Integrated Vector Management – generation and use of evidence for more effective vector control

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Submitted to Durham University for

the degree of Doctor of Philosophy

December 2016

Abstract

Vector-borne diseases (VBD) such as malaria, dengue and leishmaniasis have a major public health impact primarily in low and middle income countries in the tropics. Vector control methods including long-lasting insecticidal nets and indoor residual spraying contribute substantially to control of VBDs, particularly malaria. However, progress is being hampered by a number of factors including a lack of human, infrastructural and financial resources, and is threatened by the development of insecticide resistance. The World Health Organization (WHO) strongly advocates the use of Integrated Vector Management (IVM), a policy which has the potential to overcome many of the challenges facing vector control. IVM calls for evidence-based and adaptive use of vector control tools and involvement of multiple sectors to control VBDs. This thesis brings together work on the theme of IVM and the generation and use of evidence for better vector control programming. Specifically I ask how do we develop high quality evidence to improve the effectiveness of vector control?

The writer has been a principal author of a recently published WHO Toolkit for IVM in sub-Saharan Africa (Volume II of this thesis). This toolkit for vector control programme managers builds on previous WHO guidance by providing practical detail on how to plan, implement, and monitor and evaluate an IVM programme. In order to provide guidance on choice of vector control interventions in the IVM toolkit, it was necessary to systematically review the evidence from field trials of vector control tools. Two systematic reviews are presented evaluating the efficacy of insecticide-treated nets, curtains and screening against non-malaria VBDs, and the efficacy of topical repellents against malaria. These found that: i) insecticide-treated materials in the home (nets, curtains and screening) are protective against cutaneous leishmaniasis and may be protective against dengue and Japanese encephalitis, ii) topical repellents are not protective against falciparum or vivax malaria in endemic populations. Systematic reviews revealed a paucity of well-conducted efficacy studies of vector control interventions which hinders evidence-based policy-making. A critical analysis of vector control study design and conduct is presented. This analysis identified common failings with vector control trials including a lack of randomisation and blinding, poor choice of outcome measures, lack of replication, no sample size calculations and contamination between clusters in cluster-randomised trials. Many of these failings could be easily rectified to produce better quality evidence and prevent waste in research.

As well as evidence-based policy making on vector control interventions, IVM calls for use of evidence throughout the lifetime of the programme through entomological and epidemiological surveillance and monitoring and evaluation to choose and target interventions, measure their

effectiveness and adapt the programme over time. One entomological parameter which should be measured is insecticide resistance. A study of the spatial and temporal pattern of knockdown resistance (*kdr*) resistance in *Anopheles gambiae* s.l. in a setting of high vector control use in the Upper River Region of The Gambia is presented which found that: i) *An. arabiensis* was the most common member of the species complex, ii) the odds of *kdr* were 24 times higher in *An. gambiae s.s.* in villages with both IRS and LLINs and 14 times higher in villages with LLINs alone, iii) the *kdr* mutation was more common in mosquitoes in the second year of the study and with increasing distance from the river.

The result of this work is the IVM Toolkit for sub-Saharan Africa. IVM provides a logical framework to think through vector control and advocates for a more locally tailored and adaptive approach which engages partners within and beyond the health sector. Compared to current vector control, IVM has the potential to be more effective (through evidence-based use of interventions), cost-effective (through implementation of cost effective interventions and sharing of resources across sectors), sustainable (through engagement and mobilisation of communities and the non-health sector) and ecologically sound (through the use of non-insecticide-based tools). However, there are a number of challenges to utilisation of IVM. While this thesis outlines the theoretical framework for IVM, it does not test its use by programmes, and in fact there are few good examples of IVM in practice available. Policies and organisational structures of vector control programmes are currently not in support of IVM. Lack of resources (infrastructural, human and financial) hampers implementation of this more knowledge-intensive and adaptive approach to vector control. Deeply engrained silos and lack of political support may impede partnership working within and across sectors. An increased focus on vector control in the light of the recent Zika virus disease outbreak and high-level policy changes at WHO including development of the forthcoming Global Vector Control Response should galvanise support for vector control and reorientation of programmes towards an IVM approach. IVM can be implemented if there is additional and sustained financing for vector control, an investment in human resources and infrastructure, and more commitment to working across sectors. It is important to grasp this opportunity in order to exploit fully the potential of vector control to control and eliminate VBDs in the future.

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Abbreviations

AIDS	acquired immunodeficiency syndrome
BCC	behaviour change communication
CBA	controlled before-and-after study
CDC	Centers for Disease Control and Prevention
CI	confidence interval
DDT	dichlorodiphenyltrichloroethane
DEET	*N,N*-diethyl-m-toluamide
DNA	deoxyribonucleic acid
EPOC	Effective Practice and Organization of Care
EQUATOR	Enhancing the QUAlity and Transparency Of health Research
GDP	gross domestic product
GMEP	Global Malaria Elimination Programme
GMP	Global Malaria Programme
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GVCR	Global Vector Control Response
HAT	human African trypanosomiasis
HIV	human immunodeficiency virus
HLC	human landing catch
IEC	Information, education, communication
IPM	integrated pest management
IRS	indoor residual spraying
ITC	insecticide-treated curtain
ITN	insecticide-treated net
ITS	insecticide-treated screening
ITS	interrupted time series
IVC	integrated vector control
IVM	integrated vector management
kdr	knockdown resistance
LLIN	long-lasting insecticidal net
LT	light trap
LSM	larval source management
MDA	mass drug administration
MDAST	malaria decision analysis support tool
MFI	(Khartoum) Malaria Free Initiative
MoA	mode of action
MPAC	Malaria Policy Advisory Committee
NGO	non-governmental organisation
NR	not reported
NTD	neglected tropical disease
OCP	Onchocerciasis Control Programme
OR	odds ratio
PDR	People's Democratic Republic
PE	protective efficacy

PMD	*p*-Menthane-3,8-diol
POP	persistent organic pollutant
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSC	pyrethrum spray catch
PWD	public works department
R&D	research and development
RBM	Roll Back Malaria
RCT	randomised controlled trial
SCI	Southern Cone Initiative
SDG	Sustainable Development Goal
SSA	sub-Saharan Africa
STAG	Strategic and Technical Advisory Group
TPP	target product profile
TVA	Tennessee Valley Authority
URR	Upper River Region
USA	United States of America
VBD	vector-borne disease
VCAG	Vector Control Advisory Group
VCNA	vector control needs assessment
VOI	value-of-information
WHA	World Health Assembly
WHO	World Health Organization

Declaration

The work contained in this thesis has not been submitted elsewhere for any other degree or qualification and is the authors own work unless otherwise stated.

Statement of Copyright

Acknowledgements

First and foremost, I am indebted to Professor Steve Lindsay for his tireless support and guidance, and for sharing his immense knowledge and enthusiasm for vector control with me.

I am extremely grateful to the Bill and Melinda Gates Foundation who were the main funder of this research through a grant to develop a framework for integrated vector control (OPP1053338).

Collection of data for chapter 6 on the spatial and temporal distribution of knock-down resistance was funded by the UK Medical Research Council (grant number MRC GO900220). I am grateful to everyone involved in the original study including the communities, NMCP managers and staff, field, laboratory and data management staff from the Medical Research Council Unit in The Gambia and Basse demographic surveillance unit, as well as members of the Trial Steering Committee and the Data Safety and Monitoring Board. Special thanks to Margaret Pinder for study coordination and Musa Jawara for overseeing the entomological data collection.

I would like to thank my co-authors on papers included in my thesis: Ramesh Dhiman, Uriel Kitron, Tom Scott, Henk van den Berg, Vanessa Chen-Hussey, James Logan, Marleen Boelaert, Immo Kleinschmidt, Margaret Pinder and Lucy Tusting. I would also like to thank those involved in meetings during development of the IVM toolkit and expert review panels for this document, but in particular; Raman Velayudhan, Rajpal Singh Yadav, Dave Smith, Willem Takken and Marlize Coleman. Thanks also to Laura Turnbull-Lloyd in the Geography Department of Durham University for guidance on using ArcGIS, and to Rachel Simpson, School of Biosciences for administrative assistance.

Lastly, I thank mam, dad and my brother Stephen for their invaluable support and encouragement over the years.

Introduction

Over 80 % of the global population, or 5.5 billion people, live in areas at risk from one vector-borne disease (VBD) [1]. VBDs are diseases transmitted by arthropod vectors, such as malaria, dengue and leishmaniasis. These diseases result in a large burden of morbidity and mortality that predominantly falls on low and middle income countries in the tropics and sub-tropics, particularly the poor. Vector control tools including long-lasting insecticidal nets (LLINs), indoor residual spraying (IRS) and larval source management play a major role in control of these diseases. The World Health Organization (WHO) has since 2004 advocated for the use of Integrated Vector Management (IVM) for control and/or elimination of VBDs globally [2]. IVM calls for the evidence-based and adaptive use of vector control tools and involvement of multiple sectors in vector control. Briefly, it involves the use of a range of proven vector control tools from within and outside the health sector, used either alone or in combination, and selected based on knowledge of the local vector ecology and disease epidemiology. IVM is accompanied by vector surveillance and monitoring and evaluation so that control activities can be adapted over time and impacts can be evaluated. IVM aims to make vector control more efficacious, cost effective, ecologically sound and sustainable [3].

Application of IVM relies on evidence-based policy-making in order to know which vector control tools are effective against which VBD, and where, when and how they should be deployed. Policy formulation on a particular vector control product at WHO is based on evidence from different field trials of vector control tools which is synthesised using a systematic review. A systematic review involves systematically identifying all the studies of a particular vector control tool, selecting these on the basis of inclusion and exclusion criteria, assessing the quality of each study, synthesising the findings and interpreting the findings in an impartial fashion. Study findings are often summarised using meta-analysis which generates a summary effect measure giving due weight to the size of the studies included. The evidence base on vector control for malaria is relatively strong and a number of high quality systematic reviews and meta-analyses are available [4-7]. However, the evidence base on vector control tools for other VBDs is weaker. For example, there are no 'gold standard' Cochrane Collaboration reviews on vector control of dengue, leishmaniasis, lymphatic filariasis, Japanese encephalitis, onchocerciasis or Chagas disease. There are several possible reasons for this including a longstanding biomedical focus on prevention and treatment of these diseases and the fact that many VBDs are neglected tropical diseases. The quality of the design and conduct of vector control studies has been highlighted as a problem in previous systematic reviews, one of which, evaluating the effect of larvivorous fish on malaria, did not even include epidemiological outcomes [7]. Epidemiological outcomes are important since public health practitioners are interested in

reductions in disease or infection, rather than reductions in vectors which may not correlate well with health outcomes. The issue of waste in research studies was the focus of a recent Lancet series [8, 9] and is particularly important in vector control since poorly conducted studies not only waste resources but also delay policy-making and deployment of effective products.

In order to adopt an IVM approach, deployment of proven vector control tools should also be evidence-based to maximise effectiveness given a fixed set of resources. Interventions should be targeted to particular geographic areas and populations based on routine entomological and epidemiological surveillance data. For example, determinants of malaria in populations such as close proximity to mosquito breeding sites or poor housing, or rising insecticide resistance should inform the best choice of intervention to implement in a particular setting. Feedback from monitoring and evaluation can then be used to adapt interventions over time.

The overarching theme of the thesis is **the generation and use of evidence to support better vector control programming**. The writer has been a principal author of a recently published World Health Organization Toolkit for IVM in sub-Saharan Africa [10]. The rationale for this piece of work is that a common critique of IVM has been that there is no practical guidance for country programmes on how to go about planning, implementing and evaluating IVM. The toolkit was developed in order to bridge this gap. A description is provided of how this toolkit was formulated and structured, as well as a critical analysis and suggestion of next steps for operationalising the toolkit in country vector control programmes (Chapter 2).

In order to make evidence-based recommendations on vector control tools in the toolkit, it was necessary to conduct systematic reviews. The results of two systematic reviews are presented in this thesis. The first evaluates the efficacy of insecticide-treated nets, curtains and screening against VBD other than malaria (Chapter 3). The aim here is to determine whether these interventions, typically rolled out for malaria control have collateral benefits on other VBD that may be co-endemic with malaria. The second systematic review and meta-analysis evaluates the efficacy of topical repellents against malaria in endemic populations (Chapter 4). Topical repellents are often recommended as a personal protection measure for malaria and other VBDs but their efficacy has not been systematically assessed. These systematic reviews identified a dearth of well-designed and conducted field studies of vector control. A critical analysis of the common failings in vector control study design and conduct is presented, along with suggestions for improvement (Chapter 5).

As well as evidence-based policy making on vector control interventions, IVM calls for evidence-based decision making throughout the life of the programme. Surveillance and monitoring and

evaluation should enable programmes to choose and target interventions, measure their effectiveness and adapt the programme over time. Entomological surveillance, including insecticide resistance monitoring is therefore a crucial component of IVM programmes. In particular, insecticide resistance in malaria vectors in sub-Saharan Africa has been increasing in prevalence and intensity and may lead to loss of effectiveness of vector control tools such as LLINs, which have contributed massively to reductions in malaria in the past 10 years [11]. One of the principal routes through which vectors become resistant to pyrethroids and dichlorodiphenyltrichloroethane (DDT) is through mutations in a sodium-gated channel which is a binding site for the insecticides – this is said to confer knock-down resistance (*kdr*) to the insecticide. A secondary analysis of entomological data from a clinical trial in The Gambia is presented which explores spatial and temporal heterogeneity in *kdr* mutations in a setting of high vector control use (Chapter 6). Based on the findings, recommendations for continued insecticide resistance monitoring in The Gambia are given.

Lastly, the final chapter summarises the findings of the research, study limitations and discusses the implications of the research in the wider context (Chapter 7).

Aims and Objectives

Goal

To improve the effectiveness of vector control for the prevention, control and elimination of vector-borne diseases through evidence-based decision making.

Aim

To conduct a critical analysis of the generation and use of evidence in vector control, in relation to i) policymaking on vector control and ii) entomological monitoring for insecticide resistance.

Hypotheses

It is hypothesised that:

1. Development of a 'how-to' guide on planning, implementing and evaluating IVM will be informative and valuable for programme managers in sub-Saharan Africa and help to improve the efficiency and effectiveness of VBD control.

2. Insecticide-treated materials in the home (nets, curtains and screening) will be efficacious against VBDs other than malaria.

3. Given the personal protection against biting provided by topical repellents, they will be effective at preventing malaria in endemic populations.

4. A critical analysis of the design and conduct of vector control efficacy trials will be useful to improve future studies and generate a more robust evidence base on vector control interventions.

5. *i)* *Anopheles arabiensis* and *An. coluzzii* will be found in close proximity to the River Gambia and will be associated with rice fields, swamps and other water bodies.

   ii) Knockdown mutations *(kdr)* mutations will be more common in villages that received IRS with DDT and LLINs than LLINs alone due to the selection pressure contributed by the double intervention.

   iii) *Kdr* mutations will be low in *An. coluzzii* and *An. arabiensis* but more common in *An. gambiae* s.s.

Research Questions

The thesis aims to answer the overarching research question: How do we develop high quality evidence to support IVM and improve the effectiveness of vector control? To address this question, there are several sub-research questions which will be addressed:

1. Is it possible to develop practical guidance for vector control programmes in sub-Saharan Africa on how to plan and implement IVM?
2. Are insecticide-treated nets, curtains and screening effective against vector-borne diseases other than malaria?
3. Are topical repellents effective against malaria in endemic populations?
4. Is it possible to improve the design and conduct of field trials of vector control interventions in order to improve the quality of evidence to support evidence-based policy making?
5. What is the spatial and temporal distribution of *kdr* in the Upper River Region of The Gambia and is this associated with members of the *An. gambiae* species complex?

Objectives

1. Review existing literature on Integrated Vector Management (IVM) – a World Health Organization (WHO) policy which calls for the use of evidence-based vector control (**Chapter 1**).

2. Describe and critically analyse the development of the WHO Toolkit for IVM in sub-Saharan Africa, of which the author was a lead contributor (**Chapter 2**).

3. Evaluate the efficacy of insecticide-treated nets, curtains and screening against vector-borne diseases other than malaria, using a systematic review and meta-analysis (**Chapter 3**).

4. Evaluate the efficacy of topical repellents against malaria in endemic populations, using a systematic review and meta-analysis (**Chapter 4**).

5. Conduct a critical analysis of the design and conduct of vector control efficacy trials and provide recommendations for future studies (**Chapter 5**).

6. Present a secondary analysis exploring the spatial and temporal pattern of knock-down resistance in the *Anopheles gambiae* complex using data from a study in The Gambia which involved intensive use of LLINs and IRS using dichlorodiphenyltrichloroethane (DDT), and give recommendations for continued insecticide resistance monitoring (**Chapter 6**).

Thesis Overview

Chapter 1 reviews the existing literature on Integrated Vector Management (IVM). It describes the worldwide burden of vector-borne diseases (VBDs), history of vector control, challenges to effective and sustainable vector control, the IVM policy as advocated by the World Health Organization (WHO) and challenges to IVM implementation.

Chapter 2 describes the development of the WHO Toolkit for IVM in sub-Saharan Africa and critically analyses the output and discusses next steps for operationalising the document.

Chapter 3 assesses the efficacy of insecticide-treated nets, curtains and screening against VBDs, excluding malaria.

Chapter 4 assesses the efficacy of topical repellents against falciparum and vivax malaria in endemic populations.

Chapter 5 is a critical analysis of the design and conduct of phase III field trials of vector control interventions. It outlines common failings with design and conduct of vector control trials and provides a framework for the critical evaluation of vector control field trials.

Chapter 6 is a secondary analysis which explores the spatial and temporal distribution of knock-down resistance in the *Anopheles gambiae* complex in the Upper River Region of The Gambia utilising secondary data from a clinical trial of intensive vector control use.

Chapter 7 discusses the main findings of the thesis, study limitations, wider implications of the research, the way forward for IVM as a policy and future directions.

Volume II of the thesis is the WHO Toolkit for IVM in sub-Saharan Africa.

Contributions

Some of the work in this thesis is reproduced from published manuscripts in which Anne Wilson was first author.

Chapter 1 and 2 use material from a World Health Organization (WHO) document entitled A Toolkit for Integrated Vector Management in sub-Saharan Africa released in 2016. This document was largely written by Anne Wilson but was revised following discussions with a large number of contributors who attended expert review meetings. The full list of contributors is available in the published WHO document.

Chapter 3 was published as Wilson *et al*., 2014 (PLoS Neglected Tropical Diseases 8: e3228). Anne Wilson and Steve Lindsay conceived the study. Anne Wilson searched the literature and identified relevant studies for inclusion in collaboration with Steve Lindsay. Anne Wilson and a contract research organisation GVK Bio, Hyderabad India extracted data from published papers. Anne Wilson conducted the meta-analysis and wrote the draft of the paper. Steve Lindsay, Ramesh Dhiman, Uriel Kitron, Tom Scott and Henk van den Berg contributed to the final paper.

Chapter 4 was published as Wilson *et al*., 2014 (Malaria Journal 13:446). Anne Wilson, Steve Lindsay and Vanessa Chen-Hussey conceived the study. Anne Wilson searched the literature and identified relevant studies for inclusion in collaboration with Steve Lindsay. Anne Wilson and Vanessa Chen-Hussey extracted data from published papers. Anne Wilson conducted the meta-analysis and wrote the draft of the paper. Vanessa Chen-Hussey, James Logan and Steve Lindsay contributed to the final paper.

Chapter 5 was published as Wilson *et al*., 2015 (Trends in Parasitology 31:380-90). Anne Wilson identified vector control studies, conducted a critical analysis and outlined a framework for study improvement. Anne Wilson wrote the draft of the paper and Marleen Boelaert, Immo Kleinschmidt, Margaret Pinder, Tom Scott, Lucy Tusting and Steve Lindsay contributed to the final manuscript.

Chapter 6 describes unpublished work. Anne Wilson conceived and designed the secondary analysis with guidance from Steve Lindsay. Responsibilities during primary data collection are outlined in Pinder *et al*., 2015 (Lancet 385: 1436–46). Entomological data cleaning was conducted by Anne Wilson, with support from Margaret Pinder. Anne Wilson conducted data analysis, interpreted the data and wrote the chapter.

Chapter 1: Integrated Vector Management: an evidence-based, adaptive and multi-sectoral approach to control of vector-borne diseases globally

Abstract

Vector-borne diseases (VBDs) such as malaria, dengue and leishmaniasis contribute substantially to the global burden of disease and are most common in low and middle income countries in tropical and sub-tropical zones. One method by which they can be controlled is vector control, for example long-lasting insecticidal nets or indoor residual spraying for malaria. Vector control has historically been hugely successful in controlling VBDs but there are challenges to its effective implementation including funding and resource constraints and insecticide resistance, and pressures which are serving to increase VBDs such as population movement and environmental deterioration. The World Health Organization recommended approach for vector control is Integrated Vector Management (IVM). IVM is characterised by evidence-based and adaptive use of vector control tools and importantly, the use of interventions from within and outside the health sector. While a wholly sensible approach to vector control, particularly in the current climate, IVM, conceptualised in the early 2000s is not a new policy and has not gained much traction. The reasons for this are discussed including a lack of political will, insufficient understanding of IVM, lack of evidence on IVM and difficulties establishing and sustaining intersectoral collaboration.

Epidemiology, burden and distribution of vector-borne diseases

Vector-borne diseases (VBDs) are infections transmitted by infected arthropod species such as mosquitoes, triatomine bugs, blackflies and tsetse flies (Table 1.1). Malaria, leishmaniasis, lymphatic filariasis dengue, Chagas disease and other VBDs disproportionately affect communities living in low and middle income countries in tropical and sub-tropical zones. VBD typically affect the poor and those lacking access to safe housing, safe water, sanitation and health services. VBD contribute significantly to the global burden of disease, accounting for 17% of the global estimated burden of all infectious diseases [12]. It is estimated that over 80% of the global population live in regions of the world at risk from one VBD, equating to 5.5 billion people [1]. Many of these VBD are co-endemic and it is estimated that more than half the world's population live in areas where at least two different VBD are present (Figure 1.1) [1].

VBDs are a major threat to health and wellbeing. The most well-known VBD, malaria, is a major cause of morbidity and mortality, particularly in sub-Saharan Africa (SSA), with 3.2 billion people at risk worldwide (half the world population) (Table 1.2) [13]. Many VBDs are classed as neglected tropical diseases (NTDs), for example Chagas disease, human African trypanosomiasis (HAT), leishmaniasis and lymphatic filariasis [14]. These diseases have long suffered from a perceived low burden of disease, lack of prioritisation and investment. While less deadly than malaria, vector-borne NTDs still result in high levels of morbidity. For example, onchocerciasis results in blindness, Chagas disease in its late stages can cause heart failure, chikungunya results in debilitating joint pain and Japanese encephalitis can cause permanent damage to the nervous system. Many VBD are associated with stigma and social exclusion due to the manifestations of the infection, for example elephantiasis caused by lymphatic filariasis [15, 16]. Illness and disability means that those affected are not able to work to support themselves and their family which along with medical costs causes a heavy burden on communities. VBDs also place a large strain on health services due to costs of prevention and treatment.

It is no surprise therefore, that on a larger scale, VBD are a major cause of poverty and underdevelopment in many countries. For example, malaria endemic countries are on average poorer by more than five-fold and have lower rates of economic growth than non-malaria endemic countries with an average growth of per-capita GDP of 0.4% per year versus 2.3% between 1965 and 1990 [17]. The global cost of Chagas disease was estimated to be over 7 billion US$ per year in 2013, including lost productivity [18]. Dengue and other *Aedes*-borne infections are a growing threat worldwide and the estimated annual global cost of dengue illness in 2013 was 8.9 billion US$ [19].

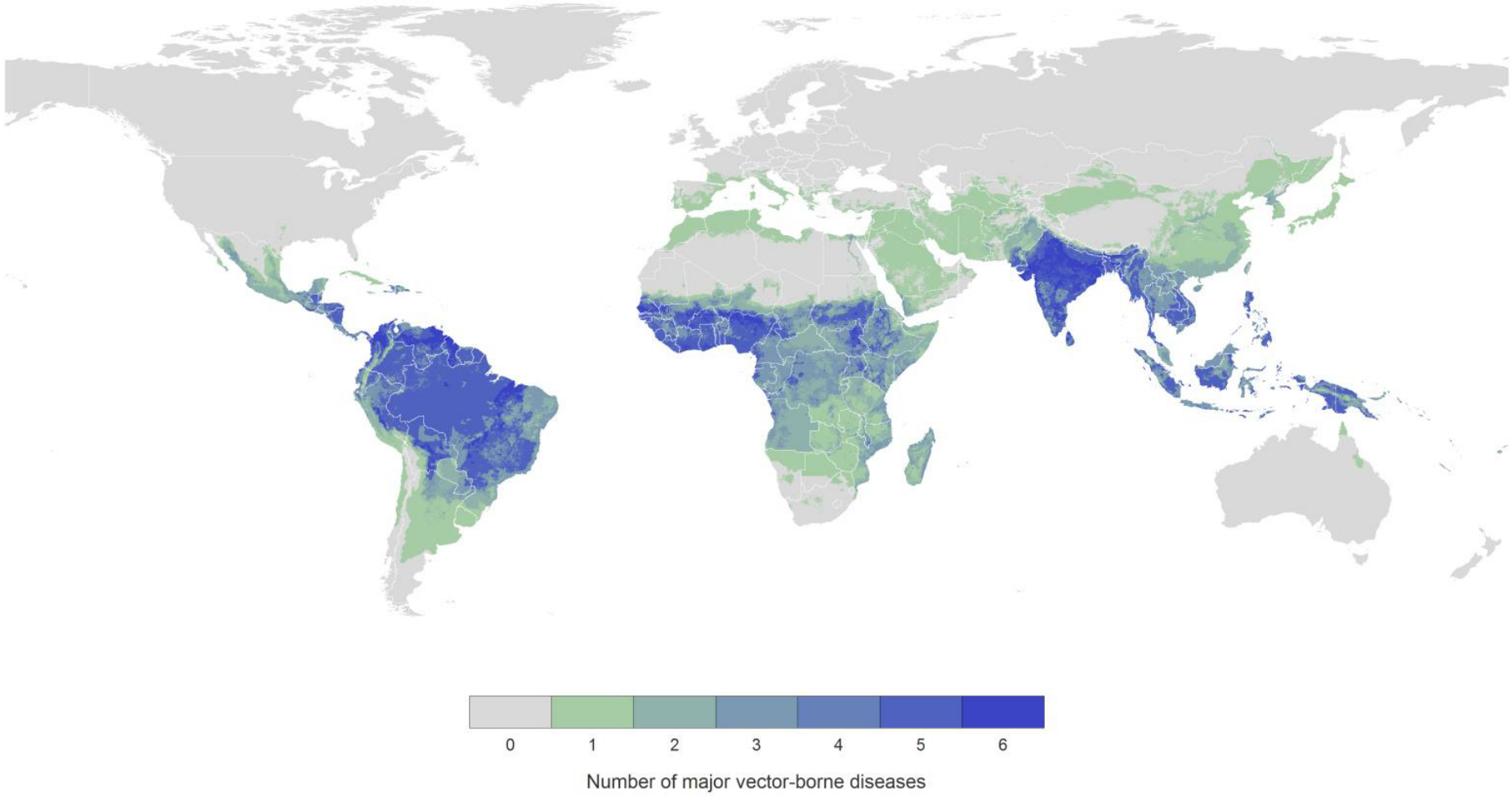

Figure 1.1: Combined global distribution of 7 major vector-borne diseases (malaria, lymphatic filariasis, leishmaniasis, dengue, Japanese encephalitis, yellow fever and Chagas disease)

Reproduced from [1]. Colours indicate the number of vector-borne diseases that pose a risk at each 5 x 5 km grid cell.

Table 1.1: Major vector-borne diseases, vectors, geographical distribution and control measures

Disease	Infectious organism	Vector	Geographical distribution	Control measures
Malaria	*Plasmodium* species	Mosquitoes*: Anopheles* spp.	Sub-Saharan Africa, Asia and South America.	• Vector control • Chemoprevention (pregnant women / children in areas of seasonal transmission)
Lymphatic filariasis	Roundworms: *Wuchereria bancrofti*, *Brugia malayi*, *Brugia timori*	Mosquitoes: *Anopheles* (rural sub-Saharan Africa), *Culex quinquefasciatus* (Americas, Asia and urban sub-Saharan Africa), *Aedes* and *Mansonia* spp. (Pacific and Asia)	Sub-Saharan Africa, South America, Caribbean, South Asia, South East Asia and Pacific	• Vector control • Mass treatment with albendazole plus diethylcarbamazine or ivermectin (where onchocerciasis is co-endemic)
Dengue	Dengue virus	Mosquitoes: *Aedes aegypti* and *Aedes albopictus*	Asia, Pacific, South America	• Vector control
Leishmaniasis	*Leishmania species: L. major, L. infantum, L. braziliensis*	Sandflies: *Phlebotomus* spp. (Old World) *and Lutzomyia* spp. (New World)	Asia, the Middle East, Africa, southern Europe and South America	• Vector control
Chagas disease	*Trypanosoma cruzi*	*Triatomid* bugs	South America	• Vector control
Trachoma	*Chlamydia trachomatis*	Flies: *Musca sorbens*	Mainly Sub-Saharan Africa	• SAFE strategy: **S**urgery, **A**ntibiotics, **F**acial cleanliness, **E**nvironmental change to increase access to water and sanitation
Onchocerciasis	*Onchocerca volvulus*	*Simulium* spp. (Black fly)	Sub-Saharan Africa and South America	• Vector control • Mass treatment with ivermectin
Japanese encephalitis	Japanese encephalitis virus	Mosquitoes: *Culex* spp., particularly *Culex tritaeniorhynchus*	Asia	• Vector control • Vaccination (travellers)
Human African trypanosomiasis	*Trypanosoma brucei gambiense* and *T. b. rhodesiense.*	*Glossina* spp. (Tsetse fly)	Sub-Saharan Africa	• Vector control
Yellow fever	Yellow fever virus	Mosquitoes: *Aedes* spp. and *Haemogogus* spp.	Africa, South America	• Vector control • Vaccination (travellers / outbreak)
Chikungunya	Chikungunya virus	Mosquitoes: *Aedes* spp. particularly *Ae. aegypti* and *Ae. albopictus*	Sub-Saharan Africa, Asia, Indian and Pacific Oceans, North and South America, Caribbean, Europe.	• Vector control
Zika virus disease	Zika virus	Mosquitoes: *Aedes aegypti* and *Aedes albopictus*	South America, Caribbean, North America, Asia, Pacific	• Vector control

Table 1.2: Burden of vector-borne diseases worldwide

	Data source	Estimated cases worldwide in 2015 [thousands, (95% uncertainty interval)]	Estimated global all-age DALYs in 2015 [thousands, (95% uncertainty interval)]	Estimated all age deaths worldwide in 2015 [thousands, (95% uncertainty interval)]
Malaria	World Malaria Report 2016 [20]	212,000 (range: 148,000 – 304,000)	Not available	429.0 (range: 235.0 – 639.0)
	Global Burden of Disease 2015 [21-23]	295 717.3 (257 568.4 to 338 449.0)	55 769.6 (42 478.4 to 69 078.5)	730.5 (555.8 to 904.0)
Dengue	Global Burden of Disease 2015 [21-23]	Incidence: 79 609 (53 784–169 704) Prevalence: 4730.0 (2654.1 to 10 254.2)	1892.2 (1266.7 to 2925.2)	18.4 (11.8 to 22.7)
Cutaneous and mucocutaneous leishmaniasis		3895.9 (3324.6 to 4767.5)	41.5 (19.4 to 81.0)	-
Visceral leishmaniasis		60.8 (57.5 to 64.7)	1377.4 (965.4 to 1863.8)	24.2 (17.1 to 32.5)
Yellow fever		2.8 (0.8 to 7.7)	329.8 (66.9 to 898.1)	5.1 (1.1 to 14.2)
Chagas disease		6653.6 (5750.5 to 7575.6)	236.1 (211.8 to 265.3)	8.0 (7.5 to 8.6)
Human African trypanosomiasis		10.7 (6.0 to 17.0)	202.4 (104.6 to 322.3)	3.5 (1.8 to 5.7)
Lymphatic filariasis		38 464.1 (31 328.2 to 46 783.0)	2075.0 (1120.5 to 3311.5)	-
Onchocerciasis		15 531.5 (11 963.5 to 19 993.8)	1135.7 (545.8 to 2005.7)	-
Trachoma		3557.1 (2940.5 to 4321.8)	279.2 (192.5 to 396.2)	-

The distribution of VBDs in geographic areas and populations is determined by the interplay between vectors, pathogens, humans and the environment (Figure 1.2). The distribution and abundance of VBDs is broadly dependent on climate. Temperature affects the development, biting and survival of vectors and the development, survival and reproduction of pathogens within the vectors [24]. Vectors with aquatic developmental stages, such as mosquitoes are highly dependent on rainfall, as are vectors without aquatic stages that depend on humidity, such as sandflies. As well as temperature and rainfall, the distribution of vectors on a more local scale is driven by land use, which determines the presence of suitable habitats and host density. As a consequence of the interaction between these determinants, diseases can vary markedly in time and space. Some diseases such as malaria may be more stable in their geographic distribution over time, while others such as dengue may be patchier in their distribution and vary from year to year. Human determinants of VBD include where people live, attitudes and practices toward VBD and access to diagnosis and treatment. Diseases may be unequally distributed within the population because

some individuals or communities may be more at risk of disease than others due to poorer environmental and social conditions, and lack of access to preventative and curative health services. For example, research shows that within communities the poorest children are twice as likely to contract malaria than the least poor [25]. Typically, 80% of the disease burden is experienced by 20% of the population [26]. Animals may also play a role in determining disease distributions where they act as reservoir hosts. For example, game animals and livestock for HAT and pigs and birds for Japanese encephalitis. Detail on the epidemiology and burden of the major VBDs is given in Box 1.1.

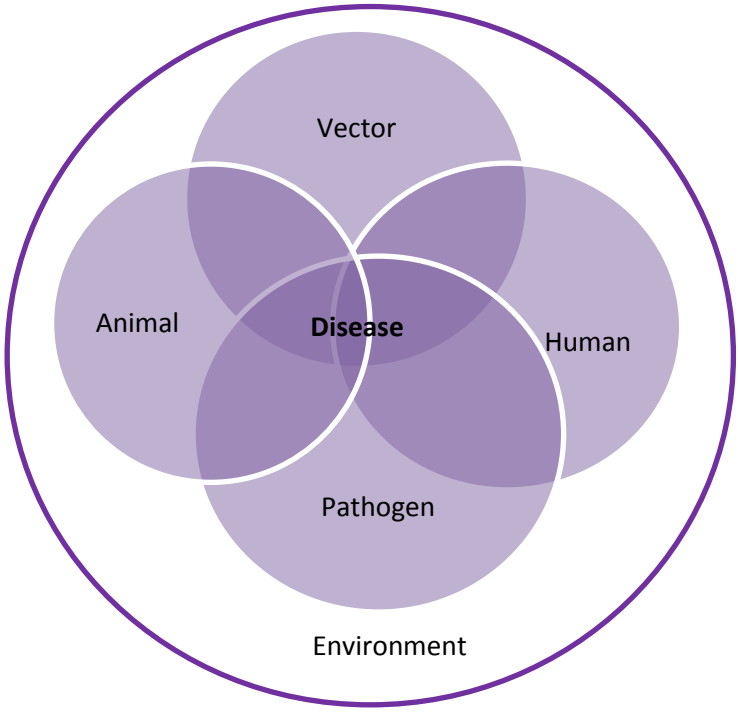

Figure 1.2: The pathogen, vector, human, animals and environment depicted as five categories of determinants of vector-borne diseases

Box 1.1: Epidemiology, burden and control of the main vector-borne diseases

There were an estimated 212 million malaria cases and 429,000 malaria deaths worldwide in 2015 [20]. Malaria is caused by the *Plasmodium* parasite which is transmitted by female *Anopheles* mosquitoes. There are five *Plasmodium* species that cause disease in humans but the most important in terms of burden are *Plasmodium falciparum* which is prevalent in sub-Saharan Africa (SSA), and *P. vivax* which is more common in central Asia and South America [27, 28]. SSA carries a disproportionately high share of the malaria burden with 90% of cases and 92% of malaria deaths in 2015 [20]. The burden is becoming increasingly focal with only 13 countries accounting for 76% of malaria cases and 75% deaths globally in 2015, the majority of these in SSA [20]. In high transmission

areas, children aged under five years are highly susceptible to malaria infection, illness and death and accounted for 70% of all malaria deaths in 2015 [20]. Vector control tools such as long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) of insecticide play a large role in control of malaria, alongside diagnosis and effective treatment of infections, and chemoprevention in some population groups [13]. Larval source management (LSM) is recommended as a supplementary vector control method [29].

Viral infections transmitted by *Aedes* mosquitoes such as dengue, chikungunya and Zika are becoming an increasing problem primarily due to urbanisation which has expanded the habitat of the vector. These infections most often appear as outbreaks which as well as causing economic and social disruption, can rapidly overload weak health systems due to high caseloads. Dengue, a debilitating and sometimes fatal viral infection is the world's fastest growing VBD. The number of incident dengue cases have more than doubled in the past decade from 32.7 million cases in 2005 to 79.6 million cases in 2015 [22]. Some researchers have estimated the number of dengue cases to be even higher (96 million cases in 2010) [30]. Outbreaks of Chikungunya and Zika virus are normally maintained in a sylvatic cycle of transmission between non-human primates and forest-dwelling mosquitoes but outbreaks can occur when the virus spills over into urban transmission cycles. Human chikungunya infections which result in fever and severe joint pain have been at relatively low levels but outbreaks have been more frequent since the early 2000s with outbreaks in SSA, the Indian Ocean and Asia since 2005 and the Caribbean, Central America, northern South America and Florida since 2013. More recently, Zika virus has hit the headlines due to its association with microcephaly and Guillain-Barré syndrome. Prior to 2007, the virus was circulating in Asia and Africa but only 14 cases had been identified and so the virus was of little concern to humans [31]. In 2007 there was an outbreak in Yap State, Federated States of Micronesia in the western Pacific Ocean with 49 confirmed and 59 probable cases of Zika virus infection [31]. Since then, outbreaks have been increasingly large with an estimated 440,000-1,300,000 cases in the most recent Brazil outbreak in 2016 [31]. There is no specific treatment for dengue, chikungunya or Zika and therefore prevention and control relies exclusively on vector control interventions [32].

Yellow fever, transmitted by *Aedes* and *Haemogogus* mosquitoes, is endemic in Africa, Central and South America. There are three different transmission cycles – forest (sylvatic), intermediate and urban - depending on the mosquito and its habitat [33]. In forest areas the virus cycles between non-human primates and forest-dwelling mosquitoes and isolated yellow fever cases can occur when individuals enter the forest. Outbreaks occur when semi-domestic mosquitoes infect both monkeys

and people (intermediate cycle) or when infected individuals introduce the virus into heavily populated urban areas where people are typically non-immune due to lack of vaccination (urban cycle). There were an estimated 2800 yellow fever cases worldwide in 2015 [22]. However, underreporting and lack of diagnostic capability is a problem in many areas [34] and other studies estimate that there were 130,000 cases and 78,000 deaths in Africa alone in 2013 [35]. Accelerated urbanisation, particularly in SSA, is creating ideal conditions for transmission (high vector and population density) leading to outbreaks such as those in Angola and Democratic Republic of Congo in late 2015/early 2016 [36].

Japanese encephalitis, caused by a flavivirus related to dengue and yellow fever viruses and is transmitted by culicine mosquitoes (mainly *Culex tritaeniorhynchus*) [37]. The virus exists in a transmission cycle between mosquitoes which tend to lay eggs in rice paddies and other water bodies, pigs and/or water birds (enzootic cycle). 24 countries in south-east Asia and the western Pacific covering a population of more than 3 billion people are at risk of Japanese encephalitis [38]. Although the disease is vaccine preventable, it is the leading cause of viral encephalitis in Asia and primarily affects children. There are an estimated 67,900 Japanese encephalitis cases annually [38].

Lymphatic filariasis is caused by infection with filarial parasites which are transmitted by either *Culex* (urban and semi-urban areas), *Anopheles* (rural areas), *Aedes* or *Mansonia* (Asia and the Pacific) mosquitoes [39, 40]. Infection can result in an altered lymphatic system and abnormal enlargement of body parts (elephantiasis) which causes pain, severe disability and social stigma [15, 16]. 1.1 billion people in 55 countries are currently at risk of lymphatic filariasis and require preventive chemotherapy to control the infection [41]. More than 38 million people are affected by the disease [22]. The World Health Organization (WHO) advocates for the use of vector control alongside mass drug administration (MDA) to control and eliminate lymphatic filariasis [42].

Chagas disease, a condition common in South America, is caused by infection with *Trypanosoma cruzi* which is transmitted by triatomine bugs [43, 44]. The disease is common in poor rural and suburban areas since the bug lives in cracks in walls and roofs of poorly constructed housing. Infection is curable if treated early but if left un-treated many chronically infected people develop cardiac, digestive or neurological problems. There were over 6.5 million cases of Chagas disease and 8000 deaths in 2015 [22]. Vector control such as IRS, house and environmental improvement is recommended alongside effective treatment, screening of donors and newborns of infected mothers for control of the disease [44].

There are three different types of leishmaniasis – visceral (Kala-Azar), cutaneous and mucocutaneous – which are caused by *Leishmania* parasites and transmitted by the bite of a female sandfly [45, 46]. The sandflies are found in inter-tropical and temperate regions of the world and thrive in cracks in buildings, household rubbish and burrows of some rodents. Visceral leishmaniasis occurs in Asia, east Africa and South America (Brazil). It is associated with fever, weight loss, swelling of the spleen and liver, and anaemia, and can be fatal. There were over 60,000 cases of visceral leishmaniasis wordwide in 2015 and over 24,000 deaths from the disease [22]. Cutaneous leishmaniasis is present in the Middle East, Central Asia and South America. It causes ulceration of the skin which results in scarring and social exclusion [47]. Mucocutaneous leishmaniasis occurs in Bolivia, Brazil and Peru and is associated with debilitating and stigmatising lesions which can destroy the mucus membranes of the nose and mouth. There were almost 4 million cases of cutaneous and mucocutaneous leishmaniasis worldwide in 2015 [22]. The WHO recommends vector control measures such as IRS and LLINs for endophillic species and environmental management, in combination with control of any reservoir hosts and early diagnosis and treatment of the disease [48].

Human African trypanosomiasis (HAT) or sleeping sickness affects 36 countries in SSA and is caused by parasites of the genus *Trypanosoma* which are transmitted by tsetse flies [49]. There were an estimated 10,700 HAT cases and 3,500 deaths worldwide in 2015 [22]. There are two forms depending on the parasite involved. *Trypanosoma brucei gambiense* causes the majority of HAT cases and is found in West and Central Africa, while *Trypanosoma brucei rhodesiense* is found in East and Southern Africa. Infection can progress to a debilitating neurological stage characterised by confusion, altered behaviour, sensory disturbances and poor coordination. Progression to this stage occurs in months with Rhodesian HAT but Gambian HAT often has a long asymptomatic period when people act as a reservoir of infection. HAT occurs in poor, remote populations with no access to healthcare or where populations have been displaced. Control of HAT relies on reduction of the parasite reservoir (human and/or animal) and/or vector control [49]. Vector control techniques such as insecticide-treated traps and targets play a larger role in control of Rhodesian HAT since this is a zoonotic infection with game animals as the main reservoir, versus Gambian HAT where humans are the main reservoir and diagnosis and treatment plays a bigger role.

Onchocerciasis or river blindness is caused by the filarial worm *Onchocerca volvulus* which is transmitted by the bite of infected blackflies (*Simulium* species). Onchocerciasis is a major cause of blindness in many West and Central African countries but is also a problem in parts of South America

[50-52]. Approximately 120 million people are at risk of onchocerciasis and there were almost 15 million cases worldwide in 2015 [22, 53]. The WHO primarily recommends MDA using ivermectin for control of onchocerciasis, alongside larviciding to kill blackfly larvae in some areas [54].

Trachoma is an infection of the eyes caused by the bacterium *Chlamydia trachomatis* which can be transmitted by flies (*Musca sorbens*) which pick up discharge from an infected child's eyes. The disease is predominantly found in SSA and although infections initially occur in children, repeated infections can result in blindness in adulthood. There were over 3.5 million prevalent trachoma cases in 2015 [22]. Trachoma which is largely controlled through use of surgery, antibiotics, facial cleanliness and environmental sanitation (SAFE strategy), rather than vector control [55].

Vector control

Vector control aims to limit the transmission of pathogens by preventing human contact with the vector. Vector control methods such as long-lasting insecticidal nets (LLINs), indoor residual spraying (IRS) and larval source management (LSM) play a large role in disease control. For some diseases, such as dengue, chikungunya, Zika and west Nile virus, vector control is currently the only method we can use to protect populations. A wide range of vector control tools exist; which can be broadly classified into chemical-based and non-chemical-based tools for control of either adult or immature forms of the vector (Table 1.3). Tools targeting the immature stages of vectors can act by killing the immature vector (e.g. chemical or biological larvicides and predator species) or by removing suitable aquatic habitats (e.g. habitat modification or manipulation). Tools targeting the adult stages of vectors can function by killing the vector (e.g. IRS, space spraying) and/or preventing the vector from biting human hosts (e.g. topical and spatial repellents). This leads us to a central concept in vector control: the concept of community and personal protection. At sufficiently high coverage, vector control tools such as IRS can provide community protection, whereby even those not covered by the intervention receive benefit as a result of mass killing of vector populations. Interventions such as topical repellents (except possibly when they are used at extremely high coverage) provide only personal protection from biting. Some studies have shown that LLINs can provide both personal and community protection [56-58], although not all studies have demonstrated this effect [59]. There are also a large number of experimental vector control tools (not included in the table) which are not yet recommended for routine use. These include *Wolbachia*, a bacterium which when introduced into *Aedes* mosquitoes prevents dengue virus transmission; sterile insect technique in which sterile male mosquitoes are released; and approaches involving genetic engineering of mosquitoes such as gene drive [60-63].

Table 1.3: Categories and examples of vector control methods

Chemical	Immature	Chemical larvicides e.g. temephos or pyriproxyfen
	Adult	Long-lasting insecticidal nets (LLINs)
		Insecticide-treated materials for personal protection e.g. insecticide-treated clothing
		Indoor residual spraying (IRS)
		Space spraying
		Insecticidal treatment of habitat e.g., focal, perifocal, ground or aerial spraying
		Insecticide-treated cattle
		Insecticide-treated traps and targets
		Topical repellent e.g. N,N-diethyl-meta-toluamide (DEET), picaridin
		Spatial repellent
Non-chemical	Immature	Biological larvicides e.g. *Bacillus thuringiensis* var. *israelensis*
		Predator species e.g. predatory fish or invertebrates
		Habitat modification i.e. a permanent change of land and/or water. e.g. drainage of surface water; land reclamation and filling; coverage of large water storage containers or complete coverage of water surfaces with a material that is impenetrable to mosquitoes (for example, expanded polystyrene beads.
		Habitat manipulation i.e. a recurrent activity e.g. water-level manipulation, flushing of streams, drain clearance, rubbish disposal, regular emptying and cleaning of domestic containers (e.g. flower pots, animal drinking water troughs), or exposing habitats to the sun depending on the ecology of the vector.
		Regulatory measures e.g. removal of man-made aquatic habitats, appropriate waste disposal etc
	Adult	House improvement and screening
		Removal trapping

Much of the principles behind vector control come from malaria and the theory of vectorial capacity developed by George MacDonald in the 1950s, known as the Ross-Macdonald model [64, 65]. Vectorial capacity describes the total number of potentially infectious bites that would eventually arise from all the mosquitoes biting a single perfectly infectious (i.e., all mosquito bites result in infection) human on a single day. The formula for vectorial capacity (*V*) includes a number of important elements of the life history of the mosquito which matter for transmission:

$$V = \frac{ma^2p^n}{-\ln(p)}$$

where *n* is the length of the parasite's extrinsic incubation period in days, *m* is the ratio of mosquitoes to humans, *p* is mosquito survival through one day and *a* is the human biting rate [66]. The vectorial capacity equation can help us to prioritise vector control interventions. It shows that reducing mosquito survival, for example by killing adult mosquitoes using IRS is the most effective

way of reducing disease transmission [65], compared to interventions that reduce mosquito population density such as those attacking larval stages (e.g. LSM or environmental management) [67, 68]. While useful, the vectorial capacity approach is a simplification of the situation, for example it does not fully consider the aquatic stage of the mosquito and its application to non-mosquito vectors is also unclear.

