bank (2019) *The World Bank in DRC: Democratic Republic of Congo Overview*. Available at: https://www.worldbank.org/en/country/drc/overview (Accessed: 15 April 2020).

Thompson, P. B. (2018) 'The roles of ethics in gene drive research and governance', *Journal of Responsible Innovation*. Routledge, 5(sup1), pp. S159–S179. doi: 10.1080/23299460.2017.1415587.

U.S. Bureau of Labour Statistics (2019) *Consumer Price Index*. Available at: https://www.bls.gov/news.release/archives/cpi_12112019.htm (Accessed: 28 December 2019).

Umweltbundesamt (2020) *Gene Drive Organisms: Implications for the Environment and Nature Conservation*. doi: 10.1016/J.CUB.2013.

UN-the Secretariat of the Convention on Biological Diversity (2011) *Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety*.

Vector Link (2019) *Democratic Republic of the Congo*. Available at: https://pmivectorlink.org/where-we-work/drc/.

Wedell, N., Price, T. A. R. and Lindholm, A. K. (2019) 'Gene drive: Progress and prospects', *Proceedings of the Royal Society B: Biological Sciences*. Royal Society Publishing, 286(1917). doi: 10.1098/rspb.2019.2709.

Weiss, D. J. *et al.* (2019) 'Mapping the global prevalence, incidence, and mortality of Plasmodium falciparum, 2000–17: a spatial and temporal modelling study', *The Lancet*. Lancet Publishing Group, 394(10195), pp. 322–331. doi: 10.1016/S0140-6736(19)31097-9.

White, M. T. *et al.* (2011) 'Costs and cost-effectiveness of malaria control interventions--a systematic review.', *Malaria journal*. England, 10, p. 337. doi: 10.1186/1475-2875-10-337.

WHO/TDR and FNIH (2014) 'Guidance Framework for testing genetically modified mosquitoes', p. 159. Available at: http://r4d.dfid.gov.uk/Output/197475/Default.aspx.

WHO (2001) *Country groupings*. Available at: https://www.who.int/quantifying_ehimpacts/global/ebdcountgroup/en/ (Accessed: 28 February 2020).

WHO (2003) *WHO guide to cost-effectiveness analysis*. Edited by T. TAN-TORRES EDEJER et al. Switzerland: WHO. Available at: https://www.who.int/choice/publications/p_2003_generalised_cea.pdf (Accessed: 19 March 2020).

WHO (2005) *Malaria control in complex emergemcies: an inter-agency handbook*.

WHO (2010) *World Malaria Report*. Available at: https://www.who.int/malaria/world_malaria_report_2010/worldmalariareport2010.pdf?ua=1 (Accessed: 5 May 2020).

WHO (2014a) 'Severe malaria', *Tropical medicine & international health : TM & IH*. John Wiley & Sons, Ltd, 19 Suppl 1, pp. 7–131. doi: 10.1111/tmi.12313_2.

WHO (2014b) 'Status report on artemisinin resistance (January 2014)', *WHO*. World Health Organization.

WHO (2015a) 'Global technical strategy for malaria 2016-2030', *WHO Geneva*, pp. 1–35. Available at: http://apps.who.int/iris/bitstream/10665/176712/1/9789241564991_eng.pdf?ua=1.

WHO (2015b) *Indoor residual spraying: an operational manual for indoor residual spraying (IRS) for malaria transmission control and elimination – 2nd ed.* Available at: https://apps.who.int/iris/bitstream/handle/10665/177242/9789241508940_eng.pdf;jsessionid=F52653E3A627EEA36605CF75D5DE5FF7?sequence=1 (Accessed: 14 March 2020).

WHO (2016a) *Democratic Republic of the Congo Statistics*. Available at: http://www.who.int/countries/cod/en/.

WHO (2016b) *World Malaria Report*.

WHO (2018a) 'High burden to high impact: a targeted malaria response', p. 186. doi: 10.1071/EC12504.

WHO (2018b) *World Malaria Report. 2018. ISBN 978 92 4 156469 4.* doi: ISBN 978 92 4 1564403.

WHO (2019a) *Metrics: Disability-Adjusted Life Year (DALY)*. Available at: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html.

WHO (2019b) *Overview of malaria elimination, WHO*. World Health Organization.

WHO (2019c) *World Malaria Report*. Available at: https://www.who.int/publications-detail/world-malaria-report-2019.

WHO (2020a) *CHOosing Interventions that are Cost Effective (WHO-CHOICE)-Democratic Republic of the Congo, WHO*. World Health Organization. Available at: https://www.who.int/choice/country/cod/cost/en/ (Accessed: 16 April 2020).

WHO (2020b) *Coronavirus disease 2019*. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (Accessed: 16 February 2020).

WHO (2020c) *Malaria eradication: benefits , future scenarios A report of the Strategic Advisory Group*. Geneva.

WHO (2020d) *WHO | Democratic Republic of the Congo*. World Health Organization. Available at: https://www.who.int/countries/cod/en/ (Accessed: 15 April 2020).

WHO (2020e) *WHO | Metrics: Disability-Adjusted Life Year (DALY)*. Available at: https://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/ (Accessed: 23 February 2020).

Willey, B. A. *et al.* (2012) 'Strategies for delivering insecticide-treated nets at scale for malaria control: a systematic review', *Bulletin of the World Health Organization*. World Health Organization, p. 672. doi: 10.2471/BLT.11.094771.

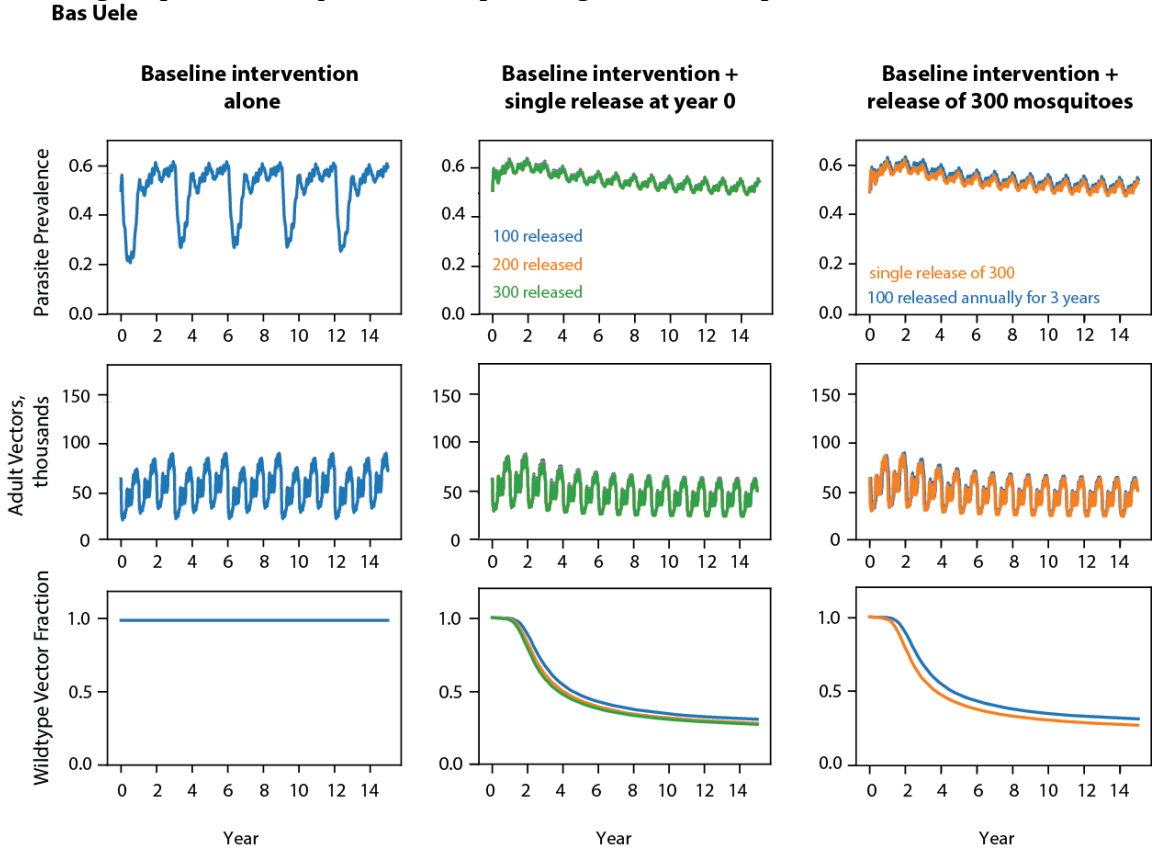
Windbichler, N., Papathanos, P. A. and Crisanti, A. (2008) 'Targeting the X chromosome during spermatogenesis induces Y chromosome transmission ratio distortion and early dominant embryo lethality in Anopheles gambiae', *PLoS Genetics*, 4(12). doi: 10.1371/journal.pgen.1000291.

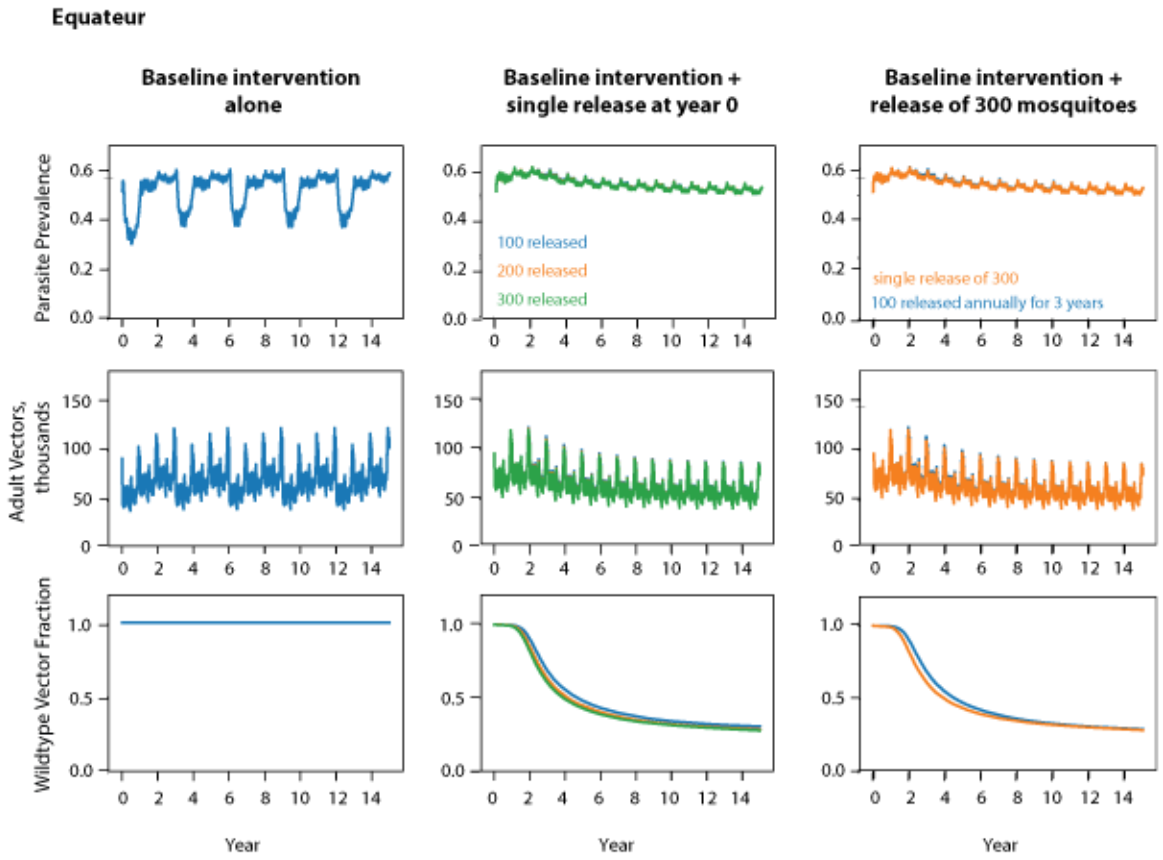
Zelman, B. *et al.* (2014) 'Costs of eliminating malaria and the impact of the global fund in 34 countries', *PloS ONE*. Public Library of Science, 9(12), pp. 1–17. doi: 10.1371/journal.pone.0115714.

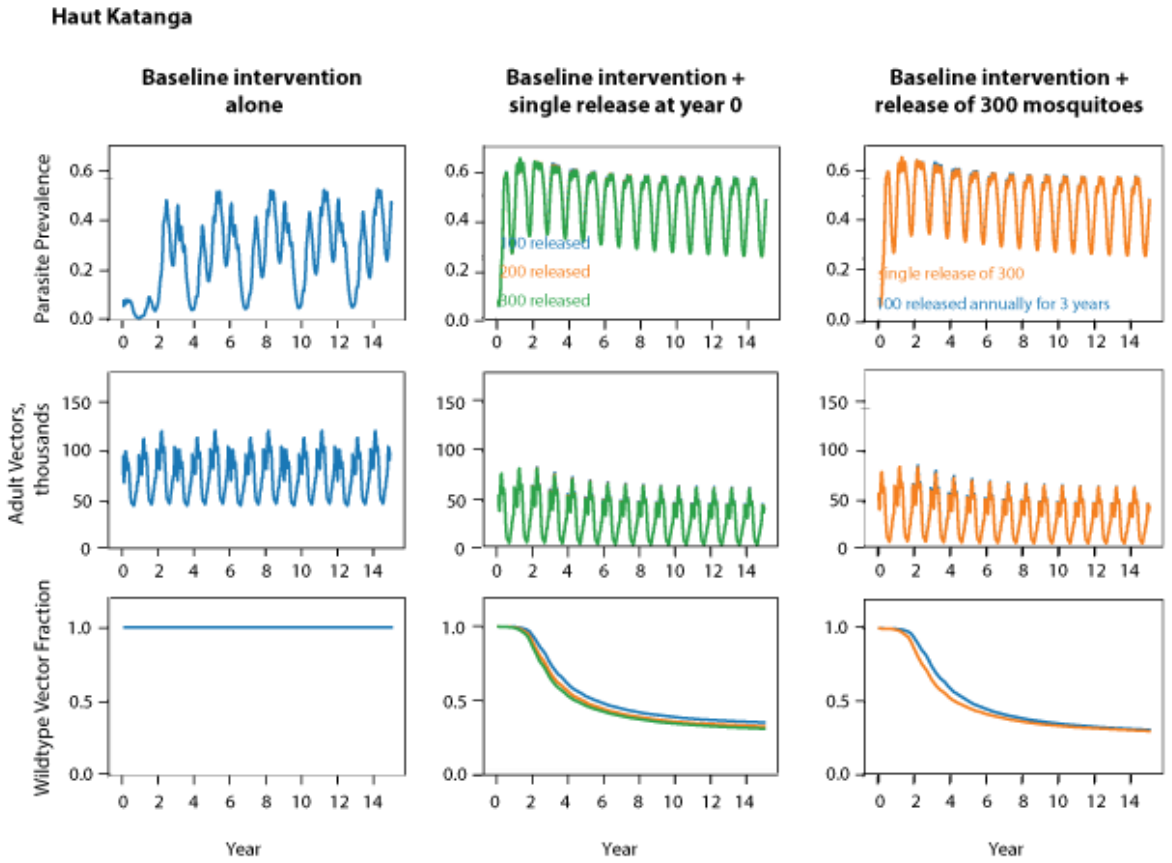
Appendices

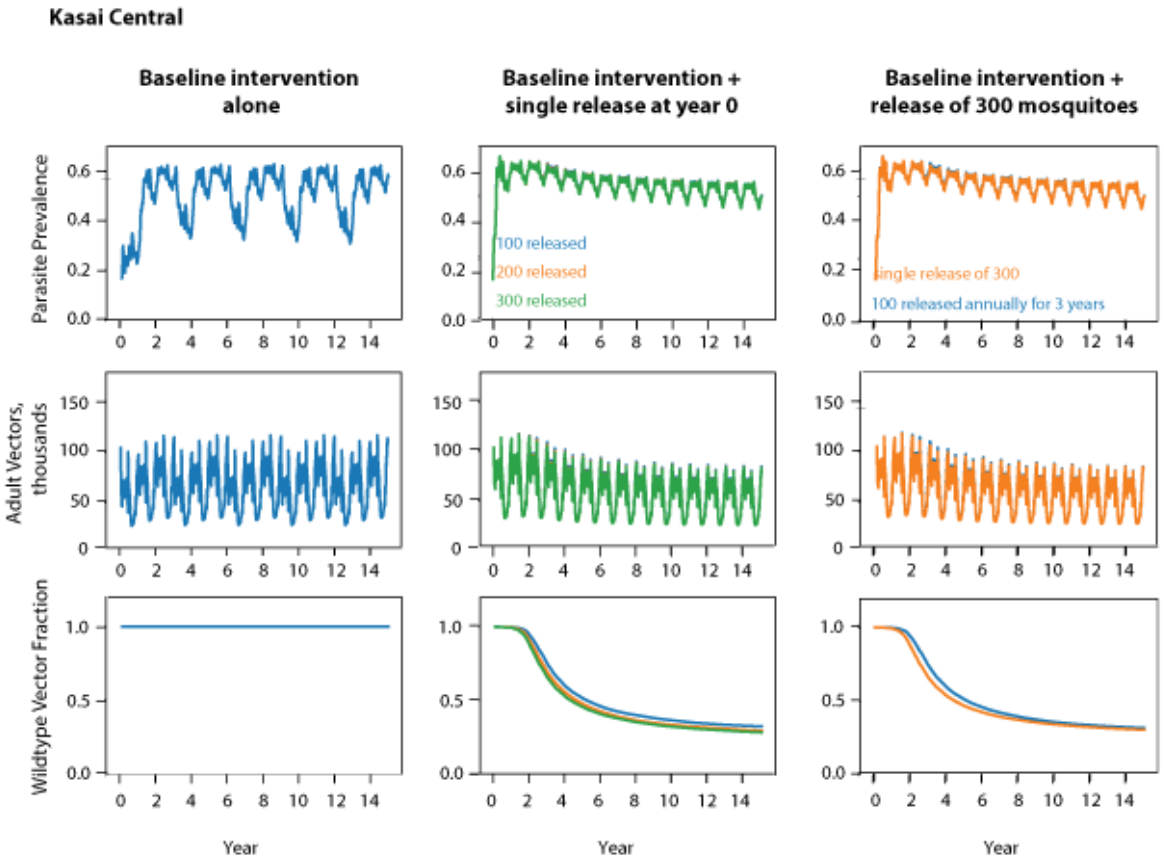
Appendix 1: Simulation outputs – non-spatial framework

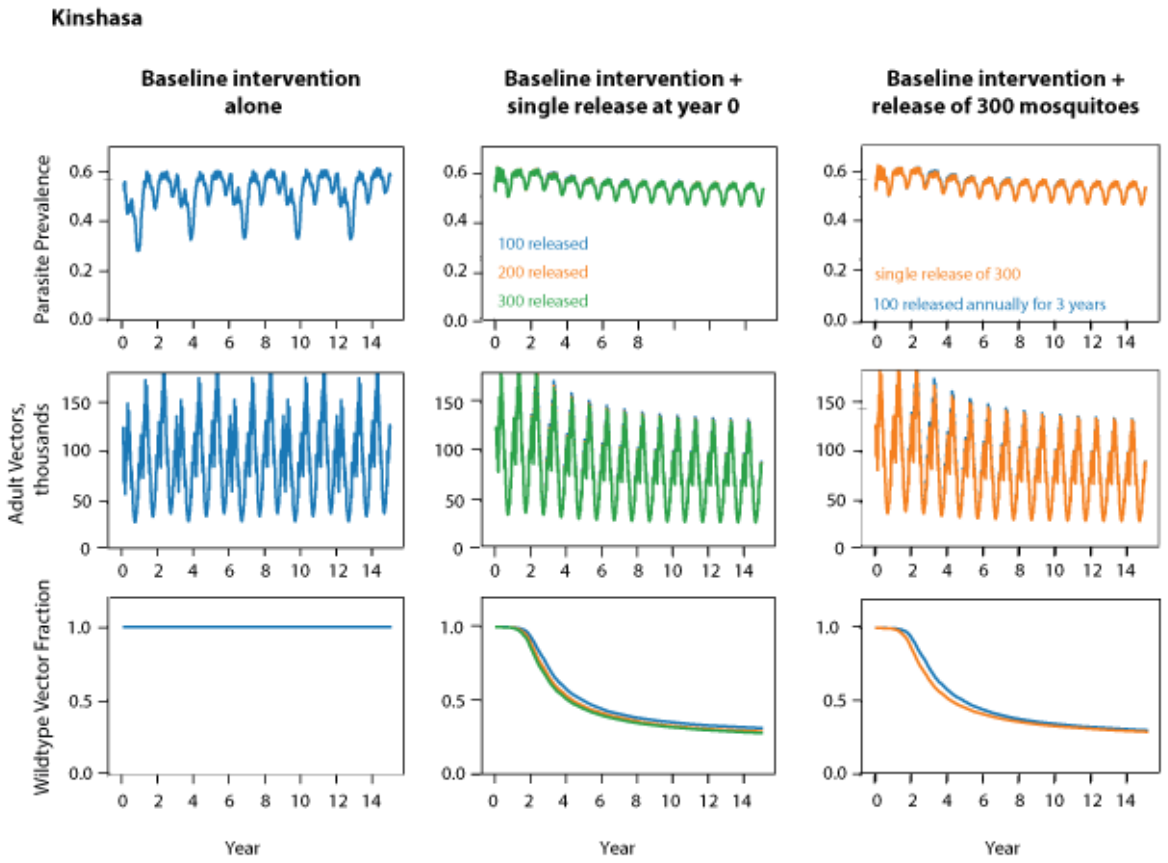
Appendix 1.1 Modeling outputs of mosquito release planning within non-spatial framework in selected locations in DRC

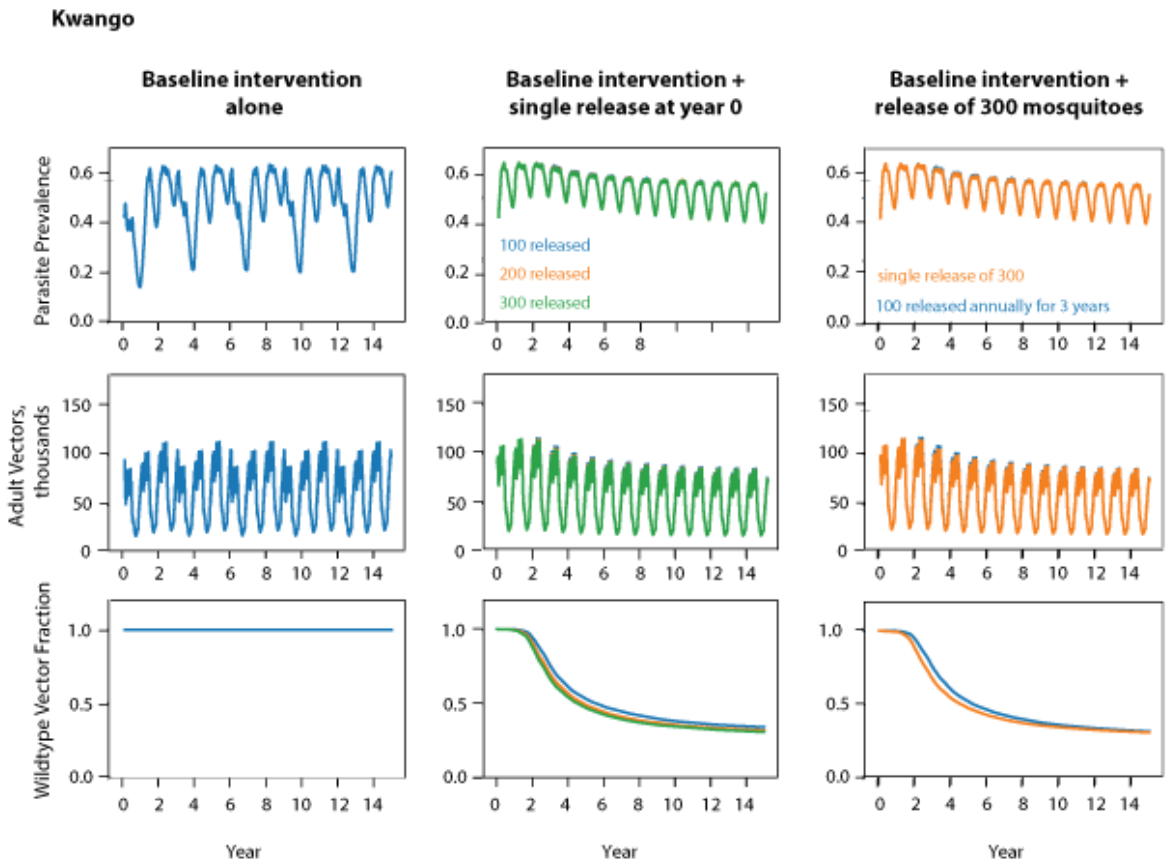


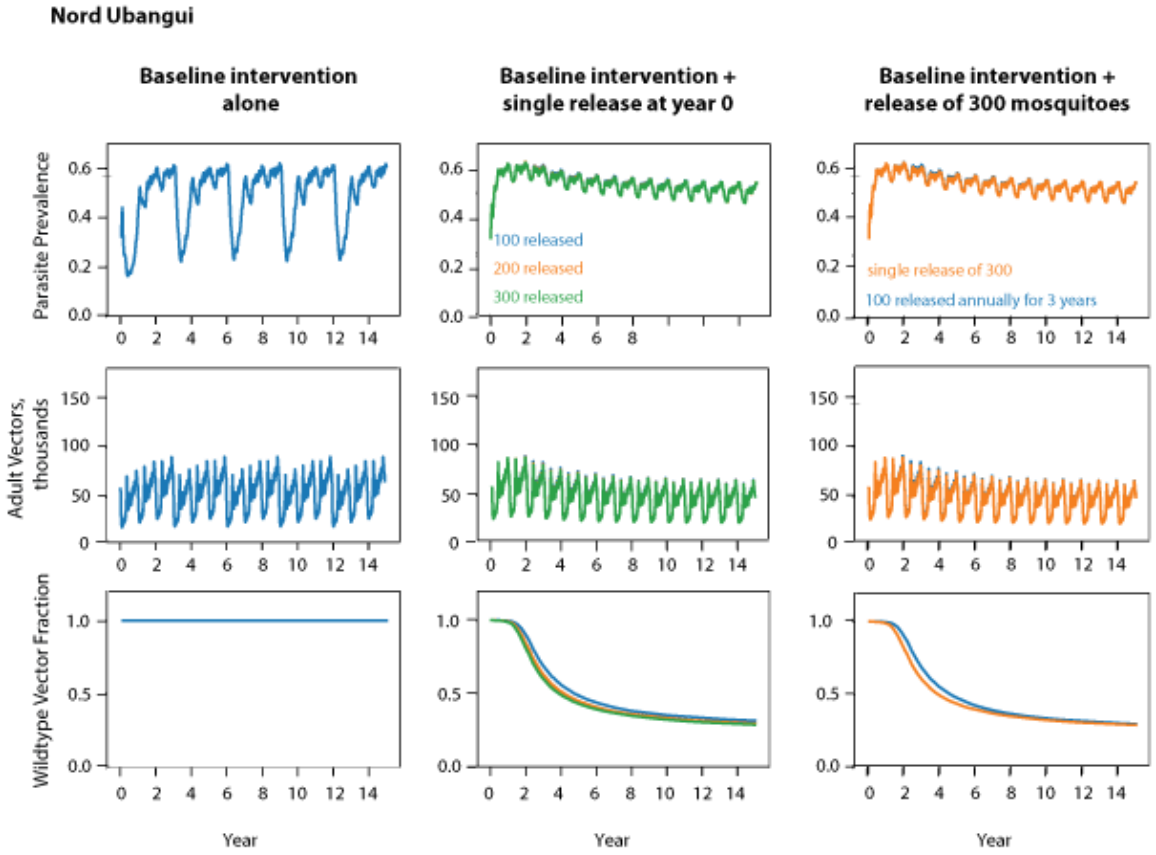

Equateur
Baseline intervention alone
Baseline intervention + single release at year 0
Baseline intervention + release of 300 mosquitoes
Parasite Prevalence
Adult Vectors, thousands
Wildtype Vector Fraction
100 released
200 released
300 released
single release of 300
100 released annually for 3 years
Year