History of vector control

Discovery of transmission of malaria and yellow fever by mosquitoes

In 1897 ground-breaking work by Sir Ronald Ross showed that *Anopheles* mosquitoes transmitted malaria parasites [69]. Three years later Major Walter Reed and colleagues experimentally confirmed transmission of the yellow fever virus by *Ae. aegypti*, a hypothesis that had been proposed by a Cuban physician named Finlay some years earlier [70, 71]. However, vector control was taking place even before the transmission route of these diseases was elucidated, mainly due to an awareness of the connection between fevers and proximity of swamps and marshes. For example, historical reports from Greek (circa 550 B.C.) and Roman times talk of large drainage schemes and reductions in "plague" and fever [72, 73]. There is also a history of the use of mechanical vector control methods, such as sleeping in high buildings where mosquitoes were unable to fly due to wind or use of bednets in Egypt (as noted by Herodotus 484-425 B.C.), use of bednets by the Romans and bed curtains (as noted by Marco Polo during his travels to India in the thirteenth century) [72]. Furthermore, larviciding was recommended in the USA for yellow fever control in the late 1700s [74, 75].

Environmental management as the primary tool for control of vector-borne diseases

Following Ross's discovery, much of the focus on malaria control was on elimination of anophelines, primarily by changing the aquatic habitats of the vector. For example, drainage carried out mainly for agricultural reasons in the central part of the USA during the early nineteenth century led to reductions in malaria [72]. There was also a focus on housing improvements such as screening of doors and windows. For example, the experiments of Angelo Celli among railway worker settlements in Italy during 1899-1900 [76].

Environmental management was used successfully in the early 1900s in both Malaysia and Indonesia. Sir Malcolm Watson, a British doctor joined the Malayan Medical Service in 1900 where he led vector control efforts [77]. Drainage of breeding sites controlled malaria in two coastal towns in the state of Selangor and allowed resumption of port development. Later, Watson's work

expanded to lowland areas where he controlled *An. umbrosus* by clearing the forest within 0.5 miles of plantation labourer houses so that breeding sites were exposed to the sun, and also to hilly regions in 1909 where subsoil drainage was successful against *An. maculatus.* Watson also oversaw successful drainage schemes in Singapore in 1911 where local malaria transmission was practically eliminated [77]. The Dutch zoologist Nicolaas Hendrik Swellengrebel was inspired by discussions with Watson and that Watson was able to limit the scope of control measures to species which are proven vectors [78]. Swellengrebel set out to replicate the work throughout the Indonesian archipelago between 1920 and 1935 and termed his own methods "species sanitation". Swellengrebel aimed to control malaria primarily through environmental management, such as filling in or draining ponds and lagoons, maintaining and flushing drains or planting shade trees depending on the vector present and its bionomics.

Draining of the Pontine marches near Rome, Italy from 1922 onwards was highly successful in malaria control against the Italian malaria vector *An. labranchiae* [79]. This was done as part of the three-pronged *bonifica integrale* campaign instigated by Mussolini which also consisted of agricultural improvements, and hygienic measures such as house screening and quinine distribution.

Another excellent example of the use of environmental management for malaria control is that of the Zambian copper mines launched in 1929 and implemented for two decades [80]. Here, control measures including vegetation clearance, modification of river boundaries, draining swamps, oil application to open water bodies and house screening were effective in reducing malaria-related mortality, morbidity and incidence rates by 70-95%.

Environmental management was also being implemented in the southern USA. The Tennessee Valley Authority (TVA) was set up in 1933 to exploit the Tennessee River's potential for hydroelectric power and improve the land and waterways for development of the region [81]. At the time, the region was highly malaria endemic and so creation of artificial lakes would only exacerbate the problem. Implementation of vector control methods included regulation of water levels in the lakes, shoreline improvements such as deepening or diking and draining, larviciding and later DDT spraying. Massive reductions in malaria were seen and malaria was essentially eliminated by the late 1940s.

Control of yellow fever in the Americas at the start of the 19th century was also heavily reliant on environmental management. At this time, the USA had taken control of Cuba following the end of the Spanish-American war but outbreaks of yellow fever and malaria were taking the lives of many US soldiers [82]. In 1901, Major W.C. Gorgas, Chief Sanitary Officer was asked to initiate a

programme for the elimination of *Ae. aegypti*, work he carried out with J. A. Le Prince [83]. The programme comprising of drainage or oiling of standing water, fumigation and isolation of yellow fever patients with screening and netting was highly successful and was later enlarged to include also *Anopheles* control. In 1904, Gorgas became Chief Sanitary Officer in the building of Panama Canal, and again with the aid of Le Prince, removed yellow fever and kept malaria at low levels [83]. Methods included screening living quarters, draining or filling standing water, installing drains, larviciding using oil or Paris Green [84]. After these successes, campaigns were also launched by Joseph White in Havana, Oswaldo Cruz in Rio de Janeiro and Emilio Ribas in Santos [85]. A period of apathy followed but this was brought to a halt by an epidemic of yellow fever in Rio de Janeiro in 1928 in which *Ae. aegypti* levels were again at high levels. The Cooperative Yellow Fever Service, a collaboration between the Brazilian Government and the Rockefeller Foundation, was set up under the direction of Fred Soper with the aim of eradicating *Ae. aegypti* from Brazil. From 1930-34 Soper led a well-organised campaign, with control measures including oiling of water containers and house searches for larvae and adults. Campaigns initiated by the Cooperative Yellow Fever Service also succeeded in eliminating the highly efficient malaria vector *An. gambiae* from the north-east of Brazil in 1942 using larviciding with Paris Green and house spraying with short-acting pyrethroids [86].

In the late 1800s, colonial expansion in SSA and massive outbreaks of HAT led to a number of scientific missions to study the disease including that of pathologist and microbiologist David Bruce and colleagues who in 1903 provided conclusive evidence that sleeping sickness was transmitted via *Glossina palpalis* (now *G. fuscipes*) [87, 88]. Environmental management such as bush clearance and game destruction were widely practised, along with trapping of tsetse flies, particularly in east Africa [87].

Post-World War 2 era and the advent of DDT

With the addition of the first residual insecticide dichloro-diphenyl-trichloroethane (DDT) to the vector control toolbox in the 1940s, the popularity of insecticide-based control increased and malaria eradication became a more realistic proposition. Support for an eradication approach and IRS using DDT was also bolstered by findings from Macdonald's mathematical model in the 1950s which showed that malaria transmission was highly sensitive to reductions in mosquito longevity [89, 90]. DDT contributed to the eradication of malaria in the USA and southern European countries such as Italy, Spain and Greece [91, 92]. Spurred on by malaria control successes such as TVA and Malaria Control in War Areas programme to control malaria around military training bases in the southern United States [93], the US National Malaria Eradication Programme was set up in 1947 [91]. This was a joint undertaking by state and local health agencies of 13 south eastern states and

the Communicable Disease Center of the US Public Health Service. Indoor DDT spraying, drainage and removal of mosquito breeding sites and insecticide spraying was able to eliminate transmission and in 1949 the country was declared free of malaria as a significant public health problem. In 1955 the World Health Organization (WHO) launched the Global Malaria Eradication Programme (GMEP) based largely on indoor residual spraying with DDT and other residual insecticides, larval control and anti-malarial drugs [94, 95]. The GMEP succeeded in eliminating malaria from large parts of the world, particularly those with more temperate climates and seasonal transmission. However, the GMEP faced a number of problems including drug and insecticide resistance, lack of community participation and funding challenges and was abandoned in 1969 after it was realised that elimination was not possible everywhere with the available tools [94].

In 1947 Brazil called for elimination of *Ae. aegypti* across the whole South American continent, a task which was coordinated by the Pan-American Sanitary Bureau [96]. Brazil was encouraged by the success of the Cooperative Yellow Fever Service in north-east Brazil, but also aware that *Ae. aegypti* could not be eradicated from Brazil unless frontiers and ports were protected. Container inspections, oiling of breeding sites and later perifocal spraying of DDT in water containers and nearby walls succeeded in eradicating *Ae. aegypti* from large parts of South America during the 1950s and 1960s.

The advent of DDT also saw its use for tsetse control. Ground spraying of DDT was carried out from the 1950s till mid 1970s by tsetse control programmes in large parts of east Africa, combined with screening, treatment and follow-up of patients [87]. However, high costs and concerns about environmental impact of DDT meant that spraying was discontinued [88].

Failure of the GMEP – what next for malaria?

After the failure of the GMEP, many countries reverted back to malaria control, although the WHO reaffirmed that eradication was still the ultimate goal [97]. During the 1970s and 1980s there was a deterioration of the malaria problem with epidemics in the Indian subcontinent (1973-1976) and Turkey (1977) and focalisation of the malaria problem in SSA and other areas of limited socioeconomic development such as India, Brazil and Sri Lanka [95, 98]. The economic crisis in the early 1970s meant less funding for malaria control, oil shortages led to increases in insecticide prices, drug and insecticide resistance were increasing and there was a focus on implementation rather than an flexible approach and linking with researchers [94]. At this time, the WHO called for a more tactical approach to malaria control based on the biological, social, ecological and economic determinants of malaria. This approach was endorsed by the World Health Assembly (WHA) in 1978 [99] and further developed at the Seventeenth WHO Expert Committee on Malaria in 1979 [100]. In

the early 1990s, the WHO devised a new global malaria control strategy with member states and this was endorsed by the WHA in 1993 [101].

A renewed focus on research led to new vector control tools becoming available. In the early 1970s, second generation pyrethroids were developed (permethrin, cypermethrin and deltamethrin) which were safe to use for impregnation of bednets [102]. Following pioneering trials on bednets including those in The Gambia in the 1980s which showed huge impacts on malaria and mortality [59, 103, 104], the WHO recommended the use of insecticide-treated bednets for children and pregnant women [105]. The WHO position statement was later strengthened in 2007 to recommend the use of LLINs (with long-lasting pyrethroid formulations that lasted for 3 years) which should be distributed either free or highly subsidised and used by all community members, not just high risk groups [106].

Political will and resources for malaria were increasing and in 2007 malaria eradication hit the agenda again following calls by Bill and Melinda Gates to eradicate malaria with massive scale up of existing tools and other novel tools not yet available [107]. LLINs have been scaled up rapidly since 2000 and an estimated 53% of the population of SSA were sleeping under a LLIN in 2015 [20]. IRS is only used in particular areas and therefore only 3.1% of the global population at risk was covered by this intervention in 2015 [20]. Both interventions have had considerable public health impact. There has been a decline in malaria infection by over 50% in SSA and an estimated 663 million clinical cases averted worldwide since 2000, with LLINs and IRS being responsible for an estimated 68% and 13% of the cases averted, respectively [11].

Neglected tropical diseases – lagging behind in vector control

Vector control for vector-borne NTDs such as lymphatic filariasis, onchocerciasis, Chagas disease and leishmaniasis took much longer to gain traction compared to efforts against anopheline and *Aedes* vectors.

Notwithstanding the early discovery by Sir Patrick Manson of transmission of *Wuchereria bancrofti* by mosquitoes in 1900 [108, 109], vector control against lymphatic filariasis has played a lesser role than for other VBDs. While vector control is advocated by the WHO [39], much of the focus is on use of mass drug administration (MDA) to eliminate microfilariae from the blood of infected individuals in order to interrupt transmission of infection by mosquitoes. Despite this, there are several examples from the Pacific region of elimination of lymphatic filariasis using vector control alone – IRS using DDT against *Anopheles* vectors in the Solomon Islands and Papua New Guinea [110-112] and sanitation campaigns against culicine vectors in Australia [113]. Polystyrene beads used in pit

latrines against culicine vectors have also been shown to augment MDA in India and Zanzibar in the 1980s and 1990s [114-116].

Vector control has also played an important role in control of onchocerciasis in Africa. Aerial larviciding was responsible for the near-elimination of river blindness from much of West Africa as part of the Onchocerciasis Control Programme (OCP) from 1974 to 2002 [50, 52]. Furthermore, several of the countries in the African Programme for Onchocerciasis Control, a campaign launched in 19 African countries not covered by the OCP, have successfully used ground larviciding [52, 117].

Vector control has also been highly effective against Chagas disease as shown by the Southern Cone Initiative (SCI) initiated in 1991 in Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay [118-120]. Vector control against the vector *Triatoma infestans* focused mainly on IRS, house improvements and community education. Over 14 years, the SCI resulted in a decline in infestation rate and a sharp decline in the infection rates of children born since the programme began, with interruption of transmission in many countries.

Leishmaniasis transmitted by sandflies can also be controlled using vector control, with most programmatic success being seen with IRS. IRS used for malaria control has shown concomitant effects on both cutaneous leishmaniasis [121, 122] and visceral leishmaniasis [123-125]. A visceral leishmaniasis elimination initiative launched by India, Bangladesh and Nepal in 2005 which incorporates an IRS component has seen a 75% reduction in cases to 2014 [126].

Scaling down of tsetse campaigns and neglect of surveillance activities led to an increase in HAT cases by the turn of the century. Renewed efforts are underway to eliminate *gambiense* and *rhodesiense* HAT through reduction of the parasite reservoir (human and/or animal) and/or vector control, such as traps and targets that attract host-seeking tsetse flies [49, 127]. Increased control efforts have coincided with plummeting case numbers. According to the WHO there has been a 90% reduction in *gambiense* HAT cases and a 89% reduction in *rhodesiense* HAT cases between 1999 and 2015 [128].

Challenges to effective and sustainable vector control

Although progress has been made in reducing VBD endemicity, sustaining and advancing these gains requires intensification of control efforts and vector control faces a number of key challenges.

Insecticide resistance

Possibly the greatest challenge facing vector control is the development of insecticide resistance. Current vector control is heavily reliant on insecticides and unfortunately vectors are increasing becoming resistant to these chemicals. Insecticide resistance is present in a number of vectors including *Aedes* mosquitoes, culicine mosquitoes, sandflies, blackflies and triatoma bugs [129-131], but most worrying is insecticide resistance in *Anopheles* vectors which has been identified in 64 countries with ongoing malaria transmission [132]. The massive deployment of LLINs and IRS, along with use of the same insecticide classes for agriculture and in consumer products such as aerosols has increased selection pressure on mosquitoes to develop resistance to insecticides [133].

WHO-recommended insecticides used for malaria vector control belong to one of only four classes: pyrethroids, organochlorines (e.g. 1,1,1-trichloro-2,2-bis (p-chlorophenyl)-ethane, DDT), organophosphates and carbamates, with pyrethroids being the only class currently recommended for use on LLINs [132]. There are two main insecticide resistance mechanisms – metabolic resistance and target site resistance – which have multiple forms and are of varying importance for different insecticide classes [132]. Metabolic resistance involves a change or amplification in the enzymes that metabolise the insecticide meaning that a lower amount of insecticide eventually reaches the target site [134]. Target site resistance involves a genetic mutation which directly impacts on the target site of the insecticide thereby reducing or eliminating the effect of the insecticide. Two different point mutations in the voltage-gated sodium channel gene – the target site for pyrethroids and organochlorines confer knockdown resistance (*kdr*) to these insecticides in the *An. gambiae* complex [135-137]. Since the discovery of the *kdr* mutations in the late 1990s and early 2000s, additional target site mutations have also been discovered [138]. An additional problem is cross resistance which occurs when resistance to one insecticide confers resistance to another insecticide, even where the insect has not been exposed to the latter product. Pyrethroids and DDT share a common mode of action and therefore *kdr* mutations in malaria vectors can confer cross resistance to both DDT and pyrethroids [135]. Insecticide resistance genes may start out as rare events but with repeated exposure to an insecticide they increase in frequency over time. This increase becomes exponential once the gene reaches a certain frequency ('tipping point') and the gene can become stable in the population [132]. Resistance is generally measured using phenotypic assays, chiefly WHO tube tests in which mosquitoes are exposed to a discriminating dose of insecticide and

their mortality measured (mortality of less than 90% indicating resistance) [139]. The presence of molecular markers of resistance such as *kdr* can also be measured.

Insecticide resistance has been reported in all major malaria vectors and involves all classes of insecticide (but particularly pyrethroids) [132]. In some places anopheline mosquitoes have developed resistance to all four classes of insecticides available [132]. The strength and distribution of insecticide resistance has been increasing over time (Figure 1.3). According to the 2016 World Malaria Report, of 73 malaria endemic countries reporting insecticide resistance monitoring data since 2010, 60 reported resistance to at least one insecticide class and 50 reported resistance to two or more insecticide classes [20].

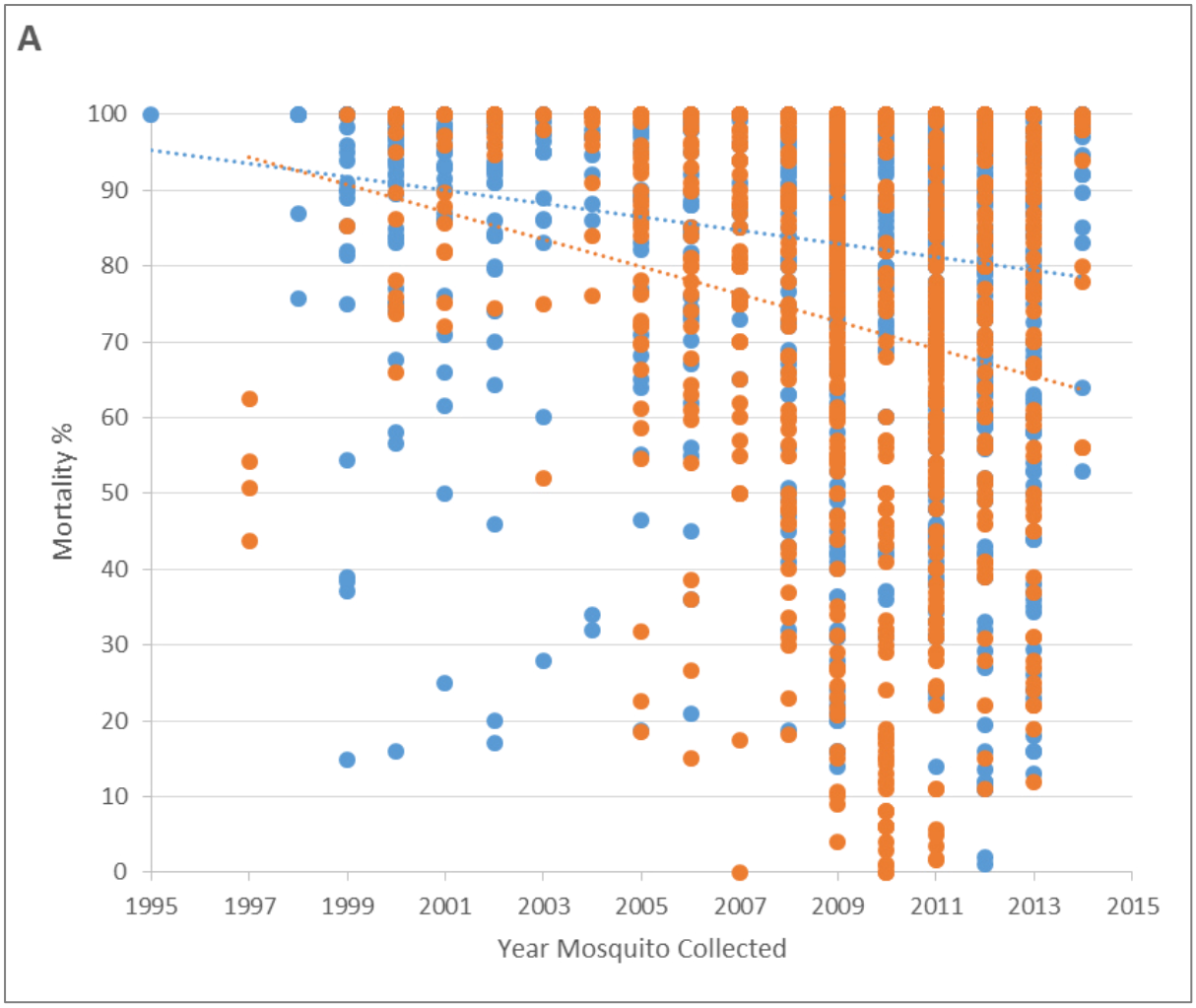

Figure 1.3: Changes in pyrethroid mortality in *Anopheles gambiae* sensu lato over time
Percentage mortality of *Anopheles gambiae* sensu lato (s.l.) exposed to 0.05% deltamethrin (blue) or 0.75% permethrin (orange) in WHO susceptibility bioassays. Data from 1995 to 2015 were extracted from IR Mapper (http://www.irmapper.com/) in August 2015 and supplemented with a literature search for 2014 and 2015 data. Each dot represents a data point extracted from IR Mapper or from the literature search and the dotted lines show trend lines for the mortality rates for each insecticide.
Reproduced from [133] with permission.

There is an urgent need to determine whether insecticide resistance is reducing the effectiveness of malaria vector control. Unfortunately, this is a highly complex task and the findings are far from conclusive.

Although indirect, the most convincing evidence for an effect of insecticide resistance on malaria transmission comes from control programmes where a change in class of insecticide used coincided with an improvement in malaria control. For example, a switch in IRS insecticides from DDT and pyrethroids to the carbamate bendiocarb in Uganda resulted in a marked improvement in slide positivity rates between 2007 and 2011 [140]. Similarly, in Ghana a switch in IRS insecticide to pirimphos-methyl after discovery of pyrethroid resistance coincided with a noticeable impact on key indicators of malaria transmission [141]. Both of these examples demonstrate the added value of using different classes of insecticide for LLINs and IRS. The most oft cited example of insecticide resistance impacting on control is that of KwaZulu-Natal, South Africa where there was an increase in malaria cases in the 1990s which coincided with a switch in IRS from DDT to deltamethrin [142]. Resistance to pyrethroids was widespread in *An. funestus* [138] and there was a decrease in malaria cases when IRS switched back to DDT in 2000. However, the fact that this reduction in malaria cases could also be attributed to a switch in first line malaria treatment from sulfadoxine-pyrimethamine to artemether-lumefantrine in 2001 [143] highlights the problem of confounding which means it is difficult to attribute programme failure to insecticide resistance. Also in support of an effect of insecticide resistance on malaria transmission is work by Churcher *et al.* [144]. This study used transmission dynamics models based on experimental hut data to show that even low levels of resistance would increase the incidence of malaria due to reduced mosquito mortality and lower overall community protection over the life-time of the net.

Other studies suggest that the effect of insecticide resistance may be exaggerated. Despite widespread detection of insecticide resistance in mosquitoes, a systematic review did not find evidence that insecticide resistance was attenuating the effect of insecticide-treated nets on mosquito mortality in experimental hut trials and cone bioassays [145]. However, there was high variability in study design and many of the studies included were conducted before the most potent pyrethroid-resistance mechanisms took hold [133]. Several field studies have shown no reduction in effectiveness of LLINs in areas of pyrethroid resistance. For example, a cohort study in an area of moderate pyrethroid resistance in Malawi found that children using LLINs had a 30% reduced odds of malaria infection compared to children not using LLINs [146]. A four country (Benin, Cameroon, Kenya and Sudan) observational study has also been conducted to quantify the potential loss of epidemiological effectiveness of LLINs and IRS due to decreased susceptibility of malaria vectors to

insecticides [147]. Unpublished results presented at the American Society of Tropical Medicine and Hygiene 2016 Annual Meeting do not suggest that insecticide resistance was reducing the effectiveness of vector control [148]. However, as an observational study this also has some limitations including known and unknown confounding factors such as differing transmission intensity and vector ecology between sites. The reason for these findings may be explained by the results of recent studies which suggest that insecticide-based control may still be able to reduce malaria transmission despite high levels of resistance. For example, a study by Kristan *et al.* suggests that in resistant mosquitoes (homozygous for *kdr*-east mutation) sub-lethal doses of pyrethroids can interfere with parasite development [149]. Another study shows that while insecticide resistant mosquitoes may survive initial contact with insecticide there are delayed mortality effects which can reduce the lifespan of even highly resistant strains of *An. gambiae* by 50%, therefore reducing their malaria transmission potential by up to two thirds [150].

It is clear that further study of insecticide resistance is required. However, if the effectiveness of malaria vector control is reduced or at the extreme, control failure occurs, the results could be catastrophic. Modelling suggests that if pyrethroids fail, about 50% of the benefits of vector control would be lost, meaning that at the current level of LLIN and IRS coverage there would be approximately 120,000 deaths among children under 5 and 26 million malaria cases not averted [132].

Funding and political will

A major challenge to vector control is how to sustain sufficient and predictable levels of domestic and international funding for vector control. Maintaining strong political support and collaboration at the highest levels is difficult due to competing priorities and limited resources, and will become increasingly so given the likely protracted nature of VBD elimination. The WHO Global Technical Strategy for Malaria 2016-2030 estimates the cost of achieving the 2030 malaria goals (reducing malaria mortality and incidence rates by 90%, and eliminating the disease in at least 35 more countries) to be 101.8 billion US$ (not including research and development) [13]. Global financing for malaria control and elimination was 2.9 billion US$ in 2015, which represents only 46% of the Global Technical Strategy 2020 annual investment milestone of 6.4 billion US$ [20, 151].

There is still very little funding allocated to NTDs despite the renewed focus on NTDs from the international public health community, including the ambitious London Declaration of 2012 in which partners pledged to control Chagas disease, visceral leishmaniasis and onchocerciasis and eliminate lymphatic filariasis, HAT and trachoma by 2020 [152]. Analysis shows that NTDs were responsible

for only 0.6% of Official Development Assistance in 2012, compared to 6.8% for malaria and 47.2% for HIV/AIDS [153].

Weak health systems and vector control programmes

Countries face a lack of skilled personnel, in particular public health entomologists, vector control technicians and allied fields, such as sanitary engineers [154]. Under-resourcing leads to poor execution of vector control and surveillance. In many countries senior entomologists are retiring and there are no training programmes available for the next generation of public health entomologists and vector control technicians. Shortages of funding and a lack of career pathways causes low motivation. As a result, attrition of trained individuals due to reallocation to other health areas, the agricultural sector or abroad leads to inconsistent vector control efforts.

Many country health systems are weak and therefore do not support effective vector control. For example, logistic and delivery systems need to be effective to achieve and sustain high coverage of interventions. Weak systems for surveillance and monitoring and evaluation mean that programmes are not able to target interventions well or track progress against entomological and epidemiological indicators so that they can make changes for more effective vector control. Vector control programmes typically do not put enough emphasis on understanding and engaging communities which means that compliance with vector control, particularly personal protective measures is not optimal.

These systems and operational challenges are crucial given that a review of malaria resurgence events between the 1930s and 2000s found that 91% (68/75) could be attributed, at least in part, to weakening of malaria control programmes through financial and operational threats [155]. More recently, outbreaks of Zika have been attributed to weak vector control programmes which have failed to adequately control *Ae. aegypti* [156].

Environmental and social change

The distribution and burden of VBD is affected by changes in the environment and socioeconomic conditions which result in re-emergence of VBDs, including geographic spread to new areas, extension of the transmission season in endemic areas or reoccurrence of VBDs after an extended period of absence [157].

Urbanisation is a particular problem since 54% of world's population live in cities and this proportion is expected to rise to two thirds by 2050 [158]. Most of the increase in urbanisation is occurring in Africa and Asia, which are projected to become 56% and 64% urban, respectively by 2050 [158]. Urban environments in tropical climes with high population density and often accompanied by environmental deterioration provide an ideal habitat for *Ae. aegypti* which has

adapted to live in and around homes and feed preferentially on humans. Development of cheap plastics and rubber and a lack of refuse collection has allowed *Ae. aegypti* to flourish in small bodies of water found in discarded plastic containers, plant pots, gutters, tires and water-storage containers that abound in modern urban environments [159]. Lack of piped water or insecure water supply in many tropical cities means that water is often stored in water containers inside homes which provide an ideal habitat for *Ae. aegypti* to lay its eggs.

As countries develop, socioeconomic and population growth has led to increasing demand for energy, transport, food and natural resources. Environmental changes such as agricultural expansion and intensification, water resource development, deforestation and natural resource exploitation have created enabling conditions for VBDs [157]. For example, the building of dams is sometimes associated with an increase in malaria incidence in the vicinity since the newly created standing water serves as a breeding site for *Anopheles* larvae [160]. Another example is increased transmission of Chagas disease, a typically rural disease, in peri-urban slums in Brazil due to deforestation, forest fragmentation and urbanisation which has led to invasion of suburban areas by triatomines [161, 162]. Climate change may also be impacting on transmission of some VBD, with models predicting an increase in malaria and dengue burden [163], although others believe that malaria transmission potential could be reduced by climate change [164].

Human factors such as poverty, social inequality, population movement and deterioration in living conditions due to political upheaval, natural disasters, conflict and migration for employment are also affecting the burden and distribution of VBDs. Population movement can introduce non-immune individuals into endemic areas or infected individuals into susceptible populations with competent vectors. For example, mobile and migrant populations in the Mekong region of south-east Asia who conduct forest-related activities are highly vulnerable to malaria [165].

An increase in international air travel and trade means that VBDs once confined to a particular locale present a wider threat to global health due to introduction of vectors in new locations and pathogen movement [157, 166]. There are numerous historical examples of vector invasion such as movement of *Ae. aegypti* from West Africa which facilitated yellow fever epidemics in north American port cities in the 19th and early 20th centuries, *An. gambiae* invasion of north eastern Brazil in 1930 and worldwide dispersion of *Ae. albopictus* through ship-borne transportation of eggs and larvae in tyres [167]. Air travel is probably more important in movement of pathogens, via infected human passengers, rather than vector movement [166]. For example, air travel has the potential to spread Zika rapidly, similar to previous experiences with chikungunya [168, 169].

Zoonotic pathogens

There is also the threat of zoonotic pathogens spilling over into transmission cycles involving humans and adapting to be vectored by human specialist vectors such as *An. gambiae* and *Ae. aegypti* [157, 170, 171]. Dengue, chikungunya and yellow fever have all altered their host range from non-human primate reservoirs to humans, mediated by an ecologically and separately evolving urban endemic transmission cycle [33]. Research by Jones *et al.* shows that since 1940 over 335 new human infections have been newly recognised, and that worryingly 29% of new human diseases are transmitted by vectors [172]. In the future, other viruses may emerge that could be transmitted by *Ae. aegypti* or other mosquitoes and these viruses could be potentially more pathogenic than those circulating currently.

Insufficiency of current vector control toolbox

There is increasing recognition that in order to control VBD more effectively and/or drive VBD to zero, multiple interventions need to be applied and that this may not be achievable with the current tools available [173-176]. As well as combatting insecticide resistance, new tools are urgently needed to tackle residual malaria transmission i.e. malaria transmission that persists despite achieving universal coverage with LLINs and/or IRS to which vector populations are fully susceptible [177]. In some settings, specific behaviours of the vector population such as avoidance of contact with insecticide-treated surfaces, outdoor biting, feeding on animals or outdoor resting behaviour mean that malaria transmission can be sustained despite high coverage with LLINs and/or IRS. Chagas disease vector control is also facing similar problems since vector control targeted at homes, while effective against domestic vector populations, is ineffective against sylvatic vector populations and must be sustained to prevent reinfestation of homes by wild vectors [178-180].

Data from the 2015 G-FINDER report produced by the policy think tank Policy Cures shows that research and development (R&D) investment in malaria (610 million US$ in 2014) dwarfs that for other VBDs (Table 1.4) [181]. For each VBD, there is less investment in vector control R&D compared to drugs, diagnostics and vaccines. For example, for malaria only 18 million US$ (3% of total R&D investment) was on vector control. It is promising to note that 25% of dengue R&D investment (21 million US$ in 2014) was on vector control which represents an increase from 8% in 2010. However, there is negligible or no investment in vector control R&D for other VBDs such as lymphatic filariasis.

Table 1.4: Research and development funding by product type by vector-borne disease in 2014

VBD	Global disease burden [20-23]		Investment in research and development (US $, millions) (% is given in parentheses)						
	Morbidity (estimated cases in 2015, thousands)	Mortality (estimated all age deaths in 2015, thousands	Diagnostics	Vector control	Vaccines (preventive)	Vaccines (therapeutic)	Drugs	Basic research	**Total**
Malaria	212,000	429.0	19 (3%)	18 (3%)	173 (28%)		214 (35%)	164 (27%)	**610**
Dengue	79,609 (53,784–169,704) (incidence)	18.4	5.4 (6%)	21 (25%)	*		20 (23%)	39 (45%)	**87**
Human African trypanosomiasis	10.7	3.5	2.7 (5%)	-	-		24 (50%)	22 (45%)	**48**
Leishmaniasis	3956.7	24.2	1.1 (2%)		5.1 (11%)	1.6 (3%)	15 (32%)	23 (49%)	**47**
Chagas disease	6653.6	8.0	1.4 (6%)	-	0.6 (3%)	0.2 (1%)	12 (55%)	8.3 (38%)	**22**
Lymphatic filariasis	38,464.1	-	0.2 (1%)	<0.1 (<1%)			14 (67%)	5.3 (25%)	**21**
Onchocerciasis	15,531.5	-	0.1 (1%)	<0.1 (<1%)	<0.1 (<1%)		8.3 (87%)	1.1 (12%)	**9.5**
Trachoma	3557.1	-	2 (29%)	-	4.7 (69%)		-	-	**6.8**

- indicates no reporting funding, greyed out box indicates category not included in G-FINDER
* commercial dengue vaccine programme excluded from G-FINDER
Source: [181]

As well as financial barriers, there are technical and programmatic barriers to vector control innovation including the relatively small and unpredictable market for vector control which is largely due to reliance on a small number of donors such as the Global Fund for AIDS, Tuberculosis and Malaria [182]. Initiatives have been set up to overcome these barriers and fast-track the development of new public health insecticides and new paradigms in vector control, for example the Innovative Vector Control Consortium, a product development partnership [183].

Integrated Vector Management

What is Integrated Vector Management?

The WHO recommended approach for control of VBDs globally is known as Integrated Vector Management (IVM) and is defined by the WHO as a "rational decision-making process for the optimal use of resources for vector control" [184]. In simpler terms, IVM is an evidence-based, adaptive and multi-sectoral approach to vector control. Briefly, it involves the use of a range of proven vector control tools used either alone or in combination selected based on knowledge of the local vector ecology and disease epidemiology. IVM is accompanied by vector surveillance and monitoring and evaluation so that control activities can be adapted over time and impacts can be evaluated. Importantly IVM utilises tools from within and outside the health sector, for example harnessing community groups to conduct environmental management for mosquito control.

The WHO highlighted the five major elements of an IVM strategy as: i) advocacy, social mobilisation and legislation, ii) collaboration within the health sector and with other sectors, iii) an integrated approach, iv) evidence based decision making and v) capacity building [2] (Table 1.5).

Table 1.5: Key elements of an integrated vector management (IVM) strategy

	Element	Description
1	Advocacy, social mobilisation and legislation	• Principles of IVM promoted and integrated into policies in all relevant ministries, organisations and civil society. • Establishment / strengthening of regulatory and legislative controls for public health. • Community engagement and empowerment to increase sustainability.
2	Intrasectoral and intersectoral collaboration	• Collaboration within the health sector and with other sectors (public and private). • Planning and decision-making delegated to the lowest possible level (subsidiarity).
3	Integrated approach	• Addresses several diseases using vector control tools, often

		in combination and synergistically. • Utilises chemical and non-chemical vector control methods. • Integrates with other disease control methods, such as drugs and vaccines.
4	Evidence-based decision making	• Strategies and interventions are adapted to local vector ecology and disease epidemiology and are guided by operational research and monitoring and evaluation.
5	Capacity building	• Availability of infrastructure, financial and human resources at central and local level.

Adapted from WHO Handbook for IVM (2012) [3]

i) Integrated approach

IVM involves the use of a range of proven vector control methods used either alone or in combination. Tools which are partially effective can be combined additively or synergistically with more effective methods to improve the overall effectiveness of vector control. Vector control tools can be chemical or non-chemical and IVM can also supplement the use of vaccines, MDA or diagnosis and treatment for integrated disease control. By encouraging the diversification of vector controls used, IVM also provides a framework through which countries can reduce reliance on insecticides and extend the useful life of insecticides by reducing the selection pressure for resistance development.

IVM, in certain situations, can address several diseases concurrently. The reasons for this are twofold. Firstly, some interventions are effective against several vectors. For example, LLINs are effective against malaria, lymphatic filariasis, leishmaniasis and dengue [185]. Secondly, some vectors can transmit several diseases. For example, *Anopheles* mosquitoes transmit both malaria and lymphatic filariasis in rural areas of SSA [42, 186], and *Aedes* mosquitoes transmit dengue, chikungunya, Zika and yellow fever. Where diseases are co-endemic there is an opportunity for integrated control, for example by jointly planning, implementing and monitoring and evaluating VBD control. However, IVM does not necessarily have to be used for cross-disease control.

ii) Evidence-based decision making

Selection and implementation of vector control methods should be guided based on knowledge of the local vector ecology and epidemiological situation. IVM programmes should be accompanied by monitoring and evaluation of the effect on both the vector and disease which serve to troubleshoot implementation and evaluate the impact of the programme. In addition, operational research priorities should also be identified and studies conducted to inform the programme.

iii) Intrasectoral and intersectoral collaboration

IVM should be a collaborative effort both within the health sector and with other sectors. For example, VBD control programmes should link with other VBD control programmes, centralised functions (human resources, health information systems, logistics and stores) and private, faith-based and other health providers. Through effective coordination it may be possible to share resources in planning, implementing, surveillance and monitoring and evaluation and reduce overlap and duplication.

Collaboration between the health sector and with other sectors such as government ministries (e.g. agriculture, education, housing and public works), local government, the private sector, research and academic institutions, civil society and non-governmental organisations (NGOs) should be strengthened. This is important because often the non-health sector is unaware of how their actions or inactions contribute to VBD and many determinants of VBD such as agriculture, urban development, sanitation, and housing are outside the scope and jurisdiction of conventional VBD control programmes. IVM calls for programmes to make non-health actors aware of their contribution and responsibilities towards VBD and seek their buy-in sought for implementation of interventions such as housing improvement and environmental management. Other options for intersectoral involvement include involving academic and research institutions to assist with training, the design and implementation of operational research studies or sharing of laboratory facilities, for example insectaries. Also NGOs and civil society groups can mobilise and engage communities for VBD prevention and communities can for example take part in participatory mapping of diseases and their determinants or clean-up campaigns to remove aquatic habitats.

IVM embraces the principle of subsidiarity in which planning and decision making is performed at the lowest possible level. It is essential therefore that responsibility for essential functions is allocated to appropriate levels in overall system (e.g. national, provincial, district, community).

iv) Advocacy, social mobilisation and legislation

IVM needs to be communicated effectively, promoted and integrated into policies in relevant ministries, organisations and civil society. Regulatory and legislative controls for public health need to be established or strengthened. Involvement and engagement of communities can help to increase the sustainability of IVM and so efforts should be made towards social mobilisation.

v) Capacity building

IVM is knowledge intensive and needs skilled personnel at national, sub-national, district and village level to collect and make use of data effectively for decision making. Capacity building should be

conducted to upgrade and maintain the knowledge and skills of vector control staff. The WHO provides a core structure for training curricula on IVM covering introduction to vectors of human disease, planning and implementation, organisation and management, policy and institutional arrangements, advocacy and communication, and monitoring and evaluation [187]

How does IVM differ from current vector control?

IVM is said to represent a paradigm shift from standard vector control practice because of its integrated holistic, ecological approach. Thomas *et al.* outlined the major differences between current vector control and IVM in terms of three categories – problem definition, control strategy and implementation (Figure 1.4) [188].

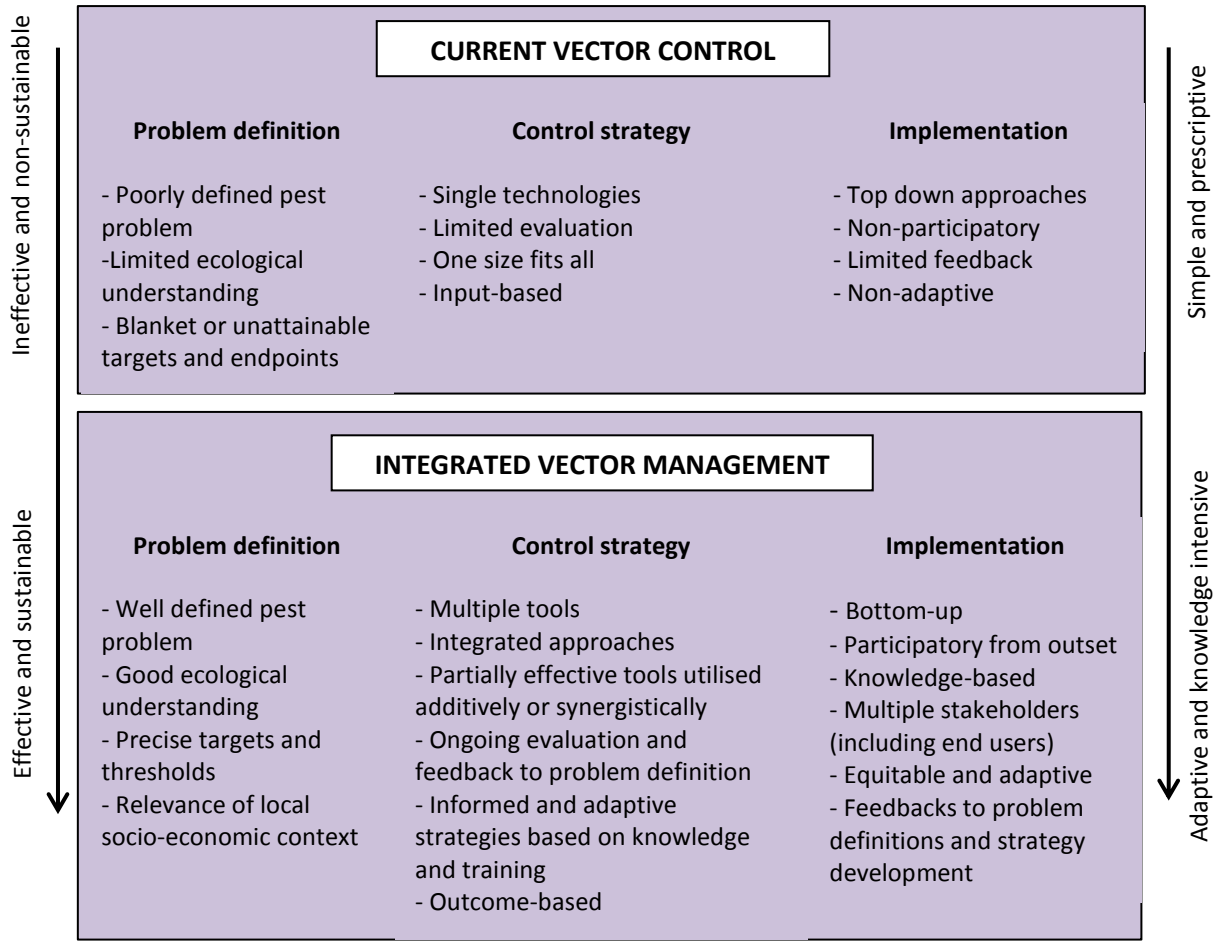

Figure 1.4: Features of current vector control strategies compared with IVM [Adapted from [188]]

In contrast to the majority of current vector control programmes, IVM is based on a good understanding of the ecological factors determining the distribution and densities of different vector species and their bionomics, as well as human determinants of VBD such as socioeconomic factors, population movement and behaviour i.e. the VBD problem is well defined. IVM calls for a more

ecological approach to vector control based on an awareness of the ecological and environmental changes which can affect the vector, pathogen and hosts [189]. In terms of control strategy, IVM is characterised by the use of multiple vector control tools used in combination where possible, and approaches adapted to the control area, rather than a one-size-fits-all approach and the use of single tools which characterise current vector control. IVM encourages the use of both chemical and non-chemical vector control methods.

The collection of entomological and epidemiological data through monitoring and evaluation is crucial in IVM in order to inform and adapt ongoing control efforts (in terms of tools used and implementation strategy) through a feedback loop and to measure impact. In current vector control programmes, monitoring and evaluation is generally weak and programme activities are often not linked with vector surveillance or epidemiological surveillance data. Rather than the top-down vertical approach of current vector control where activities are driven from higher administrative levels, IVM is characterised by a bottom-up approach whereby planning, implementation and evaluation of vector control is delegated to the lowest administrative level. IVM is therefore well suited to countries with decentralised decision-making and finances. Community involvement, generally overlooked in standard practice vector control, is key to IVM. Equally important is collaboration with other stakeholders such as industry, government ministries (e.g. agriculture, education, housing and public works), local government, research and academic institutions, civil society and NGOs. Collaboration within the health sector, for example between the different disease control programmes is also essential, compared to routine vector control in which disease control programmes traditionally work in 'silos'.

History of IVM policy

IVM is modelled on the concept of Integrated Pest Management (IPM) which was developed in the agricultural sector in the 1950s [190]. IPM is an ecological approach to crop production and protection that combines different management strategies and practices to grow healthy crops and minimize the use of pesticides. Chemical pesticides had a minor role in IPM, if any, and if used were always in combination with a non-insecticide based tool. In parallel in the 1980s, there was increased interest in finding alternatives to the use of residual insecticides in vector control due to concerns over insecticide resistance, environmental contamination and human safety. This led to formation of the integrated vector control (IVC) concept based on the principles of IPM. The IVC approach consisted of use of a several vector control measures either simultaneously or sequentially including personal protection, habitat management, source reduction, insecticides as larvicides or adulticides and biological control [191]. IVC stated that "although as a rule, chemical control methods should be considered as a supplement to basic sanitation, they must continue to be

employed as the principal means for obtaining rapid and maximum control of a vector, especially during epidemics…".

In 1997 a World Health Assembly resolution (WHA 50.13) was passed which called on member states to reduce reliance on insecticides for control of VBD, and develop and adopt alternative methods of disease control [192]. Between 1998 and 2001 the idea of IVC was revitalised during inter-governmental negotiations on a legally binding instrument to limit the use of persistent organic pollutants (POPs). This led to the Stockholm Convention on POPs in 2001 which recommended the "implementation of suitable alternative (vector control) products, methods and strategies" to reduce and eventually phase out the use of DDT [193]. In 2004 the WHO released the Global Strategic Framework for IVM which set out "new and broad principles and approaches to vector control that are applicable to all vector-borne diseases" [2]. This document called for the integrated use of all available and effective measures whether these are chemical, biological or environmental.

In May 2007, a group of experts met at WHO to review the status of IVM and develop a global strategic plan to advance the development and promotion of the IVM approach [194]. The key recommendations of the consultation were to: i) increase advocacy and social mobilisation to articulate the need for IVM, ii) build capacity of human resources and infrastructure, iii) conduct operational research and monitoring and evaluation to strengthen the evidence base on IVM, and iv) establish an institutional framework to promote and implement IVM.

A consultation was held in December 2008 on the development of global action plan for IVM for period 2009-2011 [195]. The objective of the consultation was to develop a global action plan on IVM, identify the roles of partners, review the status of IVM and develop a guidance document on national IVM policy. Specific recommendations from the meeting were to launch a global advocacy strategy, strengthen capacity through development of a training package, establish a network on IVM to strengthen the evidence base and data-sharing for IVM, including the documentation of case examples and finally to develop a system for the evaluation of IVM.

In the same year, the WHO issued a position statement on IVM [184]. In this document, member states were encouraged to accelerate the preparation of national policies and strategies and international agencies, donors and other stakeholders were encouraged to support the capacity building necessary for IVM implementation. The WHO Global Plan to Combat NTDs 2008-2015 highlighted strengthening IVM as a strategic area for action [196]. In 2012 a Handbook on IVM targeted at vector control programme managers was released by the WHO and provides an operational framework to transition vector control programmes towards IVM [3].