Haut Katanga
Baseline intervention alone
Baseline intervention + single release at year 0
Baseline intervention + release of 300 mosquitoes
Parasite Prevalence
Adult Vectors, thousands
Wildtype Vector Fraction
100 released
200 released
300 released
single release of 300
100 released annually for 3 years
Year

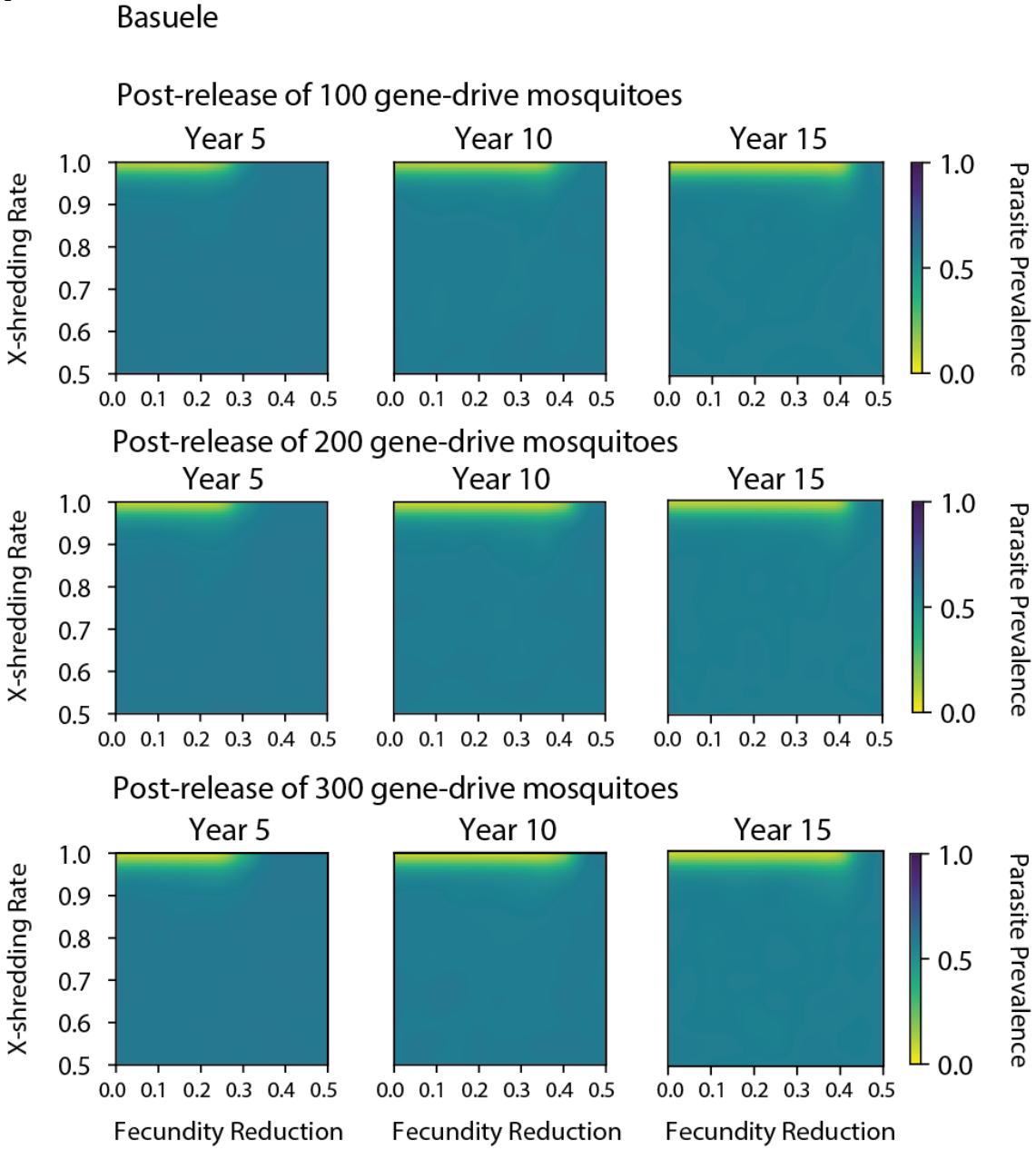

Kasai Central
Baseline intervention alone
Baseline intervention + single release at year 0
Baseline intervention + release of 300 mosquitoes
Parasite Prevalence
Adult Vectors, thousands
Wildtype Vector Fraction
100 released
200 released
300 released
single release of 300
100 released annually for 3 years
Year

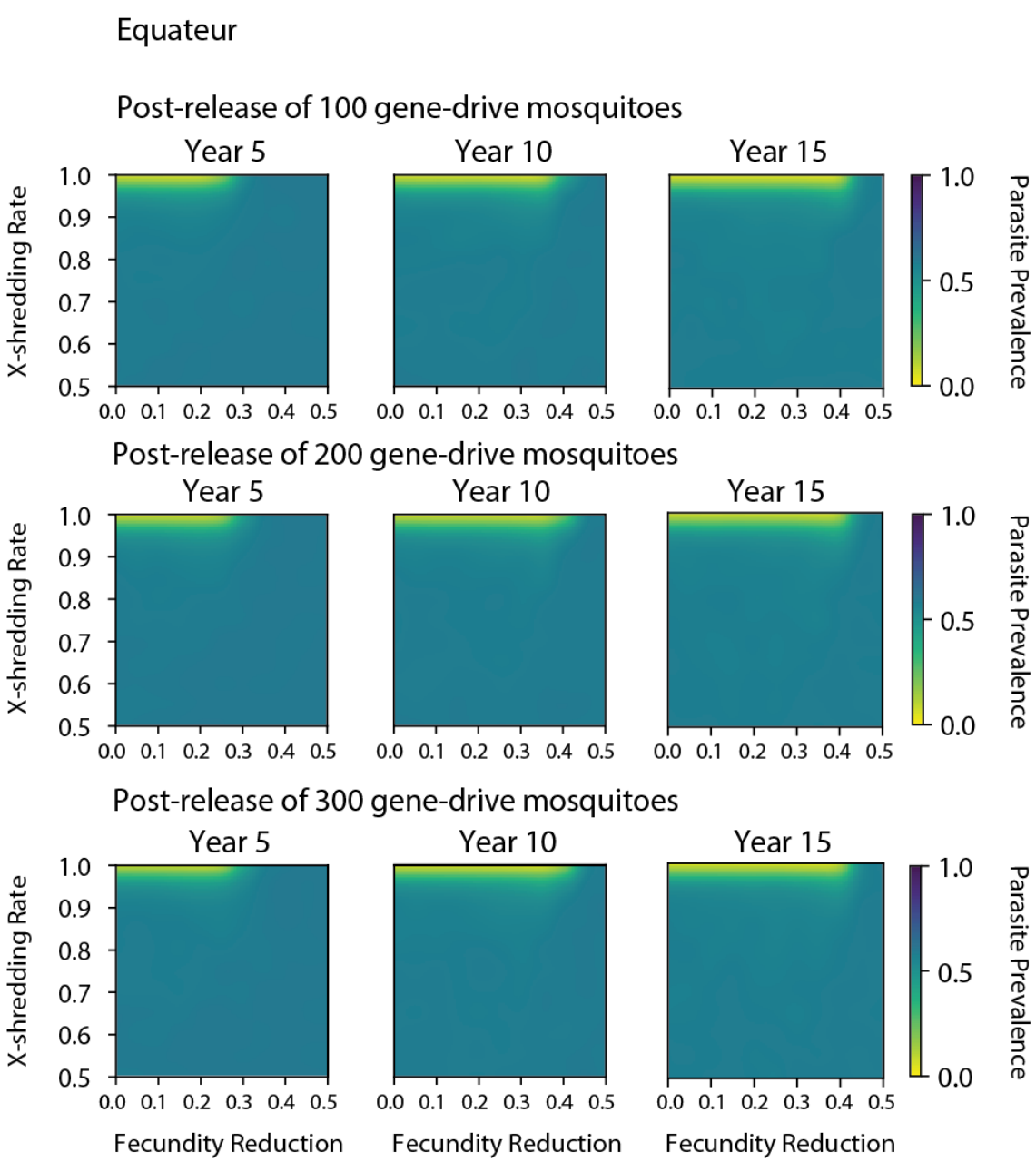

Kinshasa
Baseline intervention alone
Baseline intervention + single release at year 0
Baseline intervention + release of 300 mosquitoes
Parasite Prevalence
Adult Vectors, thousands
Wildtype Vector Fraction
100 released
200 released
300 released
single release of 300
100 released annually for 3 years
Year

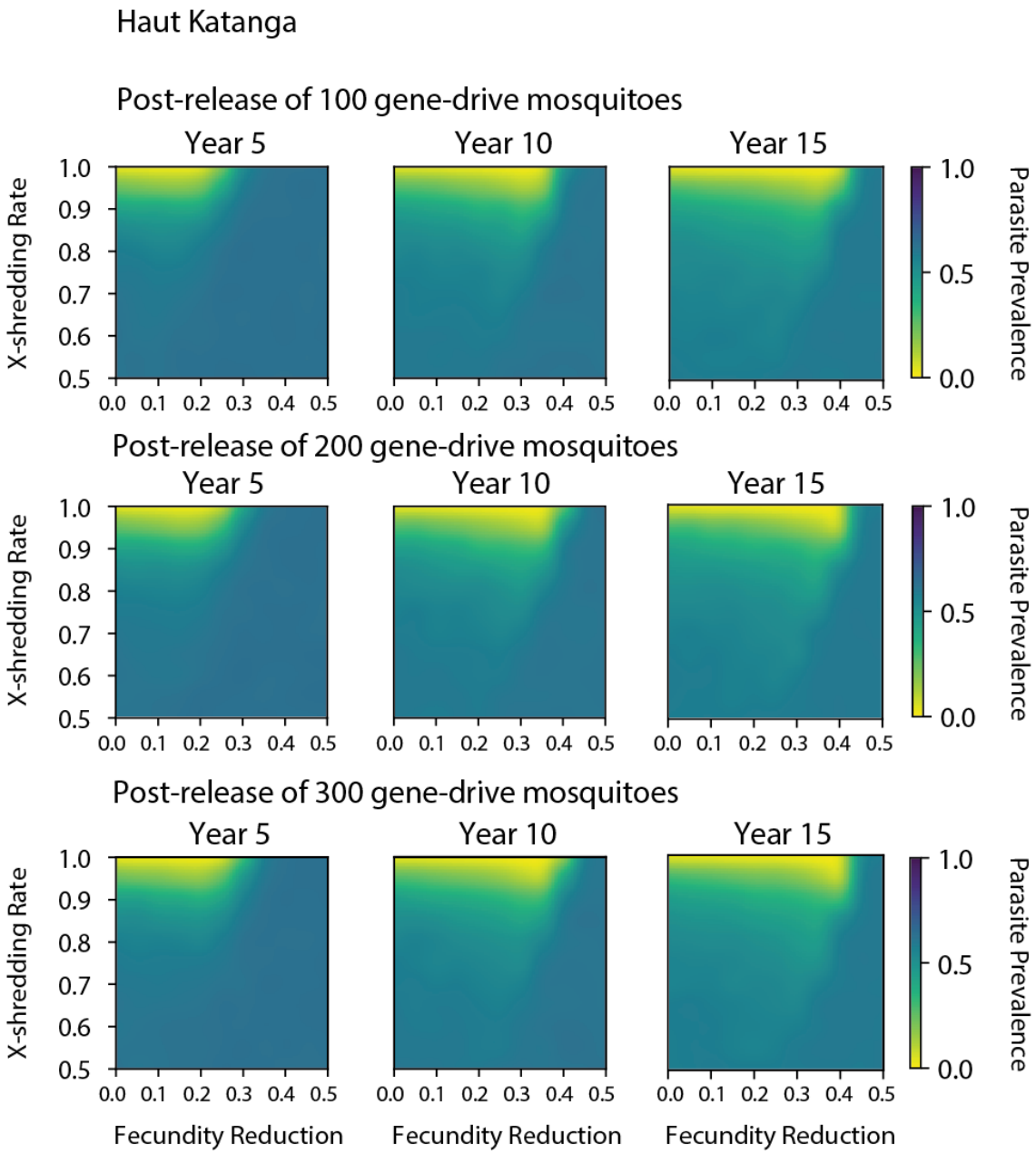

Kwango
Baseline intervention alone
Baseline intervention + single release at year 0
Baseline intervention + release of 300 mosquitoes
Parasite Prevalence
Adult Vectors, thousands
Wildtype Vector Fraction
100 released
200 released
300 released
single release of 300
100 released annually for 3 years
Year

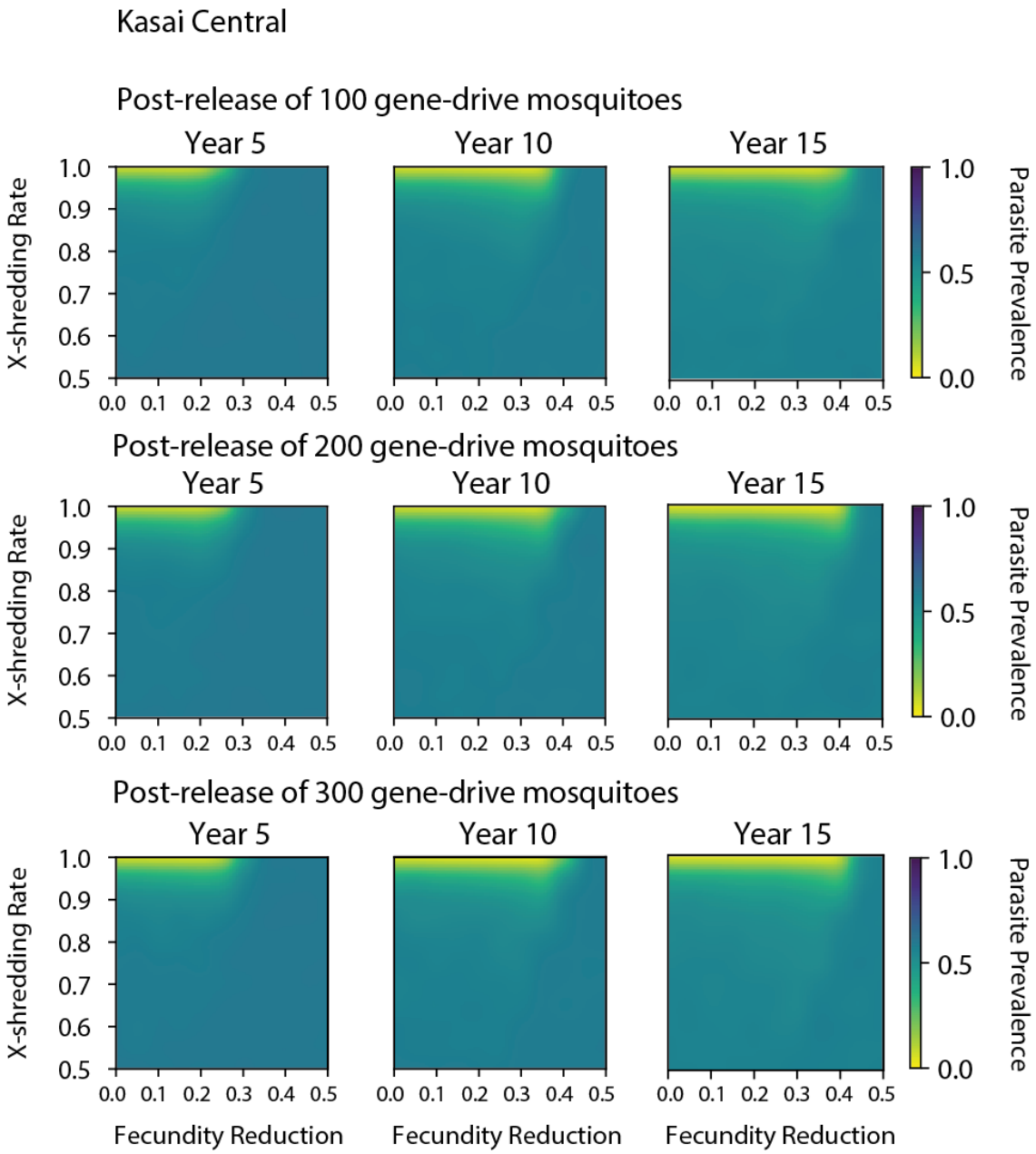

Nord Ubangui
Baseline intervention alone
Baseline intervention + single release at year 0
Baseline intervention + release of 300 mosquitoes
Parasite Prevalence
Adult Vectors, thousands
Wildtype Vector Fraction
100 released
200 released
300 released
single release of 300
100 released annually for 3 years
Year

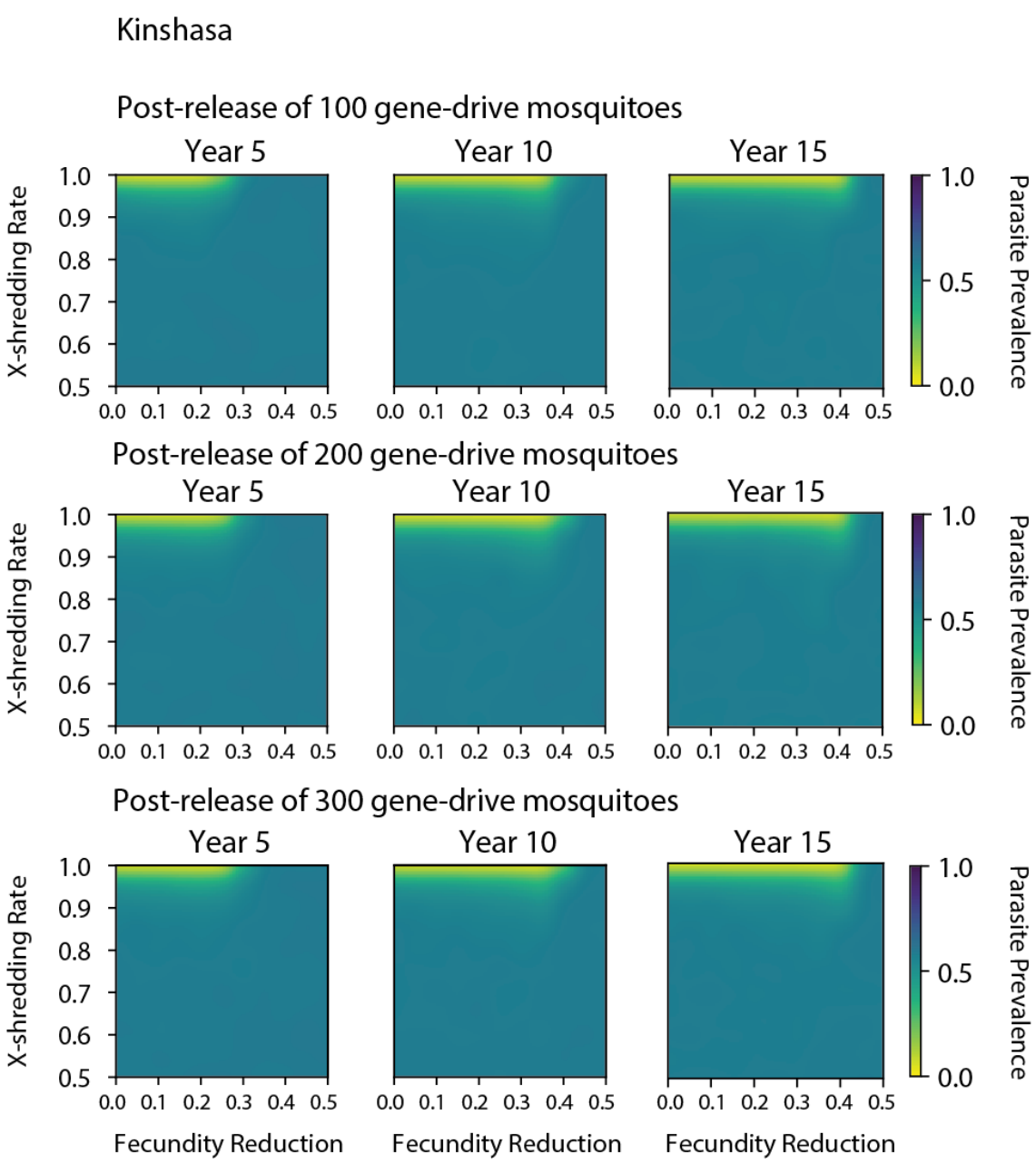
Appendix 1.2 Simulation outputs after single release of 100, 200, and 300 gene drive mosquitoes within non-spatial framework in eight study locations at 5, 10 and 15-year post-release.