IVM is referenced in both the Roll Back Malaria (RBM) Action and Investment to Defeat Malaria 2016-2030 document [151] and the WHO Global Technical Strategy for Malaria 2016-2030 [13]. These documents highlight the need for intersectoral collaboration and reinforce that malaria vector control should be implemented in a wider framework of IVM.

More recently, the WHO has released a Toolkit on IVM for SSA giving countries practical advice on how to go about planning and implementing IVM [10]. Toolkits are also under preparation for Latin America and the Caribbean and Asia.

As well as policy generation at global level, regional WHO offices and subsequently, member states have been working in parallel on IVM policy and training workshops. For example, the African region was the first to develop an IVM framework for vector control in 2001 [197, 198], along with guidelines for management of IVM and vector control needs assessment in 2003 [199, 200].

IVM Case Studies

There are few contemporary rigorously conducted evaluations of IVM and programmatic experiences are often not shared outside of programmes, instead being documented in reports, policy documents and annual operational plans which are not made publically available. Most programme examples include some but not all of the elements of IVM, and most are focused solely on malaria. Probably the best IVM programme example is that of the Khartoum Malaria Free Initiative in Sudan launched in 2002 which incorporates many of the elements of IVM and has led to declines in parasite prevalence and malaria deaths (Table 1.6) [201-203]. In Khartoum the malaria vector *An. arabiensis* breeds largely in irrigation canals, pools created from broken water pipes, water basins and storage tanks and so vector control measures consist of larviciding and environmental management.

Table 1.6: Khartoum Malaria Free Initiative (MFI) as an example of IVM

Element of IVM	Role in Khartoum Malaria Free Initiative (MFI)
Advocacy, social mobilisation and legislation	• Strong political support at State and Federal Level. • Generate strong community support through distribution of information leaflets, radio broadcasts and television coverage, health education in schools in collaboration with the Ministry of Education, the organisation of an annual 'Khartoum State Malaria Day', public meetings and the establishment of malaria control committees and societies. • Legislative measures put in place e.g. removal of water basins and storage tanks is enforceable by law. e.g. LLINs are exempt from import tax to encourage sales in the private sector.
Intrasectoral and intersectoral	• Close collaboration between the State and Federal Ministry of Health. • Close collaboration with Farmers Union and the Ministry of Agriculture to

collaboration	enforce compulsory regular drying of irrigated fields in government and private irrigation schemes. • Partnership between Ministry of Health and Public Works Department (PWD) to repair or replace broken water pipes, with resource sharing (Malaria Free Initiative (MFI) is responsible for surveillance, reporting and transportation while the PWD provides engineers and equipment). • Collaboration with the Ministries of Irrigation and Agriculture to repair leakages from irrigation canals and clear vegetation around canals. • Community involvement in vector control e.g. schools and pupils involved in mosquito larval control activities.
Integrated approach	• As well as vector control, the MFI comprises also case management and epidemic surveillance. Case management is strengthened through training on malaria diagnosis and case management and provision of antimalarial drugs through the 'revolving drugs fund'.
Evidence-based decision making	• Entomological sentinel surveillance sites established in Khartoum (and countrywide) visited monthly. • Epidemiological surveillance to monitor and evaluate impact of MFI.
Capacity building	• MFI employs 14 trained medical entomologists, 60 public health officers, 180 sanitary overseers, 360 assistant sanitary overseers and 1170 spraying men who undertake larviciding and environmental management. • National training site established at Blue Nile National Institute for Communicable Diseases at University of Gezira which offers a masters degree in medical entomology and vector control in collaboration with other international universities and WHO Eastern Mediterranean Regional Office.
MFI = Malaria Free Initiative, PWD = Public Works Department	

Another good example, also focusing on malaria, comes from Zambia [204, 205]. In response to a high malaria burden, Zambia adopted a new National Malaria Treatment and Control Policy with IVM as the strategic approach to vector control in 2003 (Table 1.7). IVM was introduced and implemented in accordance with WHO recommendations in three steps; introduction, consolidation and expansion phase [206]. Some of the notable achievements were: designation and training of a national IVM focal point to spearhead IVM and develop the National Action Plan, conducting a comprehensive vector control needs assessment, development of country specific IVM guidelines, upgrading of the national entomology laboratory and constituting a national IVM steering committee.

Table 1.7: IVM for malaria control in Zambia

Element of IVM	Role in Zambia IVM Programme
Advocacy, social mobilisation and legislation	• Established policy, legal and regulatory framework including development of new malaria strategic plan (2006-2011) and review of key legal documents e.g. Public Health Act Chapter 295 and Mosquito Extermination Acts • Removed taxes and tariffs on LLINs and insecticides for malaria control • Enhanced community participation e.g. spray operators for IRS, applicators for larviciding and those supporting LLIN delivery were selected from communities.
Intrasectoral and intersectoral collaboration	• IVM steering committee has broad participation from public sector (Ministry of Defence, Environment, Agriculture, Housing and Local Government), research institutions, higher learning institutions, local authorities, private sector (mining, chemical and agriculture), non-governmental organisations (NGOs) and multi-/bilateral development partners (e.g. United States Agency for International Development, WHO, Global Fund for AIDS, Tuberculosis and Malaria). • Working group on DDT under the National Implementation Plans also set up to ensure adherence to Stockholm Convention on DDT usage • Broad intersectoral collaboration. For example, Ministry of defence provides transport and staff; mining and agricultural companies provide technical assistance on capacity building, additional workforce and supplement government efforts on increasing intervention coverage; NGOs lead social marketing of LLINs and coordinate distribution • Collaboration within health sector for example between national malaria control centre, medical stores, provincial and district health offices. • IVM committee established in Ministry of Health dealing with priority issues on implementation, capacity building, financing and monitoring and evaluation and encouraging linkages between malaria and other VBD control programmes e.g. schistosomiasis, trypanosomiasis.
Integrated approach	• Interventions used in combination – scale up of IRS and LLINs, and environmental management (canalisation, draining and land filling) and larviciding implemented by local authorities and communities as supplementary interventions.
Evidence-based decision making	• Geographical, epidemiological, entomological and ecological assessments carried out at district level to ensure that methods are based on knowledge of factors influencing local vector biology, disease transmission and morbidity. • Operational research looking at feasibility of using bio-larvicides. • Established IVM monitoring and evaluation indicators which have been included in national action plan.
Capacity building	• Vector control unit established at National Malaria Control Programme with postgraduate level staff. • Training of trainers (provincial and district level personnel i.e. Environmental

	Health Technicians, Programme Managers, Coordinators and Supervisors) on IVM. • Annual district training for District Health Management Teams, local authorities and communities with technical support drawn from public sector and private sector partners. • Training of community operators for IRS/larviciding/LLIN delivery and supervision by trained environmental health officers

Challenges to implementation of IVM

According to WHO, 68 out of 110 WHO member states have adopted an IVM policy (R. Velayudhan, pers. comm.). However, the proportion of countries using IVM in practice is unclear. IVM has been around since the 1980s and therefore is not a new approach to vector control. However, the general feeling is that despite being a wholly sensible approach to vector control, it is a policy which has never really gained any traction, despite numerous relaunches and new initiatives from WHO. Here, I briefly review the three key reasons for this. These are neatly summarised by Ellis and Wilcox who state that for ecological approaches to VBD control "…..the idea and policy impetus behind them generally has been out in front of the science (the conventional hypothesis-driven experimental evidence) and the capacity of academic and public health institutions to readily grasp and implement them" [189].

Firstly, IVM can be a difficult and abstract concept to understand and is seen as being overly complex by some. IVM has not been well articulated by WHO in the past which is exemplified by the official WHO definition of IVM as a "rational decision-making process for the optimal use of resources for vector control" [184]. This definition lacks clarity. The same reasons stated by WHO with regard to slow uptake of IVC also apply to IVM today [207]. For example, an over-estimation of the requirements of integrated control, misconception of some programmes that IVC meant stopping the use of pesticides altogether and a lack of information on the advantages of IVC including comparative costs, effectiveness, benefits and risks. IVM adopts a holistic, integrated and ecosystem approach which rekindles the spirit of historical vector control according to the Dutch and Italian schools and others. However, until the recent Toolkit for IVM there has been no operationally explicit description of how to do IVM [10]. Nevertheless, it is acknowledged that implementation of locally adapted and integrated vector control approaches based on entomological and epidemiological surveillance and monitoring and evaluation can be daunting, particularly for programmes that do not collect or utilise data in this way currently.

Secondly, although the WHO maintains that IVM will improve the efficacy, cost effectiveness, ecological soundness and sustainability of vector control interventions with the available tools and resources [3], the evidence base for this is limited. Apart from the case studies of Sudan and Zambia mentioned previously, there are no well documented examples of IVM. A particular weakness is the lack of rigorous economic evaluations of an IVM programme versus routine vector control since cost savings would be a huge driver for programmes and funders.

Thirdly, there is a lack of capacity in vector control programmes to implement IVM, as well as organisational and structural barriers such as a general lack of intersectoral linkage. IVM is adaptive and knowledge intensive, with implications on resources. For example, human resources, in particular public health entomology capacity and infrastructure (e.g. insectaries) are required to plan, implement and monitor and evaluate an IVM programme. Staff retention is a major issue in control programmes, as poorly paid vector control specialists with no room for career progression often move to the agricultural and private sectors. Often there is little linkage between research and programmes which means that research findings are not adopted by ministries for implementation. Political will is often lacking. Programme Managers who are supposed to be driving IVM are often clinicians rather than vector control experts who favour case management and chemoprevention rather than vector control methods and so IVM falls down the priority list [208]. Achieving and sustaining multisectoral collaboration is difficult [209]. Mutero *et al.* noted that financial constraints, culture of organisational independence or silos, lack of political will, poor planning and communication are all barriers to IVM in Uganda [210]. Countries tend not to have integrated VBD control programmes which are responsible for all VBDs, and if they do collaboration between units may be weak or non-existent. For example in Mali, the Ministry of Health has separate control programmes in charge of malaria and NTDs but there is limited collaboration between these programmes and NTD control relies solely on MDA and not vector control [211]. However, integration is compromised if other VBD programmes are not brought on board or if programmes are unaware of the effects of other VBDs, and how integration can have added impact [208]. Funding of IVM is also problematic. Often a lack of comprehensive policy means it is hard to mobilise and distribute cross sectoral resources for vector control. External donor funding is generally siloed for specific diseases and often mandated for single interventions, so there is little flexibility for programmes to mix major and supplementary interventions towards IVM that will maximise impact [208].

Conclusion

VBDs are a huge burden on developing countries in tropical and sub-tropical zones. There is an urgent need to reduce morbidity and mortality from these diseases, and stakeholders are aligned

behind the United Nations Sustainable Development Goal 3 which aims to end epidemics of malaria, NTDs and other communicable diseases by 2030 [212]. For many VBDs, vector control remains the primary method by which they can be controlled. Historically and more recently, with the example of malaria [11], vector control has been hugely successful. However, vector control, as currently practised is not effective everywhere, as evidenced by the increasing burden of *Aedes*-borne diseases and other challenges such as insecticide resistance are looming. IVM is a wholly sensible approach to VBD control and is potentially more effective, efficient and sustainable than current standard practice vector control. However, transitioning programmes to a more holistic and evidence-based approach is not easy and one of the main gaps is a lack of guidance on how to plan, implement and evaluate IVM.

Chapter 2: Development of the World Health Organization Toolkit for IVM in sub-Saharan Africa

Abstract

In 2012 The Bill & Melinda Gates Foundation provided funding for development of an operational framework for integrated vector control. The project had several workstreams one of which aimed to provide the World Health Organization (WHO) with a practical toolkit on Integrated Vector Management (IVM) for vector control managers at the national and regional levels. The document was developed in close collaboration with vector control experts, and the Department of Neglected Tropical Diseases and Global Malaria Programme at WHO, and was reviewed by an independent panel of experts. The research identified several major findings including the need: i) to have a clearer definition of what IVM is; ii) to base the toolkit on existing documentation where possible to avoid repetition; iii) for regional toolkits (sub-Saharan Africa, Latin America and the Caribbean, and Asia); and iv) to make the toolkit applicable to both well-resourced and under-resourced programmes. The need to give evidence-based recommendations on vector control tools was also highlighted rather than simply a list of possible tools which could be used which is often the case in WHO guidance. The toolkit conceptualises IVM as a cyclical process with multiple rounds of situational analysis, planning, design, implementation and monitoring and evaluation, accompanied by operational research. The development and thinking behind the toolkit is further explained, along with a critical analysis of the work and suggested next steps to move the document into policy and practice in country programmes, including development of training materials and a web-based resource.

Operational framework for integrated vector control – project and milestones

Durham University was awarded a grant in November 2012 by the Bill & Melinda Gates Foundation to develop an operational framework for integrated vector control. The goal of the grant was the 'Development of an actionable, global, strategic framework based on Integrated Vector Management (IVM) principles, supported by mathematical modelling'. The project aimed to provide the World Health Organization (WHO) with a practical toolkit on IVM for control managers at the national and regional levels. As well as development of a toolkit providing a detailed description of how to do IVM, the project included three additional workstreams. The first aimed to systematically review the evidence on the efficacy of vector control tools against VBDs. The second, led by the Swiss Tropical and Public Health Institute, used mathematical modelling to explore how vector control interventions could impact more than one vector-borne disease (VBD) using the example of malaria and lymphatic filariasis transmitted by *Anopheles gambiae* [213]. The third workstream led by the University of Oxford and the London School of Hygiene and Tropical Medicine aimed to generate global environmental risk maps for VBDs based on occurrence records and biologically relevant environmental covariates [1, 214, 215].

The toolkit on IVM was developed in close collaboration with colleagues in the Department of Neglected Tropical Diseases and Global Malaria Programme at WHO. Two meetings were held with vector control experts from around the world, including academics, donors (e.g. Global Fund for AIDS, TB and malaria), implementing agencies (e.g. RTI International) and vector control programme managers. The first meeting was held in Palm Springs, USA in September 2013 when 22 experts met to agree the general structure & content of the IVM toolkit. It was decided at this meeting that three regional (sub-Saharan Africa, SSA, Latin America and the Caribbean, and Asia) toolkits were required, which was not anticipated in the initial scope of the grant. In April 2014, 18 experts met in Durham, UK to revise the first detailed draft of the toolkit.

In January 2015 the IVM toolkit for SSA was reviewed at a 2-day informal consultation meeting held at WHO, Geneva by an independent group of experts comprising vector control experts, funders, programme managers and staff from the WHO Eastern Mediterranean and African regional offices. The revised document was submitted to WHO for final approval by 1st April 2015 and following copy editing was published in June 2016. The IVM toolkit for SSA has been distributed by the WHO to country and regional offices. A draft IVM toolkit for Latin America and the Caribbean was also prepared and discussed at an informal consultation meeting held in August 2015 in Havana, Cuba. This document was revised and submitted to the Pan-American Health Organization for review by their technical committee which is still ongoing. A draft IVM toolkit for Asia is also under review.

Development of the IVM Toolkit for sub-Saharan Africa

The toolkit for IVM in SSA (Volume II of thesis) aims to provide detail on the planning and implementation of IVM in the region. It is an extension of earlier guidance and teaching material provided by the WHO. In particular, it complements a series of WHO guidance documents published in 2012; *Handbook for IVM, Monitoring and Evaluation Indicators for IVM, Guidance on policy-making for IVM*, and *Core structure for training curricula on IVM* [3, 187, 216]. The structure is largely based on that set out in the Handbook for IVM which outlined the key steps in planning and implementation of IVM as: understanding the disease situation and local determinants of disease, selection of vector control methods, requirements and resources, implementation strategy, generating an evidence base, vector surveillance and monitoring and evaluation) [3].

The toolkit is designed to help national and regional level programme managers to design and run large IVM programmes. It was written with two audiences in mind – well-resourced and funded programmes such as that of South Africa and programmes with minimal resources such as that in The Gambia. 'Top tip' boxes included throughout the text highlight the key points and minimum activities required by programmes which serve as an aid for under-resourced and time-poor programme managers (Figure 2.1).

KEY POINT

It is essential that a steering committee is set up to oversee the IVM programme. The committee should comprise members of the different disease control programmes, as well as representatives of other sectors.

Figure 2.1: Example of text box in the IVM Toolkit for sub-Saharan Africa highlighting a key point

The toolkit provides guidance on where VBD are endemic and what interventions should be implemented, systems for operational research, vector surveillance and monitoring and evaluation, and highlights useful case studies on various aspects of IVM throughout the document. Compared to other WHO documents, the toolkit recommends only vector control tools that have evidence to support their use. The vector control tools recommended are based on the findings of systematic reviews and meta-analyses, two of which are included in this thesis (Chapter 3 and 4). Since each VBD has a number of guidelines and policy documents which have been released by WHO and other partners, the toolkit aimed to reference existing documents where possible to direct readers to the

reference materials. In terms of diseases, the toolkit focuses on malaria, lymphatic filariasis, dengue, leishmaniasis, onchocerciasis, human African trypanosomiasis and schistosomiasis. To a lesser extent it also includes information on other viral diseases (Rift Valley fever, West Nile fever, chikungunya, yellow fever) and trachoma. The toolkit also encourages programmes to be vigilant for new and re-emerging diseases. The IVM toolkit for SSA focuses mainly on malaria since this is the VBD with the largest burden in the region and is generally the most well-funded. The majority of experience in vector control is on malaria and therefore there is an opportunity for other VBD programmes to learn from these examples.

Summary of toolkit for IVM in sub-Saharan Africa and its development

Section 1 outlines the importance of VBD and explains in simple terms what IVM is. This is necessary because IVM has generally been poorly understood and perceived as being overly complicated in the past. Section 2 provides a framework for planning and implementation of IVM. As described in the WHO Handbook for IVM, IVM should follow a cyclical process with multiple rounds of situational analysis, planning, design, implementation and monitoring and evaluation. This is depicted in Figure 2.2 which is the most important figure in the toolkit. It differs from the original figure in the Handbook on IVM in that it includes operational research running alongside and feeding into the programme activities. Operational research is a weak component of many vector control programmes and so it is important to emphasise its role in addressing operational problems which could lead to more effective control of VBDs.

Also included in Section 2 is an explanation of the policy, legislative and management framework required to support IVM. It describes the need for alignment of policies that relate to VBD and IVM through either policy formulation or reform, both within and outside the health sector. It describes policy instruments that should be employed to ensure that these policies become practice including formation of an IVM steering committee chaired by the Minister of Health with defined terms of reference to guide planning and implementation of IVM. The importance of securing strong political will and support at the government level is stressed. This is hugely important to sustain the IVM approach over time and without political support it will be difficult to ensure that intrasectoral, and particularly intersectoral collaboration occurs. The section also discusses the importance of conducting a Vector Control Needs Assessment (VCNA) as a first step in moving towards IVM.

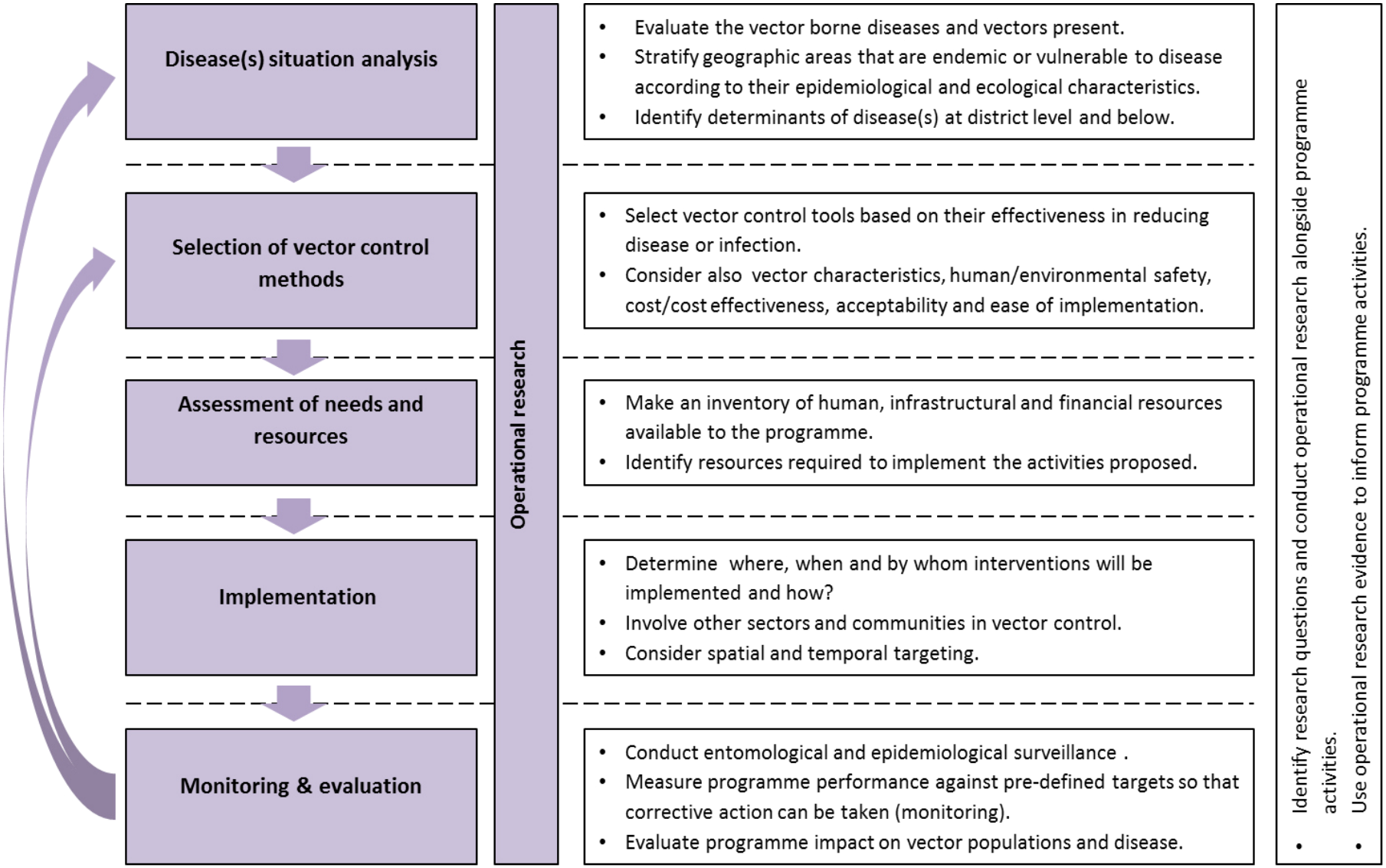

Figure 2.2: Schematic indicating steps in IVM implementation and monitoring & evaluation feedback loop
[modified from [3]]

Section 3 provides detail on conducting a disease situation analysis. In contrast to previous WHO documentation on IVM, the toolkit recommends conducting a disease situation analysis at broad (i.e. national/first administrative) level and local level (district and below) (Figure 2.3).

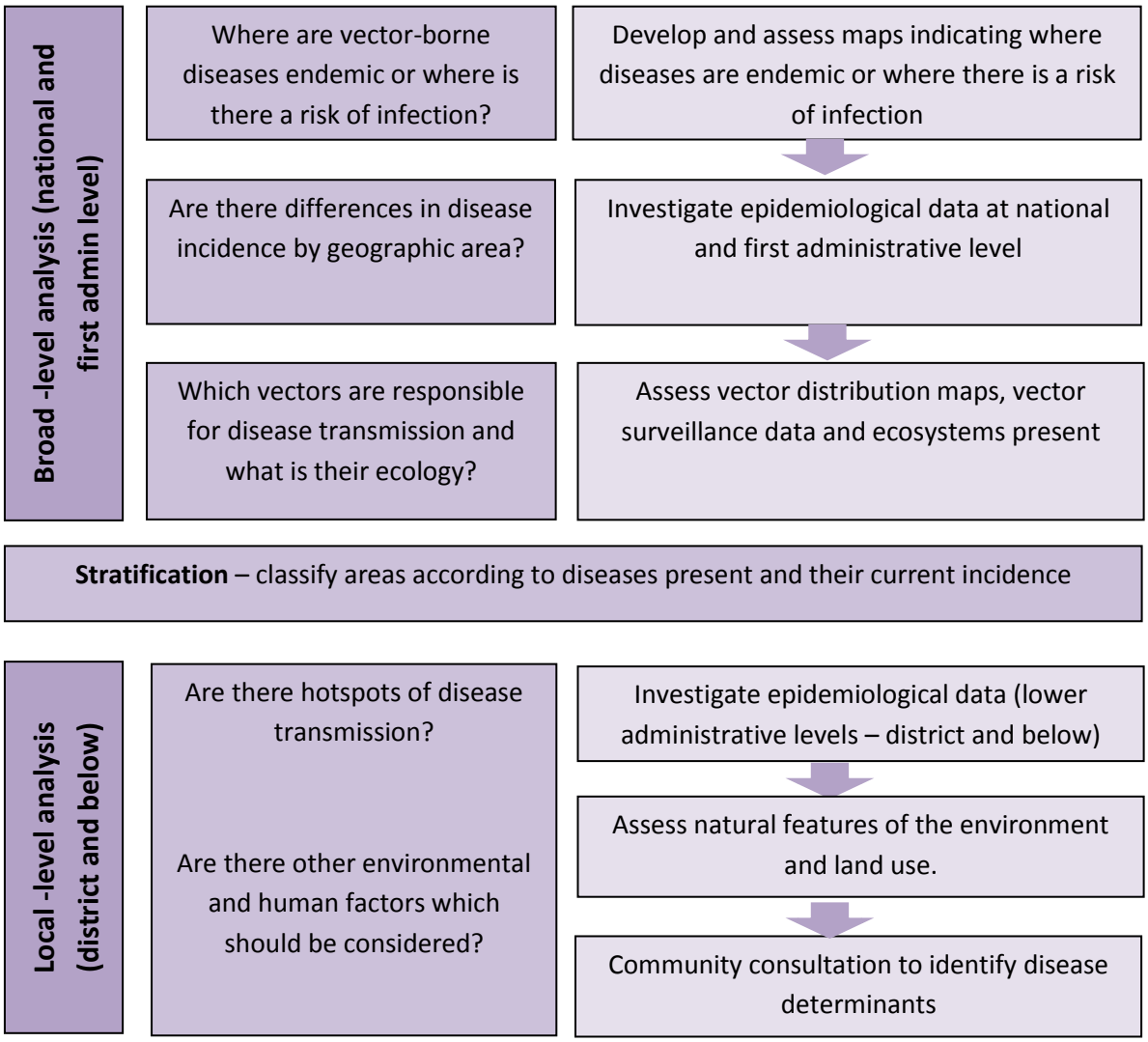

Figure 2.3: Flowchart indicating steps in conducting disease assessment for IVM

This fits well with the decentralised nature of vector control in many countries and the often focal nature of VBD transmission. Maps produced as part of the complementary workstream of the grant which illustrate risk of VBDs in SSA (accurate to first administrative level) are included, along with relevant vector population maps such as those by Sinka *et al.* [217]. This allows countries to visualise where there is a risk of VBDs in their country (particularly useful where health information systems are weak), where VBDs may overlap and may encourage additional data collection to resolve uncertainties. The toolkit revisits the often neglected ecosystem basis for assessing risk of VBDs as applied by Schapira and Boutsika (for malaria) [218] and others. This system encourages

stratification of areas into ecotypes (e.g. riceland, plantations etc) to supplement available epidemiological and entomological data in order to determine VBD risk and opportunities for control and intersectoral action.

Section 4 outlines broad considerations when selecting vector control tools for use such as cost, cost effectiveness, community acceptability and human and environmental safety, and provides detail on the efficacy of vector control tools for different diseases. The idea behind this section is to provide evidence-based information on efficacy rather than a 'shopping list' of tools which is the case in some WHO documents previously. The toolkit makes clear that vector control tools should be chosen on the basis of their efficacy primarily against epidemiological parameters (prevalence or incidence of infection/disease), rather than entomological parameters, although the latter may be useful in limited circumstances or in support of an epidemiological outcome. In this section we separated vector control tools into three categories in a 'traffic light' system: WHO recommended tools (green), tools with some evidence or evidence to recommend their use in certain settings or populations (amber) and lastly tools for which there is currently insufficient evidence to recommend their use (red). The separation of tools into these categories is based on rigorous systematic reviews where possible (and where there should be normative guidance from WHO), but otherwise is based on WHO guidance (often not supported by systematic reviews) and expert opinion. The document also provides a matrix which shows vector control tools recommended across diseases so programmes can see where there might be synergies in application of tools.

Section 5 outlines strategies for evaluating needs and resources required for IVM. Section 6 gives more detail on strategies for implementing IVM including considering **where**, **when** and by **whom** the interventions will be delivered and **how**. The section gives some guidance on targeting of interventions in time and space, rather than the blanket coverage approach of interventions which is often used but may not be the most effective or efficient use of resources. While oversight of delivery and implementation of vector control remains the remit of the health sector, the toolkit stresses that other sectors such as the private sector and the community should be involved where possible. A review of the literature and consultation with experts identified several good examples of multisectoral involvement in vector control which are included in this section, for example farmer field schools linking education on agriculture and vectors to reduce crop pests and vectors [219] and involvement of the mining company Anglo Gold Ashanti in malaria treatment and vector control in Ghana [220]. Programmes are encouraged to adapt and replicate these examples in their own settings.

The topic of section 7 is operational and implementation research which also gives guidance on pilot testing and scaling up recommended vector control interventions. Here it was necessary to develop the thinking around minimum recommendations for pilot study design so that even under-resourced vector-control programmes should be able to conduct relatively robust randomised studies. A table outlining minimum and optimal requirements (e.g. randomisation, duration of pre-intervention data, replication of study units etc) for a pilot study is given.

Section 8 discusses vector surveillance. A useful framework for entomological surveillance first described in a WHO Manual on Practical Entomology in Malaria from 1975 [221] is reproduced in this section. Expert opinion was used to draw up a list of recommended entomological indicators and vector sampling tools by disease. Guidance is also given on procedures for identifying sentinel sites for entomological surveillance. Much of the information available on selection of sentinel sites is buried in historical malaria literature [221]. The toolkit brings this information together and shows how the same criteria for selection can be applied across diseases which could lead to synergies if sentinel sites are co-located.

Section 9 discusses monitoring and evaluation which is an often neglected aspect of vector control. Tracking the progress of IVM against set indicators is crucial to generate feedback on the programme which can be used to influence future planning and implementation of IVM. This section builds on information provided in the 2012 WHO document on Monitoring and Evaluation Indicators for IVM [222] and gives examples of a logical framework for a vector control programme, data sources for the different IVM indicators, data management and data flows.

Critical analysis of the IVM Toolkit for sub-Saharan Africa

Since being involved in development of the toolkit, the author has reflected on the process and the end-product and identified several limitations.

Firstly, the toolkit was produced following a traditional research process (termed by Gibbons *et al* as mode 1 research) which is researcher driven, subject to peer review and based on a positivist epistemology [223]. Although the toolkit was produced with the involvement of several current or ex-programme managers from Nigeria (project writing workshop) and Cameroon (WHO expert meeting), the toolkit was not piloted before being made available by WHO and indeed a more participatory approach could have been adopted. Co-production is the collaborative generation of knowledge in the context of its application by academics in partnership with others, whereby researchers and practitioners with distinct values, norms and tacit knowledge come together to solve a particular problem [223]. This has been termed by Gibbons *et al* as mode 2 research or more broadly as 'integrated knowledge translation' [223, 224]. There is growing evidence to suggest

that knowledge that is co-produced has a better chance of being implemented [225-227], although this approach is not widely practised, particularly in global health. Co-production is thought to increase uptake of findings through a variety of mechanisms including improved mutual understanding and communication between researchers and practitioners, development of a shared vision, capacity development and increased relevance of the outputs [228, 229]. If the toolkit had been produced using a co-design approach with vector control programmes, for example following the theoretical framework outlined by Kitson *et al* [230] this may have enhanced the relevance and ownership of the IVM toolkit, and perhaps generated better commitment to its uptake.

Secondly, the IVM tookit is a large document (221 pages) which was unavoidable given the breadth of the subject area and need to cover all VBDs pertinent to SSA. The toolkit is available in printed and electronic format via the WHO website and there are no plans or funding as yet for updating of the material. The toolkit is a generic document which provides guidance on IVM but it cannot be taken as a standalone how-to guide for IVM in countries. The toolkit instead provides a framework for IVM, and high-level guidance and the actual steps on the ground will need be elaborated by countries through formulation of their own IVM policies. This process is typically facilitated by the regional and country WHO offices who support countries to develop their policies and conduct training courses. In this regard, the WHO Eastern Mediterranean Regional Office is particularly active and it is hoped that the toolkit will aid the development of IVM Strategic Plans and training materials in these countries. The document is aimed at programme managers at national and regional level but generally does not provide sufficient detail for district level managers.

Another limitation is in development of the maps showing risk of VBDs. Some of these maps, such as those for the different types of malaria, are based on a large amount of information on sub-national disease endemicity and therefore are likely to be very reliable. However, the predicted extents of maps for other VBD such as those for dengue and leishmaniasis which are based on fewer occurrence data points are less certain and possibly overestimate the geographic area at risk of infection.

Unfortunately, Section 4 which details recommended vector control tools is based in part on a narrative review of efficacy studies and other documents rather than systematic reviews. This is because 18 months (plus no-cost extension) project lifespan was insufficient time to complete systematic reviews of all vector control tools against all diseases, as was the original intention. Given that a typical traditional systematic review of a single intervention against a single disease takes between 6 and 12 months [231], the timelines were unfortunately underestimated in the grant proposal.

Next steps for the IVM toolkit for SSA

There are several recommendations in order to translate the material in the IVM toolkit into policy and practice. Firstly, WHO regional and country offices should work with countries to develop or update country policies, for example the IVM Strategic Plan based on the material in the regional IVM toolkit. Secondly, training materials should be updated at global and/or regional level according to the material in the toolkit. Thirdly, ideally we would have funding to translate the toolkit into a web-based system to allow easy navigation of the material, linking to existing documents and updating of the risk maps. Visualisation of the risk maps would be improved by allowing users to zoom in, and manipulate the maps to show areas of disease co-endemicity. Functionality could be added to allow, for example sharing of case studies of IVM or lessons learnt in intersectoral collaboration. Lastly, translation of the IVM SSA toolkit into French and Portuguese would aid its uptake by Francophone and Lusophone countries.

The issue of capacity and capability to implement the IVM toolkit is an important one. As mentioned in Chapter 1, routine vector control already faces a problem of lack of financial, human and infrastructural resources. The current resource situation and future requirements should be elucidated through a VCNA (mandated as part of IVM) which will inform development of a fully-costed Vector Control Strategic Plan. The knowledge-intensive and adaptive nature of IVM means that some resource requirements will be different under IVM compared to routine vector control. For example, IVM places a large emphasis on surveillance, and monitoring and evaluation. Programmes need capable field staff trained in entomological surveillance, supported by necessary infrastructure including entomological laboratories and insectaries. Capacity needs to be strengthened in data management and analysis, for example through adoption of a database which links entomological, epidemiological and intervention data. Programmes could streamline surveillance activities by investing in new technologies such as geographic information systems and information communication technology. It is unclear whether IVM would require more financial resources than routine vector control and this has not been systematically evaluated. However, it is expected that there will be overall resource savings through targeted and adaptive application of vector control and through use of resources from outside the health sector. Nevertheless, vector control certainly requires greater investment than it receives currently.

Chapter 3: The efficacy of insecticide-treated nets, curtains and screening on vector-borne diseases, excluding malaria: a systematic review and meta-analysis.

Adapted from: Wilson AL, Dhiman R, Kitron U, Scott TW, van den Berg H, Lindsay SW. Benefit of insecticide-treated nets, curtains and screening on vector-borne diseases, excluding malaria: a systematic review and meta-analysis. PLoS Neglected Tropical Diseases. 2014;8:e3228.

Abstract

Insecticide-treated nets (ITNs) are one of the main interventions used for malaria control. However, these nets may also be effective against other vector-borne diseases (VBDs). We conducted a systematic review and meta-analysis to estimate the efficacy of ITNs, insecticide-treated curtains (ITCs) and insecticide-treated house screening (ITS) against Chagas disease, cutaneous and visceral leishmaniasis, dengue, human African trypanosomiasis, Japanese encephalitis, lymphatic filariasis and onchocerciasis.

MEDLINE, EMBASE, LILACS and Tropical Disease Bulletin databases were searched using intervention, vector- and disease-specific search terms. Cluster or individually randomised controlled trials, non-randomised trials with pre- and post-intervention data and rotational design studies were included. Analysis assessed the efficacy of ITNs, ITCs or ITS versus no intervention. Meta-analysis of clinical data was performed and percentage reduction in vector density calculated.

21 studies were identified which met the inclusion criteria. Meta-analysis of clinical data could only be performed for four cutaneous leishmaniasis studies which together showed a protective efficacy of ITNs of 77% (95%CI: 39% - 91%). Studies of ITC and ITS against cutaneous leishmaniasis also reported significant reductions in disease incidence. Single studies reported a high protective efficacy of ITS against dengue and ITNs against Japanese encephalitis. No studies of Chagas disease, human African trypanosomiasis or onchocerciasis were identified.

There are likely to be considerable collateral benefits of ITN roll out on cutaneous leishmaniasis where this disease is co-endemic with malaria. Due to the low number of studies identified, issues with reporting of entomological outcomes, and few studies reporting clinical outcomes, it is difficult to make strong conclusions on the effect of ITNs, ITCs or ITS on other VBDs and therefore further studies be conducted. Nonetheless, it is clear that insecticide-treated materials such as ITNs have the potential to reduce pathogen transmission and morbidity from VBDs where vectors enter houses.

Introduction

Integrated Vector Management (IVM) aims to make vector control more effective, cost effective and sustainable [3]. IVM can involve the use of multiple vector control tools against a single disease or alternatively a single tool against multiple diseases. The latter occurs when vector control interventions are active against more than one disease and vector-borne diseases (VBDs) overlap in their distribution. In order to make use of shared interventions across diseases, it is necessary to know whether interventions are effective against more than one disease. This was the rationale for conducting this review. We considered insecticide-treated bednets (ITNs) since this intervention has been rolled out already on a large scale for malaria vector control.

ITNs are highly effective against malaria, reducing all-cause child mortality by 17% and uncomplicated *Plasmodium falciparum* episodes in areas of stable transmission by 50%, compared to no nets [4]. ITNs form the mainstay of malaria vector control in many malaria endemic areas, particularly in sub-Saharan Africa (SSA) [20]. The proportion of the population at-risk in SSA sleeping under an ITN was 53% in 2015, increasing from 5% in 2005 and 30% in 2010 [20], although more work is needed to achieve universal coverage [13]. Outside of SSA, ITNs are used for malaria control in a number of countries including those in Asia (e.g. India, Indonesia, Myanmar), eastern Mediterranean (e.g. Afghanistan, Iran), western Pacific (e.g. Papua New Guinea) and the Americas (e.g. Haiti) [20]. More recently conventional ITNs have been replaced by long-lasting insecticidal nets (LLINs) that maintain effective levels of insecticide for at least three years meaning that re-treatment with insecticide is not necessary. Since 2007 the WHO recommends only use of LLINs and not conventional ITNs [106]. For the purpose of this review we refer to ITNs without distinguishing between conventional ITNs or LLINs.

ITNs are likely to be effective against multiple vectors and VBDs since a substantial proportion of transmission occurs indoors, but this has not been systematically assessed. As such there may be unknown collateral benefits of ITN roll-out on VBDs in addition to malaria. ITNs, as well as insecticide-treated curtains (ITC) and insecticide-treated screening (ITS) are likely to function in the same way. Disease vectors are attracted to host odours emanating either from people sleeping under ITNs or from people within houses in the case of ITCs and ITS. Vectors then coming into contact with these materials are deterred or killed and thus it can be said that the ITN and house are acting as 'baited traps'. ITC and ITS may also be working to some extent to prevent vectors from entering houses (household level protection) rather than personal protection in the case of ITNs.

We conducted a systematic review to assess the efficacy of ITNs, ITCs or ITS against eight VBDs prioritised by the WHO in the Handbook for IVM [3]: Chagas disease, cutaneous and visceral

leishmaniasis, dengue, human African trypanosomiasis, Japanese encephalitis, lymphatic filariasis and onchocerciasis. In this study we assessed the effect of ITNs, ITCs and ITS on clinical and entomological outcomes.

Methods

Literature search

The review was carried out according to a protocol and analytical plan that was prepared in advance. A systematic search of published literature was performed in April 2013 and repeated in June 2014 using intervention-specific search terms (for example ITN / LLIN / bednet / curtain / pyrethrins), as well as vector and disease specific search terms. Medical Subject Heading (MeSH) and Health Sciences Descriptor (DeCS) terms were used where appropriate. More detail on the search terms used is given in Appendix 3.1. MEDLINE (1950 -), EMBASE (1980 -) and LILACS (1982 -) databases were searched and no language restrictions were applied. In April 2013 we also searched the Tropical Disease Bulletin (1912 -) database. In addition, we reviewed the reference lists of key review articles and consulted with experts to identify further studies.

Anne Wilson (AW) screened the search results for potentially relevant studies and full text documents were obtained for those publications deemed to be relevant. Foreign language studies were evaluated by a native speaker in consultation with AW. The articles were scrutinised to ensure that multiple publications from the same study were included only once.

Study inclusion and exclusion criteria

Studies were assessed against inclusion and exclusion criteria by AW and Steve Lindsay (SL) independently. Studies were included if they compared the efficacy of ITNs, ITCs or ITS versus no intervention (control group) in disease endemic areas. Excluded studies and reasons for their exclusion are detailed in Appendix 3.2. We sought to compare the efficacy of ITNs, ITCs and ITS versus no intervention, rather than assess the efficacy of untreated bednets, curtains or screening or compare these untreated materials to ITNs, ITCs or ITS. We took this decision because bednets being rolled out for malaria control are insecticide-treated. Studies using hand-impregnated nets or factory manufactured LLINs were included. Throughout this chapter, the term 'ITNs' refers to both regular ITNs and LLINs. Studies assessed the effect of the intervention on either i) clinical outcomes (incidence or prevalence of disease or infection – whether this was confirmed by the patient, clinical diagnosis or diagnostically differed by study) and / or ii) entomological outcomes (including human biting rate, adult vector density and *Stegomyia* indices, pupal/demographic indices, oviposition rates or ovitrap positivity for dengue vectors). Adult vector density was measured using a number of techniques including US Centers for Disease Control and Prevention (CDC) light traps, sticky traps,

pyrethrum spray catches and resting catches using aspirators. Larval indices extracted for dengue were house index (percentage of houses infested with larvae and/or pupae), container index (percentage of water containers infested with active immatures) and Breteau index (number of positive containers per 100 houses). We also extracted data on pupae per person (number of pupae collected over the total number of inhabitants of the households inspected), oviposition rates (mean number of *Aedes aegypti* eggs per trap) and ovitrap positivity (percentage of traps positive for *Aedes* eggs).

In terms of study designs, we included i) randomised controlled trials (cluster level or individual randomisation), ii) non-randomised trials with pre- and post-intervention data (for both control and intervention areas) and iii) rotational studies (provided there was baseline data or allocation was random or interventions/ collectors were rotated appropriately e.g. each house received each intervention). A rotational design is when an intervention(s) is moved between sampling sites for set time periods or, in the case of human landing catches, collectors are rotated between interventions.

Studies performed under laboratory or semi-field conditions (for example, experimental huts) were excluded. We also excluded non-randomised trials without baseline data (for both control and intervention areas), non-controlled programme evaluations and observational studies in which clusters or individuals were not purposely allocated to intervention and control groups.

Data extraction and analysis

Data were extracted from the publications into a pre-designed data extraction form in Microsoft Word (Appendix 3.3), along with data tables and graphs. Graphs were digitised using Engauge Digitizer software (version 5.1, http://digitizer.sourceforge.net/). Preliminary analysis of data tables was conducted in Microsoft Excel. Analysis assessed the efficacy of ITNs, ITCs or ITS compared to no intervention. We used un-adjusted measures (clinical and entomological) throughout. This was for consistency because different studies adjust for different covariates. However, adjusted values, where available are reported for comparison.

Clinical outcomes were reported as either risks or rates of disease or infection in the published papers. Meta-analysis of clinical data (unadjusted risk of disease or infection) was performed in Stata 13 using the *metan* command (StataCorp, Texas, USA). Pre-intervention risk ratios were plotted on forest plots alongside post-intervention risk ratios to show comparability of groups at baseline. Statistical heterogeneity was assessed using a χ^2 test. Due to the small number of studies in each comparison, we deemed there to be heterogeneity if the χ^2 test p value was less than 0.1 [232]. If heterogeneity was found, a summary effect measure was calculated using random effect

meta-analysis rather than fixed effect meta-analysis. Protective efficacy (PE) was calculated as PE = 1− (risk ratio of clinical disease or infection during the intervention period) × 100%. PE (or relative risk reduction) can be interpreted as the percentage reduction in risk of clinical disease or infection associated with the intervention. Standard formulas were used to calculate 95% confidence intervals for risk or rate ratios [233].

Entomological outcomes are reported as means with 95% confidence intervals (CI), where these are reported in the published paper or could be calculated. If there were zero events then we estimated the upper 95% CI as 100 x (3.7/N) where N is the sample size [234]. For entomological outcomes, where data were available for multiple intervention and control sites, we took the average values of the outcome measure, applying equal weight to all sites. A similar approach was taken if data were available for multiple timepoints within a year or transmission season, either pre- or post-intervention. We could not use meta-analysis to analyse the entomological data due to inadequate reporting in the published manuscripts. In almost all the studies the standard error for mean vector density was not reported and could not be calculated from the data presented in the papers. For studies with baseline/post intervention data for control and intervention sites we calculated the percentage reduction in vector density using a difference in differences approach. We estimated the effect of the intervention (J) using the formula J=(q1/q0)/(p1/p0), where q1 and q0 are, respectively, the entomological indicators (mean density, or biting rate) observed in the intervention and control areas post-intervention respectively and p1 and p0 are the corresponding baseline estimates of these entomological indicators [6]. We calculated the percentage reduction in entomological indicators as 100 x (1 - J). For studies in which only post intervention data were available we calculated the percent reduction in the outcome in the treatment group compared to the control group using the formula 100 x (1-(q1/q0) [6]. We were not able to calculate confidence intervals around percentage reductions due to heterogeneity in study designs; e.g. different follow up periods pre- and post-intervention and the way in which the data was reported e.g. the total vector count was reported rather than individual observations.

We followed recommendations made by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group where possible [235, 236] (Appendix 3.4).

Risk of bias and study quality assessment

AW and SL assessed independently the risk of bias in the included studies using a risk of bias assessment form. This form was developed for the purposes of this review to assess entomological studies and was adapted from the Effective Practice and Organisation of Care (EPOC) risk of bias assessment form [237] (Appendix 3.5). A judgement of high, low or unclear risk of bias was given for a number of parameters. An overall bias assessment (high / medium / low) was made based on the modal bias risk.

We developed a tool for assessing study quality which primarily concerns the study design and downgrades the score given to the study depending on whether sample size calculations were performed (overall and for entomological sampling), the length of the follow up period and risk of bias (Appendix 3.6). This was loosely based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system of rating quality of evidence [238], but adapted for entomological studies. For the purposes of the quality assessment, we deemed a trial to be a randomised controlled trial if the published paper stated that groups were randomised to intervention or control, even if the process of sequence generation was not described in the paper.