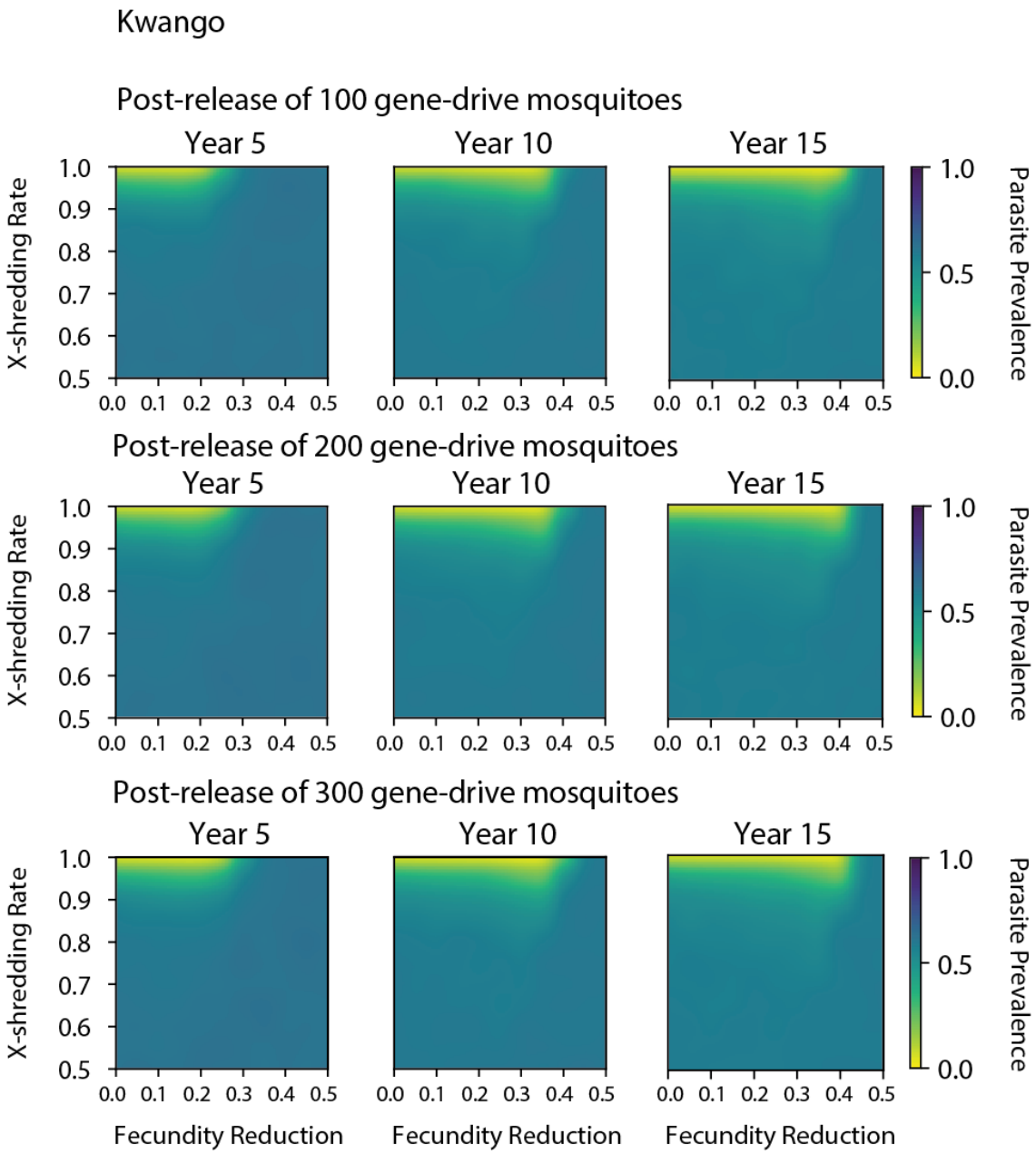


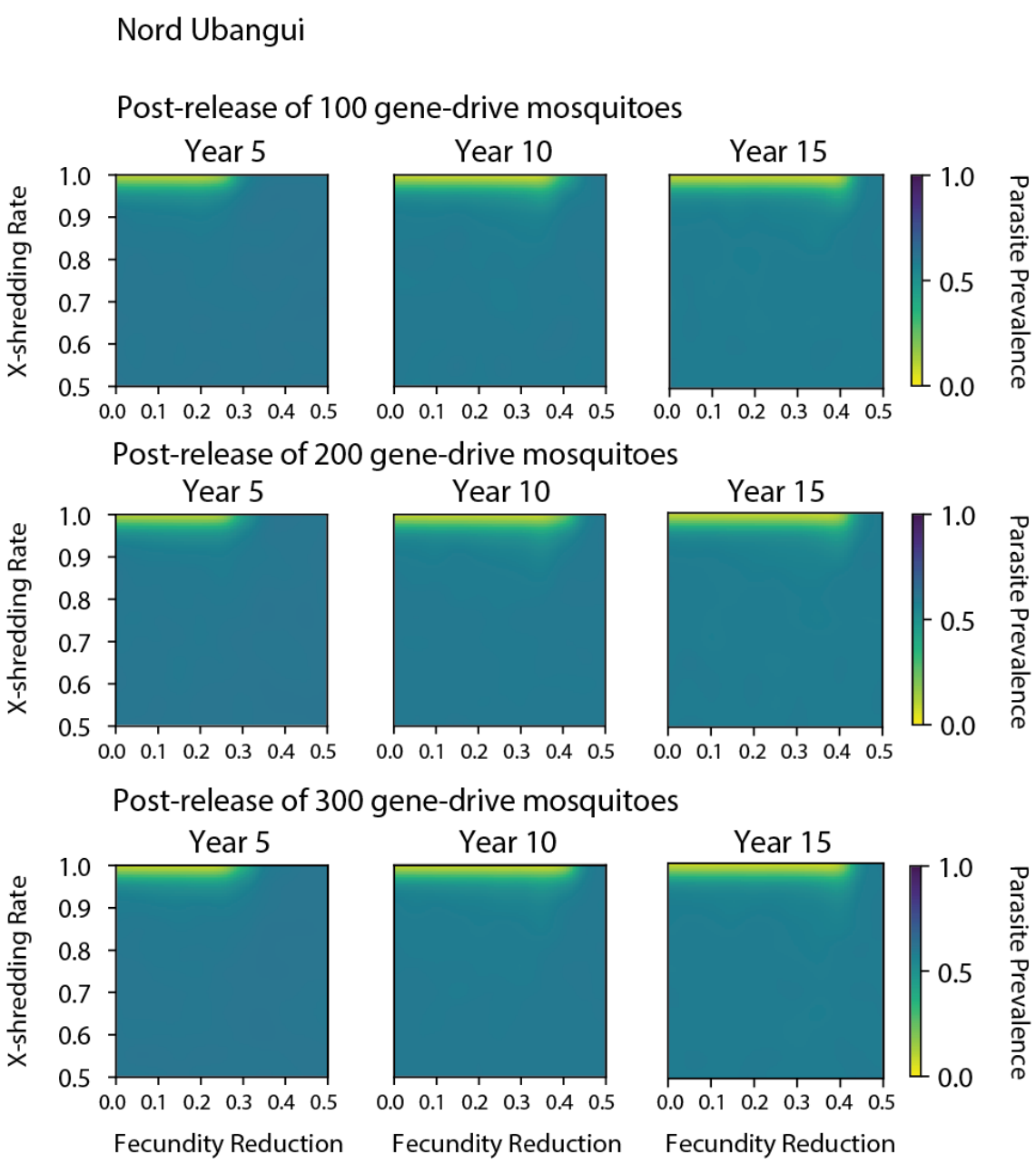

Equateur
Post-release of 100 gene-drive mosquitoes
Year 5
Year 10
Year 15
Post-release of 200 gene-drive mosquitoes
Year 5
Year 10
Year 15
Post-release of 300 gene-drive mosquitoes
Year 5
Year 10
Year 15
X-shredding Rate
1.0
0.9
0.8
0.7
0.6
0.5
0.0 0.1 0.2 0.3 0.4 0.5
Fecundity Reduction
Parasite Prevalence
1.0
0.5
0.0


Haut Katanga
Post-release of 100 gene-drive mosquitoes
Year 5
Year 10
Year 15
X-shredding Rate
1.0
0.9
0.8
0.7
0.6
0.5
0.0 0.1 0.2 0.3 0.4 0.5
Parasite Prevalence
1.0
0.5
0.0
Post-release of 200 gene-drive mosquitoes
Post-release of 300 gene-drive mosquitoes
Fecundity Reduction

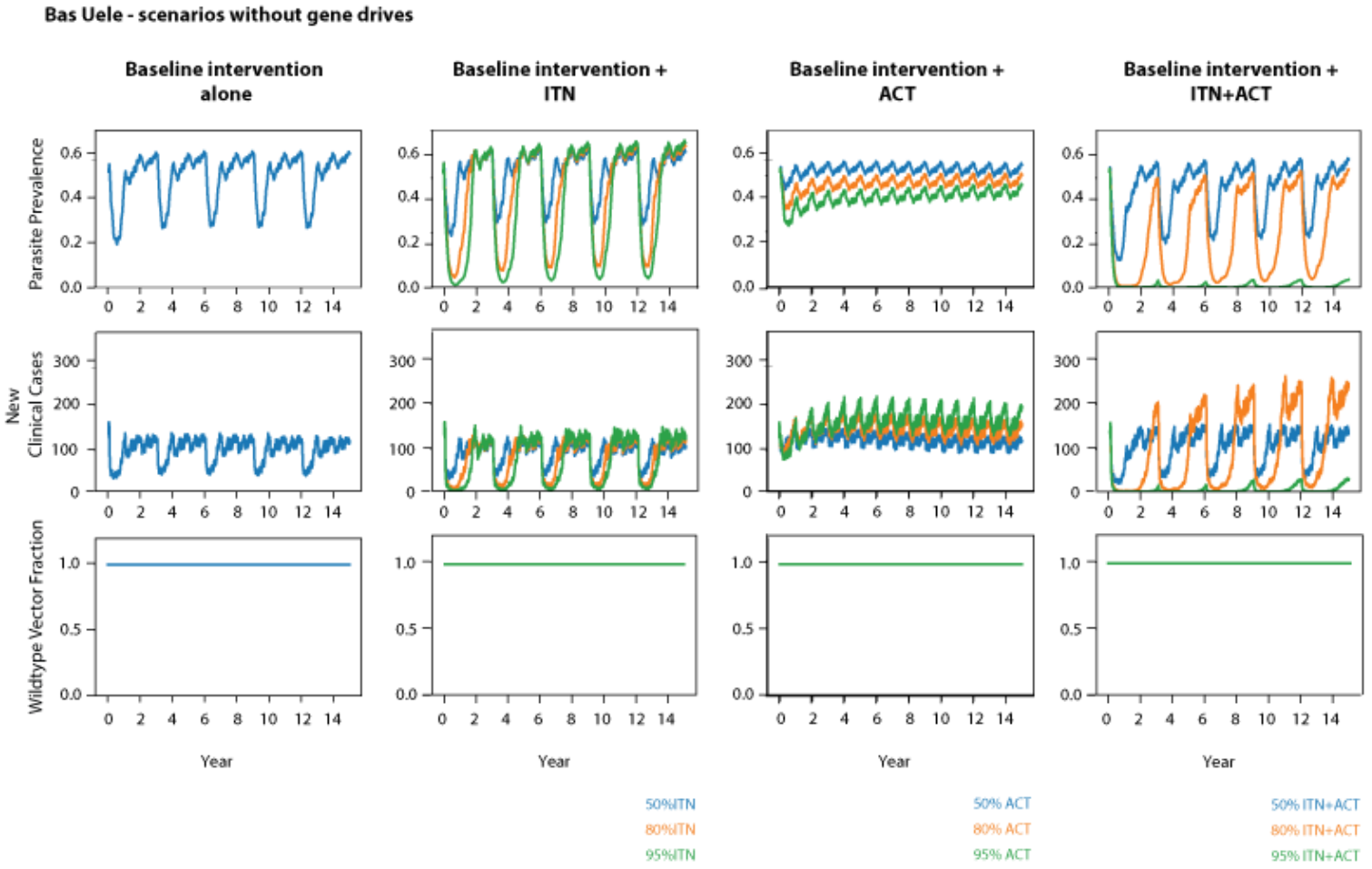

Kasai Central
Post-release of 100 gene-drive mosquitoes
Year 5
Year 10
Year 15
X-shredding Rate
Parasite Prevalence
Post-release of 200 gene-drive mosquitoes
Post-release of 300 gene-drive mosquitoes
Fecundity Reduction

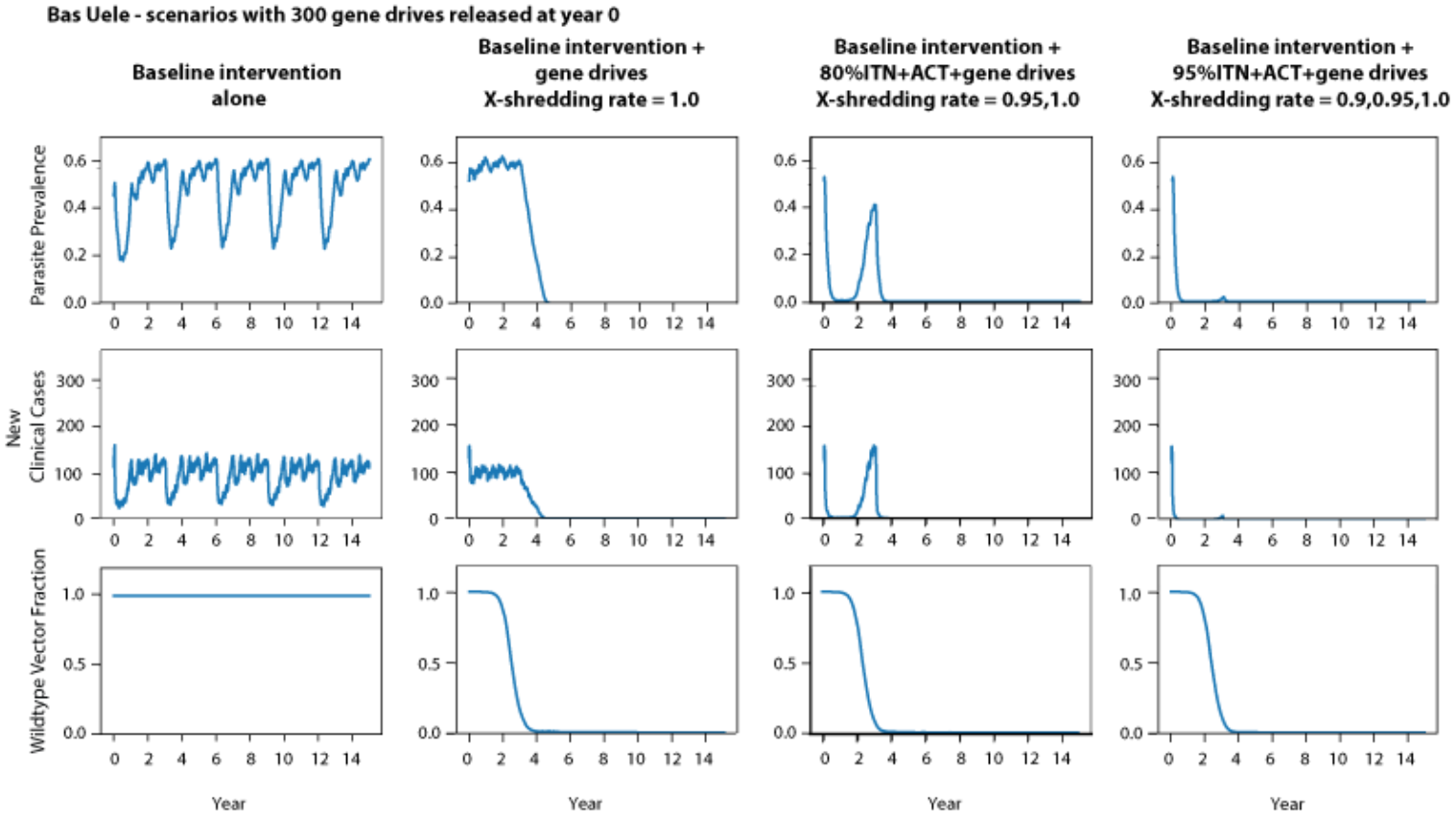

Kinshasa
Post-release of 100 gene-drive mosquitoes
Year 5
Year 10
Year 15
X-shredding Rate
Parasite Prevalence
Post-release of 200 gene-drive mosquitoes
Post-release of 300 gene-drive mosquitoes
Fecundity Reduction

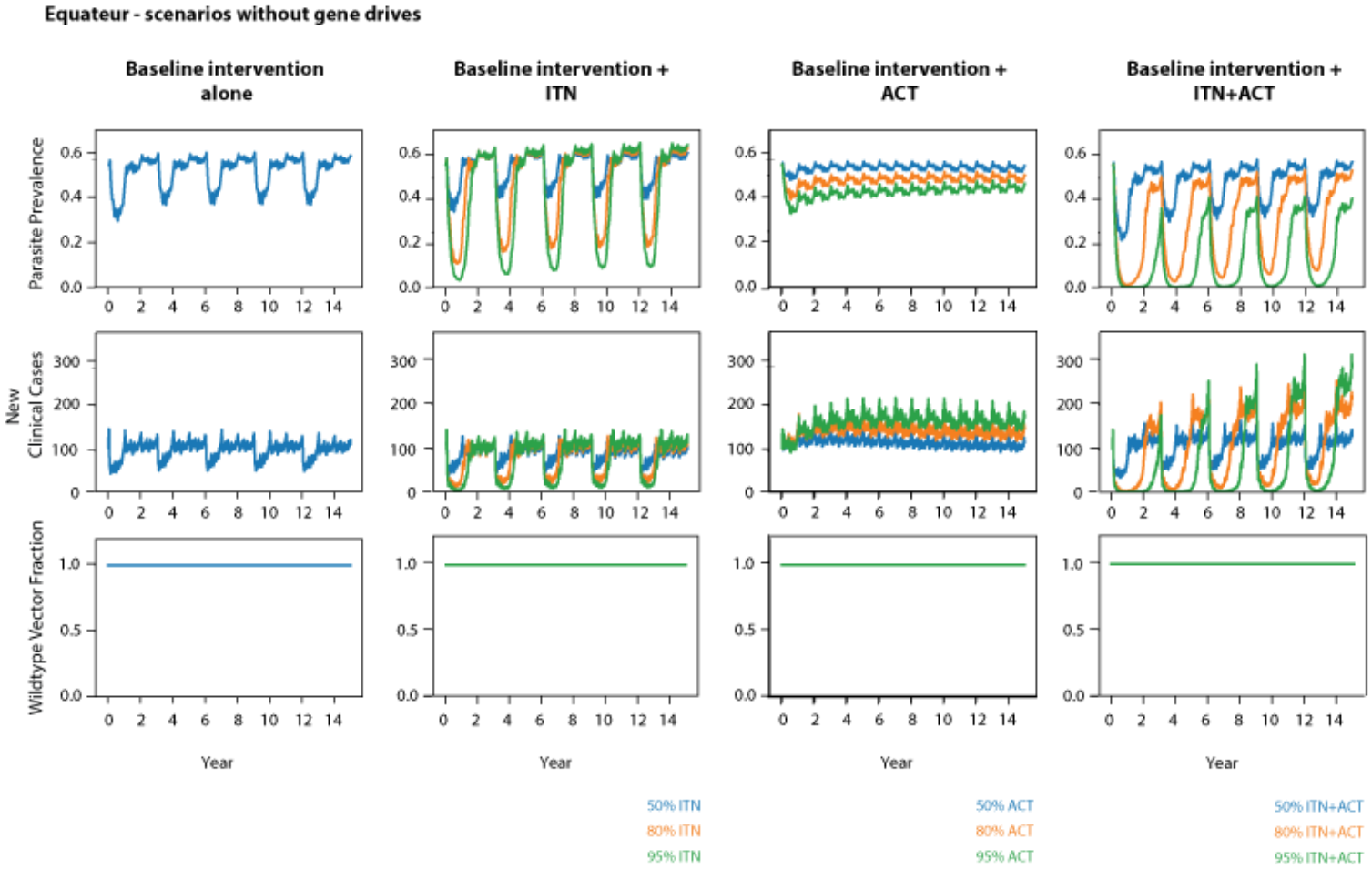

Kwango
Post-release of 100 gene-drive mosquitoes
Year 5
Year 10
Year 15
X-shredding Rate
Parasite Prevalence
Post-release of 200 gene-drive mosquitoes
Post-release of 300 gene-drive mosquitoes
Fecundity Reduction

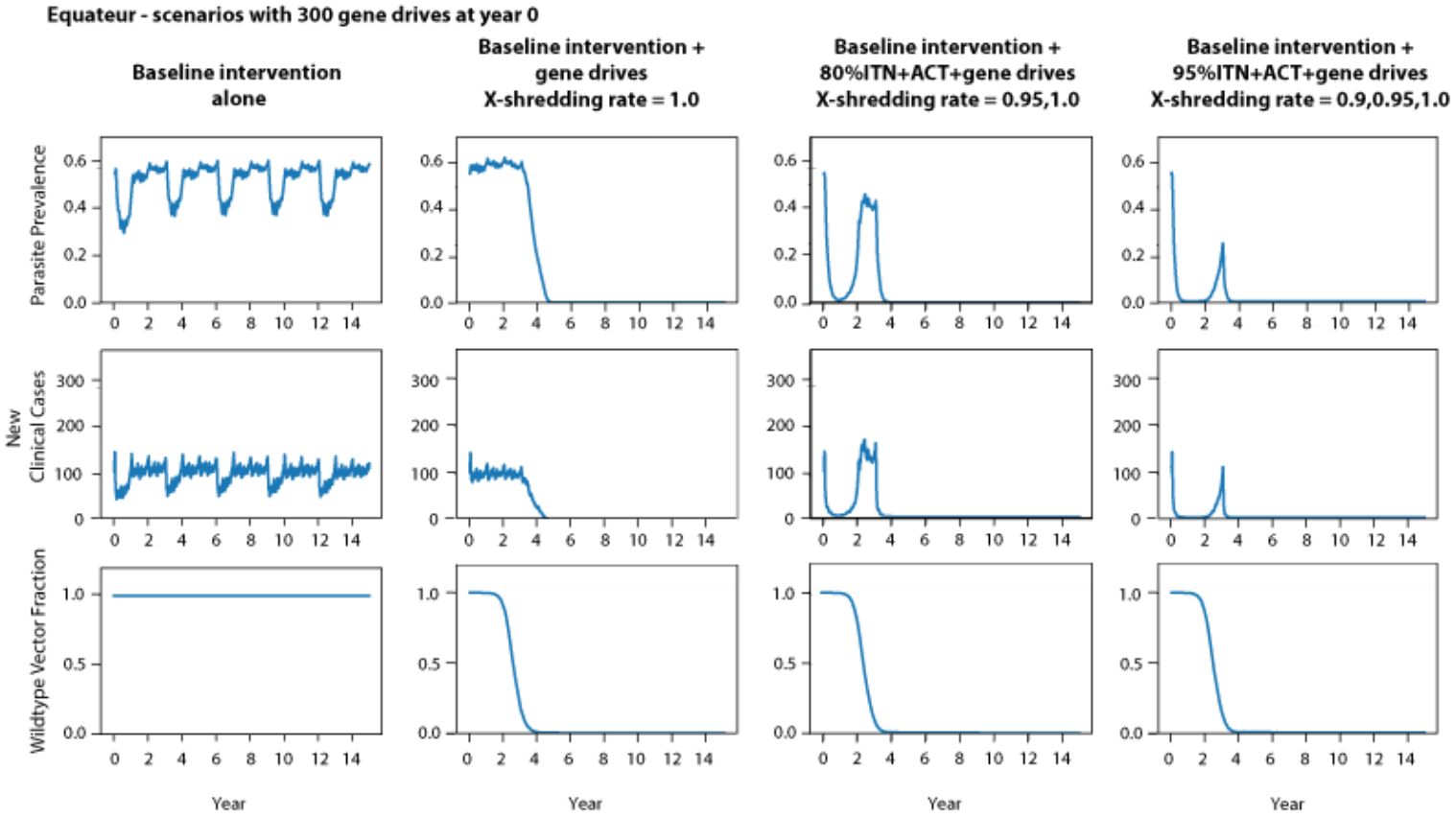

Nord Ubangui
Post-release of 100 gene-drive mosquitoes
Year 5
Year 10
Year 15
X-shredding Rate
1.0
0.9
0.8
0.7
0.6
0.5
0.0 0.1 0.2 0.3 0.4 0.5
Parasite Prevalence
1.0
0.5
0.0
Post-release of 200 gene-drive mosquitoes
Year 5
Year 10
Year 15
X-shredding Rate
Parasite Prevalence
Post-release of 300 gene-drive mosquitoes
Year 5
Year 10
Year 15
X-shredding Rate
Parasite Prevalence
Fecundity Reduction
Fecundity Reduction
Fecundity Reduction

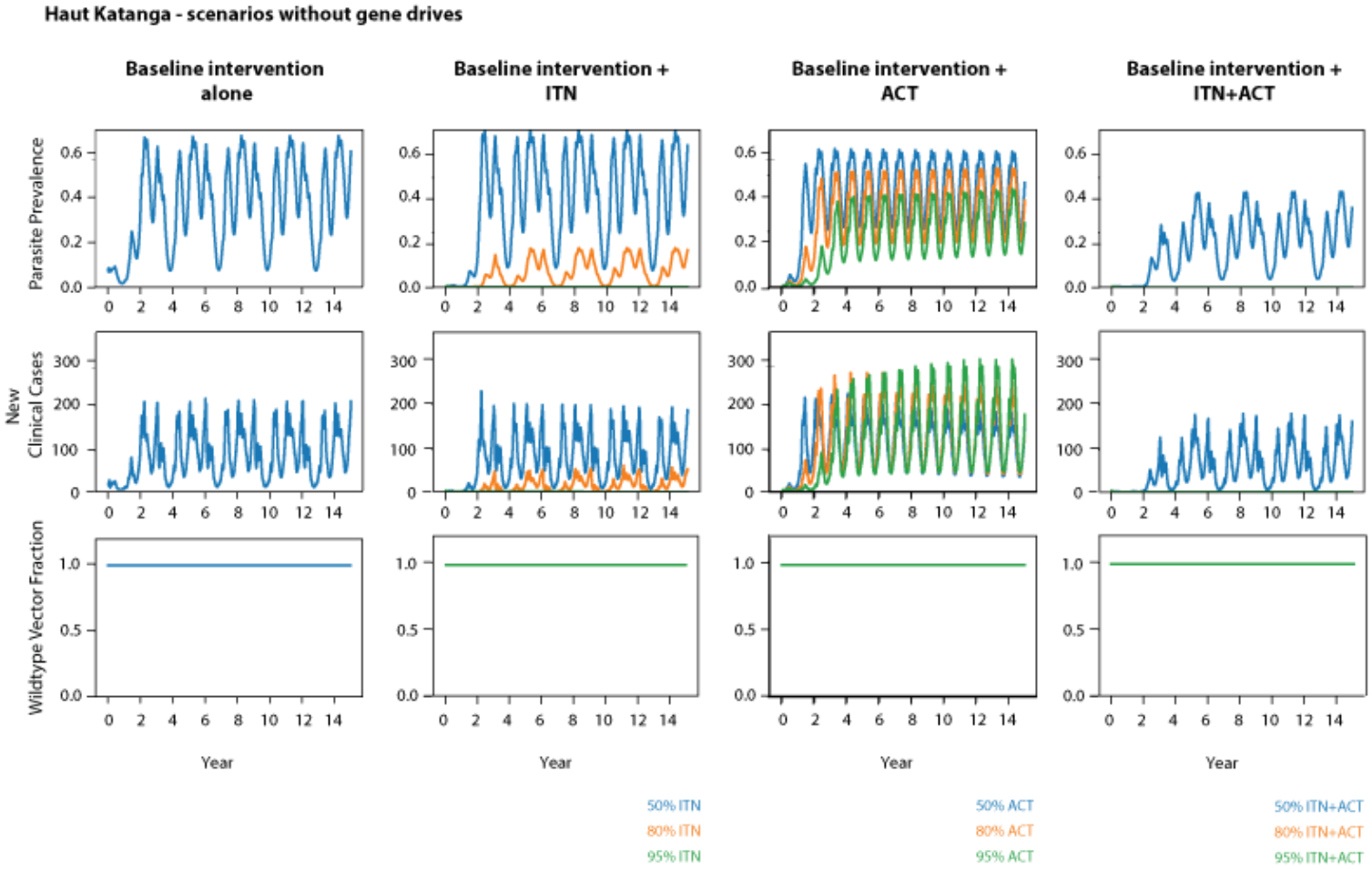
Appendix 2: Simulation outputs – spatial framework

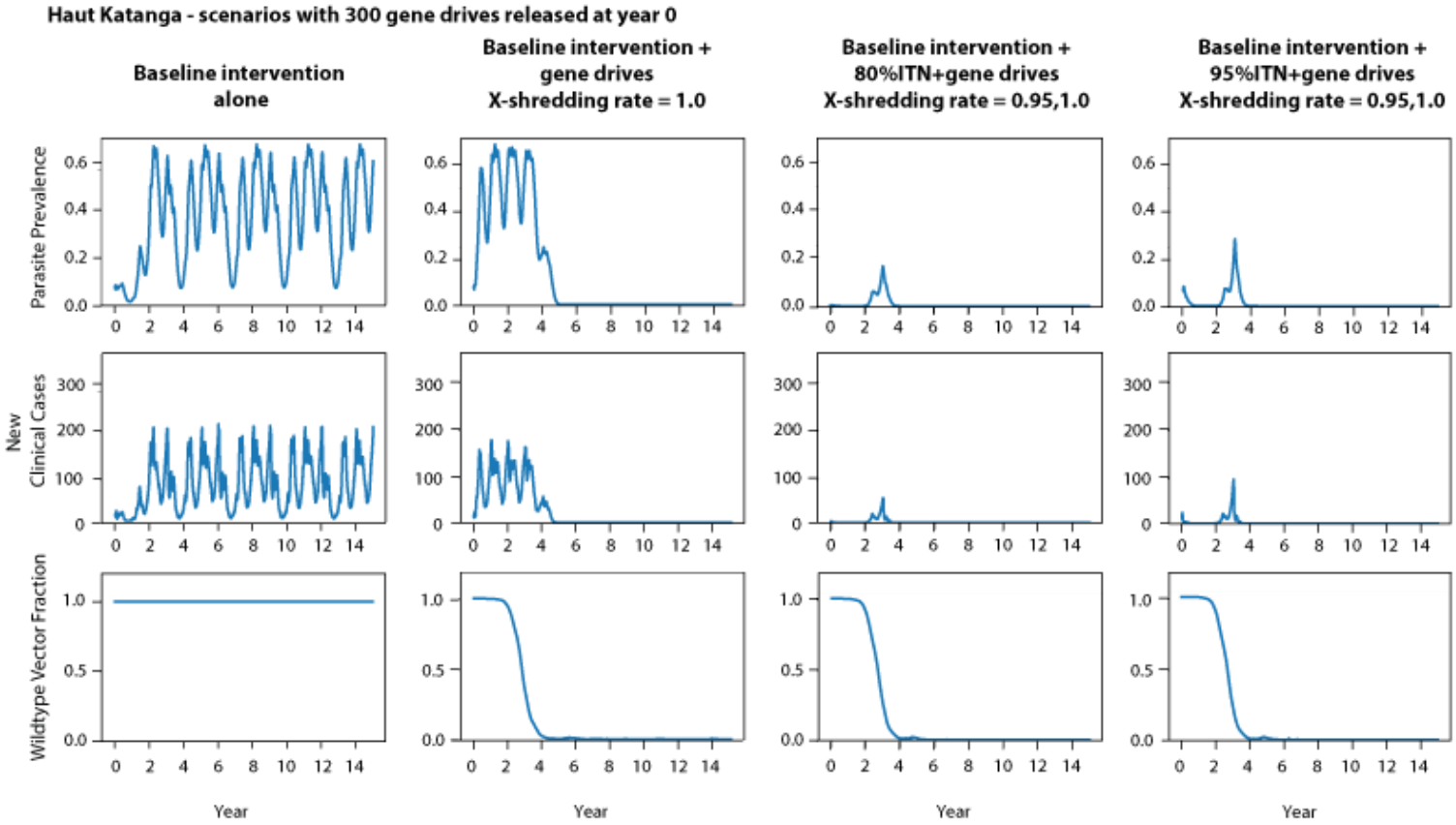


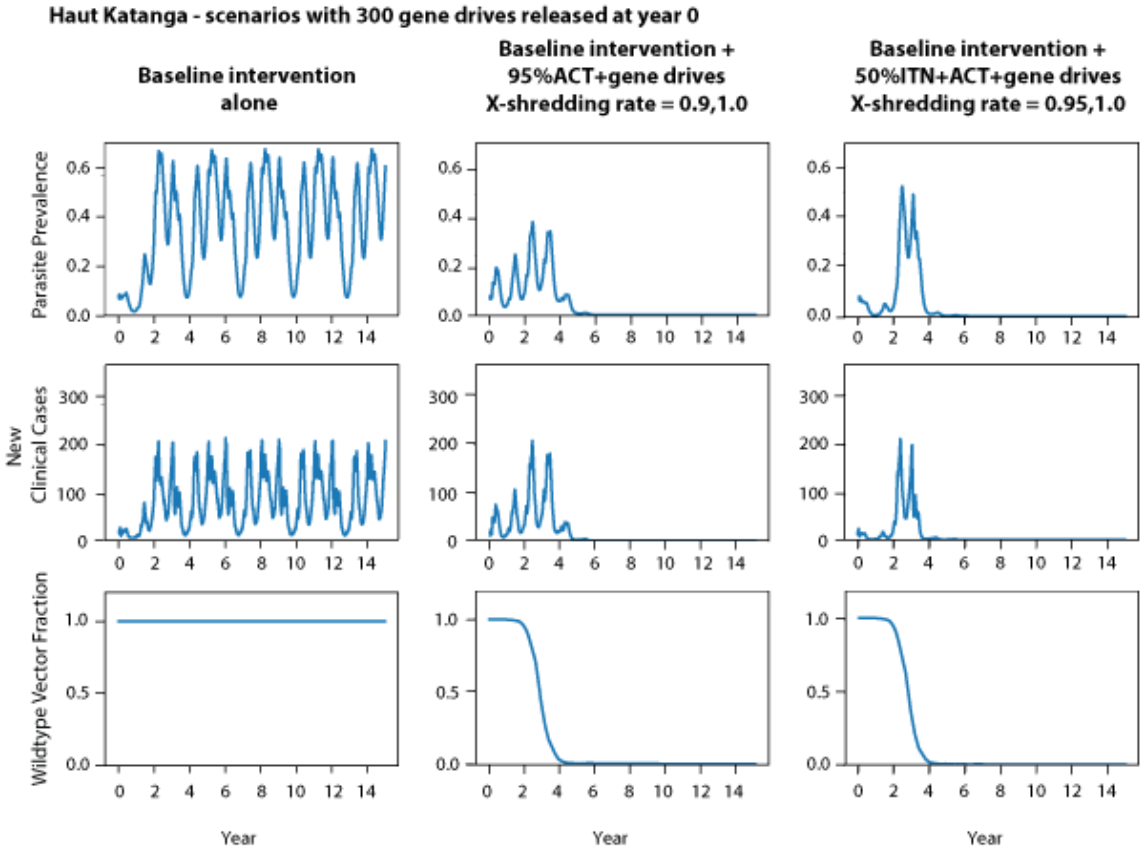

Bas Uele - scenarios with 300 gene drives released at year 0
Baseline intervention alone
Baseline intervention + gene drives X-shredding rate = 1.0
Baseline intervention + 80%ITN+ACT+gene drives X-shredding rate = 0.95,1.0
Baseline intervention + 95%ITN+ACT+gene drives X-shredding rate = 0.9,0.95,1.0
Parasite Prevalence
New Clinical Cases
Wildtype Vector Fraction
Year

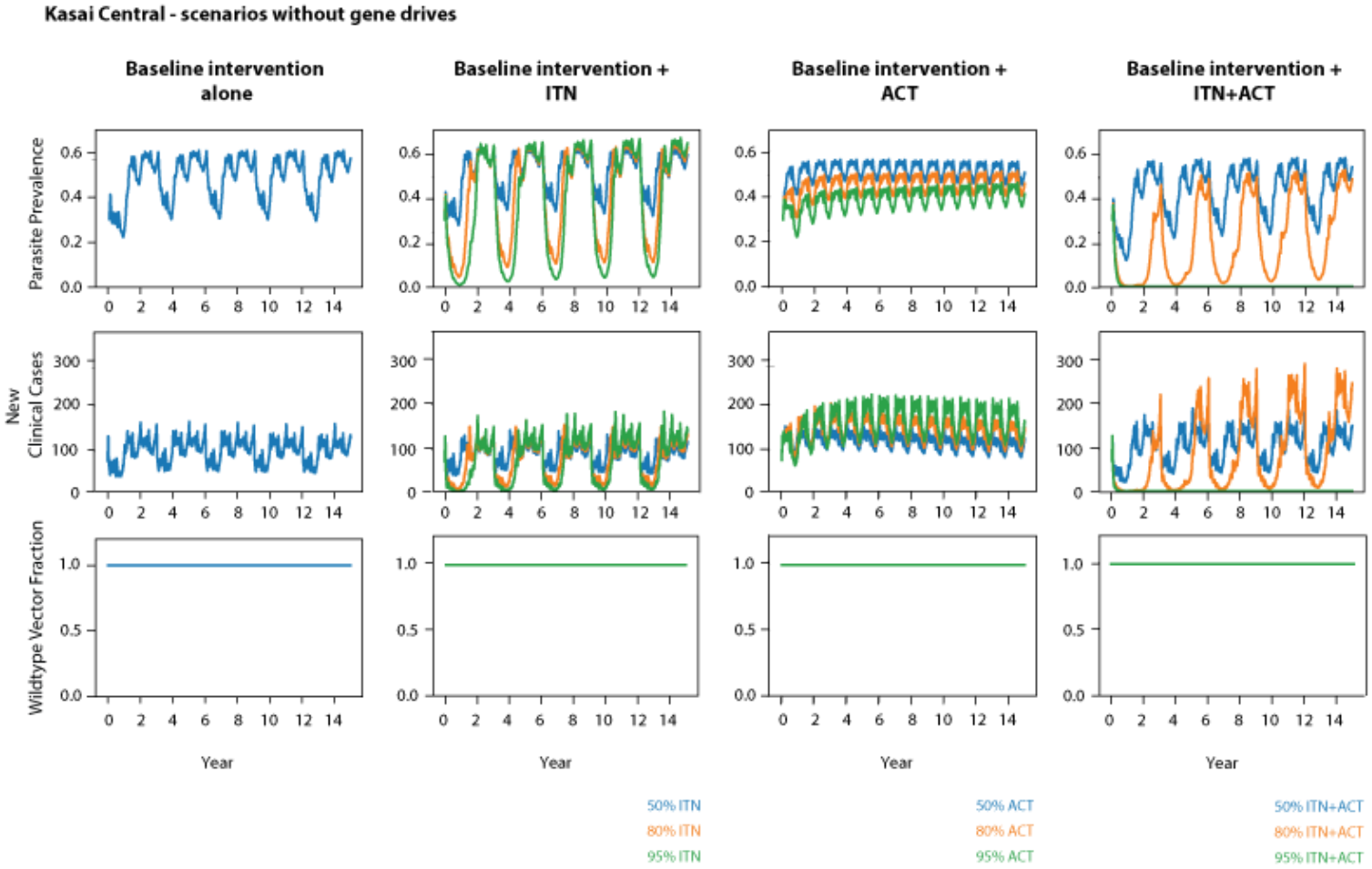

Equateur - scenarios without gene drives
Baseline intervention alone
Baseline intervention + ITN
Baseline intervention + ACT
Baseline intervention + ITN+ACT
Parasite Prevalence
New Clinical Cases
Wildtype Vector Fraction
Year
50% ITN
80% ITN
95% ITN
50% ACT
80% ACT
95% ACT
50% ITN+ACT
80% ITN+ACT
95% ITN+ACT

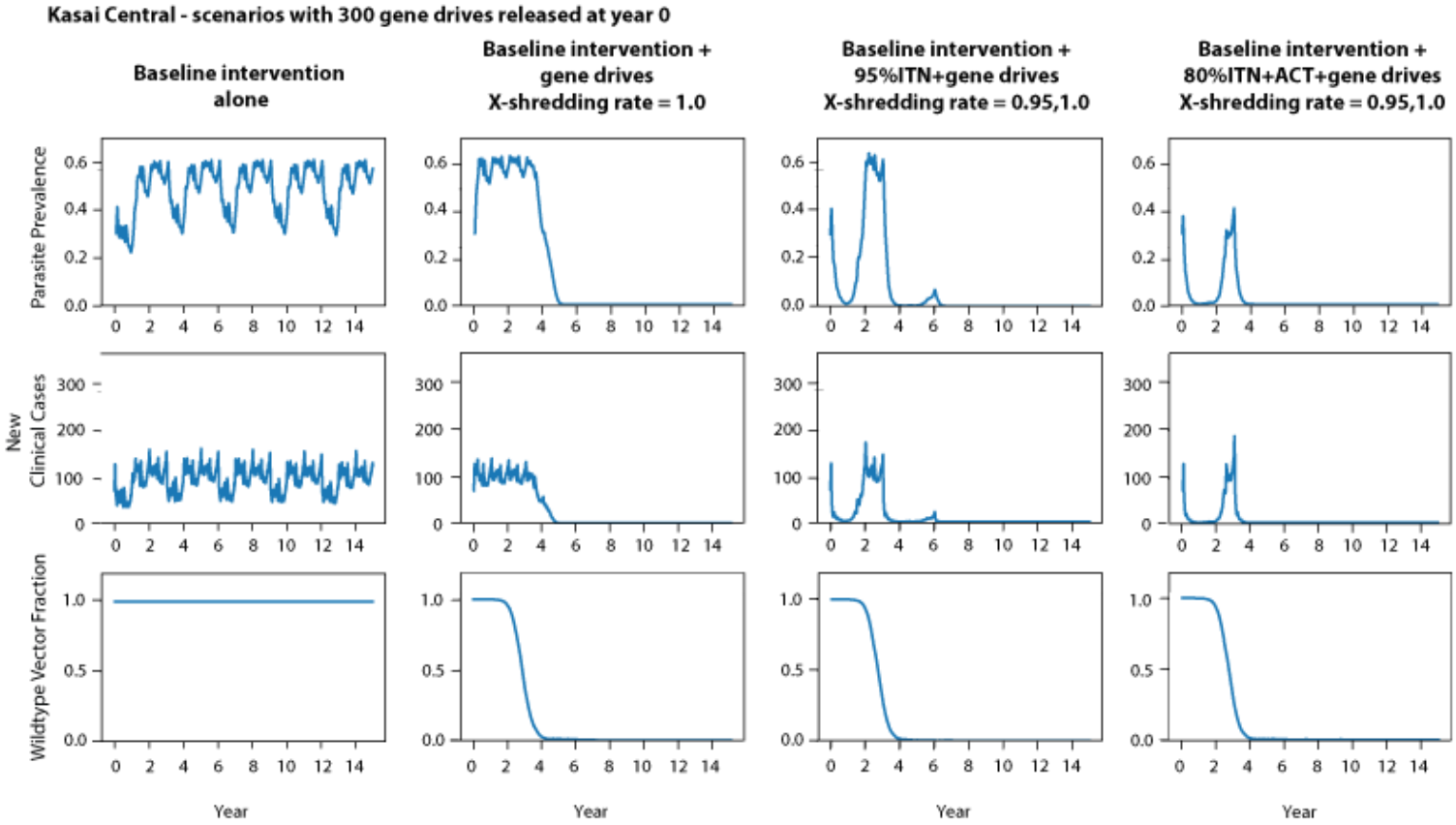

Equateur - scenarios with 300 gene drives at year 0
Baseline intervention alone
Baseline intervention + gene drives X-shredding rate = 1.0
Baseline intervention + 80%ITN+ACT+gene drives X-shredding rate = 0.95,1.0
Baseline intervention + 95%ITN+ACT+gene drives X-shredding rate = 0.9,0.95,1.0
Parasite Prevalence
New Clinical Cases
Wildtype Vector Fraction
Year

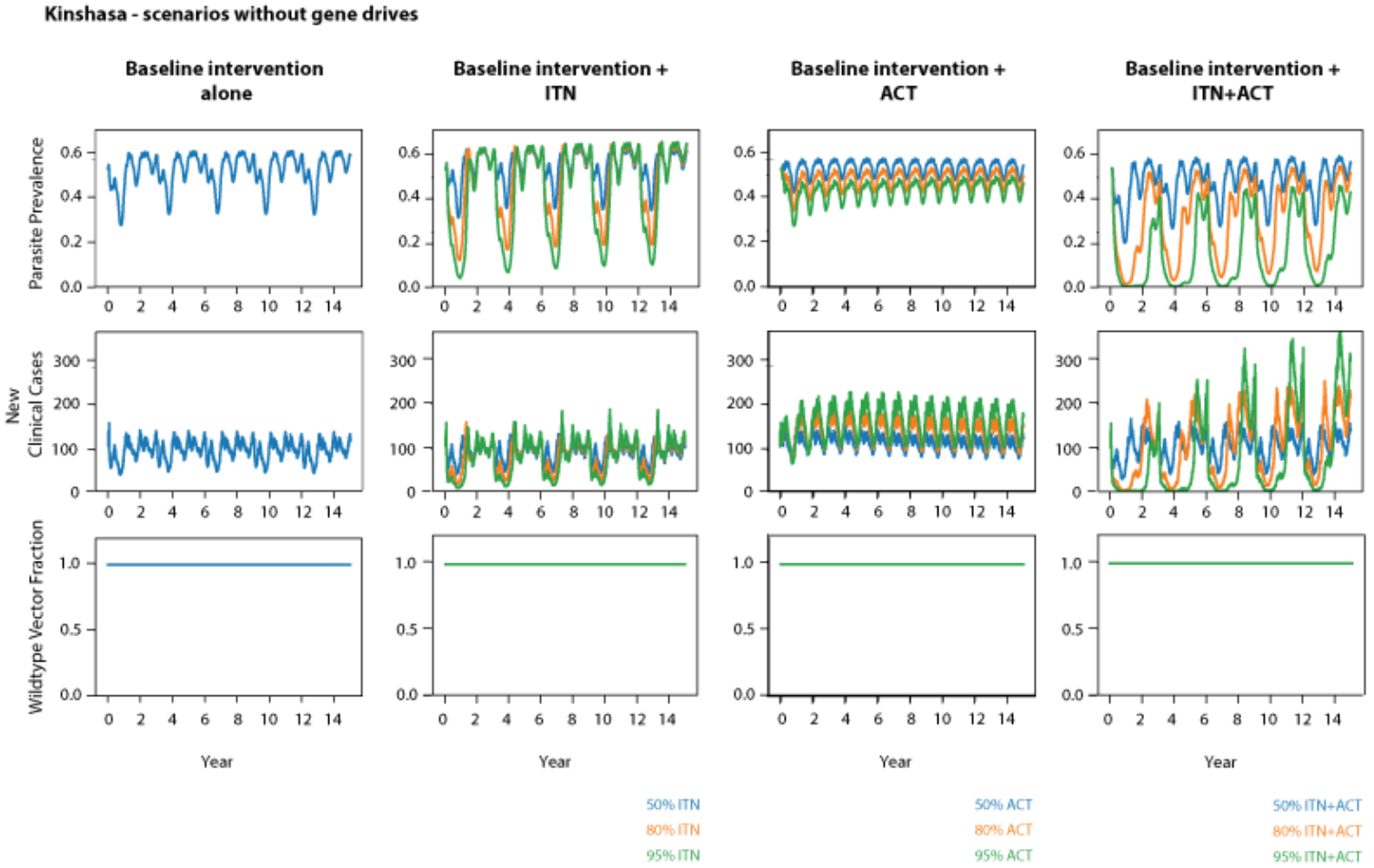

Haut Katanga - scenarios without gene drives
Baseline intervention alone
Baseline intervention + ITN
Baseline intervention + ACT
Baseline intervention + ITN+ACT
Parasite Prevalence
New Clinical Cases
Wildtype Vector Fraction
Year
50% ITN
80% ITN
95% ITN
50% ACT
80% ACT
95% ACT
50% ITN+ACT
80% ITN+ACT
95% ITN+ACT

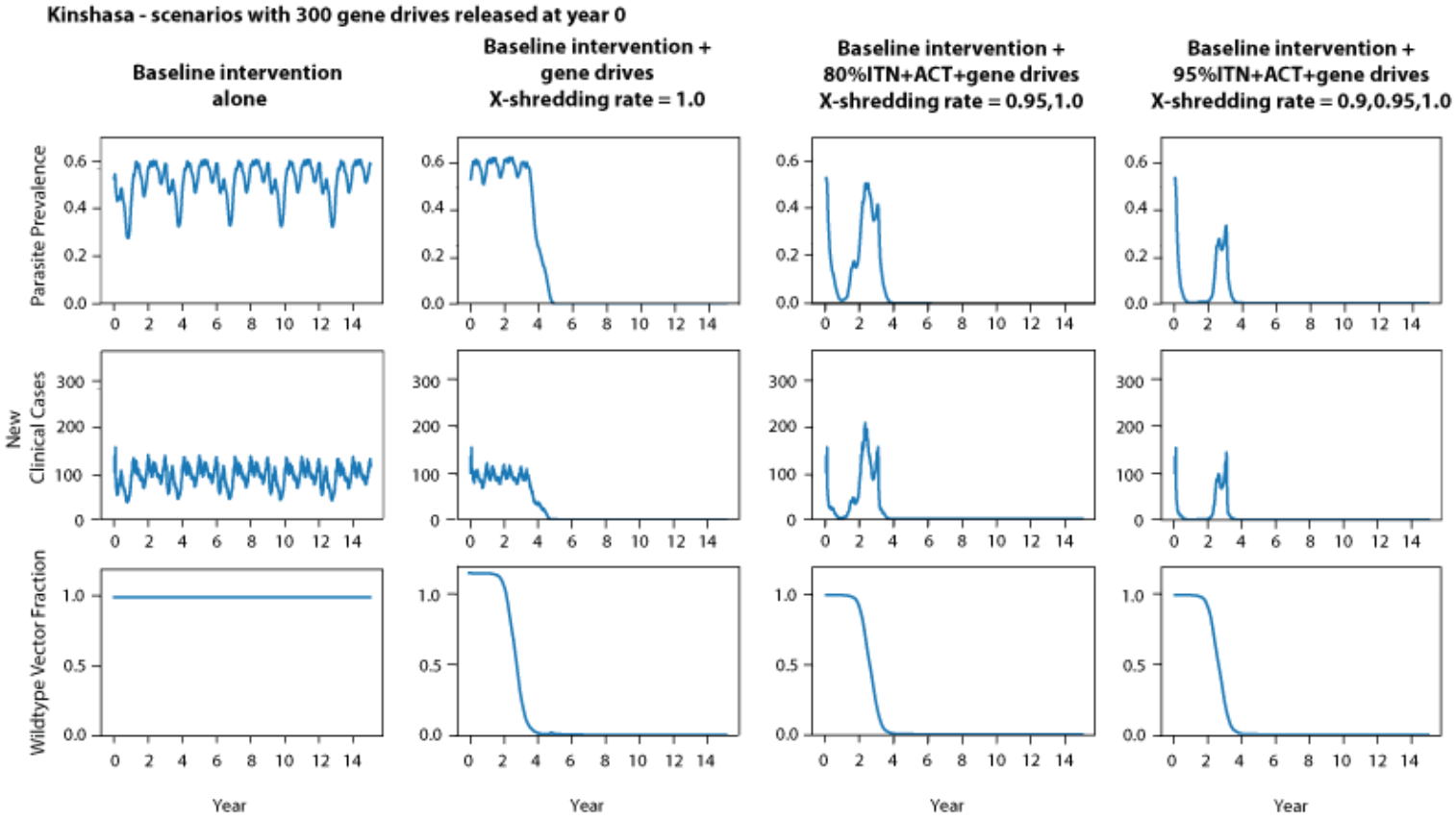

Haut Katanga - scenarios with 300 gene drives released at year 0
Baseline intervention alone
Baseline intervention + gene drives X-shredding rate = 1.0
Baseline intervention + 80%ITN+gene drives X-shredding rate = 0.95,1.0
Baseline intervention + 95%ITN+gene drives X-shredding rate = 0.95,1.0
Parasite Prevalence
New Clinical Cases
Wildtype Vector Fraction
Year