Results

Summary of studies identified and risk of bias and quality assessment

The initial systematic literature search identified 19,113 unique records (Figure 3.1). 18,617 records were excluded based on review of the title and abstract. 496 full text records were reviewed and of these 310 studies met the inclusion / exclusion criteria across all types of vector control intervention. The update of the search in June 2014 identified 1,991 unique records, of which 125 full-text records were reviewed and 2 studies met the inclusion / exclusion criteria. In total, 21 studies assessed the efficacy of ITNs, ITCs or ITS versus no intervention and the split of these by disease was nine cutaneous leishmaniasis, five dengue, one Japanese encephalitis, three lymphatic filariasis and three visceral leishmaniasis. Summary tables of the studies identified are given in Appendix 3.7. Only nine of the 21 studies included reported the level of insecticide resistance in the study area or conducted an insecticide bioassay. Of the 21 studies identified, fifteen were deemed to be at low risk of bias, three at medium risk and three at high risk of bias [239] (Appendix 3.8). Twelve studies were deemed to be of high quality, three medium quality and six low quality (Appendix 3.9). No studies that met the inclusion and exclusion criteria were found assessing the efficacy of ITNs, ITCs or ITS against Chagas disease, human African trypanosomiasis or onchocerciasis.

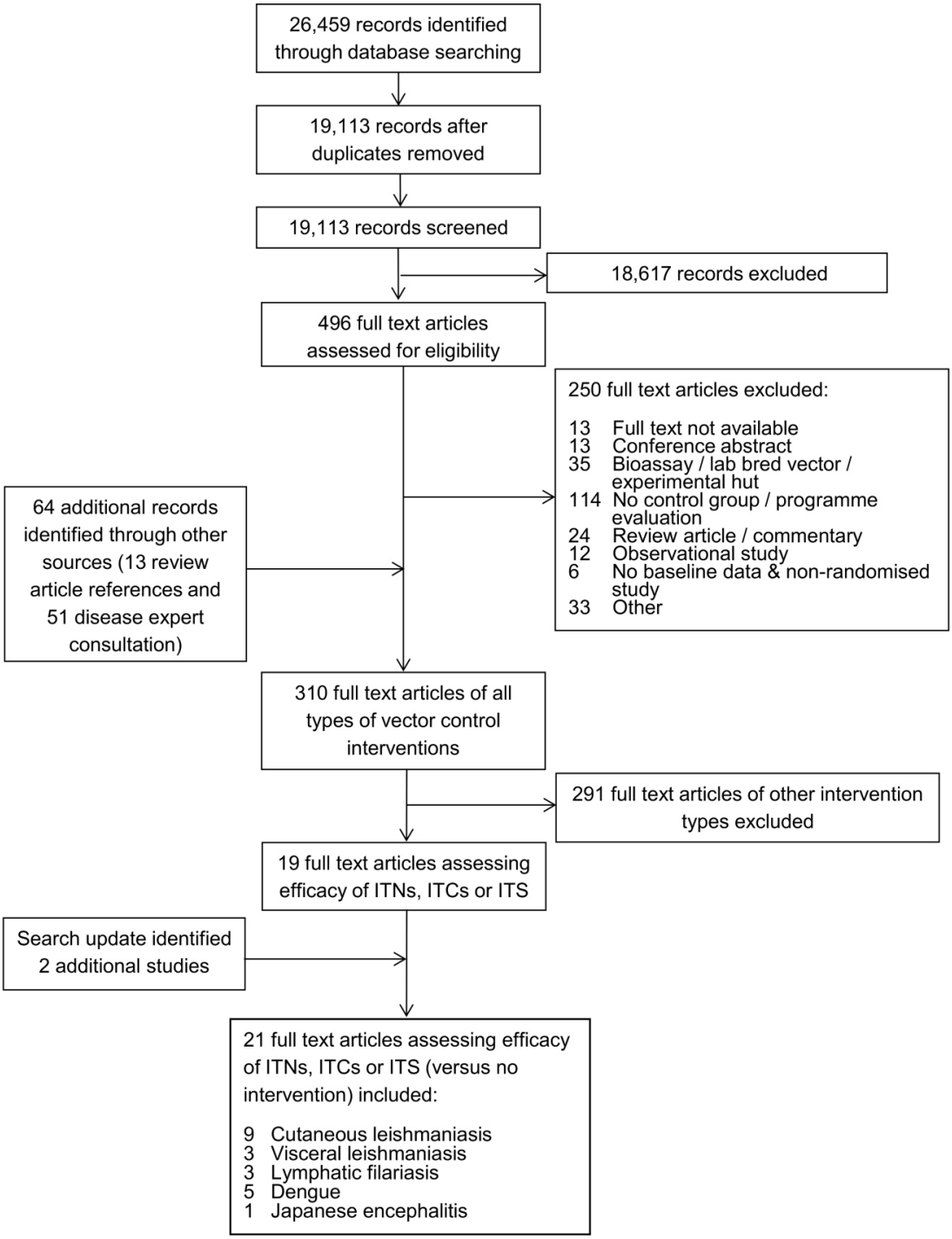

Figure 3.1: Flowchart of study inclusion for studies evaluating the efficacy of insecticide-treated nets, curtains and screening against vector-borne diseases other than malaria
(adapted from [235])
ITN = insecticide-treated net, ITC = insecticide-treated curtain, ITS = insecticide-treated screening

Efficacy of ITNs and ITCs against cutaneous leishmaniasis

A total of six studies assessing the efficacy of ITNs against cutaneous leishmaniasis were identified [239-244]. Of these three reported clinical data only, one reported entomological data only, and two reported both clinical and entomological data. Of the studies reporting clinical data, this was

generally either a symptom questionnaire administered to participants or examination of lesions. Two studies utilised either a leishmanin skin test [244] or microscopic examination of skin scrapings from an active lesion [245].

Random effects meta-analysis of the efficacy of ITNs was conducted on data from four studies conducted in Iran (2 studies), Afghanistan and Colombia [241-244] (Figure 3.2, Table 3.1). Pre-intervention incidence of cutaneous leishmaniasis was comparable in intervention and control groups in the three studies that reported this data, with 95% confidence intervals for the risk ratio crossing the null value. Random effect meta-analysis indicated a PE of ITNs against cutaneous leishmaniasis of 77% (95% CI: 39% - 91%, P=0.003). Clinical data from one study in Turkey [239] was not suitable for meta-analysis because this study did not report numbers of cases or population at risk. Alten *et al.* reported a significant reduction in incidence of cutaneous leishmaniasis in ITN clusters, while incidence in control areas either stayed the same or increased. However, this study was deemed to be at high risk of bias and low quality.

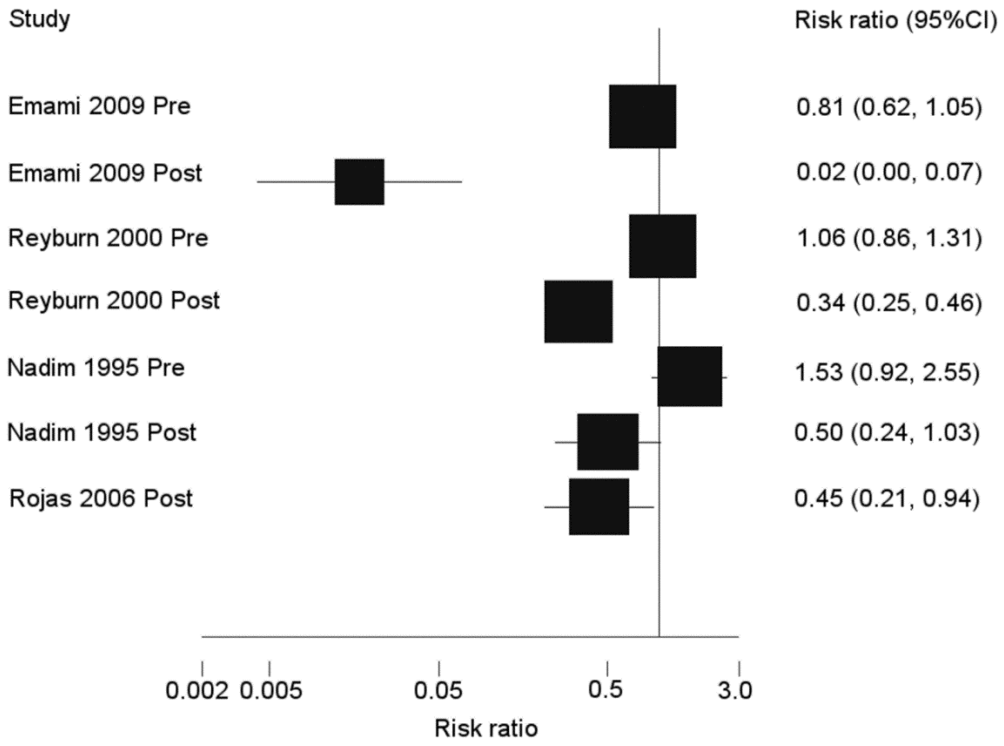

Figure 3.2: Forest plot (random effects meta-analysis) indicating efficacy of ITNs against cutaneous leishmaniasis
The forest plot displays post-intervention risk ratios and pre-intervention risk ratios separately to show comparability of groups at baseline.

Table 3.1: Effect of insecticide-treated nets, insecticide-treated curtains and insecticide-treated screening against vector-borne diseases

Disease	Intervention	Study	Unadjusted PE (95% CI, p value)	Adjusted PE (95% CI, p value)	Covariates adjusted for
Cutaneous leishmaniasis	ITN	Emami 2009 [241]	98% (93%, 100%, p<0.001)	NR	NR
		Nadim 1995 [242]	50% (-3%, 76%, p=0.06)	NR	NR
		Reyburn 2000 [243]	66% (54%, 75%, p<0.001)	69% (45%, 82%, p<0.001)	Intra-household clustering
		Rojas 2006 [244]	55% (6%, 79%, p=0.03)	55% (-14%, 82%)	Age, residence located on the periphery, roof of thatch, distance to the forest <50m, community participation score and prevalence of infection in children <5 years old
		Alten 2003 [239]	37%	NR	NR
	ITC	Kroeger 2002 [246]	93% (-16%, 100%, p=0.06)	NR	NR
	ITC and ITS	Noazin 2013* [245]	16% (2%, 28%, p=0.03)	NR	NR
Visceral leishmaniasis	ITN	Picado 2010 [247]	Cases: 4% (-81%, 48%, p=0.9) Infection: 0.3% (-15%, 14%, p=0.97)	Cases: -15% (-116%, 39%, p=0.64) Infection: 11% (-64%, 52%, p=0.68)	Clustering, age group, sex, times sprayed, and socioeconomic status.
Dengue	ITS	Nguyen 1996 [248] Igarashi 1997 [249]	81% (53%, 92%, p<0.001)	NR	NR
Japanese encephalitis	ITN	Dutta 2011 [250]	67% (44%, 80%, p<0.001)	NR	NR

* study reported rates only, ITN = insecticide-treated nets, ITC = insecticide-treated curtains, ITS = insecticide-treated screening, PE = protective efficacy, CI = confidence interval, NR = not reported

Table 3.2: Effect of insecticide-treated nets and insecticide-treated curtains on density of sandfly vectors of cutaneous leishmaniasis

Study	Vector species	Surveillance method	Measure	Control (Mean and 95% CI)		Intervention (Mean and 95% CI)		% reduction in vector density	Adjusted % reduction (95% CI, p value)	Covariates adjusted for
				Pre	Post	Pre	Post			
Insecticide-treated nets										
Alexander 1995 [240]	*Lutzomyia lichyi, L. youngi, L. columbiana*	HLC	No. of sandflies caught per man hour (biting inside net)		3.29		0.14	**96%**	NR	NR
Alten 2003 [239]	*Phlebotomus papatasi, P. sergenti*	CDC LT and sticky trap (exophilic and endophilic species, respectively)	Mean no of female *P. papatasi* and *P. sergenti* / month		88.8		132.2	**-49%**	NR	NR
Emami 2009 [241]	*P. papatasi, P. sergenti*		Mean no of female *P. sergenti* captured / month	615	214	385	140	**-5%**	NR	NR
Insecticide-treated curtains										
Alexander 1995 [240]	*L. lichyi, L. youngi, L. columbiana*	HLC	No. of sandflies caught per man hour (biting)		3.29		1.5	**54%**	NR	NR
Kroeger 2002 [246]	*L. youngi, L. ovallesi*	CDC LT	Mean no of sandflies per trap	19.5	20.0	15.1	2.1	**87%**	NR	NR
Majori 1989 [251]	*P. duboscqi*	PSC	Density of sandflies per single PSC	47	71	40	1	**98%**	NR	NR

where CDC LT = US Centers for Disease Control and Prevention light traps, HLC = human landing catches, PSC = pyrethrum spray catches and NR = not reported.

Table 3.3: Effect of insecticide-treated nets on density of sandfly vectors of visceral leishmaniasis

Study	Vector species	Surveillance method	Measure	Control (Mean and 95% CI)		Intervention (Mean and 95% CI)		% reduction in vector density	Adjusted % reduction (95% CI, p value)	Covariates adjusted for
				Pre	Post	Pre	Post			
Insecticide-treated nets										
Elnaiem 1999 [252]	*Phlebotomus orientalis*	HLC	Mean number of *P. orientalis* females landing to bite per volunteer / per night		32 (15.7, 48.3)		0 (0, 31)	**100%**	NR	NR
Joshi 2009 [253]	*P. argentipes, P. papatasi*	CDC LT	Number of sandflies per house (trap) per night (unadjusted mean)	9.41 (6.97, 12.71)	12.15 (8.68, 17)	9.92 (7.28, 13.53)	8.32 (5.56, 12.45)	**35%***	Model coefficient reported only (-0.42, p=0.04)	Clustering (country /cluster), type of wall and dwelling
Picado 2010 [254]	*P. argentipes*	CDC LT	Mean number of female *P. argentipes* per LT night	2.62	1.57	2.18	0.55	**58%**	11.6% (95%CI 2.10– 20.2%), p = 0.016	Clustering (country/ cluster), baseline mean density, IRS carried out by ministry in some clusters

where CDC LT = US Centers for Disease Control light traps, HLC = human landing catches and NR = not reported.

* paper reports unadjusted PE as 43.7% (reduction in count = -4.34, 95% CI: -8.57, -0.10 and model coefficient: -0.43, p=0.04)

Table 3.4: Effect of insecticide-treated nets and insecticide-treated curtains on lymphatic filariasis vectors

Study	Vector species	Surveillance method	Measure	Control (Mean and 95% CI)		Intervention (Mean and 95% CI)		% reduction in vector density	Adjusted % reduction (95% CI, p value)	Covariates adjusted for
				Pre	Post	Pre	Post			
Insecticide-treated nets										
Bøgh 1998 [255]	*Anopheles gambiae s.l.*	PSC	Geometric mean no. of indoor resting female mosquitoes per house	29.7	12.3	17	0.1	**99%**	NR	NR
	An. funestus			20.4	33.4	19.7	0.7	**98%**	NR	NR
	Culex quinquefasciatus			14.6	5.0	7.7	2.2	**17%**	NR	NR
Charlwood 1987 [256]	*An. punctulatus*	Aspirator	No. of indoor resting *An. punctulatus* females	-	67.7	-	2	**97%**	NR	NR
Insecticide-treated curtains										
Poopathi 1995 [257]	*Cx. quinquefasciatus*	HLC	Average man biting (landing) density per man hour	133.5	62.8	91.5	7.5	**83%**	NR	NR
		Aspirator	Average indoor resting density per man hour	55.0	55.9	42.5	9.0	**79%**	NR	NR

where HLC = human landing catches and PSC = pyrethrum spray catches.

Studies assessing the efficacy of ITNs reported mixed results in terms of effect on sandfly density ranging from a relative *increase* of 49% to a relative reduction of 96% (Table 3.2). Although Emami *et al.* reported a highly significant PE against cutaneous leishmaniasis in Iran, no effect on the mean number of *Phlebotomus sergenti* captured per month was detected in this study [241]. Similarly, Alten *et al.* reported a beneficial effect of ITNs on clinical disease in Turkey and a percentage increase in vector density relative to the control group was documented [239].

Three studies conducted in Colombia, Venezuela and Burkina Faso assessed the efficacy of ITCs against cutaneous leishmaniasis [240, 246, 251]. Two studies reported entomological data while one reported both clinical and entomological data. Kroeger *et al.* demonstrated a high PE against cutaneous leishmaniasis of 93% (95% CI: -16% - 100%, p=0.06) in Venezuela (Table 3.1) [246]. Studies that measured the entomological effect of ITCs demonstrated a high percentage reduction in vector density of 54%, 87% and 98% (Table 3.2). However, the 98% reduction was observed in a study that was deemed to be of low quality due to the study design employed (non-randomised pre-post design), few sampling sites for entomological data and short period of follow up.

A study which assessed the efficacy of ITCs and ITS against cutaneous leishmaniasis in Iran reported a PE of 16% (95% CI: 2% - 28%, p=0.03) [245]. This study was deemed to be of low quality due to the study design (non-randomised pre-post design) and high risk of bias.

Efficacy of ITNs against visceral leishmaniasis

Three studies assessing the efficacy of ITNs on visceral leishmaniasis were identified [247, 252-254]. Two studies reported only entomological data and one reported both clinical and entomological data. The Picado *et al.* study [247] did not show a significant effect on incident *Leishmania donovani* infections (PE: 0.3%, 95%CI: -15% - 14%, p=0.97) or incident cases of visceral leishmaniasis (PE: 4%, 95%CI: -81% - 48%, p=0.9) in India and Nepal (Table 3.1). The same study, however, did appear to show an effect on vector density with a relative reduction in the mean number of *P. argentipes* females per light trap night of 57% [254] (Table 3.3). Two studies conducted in Sudan [252] and Bangladesh, India and Nepal [253] demonstrated a 100% and 35% (95% CI: -56% to 75%) reduction in vector density, respectively (Table 3.3).

No studies were identified which assessed the efficacy of ITCs or ITS against visceral leishmaniasis.

Efficacy of ITNs and ITCs against lymphatic filariasis

Two studies assessing the efficacy of ITNs against lymphatic filariasis were identified, both of which collected entomological data only [255, 256]. ITNs generally were associated with a high level of protection against *Anopheles* species, with approximately a 98% reduction in vector density in the

two studies conducted in Kenya and Papua New Guinea (Table 3.4). Bøgh *et al.* reported a lower percentage reduction in *Culex quinquefasciatus* density of 16% [255].

One study conducted in India assessing the efficacy of ITCs hung in eaves and doorways against lymphatic filariasis vectors was identified [257]. Poopathi *et al.* detected an 82% reduction in man biting density and a 79% reduction in indoor resting density of *Cx. quinquefasciatus* [257] (Table 3.4). However, this study was deemed to be of low quality mainly due to the study design employed (non-randomised pre-post design), few sampling sites for entomological data and short period of follow up.

Efficacy of ITNs, ITCs and ITS against dengue

One study conducted in Haiti assessed the efficacy of ITNs against dengue [258]. Based on the five month post-intervention survey this study showed that ITN use was associated with a 36% reduction in pupae per person and 77% reduction in indoor ovitrap positivity. However, the study reported that ITNs were associated with a 56% increase in house index, 143% increase in container index, 60% increase in Breteau index and 20% increase in outdoor ovitrap positivity. The bioassay results on new nets from this study site indicated only 30% mortality of *Ae. aegypti* suggesting that insecticide resistance may have been a problem.

Three studies were identified that assessed the efficacy of ITCs against dengue vectors [259-261]. Kroeger *et al.* demonstrated in Mexico a beneficial effect of ITCs on house index (25% reduction) and pupae per person (39% reduction), but reported a relative *increase* in Breteau index of 10% based on the 12 month follow up survey [259]. The authors, however, reported a community-level effect of the ITCs which meant that benefits in terms of reductions in mosquito populations spilt over into control areas. They postulate that this is why there is no significant difference between intervention and control arms. Breteau and house indices from an external control area closely follow seasonal rainfall patterns and do not show similar reductions as in the study intervention and control areas. In Thailand Lenhart *et al.* did not detect a beneficial effect of ITCs on house index, container index, Breteau index or pupae per person, with relative *increases* of 15%, 20%, 3% and 37%, respectively at the nine-month time point [260]. ITCs did, however, show a beneficial effect on indoor and outdoor oviposition rates with reductions of 44% and 49% in mean numbers of eggs per trap, respectively at the six month time point, although no significant difference between control and ITC arms was reported at three or nine months. Another study in Thailand where houses generally had a more closed design reported a 56% reduction in house index, 67% reduction in Breteau index and 63% reduction in pupae per person index six months after the start of the intervention [261]. At the 6-month follow up survey 71% of households had at least one ITC. However, at the 18-month follow

up survey when ITC coverage had fallen to only 33% a much lower effect on entomological parameters was observed (26% reduction in house index, 8% reduction in Breteau index and 111% increase in pupae per person index).

A study of ITS reported a beneficial effect on both house index and density index (adult *Ae. aegypti*) in Vietnam. In the intervention arm both house and density index were reduced to zero one month after installation of the screening and remained at zero for the duration of the epidemic season (eight months post intervention), compared to the control arm in which seasonal peaks in both indices were observed [248, 249]. The same study also reported a PE of ITS against immunoglobulin M seropositivity of 80% (95% CI: 53 – 92%, p<0.001) compared to the control group (Table 3.1). This study used a non-randomised pre-post design and was deemed to be of low quality.

Efficacy of ITNs against Japanese encephalitis

A single study by Dutta *et al.* assessed the efficacy of ITNs against Japanese encephalitis vectors and seroconversion in India [250]. This study was deemed to be of low quality due to the study design employed (non-randomised pre-post design) and low number of sampling sites for entomological data. No effect of ITNs on mean density of adults of the *Cx. vishnui* group was observed (reduction of -3.5%). The risk of seroconversion against Japanese encephalitis virus was comparable across groups at baseline, but the risk was significantly lower in the ITN group compared to the control during the two year post intervention period (PE: 67%, 95%CI: 44 – 80%, p<0.001) (Table 3.1).

Discussion

This review shows the potential for ITNs, ITCs and ITS to reduce VBDs. Of particular note is the evidence on high protective efficacy of ITNs against cutaneous leishmaniasis, which suggests that there may be considerable collateral benefits of ITN roll out where cutaneous leishmaniasis and malaria are co-endemic. There is also good evidence of the efficacy of ITC and ITS against cutaneous leishmaniasis. Weaker evidence exists for the effect of ITS on dengue and ITNs on Japanese encephalitis, but these interventions look promising. Further studies should be conducted to confirm these findings. The potential of ITNs, ITCs and ITS against Chagas disease, human African trypanosomiasis and onchocerciasis remains untested. In several studies the pattern of reduction in disease incidence was not matched by reductions in entomological parameters. This is not unsurprising given the complicated relationship between vector density and risk of human infection, particularly when vector infection rate is not taken into account.

Meta-analysis showed that ITNs were able to reduce the incidence of cutaneous leishmaniasis by 77%. This finding provides support for WHO's recommendation that ITNs should be used as a vector

control method against this disease [48]. The level of protective efficacy found compares favourably with the 50% protective efficacy of ITNs against *P. falciparum* malaria shown by Lengeler [4]. Studies by Kroeger *et al.* [246] and Noazin *et al.* [245] reported significant effects of ITC and ITC/ITS on clinical outcomes. Based on maps of cutaneous leishmaniasis [214] and *P. falciparum* endemicity [28] there are large areas, particularly in South America, where these diseases are likely to be co-endemic, suggesting that collateral benefits of ITN roll out may be significant. Similar reductions in vector density were not observed which may be due to the ecology of the vector species or differences in collection techniques. For example studies by Alten *et al.* and Emami *et al.* sampled both endophilic and exophilic species [239, 241].

Clinical evidence from one study suggested that ITNs were not effective against visceral leishmaniasis [247]. However, in this study Picado *et al.* suggested that *L. donovani* transmission may have been occurring outside the home where ITNs would have little impact on preventing sandfly-human contact. In Africa observational studies led to mixed results – several studies have shown treated bednets to be protective against visceral leishmaniasis [262, 263], while others have shown no effect of ITNs on *L. donovani* infection rate in *P. orientalis*, although the number of infected *P. orientalis* identified was small in all villages [264]. In south Asia, several observational studies have shown use of (untreated) bednets to be protective against visceral leishmaniasis [265, 266].

The efficacy of ITNs in preventing leishmaniasis transmission is dependent on a number of key variables related to vector biology, type of nets and human behaviour. Studies have shown protection is dependent on mesh size of the nets – nets designed to be cooler which have large holes are more likely to let sandflies though, even if they are insecticide-treated [267]. ITNs are likely to be more effective where sandflies bite indoors at night and where people use ITNs consistently [125, 268]. ITCs and ITS may be advantageous over ITNs because these interventions are in place all the time and since there is no need to set them up at night, compliance is less of an issue [245]. In general, where transmission is occurring inside the home or where vectors rest indoors, we would expect ITNs, ITCs or ITS to have a beneficial effect, irrespective of whether the vectors are transmitting cutaneous or visceral leishmaniasis. It is important to have a sound grasp of sandfly biology and human behaviour in a particular setting in order to understand where transmission is occurring or where vectors rest before planning specific intervention strategies.

There were no studies that met the selection criteria, which reported the efficacy of ITNs against lymphatic filariasis infection. In much of SSA and parts of the western Pacific, *Anopheles* mosquitoes transmit both lymphatic filariasis and malaria and so theoretically ITNs should have a beneficial

effect on both diseases [186]. Observational studies have shown a beneficial effect of ITNs on lymphatic filariasis transmission where the disease is transmitted by *Anopheles* mosquitoes [269-272] and ITNs may be particularly useful in areas co-endemic for lymphatic filariasis and *Loa Loa* where mass drug administration of ivermectin is contraindicated due to serious adverse events [273]. However, to our knowledge no randomised controlled trials have been performed in these settings. Such a study would need to be of long duration to show a reduction in microfilaraemia given that adult worms have lifespans of between four and 10 years [274, 275]. Alternatively, a study could use incidence of new infections in young children as an outcome [276]. The efficacy of ITNs, ITCs and ITS against *Culex* vectors of lymphatic filariasis, which are predominant in urban areas [277], needs further assessment. Bøgh *et al.* reported a 16% reduction in indoor resting density of *Cx. quinquefasciatus* compared to a 98% reduction in *Anopheles* species [255], presumably because *Culex* are less susceptible than *Anopheles* to pyrethroids [278-280]. Another explanation may be that transient reductions in vector density are masked because *Culex* populations are massive and the population can rapidly replace itself or immigrate. Poopathi *et al.* assessed the effect of insecticide-treated eave and door curtains and reported an 82% reduction in human biting density of *Cx. quinquefasciatus* [257]. It may be the door curtain component of this intervention which is of greatest importance given the findings of a study by Njie *et al.* who reported that culicines enter houses via the door rather than the eaves [281].

There is an increasing focus on indoor vector control for dengue [282] because *Ae. aegypti* rest, feed, mate and reproduce inside houses [283]. Targeting adult *Ae. aegypti* shifts the age structure of the vector population to younger mosquitoes, which is likely to have a large effect on human infections due to the relatively long extrinsic incubation period of the dengue virus in the mosquito [284]. However, since transmission of dengue occurs mostly during the daytime the use of bednets has rarely been considered as a control strategy. Studies identified in this review reporting an effect of ITCs and ITS on *Ae. aegypti* infestation levels [248, 249, 259, 261] suggest that vectors are coming into contact with these interventions indoors. The likelihood of the vector coming into contact with the ITN, ITC or ITS will depend on a number of factors including the size of the home and construction. For example, Lenhart *et al.* state that the open construction of the homes in their study conducted in Thailand may explain why ITCs did not show any effect [260]. It is generally recognised that greater coverage of the intervention will result in mass killing, reduced vector survival and greater reductions in transmission; i.e. a community level effect. This was apparent in two of the dengue studies included in this review. In one study use of ITCs in intervention areas led to a community level effect whereby larval indices were reduced in neighbouring control areas [259]. A study by Vanlerberghe reported that a reduction in ITC coverage over time led to a reduced

effect on entomological parameters [261]. A similar pattern of coverage dependent effects of ITCs on *Ae. aegypti* larval and pupal/demographic indices was reported in another study in Venezuela, which suggested that at least 50% coverage of ITCs was necessary to reduce *Ae. aegypti* infestation levels by 50% [285].

Entomological data from studies on the efficacy of ITCs and ITNs against the dengue vector *Ae. aegypti* were inconsistent across the different indices measured. Focks and others have questioned the reliability and sensitivity of traditional immature *aegypti* indices (the house, container, and Breteau indices) and there is growing consensus that these indices are of little value in predicting risk of human infection [286]. Ovitraps are also not recommended for assessing vector abundance because measures are often biased by competition from natural oviposition sites [282]. Instead pupal/demographic indices (for example pupae per person) are a better proxy for adult vector abundance or measurement of adult vector density itself [286, 287] and are more appropriate for assessing transmission risk and directing control operations [288, 289]. The ideal would be to have a measure similar to the entomological inoculation rate for malaria transmission (incorporating both adult density and infection rate). However, adult *Ae. aegypti* are difficult to catch in appreciable numbers (though this is likely to improve with development of new adult monitoring tools) and only small proportion of adults are infected so it is difficult to detect infection [290].

The absence of studies of the two human trypanosome vectors and black flies is noteworthy. For black flies and tsetse flies, the predominantly outdoor exposure may be the main underlying reason, although there is some evidence that tsetse flies do come indoors [291, 292]. For triatomines, the absence of intensive bednet campaigns in Chagas disease endemic areas (which are often non-malarious, especially for the main vector *Triatoma infestans*), and the general lack of attention to improved housing may be among the principal underlying factors for the lack of studies.

Our review has several limitations that should be noted. We focused on a number of important neglected tropical diseases. This group of diseases is well-named because few studies were identified, despite conducting a comprehensive database search and contacting disease experts. We also relaxed the inclusion criteria somewhat in terms of study designs to include non-randomised studies with pre- and post-intervention data. We did not, however, do a full search of the grey literature which may mean that publication bias was introduced resulting in over-reporting of studies demonstrating that ITNs, ITCs and ITS were protective. We did not request further information from authors if reporting of methods or results was unclear in the published paper. Due to the few studies identified, summary estimates could only be generated using meta-analysis for cutaneous leishmaniasis. Studies were generally at low risk of bias but were of mixed quality. The

main problems identified were with study design; e.g. short periods of follow up and incomplete reporting in the published papers; e.g. the method of sequence generation for randomisation was not reported. We took a cautious approach and did not calculate confidence intervals for entomological outcomes. This was due to i) heterogeneity in study designs e.g. differences in follow up periods pre- and post-intervention and between studies, studies involving single houses and entomological parameters measured once versus studies with multiple clusters and measurements over an extended time period and ii) incomplete reporting in the published papers e.g. confidence intervals and standard deviations omitted. Without knowing the uncertainty around percentage reductions it was not possible to make any conclusions regarding the entomological effect of interventions. Improved reporting of entomological data in studies and standardisation of study design and conduct should be a priority. Entomological data should always be assessed in combination with a clinical outcome where possible, and clinical outcomes with standardised diagnostic techniques and case definitions should remain the gold standard outcome for assessing the efficacy of vector control interventions.

Less than half of the studies we considered reported the results of bioassays for efficacy of the insecticide used. In one of the studies conducted in Haiti there was some indication of resistance [258]. However, many of the studies were conducted prior to the early 2000s before the advent of pyrethroid resistance [293], including those against cutaneous leishmaniasis that show a high PE. It is not possible, therefore, to say whether this level of efficacy would be observed today. Currently pyrethroids are the only class of insecticides suitable for use on LLINs and increasing coverage of pyrethroid-treated materials to control multiple VBD is likely to increase selection pressure for development of resistance. Indeed, pyrethroid resistance has been detected in a number of non-malaria vectors including *Cx. quinquefasciatus* [294-296], sand flies [297], *Ae. aegypti* and *Ae. albopictus* [130]. Even if pyrethroid resistance increases, it is likely that ITNs, ITC and ITS will still afford some level of protection against vectors due to a barrier effect. However, it would be sound to use insecticide-treated materials as part of an IVM strategy including other vector control tools that do not rely on insecticide such as larval source management or make sure that different insecticide classes are used for IRS/fogging etc (if appropriate). In the meantime, new types of insecticide-treated materials, for example LLINs impregnated with insecticides with two different modes of action, are being developed which are showing promise against insecticide resistant malaria vectors [298, 299].

In terms of collateral benefits there may also be beneficial effects of ITNs, curtains and screening on preventing household pests such as headlice, cockroaches and rodents which although not

systematically assessed in this review are important benefits which increase acceptability and encourage compliance with interventions [300, 301]. There is also evidence of a beneficial effect of insecticide-treated materials against bedbugs [302], although a study in Tanzania suggested that roll-out of ITNs led to pyrethroid resistance in bedbugs over time [303].

In conclusion, ITNs, ITCs and ITS have great potential to reduce VBDs. The biological insight that follows from this conclusion is that a substantial proportion of the vector population must be resting or feeding indoors. However, it is important to conduct entomological surveillance to understand vector behaviour in specific settings before rolling out these interventions. Evidence on efficacy of ITNs, ITC and ITS against multiple VBDs should be paired with maps of disease co-endemicity in order to prioritise and focus resources to areas of greatest disease burden. The use of interventions against multiple diseases has the potential to reduce costs and make better use of financial and human resources. This requires functional coordination between disease-specific programmes on planning, implementation and monitoring and evaluation with sharing of existing infrastructure and competencies. Beneficial effects on multiple VBDs will serve to increase the cost effectiveness of insecticide-treated materials and this may help to bolster the case for vector control funding. This review demonstrates some promising results, but highlights the urgent need for further well conducted studies. The efficacy of ITNs, ITCs and ITS against VBDs needs to be rigorously tested in randomised controlled trials with standardised clinical outcomes.

Chapter 4: Are topical insect repellents effective against malaria in endemic populations? A systematic review and meta-analysis

Adapted from: Wilson AL, Chen-Hussey V, Logan JG, Lindsay SW. Are topical insect repellents effective against malaria in endemic populations? - a systematic review and meta-analysis. Malaria Journal. 2014;13:446.

Abstract

Recommended vector control tools against malaria, such as long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS), mainly target mosquitoes that rest and feed on human hosts indoors. However, in some malaria-endemic areas, such as Southeast Asia and South America, malaria vectors primarily bite outdoors meaning that LLINs and IRS may be less effective. In these situations the use of topical insect repellents may reduce outdoor biting and morbidity from malaria. A systematic review and meta-analysis was conducted to assess the efficacy of topical insect repellents against malaria.

Studies were identified using database searches (MEDLINE, EMBASE, Web of Science and clinical trials registers), as well as reference list searches and contact with researchers. Randomised and non-randomised controlled trials were included that assessed the effect of topical repellents (all active ingredients and concentrations) on *Plasmodium falciparum* or *Plasmodium vivax* malaria or infection in malaria-endemic populations. Meta-analysis of clinical data was conducted in order to generate summary risk ratios.

Ten trials met the inclusion criteria. Studies varied in terms of repellent active ingredient and formulation, co-interventions, study population, compliance, and follow-up period. Topical repellents showed an 18% protective efficacy against *P. falciparum* malaria, although this was not significant (95% CI: -8%, 38%). Similarly, the average protective efficacy of topical repellents against *P. vivax* malaria did not reach significance (protective efficacy: 20%, 95% CI: -37%, 53%). Exclusion of non-randomised trials from the meta-analysis did not alter the findings.

Although topical repellents can provide individual protection against mosquitoes, the results of this meta-analysis indicate that topical repellents are unlikely to provide effective protection against malaria. However, there was substantial heterogeneity between studies included and the relatively small number of studies meant that this heterogeneity could not be fully explored in the analysis. Further well-designed trials of topical repellents at appropriate doses and alternative modes of repellent delivery, such as spatial repellents and long-lasting insecticide-treated clothing, are required.

Introduction

Malaria is a major cause of morbidity and mortality in developing countries. In 2015, the World Health Organization (WHO) estimated that there were 212 million cases of malaria, which caused approximately 429,000 malaria deaths [20]. The parasites that cause malaria, primarily *Plasmodium falciparum* and *Plasmodium vivax*, are transmitted by the bite of female mosquitoes belonging to the genus *Anopheles*. Vector control plays a major part in malaria control and recommended vector control tools include long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS). Both tools have contributed to the large declines in malaria observed over the past decade. It is therefore of great concern that insecticide resistance in malaria vectors is widespread in sub-Saharan Africa (SSA), particularly to pyrethroids, the only insecticide class suitable for impregnation of LLINs [293].

Both LLINs and IRS aim to control malaria vectors that feed on human hosts and rest indoors. However, in many malaria-endemic areas, including southeast Asia and south America, biting occurs mainly outdoors. For example, the most important malaria vectors in the Greater Mekong Subregion in Southeast Asia are *Anopheles dirus*, *Anopheles minimus* and *Anopheles maculatus* which often bite outdoors and prior to 22.00 hours before people who own LLINs are protected by them [304, 305]. Outdoor-biting is a huge challenge in the Greater Mekong, where artemisinin resistance has also been found and the race is on to eliminate malaria before resistance spreads further [306]. Scale up of LLINs in SSA has been associated with a change in vector dominance from the predominantly indoor biting vector *Anopheles gambiae* s.s. to the outdoor biting vector *Anopheles arabiensis* [307-309]. There is also evidence of behavioural resistance of malaria vectors in response to the wide-scale use of IRS and LLINs [310]. Malaria vectors may be adapting their behaviour to early evening and dawn biting in response to reduced availability of blood meals at night when people are sleeping under LLINs. Indeed, studies in SSA [308, 311] and the Pacific [312, 313] have reported an increase in early evening biting of malaria vectors following roll-out of LLINs or IRS. Increasing development of urban areas and availability of electricity means that people are staying awake for longer and are exposed to outdoor-biting mosquitoes in the evening [314]. In addition, some populations groups, for example hunters, rubber tappers or forest workers that are active at night or sleep in the forest [315-317] are at high risk of malaria transmission from outdoor-biting mosquitoes. Based on this information, there is a need for vector control tools to protect people against outdoor-biting vectors.

Topical insect repellents protect users from mosquito bites as people go about their daily activities and therefore offer a potential tool against outdoor-biting mosquitoes. It is likely that people have been using repellents to prevent insect bites since prehistory [318]. Early repellents were largely

plant derived and include some repellents that are still in use today, such as citronella (oil derived from plants of the *Cymbopogon* genus), neem (leaves from *Azidarachta indica*) and lemon eucalyptus (*Eucalyptus maculata citriodon*). *N,N*-diethyl-m-toluamide (DEET), developed in the 1950s, is the most effective repellent available [319]. Topical insect repellents are very successful at reducing outdoor biting at any time of the day from a wide range of insects, but this protection is short-lived. For example, the current 'gold standard' repellent, DEET, applied topically will provide approximately six hours of protection under field conditions, although this is dependent on the formulation [320, 321].

A number of trials of topical repellents against malaria have been conducted but it is necessary to synthesise the results of these trials in order to inform policy decisions on use of topical repellents. Narrative and systematic reviews of topical insect repellents for personal protection have been conducted but these did not use meta-analysis [322-324]. Therefore, a systematic review and meta-analysis of randomised and non-randomised controlled trials was conducted to determine the efficacy of topical insect repellents against *P. falciparum* and *P. vivax* malaria or infection in malaria-endemic populations.

Methods

Literature search

Recommendations made by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group were followed where possible [235, 236] (Appendix 4.1).

A systematic search of the literature was performed in January 2014 and updated in July 2014. Medline (1946-), Embase (1980-) and Web of Science databases were searched using search terms including 'malaria' and 'insect repellents' and using MeSH terms where appropriate (Appendix 4.2). No language restrictions were placed on this search. In addition, clinical trials databases [325, 326] were searched, reference lists of identified manuscripts were checked and researchers were contacted to identify ongoing studies.

Anne Wilson (AW) screened the abstracts of the citations identified for potentially relevant studies and full text documents were obtained for those publications deemed to be relevant. The articles were scrutinised to ensure that multiple publications from the same study were included only once.

Study inclusion and exclusion criteria

Studies identified were assessed against inclusion and exclusion criteria by AW and Steve Lindsay (SL). Randomised and non-randomised controlled trials of topical repellents in endemic populations were included. Trial interventions included any topical insect repellent, regardless of active

ingredient or concentration used. Studies including co-interventions (usually insecticide-treated nets (ITNs) or LLINs) were included. Control arms received either no repellent, placebo repellent or co-interventions. Studies were included if they assessed the efficacy of topical repellents against either *P. falciparum* or *P. vivax* malaria cases or infection (self-reported or diagnostically confirmed using microscopy or a rapid diagnostic test). Both incidence and prevalence measures were included. Studies in travellers to malaria-endemic regions were excluded since the susceptibility of these populations to malaria and other factors, such as trial duration and compliance, would likely differ. Studies of insect repellent impregnated clothing and spatial repellents were also excluded. Studies assessing only entomological outcomes and arm-in-cage/laboratory studies/semi-field studies were excluded since the focus was primarily on determining whether repellents impacted on malaria morbidity.

Data extraction and analysis

AW and Vanessa Chen-Hussey independently extracted data from included studies into a standardised form capturing data on trial location, study population, randomisation, blinding methods, repellent formulation, estimated coverage or compliance and method of estimation, type of control, co-interventions, outcome measures, and length of follow-up from each trial. If these were not presented in the report, the trial location was used to find malaria endemicity, *Plasmodium* species and *Anopheles* vectors present. Where the *Plasmodium* species was not determined, the protective efficacy was attributed to the most common *Plasmodium* species which was identified either from the manuscript or expert opinion.

Clinical outcomes were reported as either risks, odds or rates of disease or infection in the published papers. For consistency across studies, risks of disease or infection were used in the meta-analysis. In the few cases where studies reported rates, risks were calculated using data on the number of cases and size of the study populations which was included in the published papers. The meta-analysis was conducted using unadjusted data. This decision was taken due to the small number of trials identified that reported adjusted effect estimates and the inconsistency across measures reported (adjusted rate and odds ratios). The *metan* command was used to perform meta-analysis in Stata 13 (StataCorp, Texas, USA). Due to the higher risk of bias in studies that were non-randomised, the meta-analysis was conducted both including and excluding these studies. Statistical heterogeneity was assessed using a χ^2 test. Due to the small number of studies in each comparison, the data were said to be heterogeneous if the χ^2 test p value was less than or equal to 0.1 [327]. The I^2 statistic was used to quantify the degree of heterogeneity. I^2 was calculated as $I^2 = ((Q - d.f.)/Q) \times 100\%$, where Q is the χ^2 statistic and d.f. is the number of degrees of freedom. Due to the high levels of statistical heterogeneity found and the *a priori* assessment that the studies were indeed

heterogeneous (different repellent types, study sites, etc.), the summary effect measure was calculated using random effect meta-analysis, rather than fixed effect meta-analysis. Protective efficacy (PE) was calculated as PE = 1− (risk ratio of clinical disease or infection during the intervention period) × 100%. PE (or relative risk reduction) can be interpreted as the percentage reduction in risk of clinical disease or infection associated with the intervention. A standard formula was used to calculate 95% confidence intervals for risk ratios [233].

Risk of bias assessment

AW assessed the risk of bias in the studies using the Effective Practice and Organization of Care (EPOC) risk of bias assessment form [237]. Risk of bias for each of the domains was graded as low, high or unclear risk.

Results

Study selection

The initial systematic literature search identified 1,736 unique records (Figure 4.1). 1,699 records were excluded based on review of the title and abstract. The majority of these studies related to use of insecticide-treated materials (e.g. LLINs) or chemoprophylaxis in travellers, or described risk factors for malaria. 37 full text records were reviewed and of these eight studies met the inclusion/exclusion criteria. Contact with experts identified one additional study [314]. The update of the search in July 2014 identified two additional studies – one of which was published [328]. The second study was identified from Clinicaltrials.gov [325] (Identifier: NCT01663831) and could not be included because the data were still being analysed. Therefore, the total number of studies included in the review was ten. One of these studies was available as a study report [314] but was later published as a peer-reviewed manuscript [329]. We used figures from the manuscript for our analysis.

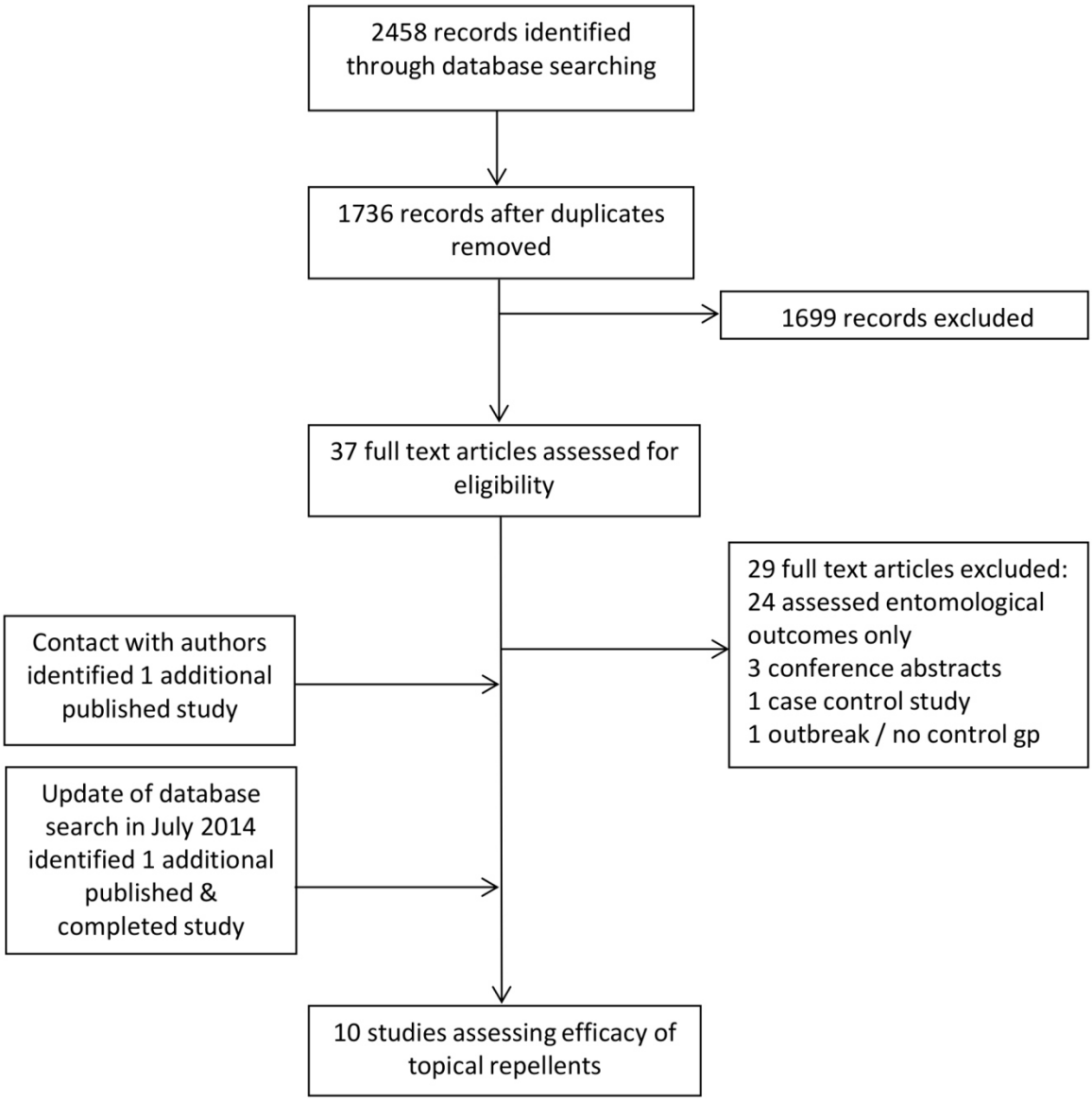

Figure 4.1: Flow chart of study inclusion for studies evaluating the efficacy of topical insect repellents against malaria
(adapted from [235])

Study characteristics and risk of bias

The ten studies identified were conducted in Africa (Ethiopia, Ghana, Tanzania), Asia (India, Lao People's Democratic Republic (PDR), Pakistan, Thailand) and South America (Bolivia and Ecuador and Peru) (Appendix 4.3). Three studies assessed the effect of repellents on *P. falciparum* malaria/infection [329-331], five studies assessed the effect on both *P. falciparum* and *P. vivax* malaria/infection [328, 332-335] and two studies did not determine the *Plasmodium* species [336, 337]. Four studies measured malaria incidence [329, 331, 336, 337], four studies measured incidence of infection [332-335] and two measured parasite prevalence [328, 330]. Studies utilised a

range of topical insect repellents, the most common being DEET and four of the ten studies used ITNs or LLINs as a co-intervention.