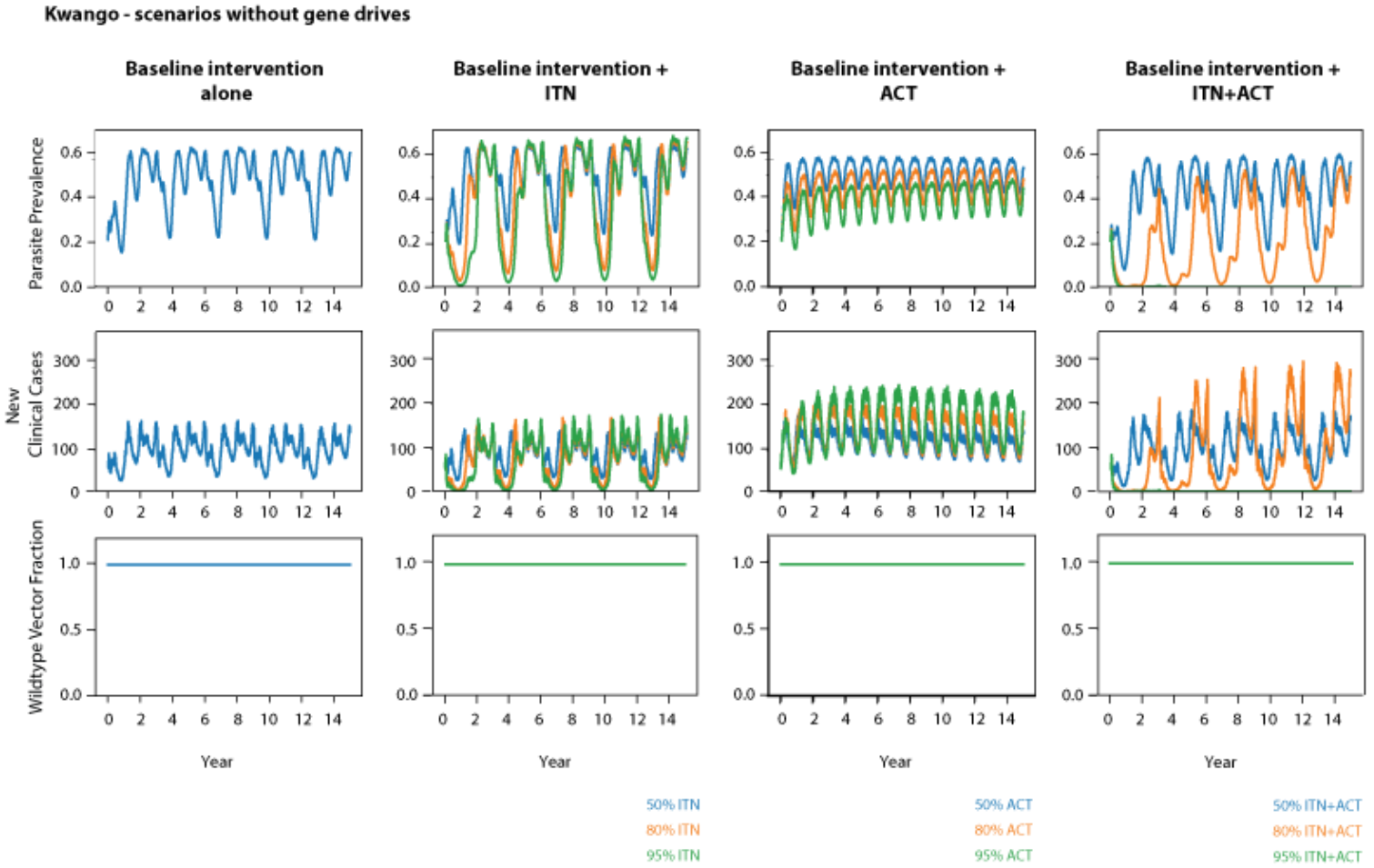

Haut Katanga - scenarios with 300 gene drives released at year 0
Baseline intervention alone
Baseline intervention + 95%ACT+gene drives X-shredding rate = 0.9,1.0
Baseline intervention + 50%ITN+ACT+gene drives X-shredding rate = 0.95,1.0
Parasite Prevalence
New Clinical Cases
Wildtype Vector Fraction
Year
Year
Year

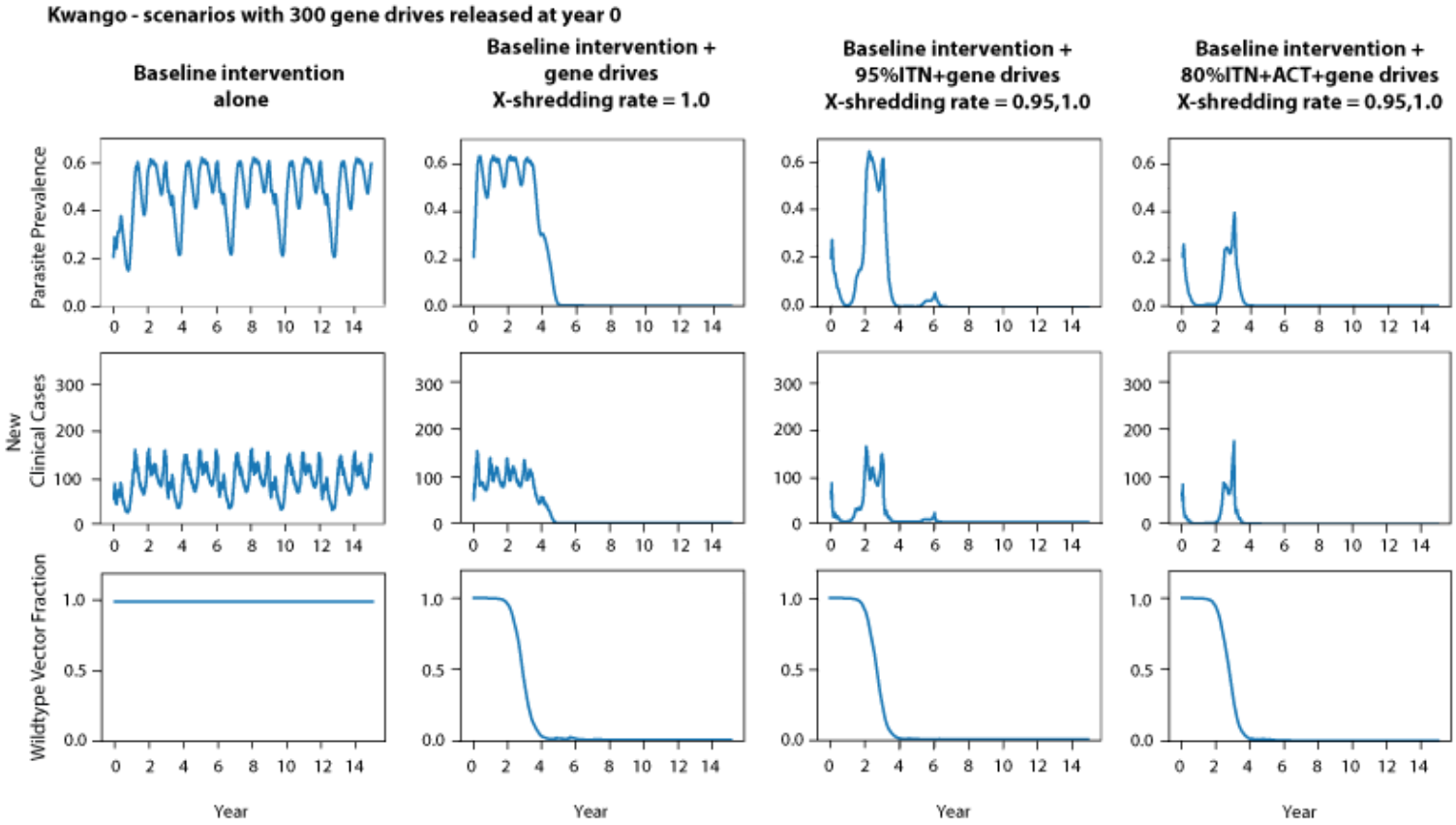

Kasai Central - scenarios without gene drives
Baseline intervention alone
Baseline intervention + ITN
Baseline intervention + ACT
Baseline intervention + ITN+ACT
Parasite Prevalence
New Clinical Cases
Wildtype Vector Fraction
Year
50% ITN
80% ITN
95% ITN
50% ACT
80% ACT
95% ACT
50% ITN+ACT
80% ITN+ACT
95% ITN+ACT

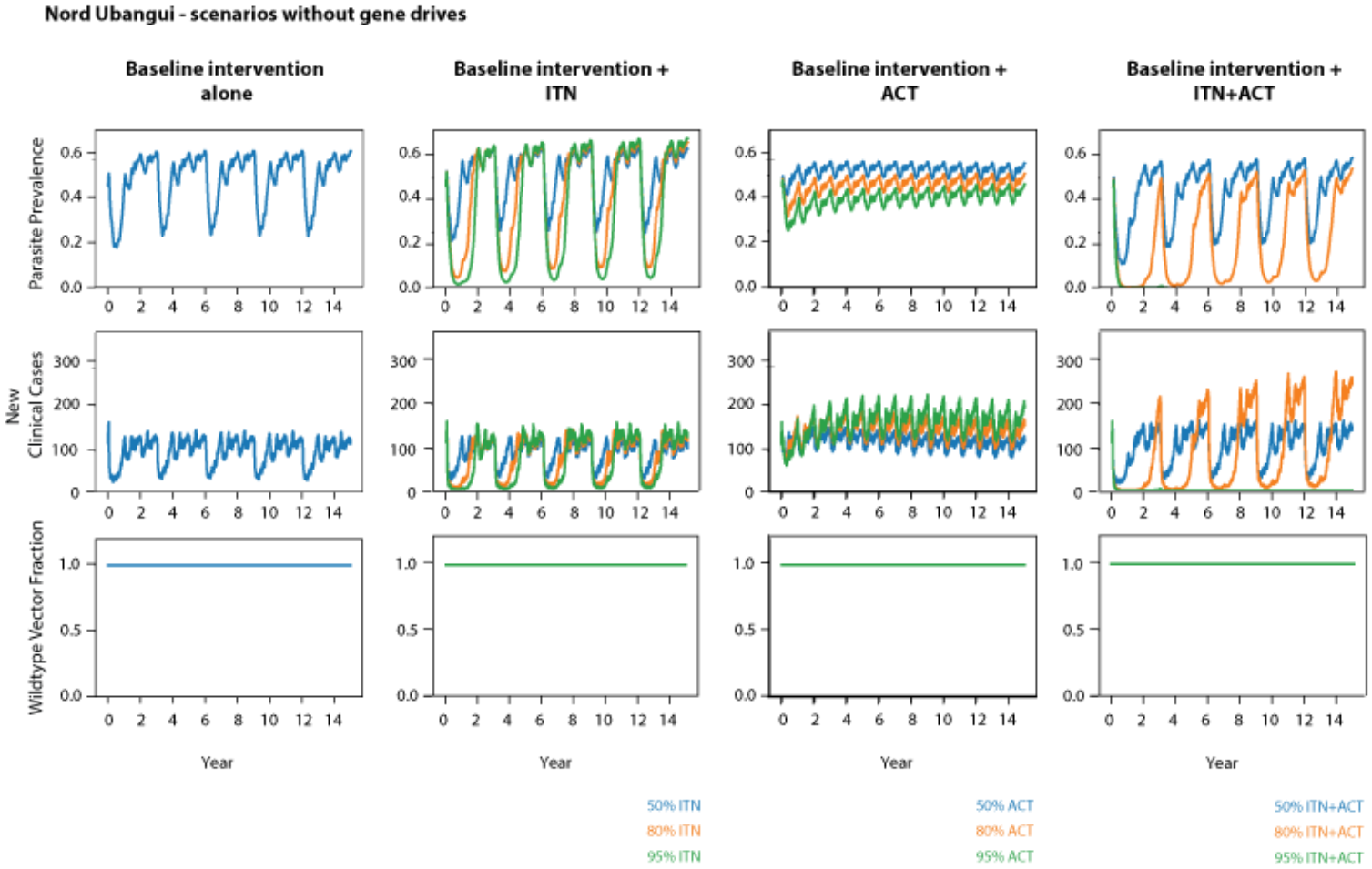

Kasai Central - scenarios with 300 gene drives released at year 0
Baseline intervention alone
Baseline intervention + gene drives X-shredding rate = 1.0
Baseline intervention + 95%ITN+gene drives X-shredding rate = 0.95,1.0
Baseline intervention + 80%ITN+ACT+gene drives X-shredding rate = 0.95,1.0
Parasite Prevalence
New Clinical Cases
Wildtype Vector Fraction
Year

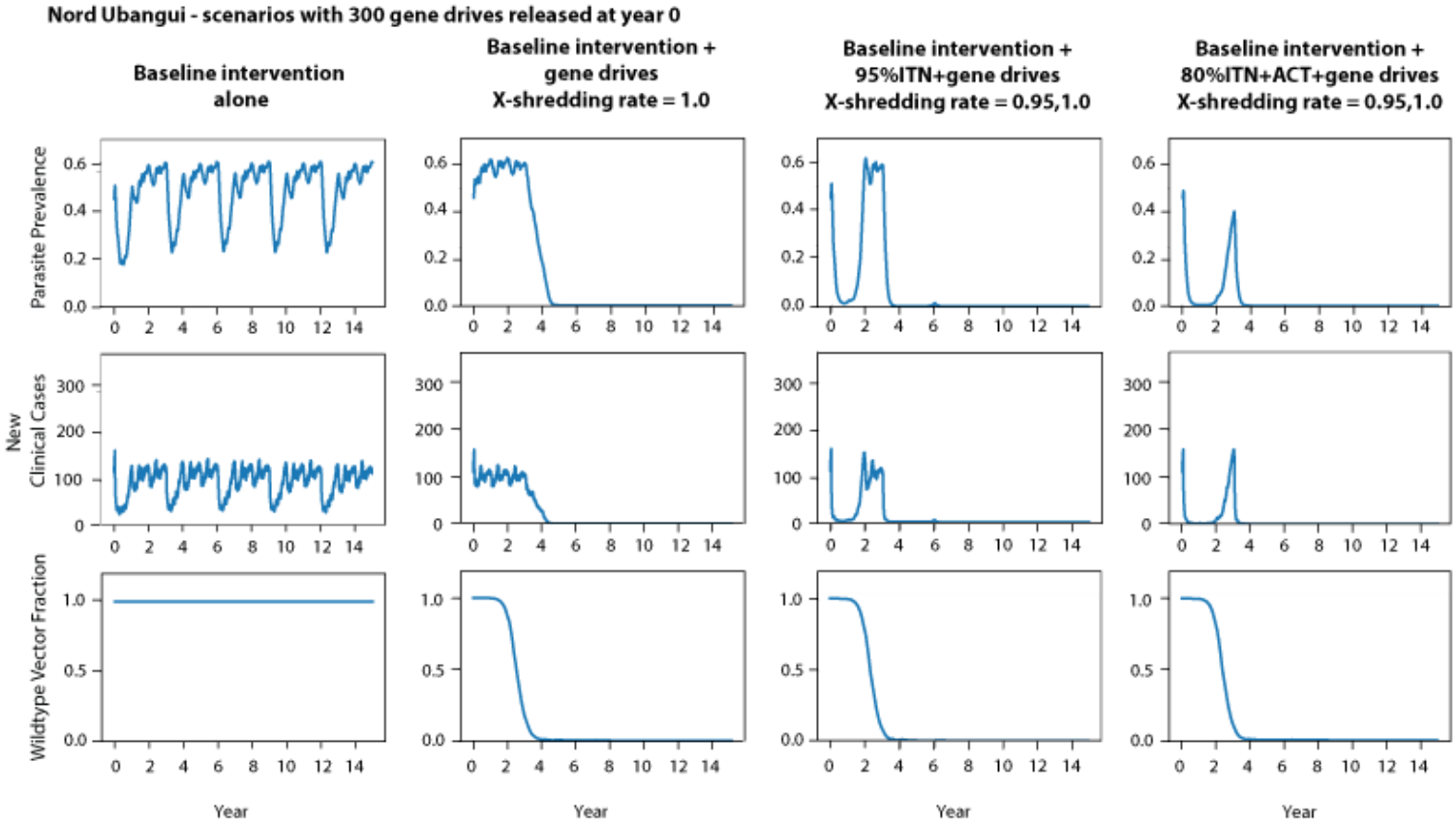

Kinshasa - scenarios without gene drives
Baseline intervention alone
Baseline intervention + ITN
Baseline intervention + ACT
Baseline intervention + ITN+ACT
Parasite Prevalence
New Clinical Cases
Wildtype Vector Fraction
Year
50% ITN
80% ITN
95% ITN
50% ACT
80% ACT
95% ACT
50% ITN+ACT
80% ITN+ACT
95% ITN+ACT


Kinshasa - scenarios with 300 gene drives released at year 0
Baseline intervention alone
Baseline intervention + gene drives X-shredding rate = 1.0
Baseline intervention + 80%ITN+ACT+gene drives X-shredding rate = 0.95,1.0
Baseline intervention + 95%ITN+ACT+gene drives X-shredding rate = 0.9,0.95,1.0
Parasite Prevalence
New Clinical Cases
Wildtype Vector Fraction
Year


Kwango - scenarios without gene drives
Baseline intervention alone
Baseline intervention + ITN
Baseline intervention + ACT
Baseline intervention + ITN+ACT
Parasite Prevalence
New Clinical Cases
Wildtype Vector Fraction
Year
50% ITN
80% ITN
95% ITN
50% ACT
80% ACT
95% ACT
50% ITN+ACT
80% ITN+ACT
95% ITN+ACT


Kwango - scenarios with 300 gene drives released at year 0
Baseline intervention alone
Baseline intervention + gene drives X-shredding rate = 1.0
Baseline intervention + 95%ITN+gene drives X-shredding rate = 0.95,1.0
Baseline intervention + 80%ITN+ACT+gene drives X-shredding rate = 0.95,1.0
Parasite Prevalence
New Clinical Cases
Wildtype Vector Fraction
Year


Nord Ubangui - scenarios without gene drives
Baseline intervention alone
Baseline intervention + ITN
Baseline intervention + ACT
Baseline intervention + ITN+ACT
Parasite Prevalence
New Clinical Cases
Wildtype Vector Fraction
Year
50% ITN
80% ITN
95% ITN
50% ACT
80% ACT
95% ACT
50% ITN+ACT
80% ITN+ACT
95% ITN+ACT


Nord Ubangui - scenarios with 300 gene drives released at year 0
Baseline intervention alone
Baseline intervention + gene drives X-shredding rate = 1.0
Baseline intervention + 95%ITN+gene drives X-shredding rate = 0.95,1.0
Baseline intervention + 80%ITN+ACT+gene drives X-shredding rate = 0.95,1.0
Parasite Prevalence
New Clinical Cases
Wildtype Vector Fraction
Year

Appendix 3: Economic evaluation

Appendix 3.1 Case calculation

From the model outputs, the following elements were calculated (Table 16).

Table 16 Elements and values used in case calculation

Element	Value used in case calculation
Statistical Population	Average of all simulations in the same scenario
Parasite Prevalence	Average of all simulations in the same scenario
New Diagnostic Prevalence	Average of all simulations in the same scenario
New Clinical Cases	Sum of all simulations in the same scenario
New Severe Cases	Sum of all simulations in the same scenario

Proportions by age group of severe cases, clinical cases and population were identified for each province (Table 17).

Notes for Table 18-24:

ITNs: Insecticide treated nets

ACT: Artemisinin-based Combination Therapy

Drives, gene drive mosquitoes: Driving-Y gene drive mosquitoes

Green fields: Scenarios achieved malaria elimination

Grey fields: Not applicable

Table 17 Proportions by age group of severe cases, clinical cases, and population of all target province.

Age group / Province	0-1	2-5	5-10	11-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70	71-75	76-80	84-85	85+
Bas Uele																			
severe cases proportion by age group	0.167415453	0.629029868	0.181041719	0.020439398	0.00187608	0.000197482	0	0	0	0	0	0	0	0	0	0	0	0	0
clinical cases proportion by age group	0.086693	0.362856	0.339189	0.153713	0.039665	0.013556	0.003328	0.000794	0.000144	3.69E-05	3.46E-06	3.46E-06	3.46E-06	2.31E-06	0	2.31E-06	0	4.61E-06	5.77E-06
population proportion by age group	0.036339	0.13093	0.136962	0.116454	0.09364	0.077908	0.0685	0.057051	0.046045	0.038474	0.032133	0.027782	0.025281	0.019788	0.016667	0.012193	0.011474	0.009049	0.04333
Kwango																			
severe cases proportion by age group	0.148491759	0.611329948	0.209598839	0.026795895	0.003109775	0.000570125	0.000103659	0	0	0	0	0	0	0	0	0	0	0	0
clinical cases proportion by age group	0.072944286	0.343055744	0.343783851	0.170066291	0.048435282	0.016226922	0.004113633	0.000998616	0.000244292	6.55E-05	1.07E-05	7.15E-06	3.22E-05	1.19E-06	1.19E-06	3.57E-06	2.38E-06	1.19E-06	5.96E-06
population proportion by age group	0.035955279	0.132740831	0.136298601	0.116651454	0.094788791	0.079612239	0.068619286	0.05640745	0.045366958	0.038724517	0.033284557	0.027125205	0.02329255	0.019384453	0.015120923	0.012741631	0.011847339	0.010066822	0.041973603
Haut Katanga																			
severe cases proportion by age group	0.035849533	0.45594547	0.400908861	0.091391062	0.014137844	0.00176723	0	0	0	0	0	0	0	0	0	0	0	0	0
clinical cases proportion by age group	0.029057532	0.234311	0.344749352	0.233695651	0.099719101	0.041712074	0.011788554	0.003508887	0.001047499	0.000267746	4.70E-05	1.41E-05	9.39E-06	1.88E-05	4.70E-06	2.35E-05	0	4.70E-06	2.35E-05
population proportion by age group	0.035621264	0.131640058	0.140624474	0.112574953	0.094315687	0.0831601	0.066308782	0.0563435	0.045239059	0.038846543	0.032763189	0.027514622	0.022783395	0.020027513	0.015709852	0.012902395	0.011901788	0.009500466	0.042218168
Kinshasa																			
severe cases proportion by age group	0.198858914	0.634465187	0.150889049	0.013958899	0.001661774	0.000166177	0	0	0	0	0	0	0	0	0	0	0	0	0

clinical cases proportion by age group	0.0930 33968	0.3836 3066	0.3468 23529	0.1321 52941	0.0318 37038	0.0096 98306	0.0021 34381	0.0005 28733	0.0001 20332	2.07E-05	7.29E-06	1.22E-06	2.43E-06	1.22E-06	0	1.22E-06	1.22E-06	1.22E-06	3.65E-06
population proportion by age group	0.0348 54418	0.1285 88723	0.1389 02615	0.1143 05328	0.0981 18503	0.0802 17104	0.0685 64969	0.0566 82031	0.0465 28368	0.0383 96236	0.0305 32002	0.0275 74711	0.0235 90245	0.0201 29133	0.0157 59495	0.0143 06103	0.0113 70426	0.0090 65078	0.0425 14509
Nord Ubangui																			
severe cases proportion by age group	0.1445 44375	0.6191 93518	0.2102 68828	0.0233 24768	0.0025 20261	0.0001 48251	0	0	0	0	0	0	0	0	0	0	0	0	0
clinical cases proportion by age group	0.0767 97092	0.3506 13189	0.3487 98176	0.1594 9297	0.0446 74331	0.0151 92817	0.0033 7267	0.0008 25108	0.0001 60281	4.63E-05	6.77E-06	2.26E-06	2.26E-06	4.51E-06	2.26E-06	4.51E-06	1.13E-06	2.26E-06	1.13E-06
population proportion by age group	0.0344 43485	0.1286 19586	0.1396 18443	0.1165 71197	0.0967 20204	0.0835 86417	0.0656 09893	0.0534 91466	0.0452 34476	0.0369 90829	0.0329 74566	0.0260 46653	0.0234 70476	0.0203 32609	0.0157 58208	0.0140 76846	0.0121 53909	0.0106 76958	0.0436 23778
Equateur																			
severe cases proportion by age group	0.2059 43407	0.6211 62458	0.1580 90245	0.0137 11352	0.0008 7403	0.0001 09254	5.46E-05	5.46E-05	0	0	0	0	0	0	0	0	0	0	0
clinical cases proportion by age group	0.0984 76491	0.3825 49417	0.3415 91116	0.1323 0177	0.0313 58964	0.0103 09649	0.0026 8312	0.0005 45009	0.0001 28167	3.35E-05	7.19E-06	1.20E-06	2.40E-06	2.40E-06	0	2.40E-06	0	3.59E-06	3.59E-06
population proportion by age group	0.0369 29681	0.1300 75843	0.1387 10856	0.1132 3926	0.0944 93663	0.0806 40658	0.0679 41475	0.0571 68634	0.0463 32544	0.0401 64916	0.0316 39793	0.0271 71395	0.0235 975	0.0177 91363	0.0164 81759	0.0134 10055	0.0113 709	0.0099 51817	0.0428 87887
Kasai Central																			
severe cases proportion by age group	0.1460 08666	0.6156 0679	0.2119 91436	0.0238 03596	0.0021 41328	0.0004 48185	0	0	0	0	0	0	0	0	0	0	0	0	0
clinical cases proportion by age group	0.0759 99463	0.3477 72097	0.3498 84146	0.1621 27403	0.0445 96741	0.0149 48361	0.0035 86148	0.0008 47552	0.0001 75434	3.65E-05	1.03E-05	0	2.28E-06	1.14E-06	2.28E-06	2.28E-06	2.28E-06	1.14E-06	4.56E-06
population proportion by age group	0.0355 06629	0.1300 14674	0.1387 9462	0.1171 11024	0.0953 0856	0.0795 91956	0.0685 81084	0.0552 59866	0.0459 76557	0.0371 61493	0.0305 82878	0.0278 67002	0.0225 38869	0.0196 2572	0.0157 27409	0.0145 08737	0.0114 33646	0.0105 396	0.0438 69676

Table 18 Number of total new clinical cases and total new severe cases by study location over 15 years

Province	Intervention	Coverage	without drives			with drives				Year
			Mean Statistical population	Total new clinical cases	Total new severe cases	Intervention	Mean Statistical population	Total new clinical cases	Total new severe cases	
Bas Uele	**Baseline: 50%ITNs+19%ACT**		25,033	155,333	2,844	300 drives only	24,997	125,079	2,501	0-5
			25,026	161,913	2,502		25,002	0	0	6-10
			25,025	168,276	2,661		25,016	0	0	11-15
	ITNs	50	25,012	150,703	3,016					0-5
			25,020	153,276	2,571					6-10
			25,027	157,145	2,726					11-15
		80	25,013	116,171	2,529					0-5
			25,021	135,341	2,527					6-10
			25,013	161,841	2,892					11-15
		95	25,007	90,185	2,108					0-5
			24,998	125,506	2,565					6-10
			24,980	158,505	2,949					11-15
	ACT	50	25,010	209,267	3,017					0-5
			25,010	200,843	2,456					6-10
			25,019	187,051	2,356					11-15
		80	25,008	241,770	2,536					0-5
			25,008	251,771	2,234					6-10
			25,014	236,447	2,110					11-15
		95	24,997	246,793	2,056					0-5
			24,970	292,198	2,093					6-10
			24,972	284,241	1,969					11-15

Province	Intervention	Coverage	without drives			with drives				Year
			Mean Statistical population	Total new clinical cases	Total new severe cases	Intervention	Mean Statistical population	Total new clinical cases	Total new severe cases	
	ITNs+ACT	50	25,002	161,424	2,421					0-5
			25,016	182,483	2,361					6-10
			25,019	197,407	2,557					11-15
		80	25,004	59,343	758	80% ITNs+ACT+Drives X-shred 0.95,1.0	25,003	41,924	533	0-5
			25,007	173,300	2,189		25,000	0	0	6-10
			25,027	234,342	2,460		25,006	0	0	11-15
		95	24,995	37,888	546	95% ITNs+ACT+Drives X-shred 0.9,0.95,1.0	24,997	4,873	70	0-5
			25,008	4,620	56		24,996	0	0	6-10
			25,006	10,760	134		24,995	0	0	11-15
Equateur	**Baseline: 50%ITNs+19%ACT**		25,083	157,703	2,775	300 drives only	25,091	124,042	2,373	0-5
			25,080	161,958	2,474		25,082	0	0	6-10
			25,085	166,337	2,625		25,068	0	0	11-15
	ITNs	50	25,082	151,915	2,908					0-5
			25,066	153,039	2,548					6-10
			25,083	155,620	2,676					11-15
	ITNs	80	25,073	124,781	2,520					0-5
			25,053	138,338	2,467					6-10
			25,069	159,951	2,873					11-15
	ITNs	95	25,065	104,855	2,239					0-5
			25,077	129,165	2,504					6-10
			25,049	160,012	2,911					11-15
	ACT	50	25,074	203,121	2,852					0-5
			25,048	195,293	2,433					6-10

Province	Intervention	Coverage	without drives			with drives				Year
			Mean Statistical population	Total new clinical cases	Total new severe cases	Intervention	Mean Statistical population	Total new clinical cases	Total new severe cases	
			25,039	183,858	2,347					11-15
	ACT	80	25,090	241,276	2,439					0-5
			25,062	247,075	2,207					6-10
			25,062	234,362	2,141					11-15
	ACT	95	25,058	256,287	2,037					0-5
			25,043	291,647	2,020					6-10
			25,051	282,991	1,944					11-15
	ITNs+ACT	50	25,098	168,925	2,394					0-5
			25,094	184,175	2,340					6-10
			25,099	194,985	2,510					11-15
	ITNs+ACT	80	25,074	189,486	2,166	80% ITNs+ACT+Drives X-shred 0.95,1.0	25,079	64,095	766	0-5
			25,074	189,486	2,166		25,078	20	0	6-10
			25,048	245,922	2,432		25,063	0	0	11-15
	ITNs+ACT	95	25,081	23,089	241	95% ITNs+ACT+Drives X-shred 0.9,0.95,1.0	25,078	15,868	167	0-5
			25,083	117,814	1,319		25,070	1	0	6-10
			25,084	192,273	1,920		25,063	0	0	11-15
Haut Katanga	**Baseline: 50%ITNs+19%ACT**		25,117	104,503	2,157	300 drives only	25,140	131,114	2,807	0-5
			25,088	152,233	2,695		25,116	0	0	6-10
			25,083	162,492	2,610		25,108	0	0	11-15
	ITNs	50	25,124	110,930	2,497					0-5
			25,087	143,813	2,753					6-10
			25,050	151,991	2,678					11-15
	ITNs	80	25,138	51,424	1,225		25,133	75,747	1,760	0-5

Province	Intervention	Coverage	without drives			with drives				Year
			Mean Statistical population	Total new clinical cases	Total new severe cases	Intervention	Mean Statistical population	Total new clinical cases	Total new severe cases	
			25,108	122,359	2,921	80% ITNs+Drives X-shred 0.95,1.0	25,120	3,012	54	6-10
			25,083	142,545	2,776		25,095	2,139	60	11-15
	ITNs	95	25,143	14,204	340	95% ITNs+Drives X-shred 0.95,1.0	25,137	36,331	909	0-5
			25,118	61,922	1,702		25,109	32	1	6-10
			25,115	76,098	1,691		25,093	0	0	11-15
	ACT	50	25,137	187,628	2,899					0-5
			25,096	204,065	2,556					6-10
			25,081	185,847	2,301					11-15
	ACT	80	25,149	184,336	2,127					0-5
			25,135	245,972	2,354					6-10
			25,147	234,421	2,099					11-15
	ACT	95	25,137	141,668	1,367	95% ITNs+ACT+Drives X-shred 0.95,1.0	25,140	90,036	864	0-5
			25,130	249,003	2,160		25,118	609	6	6-10
			25,081	268,783	2,044		25,099	0	0	11-15
	ITNs+ACT	50	25,128	83,761	1,373	50% ITNs+ACT+Drives X-shred 0.9,0.95,1.0	25,137	52,364	885	0-5
			25,109	167,675	2,634		25,125	257	4	6-10
			25,109	185,693	2,491		25,111	0	0	11-15
	ITNs+ACT	80	25,146	812	9					0-5
			25,120	0	0					6-10
			25,102	0	0					11-15
	ITNs+ACT	95	25,138	601	6					0-5
			25,090	0	0					6-10
			25,039	0	0					11-15

Province	Intervention	Coverage	without drives			with drives				Year
			Mean Statistical population	Total new clinical cases	Total new severe cases	Intervention	Mean Statistical population	Total new clinical cases	Total new severe cases	
Kasai Central	**Baseline: 50%ITNs+19%ACT**		25,241	155,113	2,822	300 drives only	25,257	142,065	2,815	0-5
			25,168	162,589	2,538		25,222	0	0	6-10
			25,133	169,020	2,656		25,196	0	0	11-15
	ITNs	50	25,247	151,945	3,029					0-5
			25,209	154,186	2,616					6-10
			25,190	158,365	2,716					11-15
	ITNs	80	25,250	112,976	2,442					0-5
			25,232	136,908	2,616					6-10
			25,200	159,863	2,841					11-15
	ITNs	95	25,270	86,449	1,969	95% ITNs+Drives X-shred 0.95,1.0	25,263	60,304	1,444	0-5
			25,243	128,463	2,674		25,226	2,314	44	6-10
			25,226	157,310	2,921		25,193	0	0	11-15
	ACT	50	25,224	211,391	3,037					0-5
			25,187	202,475	2,455					6-10
			25,153	186,545	2,362					11-15
	ACT	80	25,248	254,619	2,253					0-5
			25,248	254,619	2,253					6-10
			25,204	237,084	2,122					11-15
	ACT	95	25,264	246,029	2,073					0-5
			25,230	294,574	2,096					6-10
			25,202	284,843	1,960					11-15
	ITNs+ACT	50	25,273	159,515	2,376					0-5
			25,248	185,191	2,416					6-10

Province	Intervention	Coverage	without drives			with drives				Year
			Mean Statistical population	Total new clinical cases	Total new severe cases	Intervention	Mean Statistical population	Total new clinical cases	Total new severe cases	
			25,199	198,238	2,519					11-15
	ITNs+ACT	80	25,241	45,586	549	80% ITNs+ACT+Drives X-shred 0.95,1.0	25,248	35,111	427	0-5
			25,198	165,632	2,190		25,211	6	0	6-10
			25,180	226,245	2,473		25,191	0	0	11-15
	ITNs+ACT	95	25,244	3,564	37					0-5
			25,198	0	0					6-10
			25,163	0	0					11-15
Kinshasa	**Baseline: 50%ITNs+19%ACT**		25,005	155,657	2,711	300 drives only	25,016	126,988	2,424	0-5
			25,002	158,639	2,451		25,014	0	0	6-10
			25,031	164,132	2,656		25,020	0	0	11-15
	ITNs	50	25,007	149,696	2,844					0-5
			25,005	149,743	2,529					6-10
			25,007	153,349	2,703					11-15
	ITNs	80	25,038	125,770	2,526					0-5
			25,055	138,130	2,500					6-10
			25,053	156,697	2,812					11-15
	ITNs	95	25,040	107,862	2,296					0-5
			25,036	128,886	2,463					6-10
			25,013	155,606	2,870					11-15
	ACT	50	25,024	198,951	2,786					0-5
			25,032	192,067	2,407					6-10
			25,001	181,160	2,351					11-15
	ACT	80	25,012	238,144	2,408					0-5

Province	Intervention	Coverage	without drives			with drives				Year
			Mean Statistical population	Total new clinical cases	Total new severe cases	Intervention	Mean Statistical population	Total new clinical cases	Total new severe cases	
			25,027	242,319	2,167					6-10
			25,035	230,067	2,086					11-15
	ACT	95	24,992	259,435	2,009					0-5
			24,966	287,748	1,972					6-10
			24,970	278,733	1,909					11-15
	ITNs+ACT	50	25,016	168,056	2,415					0-5
			25,029	181,601	2,348					6-10
			25,025	191,171	2,523					11-15
	ITNs+ACT	80	25,002	109,847	1,247	80% ITNs+ACT+Drives X-shred 0.95,1.0	25,016	72,991	854	0-5
			24,998	192,229	2,115		25,017	96	1	6-10
			24,996	242,540	2,377		25,019	0	0	11-15
	ITNs+ACT	95	25,004	39,257	383	95% ITNs+ACT+Drives X-shred 0.9,0.95,1.0	25,016	30,572	301	0-5
			25,000	143,388	1,522		25,026	20	0	6-10
			25,005	218,196	2,072		25,026	0	0	11-15
Kwango	**Baseline: 50%ITNs+19%ACT**		24,991	149,875	2,785	300 drives only	24,990	114,117	2,814	5th
			25,006	160,721	2,583		24,998	4,171	78	10th
			25,023	167,975	2,678		25,002	0	0	15th
	ITNs	50	24,997	147,034	3,021					0-5
			25,000	151,576	2,610					6-10
			24,992	156,841	2,725					11-15
	ITNs	80	24,977	109,618	2,407					0-5
			24,965	135,206	2,619					6-10
			24,998	157,028	2,838					11-15

Province	Intervention	Coverage	without drives			with drives				Year
			Mean Statistical population	Total new clinical cases	Total new severe cases	Intervention	Mean Statistical population	Total new clinical cases	Total new severe cases	
	ITNs	95	24,982	83,633	1,943	95% ITNs+Drives X-shred 0.95,1.0	24,990	57,058	1,407	0-5
			24,991	128,135	2,722		24,998	2,085	39	6-10
			25,010	155,308	2,879		25,002	0	0	11-15
	ACT	50	24,986	207,462	3,038					0-5
			24,987	201,632	2,483					6-10
			24,998	185,376	2,355					11-15
	ACT	80	24,980	237,834	2,531					0-5
			24,990	251,978	2,237					6-10
			24,990	234,101	2,122					11-15
	ACT	95	25,008	241,462	2,060					0-5
			25,018	294,059	2,086					6-10
			25,028	284,109	1,965					11-15
	ITNs+ACT	50	24,997	153,532	2,353					0-5
			24,986	181,943	2,409					6-10
			24,990	195,046	2,516					11-15
	ITNs+ACT	80	24,961	42,930	522	80% ITNs+ACT+Drives X-shred 0.95,1.0	24,976	31,612	380	0-5
			24,969	164,907	2,182		24,990	5	0	6-10
			24,952	219,305	2,420		25,004	0	0	11-15
	ITNs+ACT	95	24,993	2,858	27					0-5
			25,017	0	0					6-10
			25,022	0	0					11-15
Nord Ubangui	**Baseline: 50%ITNs+19%ACT**		25,097	153,394	2,793	300 drives only	25,108	126,729	2,518	0-5
			25,086	160,764	2,501		25,086	0	0	6-10

Province	Intervention	Coverage	without drives			with drives				Year
			Mean Statistical population	Total new clinical cases	Total new severe cases	Intervention	Mean Statistical population	Total new clinical cases	Total new severe cases	
			25,101	168,847	2,690		25,087	0	0	11-15
	ITNs	50	25,125	149,791	3,015					0-5
			25,110	152,559	2,582					6-10
			25,100	156,869	2,719					11-15
	ITNs	80	25,104	110,640	2,426					0-5
			25,076	133,345	2,520					6-10
			25,070	160,853	2,886					11-15
	ITNs	95	25,119	241,884	2,038	95% ITNs+Drives X-shred 0.95,1.0	25,109	57,788	1,391	0-5
			25,094	123,599	2,608		25,080	284	5	6-10
			25,088	156,701	2,952		25,072	0	0	11-15
	ACT	50	25,116	211,069	3,019					0-5
			25,081	202,464	2,463					6-10
			25,033	186,723	2,345					11-15
	ACT	80	25,098	240,919	2,499					0-5
			25,079	251,931	2,233					6-10
			25,075	236,284	2,103					11-15
	ACT	95	25,108	84,198	1,999					0-5
			25,115	290,819	2,085					6-10
			25,076	284,012	1,984					11-15
	ITNs+ACT	50	25,098	157,253	2,368					0-5
			25,069	181,241	2,361					6-10
			25,048	197,503	2,540					11-15
	ITNs+ACT	80	25,099	45,683	580		25,113	31,520	392	0-5

Province	Intervention	Coverage	without drives			with drives				Year
			Mean Statistical population	Total new clinical cases	Total new severe cases	Intervention	Mean Statistical population	Total new clinical cases	Total new severe cases	
			25,086	164,301	2,146	80% ITNs+ACT+Drives 0.95,1.0	25,098	0	0	6-10
			25,070	224,904	2,457		25,083	0	0	11-15
	ITNs+ACT	95	25,113	4,164	50					0-5
			25,084	0	0					6-10
			25,101	0	0					11-15

Table 19 Number of untreated uncomplicated cases over 15 years by study location in scenarios without gene drives

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
Bas Uele	**Baseline-50%ITN+19%ACT**		10,908	45,654	42,677	19,340	4,991	1,706	419	100	18	5	0	0	0	0	0	0	0	1	1	0-5
			11,370	47,588	44,485	20,159	5,202	1,778	437	104	19	5	0	0	0	0	0	0	0	1	1	6-10
			11,817	49,459	46,233	20,952	5,406	1,848	454	108	20	5	0	0	0	0	0	0	0	1	1	11-15
	ITNs	50	13,065	54,683	51,117	23,165	5,978	2,043	502	120	22	6	1	1	1	0	0	0	0	1	1	0-5
			13,288	55,617	51,989	23,560	6,080	2,078	510	122	22	6	1	1	1	0	0	0	0	1	1	6-10
			13,623	57,021	53,302	24,155	6,233	2,130	523	125	23	6	1	1	1	0	0	0	0	1	1	11-15
		80	10,071	42,153	39,404	17,857	4,608	1,575	387	92	17	4	0	0	0	0	0	0	0	1	1	0-5
			11,733	49,109	45,906	20,804	5,368	1,835	450	107	20	5	0	0	0	0	0	0	0	1	1	6-10
			14,030	58,725	54,895	24,877	6,419	2,194	539	128	23	6	1	1	1	0	0	0	0	1	1	11-15
		95	7,818	32,724	30,590	13,863	3,577	1,223	300	72	13	3	0	0	0	0	0	0	0	0	1	0-5
			10,881	45,541	42,570	19,292	4,978	1,701	418	100	18	5	0	0	0	0	0	0	0	1	1	6-10
			13,741	57,514	53,763	24,364	6,287	2,149	528	126	23	6	1	1	1	0	0	0	0	1	1	11-15
	ACT	50	9,071	37,967	35,491	16,084	4,150	1,418	348	83	15	4	0	0	0	0	0	0	0	0	1	0-5

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			8,706	36,438	34,062	15,436	3,983	1,361	334	80	14	4	0	0	0	0	0	0	0	0	1	6-10
			8,108	33,936	31,723	14,376	3,710	1,268	311	74	13	3	0	0	0	0	0	0	0	0	1	11-15
		80	4,192	17,546	16,401	7,433	1,918	656	161	38	7	2	0	0	0	0	0	0	0	0	0	0-5
			4,365	18,271	17,080	7,740	1,997	683	168	40	7	2	0	0	0	0	0	0	0	0	0	6-10
			4,100	17,159	16,040	7,269	1,876	641	157	38	7	2	0	0	0	0	0	0	0	0	0	11-15
		95	1,070	4,478	4,185	1,897	489	167	41	10	2	0	0	0	0	0	0	0	0	0	0	0-5
			1,267	5,301	4,956	2,246	579	198	49	12	2	1	0	0	0	0	0	0	0	0	0	6-10
			1,232	5,157	4,821	2,185	564	193	47	11	2	1	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	6,997	29,287	27,377	12,406	3,201	1,094	269	64	12	3	0	0	0	0	0	0	0	0	0	0-5
			7,910	33,108	30,948	14,025	3,619	1,237	304	72	13	3	0	0	0	0	0	0	0	0	1	6-10
			8,557	35,815	33,479	15,172	3,915	1,338	329	78	14	4	0	0	0	0	0	0	0	0	1	11-15
		80	1,029	4,307	4,026	1,824	471	161	40	9	2	0	0	0	0	0	0	0	0	0	0	0-5
			3,005	12,577	11,756	5,328	1,375	470	115	28	5	1	0	0	0	0	0	0	0	0	0	6-10
			4,063	17,006	15,897	7,204	1,859	635	156	37	7	2	0	0	0	0	0	0	0	0	0	11-15
		95	164	687	643	291	75	26	6	2	0	0	0	0	0	0	0	0	0	0	0	0-5
			20	84	78	36	9	3	1	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			47	195	182	83	21	7	2	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Equateur	**Baseline-50%ITN+19%ACT**		12,579	48,867	43,635	16,900	4,006	1,317	343	70	16	4	1	0	0	0	0	0	0	1	1	0-5
			12,919	50,185	44,812	17,356	4,114	1,352	352	71	17	4	1	0	0	0	0	0	0	0	0	6-10
			13,268	51,542	46,024	17,825	4,225	1,389	362	73	17	5	1	0	0	0	0	0	0	0	0	11-15
	ITNs	50	14,960	58,115	51,893	20,099	4,764	1,566	408	83	19	5	1	0	0	0	0	0	0	1	1	0-5
			15,071	58,545	52,277	20,247	4,799	1,578	411	83	20	5	1	0	0	0	0	0	0	1	1	6-10
			15,325	59,532	53,158	20,589	4,880	1,604	418	85	20	5	1	0	0	0	0	0	0	1	1	11-15
		80	12,288	47,735	42,624	16,509	3,913	1,286	335	68	16	4	1	0	0	0	0	0	0	0	0	0-5
			13,623	52,921	47,255	18,302	4,338	1,426	371	75	18	5	1	0	0	0	0	0	0	0	0	6-10
			15,751	61,189	54,638	21,162	5,016	1,649	429	87	21	5	1	0	0	0	0	0	0	1	1	11-15
		95	10,326	40,112	35,818	13,872	3,288	1,081	281	57	13	4	1	0	0	0	0	0	0	0	0	0-5
			12,720	49,412	44,122	17,089	4,050	1,332	347	70	17	4	1	0	0	0	0	0	0	0	0	6-10
			15,757	61,213	54,659	21,170	5,018	1,650	429	87	21	5	1	0	0	0	0	0	0	1	1	11-15
	ACT	50	10,001	38,852	34,692	13,437	3,185	1,047	272	55	13	3	1	0	0	0	0	0	0	0	0	0-5

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			9,616	37,355	33,355	12,919	3,062	1,007	262	53	13	3	1	0	0	0	0	0	0	0	0	6-10
			9,053	35,167	31,402	12,162	2,883	948	247	50	12	3	1	0	0	0	0	0	0	0	0	11-15
		80	4,752	18,460	16,484	6,384	1,513	497	129	26	6	2	0	0	0	0	0	0	0	0	0	0-5
			4,866	18,904	16,880	6,538	1,550	509	133	27	6	2	0	0	0	0	0	0	0	0	0	6-10
			4,616	17,931	16,011	6,201	1,470	483	126	26	6	2	0	0	0	0	0	0	0	0	0	11-15
		95	1,262	4,902	4,377	1,695	402	132	34	7	2	0	0	0	0	0	0	0	0	0	0	0-5
			1,436	5,578	4,981	1,929	457	150	39	8	2	0	0	0	0	0	0	0	0	0	0	6-10
			1,393	5,413	4,833	1,872	444	146	38	8	2	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	8,318	32,311	28,852	11,175	2,649	871	227	46	11	3	1	0	0	0	0	0	0	0	0	0-5
			9,068	35,228	31,456	12,183	2,888	949	247	50	12	3	1	0	0	0	0	0	0	0	0	6-10
			9,601	37,296	33,302	12,898	3,057	1,005	262	53	12	3	1	0	0	0	0	0	0	0	0	11-15
		80	3,732	14,498	12,945	5,014	1,188	391	102	21	5	1	0	0	0	0	0	0	0	0	0	0-5
			3,732	14,498	12,945	5,014	1,188	391	102	21	5	1	0	0	0	0	0	0	0	0	0	6-10
			4,844	18,815	16,801	6,507	1,542	507	132	27	6	2	0	0	0	0	0	0	0	0	0	11-15
		95	114	442	394	153	36	12	3	1	0	0	0	0	0	0	0	0	0	0	0	0-5
			580	2,253	2,012	779	185	61	16	3	1	0	0	0	0	0	0	0	0	0	0	6-10
			947	3,678	3,284	1,272	301	99	26	5	1	0	0	0	0	0	0	0	0	0	0	11-15
Haut Katanga	**Baseline-50%ITN+19%ACT**		2,460	19,834	29,182	19,782	8,441	3,531	998	297	89	23	4	1	1	2	0	2	0	0	2	0-5
			3,583	28,893	42,511	28,817	12,296	5,143	1,453	433	129	33	6	2	1	2	1	3	0	1	3	6-10
			3,824	30,840	45,375	30,759	13,125	5,490	1,551	462	138	35	6	2	1	2	1	3	0	1	3	11-15
	ITNs	50	3,223	25,992	38,243	25,924	11,062	4,627	1,307	389	116	30	5	2	1	2	1	3	0	1	3	0-5
			4,179	33,697	49,580	33,609	14,341	5,999	1,695	505	151	39	7	2	1	3	1	3	0	1	3	6-10
			4,416	35,613	52,399	35,520	15,156	6,340	1,791	533	159	41	7	2	1	3	1	4	0	1	4	11-15
		80	1,494	12,049	17,728	12,018	5,128	2,145	606	180	54	14	2	1	0	1	0	1	0	0	1	0-5
			3,555	28,670	42,183	28,595	12,202	5,104	1,442	429	128	33	6	2	1	2	1	3	0	1	3	6-10
			4,142	33,400	49,142	33,312	14,214	5,946	1,680	500	149	38	7	2	1	3	1	3	0	1	3	11-15
		95	413	3,328	4,897	3,320	1,416	592	167	50	15	4	1	0	0	0	0	0	0	0	0	0-5
			1,799	14,509	21,348	14,471	6,175	2,583	730	217	65	17	3	1	1	1	0	1	0	0	1	6-10
			2,211	17,831	26,235	17,784	7,588	3,174	897	267	80	20	4	1	1	1	0	2	0	0	2	11-15
	ACT	50	2,726	21,982	32,342	21,924	9,355	3,913	1,106	329	98	25	4	1	1	2	0	2	0	0	2	0-5