Risk of bias assessment found that studies were generally at low risk of bias, although poor description in the published papers meant that many parameters could only be classified as 'unclear' (Appendix 4.4). Seven studies were reported as being randomised trials (although the randomisation process was not well described in several papers), and it was assumed that three trials making no mention of randomisation were non-randomised [330, 331, 337]. In one of these studies by Vittal *et al*., baseline malaria incidence was significantly lower in the intervention group compared to control group [337], and in another by Dadzie *et al.* baseline malaria prevalence was significantly greater in the intervention village at baseline, although this would most likely serve to bias the effect size downwards [330]. The study in Tanzania reported that socio-economic status was higher in the control arm, suggesting that randomisation was imbalanced [329]. Only one study identified [336] did not use diagnostic confirmation of malaria, instead relying on self-reporting which the researchers 'validated'. This study reported that agreement between self- and professional-diagnosis (including diagnostic confirmation) was 80-90%.

Results of individual studies

Of the nine studies that assessed the efficacy of topical repellents against *P. falciparum* malaria, only one of these by Rowland *et al*. reported a significant protective efficacy [334]. Only one of the seven studies that assessed the efficacy of topical repellents against *P. vivax* malaria reported a significant protective efficacy [332]. Individual study results are reported in Tables 4.1 and 4.2.

Table 4.1: Efficacy of topical repellents against *Plasmodium falciparum*

Study	Repellent		Control		Risk ratio (95% confidence intervals)
	Cases	Population at risk	Cases	Population at risk	
Chen-Hussey *et al*. [333]	35	3,947	33	3,961	1.06 (0. 66-1.71)
Dadzie *et al*. [330]	54	205	47	204	1.14 (0.81-1.61)
Deressa *et al*. [1] [328]	23	2,399	19	2,273	1.15 (0.63 - 2.10)
Dutta *et al.* [331]	-	-	-		Yr 1: 1.16 (0.85-1.58), Yr 2: 1.20 (0.83-1.72)
Hill *et al*. [332]	1	2,041	6	1,967	0.16 (0.02-1.33)
Kroeger *et al*. [2] [336]	8.5%		6.7%		1.27[3]
McGready *et al*. [4] [335]	40	379	30	202	0.71 (0.46-1.11)
Sangoro *et al.* [5] [329]	115	2,224	137	2,202	0.83 (0.65-1.06)
Rowland *et al*. [334]	23	618	47	530	0.42 (0.26-0.68)

[1] Denominator is average of two follow up surveys, number of infections is combined total from two follow-up surveys - based on assumption that infections at 2-month time point were new infections (1 month between follow-up surveys); [2] Trial conducted in two sites. This data is from Ecuador where according to manuscript 86% of cases were usually due to *P. falciparum*. Since parasite species of cases was not determined, we are attributing these cases to *P. falciparum*; [3] Counts and denominators not reported in manuscript so unable to calculate 95% confidence intervals; [4] Cases and denominator back-calculated from percentages and confidence intervals reported in paper; [5] number of cases/denominator taken from published manuscript not study report;

Table 4.2: Efficacy of topical repellents against *Plasmodium vivax*

Study	Repellent		Control		Risk ratio (95% confidence intervals)
	Cases	Population at risk	Cases	Population at risk	
Chen-Hussey *et al*. [333]	14	3,947	16	3,961	0.88 (0.43-1.80)
Deressa et al. [1] [328]	21	2,399	17	2,273	1.17 (0.62 - 2.21)
Hill *et al*. [332]	14	2,041	66	1,967	0.20 (0.12-0.36)
Kroeger *et al*. [2] [336]	17.9%		24.1%		0.74[3]
McGready *et al*. [4] [335]	67	316	70	266	0.81 (0.60-1.08)
Rowland *et al*. [334]	103	618	62	530	1.42 (1.06-1.91)
Vittal *et al*. [5] [337]	8	228	13	411	1.11 (0.47-2.64)

[1] Denominator is average of two follow up surveys, number of infections is combined total from two follow-up surveys - based on assumption that infections at 2-month time point were new infections (1 month between follow-up surveys); [2] Trial conducted in two sites. This data is from Peru where according to manuscript 86% of cases were usually due to *P. vivax*. Since parasite species of cases was not determined, we are attributing these cases to *P. vivax*; [3] Counts and denominators not reported in manuscript so unable to calculate 95% confidence intervals; [4] Cases and denominator back-calculated from percentages and confidence intervals reported in paper; [5] Number of cases is combined total from two years of follow up.

Synthesis of results

Two studies could not be included in the meta-analysis. The trial conducted by Kroeger *et al*. in Ecuador and Peru did not report numbers of cases or denominators [336]. This was also the only study included which relied on self-reported malaria incidence. Dutta *et al.* seemed to misinterpret the results of their study in the published paper stating that risk ratios greater than 1 were protective [331]. Attempts to contact the authors to clarify and obtain the study data were unsuccessful and so this study was excluded from the meta-analysis.

The combined summary risk ratio for the effect of topical repellents on *P. falciparum* malaria or infection was 0.82 (95% CI: 0.62, 1.08, p=0.2) (Figure 4.2). There was substantial heterogeneity across studies (χ^2 p value=0.01, I^2=62%). Similarly the protective efficacy of topical repellents against *P. vivax* malaria or infection was not significant (risk ratio: 0.80 (95%CI: 0.47, 1.37, p=0.4) (Figure 4.3). There was considerable heterogeneity across studies (χ^2 p value <0.001, I^2=87%). When non-randomised trials were excluded from the meta-analysis, the risk ratios did not change substantially (*P. falciparum* risk ratio: 0.76, 95%CI: 0.55, 1.03, p=0.08, *P. vivax* risk ratio: 0.76, 95%CI: 0.42, 1.39, p=0.4).

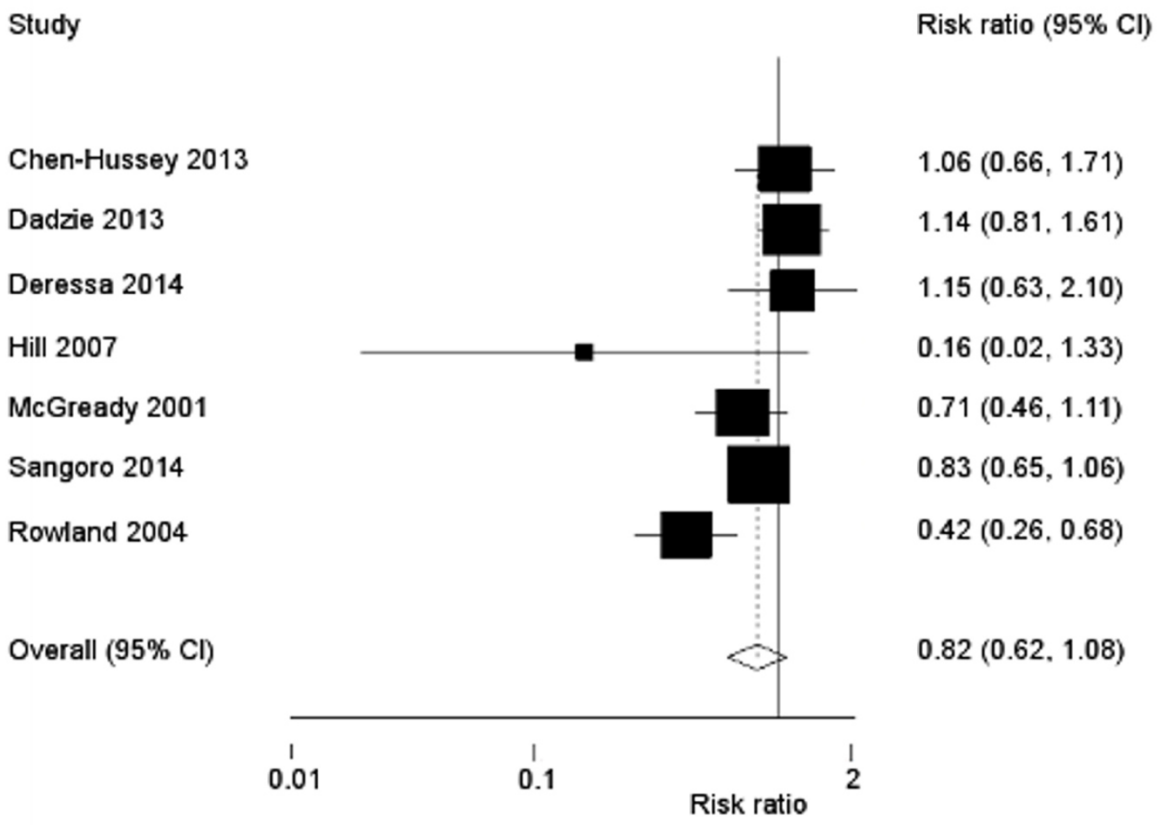

Figure 4.2: Forest plot showing risk ratios and summary effect estimate of topical insect repellent against *Plasmodium falciparum* malaria (random effects meta-analysis)

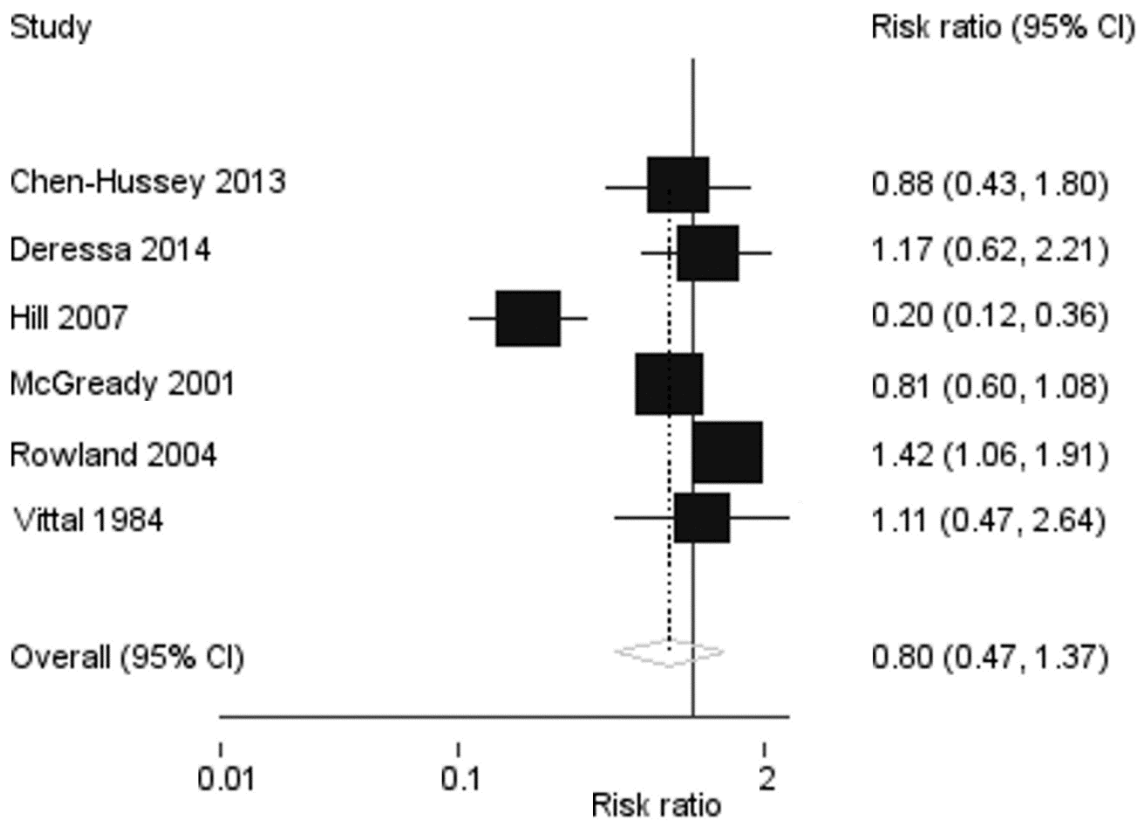

Figure 4.3: Forest plot showing risk ratios and summary effect estimate of topical insect repellent against *Plasmodium vivax* malaria (random effects meta-analysis)

Discussion

This meta-analysis did not show a significant protective effect of topical repellents against either *P. falciparum* (18%, 95% CI: -8%, 38%) or *P. vivax* malaria or infection (20%, 95% CI: -37%, 53%). Calculating the summary effect measure excluding non-randomised trials, did not alter the conclusion – no significant protective effect of topical repellents was observed.

Heterogeneity was high in the meta-analysis indicating substantial variance between the studies. Sources of heterogeneity included varying background rates of malaria, outcome measures (malaria cases or infection), follow-up periods, characteristics of participants (e.g., age), active ingredients, concentration and formulation of the repellent, user compliance, and co-interventions. Due to the small number of studies identified, it was not possible to conduct subgroup analysis to account for some of these important differences between studies. The most obvious difference was in study location, which would lead to varying background malaria rates. The interventions also varied; DEET,

permethrin and *p*-Menthane-3,8-diol (PMD) were all used at different concentrations and formulations. Compliance varied greatly between studies from 58% in Lao PDR to 98% in Bolivia.

There is strong evidence from a large number of studies that topical repellents protect from mosquito bites [338-343]. Studies included in the review also demonstrated high protection of the repellents against mosquito bites. For example, Moore *et al*. reported a high level of protection from *An. gambiae s.l.* biting in a field trial using human-landing catches in Tanzania [314] and Dadzie *et al.* reported that the biting pressure of *Anopheles* on unprotected individuals averaged 86 bites/man/night, which was significantly reduced to 9 bites/person/night among collectors using the NO MAS repellent [330]. However, the results of this meta-analysis suggest that protection from biting in controlled entomological studies does not translate into protective efficacy against clinical malaria. There are a number of potential reasons for this that are discussed briefly here. Firstly, compliance with repellent use may be suboptimal and vary amongst the study population. A mathematical model developed by Kiszewskia and Darling indicates that the probability of avoiding infections is highly sensitive to small changes in compliance and product efficacy – both of which are exponential parameters in the model [344]. In a study setting, compliance is difficult to measure as direct observation is only practicable in a small number of participants. Most of the trials used a combination of self-reported data confirmed by a small number of direct observations. Self-reported data may be unreliable due to courtesy bias whereby participants report using repellent even though they have not used it. It is also difficult to standardise repellent use given that participants may use varying amounts of the lotion each time they apply it leading to varying repellent effects. Secondly, the duration of protection from biting provided by repellents is relatively short. Even though participants may apply the lotion correctly in early evening, waning of the effect of the repellent may mean that participants are unprotected during the night and early morning. The risk of malaria may be even greater if the participant perceives they are protected and so does not comply with use of personal protective measures, such as LLINs. Thirdly, in some of the studies LLINs were used as a co-intervention – indeed, it is unethical to deny LLINs from control groups since they are considered standard best practice. However, this means that the study needs to show an effect of repellents on top of LLINs, an already highly effective intervention. This poses a problem of 'statistical power, and the law of diminishing returns' as noted by Lines and Kleinschmidt [345], whereby large sample sizes are required to have sufficient power to show a small increase in protection on top of LLINs. Lack of power may have been a problem in some of the studies. For example, in Thailand [335] and Tanzania [314, 329] reductions in malaria rates were recorded in repellent users, but the lower than expected overall malaria rates meant that sample sizes were too low for this reduction to reach significance.

Compliance with preventive measures such as topical repellents is dependent on a number of factors including acceptability of the product and biting nuisance. Ensuring high compliance with repellent use is critical in order to prevent diversion of malaria vectors to non-repellent-using individuals, especially if the vector species are strongly anthropophilic. A study in Tanzania showed that placebo users living in a village where 80% of the households used 15% DEET had over four times more mosquitoes resting in their dwellings in comparison to households in a village where nobody used repellent [346]. Some of the better designed studies included in this review attempted to reduce this diversion effect by enrolling a relatively small proportion of the population from villages/camps [314, 333, 334], but this was not the case with all studies or was not described in the papers.

This review assessed the efficacy of topical insect repellents against malaria in endemic populations but did not look at their efficacy when used by travellers. Malaria risk (due to for example immunity or living accommodation) and repellent use is likely to be different in endemic populations and travellers and so the data cannot be extrapolated between these two populations. Since topical repellents are able to reduce biting rates when used correctly [341], it is recommended that travellers continue to use them [323, 347, 348].

This review has a number of limitations which should be noted. Firstly, despite a comprehensive literature search of several databases, clinical trials registers and contact with researchers there is a possibility of missing some relevant studies. However, although a systematic search of grey literature databases was not conducted it is likely that all relevant studies were identified. While ten studies might be considered modest in order to make conclusions on a vector control tool, this is comparable to other systematic reviews of vector control tools (Cochrane reviews on ITNs = 22 studies [4], IRS = 6 studies [5], larvivorous fish = 12 studies [7], larval source management = 13 studies [6]). Studies were generally at low risk of bias, although many bias parameters could only be rated as 'unclear' given the poor reporting in the published studies. Efforts should be made to improve reporting of vector control studies.

Although entomological evidence is available that topical repellents protect individuals from mosquito bites, the results of this meta-analysis suggest they are ineffective at preventing malaria morbidity. However, there was substantial heterogeneity between studies and the relatively small number of studies identified meant that the effect of this heterogeneity on the summary effect estimate could not be assessed. Therefore it is recommended that further well-designed trials of topical repellents at appropriate doses be conducted. Additionally, research should focus on alternative modes of repellent delivery such as spatial repellents and long-lasting insecticide-treated

clothing, which rely less on compliance. Although repellents do not seem to be effective against malaria, they may be effective against other diseases vectored by insects, including dengue and leishmaniasis [244]. Studies of topical repellents against other VBDs should therefore be conducted.

Chapter 5: Advancing evidence-based vector control: a critical analysis of vector control study design and conduct and potential solutions to improve the quality of vector control trials

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Adapted from: Wilson AL, Boelaert M, Kleinschmidt I, Pinder M, Scott TW, Tusting L, Lindsay SW. Evidence-based vector control? Improving the quality of vector control trials. Trends in Parasitology. 2015;31:380-90.

Abstract

Vector-borne diseases such as malaria, dengue and leishmaniasis cause a high level of morbidity and mortality. Although vector control tools can play a major role in controlling and eliminating these diseases, in many cases the evidence base for assessing the efficacy of vector control interventions is limited or not available. Studies assessing the efficacy of vector control interventions are often poorly conducted which limits the return on investment of research funding. Here, we outline the principal design features of phase III vector control field studies, highlight major failings and strengths of published studies and provide guidance on improving the design and conduct of vector control studies. It is hoped that this critical assessment will increase the impetus for more carefully considered and rigorous design of vector control studies.

Evidence-based policy-making on vector control

Vector-borne diseases (VBDs) such as malaria, dengue and leishmaniasis are responsible for considerable morbidity and mortality and fall disproportionately on the poorest communities in the developing world [17, 349-351]. One of the key methods by which VBDs can be controlled and eliminated is through vector control [83, 86, 110, 120, 352, 353]; e.g., long-lasting insecticidal nets (LLINs) for malaria or indoor residual spraying (IRS) for Chagas disease.

Development of vector control interventions follows a multi-stage process [354] (Figure 5.1). Firstly, a draft target product profile should be generated. This document guides the development process by outlining the features and performance targets of the intended vector control tool. The next step is demonstrating the proof-of-concept by conducting phase I studies (laboratory assays to determine the mode of action) and phase II (semi-field and small-scale field) studies, which generally have entomological endpoints. Large scale phase III field studies (efficacy studies – see Glossary in Appendix 5.1) are then conducted which measure the efficacy of the vector control tool against epidemiological outcomes when implemented under optimal conditions.

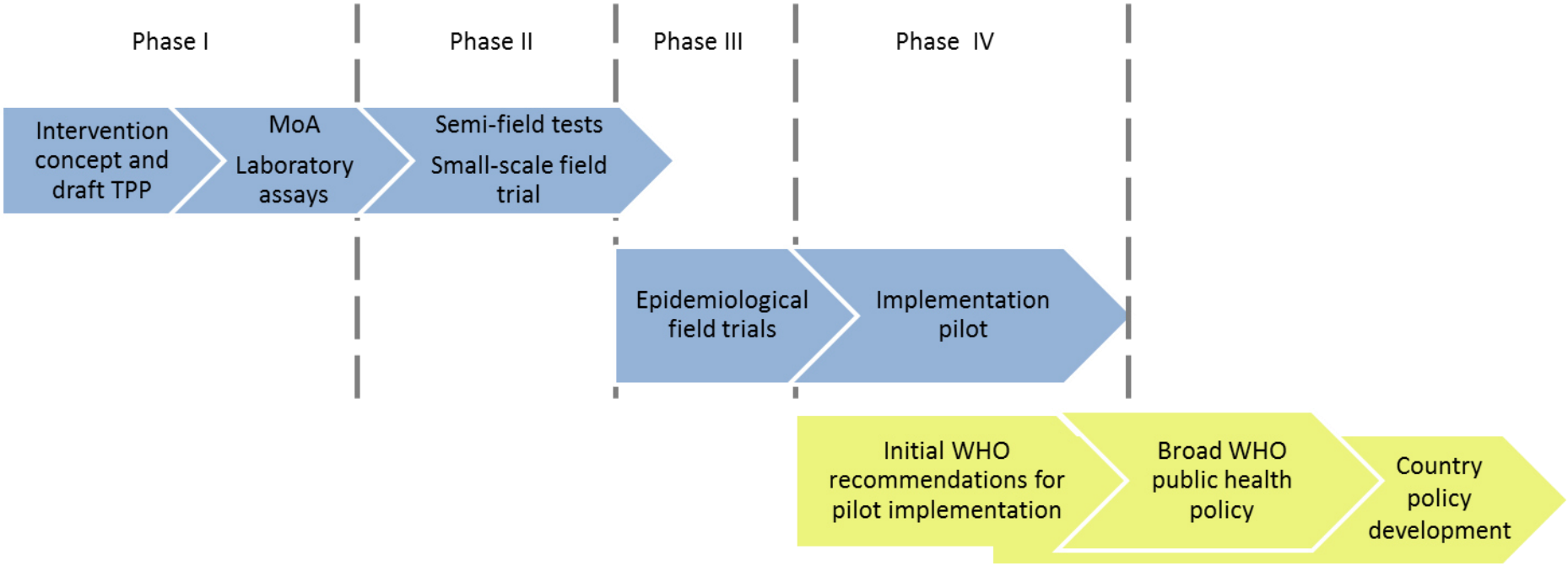

Figure 5.1: Stages in development of a new vector control product

The first step in development of a new vector control product is to define the target product profile (TPP), including target efficacy characteristics, safety and cost. Laboratory assays are then conducted to establish the mode of action (MoA) of the product followed by phase II studies (semi-field and small scale field trials) to determine the efficacy of the product against entomological outcomes. Phase III field trials to assess the efficacy of the intervention against epidemiological outcomes are then conducted and based on the results of these trials the World Health Organization (WHO) will make recommendations for pilot implementation. Phase IV pilot implementation studies assess the effectiveness of the vector control tool when it is used under 'real world' conditions and collect information on feasibility, distribution mechanisms, acceptability, cost, cost effectiveness and safety. On the basis of Phase III and Phase IV studies, WHO develop broad WHO public health policy on which many member states base country-level policy. TPP, target product profile; MoA, mode of action; WHO, World Health Organization. Adapted from [354]

Based on the results of phase III trials, the World Health Organization (WHO) will make recommendations for pilot implementation. These phase IV studies will assess the effectiveness of the vector control tool when it is delivered and used operationally (i.e., under 'real world' conditions), as well as collecting information on feasibility, distribution mechanisms, acceptability, economics and safety. Information gathered from the phase III and IV studies will enable the WHO to draw up policy recommendations and, in parallel, member states will develop country-level policy.

Evidence-based policy-making on vector control tools is now regarded as essential and is adopted by the WHO [3, 355] (Box 5.1). The quality of evidence on vector control interventions from epidemiological trials or systematic reviews needs to be rated before recommendations and policy can be formulated. Since 2008, the WHO has adopted the GRADE (Grading of Recommendations Assessment, Development and Evaluation system) methodology for evaluating evidence for policy and guideline recommendations [238, 356]. According to the GRADE methodology, an initial rating is given based on the study design. Randomised controlled trials (RCTs) are rated as high quality evidence and non-RCTs as low quality. Studies are then up- or down-graded based on several factors. RCTs can be downgraded depending on risk of bias, inconsistency, indirectness, imprecision or publication bias. Non-RCTs can be up-graded based on the effect size observed, dose response or plausible residual confounding. The final score generated can range from high (i.e., further research is very unlikely to change our confidence in the estimate of effect) to very low (i.e., very uncertain about the estimate of effect).

Box 5.1. Current policy-making process at the World Health Organization [355, 357]

The World Health Organization (WHO) has in its mandate to set, communicate, and promote the adoption of evidence-based norms, standards, policies, and guidelines. It is important that this process is streamlined because many countries rely on WHO recommendations in order to develop their own policy. Two WHO departments are responsible for the main vector-borne diseases – the Global Malaria Programme (GMP) and the Department of Control of Neglected Tropical Diseases (NTDs), which covers other VBDs including dengue, Chagas disease, leishmaniasis, human African trypanosomiasis, onchocerciasis and lymphatic filariasis. Both departments have advisory committees that provide independent strategic advice and technical input for the development of WHO policy recommendations; i.e., the Malaria Policy Advisory Committee (MPAC) and the Strategic and Technical Advisory Group (STAG) of the Department of Control of NTDs. These advisory committees are guided by standing technical expert groups and/or *ad hoc* evidence review groups that are responsible for reviewing studies on specific issues and making evidence-based

recommendations. New or innovative vector control paradigms are assessed by the WHO Vector Control Advisory Group (VCAG). This group was established in 2013 to guide the development of new vector control paradigms that have the potential for use as public health interventions. The VCAG can be consulted by innovators for advice on developing early-stage vector control paradigms and assesses proof of concept of new vector control technologies. Once satisfied that proof of principle has been established and field trials have satisfactorily demonstrated the efficacy of new forms of vector control, VCAG makes recommendations to MPAC and STAG on whether WHO guidelines should be formulated regarding the deployment of the new paradigm for public health use.

While vector control interventions are the backbone of many disease control programmes, the evidence supporting their use remains weak. Based on our experience systematically reviewing the literature [6, 25, 185, 358, 359], we have identified repeated problems with vector control studies. To advance evidence-based policy-making, the quality of evidence on vector control interventions – specifically the design, conduct, analysis and reporting of vector control studies – needs to be improved. The problem of waste in research has recently been highlighted in a Lancet series which calls for better design, conduct, analysis and reporting of studies [9, 360]. In this paper, we respond to The Lancet's demand to reduce waste in research by highlighting the essence of good study design for evaluating the efficacy of vector control interventions. Given the importance of study design and risk of bias to the GRADE assessment of quality of evidence, we firstly provide a primer on study designs and bias to illustrate the hierarchy of experimental designs for estimating intervention efficacy. Secondly, we review common failings of vector control efficacy studies in terms of their design and conduct and suggest how these studies can be improved.

General considerations on study designs for vector control studies

The methodological quality of study designs varies; so that some are better than others in being able to answer the question 'Does the intervention work?' or 'Does this intervention work better than that intervention?' [361]. In Figure 5.2 we provide a hierarchy of study designs for evaluating the efficacy of vector control interventions – ranking studies as level 1, 2a or 2b according to their methodological quality - and list non-recommended studies. We accept that different study types may be better for answering other questions, such as acceptability of the intervention [361].

RCTs are generally considered the 'gold standard' study design for evaluating the efficacy of a protective intervention since they have a low risk of selection bias [362, 363], which is arguably the

most important type of bias in experimental studies. Such is the importance of randomisation that we consider RCTs as level 1 evidence. If the number of randomisation units is sufficiently large, randomisation will ensure that in a two-armed study any factors that may affect an outcome are similar in both arms [362]. Even if one randomises, it is good practice to check the baseline characteristics of the groups are similar to verify if the randomisation was successful [364]. If there is no random allocation of intervention and control communities, potential bias can be reduced by adjusting for pre-intervention differences in the two groups using multivariate analysis (e.g., [365]). There is, however, no guarantee that this will fully control for confounders that may be unknown or unmeasured.

In vector control studies, the intervention is often allocated to a group of individuals known as a cluster (e.g., district, village or household) rather than at individual level. There are several reasons why cluster allocation is common [362]. Firstly, many vector control tools are, by their nature, applied to groups of people or communities. For example, spatial repellent may be allocated to a household, or an environmental sanitation intervention against dengue may be allocated at community level. Secondly, cluster allocation can help reduce contamination between study arms that might occur if individuals within the same community received different interventions, for example sharing of insect repellent with family members within the same household or village. Lastly, cluster allocation means that we are able to assess the community-level effect of the intervention. For example, mass killing of mosquitoes coming into contact with LLINs can reduce transmission so that indirect protection is provided to those individuals not using LLINs.

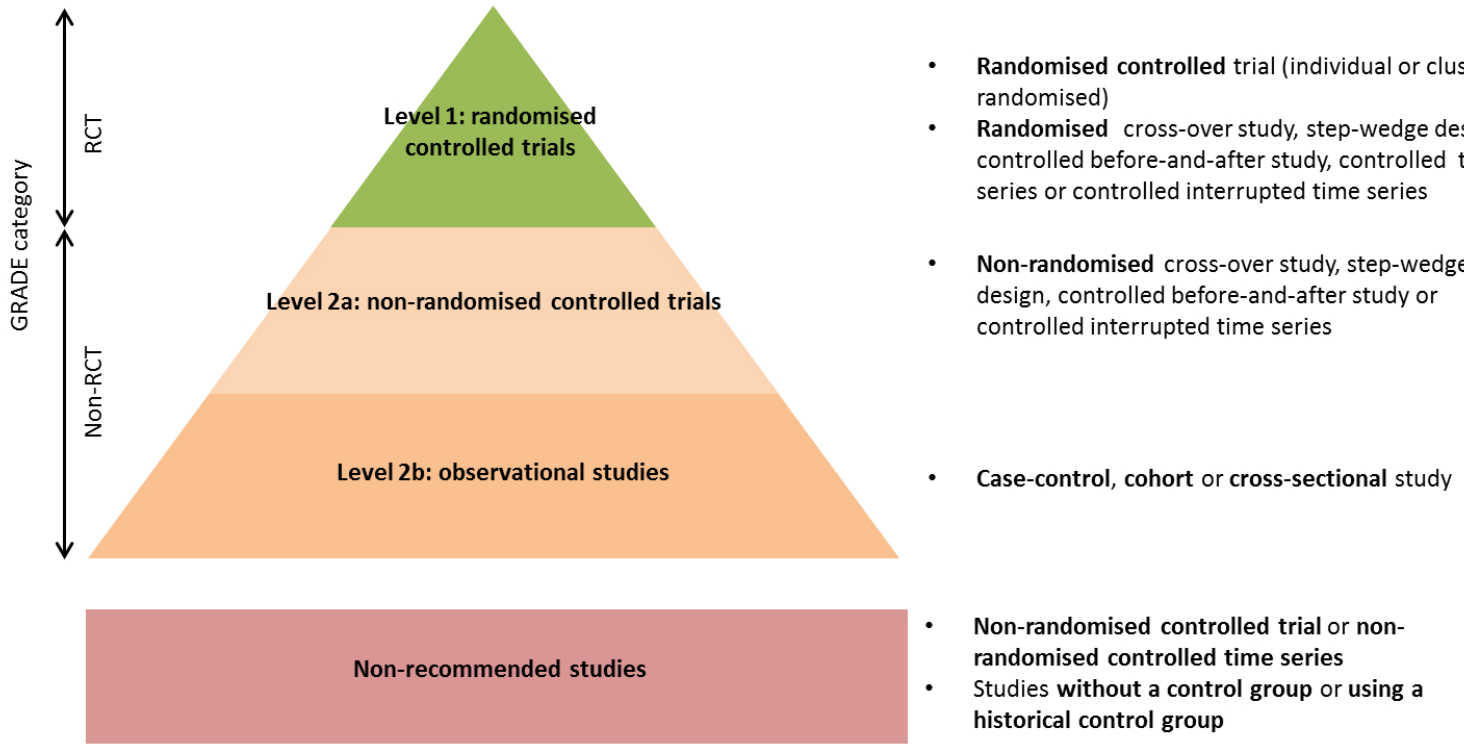

Figure 5.2: Hierarchy of study designs for assessing the efficacy of vector control interventions

Study designs for assessing the efficacy of vector control interventions can be ranked according to their methodological quality. Randomised controlled trials (level 1) are the 'gold standard' study design for evaluating the efficacy of vector control interventions. Randomisation reduces the risk of selection bias by ensuring that control and intervention groups are similar to each other. Level 1 studies include cluster or individually randomised controlled trials, as well as randomised cross-over, randomised step-wedge, randomised controlled before-and-after, randomised controlled time series and randomised controlled interrupted time series studies. Non-randomised trials (including non-randomised cross-over, non-randomised step-wedge, non-randomised controlled before-and-after and non-randomised controlled interrupted time series studies) are at a higher risk of bias and so are ranked lower (level 2a). Observational studies, such as case-control, cohort and cross-sectional studies (level 2b) provide weaker evidence on the efficacy of protective interventions than experimental designs since they can be subject to bias, due to confounding factors and flaws in measuring exposures and outcomes. Non-randomised controlled trials, non-randomised controlled time series designs and studies without a control group or using a non-contemporaneous control group are not recommended. RCT, randomised controlled trial; GRADE, Grading of Recommendations Assessment, Development and Evaluation. Adapted from [366, 367]. GRADE levels defined as in [238].

There are a number of other study design types including controlled before-and-after (CBA) studies, controlled time series, controlled interrupted time series (ITS), cross-over studies and step-wedge designs (Figure 5.3) which may be more suitable for evaluating the efficacy of some vector control tools. For example, time series or ITS are probably more appropriate for studies of human African trypanosomiasis in which vectors are highly mobile and control efforts need to be implemented over large areas [368]. Step-wedge studies involve rolling out the intervention to clusters in a staged fashion. This design is often used where logistical, practical or financial constraints make the staged roll out of the intervention desirable. We classify randomised CBA, randomised time series, randomised ITS and randomised step-wedge studies as level 1 and non-randomised CBA, non-randomised ITS and non-randomised step-wedge studies as level 2a. We do not recommend the use of non-randomised controlled trials or non-randomised time series designs since selection bias is likely to be high and there is no pre-intervention data to assess comparability of groups.

Observational studies such as case-control, cohort or cross-sectional studies (Figure 5.4) have been used to generate evidence of the efficacy of vector control interventions. However, these designs provide weaker evidence than experimental (randomised) designs since they can be subject to bias e.g., recall bias, detection bias or confounding. For this reason we have ranked these studies as level 2b.

We also do not recommend the use of studies without a control group or those using a non-contemporaneous control group. This is because longitudinal changes, such as rainfall, may impact on epidemiological outcomes and can exaggerate or mask an intervention effect.

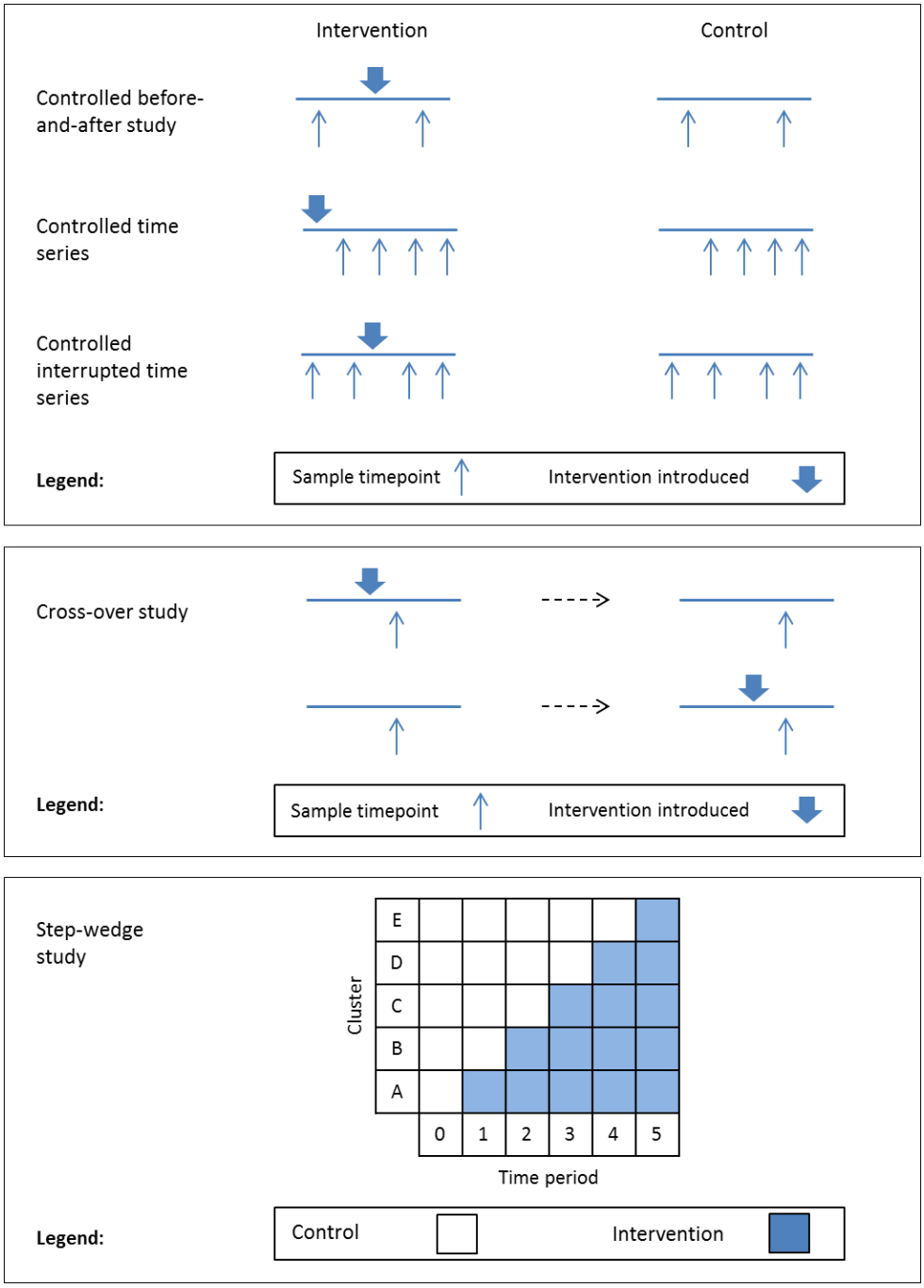

Figure 5.3. Schematic illustrating design of controlled before-and-after, controlled time series, controlled interrupted time series, cross-over and step-wedge studies

Controlled before-and-after studies involve collecting data on outcome measures before and after implementation of the intervention in the intervention group, and at the same timepoints in the control group. In controlled time series studies, data on outcome measures is collected at several timepoints once the intervention has been implemented in the intervention group, and at the same timepoints in the control group. Controlled interrupted time series studies involve collecting data on outcome measures at several timepoints before and after implementation of the intervention in the intervention group, and at the same timepoints in the control group. In cross-over studies, two groups are allocated (usually randomly) to control or intervention and outcome measures assessed once the intervention has been implemented. Following a suitable washout period, the intervention and control are switched round and outcome measures are assessed again. In a step-wedge study the intervention is rolled out randomly to clusters in a staged fashion so that by the end of the study, all clusters will have received the intervention. Adapted from [7].

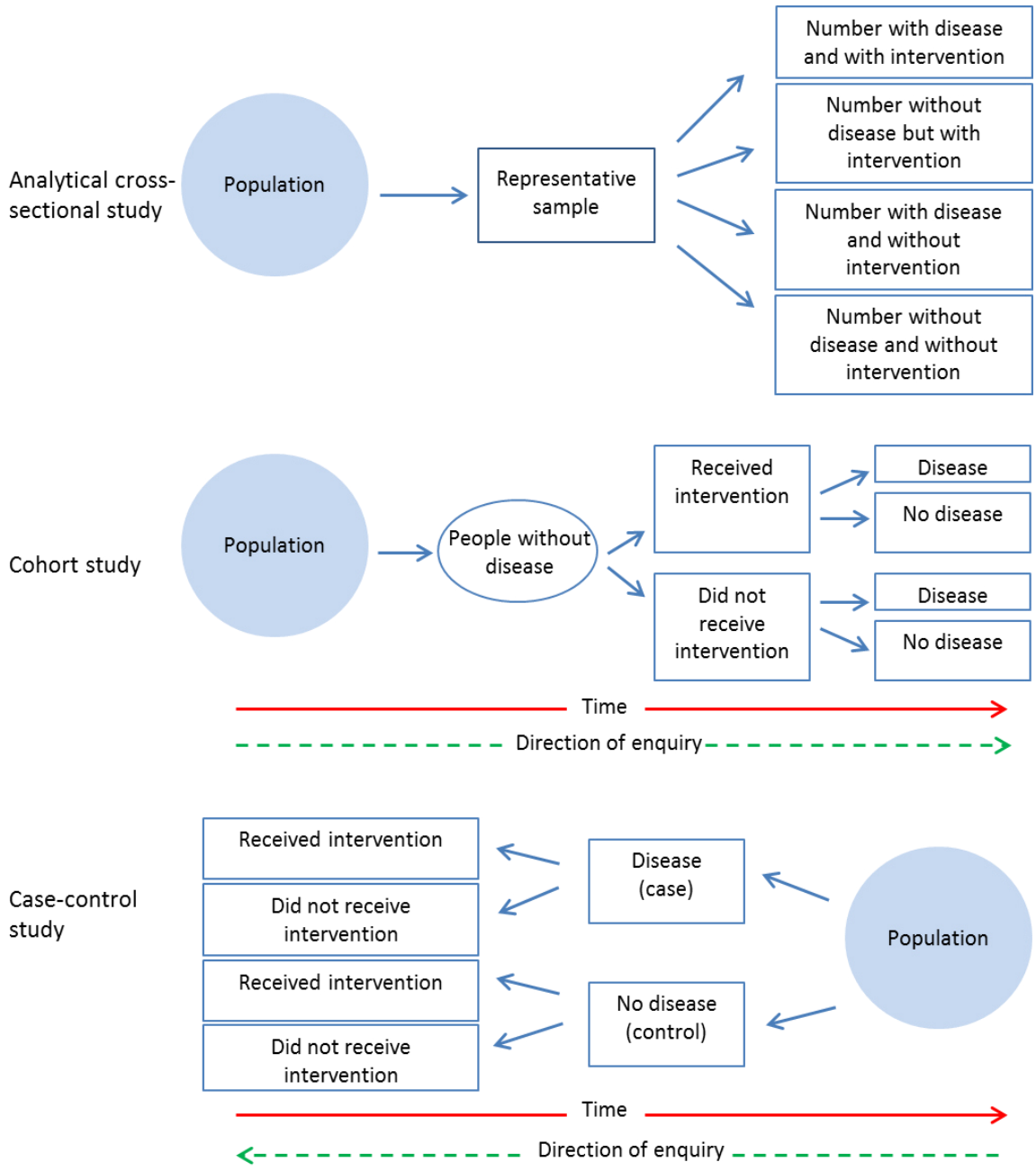

Figure 5.4. Schematic illustrating design of observational studies for vector control interventions

In an analytical cross-sectional study, a cross-sectional survey is taken from a representative sample of a population. The survey gathers information on outcomes e.g., disease/infection and exposure to the intervention from individuals at the same time so the sample can be split into four groups: those with the disease who were exposed to the intervention, those without the disease who were exposed to the intervention, those with the disease who were not exposed to the intervention and those without the disease who were not exposed to the intervention.

In a cohort study, a sample of the population is chosen that is free of disease. Individuals without the disease are split into two groups (those exposed to the intervention and those not exposed to the intervention) and are followed up over time to determine how many develop the disease or infection.

In a case-control study, individuals are selected on the basis of their disease or infection status. A group of individuals with the disease or infection (cases) and a group without the disease/infection (controls) are selected. The prevalence of exposure to the intervention is then compared between the cases and controls.

Common failings of vector control studies & recommendations

The authors have, through their involvement in a number of systematic reviews on vector control interventions [6, 25, 185, 358, 359], identified a large number of poorly designed and conducted vector control studies. Here we describe common problems with the design of vector control studies illustrated with examples and make recommendations for improvements.

Implementation and adherence to the intervention

In efficacy trials, vector control interventions should ideally be implemented in an optimal manner with attention to quality control, high coverage and user compliance. Unless these parameters are measured, it is impossible to know whether an observed lack of effect is due to low quality, coverage and/or compliance or lack of efficacy of the vector control method.

Quality control checks should be put in place to ensure that vector control interventions such as IRS are implemented optimally (e.g., correct application of insecticides and coverage of all assigned structures sites). This can be achieved through accurate record keeping, random spot checks and supervision [29, 369].

Adherence to the intervention being tested is very important. Efficacy studies usually employ specific community engagement techniques such as behaviour change communication (BCC) or information-education-communication (IEC) to encourage optimal uptake and use of the intervention where user compliance is required. For example, a study by Picado *et al* of LLINs against visceral leishmaniasis evaluated the community preference of LLIN brand (e.g. fabric, colour etc) prior to procurement; proper LLIN use (e.g. LLIN deployment, washing frequency etc) was encouraged during village meetings and through the distribution of BCC/IEC materials such as pictorial diagrams in the local language; and quarterly house-to-house visits promoted the regular and correct use of LLINs (e.g., [370]). Adherence to the intervention should be measured while taking into account that there is also the potential for introduction of bias here (e.g., courtesy bias). In some cases, innovative methods need to be identified to assess compliance. For example, an RCT of topical repellents against malaria measured compliance through self-reporting of use, the proportion of lotion used estimated from returned bottles and 'sniff checks' whereby trial staff visited villages at dusk and smelled the arms of participants to check whether lotion has been applied [333].

Choice and measurement of outcome measures

Epidemiological outcomes are necessary to demonstrate the efficacy of the intervention in protecting human populations and to ensure the relevance of these studies to public health. To date, however, many phase III studies often focus exclusively on entomological outcomes, which are

generally only useful for demonstrating proof-of-concept or as a secondary outcome in support of an epidemiological primary outcome. For example, a Cochrane systematic review on larvivorous fish for malaria control did not identify any studies with epidemiological outcomes [7]. The best epidemiological measure is incidence of clinical disease or disease-specific mortality, but for some diseases such as dengue, sero-incidence (seroconversion in sequential blood draws) and prevalence of infection in single blood draws, including age-specific antibody prevalence can be good substitutes [370, 371]. Studies should use WHO-recommended case definitions with parasitological diagnosis or serological or molecular verification [44, 48, 49, 372, 373] to allow comparison of data between studies. Outcome measures such as self-reported malaria as used by Kroeger *et al*. in a study of repellent soap [336] are unreliable.

Detection bias can be reduced by blinding outcome assessors to the identity of study arms and by the use of objective and well-standardised epidemiological and entomological outcomes. The latter should particularly be used in non-blinded studies.

Entomological data should be collected in a standardised fashion across study arms, sites and over time. Ideally these sampling tools should be automated (e.g., US Centers for Disease Control and Prevention light trap, sticky trap, other trap or target) and not depend on the ability of the fieldworker to collect specimens (e.g., human landing catches, aspiration of resting adults, and larval surveys). A number of other techniques can help avoid introduction of bias in measurement of entomological outcomes including separating the field teams that are implementing and monitoring the intervention (e.g., [374]).

Entomological endpoints are not always good predictors of epidemiological outcomes. For example, an RCT of LLINs for visceral leishmaniasis reported a reduction in sandfly density in homes, but did not show any effect on infection in study participants [247, 254]. The authors postulated that transmission was also occurring outside the home and so although there was a reduction in indoor sandfly density this did not reduce disease burden. Where possible, it is preferable to use entomological outcomes that relate to disease transmission, such as entomological inoculation rate, rather than measures that do not, such as vector density.