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			2,965	23,907	35,176	23,845	10,175	4,256	1,203	358	107	27	5	1	1	2	0	2	0	0	2	6-10
			2,700	21,773	32,035	21,716	9,266	3,876	1,095	326	97	25	4	1	1	2	0	2	0	0	2	11-15
		80	1,071	8,638	12,710	8,616	3,676	1,538	435	129	39	10	2	1	0	1	0	1	0	0	1	0-5
			1,429	11,527	16,960	11,496	4,906	2,052	580	173	52	13	2	1	0	1	0	1	0	0	1	6-10
			1,362	10,985	16,163	10,957	4,675	1,956	553	165	49	13	2	1	0	1	0	1	0	0	1	11-15
		95	206	1,660	2,442	1,655	706	295	83	25	7	2	0	0	0	0	0	0	0	0	0	0-5
			362	2,917	4,292	2,910	1,242	519	147	44	13	3	1	0	0	0	0	0	0	0	0	6-10
			391	3,149	4,633	3,141	1,340	561	158	47	14	4	1	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	1,217	9,813	14,438	9,787	4,176	1,747	494	147	44	11	2	1	0	1	0	1	0	0	1	0-5
			2,436	19,644	28,903	19,593	8,360	3,497	988	294	88	22	4	1	1	2	0	2	0	0	2	6-10
			2,698	21,755	32,009	21,698	9,259	3,873	1,094	326	97	25	4	1	1	2	0	2	0	0	2	11-15
		80	5	38	56	38	16	7	2	1	0	0	0	0	0	0	0	0	0	0	0	0-5
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	1	7	10	7	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kasai Central	**Baseline-50%ITN+19%ACT**		9,549	43,695	43,960	20,370	5,603	1,878	451	106	22	5	1	0	0	0	0	0	0	0	1	0-5
			10,009	45,801	46,079	21,352	5,873	1,969	472	112	23	5	1	0	0	0	0	0	0	0	1	6-10
			10,405	47,612	47,901	22,196	6,106	2,047	491	116	24	5	1	0	0	0	0	0	0	0	1	11-15
	ITNs	50	11,548	52,842	53,163	24,634	6,776	2,271	545	129	27	6	2	0	0	0	0	0	0	0	1	0-5
			11,718	53,622	53,947	24,998	6,876	2,305	553	131	27	6	2	0	0	0	0	0	0	0	1	6-10
			12,036	55,075	55,410	25,675	7,063	2,367	568	134	28	6	2	0	0	0	0	0	0	0	1	11-15
		80	8,586	39,290	39,528	18,316	5,038	1,689	405	96	20	4	1	0	0	0	0	0	0	0	1	0-5
			10,405	47,613	47,902	22,196	6,106	2,047	491	116	24	5	1	0	0	0	0	0	0	0	1	6-10
			12,149	55,596	55,934	25,918	7,129	2,390	573	135	28	6	2	0	0	0	0	0	0	0	1	11-15
		95	6,570	30,065	30,247	14,016	3,855	1,292	310	73	15	3	1	0	0	0	0	0	0	0	0	0-5
			9,763	44,676	44,947	20,827	5,729	1,920	461	109	23	5	1	0	0	0	0	0	0	0	1	6-10
			11,955	54,708	55,040	25,504	7,016	2,352	564	133	28	6	2	0	0	0	0	0	0	0	1	11-15
	ACT	50	8,033	36,758	36,981	17,136	4,714	1,580	379	90	19	4	1	0	0	0	0	0	0	0	0	0-5

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			7,694	35,208	35,421	16,413	4,515	1,513	363	86	18	4	1	0	0	0	0	0	0	0	0	6-10
			7,089	32,438	32,635	15,122	4,160	1,394	334	79	16	3	1	0	0	0	0	0	0	0	0	11-15
		80	3,870	17,710	17,817	8,256	2,271	761	183	43	9	2	1	0	0	0	0	0	0	0	0	0-5
			3,870	17,710	17,817	8,256	2,271	761	183	43	9	2	1	0	0	0	0	0	0	0	0	6-10
			3,604	16,490	16,590	7,688	2,115	709	170	40	8	2	0	0	0	0	0	0	0	0	0	11-15
		95	935	4,278	4,304	1,994	549	184	44	10	2	0	0	0	0	0	0	0	0	0	0	0-5
			1,119	5,122	5,153	2,388	657	220	53	12	3	1	0	0	0	0	0	0	0	0	0	6-10
			1,082	4,953	4,983	2,309	635	213	51	12	2	1	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	6,062	27,737	27,906	12,931	3,557	1,192	286	68	14	3	1	0	0	0	0	0	0	0	0	0-5
			7,037	32,202	32,398	15,012	4,129	1,384	332	78	16	3	1	0	0	0	0	0	0	0	0	6-10
			7,533	34,471	34,680	16,070	4,420	1,482	355	84	17	4	1	0	0	0	0	0	0	0	0	11-15
		80	693	3,171	3,190	1,478	407	136	33	8	2	0	0	0	0	0	0	0	0	0	0	0-5
			2,518	11,520	11,590	5,371	1,477	495	119	28	6	1	0	0	0	0	0	0	0	0	0	6-10
			3,439	15,736	15,832	7,336	2,018	676	162	38	8	2	0	0	0	0	0	0	0	0	0	11-15
		95	14	62	62	29	8	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kinshasa	**Baseline-50%ITN+19%ACT**		11,730	48,369	43,728	16,662	4,014	1,223	269	67	15	3	1	0	0	0	0	0	0	0	0	0-5
			11,955	49,296	44,566	16,981	4,091	1,246	274	68	15	3	1	0	0	0	0	0	0	0	0	6-10
			12,369	51,003	46,109	17,569	4,233	1,289	284	70	16	3	1	0	0	0	0	0	0	0	0	11-15
	ITNs	50	13,927	57,428	51,918	19,783	4,766	1,452	320	79	18	3	1	0	0	0	0	0	0	0	1	0-5
			13,931	57,446	51,934	19,789	4,767	1,452	320	79	18	3	1	0	0	0	0	0	0	0	1	6-10
			14,267	58,829	53,185	20,266	4,882	1,487	327	81	18	3	1	0	0	0	0	0	0	0	1	11-15
		80	11,701	48,249	43,620	16,621	4,004	1,220	268	66	15	3	1	0	0	0	0	0	0	0	0	0-5
			12,851	52,991	47,907	18,254	4,398	1,340	295	73	17	3	1	0	0	0	0	0	0	0	1	6-10
			14,578	60,114	54,346	20,708	4,989	1,520	334	83	19	3	1	0	0	0	0	0	0	0	1	11-15
		95	10,035	41,379	37,409	14,254	3,434	1,046	230	57	13	2	1	0	0	0	0	0	0	0	0	0-5
			11,991	49,445	44,701	17,033	4,103	1,250	275	68	16	3	1	0	0	0	0	0	0	0	0	6-10
			14,477	59,695	53,968	20,564	4,954	1,509	332	82	19	3	1	0	0	0	0	0	0	0	1	11-15
	ACT	50	9,255	38,162	34,500	13,146	3,167	965	212	53	12	2	1	0	0	0	0	0	0	0	0	0-5

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			8,934	36,841	33,307	12,691	3,057	931	205	51	12	2	1	0	0	0	0	0	0	0	0	6-10
			8,427	34,749	31,415	11,970	2,884	878	193	48	11	2	1	0	0	0	0	0	0	0	0	11-15
		80	4,431	18,272	16,519	6,294	1,516	462	102	25	6	1	0	0	0	0	0	0	0	0	0	0-5
			4,509	18,592	16,808	6,405	1,543	470	103	26	6	1	0	0	0	0	0	0	0	0	0	6-10
			4,281	17,652	15,959	6,081	1,465	446	98	24	6	1	0	0	0	0	0	0	0	0	0	11-15
		95	1,207	4,976	4,499	1,714	413	126	28	7	2	0	0	0	0	0	0	0	0	0	0	0-5
			1,339	5,519	4,990	1,901	458	140	31	8	2	0	0	0	0	0	0	0	0	0	0	6-10
			1,297	5,347	4,834	1,842	444	135	30	7	2	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	7,817	32,236	29,143	11,105	2,675	815	179	44	10	2	1	0	0	0	0	0	0	0	0	0-5
			8,448	34,834	31,492	12,000	2,891	881	194	48	11	2	1	0	0	0	0	0	0	0	0	6-10
			8,893	36,670	33,151	12,632	3,043	927	204	51	12	2	1	0	0	0	0	0	0	0	0	11-15
		80	2,044	8,428	7,620	2,903	699	213	47	12	3	0	0	0	0	0	0	0	0	0	0	0-5
			3,577	14,749	13,334	5,081	1,224	373	82	20	5	1	0	0	0	0	0	0	0	0	0	6-10
			4,513	18,609	16,824	6,410	1,544	470	104	26	6	1	0	0	0	0	0	0	0	0	0	11-15
		95	183	753	681	259	62	19	4	1	0	0	0	0	0	0	0	0	0	0	0	0-5
			667	2,750	2,487	947	228	70	15	4	1	0	0	0	0	0	0	0	0	0	0	6-10
			1,015	4,185	3,784	1,442	347	106	23	6	1	0	0	0	0	0	0	0	0	0	0	11-15
Kwango	**Baseline-50%ITN+19%ACT**		8,855	41,647	41,735	20,646	5,880	1,970	499	121	30	8	1	1	4	0	0	0	0	0	1	0-5
			9,496	44,660	44,755	22,140	6,306	2,112	536	130	32	9	1	1	4	0	0	0	0	0	1	6-10
			9,925	46,676	46,775	23,139	6,590	2,208	560	136	33	9	1	1	4	0	0	0	0	0	1	11-15
	ITNs	50	10,725	50,441	50,548	25,005	7,122	2,386	605	147	36	10	2	1	5	0	0	1	0	0	1	0-5
			11,057	51,999	52,109	25,778	7,342	2,460	624	151	37	10	2	1	5	0	0	1	0	0	1	6-10
			11,441	53,805	53,919	26,673	7,597	2,545	645	157	38	10	2	1	5	0	0	1	0	0	1	11-15
		80	7,996	37,605	37,685	18,642	5,309	1,779	451	109	27	7	1	1	4	0	0	0	0	0	1	0-5
			9,863	46,383	46,482	22,994	6,549	2,194	556	135	33	9	1	1	4	0	0	0	0	0	1	6-10
			11,454	53,869	53,984	26,705	7,606	2,548	646	157	38	10	2	1	5	0	0	1	0	0	1	11-15
		95	6,101	28,691	28,752	14,223	4,051	1,357	344	84	20	5	1	1	3	0	0	0	0	0	0	0-5
			9,347	43,958	44,051	21,792	6,206	2,079	527	128	31	8	1	1	4	0	0	0	0	0	1	6-10
			11,329	53,279	53,392	26,413	7,522	2,520	639	155	38	10	2	1	5	0	0	1	0	0	1	11-15
	ACT	50	7,567	35,585	35,661	17,641	5,024	1,683	427	104	25	7	1	1	3	0	0	0	0	0	1	0-5

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			7,354	34,585	34,659	17,145	4,883	1,636	415	101	25	7	1	1	3	0	0	0	0	0	1	6-10
			6,761	31,797	31,865	15,763	4,489	1,504	381	93	23	6	1	1	3	0	0	0	0	0	1	11-15
		80	3,470	16,318	16,353	8,090	2,304	772	196	48	12	3	1	0	2	0	0	0	0	0	0	0-5
			3,676	17,288	17,325	8,571	2,441	818	207	50	12	3	1	0	2	0	0	0	0	0	0	6-10
			3,415	16,062	16,096	7,963	2,268	760	193	47	11	3	1	0	2	0	0	0	0	0	0	11-15
		95	881	4,142	4,151	2,053	585	196	50	12	3	1	0	0	0	0	0	0	0	0	0	0-5
			1,072	5,044	5,055	2,500	712	239	60	15	4	1	0	0	0	0	0	0	0	0	0	6-10
			1,036	4,873	4,884	2,416	688	231	58	14	3	1	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	5,600	26,335	26,391	13,055	3,718	1,246	316	77	19	5	1	1	2	0	0	0	0	0	0	0-5
			6,636	31,208	31,274	15,471	4,406	1,476	374	91	22	6	1	1	3	0	0	0	0	0	1	6-10
			7,114	33,456	33,527	16,585	4,724	1,582	401	97	24	6	1	1	3	0	0	0	0	0	1	11-15
		80	626	2,945	2,952	1,460	416	139	35	9	2	1	0	0	0	0	0	0	0	0	0	0-5
			2,406	11,314	11,338	5,609	1,597	535	136	33	8	2	0	0	1	0	0	0	0	0	0	6-10
			3,199	15,047	15,079	7,459	2,124	712	180	44	11	3	0	0	1	0	0	0	0	0	0	11-15
		95	10	49	49	24	7	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Nord Ubangui	**Baseline-50%ITN+19%ACT**		9,542	43,563	43,338	19,817	5,551	1,888	419	103	20	6	1	0	0	1	0	1	0	0	0	0-5
			10,000	45,657	45,420	20,769	5,817	1,978	439	107	21	6	1	0	0	1	0	1	0	0	0	6-10
			10,503	47,952	47,704	21,813	6,110	2,078	461	113	22	6	1	0	0	1	0	1	0	0	0	11-15
	ITNs	50	11,503	52,519	52,247	23,891	6,692	2,276	505	124	24	7	1	0	0	1	0	1	0	0	0	0-5
			11,716	53,489	53,212	24,332	6,815	2,318	515	126	24	7	1	0	0	1	0	1	0	0	0	6-10
			12,047	55,000	54,716	25,020	7,008	2,383	529	129	25	7	1	0	0	1	0	1	0	0	0	11-15
		80	8,497	38,792	38,591	17,646	4,943	1,681	373	91	18	5	1	0	0	0	0	0	0	0	0	0-5
			10,240	46,752	46,510	21,268	5,957	2,026	450	110	21	6	1	0	0	1	0	1	0	0	0	6-10
			12,353	56,397	56,105	25,655	7,186	2,444	543	133	26	7	1	0	0	1	0	1	0	0	0	11-15
		95	18,576	84,808	84,369	38,579	10,806	3,675	816	200	39	11	2	1	1	1	1	1	0	1	0	0-5
			9,492	43,335	43,111	19,713	5,522	1,878	417	102	20	6	1	0	0	1	0	1	0	0	0	6-10
			12,034	54,941	54,657	24,993	7,001	2,381	529	129	25	7	1	0	0	1	0	1	0	0	0	11-15

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
	ACT	50	8,105	37,002	36,810	16,832	4,715	1,603	356	87	17	5	1	0	0	0	0	0	0	0	0	0-5
			7,774	35,493	35,310	16,146	4,522	1,538	341	84	16	5	1	0	0	0	0	0	0	0	0	6-10
			7,170	32,734	32,564	14,891	4,171	1,418	315	77	15	4	1	0	0	0	0	0	0	0	0	11-15
		80	3,700	16,894	16,806	7,685	2,153	732	163	40	8	2	0	0	0	0	0	0	0	0	0	0-5
			3,870	17,666	17,575	8,036	2,251	766	170	42	8	2	0	0	0	0	0	0	0	0	0	6-10
			3,629	16,569	16,483	7,537	2,111	718	159	39	8	2	0	0	0	0	0	0	0	0	0	11-15
		95	323	1,476	1,468	671	188	64	14	3	1	0	0	0	0	0	0	0	0	0	0	0-5
			1,117	5,098	5,072	2,319	650	221	49	12	2	1	0	0	0	0	0	0	0	0	0	6-10
			1,091	4,979	4,953	2,265	634	216	48	12	2	1	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	6,038	27,568	27,425	12,540	3,513	1,195	265	65	13	4	1	0	0	0	0	0	0	0	0	0-5
			6,959	31,773	31,608	14,453	4,048	1,377	306	75	15	4	1	0	0	0	0	0	0	0	0	6-10
			7,584	34,624	34,444	15,750	4,412	1,500	333	81	16	5	1	0	0	0	0	0	0	0	0	11-15
		80	702	3,203	3,187	1,457	408	139	31	8	1	0	0	0	0	0	0	0	0	0	0	0-5
			2,524	11,521	11,462	5,241	1,468	499	111	27	5	2	0	0	0	0	0	0	0	0	0	6-10
			3,454	15,771	15,689	7,174	2,009	683	152	37	7	2	0	0	0	0	0	0	0	0	0	11-15
		95	16	73	73	33	9	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15

Table 20 Number of untreated uncomplicated cases over 15 years by study location in scenarios with gene drives

Province	Intervention	Coverage	Gene drive X-shredding rate	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
Bas Uele	300 gene drives only			10,843	45,386	42,425	19,226	4,961	1,696	416	99	18	5	0	0	0	0	0	0	0	1	1	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15

Province	Intervention	Cov-erage	Gene drive X-shred-ding rate	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85 +	Year
	ITNs+ACT	80	0.95,1.0	727	3,042	2,844	1,289	333	114	28	7	1	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0.9,0.95 ,1.0	21	88	83	37	10	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Equateur	**300 gene drives only**			12,215	47,452	42,371	16,411	3,890	1,279	333	68	16	4	1	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				2,469	9,590	8,563	3,316	786	258	67	14	3	1	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	1,262	4,904	4,379	1,696	402	132	34	7	2	0	0	0	0	0	0	0	0	0	0	0-5
				0	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				494	1,918	1,712	663	157	52	13	3	1	0	0	0	0	0	0	0	0	0	0	11-15
		95	0.9,0.95 ,1.0	65	253	226	88	21	7	2	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				123	479	428	166	39	13	3	1	0	0	0	0	0	0	0	0	0	0	0	11-15
Haut Katanga	**300 gene drives only**			3,810	30,721	45,201	30,641	13,075	5,469	1,545	460	137	35	6	2	1	2	1	3	0	1	3	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	80	0.95,1.0	2,201	17,748	26,114	17,702	7,553	3,160	893	266	79	20	4	1	1	1	0	2	0	0	2	0-5
				88	706	1,039	704	300	126	36	11	3	1	0	0	0	0	0	0	0	0	0	6-10
				62	501	737	500	213	89	25	8	2	1	0	0	0	0	0	0	0	0	0	11-15
		95	0.95,1.0	1,056	8,513	12,525	8,491	3,623	1,515	428	127	38	10	2	1	0	1	0	1	0	0	1	0-5
				1	8	11	8	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				1	8	11	8	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	95	0.95,1.0	131	1,055	1,552	1,052	449	188	53	16	5	1	0	0	0	0	0	0	0	0	0	0-5
				1	7	10	7	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	0.95,1.0	761	6,135	9,026	6,119	2,611	1,092	309	92	27	7	1	0	0	0	0	1	0	0	1	0-5
				4	30	44	30	13	5	2	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kasai	**300 gene drives only**			10,797	49,406	49,706	23,033	6,336	2,124	509	120	25	5	1	0	0	0	0	0	0	0	1	0-5

Province	Intervention	Cov-erage	Gene drive X-shred-ding rate	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85 +	Year
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	95	0.95,1.0	4,583	20,972	21,099	9,777	2,689	901	216	51	11	2	1	0	0	0	0	0	0	0	0	0-5
				176	805	810	375	103	35	8	2	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	534	2,442	2,457	1,138	313	105	25	6	1	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kinshasa	**300 gene drives only**			11,814	48,716	44,042	16,782	4,043	1,232	271	67	15	3	1	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	1,358	5,600	5,063	1,929	465	142	31	8	2	0	0	0	0	0	0	0	0	0	0	0-5
				2	7	7	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0.9,0.95 ,1.0	120	494	446	170	41	12	3	1	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kwango	**300 gene drives only**			10,171	47,833	47,935	23,713	6,753	2,263	574	139	34	9	1	1	4	0	0	0	0	0	1	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	95	0.95,1.0	4,162	19,574	19,616	9,704	2,764	926	235	57	14	4	1	0	2	0	0	0	0	0	0	0-5
				152	715	717	355	101	34	9	2	1	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	461	2,169	2,174	1,075	306	103	26	6	2	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Nord Ubangui	**300 gene drives only**			9,732	44,433	44,203	20,212	5,662	1,925	427	105	20	6	1	0	0	1	0	1	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	95	0.95,1.0	4,438	20,261	20,156	9,217	2,582	878	195	48	9	3	0	0	0	0	0	0	0	0	0	0-5
				22	99	99	45	13	4	1	0	0	0	0	0	0	0	0	0	0	0	0	6-10

Province	Intervention	Cov-erage	Gene drive X-shred-ding rate	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85 +	Year
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	484	2,210	2,199	1,005	282	96	21	5	1	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15

Table 21 Number of severe cases (not dead) over 15 years by study location in scenarios without gene drives

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
Bas Uele	**Baseline-50%ITN+19%ACT**		359	1,348	388	44	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			316	1,186	341	39	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			336	1,262	363	41	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	50	470	1,765	508	57	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			400	1,505	433	49	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			425	1,596	459	52	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	394	1,480	426	48	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			394	1,479	426	48	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			450	1,692	487	55	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	328	1,234	355	40	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			399	1,501	432	49	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			459	1,726	497	56	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	50	235	883	254	29	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			191	719	207	23	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			183	689	198	22	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	79	297	85	10	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			70	262	75	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			66	247	71	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	16	60	17	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			16	61	18	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			15	58	17	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	189	708	204	23	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			184	691	199	22	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			199	748	215	24	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	24	89	26	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			68	256	74	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			77	288	83	9	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	4	16	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			1	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Equateur	**Baseline-50%ITN+19%ACT**		431	1,299	331	29	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			384	1,158	295	26	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			407	1,229	313	27	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	50	557	1,681	428	37	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			488	1,472	375	32	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			513	1,547	394	34	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	483	1,456	371	32	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			473	1,426	363	31	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			551	1,661	423	37	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	429	1,294	329	29	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			480	1,447	368	32	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			558	1,682	428	37	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	50	273	824	210	18	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			233	703	179	16	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			225	678	173	15	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	93	282	72	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			85	255	65	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			82	247	63	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	20	59	15	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			19	58	15	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			19	56	14	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	229	692	176	15	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			224	676	172	15	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			240	725	185	16	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	83	250	64	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			83	250	64	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			93	281	72	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	2	7	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			13	38	10	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			18	55	14	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Haut Katanga	**Baseline-50%ITN+19%ACT**		58	741	652	149	23	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			73	926	814	186	29	4	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			71	897	789	180	28	3	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	50	83	1,059	931	212	33	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			92	1,168	1,027	234	36	5	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			89	1,136	999	228	35	4	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	41	520	457	104	16	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			97	1,239	1,090	248	38	5	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			93	1,177	1,035	236	37	5	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	11	144	127	29	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			57	722	635	145	22	3	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			56	718	631	144	22	3	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	50	48	615	541	123	19	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			43	542	477	109	17	2	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			38	488	429	98	15	2	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	14	180	159	36	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			16	200	176	40	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			14	178	157	36	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	2	29	25	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			4	46	40	9	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			3	43	38	9	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
			23	291	256	58	9	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
		50	44	559	491	112	17	2	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			42	528	465	106	16	2	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
			0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
	ITNs+ACT	80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
		95	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kasai Central	**Baseline-50%ITN+19%ACT**		311	1,309	451	51	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			279	1,178	406	46	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			292	1,232	424	48	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
			411	1,735	597	67	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
		50	355	1,498	516	58	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			369	1,556	536	60	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
			332	1,399	482	54	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
	ITNs	80	355	1,498	516	58	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			386	1,627	560	63	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
			268	1,128	388	44	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
		95	363	1,532	527	59	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			397	1,673	576	65	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
			206	870	299	34	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
		50	167	703	242	27	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
	ACT		160	677	233	26	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	61	258	89	10	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			61	258	89	10	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			58	243	84	9	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	14	59	20	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			14	60	21	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			13	56	19	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	161	680	234	26	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			164	692	238	27	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			171	722	248	28	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	15	63	22	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			60	251	86	10	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			67	283	98	11	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kinshasa	**Baseline-50%ITN+19%ACT**		406	1,296	308	29	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			367	1,172	279	26	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			398	1,270	302	28	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	50	526	1,679	399	37	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			468	1,493	355	33	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			500	1,596	380	35	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	467	1,491	355	33	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			463	1,476	351	32	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			520	1,660	395	37	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	425	1,355	322	30	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			456	1,454	346	32	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			531	1,694	403	37	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	50	258	822	196	18	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			223	710	169	16	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			217	694	165	15	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	89	284	68	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			80	256	61	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			77	246	59	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	19	59	14	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			18	58	14	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			18	56	13	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	223	713	170	16	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			217	693	165	15	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			233	745	177	16	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	46	147	35	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			78	250	59	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			88	281	67	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	4	11	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			14	45	11	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			19	61	15	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kwango	**Baseline-50%ITN+19%ACT**		312	1,283	440	56	7	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			289	1,190	408	52	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			300	1,234	423	54	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	50	417	1,718	589	75	9	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			361	1,485	509	65	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			376	1,550	531	68	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	332	1,369	469	60	7	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			362	1,490	511	65	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			392	1,614	553	71	8	2	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	268	1,105	379	48	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			376	1,548	531	68	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			398	1,637	561	72	8	2	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	50	210	864	296	38	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			172	706	242	31	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			163	670	230	29	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	70	288	99	13	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			62	254	87	11	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			59	241	83	11	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	14	59	20	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			14	59	20	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			14	56	19	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	163	669	229	29	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			166	685	235	30	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			174	715	245	31	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	14	59	20	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			60	248	85	11	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			67	275	94	12	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Nord Ubangui	**Baseline-50%ITN+19%ACT**		304	1,303	443	49	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			272	1,167	396	44	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			293	1,255	426	47	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	50	405	1,737	590	65	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			347	1,487	505	56	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			366	1,567	532	59	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	326	1,398	475	53	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			339	1,452	493	55	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			388	1,663	565	63	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	274	1,174	399	44	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			351	1,502	510	57	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			397	1,700	577	64	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	50	203	870	295	33	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			166	709	241	27	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			158	675	229	25	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	67	288	98	11	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5