Traditional indicators of immature *Aedes* abundance, such as house index (percentage of houses with larvae and/or pupae), are a poor indication of adult production [286, 375]. Pupal demographic surveys (pupae per person/area index) or measurement of adult vector density are likely to be more appropriate for assessing transmission risk and directing control operations [286-289]. However, both measures are far more labour intensive than larval surveys and so may not be feasible for

routine monitoring of vector populations [372]. Because, unlike infections caused by protozoa and nematodes, dengue virus infection results in sterilising immunity, pupal and adult surveys are not consistently informative about dengue risk without an understanding of the underlying susceptibility of the human population to dengue virus [282, 376, 377].

Avoiding performance bias

Blinding of trial participants, health care providers, and researchers to the intervention received by participants can reduce performance bias. However, blinding of vector control studies is often impossible. For example, it was not possible to blind study participants in an RCT assessing the efficacy of house screening versus no house screening against malaria [378]. The study found that children living in screened homes were less likely to use bednets than children residing in homes that were unscreened, which may reflect a belief among householders that screening was a substitute for bednets. However, the effect of performance bias in this study was minimised because bednet use was carefully recorded and its effect could be adjusted for in the statistical analysis. Alternatively, an originally blinded study may become un-blinded during the study. For example, some participants in an RCT of topical repellents became aware that the placebo lotion they were allocated was not providing protection against mosquito bites which led to the withdrawal of all households in one village [333]. This kind of participant response can lead to introduction of attrition bias.

Selection of sites for entomological monitoring

Sampling sites for entomological surveys are often chosen purposively based on where high vector densities are likely e.g., sites close to suspected larval habitats or houses with un-plastered walls or wood construction for *Triatoma* surveys [379-381]. However, this does not measure average community exposure to infection and there is the potential for introduction of sampling bias if sites are not selected in a consistent way across intervention and control sites. We therefore recommend that sampling sites for entomological surveys be selected randomly. It is also possible to separate the sampling frame into strata and sample from each stratum independently, if there is likely to be substantial variation within subpopulations. For example, Joshi *et al.* stratified dwellings into two groups (houses occupied by humans alone and houses occupied by humans and animals) before using simple random sampling to select dwellings in which to measure sandfly density [253].

Contamination or spill-over effects

Contamination or spill-over effects between different study arms due to the movement of vectors [382, 383] or humans between clusters can make interpretation of study findings difficult. Spill-over which has a conservative effect (i.e., it biases results towards the null) can occur through one of two routes. Firstly, community-level effects of the intervention can reduce the transmission intensity in

neighbouring control clusters, as occurred in a study of insecticide-treated water jar covers and window curtains against dengue in Mexico and Venezuela [259]. Secondly, movement of people between intervention and control clusters (and *vice versa*) is also able to dilute the intervention effect because a person's risk of infection is proportional to the amount of time they spend in versus out of the treatment area. If the protective effect of an intervention or the sample size of the study is sufficiently large, a positive result can still be demonstrated in a superiority trial, albeit with reduced intervention effect. On the other hand, a negative finding of 'no difference' in such a trial is harder to interpret and a critical question arises. Is the lack of effect due to spill-over, or due to the absence of efficacy of the new intervention?

A more serious problem arises if the spill-over effect is anti-conservative because it exaggerates the difference in outcomes between intervention and control arms of the study. For example, topical repellents or house structural changes which have no killing effect on mosquitoes may divert vectors to non-users in the control arm of the study putting them at higher risk of infection than they would otherwise have been [346, 384].

Hayes and Moulton [362] outline a number of methods for reducing contamination including ensuring clusters are well separated, using a buffer zone so there is no common boundary between intervention and control clusters as shown in a LSM study conducted in Tanzania [385] or a 'fried egg' design where the intervention and control are administered throughout the cluster, but only the central portion is used for outcome measurement [386]. When designing these types of studies it is, therefore, important to have an estimate of how far the vector is likely to fly in seeking a blood meal or a breeding site. Geo-references of cases that make up the outcome measure should be recorded to show whether there were edge effects due to contamination. This technique has been used to estimate the size of area-wide effects in studies of LLINs for malaria control [56]. Unintended consequences of topical repellents can be avoided by randomising only a relatively low proportion of individuals or households in a village to receive the intervention [329, 333, 334]. Tackling the problem of human movement in dengue studies is more difficult because *Ae. aegypti*, feeds during the day when people are engaged in their daily activities. Potential strategies to avoid this would be to use larger cluster areas or monitor epidemiological outcomes in a sentinel cohort that is less mobile (e.g., young children) [387]. Even if these steps are taken it is a good idea to collect travel histories from study participants, particularly if the intervention is located in a household. In this way, participants can be excluded from the per-protocol study analysis if they have travelled for significant periods of time and, therefore, spent a relatively brief time being exposed to the intervention (e.g., [388]).

Contamination can also be a problem in cross-over trials if the washout period is insufficient. While cross-over trials may be suitable where the washout period is short (e.g. larvicide with a short half life [389]), they should be used with caution where interventions are persistent; e.g., dichlorodiphenyltrichloroethane (DDT) or habitat manipulation.

Need for sample size calculations

Sample size calculations are carried out prior to conducting a study in order to quantify the power the study has to show an effect of the intervention and thereby answer the study question (Box 5.2). The effect of a small sample size is on the standard error of the outcome measure; i.e., it will lead to large confidence intervals around the estimated effect, and hence poor precision. The sample size needs to be large enough to ensure that the probability of a type II error is reasonably small, generally 10% (=90% power) or 20% (=80% power). Sample size calculations should be performed for all study outcomes – whether these are epidemiological or entomological. We identified a number of studies that did not report conducting sample size calculations for epidemiological and/or entomological (e.g. [252, 255, 390-392]) outcomes, including several studies which failed to show an effect of the intervention [239, 335], indicating that the lack of an effect may simply be due to the study being underpowered. Parameters required for sample size calculations such as the prevalence or incidence of the outcome in the control group or coefficient of variation may not be readily available [370], although the former can be estimated from a survey conducted before study start if it is not known.

Box 5.2: Power and sample size calculations [233, 393, 394]

When conducting a study there are two hypotheses that need to be considered: the null hypothesis (there is no difference between the two interventions) or the alternative hypothesis (there is a difference between the two interventions, or more commonly for superiority trials, that the novel intervention is more protective than standard practice). When testing a hypothesis there are two types of error possible:

- Type I error or α = we reject the null hypothesis incorrectly; i.e., there is no effect but we report that there is.
- Type II error or β= we incorrectly do not reject the null hypothesis; i.e., there is an effect but we fail to detect it.

A number of factors need to be considered when calculating sample sizes:

- The prevalence or incidence of the outcome in the control group

- Expected effect size of the new intervention: it is important to be clear on what is the smallest size of effect we deem to be relevant from a public health or clinical perspective. For example, a study assessing the effect of house screening against exposure to malaria vectors established at the beginning of the trial that full screening or screened ceilings would be recommended if they reduced house entry by malaria mosquitoes by at least 50% [378].
- Significance level (p-value): This represents the probability of a type I error. Generally 0.05 is used, which means that we have a 5% probability of a type I error.
- Power: The power of a study is the probability of not committing a type II error or 1-β. e.g. if we have a 20% probability of a type II error then the power is 80%.

Many vector control trials use a clustered design. For cluster-randomised trials, two additional factors need to be taken into account:

- Average cluster size.
- The coefficient of variation, k, which measures the level of between-cluster variation of the outcome.

This is important because outcomes measured in individuals or sampling sites within the same cluster are likely to be correlated. A large value of k implies substantial between cluster variation in the outcome, which makes it harder to show an intervention effect, unless the sample size is increased.

It is recommended to consult an experienced statistician to assist with sample size calculations, particularly for cluster-randomised trials.

Vector control trials generally use a cluster design. Since outcomes measured in individuals or sampling sites within the same cluster are likely to be more similar than between clusters, the sample size calculation needs to take this into account and a larger sample size is required than if a non-clustered design was used (Box 5.2). Hayes and Moulton recommend the use of six clusters per arm as absolute minimum and it is generally better for cluster-randomised trials to have a higher number of smaller clusters than fewer large clusters [362]. We identified a large number of published vector control trials that used two villages [248, 337] or two areas [245, 395], one in which the intervention was introduced and the other acting as a control. This is a poor design because use of only two clusters means the intervention effect is completely confounded by study site and effectively constitutes a sample size of one [396, 397].

Deciding on the duration of the follow-up period

Insufficient periods of follow-up plague many vector control trials. For example, a RCT of topical repellents against malaria in Ethiopia conducted two malaria prevalence follow-up surveys one month and two months after the baseline survey [328]. This study is unlikely to give a true picture of the effectiveness of the repellent since compliance with the repellent would probably remain high during this short time period but decline over a longer time period. It is also worth noting that *Plasmodium falciparum* infections last on average one year [398, 399], although they can persist for up to a decade or longer [400] and it takes several years for this indicator to re-equilibrate fully following a reduction of transmission [401, 402].

For entomological outcomes, follow-up periods need to be sufficiently long and repeat measurements need to be taken to gain a picture of transmission in the area (e.g., [331, 403]). This is because there is likely to be large variation in vector density between sampling sites and across different sampling periods (night to night, week to week or over a transmission season) due to environmental factors, such as rainfall. Designs in which entomological sampling is conducted once during the follow-up period are less likely to give reliable results due to inherent variability in vector populations even if the number of sampling units is high. Longer periods of follow up with repeat measurements can be used to assess whether the effect of an intervention is waning (e.g., IRS with a short lasting insecticide) and to determine how often the intervention needs to be replaced or re-applied.

We recommend that minimum pre- and post-intervention follow-up periods be used for epidemiological and entomological data collection, the duration of which differs depending on the study design chosen and the context of pathogen transmission (Table 5.1).

Table 5.1: Minimum recommended follow-up periods by study type

Study design	Pre-intervention	Post-intervention
Randomised controlled trial	Desirable to check baseline characteristics of study population. At least one transmission season for entomological data if sampling sites are non-randomly selected. [a]	At least one transmission season (two seasons is desirable).
Controlled before-and-after study	At least one transmission season, especially if entomological sampling sites are non-randomly selected.	At least one transmission season.
Randomised controlled time series	Not applicable	Two or more transmission seasons.
Interrupted time series	Two or more transmission seasons.	Two or more transmission seasons.

Cross-over study	At least one transmission season before cross-over (and washout) and one transmission season after.

[a] Transmission season may be shorter than a one year period or a whole year if transmission is perennial.

Discussion

We have identified common problems with vector control studies and provide suggestions on how these can be improved. We also illustrate that some study designs are methodologically stronger than others. While hierarchies based on study design are somewhat controversial [404], we believe they remain useful in addressing the evidence for what interventions work, particularly when combined with a broader evaluation of the quality of the evidence as offered by GRADE [238, 356]. More specifically, the GRADE rating of evidence takes into account a number of factors in addition to study design [238, 356]. This means, for example, that a poorly conducted RCT with a high risk of bias does not necessarily constitute better evidence than a sound observational study with a large effect size.

We suggest that there are several reasons why many vector control studies have historically been designed and conducted in a less than optimum fashion. Firstly, a lack of resources may have limited the extent to which entomologists could conduct large scale, well designed studies. This may help explain the large number of two village comparison studies and studies without epidemiological outcomes. The impact of shortfalls in resources is exacerbated by issues associated with implementing environmental interventions on a large scale and the urgent need for VBD control. Secondly, medical entomologists have traditionally not been taught epidemiology or have not worked in an integrated fashion with epidemiologists. It is necessary to upgrade this aspect of the skill set of medical entomologists, include epidemiology in medical entomology course curricula and for epidemiologists to partner with entomologists in conducting intervention assessments.

New vector control tools are urgently needed to reduce the burden of VBDs. In highlighting key problems with the design and conduct of vector control tools and suggesting remedies, we hope that this manuscript will provide an impetus for up-grading the evidence base on vector control interventions. The present lack of rigorous, evidence-based vector-borne intervention assessments is an obstacle to innovation in disease reduction. It also wastes a considerable amount of money, time and energy. Improving the quality of future vector control trials will not only save valuable resources, it will also expedite the process of achieving recommendations from WHO for the roll-out of effective new interventions.

Chapter 6: Spatial and temporal distribution of knock-down resistance in the *Anopheles gambiae* complex in the Upper River Region, The Gambia

Abstract

Entomological surveillance should be conducted by vector control programmes so that they can target and adapt programme activities. One of the parameters which should be measured is insecticide resistance. Insecticide resistance in malaria vectors presents a potential threat to malaria control which is heavily reliant on insecticide-based tools such as long-lasting insecticidal nets (LLINs). Knockdown resistance (*kdr*) is one of the major markers of resistance to dichlorodiphenyltrichloroethane (DDT) and pyrethroid insecticides.

The study aimed to determine the spatial and temporal pattern of insecticide resistance in *Anopheles gambiae* in the Upper River Region of The Gambia using data from a randomised controlled trial comparing indoor residual spraying (IRS) with DDT and LLINs, treated with pyrethroids, versus LLINs alone. Entomological collections using US Centers for Disease Control and Prevention light traps were performed monthly in 32 village clusters during the malaria transmission season in 2010 and 2011. Mixed effect models with village cluster as a random effect were used to identify risk factors for *kdr* mutations.

6828 mosquitoes were identified to molecular form level: of which 71.3% were *An. arabiensis*, 15.0% *An. gambiae* s.s., 12.3% *An. coluzzii* and 1.1% hybrids. *An. gambiae* s.s. was more common in villages further away from the River Gambia in both years. *An. arabiensis* and *An. coluzzii* were predominantly wild-type at the *kdr* locus, while *An. gambiae* s.s. were predominantly homozygous west for the *kdr* mutation and this proportion increased almost to saturation from 64.8% during 2010 to 90.9% during 2011. Multivariate analysis showed that the odds of *kdr* were 23.5 higher in *An. gambiae s.s.* in villages with both IRS and LLINs (95% Confidence Intervals, CI= 16.4-33.8) and 14.0 (95%CI= 10.3-18.9) higher in villages with LLINs alone. The *kdr* mutation was also more common in the second year of the intervention than the first (odds ratio, OR = 1.7, 95%CI= 1.5-2.0) and with increasing distance from the river (OR= 1.0, 95%CI= 1.0-1.1).

The spread of *kdr* resistance occurred rapidly through *An. gambiae* s.s., the most endophilic and efficient malaria vector in The Gambia. Given the high levels of *kdr* mutation and heterogeneous spatial distribution found in the study area, longitudinal monitoring of insecticide resistance using phenotypic assays should be a priority for the malaria control programme in The Gambia.

Introduction

Integrated Vector Management (IVM) calls for evidence-based decision making by vector control programmes, including evidence-based choice of vector control tools and their implementation but also use of evidence from surveillance and monitoring and evaluation to target and adapt programme activities. Entomological surveillance is hugely important, not only to determine vector species present and their bionomics, but also susceptibility to insecticides since insecticide-based tools are currently the principal vector control interventions available to programmes, particularly for malaria.

The past 10 years have seen huge declines in malaria, particularly in sub-Saharan Africa (SSA), due to the mass deployment of long-lasting insecticidal nets (LLINs), and to a lesser extent, indoor residual spraying (IRS) [106, 405, 406]. However, this has increased selection pressure for the development of insecticide resistance in malaria vectors. The strength and distribution of insecticide resistance has been increasing over time and is now widespread in SSA [132, 407]. There is growing concern that insecticide resistance will lead to control failure which has the potential to reverse many of the gains seen in malaria control.

Malaria in The Gambia has declined substantially between 2000 and 2009 [408, 409], although a nationwide cross-sectional survey in 2012 shows continued high transmission in the eastern part of the country despite high coverage of vector control interventions [410]. As in many countries in SSA there has not been systematic measurement of insecticide resistance in The Gambia due to resource limitations and lack of awareness in the vector control community. Shortly after the introduction of permethrin-treated bednets in The Gambia in the late 1980s, there was little to no resistance to dichlorodiphenyltrichloroethane (DDT) or permethrin [411, 412]. Prior to the start of a nationwide DDT IRS campaign in 2008, DDT resistance was found in one site bordering Senegal, but mosquitoes from the site in the Upper River Region (URR) were fully susceptible to permethrin, deltamethrin and DDT, although only a small number of mosquitoes were tested [413]. Insecticide susceptibility of mosquitoes in the URR was measured using World Health Organization (WHO) tube tests during conduct of a randomised controlled trial (RCT) comparing the efficacy of LLINs versus LLINs and IRS against clinical malaria in children [388]. Tests performed in 2010 showed complete susceptibility of *An. gambiae* s.l. to DDT and permethrin (100%), while tests performed in 2011 showed some loss of susceptibility, but still high levels of mosquito mortality (mean mortality range: 88.3-94.8%). Thus insecticide resistance was probably not a reason for the study findings which showed no additional benefit of IRS on top of LLINs against clinical malaria despite high IRS and LLIN coverage [388]. However, a pilot study looking at the possibility of using alternative residual insecticides to DDT conducted in two villages in the URR just outside the RCT study area did find high levels of

insecticide resistance. The study found low mortality of *An. gambiae* s.l. when exposed to DDT (46%) and permethrin (31%) suggesting that there are pockets of high resistance in the URR [414]. More recently in 2013 there was a suggestion that insecticide resistance may be partly responsible for the heterogeneities in malaria transmission across the country, since a study found that DDT resistance measured with tube tests, was more common in villages with high malaria prevalence compared to paired villages with low malaria prevalence [415].

Mosquitoes of the *An. gambiae* complex are responsible for malaria transmission in The Gambia: namely *Anopheles coluzzii*, *An. gambiae* s.s., *An. melas* the saltwater vector found at the coast and *An. arabiensis* in the eastern part of the country, generally associated with rain fed rice fields along the edge of the alluvial soils [416-418]. In the URR only three species are present: *An. arabiensis*, *An. coluzzii*, and *An. gambiae* s.s. (Table 6.1). Previously known as M and S molecular forms, respectively, *An. coluzzii* and *An. gambiae* s.s. have been undergoing sympatric ecological diversification and are now recognised as separate species [419, 420]. This genetic divergence is thought to be in part due to distinct larval habitats which led to the evolution of reproductive isolation. Different larval ecology might affect temporal and spatial dynamics of the species and therefore have an effect on malaria transmission. *An gambiae* s.s. is generally associated with small rain-dependent breeding sites, such as puddles, while *An. coluzzii* is able to exploit semi-man-made permanent breeding sites, such as irrigated rice growing areas that are also frequented by *An. arabiensis* [421-423]. *An. coluzzii* have been shown to be more resistant to predation than *An. gambiae* s.s. which is crucial in permanent habitats [50-52]. *An. gambiae* s.s. appears to have a more rapid larval development time than *An. coluzzii* which means that it is better adapted to ephemeral breeding sites with a high risk of desiccation [424-426].

It is not clear whether there is any difference in the infection rate of wild populations of *An. gambiae* s.s. and *An. coluzzii*, with inconclusive results across studies [427-431]. Variation in susceptibility to *Plasmodium* infection in *An. gambiae* s.l. is partly due to the thioester containing protein which has anti-parasitic properties [432]. An allelic variant of the gene encoding this protein associated with resistance to experimental *P. falciparum* infections (i.e. lower oocyst burden) has been found in some *An. coluzzii* populations but not in *An. gambiae* s.s [433]. If these findings are further corroborated it suggests that *An. gambiae* s.s. are more likely to be infected with *P. falciparum* than *An. coluzzii*. Susceptibility to insecticides may also differ between the species since previous studies have found that the *kdr* mutation is more common in *An. gambiae* s.s. than *An. coluzzii* [415, 420, 434-438].

Table 6.1: Characteristics of the members of the *An. gambiae* species complex found in the Upper River Region

Characteristic	*An. arabiensis*	*An. gambiae* s.s.	*An. coluzzii*	Ref
Habitat	Water-retaining alluvial deposits with marshy vegetation or rice cultivation	Free draining soil covered with open woodland, savannah or farmland	Water-retaining alluvial deposits with marshy vegetation or rice cultivation	[417, 439]
Typical breeding site	Rice cultivation	Small rain dependent breeding sites e.g. puddles	Semi-permanent breeding sites, often created by humans e.g. rice cultivation	[417, 418, 426]
Temporal pattern	Predominant in dry season	Predominant in rainy season		[416, 418]
Larval predation	Presumably less susceptible (similar to *An. coluzzii*)	More susceptible	Less susceptible	[424, 440, 441]
Larval development time	Presumably less rapid (similar to *An. coluzzii*)	More rapid	Less rapid	[424-426]
Behaviour	Generally thought to be zoophilic but more catholic than *An. gambiae* s.s. and *An. coluzzii.* Exophagic and exophillic.	Anthropophillic. Less catholic than *An. arabiensis* in feeding habits. Endophagic and endophillic.		[217, 442]
Transmission potential / infection with *P. falciparum*	Generally said to be less efficient vector than *An. gambiae* s.s. and *An. coluzzii*	More efficient vectors than *An. arabiensis*. Unclear whether there is any difference in infection with *P. falciparum* although *An. coluzzii* may be less susceptible.		[427-431, 433, 443]
Insecticide resistance	*kdr* mutation relatively common	*kdr* mutation common	*kdr* mutation rare or absent	[415, 420, 434-438]

A greater understanding of insecticide resistance and how this varies in space and over time in the URR would be beneficial in order to plan vector control strategies and understand how to combat insecticide resistance. For example, identifying associations between land use and the members of the *An. gambiae* complex may shed light on why prevalence of the *kdr* gene is higher in some species. Identification of hotspots of resistance can help to inform the choice of vector control strategies for resistance management. The Gambia provides an ideal site in which to explore the spatial and temporal distribution of *kdr* resistance in *An. gambiae* s.l. because it lies at the interception between different ecological zones (desert to the north and rainforest to the south) and there are a range of ecological conditions within a small area. A previous study by Caputo *et al.* assessed the spatial distribution of the *An. gambiae* complex along a 400km west to east transect

following the River Gambia in 2005-6 which included 3 sampling sites in the URR [416]. This study focuses in detail on the URR and uses entomological data from 32 sampling sites to explore the temporal and spatial distribution of the *An. gambiae* species complex and *kdr* mutations. It is anticipated that *An. arabiensis* and *An. coluzzii* will be found in close proximity to the River Gambia and will be associated with rice fields, swamps and other water bodies. We expect parity of mosquitoes to increase throughout the transmission season since mosquitoes are likely to be older later in the season when breeding sites are becoming less common. *Kdr* mutations are expected to be more common in villages that received IRS-DDT and LLINs than LLINs alone due to the selection pressure contributed by the double intervention. It is anticipated that *kdr* mutations will be low in *An. coluzzii* and *An. arabiensis* but more common in *An. gambiae* s.s., as per previous studies [415, 420, 434-438].

Aim

The study aims to explore in detail the temporal and spatial distribution of the *An. gambiae* species complex and *kdr* mutations in the URR, The Gambia.

Objectives

1. Identify the temporal patterns of *An. gambiae* species complex abundance across the two years.
2. Explore the spatial distribution of the *An. gambiae* species complex in the URR.
3. Determine whether there is an association between specific waterbody types and distance to the River Gambia and members of the *An. gambiae* species complex.
4. Identify spatial and temporal patterns in the parity of *An. gambiae* s.l. caught.
5. Explore the spatial distribution and temporal patterns of *kdr* mutations in the URR.
6. Determine whether there are changes in *kdr* mutations between 2010 and 2011.
7. Determine whether there are differences in *kdr* mutations between LLIN and LLIN-IRS study arms.
8. Identify risk factors associated with *kdr* mutations, including species, study arm and time using a multivariate analysis.

Methods

Study site

The study was conducted in the URR, the most easterly administrative division in The Gambia situated more than 290km from the coast (regional capital: Basse, 13.3167° N, -14.2167° W). This is

a rural area of open Sudanian savannah characterised by tree, shrub savannah and cultivated areas. It is divided into north and south banks by the River Gambia. The south bank is more developed than the north bank and has better road access. Although the river banks are elevated to prevent flooding (which only occurs when there is exceptionally heavy rainfall), the alluvial basins alongside the river are poorly drained and often used for rice cultivation, particularly around Basse. There is a single rainy season from July to November followed by a prolonged dry season. The main malaria transmission season is during and shortly after the rains. Data on rainfall, relative humidity and maximum and minimum temperatures were obtained from the Basse weather station courtesy of The Gambia Meteorological Service, Department of Water Resources. The national malaria vector control policy is universal coverage of LLINs (LLIN use was 55% in the study villages prior to study start) and annual IRS with DDT has been carried out in the URR since 2008.

Data collection

This secondary analysis utilises entomological data from a cluster-RCT comparing the efficacy of LLINs versus LLINs and IRS with DDT against clinical malaria among children aged 6 months to 14 years in the URR of The Gambia [388]. The study design, methods and interventions, as well as the epidemiological results of the study are described in full elsewhere [388, 444].

In brief, 70 clusters of villages were randomly allocated to either LLINs or LLINs plus IRS using DDT at the start of the 2010 transmission season and the incidence of malaria in children measured during the 2010 and 2011 transmission seasons. Clusters consisted of between one and three villages and in each cluster a cohort of children were followed (between 65–213 children per cluster). LLINs (permethrin treated, 2% w/w; Olyset Nets, Sumitomo Chemicals, Japan) were distributed at the start of the study in 2010 to ensure coverage of all sleeping places and IRS with DDT (2 g/m^2, DDT 75% wettable powder; Hindustan Insecticides, New Delhi, India) was applied to dwelling rooms at the start of each season (between 15–28 July 2010 and 20 July-9 August 2011).

Entomological data collection was performed in 32 clusters (16 in each arm) in six sentinel rooms per cluster. The sample size was chosen based on the entomological endpoints of the main study – that was to detect a 60% reduction in house entering *An. gambiae* in the IRS-LLIN arm of the study with 90% power and 5% significance [388]. Clusters were a subset of those used for epidemiological data collection and were chosen purposively for logistical reasons (Figure 6.1). Using a two-stage random sampling process, six compounds were selected per cluster using a random number generator and then one house with a single occupant sleeping in it was selected per compound by spinning a bottle. Sampling was performed monthly in the six sentinel rooms per cluster from June 2010 to the end of December 2010, and then in the same houses from June 2011 to the end of December 2011.

Collections were done every two months from December 2010 to June 2010 in the same villages for the dry season sampling period. Each month/two month sampling period was termed a round. Indoor mosquitoes were collected overnight (from 19.00 h to 07.00 h) using a US Centers for Disease Control and Prevention (CDC) light trap and in each sentinel room was a single consenting adult sleeping under a bednet. Bias was reduced through the use of standardised traps, and trap catches were examined by someone other than the trap collector who was not aware of the trap location.

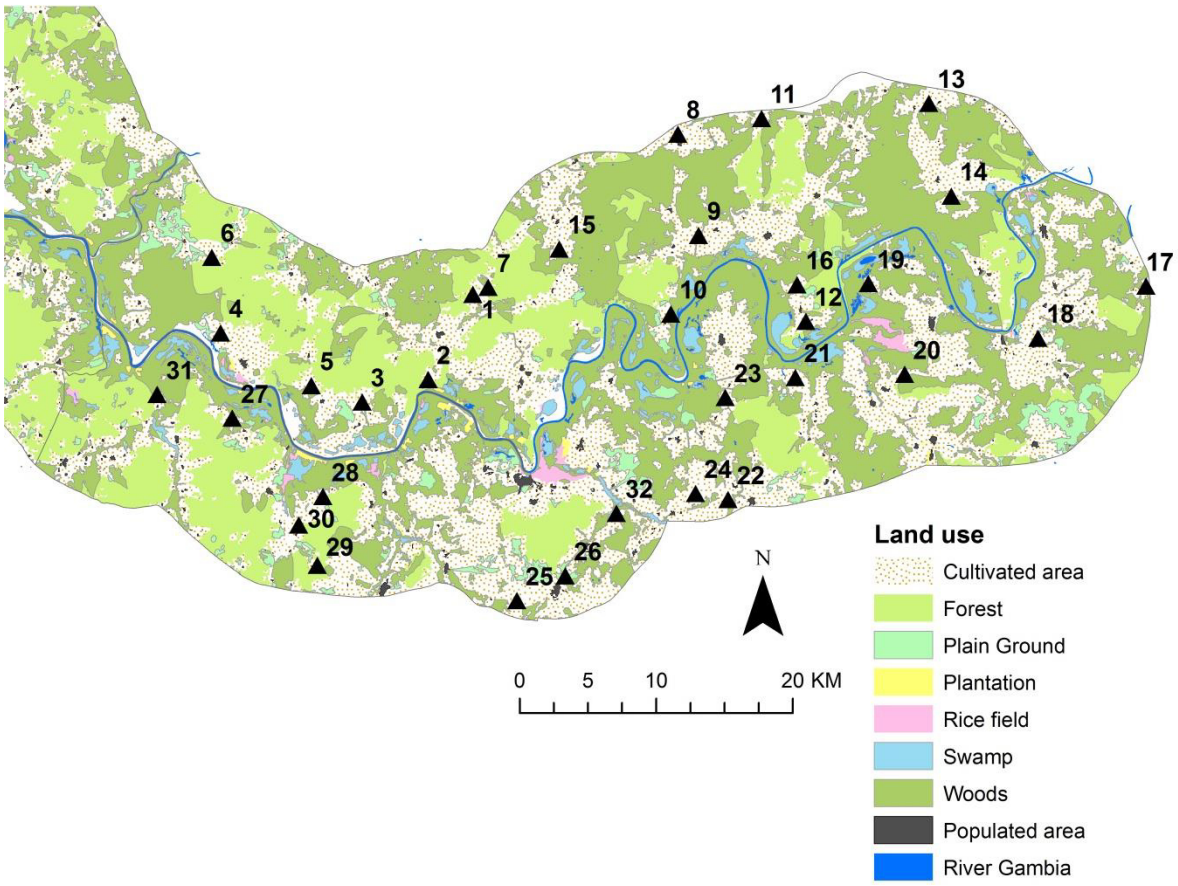

Figure 6.1: Spatial distribution of 32 entomological sampling sites in the Upper River Region of The Gambia, in relation to landcover/use

Mosquitoes were killed by freezing and were stored separately in labelled vials. Care was taken during processing to prevent any contamination between carcasses or deoxyribonucleic acid (DNA). Mosquito were identified to species morphologically using established keys [442, 445]. Mosquito parity was determined by dissection of the ovaries and examining them to see if they were parous (those that have laid eggs at least once) or nulliparous (mosquitoes that have not laid eggs). Parity

was determined for a sample of mosquitoes from each collection – ideally 25 mosquitoes from each cluster every sampling occasion; although this was not always possible if catch numbers were low as the light traps dry out the mosquitoes preventing dissection. Mosquito DNA was extracted using a Qiagen® kit (Hilden, Germany) according to the manufacturers protocol and molecular analysis using PCR was performed to identify the form (*An. arabiensis*, *An. gambiae* s.s., *An coluzzii* or hybrid) and *kdr* status (susceptible, heterozygous east or west or homozygous east or west) according to previously described methods [446-448]. Here we term a leucine to phenylalanine amino acid change at position 1014 (L1014F) found mainly in West African countries as "west" and a leucine to serine substitution at the same amino acid position (L1014S) found mainly in East African countries as "east".

Mapping and spatial analysis

Digitised maps based on aerial photography and field survey data produced by the Japan International Cooperation Agency under The Japanese Government Technical Cooperation Programme and The Government of the Republic of The Gambia from 2002 were obtained. Coordinates of villages were taken manually using a hand-held global positioning system (*Garmin* eTrex® 10) during sampling and the midpoint of population areas demarcated on the Japanese maps was used for mapping and spatial analysis.

Coordinates and shape files were plotted using ArcGIS® software (Release 10.4.1, Environmental Systems Research Institute (ESRI): Redlands, CA). Average land use classification was calculated according to the methods of Thomas and Lindsay [449]. A circular buffer of 1 km, 1.5 km and 2 km radius corresponding to the typical flight range of *An. gambiae* was generated around the midpoint of each village and was overlaid on the land cover maps. Although Thomas *et al.* found 97.2% of *An. gambiae* found within 2km of a larval habitat in central Gambia [450], the flight distance is dictated by the landscape and mosquitoes may not fly as far in the URR. The relative proportion of each land cover type within the buffer was then calculated, focusing on rice fields, swamps and water bodies (ponds and lakes); all potential mosquito breeding sites. The River Gambia was excluded since it is fast flowing and is not a suitable breeding site for *An. gambiae* s.l. [451]. Initially it was planned to set up a distance decay function (inverse Euclidean distance weighting) on the contribution of land use categories in the buffer area given that a mosquito breeding site close to a village was more likely to contribute vectors. However, this was not done since there was no discernible pattern between the three different water body types and mosquito species when plotted.

Spatial features and their associated values tend to be clustered in space and therefore we calculated the global Moran's spatial autocorrelation coefficient, I, to examine spatial independence

in variables and residuals of regressions (i.e. whether the spatial pattern in the variables is clustered, dispersed, or random). Moran's I was calculated at 1 km intervals from 1 km up to 25 km to measure the intensity of spatial clustering at each distance. Moran's I was only valid at distance of 9 km upwards since this was the shortest distance at which all sampling point locations had at least one neighbour. The z-score returned indicated the intensity of clustering, with the first peak on the graph of z taken as the spatial scale at which there was most clustering. There was said to be no clustering operating at spatial scales when the z-score p-value fell below 0.05.

Statistical analysis

The entomological dataset was double-entered using Microsoft Access and cleaned before use. Absolute numbers and proportions of mosquitoes by form and *kdr* mutation status by month were calculated. The transmission seasons were defined as 16 August- 31 December 2010 and 15 August 2011- 1 January 2012 so as to avoid the months prior to and during application of IRS and the intervening dry season. Proportions of mosquitoes by form and *kdr* mutation status over the two transmission seasons were calculated by village. Chi-squared tests were used to test for differences in variables within sampling years. Cochran-Mantel-Haenszel tests were used to determine whether there was a difference in species composition, *kdr* mutations and parity across villages between 2010 and 2011. Score test for trend in odds was used to compare proportion of parous mosquitoes across rounds within years. Linear regression was used to assess the relationship between species type and Euclidean distance from the River Gambia. Mixed effects models including village as a random effect were used to compare the odds of *kdr* mutations by species, adjusting for confounders such as study arm (LLIN-IRS versus LLIN only) and time (year 1 and 2). Hybrid forms were excluded from the model since they were few in number and absent during the second year of sampling. Reliability of numerical approximations used to estimate parameters was checked. Statistical analysis was performed using Microsoft Excel and Stata 13 (College Station, TX, USA).

Ethics

Prior to study start, meetings were held with the head of the villages to explain about the study and seek permission to catch mosquitoes in houses. Householders provided informed consent for entomological data collection in their homes. The original trial was approved by the Gambian Government and Medical Research Council Unit Joint Ethics Committee on Aug 12, 2008 (reference L2009.15) with minor amendments approved on April 30, 2010 (L2010.19; SCC1128), and by the London School of Hygiene & Tropical Medicine Ethics Committee on Sept 16, 2009 (reference 5592).

Results

Temperatures in the study area followed a similar pattern in both 2010 and 2011 with maximum temperatures reaching over 41° C in the dry season (Figure 6.2). Rainfall was above average in 2010 (total: 1116 mm), and about average in 2011 (total: 890 mm).

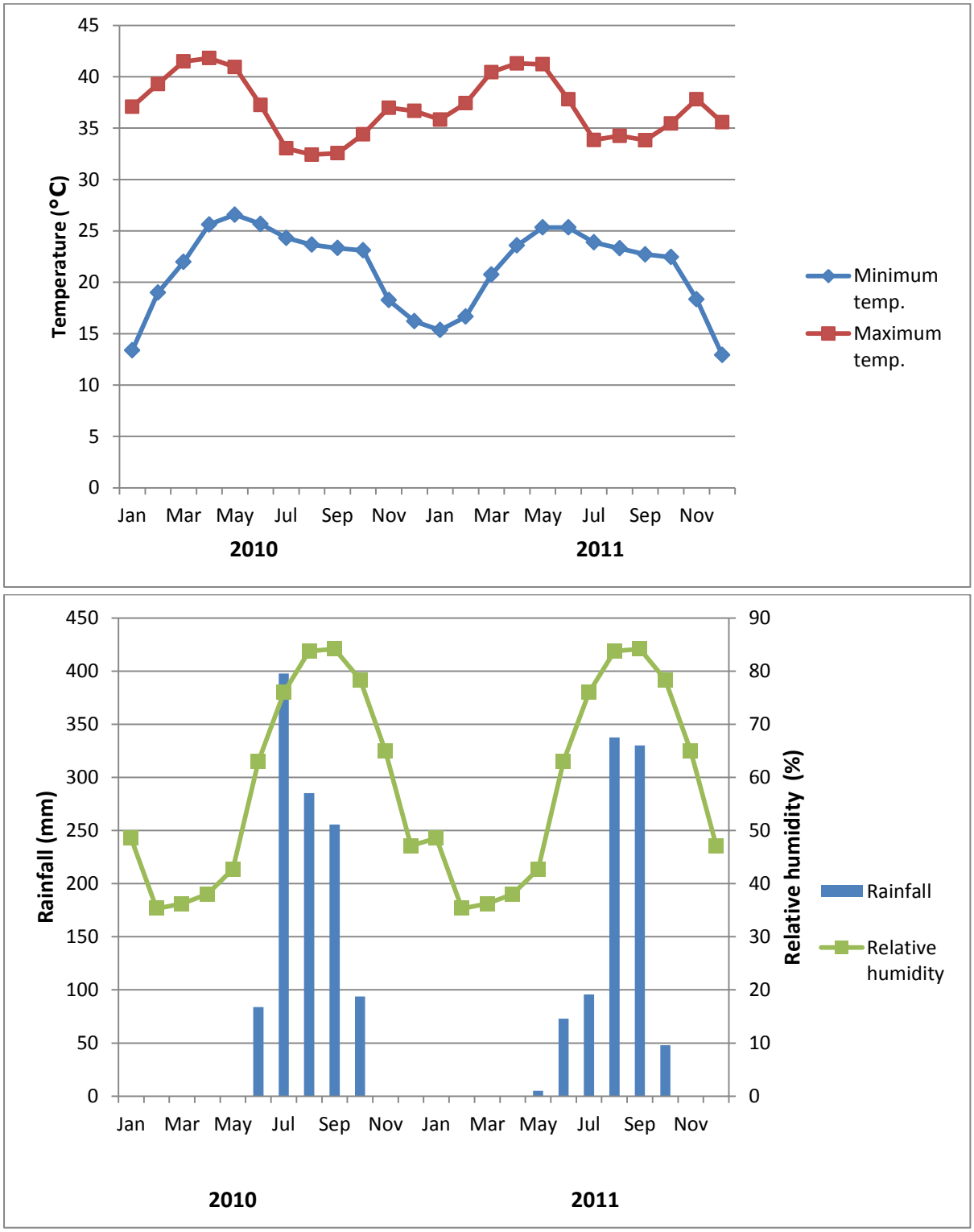

Figure 6.2: Rainfall, relative humidity and temperature at the Basse weather station during the study period 2010-2011

A total of 9682 female anophelines were caught in the 32 sampling sites over the study period, of which 6853 were *An. gambiae s.l.* Of these *An. gambiae s.l.*, 6828 were identified to species. 4864 mosquitoes were *An. arabiensis* (71.3%), 1021 *An. gambiae* s.s. (15.0%), 838 *An. coluzzii* (12.3%) and 73 *An. gambiae* s.s. and *An. coluzzii* hybrid form (1.1%) (Figure 6.3). A total of 29 mosquitoes were caught in the two dry season sampling rounds in Feb 2011 and May 2011 (of these 25 were *An. arabiensis*, 2 *An. gambiae* s.s. and 2 *An. coluzzii*).

The remainder of the analysis (unless otherwise stated) focuses on the two transmission periods spanning 16 August-31 December 2010 and 15 August 2011-1 January 2012, and excludes the intervening dry season and entomological data collected prior to administration of IRS at the start of the transmission season each year. There were proportionally fewer *An. arabiensis* in the second year compared to the first and therefore it was not appropriate to combine species data from 2010 and 2011 ($X^2_{M\text{-}H}$= 132.6, p<0.001, odds ratio= 0.48, 95%CI=0.42-0.54). During the 2010 transmission season 76.1% of *An. gambiae s.l.* were *An. arabiensis*, 12.0% *An. gambiae* s.s., 10.1% *An. coluzzii* and 1.3% hybrid form (Table 6.2). 57.8% of *An. gambiae s.l.* caught were *An. arabiensis*, 23.0% *An. gambiae* s.s. and 19.0% *An. coluzzii* during the 2011 transmission season. No hybrid forms were caught during the 2011 transmission season. There was an increase in the proportion of *An. gambiae* s.s. in 2011 compared to 2010 ($X^2_{M\text{-}H}$=8.79, p=0.003, OR = 1.40, 95%CI= 1.12-1.75).

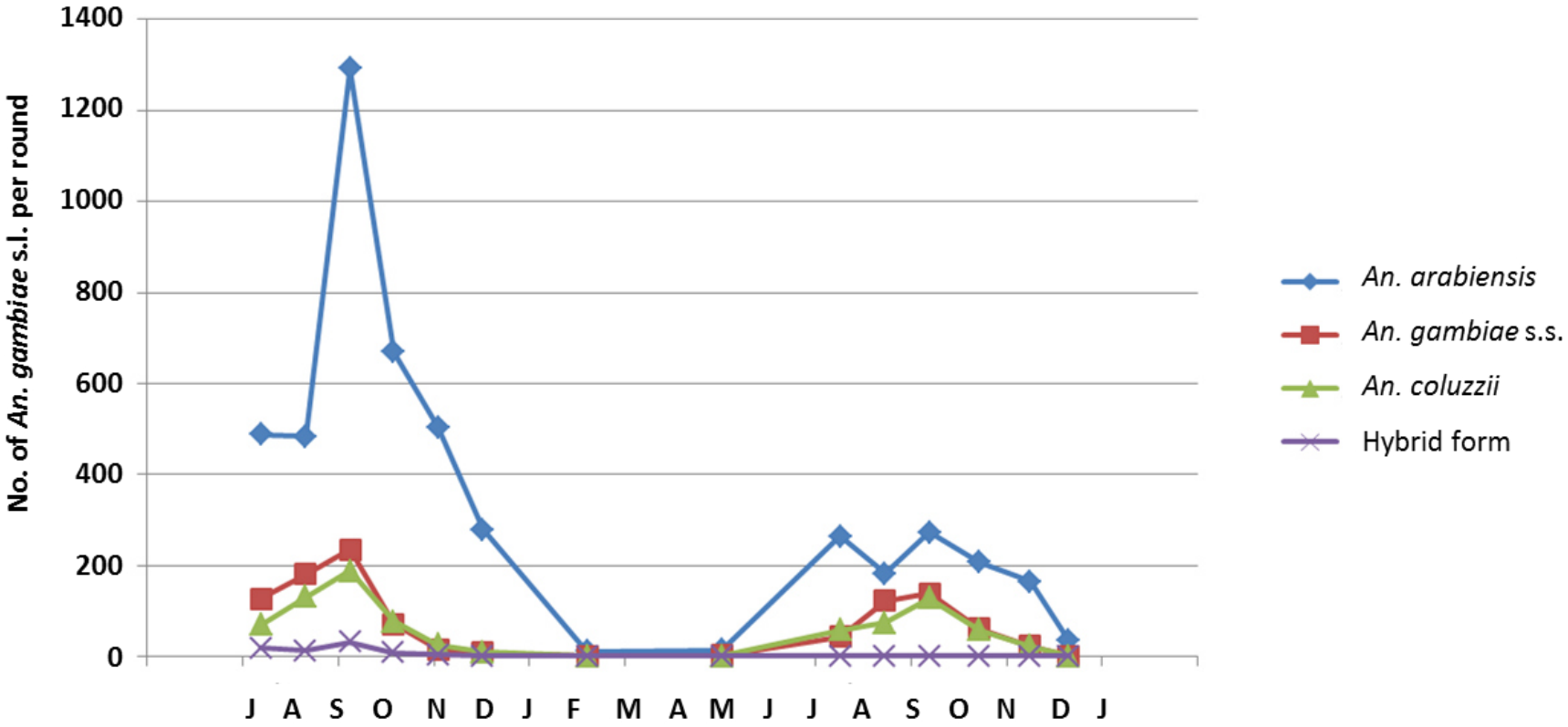

Figure 6.3: Number of *An. arabiensis*, *An. gambiae* s.s., *An. coluzzii* and hybrid (*An. gambiae* s.s. and *An. coluzzii*) caught using CDC light traps per round during 2010 and 2011

IRS using DDT was administered between 15–28 July 2010 and 20 July-9 August 2011.

Table 6.2: Characteristics of village clusters and proportion species composition during 2010 and 2011 transmission seasons

Site code	Sampling site	Study arm	Coordinates		2010					2011				
			Lat	Long	N	*An. arabiensis*	*An. gambiae* s.s.	*An. coluzzii*	Hybrid form	N	*An. arabiensis*	*An. gambiae* s.s.	*An. coluzzii*	Hybrid form
	North bank													
1	Tuba Mandinka	DDT	13.43321	-14.2502	103	75 (72.8%)	13 (12.6%)	15 (14.6%)	0	4	3 (75.0%)	0	1 (25.0%	0
2	Mbye Kunda	LLIN	13.37692	-14.2806	373	316 (84.7%)	3 (0.8%)	44 (11.8%)	0	277	194 (70.0%)	41 (14.8%)	42 (15.2%)	0
3	Changally Chewdo	DDT	13.36216	-14.3253	19	13 (68.4%)	0	3 (15.8%)	1 (5.3%)	*				
4	Kuraw Arafang	LLIN	13.40808	-14.421	128	103 (80.5%)	1 (0.8%)	22 (17.2%)	2 (1.6%)	20	12 (60.0%)	4 (20.0%)	4 (20.0%)	0
5	Jakaba	LLIN	13.37311	-14.3596	76	57 (75.0%)	6 (7.9%)	13 (17.1%)	0	12	5 (41.7%)	2 (16.6%)	5 (41.7%)	0
6	Sare Jallow	DDT	13.45815	-14.4268	10	10 (100%)	0	0	0	*				
7	Tuba Wuli	DDT	13.43777	-14.2397	38	29 (76.3%)	6 (15.8%)	3 (7.9%)	0	3	3 (100.0%)	0	0	0
8	Jecka	LLIN	13.53879	-14.1112	37	27 (73.0%)	9 (24.3%)	0	1 (2.7%)	5	3 (60.0%)	2 (40.0%)	0	0
9	Medina Saho	LLIN	13.47172	-14.0974	291	264 (90.7%)	16 (5.5%)	11 (3.8%)	0	81	59 (72.8%)	10 (12.3%)	12 (14.8%)	0
10	Limbanbulu Bambo	DDT	13.41971	-14.1164	316	245 (77.5%)	32 (10.1%)	30 (9.5%)	7 (2.2%)	202	134 (66.3%)	13 (6.4%)	54 (26.7%)	0
11	Mureh Kunda	DDT	13.54888	-14.0546	52	36 (69.2%)	16 (30.8%)	0	0	22	6 (27.3%)	15 (68.2%)	1 (4.5%)	0
12	Boro Dampha Kunda	DDT	13.41458	-14.0251	276	227 (82.2%)	14 (5.1%)	20 (7.2%)	11 (4.0%)	138	90 (65.2%)	9 (6.5%)	39 (28.3%)	0
13	Musa Kunda	DDT	13.55847	-13.9412	120	82 (68.3%)	29 (24.2%)	4 (3.3%)	5 (4.2%)	20	5 (25.0%)	14 (70.0%)	1 (5.0%)	0
14	Foday Kunda	LLIN	13.497	-13.9263	117	110 (94.0%)	5 (4.3%)	2 (1.7%)	0	13	9 (69.2%)	2 (15.4%)	2 (15.4%)	0

15	Tuba Buray	LLIN	13.463	-14.1917	53	41 (77.4%)	10 (18.9%)	2 (3.8%)	0	1	1 (100.0%)	0	0	0
16	Boro Modi Banni	LLIN	13.43877	-14.031	115	98 (85.2%)	4 (3.5%)	9 (7.8%)	4 (3.5%)	41	33 (80.5%)	4 (9.8%)	4 (9.8%)	0
	South Bank													
17	Bolibana	LLIN	13.43679	-13.7948	101	67 (66.3%)	25 (24.8%)	7 (6.9%)	2 (2.0%)	14	8 (57.1%)	5 (35.7%)	1 (7.1%)	0
18	Fantumbung	LLIN	13.40275	-13.8681	58	48 (82.8%)	7 (12.1%)	3 (5.2%)	0	32	9 (28.1%)	21 (65.6%)	2 (6.3%)	0
19	Nema	LLIN	13.43932	-13.9828	223	202 (90.6%)	3 (1.3%)	15 (6.7%)	3 (1.3%)	124	75 (60.5%)	14 (11.3%)	35 (28.2%)	0
20	Kumbul	DDT	13.37917	-13.9584	118	94 (79.7%)	12 (10.2%)	8 (6.8%)	3 (2.5%)	19	4 (21.1%	12 (63.2%)	3 (15.8%)	0
21	Perai	LLIN	13.37738	-14.0324	373	325 (87.1%)	18 (4.8%)	28 (7.5%)	2 (0.5%)	58	31 (53.4%)	13 (22.4%)	12 (20.7%)	0
22	Niji	DDT	13.29681	-14.0781	156	48 (30.8%)	88 (56.4%)	19 (12.2%)	0	91	23 (25.3%)	63 (69.2%)	4 (4.4%)	0
23	Koli Kunda	DDT	13.36431	-14.0798	118	88 (74.6%)	12 (10.2%)	17 (14.4%)	0	12	2 (16.7%)	9 (75.0%)	1 (8.3%)	0
24	Keneba	DDT	13.3009	-14.1002	50	23 (46.0%)	21 (42.0%)	6 (12.2%)	0	11	2 (18.2%)	7 (63.6%)	2 (18.2%)	0
25	Manpata Yel	DDT	13.23037	-14.221	185	101 (54.6%)	62 (33.5%)	21 (11.4%)	1 (0.5%)	33	19 (57.6%)	10 (30.3%)	4 (12.1%)	0
26	Sare Yero Cheke	LLIN	13.24672	-14.1883	91	51 (56.0%)	29 (31.9%)	11 (12.1%)	0	59	43 (72.9%)	15 (25.4%)	1 (1.7%)	0
27	Tabajang	LLIN	13.35163	-14.4133	275	190 (69.1%)	20 (7.3%)	56 (20.4%)	7 (2.5%)	55	21 (38.2%)	9 (16.4%)	25 (45.5%)	0
28	Sare Sankuleh	DDT	13.29962	-14.352	51	35 (68.6%)	7 (13.7%)	9 (17.6%)	0	21	7 (33.3%)	6 (28.6%)	8 (38.1%)	0
29	Jalali Kunda	DDT	13.25416	-14.3558	21	9 (42.9%)	8 (38.1%)	4 (19.0%)	0	11	5 (45.5%)	4 (36.4%)	2 (18.2%)	0
30	Hella Kunda	LLIN	13.2809	-14.3683	29	14 (48.3%)	4 (13.8%)	7 (24.1%)	4 (13.8%)	31	14 (45.2%)	8 (25.8%)	9 (29.0%)	0
31	Timbinto	LLIN	13.36741	-14.4639	166	137 (82.5%)	4 (2.4%)	22 (13.3%)	2 (1.2%)	33	25 (75.8%)	3 (9.1%)	5 (15.2%)	0
32	Taba Tafsir	DDT	13.28795	-14.1535	103	62 (60.2%)	24 (23.3%)	17 (16.5%)	0	45	15 (33.3%)	27 (60.0%)	3 (6.7%)	0
* No data from two villages (Changally Chewdo and Sare Jallow) in 2011														

Higher proportions of *An. arabiensis* were caught closer to the river than further away in 2010 (coefficient= -3.78, for every 1 km from the river there was a 3.78 % decrease in *An. arabiensis* percentage, 95%CI=-4.53 to -3.02, p<0.001, adjusted R^2= 49.2 %) (Figure 6.4). This negative linear relationship was not observed in 2011 (r= -0.72, 95%CI=-2.75 to 1.32, p=0.5, adjusted R^2= -0.5%). There was no evidence of an association between proportion of *An. coluzzii* caught and distance from the River Gambia in 2010 (r= -0.07, 95%CI= -0.59 to 0.45, p=0.8, adjusted r^2= -0.9%) but there was a significant negative correlation in 2011 with higher proportions being found in sampling points closer to the river compared to further away (r= -2.83, 95%CI= -3.85 to -1.81, p<0.001, adjusted r^2= 22.6%) (Figure 6.5). Higher proportions of *An. gambiae* s.s. were caught in sampling points further from the river compared to sampling points close to the river in both years (2010: r= 3.95, 95%CI= 3.5 to 4.4, p<0.001 adjusted r^2= 75.0%, 2011: r= 3.61, 95%CI= 1.68 to 5.54, p<0.001, adjusted r^2= 11.3%) (Figure 6.5). There was no evidence of an association between proportion of hybrid form caught and distance from the River Gambia in 2010 (r=0.02, 95%CI= -0.23 to 0.27, p=0.9, adjusted r^2= -1.0%). Visual inspection of graphs showing the proportion of rice field, swamp and lakes or ponds falling within 1km, 1.5km and 2km of sampling points and the proportion of the different *An. gambiae* s.l. species did not indicate any pattern and so this was not evaluated further as a variable.

Spatial autocorrelation was found in species distributions. During 2010, spatial autocorrelation in proportion of *An. arabiensis* was highest at 11 km (Moran's I=0.44, z=3.60, p<0.001) and was no longer present at 24 km. During 2011, there was less spatial autocorrelation in *An. arabiensis* (at 9 km Moran's I=0.27, z=1.89, p=0.06). During 2010, spatial autocorrelation in proportion of *An. gambiae* s.s. peaked at 14 km (Moran's I=0.35, z=3.82, p<0.001) and was no longer present at 20 km. During 2011, spatial autocorrelation in *An. gambiae* s.s. peaked at 9 km (Moran's I= 0.38, z=2.59, p=0.01) and was absent at 20 km. In 2010 spatial autocorrelation in proportion of *An. coluzzii* was highest at 11km (Moran's I=0.66, z=5.16, p<0.001) and was still present at the maximum extent of the feature class. In 2011 clustering in *An. coluzzii* was highest at 9km (Moran's I= 0.28, z=1.98, p=0.05) but absent at 13km.

It was less likely to find *An. arabiensis* indoors in the DDT and LLIN arm compared to the LLIN arm of the study in both years, adjusting for clustering (2010: OR= 0.49, 95%CI= 0.28-0.86, p=0.01; 2011: OR= 0.44, 95%CI= 0.25-0.77, p=0.004). In 2010 66.9% of mosquitoes in the LLIN-DDT arm were *An. arabiensis* compared to 81.4% in the LLIN only arm. In 2011 50.5% of mosquitoes in the LLIN-DDT arm were *An. arabiensis* compared to 63.5% in the LLIN arm. There was a significantly increased odds of *An. gambiae* s.s. in the DDT and LLIN arm compared to the LLIN arm of the study in both years, adjusting for clustering (2010: OR= 3.21, 95%CI=1.48-6.96, p=0.003; 2011: OR= 2.71, 95%CI=

1.18-6.20, p=0.02). In 2010 21.4% of mosquitoes in the LLIN-DDT arm were *An. gambiae* s.s. compared to 7.6% in the LLIN only arm. In 2011 30.0% of mosquitoes in the LLIN-DDT arm were *An. gambiae* s.s. compared to 17.9% in the LLIN only arm. There was no difference in the proportion of *An. coluzzii* caught between the DDT and LLIN arm and LLIN only arm in both 2010 and 2011, adjusting for clustering (2010: OR= 1.13, 95%CI= 0.66-1.93, p= 0.66; 2011: OR= 0.80, 95%CI= 0.40-1.60, p=0.54). Similarly, there was no difference in the proportion of hybrid forms caught between the DDT and LLIN arm and the LLIN only arm in 2010, adjusting for clustering (OR= 0.65, 95%CI= 0.17-2.41, p= 0.52).

Parity was high in the study area and ranged from 57.7% to 87.9% in villages during the 2010 transmission season and 52.2% to 93.3% during the 2011 transmission season. There was a significant difference in the proportion of mosquitoes that were parous by village cluster in 2010 (X_2= 53.8, p= 0.005) and 2011 (X_2= 49.7, p= 0.007). However, this was not associated with DDT spraying since there was no difference in the odds of mosquitoes being parous by whether the village received LLINs or LLINs with IRS in 2010 (OR=0.98, 95%CI= 0.80-1.20, X^2= 0.03, p= 0.85) or 2011 (OR=1.28, 95%CI= 0.82-2.00, X^2=1.17, p=0.28). For every increase in sampling round during the 2010 transmission season there was a significant 0.84 reduction in the odds of a mosquito being parous, adjusted for entomological cluster (95%CI= 0.78-0.92, X^2=16.74, p<0.001, test for trend in odds: X^2= 21.17, p<0.001). However, in 2011 there was no significant difference in the odds of a mosquito being parous across the rounds, adjusting for entomological cluster (adjusted OR= 0.92, 95%CI= 0.81-1.05, X^2= 1.38, p=0.24, test for trend in odds: X^2= 1.98, p=0.16). None of the 29 mosquitoes caught in the dry season sampling rounds (February 2011 and May 2011) were dissected for parity. There was no difference in parity between years, adjusting for village (X^2_{M-H}=0, p=0.98, adjusted OR= 1.00, 95%CI= 0.78 - 1.29).

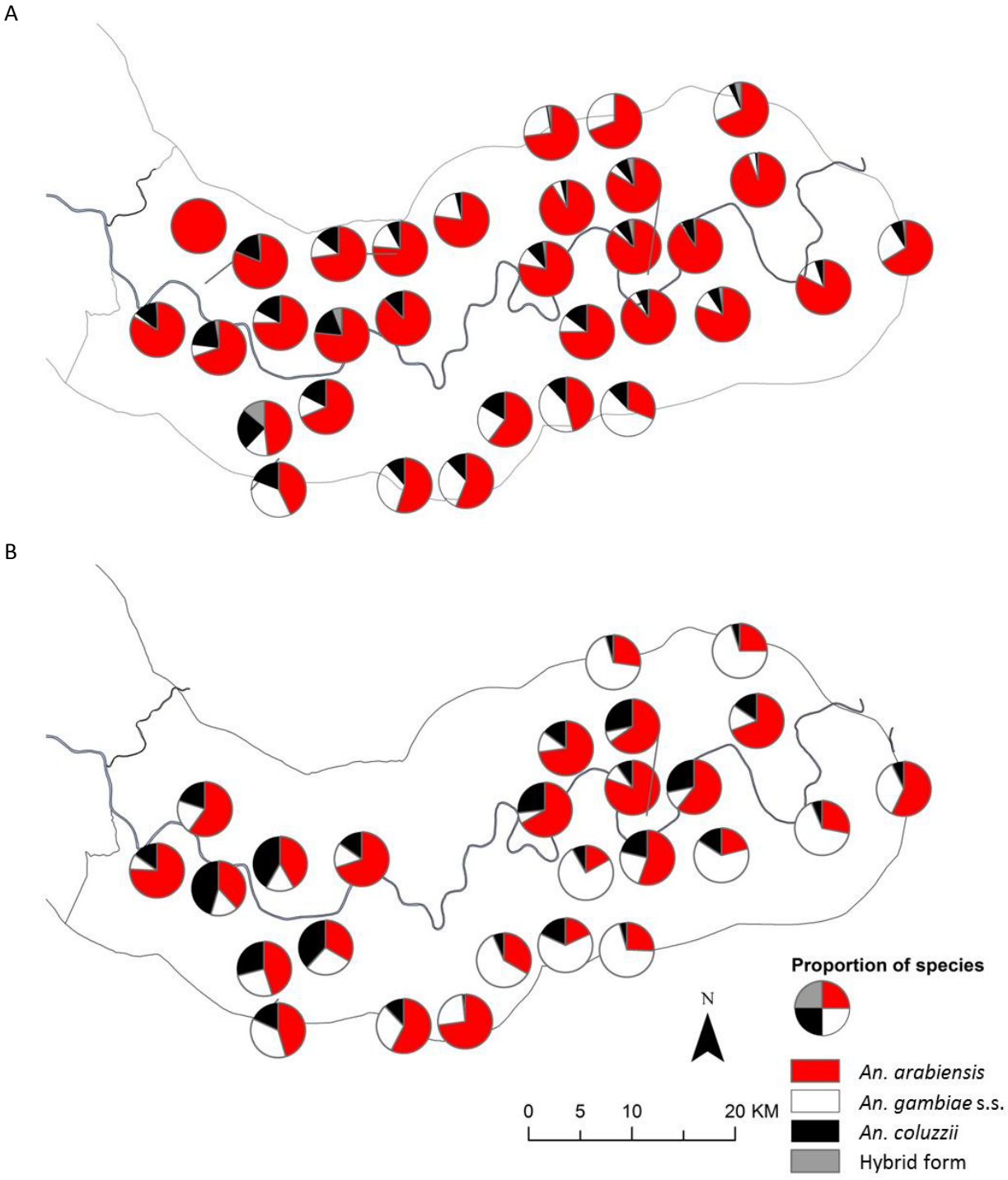

Figure 6.4: Distribution of members of the *An. gambiae* s.l. complex in the study area during 2010 (Panel A) and 2011 (Panel B) transmission seasons

Pie charts show percentage composition of species of *An. gambiae* s.l. complex at CDC light trap sampling sites, (excluding sampling sites with less than 10 mosquitoes caught in total across each transmission season).

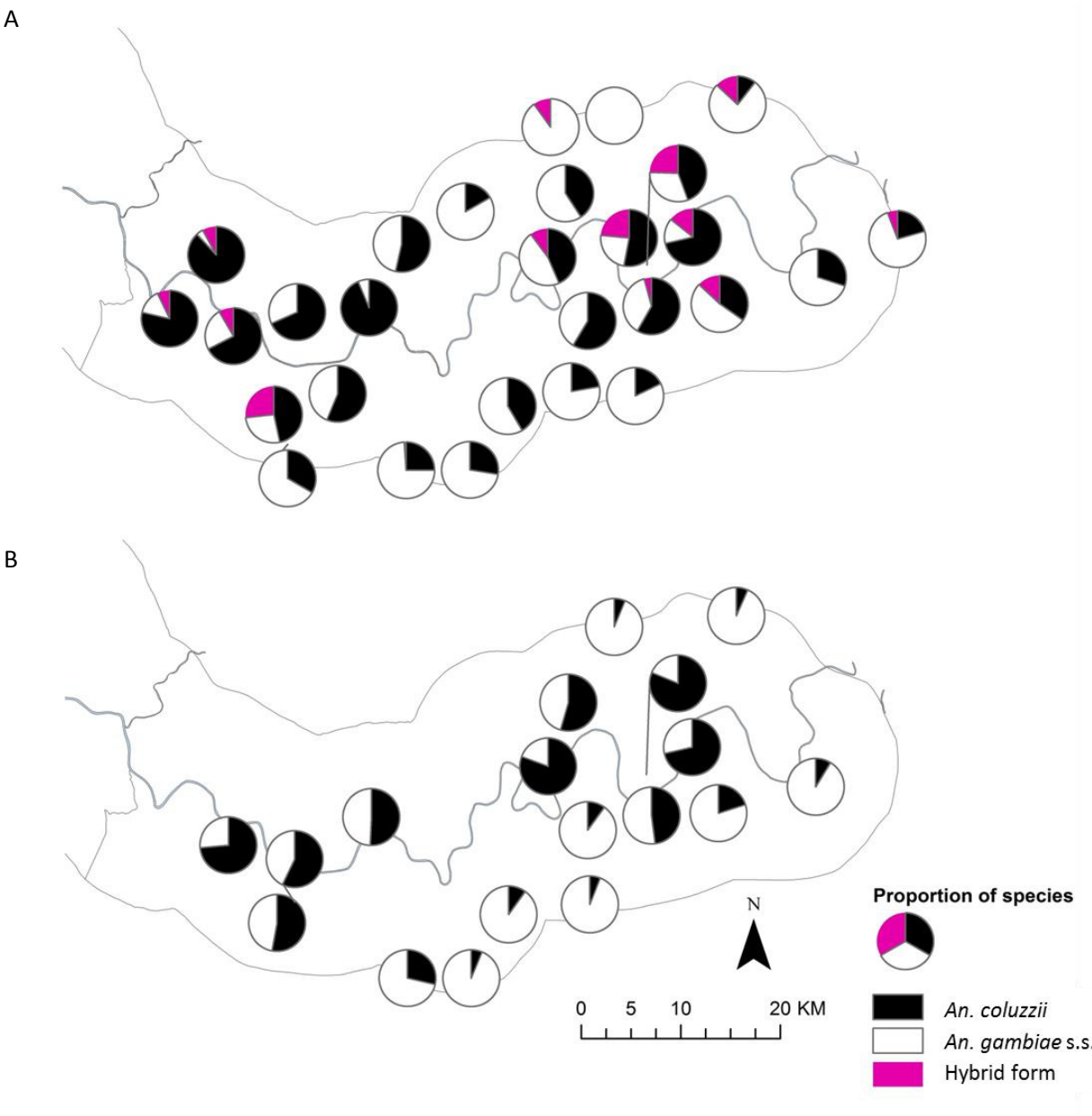

Figure 6.5: Distribution of members of the *An. gambiae* s.l. species complex (excluding *An. arabiensis*) in the study area during 2010 (Panel A) and 2011 (Panel B) transmission seasons

Pie charts show percentage *An. gambiae* s.l. species composition (excluding *An. arabiensis*) at CDC light trap sampling sites (excluding sampling sites with less than 10 mosquitoes caught in total across each transmission season).

Kdr-west and *kdr*–east mutations were found in all four species sampled but at differing levels. *An. arabiensis* were predominantly wild-type at the *kdr* locus (73.1% wild type during 2010 and 58.1% during 2011) (Table 6.3). The proportion of *An. arabiensis* with heterozygous east mutations increased between the two years (20.5% during 2010 to 28.3% during 2011) (X^2_{M-H}=28.41, p<0.001, adjusted OR = 1.56, 95%CI= 1.32-1.83). *An. gambiae* s.s. were predominantly homozygous west for

the *kdr* mutation and this proportion increased almost to saturation from 64.8% in 2010 to 90.9% in 2011 (X^2_{M-H}= 93.39, p<0.001, adjusted OR = 5.21, 95%CI= 3.73-7.29). *An. coluzzii* were predominantly wild-type at the *kdr* locus with proportions of 73.1% during 2010 and 70.9% during 2011. Hybrid forms were predominantly wild-type at the *kdr* locus during 2010 (49.1%), with lower proportions homozygous west (23.6%) and heterozygous west (12.7%).

Kdr mutations were more common in villages that received IRS and LLINs compared to LLINs alone (Table 6.4). The odds of having any type of *kdr* mutation was 1.70 times higher in the IRS and LLIN arm compared to the LLIN arm in 2010 (95%CI= 1.16-2.50, p=0.007) with 42.3% of mosquitoes carrying any *kdr* mutation in the IRS and LLIN arm and 29.0% in the LLIN only arm. Similar results were found in 2011. Mosquitoes caught in IRS and LLIN villages in 2011 had 2.26 times the odds of having any *kdr* mutation compared to mosquitoes in LLIN only villages (95%CI= 1.24-4.11, p=0.008) with 57.9% of mosquitoes carrying any *kdr* mutation in the IRS and LLIN arm and 44.5% in the LLIN only arm. This was primarily due to the higher proportion of *kdr*-west mutations, particularly homozygous-west mutations, in the IRS and LLIN arm compared to the LLIN arm. In 2010 IRS-LLIN villages had 2.55 times the odds of mosquitoes carrying homozygous-west mutations compared to the LLIN only village (95%CI= 1.22-5.36, p=0.01), while in 2011 this figure was 2.52 (95%CI= 1.20-5.29, p=0.01). There was a higher odds of a mosquito carrying the heterozygous-west mutation in 2010 (OR=2.45, 95%CI= 1.37-4.37, p=0.002) but not in 2011 (OR= 1.32, 95%CI= 0.75-2.33, p= 0.34). No significant difference in the odds of heterozygous-east or homozygous-east mutations was found between IRS-LLIN villages and LLIN villages in 2010 or 2011.

Adjusting for clustering, mosquitoes in 2011 had 1.92 times the odds (95%CI= 1.70-2.16, p<0.001) of having any *kdr* mutation compared to mosquitoes caught during 2010 (Table 6.5). Visual inspection of maps showing the distribution of *kdr* mutations shows an increase in the proportion of homozygous west mutations in villages on the south bank and in the northern part of the study area bordering Senegal between 2010 and 2011, which mirrors the increase in *An. gambiae* s.s. in the study area (Figure 6.6).

The presence of any *kdr* mutation increased away from the River Gambia (OR= 1.12, 95%CI=1.08-1.17, p<0.001) (Table 6.5). *Kdr* mutations were also more common on the south bank, with mosquitoes there having 1.61 times the odds of having any *kdr* mutation (95%CI= 1.15-2.26, p=0.006) compared to sites on the north bank (Table 6.5). Average percentage parity of mosquitoes caught in the villages was not associated with the odds of having any *kdr* mutation (OR= 2.18, 95%CI= 0.19-24.37, p=0.53). Similarly, there was no association between the odds of having any *kdr*

mutation and mean density of *An. gambiae* s.l. per trap/night/village (OR= 0.95, 95%CI= 0.88-1.04, p= 0.28) or percentage LLIN use in the villages (OR= 0.45, 95%CI= 0.02-10.71, p= 0.62).

In the final multivariate model, species, study arm, year of survey and distance from the river were associated with odds of any *kdr* mutation. Species was strongly associated with the odds of any *kdr* mutation and this association differed by study arm (i.e. study arm was an effect modifier of the association between species and *kdr* mutations) (Likelihood ratio test p<0.001). *An. gambiae* s.s. mosquitoes caught in villages in the LLIN only arm had 13.95 times the odds of having any *kdr* mutation (95%CI= 10.29-18.92, p<0.001), and *An. gambiae* s.s. in the LLIN and DDT-IRS arm had 23.54 times the odds of having any *kdr* mutation (95%CI= 16.37-33.84, p<0.001) compared to *An. arabiensis* in the LLIN only arm. *An. coluzzii* in the LLIN arm had 0.60 times the odds of any *kdr* mutation compared to *An. arabiensis* in the same study arm (95%CI= 0.46-0.77, p<0.001). There was no difference in the odds of having any *kdr* mutation among *An. coluzzii* in the DDT-IRS and LLIN arm (OR= 1.27, 95%CI= 0.95-1.70, p=0.11) and *An. arabiensis* in the DDT-IRS and LLIN arm (OR= 1.03, 95%CI= 0.84-1.26, p=0.77) compared to *An. arabiensis* in the LLIN only arm. Mosquitoes caught in 2011 had 1.71 times the odds of having any *kdr* mutation compared to those caught in 2010 (95%CI= 1.49-1.96, p<0.001). Distance from the river was linearly associated with the odds of a mosquito having any *kdr* mutation (1.03 increase in the odds for every km from the river, 95%CI= 1.00-1.06, p=0.04).

Table 6.3: *kdr* resistance status by species in the study area during 2010 and 2011 transmission seasons

Resistance status	*An. arabiensis*				*An. gambiae* s.s.				*An. coluzzii*				Hybrid form			
	2010		2011		2010		2011		2010		2011		2010		2011	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Wild type	2360	73.1	500	58.1	74	14.6	10	2.9	313	73.1	200	70.9	27	49.1		
Heterozygous West	31	1.0	18	2.1	93	18.3	12	3.5	38	8.9	35	12.4	7	12.7		
Homozygous West	44	1.4	23	2.7	329	64.8	311	90.9	66	15.4	30	10.6	13	23.6		
Heterozygous East	662	20.5	243	28.3	3	0.6	0	0.0	6	1.4	1	0.4	0	0.0		
Homozygous East	77	2.4	39	4.5	3	0.6	0	0.0	1	0.2	1	0.4	3	5.5		
N (includes missings)	3227		860		508		342		428		282		55		0	

Table 6.4: Odds of *kdr* mutations according to study arm in 2010 and 2011

Kdr mutation status	2010				2011			
	IRS-LLIN arm	**LLIN only arm**	OR (95%CI) (adjusted for clustering)	P-value	**IRS-LLIN arm**	**LLIN only arm**	OR (95%CI) (adjusted for clustering)	P-value
	Percentage	Percentage			Percentage	Percentage		
Wild type	57.5%	70.8%	0.59 (0.40-0.87)	0.008	41.9%	55.3%	0.45 (0.24-0.81)	0.009
Any *kdr* mutation	42.3%	29.0%	1.70 (1.16-2.50)	0.007	57.9%	44.5%	2.26 (1.24-4.11)	0.008
Heterozygous-west	6.4%	2.8%	2.45 (1.37-4.37)	0.002	5.2%	4.1%	1.32 (0.75-2.33)	0.34
Homozygous-west	18.2%	7.2%	2.55 (1.22-5.36)	0.013	32.9%	20.3%	2.52 (1.20-5.29)	0.014
Heterozygous- east	15.1%	17.0%	0.83 (0.67-2.38)	0.48	15.9%	17.9%	0.71 (0.41-1.23)	0.22
Homozygous-east	2.4%	1.8%	1.26 (0.87-2.21)	0.16	3.7%	2.2%	1.34 (0.53-3.36)	0.54

A

B

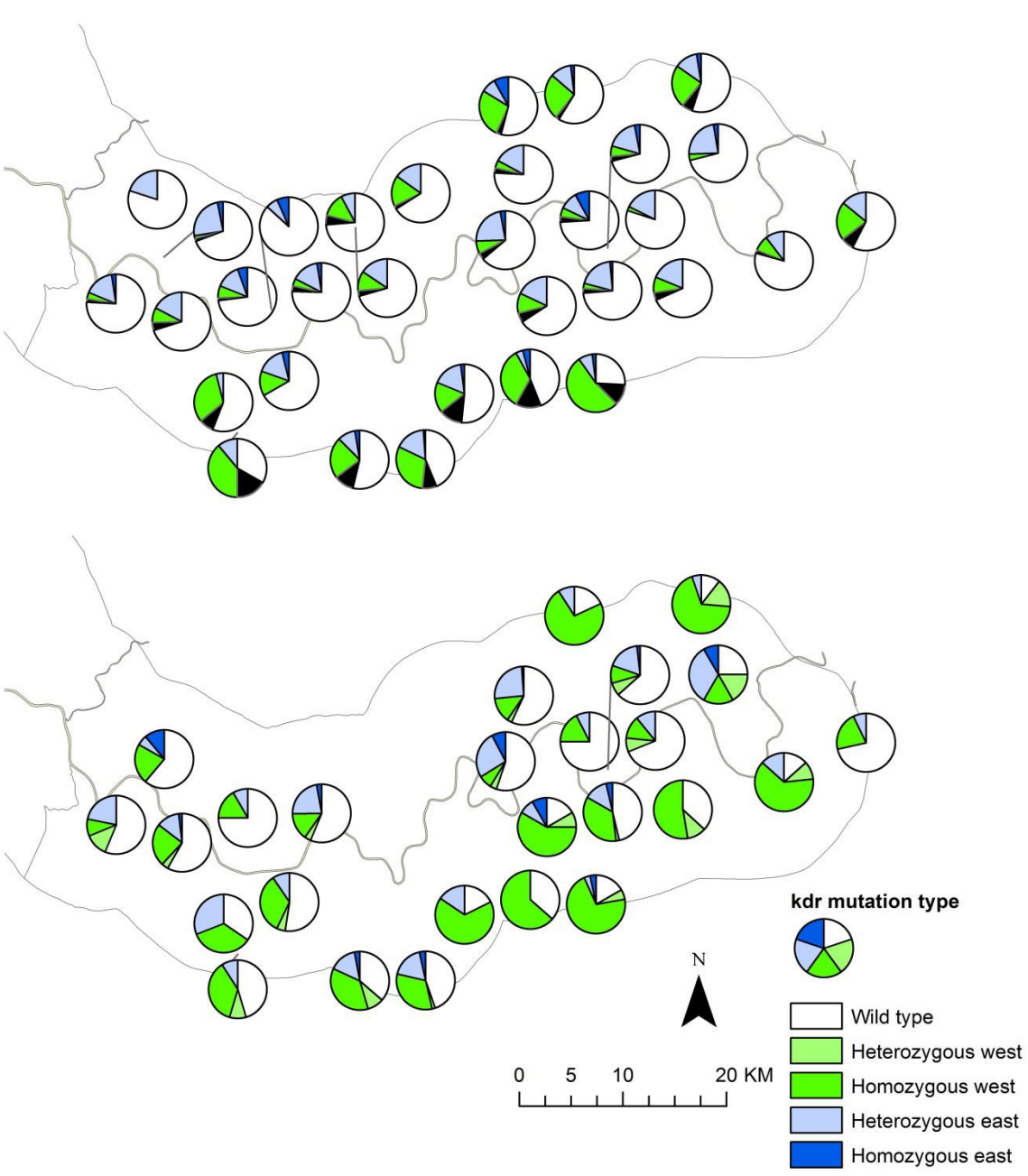

Figure 6.6: Distribution of *kdr* mutation status of *An. gambiae s.l.* in the study area during 2010 (Panel A) and 2011 (Panel B) transmission seasons

Pie charts show percentage *kdr* mutation status of *An. gambiae* s.l. complex at CDC light trap sampling sites (excluding sampling sites with less than 10 mosquitoes caught in total across each transmission season).

Table 6.5: Association between explanatory variables and the odds of having any type of *kdr* mutation (heterozygous/homozygous east/west)

Variable	n	%	Univariate analysis (adjusted for clustering on village)			Multivariate analysis		
			OR	95% CI	p-value	OR	95%CI	p-value
Species								
An. arabiensis	1360	28.6%	1					
An. gambiae s.s.	897	89.4%	19.54	15.73-24.27	<0.001			
An. coluzzii	209	25.6%	0.85	0.71-1.01	0.06			
Study arm								
LLIN only	1172	34.0%	1					
DDT-IRS and LLIN	1087	45.7%	1.59	1.13-2.25	0.008			
Year								
2010	1652	34.0%	1					
2011	858	47.7%	1.92	1.70-2.16	<0.001	1.71	1.49-1.96	<0.001
Distance from the river (km)			1.12	1.08-1.17	<0.001	1.03	1.00-1.06	0.04
Bank of River Gambia								
North	1077	33.8%	1					
South	1433	41.2%	1.61	1.15-2.26	0.006			
Parity in village (%)			2.18	0.19-24.37	0.53			
Mean female *An. gambiae* s.l. density trap/night /village			0.95	0.88-1.04	0.28			
LLIN use in village (%)			0.45	0.02-10.71	0.62			
Species and study arm interaction								
An. arabiensis / LLIN only arm						1		
An. arabiensis / DDT-IRS and LLIN arm						1.03	0.84-1.26	0.77
An. gambiae s.s. / LLIN only arm						13.95	10.29-18.92	<0.001
An. gambiae s.s. / DDT-IRS and LLIN arm						23.54	16.37-33.84	<0.001
An. coluzzii / LLIN only arm						0.60	0.46-0.77	<0.001
An. coluzzii / DDT-IRS and LLIN arm						1.27	0.95-1.70	0.11
CI = confidence interval, OR = odds ratio								

Discussion

The results show the temporal and spatial pattern of members of the *An. gambiae* complex and *kdr* mutations in the URR of The Gambia from 2010 to 2011. To the best of our knowledge this is the first study to adopt a landscape approach with intensive entomological sampling to understand factors related to the distribution of *kdr* in malaria vectors.

An. arabiensis was the most abundant species and persisted longer than the other members of the species complex into the dry season. These findings support those of Caputo *et al.* who also found *An. arabiensis* to be the dominant species [416] and others have shown *An. arabiensis* to be well adapted to dry biotopes [418, 452, 453]. We found comparable proportions of *An. gambiae* s.s. and *An. coluzzii* in both years (2010: *An. gambiae* s.s.= 12.0%, *An. coluzzii*= 10.1%, 2011: *An. gambiae* s.s.= 23.0% and *An. coluzzii*= 19.0%). In contrast Caputo *et al.* found low proportions of *An. gambiae* s.s. in the URR (5%, except for one site), compared to *An. coluzzii* (21% in 2005 and 45% in 2006) [416]. However, the sampling sites of Caputo *et al.* were generally close to the river, where we also found higher proportions of *An. coluzzii* than *An. gambiae* s.s.. 1.3% of *An. gambiae* complex mosquitoes caught during 2010 were hybrids, although none were collected in 2011. This is within the range shown by others in The Gambia (Caputo *et al.* of 0.6%-7% across the transect [416] and 7.6% in Njabakunda in the North Bank Region 30 km west of Farafenni town [454]) and supports the assertion that the frequency of hybridisation along the River Gambia is higher than that reported from other areas in west Africa, suggesting that The Gambia is an area of active speciation. However, Nwakanma *et al.* found stable proportions of the hybrid form in the two years they sampled in Njabakunda compared to our results. Our protocol for molecular analysis of species did not include retention of legs of mosquitoes for confirmatory testing if a hybrid form was found and therefore there is a chance that there was contamination in our results.

Parity differed by village but this did not appear to be due to the effects of the intervention as there was no difference by study arm. Differences in parity by member of the species complex may have been responsible for variation in the proportion of parous mosquitoes by sampling site. Unfortunately this could not be evaluated since the species of parous and nulliparous mosquitoes was not recorded as the molecular and dissection datasets were not linked. There was a reduction in proportion of mosquitoes that were parous across the sampling rounds in 2010 but no such pattern was found in 2011. This was an unexpected finding given that one would expect to see older mosquitoes towards end of the rains due to the disappearance of aquatic habitats [455]. However, this may be due to the high rainfall and flooding in 2010 which may have led to more abundant aquatic habitats across the season.

Interestingly, fewer *An. arabiensis* were caught in villages in the DDT-LLIN arm compared to the LLIN arm (2010: OR= 0.49, 95%CI= 0.28-0.86, 2011: OR= 0.44, 95%CI= 0.25-0.77), while the opposite pattern was seen with *An. gambiae* s.s (2010: OR= 3.21, 95%CI=1.48-6.96, 2011: OR= 2.71, 95%CI= 1.18-6.20). If the high prevalence of the *kdr*-west mutation in *An. gambiae* s.s. translated into phenotypic resistance, this may have given the species a competitive advantage over *An. arabiensis*. It could also be a function of sampling bias if *An. arabiensis* were more likely to be repelled and exit homes that received IRS compared to *An. gambiae* s.s., although differential repellent effects in the two species have not been reported to the best of our knowledge. This is a different pattern from what we would expect based on research in east Africa where with the scale-up of interventions, *An. arabiensis* is starting to dominate over *An. gambiae* s.s. since the latter is more endophagic and endophillic and so is being preferentially killed by LLINs [309, 456, 457].

We did not find any relationship between water bodies within 2 km of the sampling points and the species composition at that site. This may be because the small waterbodies colonised by members of the *An. gambiae* complex may not necessarily be associated with specific landcover classes. Alternatively, the digitised maps were from 2002 and so landuse may have changed somewhat from that in 2010-2011 when the entomological data were collected. In both years *An. gambiae* s.s. were more commonly found in villages away from the river which corresponds with previous studies that found that *An. gambiae* s.s. prefers free draining soil covered with open woodland savannah or farmland [421, 458]. In marked contrast, the proportion of *An. arabiensis* declined with increasing distance from the River Gambia in 2010. *An. gambiae* s.l. are not breeding in the river itself, rather proximity to river is likely to be a proxy for presence of riparian habitats [449]. This corresponds with findings of Bøgh *et al.* in the Central River Region who found *An. arabiensis* in breeding sites along the edge of the alluvial soils, particularly in areas of rice cultivation [417]. However, we did not find this pattern in 2011 and in that year, instead *An. coluzzii* was found in higher proportions in sampling sites closer to the river. The reason for this apparent switch in the species found close to the river is unclear, although it may be related to the higher rainfall and the substantial flooding that occurred in 2010 compared to 2011 where the river did not flood, which may have favoured *An. arabiensis* over *An. coluzzii*. This could also be a function of the precision of the estimates per village in 2011 due to there being fewer mosquitoes caught overall compared to 2010.

The geographic distribution of the *kdr* mutation we found largely corresponded to distribution of *An. gambiae* s.s. since the mutation was relatively rare in *An. coluzzii* and *An. arabiensis*. This finding was similar to other studies which show the *kdr*-west mutation almost at fixation in *An. gambiae* s.s. but uncommonly in *An. coluzzii* [415, 429, 434]. First detected in Benin [459], the *kdr*-west

mutation is thought to have passed from *An. gambiae* s.s. to *An. coluzzii* through introgression, coincident with increased usage of LLINs in some settings [460-463], although in some cases the mutation may have arisen independently in *An. coluzzii* [464]. Although a previous study found a limited distribution of the *kdr*-west mutation in *An. coluzzii* in Benin, Nigeria and Cameroon in the early 2000s [434], the mutation has been spreading steadily, as evidenced by our study.

Our findings do not correspond with those of Niang *et al.* who measured the frequency of the *kdr*-west mutation in sites along two transects in the Tambacounda region of Senegal, just across the border, north-east from our study site in the same years [465]. Niang *et al.* found low mean frequencies of the *kdr*-west mutation and no significant difference in *kdr*-west frequencies between species (14.4%, 21.2% and 14.7% in *An. arabiensis*, *An. gambiae* and *An. coluzzii*, respectively). The reason for this difference between our findings and those of Niang *et al.* is unclear although fewer mosquitoes were caught in Senegal which may affect the precision of these estimates.

In the univariate analysis, species, arm, year, distance from river and river bank were associated with the *kdr* mutations. There was no association between percentage LLIN use in the villages and odds of any *kdr* mutation, suggesting that a difference in coverage between villages (between 77.8% to 100% during the 2011 survey) was not a driver of insecticide resistance in the study area. There was also no association between percentage of parous mosquitoes by village and odds of *kdr* mutations. This was unexpected given that we would generally expect long-lived populations to have more *kdr*. Lastly, there was no association between the absolute number of mosquitoes per village and odds of any *kdr* mutation. This was also unexpected given that we would assume that *kdr* would be more likely to persist in higher density vector populations.

In the final multivariate model, adjusting for clustering, species, study arm, year of survey and distance from the river were associated with odds of any *kdr* mutation. We found that *kdr* mutations (particularly *kdr*-west) were more common in villages that received IRS and LLINs compared to LLINs alone. The odds of any *kdr* mutation were 23.54 higher in *An. gambiae s.s.* in villages with both IRS and LLINs (95%CI= 16.37-33.84) and 13.95 (95%CI= 10.29-18.92) higher in villages with LLINs alone. This suggests that LLINs and DDT used together provide additional selection pressure for *kdr* mutations over LLINs alone. *An. coluzzii* in the LLIN only arm had a significantly lower odds of any *kdr* mutation (OR= 0.60, 95%CI= 0.46-0.77) compared to *An. arabiensis* in the same arm. There was a 1.03 increase in the odds of any *kdr* mutation (95%CI= 1.00-1.06, p=0.04) for every km away from the river. This may suggest that there is insecticide resistance pressure acting on vector populations in The Gambia from across the border in Senegal. This is plausible given that districts surrounding the study site were part of a President's Malaria Initiative

IRS programme that was using pyrethroids (from 2007 in Velingara district to the south and east of the study site and from 2010 in Kompentoum district to the north of the study site) until a switch to carbamates in 2011 [466]. Indeed, insecticide resistance in vector populations in the two IRS districts in Senegal was high when measured in 2010 using tube tests (Velingara % mortality: permethrin=50%, DDT=52%; Kompentoum % mortality: permethrin=57%, DDT=80%) [467]. Although Niang *et al.* found lower levels of *kdr* mutations in two transects in Tambacounda region compared to us they did find low mortality to DDT (approx. 54% and 62%) and permethrin (approx. 77% and 68%) in tube tests in two sites [465].

Interestingly we found an increase in homozygous west mutation in *An. gambiae* s.s. between 2010 and 2011. This is likely to be due to the large scale deployment of permethrin-treated LLINs and IRS with DDT in the area and the increased selection pressure over time due to the second round of IRS in 2011. LLIN use by study children was only 55% at the 2010 baseline survey but LLINs were given to cover all sleeping spaces in households and coverage among study children was greater than 90% at the end of the 2011 transmission season [388]. IRS coverage was also greater than 80% at this survey [388]. A lack of longitudinal monitoring in The Gambia makes it difficult to ascertain whether there has been an increase in *kdr* mutations or phenotypic resistance over time and this should be a priority for the National Malaria Control Programme in the future. Several observational studies have shown an increase in the frequency of *kdr* mutations following implementation of vector control interventions [468-471]. However, vector control may not be the main selection pressure operating in some settings. For example, implementation of LLINs and IRS in the highlands of Burundi was associated with an increase in *kdr*-east mutations from 1% pre-spraying in 2002 to 86% in sprayed valleys by 2007 and an increase in unsprayed valleys to 67% [472].

Previous studies have highlighted a lack of decline in malaria in the eastern part of The Gambia [410, 473] and that heterogeneities in transmission may be partly due to insecticide resistance [415]. The species differences in prevalence of *kdr* mutations, if indeed this translates into a resistant phenotype, suggests that species composition will have an impact on involvement of insecticide resistance on malaria heterogeneity. Opondo *et al.* suggest that this may explain the differing levels of susceptibility to DDT and pyrethroids found by Pinder *et al.* and Tangena *et al.* in neighbouring villages in the same year [414]. Higher proportions of *An. arabiensis* caught by Pinder *et al.* (70%) versus 42% by Tangena *et al.* may have masked resistance in *An. gambiae* s.s. Our findings add weight to this hypothesis since we found no association between *An. arabiensis* and odds of any *kdr* mutation in the multivariate analysis.

There are several reasons that could explain why we observed the *kdr* mutation at such high levels in *An. gambiae* s.s. compared to the other sibling species. Firstly, differences in the indoor/outdoor biting and resting behaviour of *An. gambiae* sibling species may also be a factor influencing exposure to insecticides within the home and selection pressure for development of insecticide resistance. Unfortunately there is not much information available on the behaviour of the *An. gambiae* complex in The Gambia, in particular differences between *An. coluzzii* and *An. gambiae* s.s. If *An. gambiae* s.s. is biting indoors then it may be more likely to come into contact with insecticides on walls or LLINs. In contrast *An. arabiensis* which shows lower levels of *kdr* mutations than *An. gambiae* s.s. in our study is generally thought of as being exophillic and exophagic [474]. Differences in biting and resting behaviour have also been seen in different chromosomal forms of *An. gambiae* s.l., each chromosomal form (characterised by a different chromosomal inversion) being an indicator of adaptation to different ecological habitats [475-477]. How the chromosomal forms correspond to M (*An. coluzzii*) and S (*An. gambiae* s.s.) forms in The Gambia is unclear, although in northern savannah areas such as Mali and Burkina Faso, the M and S forms were found to correspond well to the Mopti and Savanna chromosomal forms [478] and Bockarie suggested that the Savannah form, with a 2La inversion, was mostly endophilic in southern Sierra Leone [479].

Alternatively, the observed pattern of *kdr* mutations may be due to pesticide and herbicides being used in cultivated areas favoured by *An. gambiae* s.s. for larval habitats. Several studies have reported an association between the presence of agricultural pesticides and herbicides in larval habitats and insecticide resistance [480, 481] and an increase in *kdr* frequency has also been shown in a selection experiment under controlled conditions [482]. However, pesticide use is low in the URR and largely restricted to small market gardens and so it is unlikely that this is responsible for the higher *kdr* frequency in *An. gambiae* s.s.

This study has several limitations. Firstly, the molecular analysis was restricted to *kdr* mutations and did not look at other markers of resistance such as overexpression of cytochrome P450 genes which may be involved in metabolic resistance. The study did also not verify the phenotype of the mosquitoes in bioassays. Authors of the early *kdr* studies and others showed strong correlation between *kdr* and the resistance phenotype [135, 136, 483]. In The Gambia, Opondo *et al.* showed significant association between presence of the *kdr*-west mutation in *An. gambiae* s.s. and resistance to DDT and deltamethrin [415]. This mutation was a strong predictor of resistance and effectively masked the effect of other mutations in this study (Gste2-114T which has been associated with metabolic resistance to DDT and Vgsc-1575Y which enhances the action of the 1014F mutation). However, *kdr* may only be part of the picture of insecticide resistance since target site mutations are

only one route by which mosquitoes can become resistant [484, 485]. Several studies have shown that pyrethroid LLINs were still able to kill *An. gambiae* despite high frequencies of *kdr* [486-489]. Furthermore, evidence from the Tangena *et al.* study in the same study area as ours shows poor correlation between the bioassay results and the presence of the *kdr* mutation, suggesting metabolic resistance may be contributing to the phenotype [414]. Secondly, the use of secondary data also meant that additional risk factors for insecticide resistance could not be explored in the analysis, such as household use of knockdown sprays or pesticide use on crops. Thirdly, the species composition identified in the study sites may have been biased by the use of light traps to catch indoor biting mosquitoes in human dwellings which may have favoured catching of anthropophillic and endophilic mosquitoes. Finally, this analysis used secondary data and therefore was not necessarily statistically powered for the specific analyses undertaken.

Along with studies by Betson *et al.* and Opondo *et al.* [413, 415], this work provides a baseline status of the temporal and spatial pattern of *kdr* mutations in The Gambia. High levels of *kdr* mutations were found, particularly in *An. gambiae* s.s. which tended to be found away from the River Gambia. There was a strong association between *An. gambiae* s.s. and *kdr* mutations in the multivariate model which differed according to the study arm. However, it should be noted that these data are a specific case since there was intensive vector control use during the study period. The findings of this study have implications for the planning and operationalisation of insecticide resistance monitoring and management in The Gambia. Firstly, because of the high prevalence of *kdr* found in the study it is recommended that the Gambian Malaria Control Programme monitor insecticide resistance, ideally using phenotypic assays to identify the presence and intensity of insecticide resistance countrywide and ideally at least yearly [139]. Further investigation is recommended where mortality in WHO tube tests is less than 98% as per WHO procedures [139]. Studies should be performed to elucidate the insecticide resistance mechanisms and identify drivers of resistance. Here it is important to look at how these mechanisms and drivers differ by member of the *An. gambiae* species complex, particularly if the habitats and behaviours of the members are different. The heterogeneity in *kdr* mutations observed over the URR suggests that a number of sentinel sites need to be selected, focusing on areas where different members of the species complex are dominant i.e. several sites close to the river and several sites in the savannah areas close to the Senegalese border. Where there is intensive vector control, particularly IRS, as shown by the selection pressure generated by the interventions used in this study, additionally monitoring should be conducted. The high use of insecticides in Senegal at the time of the study and potential impact on vector populations across the border in The Gambia highlights the importance of cross-border collaboration and sharing of data. If the high levels of *kdr* mutations identified in this study manifest

as cross-resistance to DDT and pyrethroids, the effectiveness of both LLIN and IRS programmes could be compromised, unless the IRS insecticide is changed. It is recommended that the programme proactively switch the IRS insecticide to a carbamate (e.g. bendiocarb) or organophosphate (e.g. pirimiphos methyl) which have different modes of action [132] and have been shown to be effective in The Gambia, in order to protect the effective lifespan of LLINs [414]. The principal vector control tools recommended by WHO for malaria control are LLINs and IRS [106, 405, 406], with larval source management recommended as a supplementary measure [29]. As part of an IVM approach, the Gambian Malaria Control Programme should consider the use of non-insecticide based tools in combination with LLINs and IRS to achieve more effective malaria vector control, prolong the effective life of insecticide-based interventions and be more environmentally sound. Environmental management could be utilised or larviciding using bacterial larvicides (although these have not been found to be effective when applied by hand in areas of extensive flooding [389]). At present The Gambia does not have an IVM policy so this should be developed as a matter of priority.