Province	Intervention	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			60	257	87	10	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			57	242	82	9	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	13	58	20	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			14	60	20	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			13	57	19	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	159	682	232	26	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			159	680	231	26	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			171	732	248	28	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	16	67	23	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			58	247	84	9	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			66	283	96	11	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15

Table 22 Number of severe cases (not dead) over 15 years by study location in scenarios with gene drives

Province	Intervention	Cover-age	Gene drive X-shred-ding rate	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
Bas Uele	**300 gene drives only**			390	1,464	421	48	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	17	62	18	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0.9,0.95, 1.0	1	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10

Province	Intervention	Cover-age	Gene drive X-shred-ding rate	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85 +	Year
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Equateur	**300 gene drives only**			455	1,371	349	30	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	29	89	23	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0.9,0.95, 1.0	1	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Haut Katanga	**300 gene drives only**			94	1,191	1,047	239	37	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	ITNs	80	0.95,1.0	59	747	656	150	23	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				2	23	20	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				2	26	23	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0.95,1.0	30	386	339	77	12	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				30	386	339	77	12	1	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	95	0.95,1.0	1	18	16	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	0.95,1.0	15	188	165	38	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kasai Central	**300 gene drives only**			382	1,612	555	62	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	95	0.95,1.0	196	827	285	32	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				6	25	9	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	12	49	17	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5

Province	Intervention	Cover-age	Gene drive X-shred-ding rate	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85 +	Year
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kinshasa	**300 gene drives only**			448	1,431	340	31	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	32	101	24	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0.9,0.95, 1.0	2	7	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kwango	**300 gene drives only**			393	1,618	555	71	8	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	95	0.95,1.0	194	800	274	35	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				5	22	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	10	43	15	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Nord Ubangui	**300 gene drives only**			339	1,451	493	55	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	95	0.95,1.0	187	801	272	30	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				1	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	11	45	15	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15

Table 23 Number of deaths over 15 years by study location in scenarios without gene drives

Province	Interven-tion	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
Bas Uele	**Baseline-50%ITN+19%ACT**		33	125	36	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			29	110	32	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			31	117	34	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	50	35	132	38	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			30	113	32	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			32	119	34	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	29	111	32	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			29	111	32	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			34	127	36	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	25	92	27	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			30	112	32	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			34	129	37	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	50	35	132	38	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			29	108	31	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			27	103	30	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	30	111	32	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			26	98	28	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			25	92	27	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	24	90	26	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			24	92	26	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			23	86	25	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	28	106	31	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			28	103	30	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			30	112	32	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	9	33	10	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			26	96	28	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			29	108	31	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	6	24	7	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5

Province	Interven-tion	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			1	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			2	6	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Equateur	**Baseline-50%ITN+19%ACT**		40	120	31	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			35	107	27	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			38	113	29	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	50	42	126	32	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			37	110	28	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			38	116	29	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	36	109	28	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			35	107	27	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			41	124	32	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	32	97	25	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			36	108	28	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			42	126	32	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	50	41	123	31	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			35	105	27	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			34	101	26	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	35	105	27	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			32	95	24	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			31	93	24	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	29	88	22	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			29	87	22	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			28	84	21	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	34	104	26	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			34	101	26	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			36	109	28	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	31	94	24	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			31	94	24	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			35	105	27	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	3	10	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5

Province	Interven-tion	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			19	57	15	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			28	83	21	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Haut Katanga	**Baseline-50%ITN+19%ACT**		5	68	60	14	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			7	86	75	17	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			7	83	73	17	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	50	6	79	70	16	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			7	87	77	18	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			7	85	75	17	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	3	39	34	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			7	93	82	19	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			7	88	77	18	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	1	11	9	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			4	54	47	11	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			4	54	47	11	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	50	7	92	81	18	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			6	81	71	16	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			6	73	64	15	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	5	67	59	14	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			6	75	66	15	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			5	67	59	13	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	3	43	38	9	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			5	69	60	14	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			5	65	57	13	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	3	44	38	9	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			7	84	74	17	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			6	79	70	16	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5

Province	Interven-tion	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kasai Central	**Baseline-50%ITN+19%ACT**		29	121	42	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			26	109	37	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			27	114	39	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	50	31	130	45	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			27	112	39	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			28	116	40	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	25	105	36	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			27	112	39	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			29	122	42	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	20	84	29	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			27	115	39	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			30	125	43	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	50	31	130	45	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			25	105	36	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			24	101	35	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	23	97	33	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			23	97	33	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			22	91	31	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	21	89	31	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			21	90	31	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			20	84	29	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	24	102	35	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			25	104	36	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			26	108	37	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	6	24	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			22	94	32	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			25	106	36	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5

Province	Interven-tion	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kinshasa	**Baseline-50%ITN+19%ACT**		38	120	28	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			34	108	26	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			37	117	28	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	ITNs	50	39	126	30	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			35	112	27	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			37	119	28	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	35	112	27	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			35	110	26	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			39	124	30	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	32	101	24	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			34	109	26	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			40	127	30	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	50	39	123	29	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			33	106	25	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			33	104	25	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	33	106	25	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			30	96	23	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			29	92	22	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	28	89	21	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			27	87	21	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			26	84	20	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	33	107	25	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			32	104	25	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			35	111	26	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	17	55	13	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			29	93	22	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			33	105	25	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	5	17	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5

Province	Interven-tion	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			21	67	16	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			29	92	22	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kwango	**Baseline-50%ITN+19%ACT**		29	118	41	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			27	110	38	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			28	114	39	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	50	31	129	44	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			27	111	38	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			28	116	40	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	25	102	35	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			27	111	38	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			29	121	41	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	20	83	28	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			28	116	40	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			30	122	42	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	50	31	129	44	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			26	106	36	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			24	100	34	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	26	108	37	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			23	95	33	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			22	90	31	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	21	88	30	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			22	89	30	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			20	84	29	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	24	100	34	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			25	102	35	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			26	107	37	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	5	22	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			23	93	32	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			25	103	35	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5

Province	Interven-tion	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Nord Ubangui	**Baseline-50%ITN+19%ACT**		28	120	41	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			25	108	37	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			27	116	39	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	50	30	130	44	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			26	111	38	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			27	117	40	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	24	105	36	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			25	109	37	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			29	124	42	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	21	88	30	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			26	112	38	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			30	127	43	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	50	30	130	44	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			25	106	36	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			24	101	34	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	25	108	37	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			22	96	33	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			21	91	31	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	20	86	29	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			21	90	31	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			20	86	29	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	24	102	35	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			24	102	35	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			26	109	37	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		80	6	25	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			22	93	31	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			25	106	36	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15

Province	Interven-tion	Coverage	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
		95	1	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15

Table 24 Number of deaths over 15 years by study location in scenarios without gene drives

Province	Intervention	Cov-erage	Gene drive X-shred-ding rate	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
Bas Uele	**300 gene drives only**			29	110	32	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	6	23	7	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0.9,0.95,1.0	1	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Equateur	**300 gene drives only**			34	103	26	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	11	33	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0.9,0.95,1.0	2	6	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Haut	**300 gene drives only**			7	89	78	18	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5

Province	Intervention	Cov-erage	Gene drive X-shred-ding rate	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Year
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	80	0.95,1.0	4	56	49	11	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0.95,1.0	2	29	25	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				2	29	25	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ACT	95	0.95,1.0	2	27	24	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	50	0.95,1.0	2	28	25	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kasai Central	**300 gene drives only**			29	121	42	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	95	0.95,1.0	15	62	21	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	4	18	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Kinshasa	**300 gene drives only**			34	107	25	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	12	38	9	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
		95	0.9,0.95,1.0	4	11	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15

Province	Intervention	Cov-erage	Gene drive X-shred-ding rate	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85 +	Year
Kwango	**300 gene drives only**			29	121	41	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	95	0.95,1.0	15	60	21	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	4	16	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
Nord Ubangui	**300 gene drives only**			25	109	37	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs	95	0.95,1.0	14	60	20	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15
	ITNs+ACT	80	0.95,1.0	4	17	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0-5
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6-10
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11-15

Appendix 3.2 Templates used for DALY calculation

Table 25 Templates for DALY calculation

	Population	Deaths	Deaths per 1,000 (5 years)	Average Age at death	Standard Life Expectation (LE)	YLLs	YLL per 1,000 (5 years)
Males							
0	0.5*total population	0.5*total deaths	1,000*deaths / population	0.1	58.9	deaths*(standard life expectancy of DRC population - avg age at death)	deaths*(standard life expectancy of DRC population - avg age at death)
1-4				2.6	61.5		
5-9				7.3	58.3		
10-14				12.9	53.5		
15-19				18.1	49.1		
20-24				22.5	45.4		
25-29				27.5	41.4		
30-34				32.6	37.2		
35-39				37.5	33.3		
40-44				42.6	29.3		
45-49				47.7	25.3		
50-54				52.6	21.6		
55-59				57.6	17.9		
60-64				62.7	14.5		
65-69				67.7	11.4		
70-74				72.6	8.8		
75-79				77.5	6.6		
80-84				82.4	4.8		
85+				89.0	0.8		
Total							

Females					
0			0.1	62.0	
1-4			2.6	64.1	
5-9			7.4	60.7	
10-14			12.6	56.4	
15-19			17.9	51.7	
20-24			22.6	47.7	
25-29			27.5	43.5	
30-34			32.6	39.2	
35-39			37.5	35.2	
40-44			42.7	31.1	
45-49			47.7	27.0	
50-54			52.6	23.1	
55-59			57.7	19.1	
60-64			62.6	15.6	
65-69			67.6	12.3	
70-74			72.6	9.4	
75-79			77.6	7.1	
80-84			82.6	5.2	
85+			90.0	0.0	
Total					

A1. YLL in study age groups

	Population	Deaths	Deaths per 1,000 (5 years)	Av. Age at death	YLLs	YLL per 1,000 (5 years)
Males						
0-4						
5-14						
15-29						
30-44						
45-59						
60-69						
70-79						
80+						
Total						
Females						
0-4						
5-14						
15-29						
30-44						
45-59						
60-69						
70-79						
80+						
Total						

B. YLD template for prevalence YLD (undiscounted and non-age-weighted)

A1. This is an optional calculation of prevalence YLD
A2. Enter prevalence rates in green cells

Severe cases (not dead)

	Population	Incidence	Incidence per 1,000	Duration (years)	Disability Weight	YLDs	YLD per 1,000
Males							
0-4	0.5*total population	0.5*severe cases, not dead	1,000*incidence / population	0.08	0.133	incidence*duration*disability weight	1,000*YLDs / population
5-14							
15-29							
30-44							
45-59							
60-69							
70-79							
80+							
Total							
Females							
0-4	0.5*total population	0.5*severe cases, not dead	1,000*incidence / population	0.08	0.133	incidence*duration*disability weight	1,000*YLDs / population
5-14							
15-29							
30-44							
45-59							

60-69						
70-79						
80+						
Total						

B. YLD template for prevalence YLD
(undiscounted and non-age-weighted)
A1. This is an optional calculation of prevalence YLD
A2. Enter prevalence rates in green cells

Uncomplicated cases

	Population	**Incidence**	**Incidence per 1,000**	**Duration (years)**	**Disability Weight**	**YLDs**	**YLD per 1,000**
Males							
0-4	0.5*total population	0.5*uncomplicated clinical cases	1,000*incidence / population	0.02	0.051	incidence*duration*disability weight	1,000*YLDs / population
5-14							
15-29							
30-44							
45-59							
60-69							
70-79							
80+							
Total							

Females

0-4	0.5*total population	0.5*uncomplicated clinical cases	1,000*incidence / population	0.02	0.051	incidence*duration*disability weight	1,000*YLDs / population
5-14							
15-29							
30-44							
45-59							
60-69							
70-79							
80+							
Total							

C. Total DALYS = YLL+YLD

	Males			***Females***			***Persons***		
Population	**DALYs**	**DALYs per 1,000 (5 years)**	**Population**	**DALYs**	**DALYs per 1,000 (5 years)**	**Population**	**DALYs**	**DALYs per 1,000 (5 years)**
Age								
0-4								
5-14								
15-29								
30-44								
45-59								
60-69								
70-79								
80+								
Total								

Appendix 3.3 Template used for cost per DALY averted calculation

Table 26 Template for cost per DALY averted calculation

Intervention	Coverage	Elimination	Cost per year (I$, millions) per one million population [i.e. cost per capita] 2000 base year	Age	Persons population	Yearly effectiveness (DALYs averted)	Yearly DALYs averted per one million population	Average yearly costs, $int	Cost per year calculation: Average cost effectiveness ($int per DALY averted)
								= cost per year*number of populations	= average yearly costs/DALYs averted

Appendix 3.4 Expansion paths by study site

Keys for Table 27-33:

- ICER: Incremental cost-effectiveness ratio
- Negative: incremental cost and incremental effect are negative
- Dominated: incremental cost is positive, and incremental effect is negative
- Undefined: incremental effect is zero
- Vector control strategies that could reach malaria elimination were highlighted in green. The first, second, third points of each expansion path were highlighted in red, orange, and yellow.
- ITNs: Insecticide treated nets
- ACT: Artemisinin-based Combination Therapy
- Drives, gene drive mosquitoes: Driving-Y gene drive mosquitoes
- NA: Not applicable

Bas Uele

Table 27 Cost effectiveness of interventions over 15 years of Bas Uele study location

					ICER ($int per DALY averted)					
					The first interval: year 1-5		The second interval: year 6-10		The last interval: year 11-15	
	Intervention	Cover-age	Malaria Elimination	Label	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound
Scenarios without gene drives	ITNs	50%	No	A	dominated	dominated	negative	negative	negative	dominated
		80%	No	B	dominated	dominated	negative	negative	negative	dominated
		95%	No	C	dominated	dominated	negative	negative	negative	dominated
	ACT	50%	No	D	negative	negative	negative	negative	negative	negative
		80%	No	E	negative	negative	negative	negative	negative	negative
		95%	No	F	**First Point**	**First Point**	negative	negative	negative	**First Point**
	ITNs & ACT	50%	No	G	dominated	dominated	negative	negative	negative	dominated
		80%	No	H	14.40	14.40	dominated	dominated	dominated	dominated
		95%	No	I	10.69	10.69	dominated	**First Point**	dominated	8.81
Scenarios with gene drives	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	NA	Yes	J	dominated	dominated	**First Point**	3,530.81	**First Point**	108.59
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	K	NA	NA	NA	NA	NA	NA
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	L	NA	NA	NA	NA	NA	NA
	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	M	NA	NA	NA	NA	NA	NA
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	50	Yes	N	NA	NA	NA	NA	NA	NA
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	O	26.80	156.99	dominated	3,980.26	undefined	121.32
	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0	95	Yes	P	19.27	119.02	undefined	3,934.21	undefined	120.00

Equateur

Table 28 Cost effectiveness of interventions over 15 years of Equateur study location

					ICER ($int per DALY averted)					
					The first interval: year 1-5		The second interval: year 6-10		The last interval: year 11-15	
	Intervention	Cover-age	Malaria Elimination	Label	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound
Scenarios without gene drives	ITNs	50%	No	A	dominated	dominated	dominated	dominated	dominated	dominated
		80%	No	B	dominated	dominated	dominated	dominated	dominated	dominated
		95%	No	C	dominated	dominated	dominated	dominated	dominated	dominated
	ACT	50%	No	D	negative	negative	dominated	negative	negative	negative
		80%	No	E	negative	negative	dominated	negative	negative	negative
		95%	No	F	**First point**	**First point**	dominated	**First point**	negative	**First point**
	ITNs & ACT	50%	No	G	dominated	dominated	dominated	dominated	negative	dominated
		80%	No	H	dominated	dominated	negative	dominated	115.07	dominated
		95%	No	I	8.98	8.98	negative	22.98	30.51	623.01
Scenarios with gene drives	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	NA	Yes	J	dominated	dominated	**First point**	105.54	**First point**	109.94
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	K	NA	NA	NA	NA	NA	NA
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	L	NA	NA	NA	NA	NA	NA
	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	M	NA	NA	NA	NA	NA	NA
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	50	Yes	N	NA	NA	NA	NA	NA	NA
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	O	32.06	187.84	dominated	117.95	17.72	122.54
	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0	95	Yes	P	20.13	124.28	dominated	116.68	16.78	121.20

Haut Katanga

Table 29 Cost effectiveness of interventions over 15 years of Haut Katanga study location

					ICER ($int per DALY averted)					
					The first interval: year 1-5		The second interval: year 6-10		The last interval: year 11-15	
	Intervention	Cover-age	Malaria Elimination	Label	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound
Scenarios without gene drives	ITNs	50%	No	A	dominated	dominated	negative	dominated	negative	negative
		80%	No	B	108.39	108.39	negative	dominated	negative	negative
		95%	No	C	15.89	15.89	negative	dominated	negative	negative
	ACT	50%	No	D	negative	negative	negative	dominated	negative	negative
		80%	No	E	negative	negative	negative	dominated	negative	negative
		95%	No	F	**First point**	**First point**	negative	dominated	negative	negative
	ITNs & ACT	50%	No	G	dominated	dominated	negative	dominated	negative	negative
		80%	No	H	14.70	14.70	undefined	undefined	undefined	undefined
		95%	No	I	12.70	12.70	undefined	**First point**	undefined	**First point**
Scenarios with gene drives	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	NA	Yes	J	dominated	dominated	**First point**	undefined	**First point**	undefined
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	K	dominated	dominated	dominated	dominated	dominated	dominated
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	L	89.34	563.77	dominated	dominated	dominated	dominated
	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	M	47.07	468.69	dominated	dominated	undefined	undefined
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	50	Yes	N	81.96	528.25	dominated	dominated	undefined	undefined
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	O	NA	NA	NA	NA	NA	NA
	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0	95	Yes	P	NA	NA	NA	NA	NA	NA

Kasai Central

Table 30 Cost effectiveness of interventions over 15 years of Kasai Central study location

					ICER ($int per DALY averted)					
					The first interval: year 1-5		The second interval: year 6-10		The last interval: year 11-15	
	Intervention	Cover-age	Malaria Elimination	Label	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound
Scenarios without gene drives	ITNs	50%	No	A	dominated	dominated	negative	negative	negative	dominated
		80%	No	B	dominated	dominated	negative	negative	negative	dominated
		95%	No	C	193.17	193.17	negative	negative	negative	dominated
	ACT	50%	No	D	negative	negative	negative	negative	negative	negative
		80%	No	E	negative	negative	negative	negative	negative	negative
		95%	No	F	**First point**	**First point**	negative	negative	negative	**First point**
	ITNs & ACT	50%	No	G	dominated	dominated	negative	negative	negative	dominated
		80%	No	H	12.45	12.45	dominated	dominated	dominated	dominated
		95%	No	I	8.06	8.06	5,516,315.92	**First point**	undefined	8.34
Scenarios with gene drives	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	NA	Yes	J	dominated	dominated	**First point**	dominated	**First point**	110.53
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	K	NA	NA	NA	NA	NA	NA
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	L	NA	NA	NA	NA	NA	NA
	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	M	NA	NA	NA	NA	NA	NA
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	50	Yes	N	NA	NA	NA	NA	NA	NA
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	O	61.93	390.79	dominated	dominated	undefined	121.73
	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0	95	Yes	P	25.18	147.57	dominated	dominated	undefined	123.52

Kinshasa

Table 31 Cost effectiveness of interventions over 15 years for Kinshasa study location

					ICER ($int per DALY averted)					
					The first interval: year 1-5		The second interval: year 6-10		The last interval: year 11-15	
	Intervention	Cover-age	Malaria Elimination	Label	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound
Scenarios without gene drives	ITNs	50%	No	A	dominated	dominated	negative	dominated	negative	dominated
		80%	No	B	dominated	dominated	negative	dominated	negative	dominated
		95%	No	C	dominated	dominated	negative	dominated	negative	dominated
	ACT	50%	No	D	negative	negative	negative	negative	negative	negative
		80%	No	E	negative	negative	negative	negative	negative	negative
		95%	No	F	**First point**	**First point**	negative	**First point**	negative	**First point**
	ITNs & ACT	50%	No	G	dominated	dominated	negative	dominated	negative	dominated
		80%	No	H	24.46	24.46	dominated	dominated	dominated	dominated
		95%	No	I	9.88	9.88	dominated	35.67	dominated	dominated
Scenarios with gene drives	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	NA	Yes	J	dominated	dominated	**First point**	107.78	**First point**	111.32
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	K	NA	NA	NA	NA	NA	NA
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	L	NA	NA	NA	NA	NA	NA
	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	M	NA	NA	NA	NA	NA	NA
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	50	Yes	N	NA	NA	NA	NA	NA	NA
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	O	35.20	206.20	dominated	120.54	undefined	124.41
	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0	95	Yes	P	21.68	133.90	dominated	119.30	undefined	123.16

Kwango

Table 32 Cost effectiveness of interventions over 15 years for Kwango study location

					ICER ($int per DALY averted)					
					The first interval: year 1-5		The second interval: year 6-10		The last interval: year 11-15	
	Intervention	Cover-age	Malaria Elimination	Label	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound
Scenarios without gene drives	ITNs	50%	No	A	negative	negative	negative	negative	negative	negative
		80%	No	B	negative	negative	negative	negative	negative	negative
		95%	No	C	negative	negative	negative	negative	negative	negative
	ACT	50%	No	D	negative	negative	negative	negative	negative	negative
		80%	No	E	negative	negative	negative	negative	negative	negative
		95%	No	F	negative	negative	negative	negative	negative	negative
	ITNs & ACT	50%	No	G	negative	negative	negative	negative	negative	negative
		80%	No	H	dominated	dominated	dominated	dominated	dominated	dominated
		95%	No	I	**First point**	**First point**	40,975.10	**First point**	undefined	**First point**
Scenarios with gene drives	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	NA	Yes	J	negative	dominated	**First point**	dominated	**First point**	undefined
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	K	NA	NA	NA	NA	NA	NA
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	L	NA	NA	NA	NA	NA	NA
	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	M	NA	NA	NA	NA	NA	NA
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	50	Yes	N	NA	NA	NA	NA	NA	NA
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	O	dominated	dominated	dominated	dominated	undefined	undefined
	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0	95	Yes	P	dominated	dominated	dominated	dominated	undefined	undefined

Nord Ubangui

Table 33 Cost effectiveness of interventions over 15 years of Nord Ubangui study location

					ICER ($int per DALY averted)					
					The first interval: year 1-5		The second interval: year 6-10		The last interval: year 11-15	
	Intervention	Cover-age	Malaria Elimination	Label	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound
Scenarios without gene drives	ITNs	50%	No	A	dominated	dominated	negative	negative	negative	negative
		80%	No	B	dominated	dominated	negative	negative	negative	negative
		95%	No	C	dominated	dominated	negative	negative	negative	negative
	ACT	50%	No	D	negative	negative	negative	negative	negative	negative
		80%	No	E	negative	negative	negative	negative	negative	negative
		95%	No	F	**First point**	**First point**	negative	negative	negative	negative
	ITNs & ACT	50%	No	G	dominated	dominated	negative	negative	negative	negative
		80%	No	H	13.30	13.30	dominated	dominated	dominated	dominated
		95%	No	I	8.38	8.38	undefined	**First point**	undefined	**First point**
Scenarios with gene drives	300 gene drive mosquitoes with X-shredding rates = 1.0 alone	NA	Yes	J	dominated	dominated	**First point**	undefined	**First point**	undefined
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	K	NA	NA	NA	NA	NA	NA
	ITNs plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	L	NA	NA	NA	NA	NA	NA
	ACT plus gene drives with X-shredding rates = 0.95 and 1.0	95	Yes	M	NA	NA	NA	NA	NA	NA
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	50	Yes	N	NA	NA	NA	NA	NA	NA
	ITNs & ACT plus gene drives with X-shredding rates = 0.95 and 1.0	80	Yes	O	63.78	402.45	dominated	dominated	undefined	undefined
	ITNs & ACT plus gene drives with X-shredding rates = 0.9, 0.95 and 1.0	95	Yes	P	25.67	150.41	dominated	dominated	undefined	undefined