Chapter 7: Discussion

Overview and summary of findings

This intention of this thesis was to develop high quality evidence to support integrated vector management (IVM) and improve the effectiveness of vector control.

Chapter 1 summarises the global burden of vector-borne diseases (VBD), the history of vector control and current challenges to implementation. It also introduces IVM, describes the inception of the policy, gives contemporary examples of IVM and critically analyses why IVM has not gained traction as a policy.

Chapter 2 summarises the development of the World Health Organization (WHO) Toolkit for IVM in sub-Saharan Africa (Volume II of thesis) which was written largely by the author of this thesis. The toolkit aims to provide practical guidance on planning and implementation of IVM for programme managers at national and regional levels. It conceptualises IVM as a cyclical process with multiple rounds of situational analysis, planning, design, implementation and monitoring and evaluation. The toolkit provides a framework for IVM, based on which country programmes can develop their own IVM policies. The toolkit has several limitations. Firstly, although vector control programme managers were involved in development of the toolkit, it was not piloted and co-production could have been used to increase ownership and uptake of the findings. Secondly, the toolkit is a large paper document and so navigation and updating of the materials will be difficult. Lastly, due to time constraints under the project grant, the evidence-based selection of vector control tools section of the toolkit is based partly on a narrative review of the evidence, rather than systematic reviews. Next steps are proposed to transition the toolkit into policy and practice in countries such as development of country policy, translation into local languages and transfer of the IVM materials including disease risk distribution maps into a web-based system.

Chapter 3 aimed to answer the research question: are insecticide-treated nets (ITNs), insecticide-treated curtains (ITCs) and insecticide-treated screening (ITS) effective against VBDs other than malaria. To answer this question a systematic review of studies measuring the efficacy of ITNs, ITCs and ITS against Chagas disease, cutaneous and visceral leishmaniasis, dengue, human African trypanosomiasis, Japanese encephalitis, lymphatic filariasis and onchocerciasis was conducted. This is of interest since roll-out of ITNs for malaria control may have collateral benefits on other VBDs where these diseases are co-endemic. It was hypothesised that insecticide-treated materials would indeed be efficacious against VBDs other than malaria. Searching bibliographic databases using intervention, vector- and disease-specific search terms identified 21 studies which met the inclusion

criteria. Studies were included if they were cluster or individually randomised controlled trials, non-randomised trials with pre- and post-intervention data or rotational design studies evaluating the efficacy of ITNs, ITCs or ITS versus no intervention against entomological and epidemiological endpoints. Meta-analysis of clinical data could only be performed for four cutaneous leishmaniasis studies which together showed a protective efficacy of ITNs of 77% (95%CI: 39% - 91%). Studies of ITC and ITS against cutaneous leishmaniasis also reported significant reductions in disease incidence. Single studies reported a high protective efficacy of ITS against dengue and ITNs against Japanese encephalitis but these studies were both deemed to be of low quality. No studies of Chagas disease, human African trypanosomiasis or onchocerciasis were identified. In conclusion, ITNs, ITCs and ITS are effective against VBD other than malaria and there are likely to be considerable benefits of ITNs on cutaneous leishmaniasis where the vectors enter houses. Unfortunately, the low number of studies identified, along with poor reporting of entomological data and few studies measuring the efficacy against epidemiological outcomes limited our ability to make conclusions on the efficacy of against other VBDs. It is therefore recommended that additional, well-conducted studies be conducted.

Chapter 4 aimed to answer the research question: are topical repellents effective against malaria in endemic populations. To answer this question, a systematic review of field trials evaluating the efficacy of topical insect repellents against malaria in endemic populations was conducted. Topical repellents are potentially of huge benefit in settings such as South East Asia and South America where malaria vectors bite outdoors and indoor interventions such as long-lasting insecticidal nets (LLINs) are less effective. It was hypothesised that topical repellents would be protective against malaria in endemic populations since topical repellents provide individual level protection against mosquito biting. Systematic searching of bibliographic databases and other sources identified 10 studies which met the inclusion criteria. Randomised and non-randomised controlled trials were included that assessed the effect of topical repellents on falciparum or vivax malaria or infection. Meta-analysis of clinical data was conducted in order to generate summary risk ratios. Topical repellents showed an 18% protective efficacy against *P. falciparum* malaria, although this was not significant (95% CI: -8%, 38%). Similarly, the average protective efficacy of topical repellents against *P. vivax* malaria did not reach significance (protective efficacy: 20%, 95% CI: -37%, 53%). While topical repellents are able to provide individual protection against mosquitoes, the initial hypothesis did not prove correct since the results of this analysis do not show any protection against malaria. However, studies included in the analysis were highly heterogeneous with varying repellent active ingredients and formulation, co-interventions, study population, compliance, and follow-up period. Relatively few studies were identified and so it was not possible to examine this heterogeneity in the

analysis, for example by conducting meta-analysis separately for each different active ingredient. It is recommended that additional well-designed trials of topical repellents at appropriate doses and alternative modes of repellent delivery, such as long-lasting insecticide-treated clothing are conducted.

Chapter 5 aimed to answer the research question: is it possible to improve the design and conduct of vector control field trials in order to improve the quality of evidence to support evidence-based policy making. Based on the experience of conducting systematic reviews included in Chapters 3 and 4, the dearth of high-quality studies evaluating the efficacy of vector control interventions was revealed. This hampers evidence-based decision making which is one of the foundations of IVM and delays policy-making and roll-out of effective new tools. To answer the research question a critical analysis of the design and conduct of phase III field trials of vector control interventions was conducted and suggestions provided on how future field trials of vector control interventions could be improved. The critical analysis identified common flaws with vector control trials such as a lack of randomisation and blinding which can introduce bias and a lack of sample size calculations which are required to ensure the study has a reasonable chance (i.e. power) to detect an intervention effect. Vector control trials also often had insufficient replicates (e.g. two village studies) which means that inferential statistics cannot separate variability due to treatment from variability due to experimental units. The chapter details study designs which are less prone to bias, such as randomised controlled trials (RCTs) which are considered the 'gold standard' study design. In conducting a study, other types of bias can be minimised, for example by blinding researchers and study participants to the intervention and randomly selecting sites for entomological monitoring. Other important considerations are the need for sample size calculations and epidemiological outcomes to quantify the public health benefit of the intervention. If taken up by those evaluating the efficacy of vector control interventions and supported by training and capacity building, the critical assessment should lead to the more rigorous design and conduct of vector control studies in the future.

Chapter 6 presents a microepidemiological study of knockdown resistance (*kdr*) mutations in the *An. gambiae* species complex in rural Gambia. This study aimed to determine the spatial and temporal distribution of *kdr* mutations in the Upper River Region of The Gambia and their association with members of the *An. gambiae* species complex. Over the two-year period (2010-2011) 71% of mosquitoes caught were *An. arabiensis*, 15.0% *An. gambiae* s.s., 12.3% *An. coluzzii* with few hybrid forms caught in the first year only. As initially hypothesised, the study found that *An. gambiae* was

more common further away from the River Gambia, while *An. arabiensis* and *An. coluzzii* were found close to the river. We initially hypothesised that *kdr* mutations would be low in *An. coluzzii* and *An. arabiensis* but more common in *An. gambiae* s.s. This was borne out in that *An. arabiensis* and *An. coluzzii* were predominantly wild-type at the *kdr* locus, while *An. gambiae* s.s. were predominantly homozygous west for the *kdr* mutation and this proportion increased almost to saturation from 65% during 2010 to 91% during 2011. *Kdr* mutations were more commonly found in villages that had received IRS with dichlorodiphenyltrichloroethane and LLINs than LLINs alone, as initially hypothesised. The odds of *kdr* were 14.0 higher in *An. gambiae s.s.* in villages with LLINs alone and 23.5 higher in villages with both IRS and LLINs, presumably due to the increased selection pressure from the double intervention. In the second year of the study, mosquitoes were 1.7 times more likely to have *kdr*. *Kdr* mutations also increased with distance from the river, which is possibly a result of intensive IRS use at the time of the study in Senegalese districts surrounding the study area. The study highlights the rapid spread of *kdr* mutations over the study period and the small scale variation in the epidemiology of insecticide resistance. It has implications for selection of sentinel sites for monitoring of insecticide resistance and cross-border collaboration and sharing of data between vector control programmes. Longitudinal monitoring of insecticide resistance using phenotypic assays should be a priority for the malaria control programme in The Gambia given the high levels of *kdr* resistance identified in this study. If *kdr* mutations translate into phenotypic resistance, the programme should consider switching the IRS insecticide to a carbamate or organophosphate. As part of an IVM approach for more effective, sustainable and ecologically sound vector control, the programme should also consider implementing non-insecticide based tools, such as environmental management.

Study limitations

While study limitations have been covered in the individual chapters of the thesis, several overarching limitations are apparent. Firstly, statistical analyses performed in Chapter 3 and 4 were limited by the small number of studies identified. This meant that I could not explore heterogeneity in terms of for example study setting or intervention used, was limited in the extent to which I could perform sensitivity analysis (although this was done for the meta-analysis of topical repellents by excluding non-randomised studies) and could not look for reporting bias in the results, for example publication bias, using funnel plots or other methods [490, 491].

There may be the potential for bias in the authors opinions on IVM due to close involvement with IVM policy development. However, it is believed that this bias is limited due to a thorough critical analysis of the flaws and potential benefits of the policy.

Future direction and wider applicability of this research

The need for more effective and sustainable vector control programmes has been increasingly recognised over the course of this PhD. Much of the impetus has come from recent outbreaks of *Aedes*-borne diseases, specifically dengue, Zika, chikungunya and yellow fever. For example, Zika has spread to 61 countries since 2015, with an estimated 0.5-1.5 million cases in Brazil alone [492, 493] and in late 2015 yellow fever re-emerged in Africa with 4,120 confirmed cases of yellow fever and 373 deaths in Angola and Democratic Republic of the Congo [494, 495]. Countries have struggled to control these epidemics, hampered by a lack of resources and capacity to conduct vector control and the absence of other effective tools – there are no effective treatments for Zika, dengue or chikungunya, a partially protective dengue vaccine and a worldwide shortage of yellow fever vaccine [496]. The threat of these VBDs in cities where policymakers and their families are at risk has galvanised support for better control. Under pressure to take action, the WHO convened an emergency meeting of the WHO Vector Control Advisory Group (VCAG) in March 2016 who recommended the scale-up of existing vector control tools and pilot testing of two new tools (*Wolbachia*-based biocontrol and OX513A transgenic mosquitoes) [156]. The poor state of vector control was highlighted by the WHO Director General Margaret Chan when she addressed the World Health Assembly in May 2016 saying "Above all, the spread of Zika, the resurgence of dengue, and the emerging threat from chikungunya are the price being paid for a massive policy failure that dropped the ball on mosquito control in the 1970s"[497].

At the WHO Executive Board meeting in 2016, member states called on the Director General to develop a Global Vector Control Response (GVCR) in collaboration with affected countries and other relevant stakeholders. The GVCR aims to reduce the burden of all VBDs through sustainable, effective and locally-adapted vector control [498]. This is to be achieved by building upon foundations of enhanced vector control capacity and improved basic and applied research with four pillars of action: i) strengthened intrasectoral and intersectoral action and collaboration; ii) enhanced entomological surveillance, and monitoring and evaluation; iii) scale-up and integration of tools and approaches; and iv) community engagement and mobilisation (Figure 7.1).

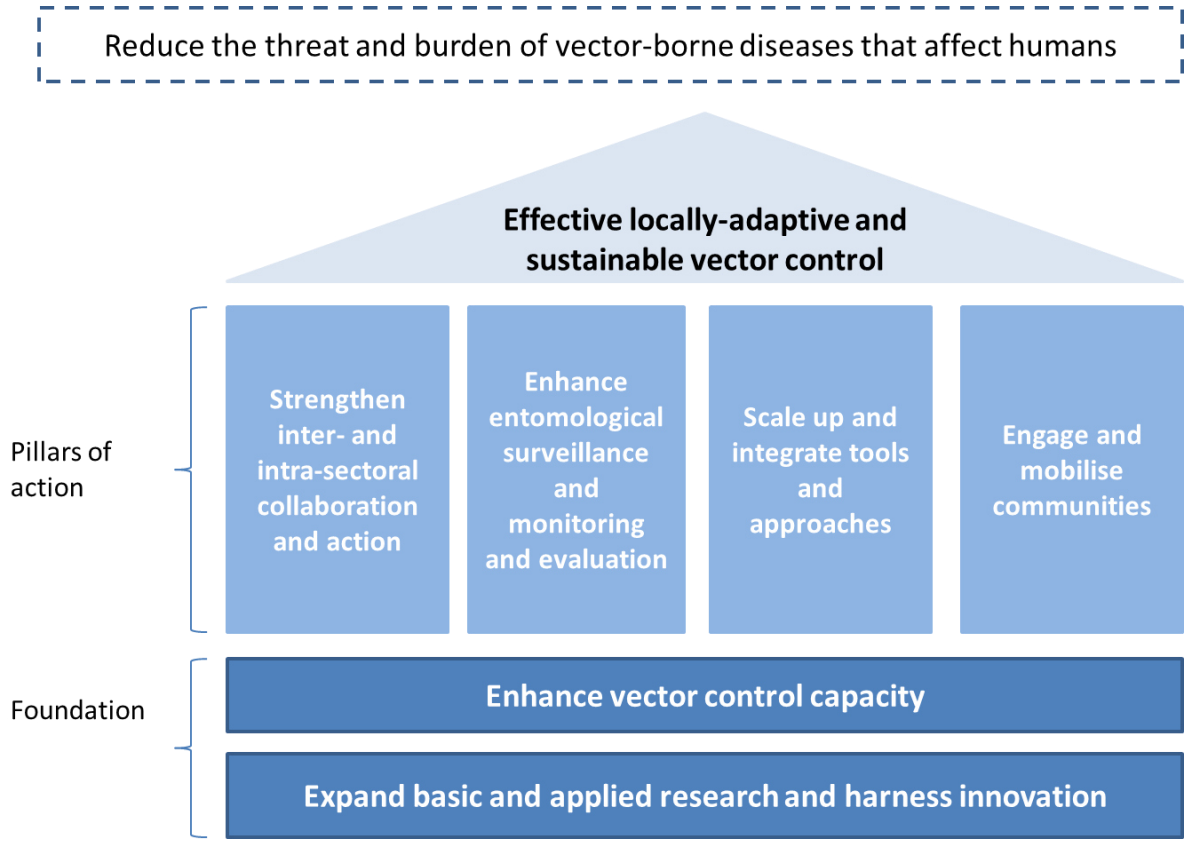

Figure 7.1: Schematic of proposed Global Vector Control Response to reduce the burden and threat of VBDs
Reproduced from [498]

The GVCR has high level political support and the strategic document will be considered by the World Health Assembly in May 2017. The GVCR is largely considered to be a "re-boot" of IVM but with a different name and draws largely from the principles outlined in Chapter 1 of this thesis and the IVM toolkit. It is expected that the GVCR will increase momentum and reinvigorate vector control, and hopefully lead to additional allocation of funds since this is much needed. The inclusion of increased capacity as a foundation of GVCR is crucial since there is a dearth of human resources at country level, particularly of public health entomologists trained in epidemiology, and monitoring and evaluation. It is anticipated that the IVM toolkit will be valuable for programmes, as initially hypothesised, since interest in the document and approach is increasing, and importantly the toolkit provides an invaluable 'how-to' guide for implementation of the GVCR.

There is an increasing push for intersectoral action against VBDs as advocated in IVM approaches, particularly against malaria. The Roll Back Malaria (RBM) Multisectoral Action Framework for Malaria [499] makes a strong case for restructuring the way countries address malaria by switching to a developmental approach, which addresses key social and environmental determinants through

a multisectoral effort. This sentiment is also echoed in the Global Technical Strategy for Malaria 2016-2030 [13] and accompanying RBM Action and Investment to Defeat Malaria 2016-2030 [151] documents, and buoyed by recent research which suggests that socioeconomic development is a possible intervention against malaria [25]. More broadly, efforts against the social determinants of health and promoting health in all policies should be harnessed to increase awareness and move towards consideration of VBDs in public policy more broadly [500, 501]. The post-2015 Sustainable Development Goals (SDGs), which are much more comprehensive and cross-cutting than the previous Millennium Development Goals provide a unique opportunity for intersectoral engagement towards control and elimination of VBDs [212]. For example, although malaria and NTDs are dealt with directly in SDG 3 - Ensure healthy lives and promote well-being for all at all ages, SDG 11 - Make cities and human settlements inclusive, safe, resilient and sustainable also calls on governments and partners to "ensure access for all to adequate, safe and affordable housing and basic services and upgrade slums" which is of huge relevance to *Aedes*-transmitted diseases. The release of the United Nations (UN) 'New Urban Agenda' at Habitat-III (UN Conference on Housing and Sustainable Urban Development) in October 2016 provides a unique opportunity to link sustainable urbanisation and VBDs [502]. Control and elimination of VBDs is also simultaneously intertwined with many of the other SDGs, for example reduction of the burden of VBDs in young children will allow more children to attend school (SDG 4 on education).

High level policy is important in giving direction but the next step is to translate this into a coordinated multi-sectoral approach in countries. Intersectoral action is challenging to initiate and sustain. Challenges of collaborative working include a lack of engagement of senior personnel (with authority to act on behalf of organisation) in the partnership, unwillingness to share resources, lack of joint funding and/or short-term funding, differing sectoral mandates, differences in values and culture of organisations, unwillingness to share information, shifting policy priorities and organisational restructuring [503, 504]. Several studies and systematic/narrative reviews have looked at what makes partnerships work. Factors include clear goals and objectives which are shared and 'owned' by the partnership, clear roles and responsibilities, strong leadership with skills in cross-organisational and -sectoral working, satisfactory accountability arrangements, a robust monitoring and evaluation framework, and importantly, the existence of trust, reciprocity and goodwill between partners [504-507]. Intersectoral action is poorly researched in the vector control field. One study in Tanzania identified barriers to intersectoral action for malaria control including differences in sectoral mandates and management culture, lack of a national coordinating body and lack of budget for intersectoral activities [508]. More effort should be put into research and documentation of case studies of intersectoral action for VBD control such as this. Identification of

good practice could have wider applicability and lead to production of how-to guides and training materials. Here there is also an opportunity to gain insights from research on working across sectors, across government and in partnerships from the health and social care and public health arenas and apply these to vector control [506, 509]. In particular, there is potential to learn from research and experiences in 'health in all policies' - an approach to public policies across sectors that takes into account health implications of decisions and seeks synergies to avoid harmful impacts on health [209, 510, 511].

This thesis highlights the need for more fundamental and operational research in vector control, which is also one of the foundations of the GVCR. Research is needed in a number of areas including basic research to identify new intervention paradigms (e.g. genetically-engineered vectors, odour-baited traps) or new active ingredients which can be applied on existing paradigms (e.g. new insecticide classes). The focus here should be on neglected tropical diseases since there is a dearth of studies in this area as demonstrated in Chapter 3 meaning that evidence-based choice of vector control tools is problematic. New tools and approaches for entomological and epidemiological surveillance and methods of better integrating these data for timely decision making are also required. Social science research is also much needed, for example to understand how to sustain community participation and behaviour change. Lastly, there is also an urgent need to increase the evidence base for IVM through documentation of case studies, and particularly economic evaluation of IVM versus standard practice vector control. Being able to make a strong economic case for IVM would be a huge benefit to advocacy.

The use of evidence to target interventions and adapt and change strategies over time is fundamental to IVM. This is in essence adaptive management which is a structured iterative process of testing assumptions, adapting and learning. Adaptive management calls for a six stage cycle consisting of problem assessment, assessment of current knowledge, identifying uncertainty and alternate hypotheses, implementation of activities, monitoring and evaluation to learn from the results. This is essentially the same process outlined in Figure 2.2. Adaptive management is an approach that was originally applied to environmental management [512, 513], but parallel concepts exist in a number of other fields including business (total quality management and learning organisations) [514] and engineering and mathematics (control theory) [515]. There is an opportunity to learn from these other disciplines and share experiences. It is widely acknowledged that there is no single 'silver bullet' for control and elimination of VBDs and that combinations of tools (drugs, vaccines and vector control) will need to be applied in locally appropriate mixes. Decision analysis tools have been developed to aid the choice of control tools, based on

mathematical models which look at the impact of tools used alone or in combination in various settings. This has, to the best of the authors knowledge, only been done for malaria so far - the Malaria Decision Analysis Support Tool (MDAST) [516] which is based on the Imperial College malaria model [176]. A further methodological development which should be applied and tested more widely in VBD control is value-of-information (VOI) analysis, which explicitly considers the uncertainty surrounding the currently available evidence to guide decision making [517]. This technique has been applied to the MDAST which when applied in countries faces knowledge gaps in a range of areas including insecticide resistance and the effectiveness of larviciding, both of which would require additional surveillance and field trials to resolve [518]. VOI analysis estimated the value of information (in terms of benefits to the programme measured in disability-adjusted life years averted and programme costs) of reducing parameter uncertainty around the knowledge gaps. These sorts of methods and tools, if effective, could help to simplify decision making around IVM, in particular targeting and choice of tools and how these should be adapted over time and space, as well as prioritising scarce resources. More generally, VOI could also have utility in helping funders improve research prioritisation on VBD control [519].

This thesis makes clear the need for rigorous study design and conduct. The hypothesis set out at the beginning of the thesis that it would be useful to synthesise common weaknesses of trials and provide guidance to improve future studies has proven correct. The manuscript on vector control study design (Chapter 5) received a high degree of interest from the vector control community and as a result I was commissioned by WHO to produce guidelines on study design and conduct aimed at product innovators. These guidelines will be reviewed by VCAG in a forthcoming meeting, and when published, will serve as a valuable resource for innovators developing new vector control tools. Pathways for VCAG review of new vector control paradigms, including data requirements are also being clarified by the WHO secretariat. This is part of a larger reform of WHO pathways for new products to deployment which has largely been spurred on by the Innovation to Impact partnership made up of global health organisations, national regulatory authorities and industry [520]. As a result of discussions on WHO transformation, the remit of the WHO prequalification process (previously only for diagnostics, drugs and vaccines) has been extended to review the quality, safety and efficacy of vector control products [521]. This much-needed reform should streamline the process and hopefully fast-track dossier review and policy-making on new vector control products. Alongside the reform of WHO pathways for new products to deployment, there is increasing discussion on under what circumstances epidemiological field trials are needed for products. RCTs are time consuming and expensive, with the average malaria vector control trial costing around £500,000 to £1 million [522]. Companies developing new vector control tools want to see early

market access for their products so that they can maximise profits before patents expire and generics are able to enter the market. There is also a huge public health need for new vector control tools. However, this needs to be balanced with the need for robust evidence of efficacy and safety of new products. The argument is made that if a vector control tool results in a reduction in biting intensity this will automatically lead to a reduction in disease, and therefore proof of entomological efficacy would be sufficient. Vontas *et al* set out a framework based on measurements of the vectorial capacity of an insect population to transmit disease and hypothesise that once RCTs establish links between entomological and epidemiological indicators then rapid evaluation of new products within the same product category may be conducted through smaller scale experiments without repetition of RCTs [354]. This may hold for vector control tools that act in a similar way to existing products e.g. a new LLIN with a new active ingredient with the same mode of action (or similar type e.g. short acting insecticide such as pyrethroid or organophosphate) as an existing active. However, tools with completely new active ingredients, combinations of active ingredients or new delivery methods (e.g. eave tubes) should probably still require epidemiological evidence. This is a hotly contested area currently and there is no consensus as yet.

More broadly, the issue of study and data quality is gaining increasing emphasis as evidence-based decision making undergoes a renaissance. Evidence-based decision making is advocated not only in medicine (evidence-based medicine) and public health, but also public and social policy, and increasingly in management [523]. Evidence-based policymaking has advantages in that it standardises practice and means that only proven and cost effective tools are used. However, it is said that a focus on 'better' evidence such as RCTs ignores other types of evidence such as tacit knowledge and professional experience, and that evidence-based policymaking strips practitioners of judgement [524]. Evidence-based policymaking assumes a rational process with a linear and direct relationship between evidence and resulting policy, in which a series of logical steps are followed (identify question, search for evidence, appraise evidence, identify best course of action and implement as policy) [525, 526]. However, it important to consider that evidence is one of many factors which shape policy and practice [527-529]. The narrow evidence-based framing of policy ignores the complexity of systems, the importance of context and local contingencies, multiple stakeholders with competing interests and the fact that research findings may be contested or subject to different interpretations. Rather than taking a rationalist view, political scientists argue that policymakers construct policy problems and fix them in a manner which corresponds to their values [530]. Thus, in reality the relationship between evidence and policy is more likely to be diffuse and indirect [531]. One model given for the utilisation of research findings in policymaking is that of 'enlightenment' or 'percolation' in which research and researchers act by providing ideas

and ways of thinking about problems, rather than providing specific answers to a particular policy question [532]. As a result of this complicated process, it may be that evidence-informed policy is all that can be achieved.

The issue of waste in research and need for more rigour was addressed in a Lancet series in 2014 [8, 9, 360] and more recently in a Royal Society article which talks about how the research culture and ranking of scientists based on high impact publications incentivises and propagates poor research methods and the abuse of statistical procedures [533]. Allied to high quality study design and conduct, is the need for accurate and transparent study reporting. Development of guidelines for study reporting is led by the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network (http://www.equator-network.org) an international initiative which seeks to improve the reliability and value of health research literature through better reporting. Given the poor reporting of entomological outcomes noted during conduct of systematic reviews in Chapter 3, I am keen to develop reporting guidelines specifically for vector control studies. Other systematic reviews have also noted this as a problem. For example, the Cochrane reviews of larval source management [6] and larvivorous fish [7] for malaria control utilised entomological outcomes but these were reported in tabular format and could not be averaged across studies to generate an average effect estimate. Reporting and analysis of entomological data in a more standardised way across studies will allow easier interpretation and comparison of study results and enable synthesis of the data using statistical methods such as meta-analysis.

The findings of Chapter 6 have implications for insecticide resistance management in The Gambia, in particular switching of the IRS insecticide to prolong the useful life of pyrethroid LLINs. The Gambia (although it does not have an IVM policy) is typical of many countries implementing malaria vector control in that it uses predominantly LLINs and IRS. There is often the misconception that this integrated use of interventions constitutes IVM. However, this is not the case. The IVM approach is more than just integration of tools, and while it does not prohibit the use of insecticide-based tools completely, these should be combined with non-insecticide based tools, where possible. The combined use of insecticide and non-insecticide based tools will not only reduce selection pressure for insecticide resistance and thus be more sustainable in the long-run but also help to reduce dependency on insecticides and therefore be safer for humans and the environment. There is also evidence from several trials that the combined use of several tools in this fashion is more effective, for example the use of microbial larvicides and LLINs in western Kenya was shown to be more effective than LLINs alone [380]. The WHO should advocate more strongly for the use of IVM as an

insecticide resistance management strategy (in particular non-insecticide based tools) since this is only briefly mentioned in the Global Plan for Insecticide Resistance Management document [132].

As well as implications for insecticide resistance monitoring in countries, the findings of Chapter 6 may have implications for the use of gene drive technologies, which are thought to have great potential in vector control [63]. In the past, genetic engineering has been difficult since altered traits typically reduce evolutionary fitness and so are eliminated by natural selection. Gene drives are able to circumvent these traditional rules and increase the likelihood that the genetic modification will be passed to offspring, which allows them to spread through populations even if they reduce the fitness of individual organisms. Gene drives could be used to alter vector populations, for example by changing the ability of the mosquito to transmit pathogens or by suppressing/eliminating vector populations, for example by causing lethality, infertility or by biasing the sex ratio. The spread of gene drives through populations will depend in part on the dynamics of mating and gene flow in the population. For example, mating barriers or geographically isolated vector populations will hinder gene drive through populations. *Kdr* genes could be informative as a marker of gene flow through populations. While several studies have looked at the population genetics of *kdr* on a country or multi-country scale [434, 534], ours does this at a finer spatial scale, at a landscape level.

Recommendations for moving IVM forward into policy and practice

The success of implementation of IVM depends on conditions including advocacy for the approach, policy and organisational reform, greater allocation of financial resources, strengthened human and infrastructural capacity and capability, increased basic and applied research, surveillance and monitoring and evaluation, more effective collaboration across sectors and community engagement. Based on the findings of this thesis and broader work on IVM, I have identified recommendations to move IVM forward into policy and practice in countries which can be divided into recommendations for high level policy makers, researchers and VBD programmes (Table 7.1).

Member states should be supported to conduct vector control needs assessments (VCNAs) as mandated by IVM and in the GVCR. VCNA will allow countries to understand their vector control situation better, identify problems, and determine opportunities and needs to re-orient their programmes in line with the GVCR (and IVM). For example, in many countries it will be necessary to restructure the vector control programme so that one department has responsibility for all VBD. This exercise should allow baseline assessment of indicators to monitor progress in implementing the GVCR. It will also allow countries to develop fully costed strategic plans for VBD control. There is no point in conducting VCNA if resources cannot be mobilised to implement the proposed plans.

Therefore, the WHO and others should lobby funders to mobilise funding for this initiative. This will require reorientation of previously siloed funding, for example from the Presidents Malaria Initiative and Global Fund for AIDS, TB and malaria that currently fund only malaria vector control and are focused primarily on vector control commodities.

Policymakers need to make a stronger case for the effectiveness of vector control and continued/increased investment. While the GVCR goes some way to achieving this, there is still some work to be done in building the evidence base. For example, WHO could partner with researchers to document existing IVM case studies or conduct prospective demonstration projects including economic analysis. Opportunities should be grasped to include VBD in the policy agendas of other sectors, the inclusion of VBD in the UN New Urban Agenda as a threat to sustainable and resilient cities being one example of this [502]. WHO should also advocate more strongly for the use of IVM as an insecticide resistance management strategy.

Building capacity and capability in vector control programmes is key to successful implementation of IVM and the GVCR. Countries should identify staffing and skill gaps, for example in vector surveillance, epidemiology, data management and analysis or geographic information systems. Training should be strengthened, for example making academic and vocational training available, establishing on-the-job training for skill upgrading and with the support of WHO, identifying national and regional networks of experts with expertise in entomology and vector control to support training. Adequate remuneration, clear job descriptions and establishment of career pathways for progression should help to stem the attrition of vector control professionals to the private and other sectors. Capacity also includes infrastructural resources such as vehicles, equipment and laboratories. These needs should have been identified in the VCNA and there may be an opportunity to share resources with other sectors here, for example sharing insectaries and entomological laboratories with research institutions.

A lack of intersectoral collaboration is currently a barrier to effective vector control. The GVCR calls for countries to establish a national inter-ministerial steering committee to oversee intersectoral activities, supported by committees with broader membership (e.g. private sector, NGOs etc) and intersectoral committees at lower administrative levels. The GVCR does not elaborate on activities beyond establishment of the committee and so here there is a need for additional research and guidance since, as noted earlier, establishing and sustaining intersectoral action is a challenging area.

Vector control programmes need to engage and mobilise communities more effectively, for example using participatory methods so that communities are supported to take responsibility for and

implement vector control. This is important for all VBD, but particularly for *Aedes* control which will require sustained effort to remove aquatic habitats from in and around the home. Programmes should establish a national plan for community mobilisation and strengthen behaviour change communication by working with community leaders, educators and the media to get messages out about VBD transmission and control.

IVM calls for surveillance and monitoring and evaluation to target and adapt vector control. The ability to collect high quality data and act on it in a timely fashion is a weakness of many programmes and so capacity needs to be built. This includes training of staff in surveillance and monitoring and evaluation, establishment of sentinel and other surveillance sites, strengthening health information systems and integration of entomological, intervention and epidemiological data on one platform.

Increased basic and applied research is needed to support implementation of IVM. For example, innovation is needed to develop new vector control tools, including new active ingredients and new paradigms. Operational research could be conducted, for example to improve delivery strategies, methods of community engagement and mobilisation or develop new surveillance tools. Countries should develop research agendas in this regard to ensure research being conducted meets their programme needs. Research findings should be reviewed and used to inform programme activities.

Table 7.1: Recommendations for moving IVM into policy and practice

High level policy makers e.g. multilateral agencies	
Support vector control needs assessment (VCNA)	Support countries to conduct situational analysis and identify needs using VCNA tools.
Support policy formulation or reform	Provide support to country programmes to formulate or reform policies on IVM, with due regard to health sector and non-health sector policies
Monitor progress of countries in implementing IVM	Establish indicators for countries (e.g. proportion with IVM focal point identified, proportion with IVM Steering Committee established) and chart progress.
Make the case for IVM	Secure more buy-in for reorientation and harmonisation of vector control programmes towards IVM by: - Document case studies of IVM. - Seeking funding for IVM demonstration projects, particularly those which include economic evaluation. - Coordinate production of information resource on IVM including case studies, relevant policies and cross-linkages to existing websites. - Advocate for IVM as an insecticide resistance management strategy, in addition to the focus on new active ingredients. - Advocating for Zika, dengue, chikungunya, yellow fever and others to

	be considered collectively as *Aedes*-transmitted diseases. - Advocating for consideration of VBDs, particularly *Aedes*-transmitted diseases as part of UN New Urban Agenda.
Lobby funders	Lobby funders to encourage the more flexible use of funds: - cross-disease funding versus siloed funding. - nuanced, adaptive use of multiple interventions rather than the current single intervention fits all approach (e.g. LLINs and malaria).
Support training and capacity building	Leverage funds for: - Building public health entomology capacity and capability. - Sharing of information on IVM between country programmes, for example through regional meetings, country exchange tours or staff secondments. Help countries / regions to establish registries of experts with expertise to support entomology and vector control.
Researchers on vector-borne diseases	
Document existing case studies	- Document existing case studies of IVM focusing on innovative and effective methods of involving other sectors in vector control, barriers and enablers of intersectoral collaboration and cross-disease benefits of IVM.
Conduct demonstration studies	- Conduct demonstration studies of IVM comparing to routine vector control, with accompanying economic evaluation.
Mathematical modelling	- Use models to determine the optimal combination of interventions to drive VBDs to zero in different eco-epidemiological settings
Develop new vector control tools	- Innovation on new vector control paradigms and active ingredients.
Establish better links with programmes and policy makers	- Aim for closer linkage with policy makers and programmes to ensure alignment of research agendas, and adoption and utilisation of research findings. - Work with programmes to develop operational research agendas, regionally and in country. - Use data to mobilise additional resources and support.
Develop new surveillance / monitoring and evaluation tools and techniques	- Develop better tools for entomological and epidemiological surveillance (e.g. new trapping methods, mobile phone reporting of cases from remote health centres, use of social media to predict outbreaks etc). - Develop systems for integration of entomological and epidemiological data for rapid evaluation, decision making and action.
Country programmes in endemic countries	
Conduct a vector control needs assessment (VCNA)	- Conduct a VCNA which will review the policy framework and institutional arrangements for vector control, review the burden of VBD and control including planning, implementation and management of operations and constraints, opportunities for addressing constraints and transitioning to IVM. - Utilise the VCNA findings to develop an IVM strategy/work plans.
Get IVM into policy	- Align policies that relate to IVM through either policy development or reform, in both the health sector and other sectors

Strengthen intersectoral action	- Establish a focal person for IVM. - Initiate an inter-ministeral steering committee to coordinate joint action across sectors, establish targets and oversee implementation and stakeholder accountability. - Look at legislation reforms, for example to mandate conduct of health impact assessments so that the impact of development in other sectors on VBD is realised and managed.
Establish better links with researchers	- In conjunction with researchers, establish a research agenda for basic and applied research. - Identify national, regional and international research institutions that the programme could partner with.
Capacity and capability	- Conduct a capacity needs assessment. - Define roles and responsibilities of different vector control cadres and establish career pathways. - Identify and train public health entomology workforce. - Establish national and regional networks of experts with expertise in entomology and vector control to support training. - Strengthen infrastructural capacity, for example insectary and entomological laboratory.
Better surveillance and use of data	- Strengthen entomological and epidemiological surveillance and integrate these data sources for more effective decision making on vector control.
Community mobilisation	- Establish plans for behaviour change communication and community mobilisation based on a good understanding of the communities in which vector control will be implemented.

Conclusion

The importance of vector control is being increasingly recognised, not only due to the massive success of malaria vector control over past 10 years but also the massive failure of *Aedes* vector control to prevent arboviral outbreaks in recent years. Vector control done well, is highly effective, as shown by historical vector control programmes and contemporary malaria vector control. However, challenges such as insecticide resistance, social and environmental change, the threat from new VBDs and weak vector control programmes mean that we cannot be complacent. IVM provides a useful framework to think through vector control and advocates for a more locally tailored and adaptive approach which engages partners within and beyond the health sector. IVM has the potential to make vector control more effective, cost effective, sustainable and ecologically sound. However, there are several conditions for its success including increased and sustainable funding, strengthened capacity and capability, and effective intersectoral collaboration. The findings of this thesis have hopefully contributed to a better understanding of the generation and use of evidence for IVM programming not least by i) demonstrating collateral benefits of insecticide-treated materials in the home on VBDs other than malaria, ii) demonstrating that topical repellents are only able to provide personal protection against biting but do not protect against clinical malaria,

iii) highlighting the issue of poor vector control study design and conduct and iv) showing differential prevalence of *kdr* resistance by member of the *An. gambiae* species complex and increases in response to vector control pressures with implications for future insecticide resistance monitoring in The Gambia. Many of the aspects of IVM have also been adopted by the GVCR. The strong political commitment behind the GVCR means that this initiative has the potential to revolutionise vector control in the future but only if adequately supported with further policy, funding and galvanisation of all stakeholders towards a common goal of VBD elimination.

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Appendix 3.1: Search terms used to identify studies of insecticide-treated nets, curtains and screening against vector-borne diseases

Search set	Medline	Embase	LILACS	Tropical Disease Bulletin
Date of search	*1st April 2013* *13th June 2014*	*2nd April 2013* *13th June 2014*	*3rd April 2013* *16th June 2014*	*8th April 2013*
1	Chagas disease (MeSH) Reduviidae (MeSH) expl Trypanosomiasis (MeSH) American trypanosomiasis	Chagas disease (Emt) expl Reduviidae (Emt) expl American trypanosomiasis	Chagas disease (DeCS)	("Chagas disease" or "american trypanosomiasis" or reduviidae)
2	Dengue (MeSH) expl Aedes (MeSH) expl	Dengue (Emt) expl Aedes (Emt) expl	Dengue (DeCS)	(dengue or aedes)
3	Trypanosomiasis (MeSH) Trypanosomiasis, African (MeSH) expl Human African trypanosomiasis Glossinidae (MeSH) expl	African trypanosomiasis (Emt) expl Human African trypanosomiasis Glossinidae (Emt) expl		("human african trypanosomiasis" or "african trypanosomiasis" or "sleeping sickness" or glossinidae)
4	Encephalitis, Japanese (MeSH) expl Culex (MeSH)	Japanese encephalitis/ (Emt) expl Culex (Emt) expl	Encephalitis, Japanese (DeCS)	("japanese encephalitis" or culex)
5	Leishmaniasis (MeSH) expl Kala Azar Psychodidae (MeSH) expl Sand fly Espundia	Leishmaniasis (Emt) expl Kala azar Psychodidae (Emt) expl Sand fly Espundia	Leishmaniasis (DeCS)	(leishmaniasis or "kala azar" or psychodidae or "sand fly")
6	Elephantiasis, Filarial (MeSH) Elephantiasis (MeSH) Lymphatic filariasis	Lymphatic filariasis (Emt) expl Lymphatic filariasis	Elephantiasis, filarial (DeCS)	("lymphatic filariasis" or elephantiasis)
7	Onchocerciasis (MeSH) expl River blindness Roble's disease Simuliidae (MeSH) Black fly	Onchocerciasis (Emt) expl River blindness Robles disease Simuliidae (Emt) expl Black fly	Onchocerciasis (DeCS)	(onchocerciasis or "river blindness" or simuliidae or "black fly")
8	Mosquito nets (MeSH) expl Pyrethrins (MeSH) Pyreth*	Bed net (Emt) expl Pyrethroid (Emt) expl Insecticide treated net	Mosquito nets (DECS) Insecticide-Treated Bednets (DECS)	"Vector control"

	ITN LLIN Insecticide treated net Long lasting insecticide treated net Bednet Insecticide-treated Insecticide-impregnated Curtain Hous* improve* Hous* design Eaves House screen* Ceiling	LLIN ITN Insecticide-treated Insecticide-impregnated Curtain Hous* improvement Hous* design Eaves House screen* Ceiling		

Appendix 3.2: Studies excluded from systematic review of insecticide-treated nets, curtains and screening against vector-borne diseases

Disease	Author and date	Reason
Visceral leishmaniasis	Basimke 1995 [1]	Permethrin-treated cloth screens measuring 1 x 9 m were fixed near the bed on the mud walls. Intervention is more akin to insecticide treated wall lining and IRS.
	Courtenay 2007 [2] Dinesh 2008 [3] Mondal 2013 [4]	Wrong comparison (ITN vs untreated net)
	Das 2010 [5] Chowdhury 2011 [6]	Data from Joshi 2009 paper included since this pools data from all three study sites (only 2 of 3 sites reported separately in Das 2010 and Chowdhury 2011)
	Mondal 2010 [7]	Comparison unclear - intervention group had existing nets dipped but unclear what proportion of control group were using un-treated nets.
	Picado 2009 [8]	Wrong comparison (Untreated net vs nothing)
	Ritmeijer 2007 [9]	Programme with staged roll out of LLINs. No control group.
Cutaneous leishmaniasis	Reyburn 2000 [10]	Chaddar data excluded – insecticide-treated Islamic cloth used as top sheet
	Jalouk 2007 [11] Tayeh 1997 [12]	Wrong comparison (ITN vs untreated net)
	Elnaiem 1999 [13]	Non-randomised study and no baseline data reported
	Maroli 1991 [14]	Paper reports two field studies with unorthodox designs. In first study CDC light trap is placed under bednet. Second study used cross-over design but no baseline data or control and each catch with treated net compared back to previous night with untreated net.
	Moosa-Kazemi 2007 [15]	Wrong comparison (ITN and treated curtain versus nothing)
	Yaghoobi-Ershadi 2006 [16]	Wrong comparison (ITN and treated curtain versus nothing / ITN and treated curtain versus untreated net and curtain / Untreated net and curtain versus nothing)
Chagas disease	Herber 2003 [17]	Wrong comparison (treated vs untreated curtain)
	Wood 1999 [18]	No numerical outcomes – reported as infestation / no infestation
	Kroeger 2003 [19]	Wrong comparison – treated vs untreated bednets
	Ferral 2010 [20]	Non-randomised study and no baseline data reported (looks to be averaged across all sites, not split by intervention and control)
Lymphatic filariasis	Ogoma 2010 [21]	Entomological data collected in local houses and experimental huts not presented separately
	Ansari 2001 [22]	Wrong comparison (treated curtain vs untreated curtain)
	Odermatt 2008 [23]	Case control study
	Weerasooriya 1996 [24]	Non-randomised study and no baseline data reported
	Pedersen 2002 [25]	No control group
Dengue	Ansari 2001 [22] Lorono Pino 2013 [26] Madarieta 1999 [27]	Wrong comparison (treated curtain vs untreated curtain)

	Vanlerberghe 2011 [28]	No control group
	Tsuzuki 2010 [29]	Case control study
Japanese encephalitis	Dapeng 1994 [30]	Non-randomised study and no baseline data reported
	Luo 1994 [31]	Case control study

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Appendix 3.3: Data extraction form for studies of insecticide-treated nets, curtains and screening against vector-borne diseases which met the inclusion/exclusion criteria

Item number	Variable Name	Variable Description
Publication Information		
1	Reference ID	Unique identifier assigned for a publication
2	Author	Authors of publication
3	Publication year	Year of publication
4	Journal	Journal/Medium in which results are published
5	Volume	Volume of the Journal
6	Issue	Issue number of the Journal
7	Pages	Start page and end page of Journal
8	Title	Title of publication or source
9	Trial number	Unique identifier for the trial.
Trial Information		
10	Trial start year	Calendar year in which trial was started (for example, baseline measurements)
11	Trial end year	Year of trial completion
12	Countries	Geographical location where the study is conducted
13	Number of arms	Number of treatment arms
14	Controlled trial	Does the trial have any control arm or not?
15	Randomisation	Is the trial randomised? Yes/no/uncertain
16	Level at which intervention was allocated	Individual / house / village / zone
17	Allocation	How were interventions allocated?
18	Blinding	Please state level of blinding - investigator, recipient of intervention, outcome assessor
19	Trial design	Design adopted for the trial: i) randomised controlled trial, ii) before-after trial (non-randomised) iii) rotational design e.g. 4 houses and types of net, each house receives each net for 1 night, similarly for personal repellents, iv) other….
20	Trial Comments	Overall trial comments if any
21	Analysis took account of cluster	Analysis section specifically mentions that they took account of clustering. NB: only relevant if study

	randomised design	is cluster randomised
Background Information		
22	Disease	Which disease are the authors trying to control using the intervention?
23	Incidence rate in location	Incidence rate of disease condition in mentioned location (baseline or historic)
24	Transmission season	When is the main disease transmission season (if reported)
25	Region	Exact location where study was conducted (name of town/s or villages and province, longitude and latitude if given)
26	Urban/Rural	Area of the trial conducted
27	Vector Species 1	Name of the main vector species
28	Vector Species 2	Name of the main vector species
29	Vector Species 3	Name of the main vector species
Treatment Description		
32	Treatment Arm 1	Type of treatment (NB: There may be multiple types of treatment within arms). E.g. treated bednet, indoor residual spraying etc
33	Treatment 1 Description	Additional information available regarding the treatment (chemical / concentration / net mesh size / residual activity of insecticide etc)
34	Treatment 1: Number of clusters?	Number of clusters (individual / house / village / zone) that received intervention
35	Treatment 1: Name of clusters / area	Name of clusters / area that received treatment
36	Treatment 1: Number of times treatment administered	
37	Treatment 1: Date treatment was administered	
REPEAT IF MORE THAN ONE TREATMENT ARM		
38	Control arm	Name of the control
39	Control description	Additional information available regarding the control
40	Number of clusters?	Number of clusters (individual / house / village / zone) that received control
41	Name of control clusters / area	Name of clusters / area that received control
42	Number of times control administered	
43	Date control was administered	
Outcome Measurement - entomological		
44	Outcome measures assessed in study	Which outcome measures were assessed in the study? Entomological / clinical / both

45	Entomological outcome	E.g. entomological inoculation rate, biting/landing density or mosquito abundance (no./trap or house).
46	Length of baseline period	State total length and dates
47	Length of post-intervention period	State total length and dates
48	Post intervention period duration	Does the post intervention period cover a whole year or transmission season?
49	Sampling method	Method used for sampling (e.g. human landing catch, aspirator, sticky trap, CDC light trap)
50	Detail on sampling method	Description of sampling method
51	Number of traps / houses	Number of traps total and number of traps per each sampling site
52	How were the sampling sites chosen?	Describe how the sites were chosen for sampling. Does the paper say they were chosen randomly? How was the random selection performed? Is this described? Or was the sampling done in ALL houses?
53	Number of times outcome was measured during baseline period	
54	Number of times outcome was measured during post-intervention period	
55	Outcome Location	Location of the outcome. Eg: Figure 2, Table 1 etc.
REPEAT IF MORE THAN ONE ENTOMOLOGICAL OUTCOME ASSESSED		
Outcome Measurement - clinical		
89	Clinical outcome	Clinical outcome assessed (e.g. prevalence of infection)
90	Patient characteristics	For example; age, previous infection (immunity) etc
91	Length of baseline period	
92	Number of times outcome was measured during baseline period	
93	Length of post-intervention period	
94	Number of times outcome was measured during post-intervention period	
95	Post intervention period duration	
96	Method of measuring clinical outcome	Clinical judgement / diagnostic test used
97	Outcome Location	Location of the outcome. Eg: Figure 2, Table 1 etc.
REPEAT IF MORE THAN ONE CLINICAL OUTCOME ASSESSED		
Tables and figures from published paper:		

Appendix 3.4: PRISMA Checklist for systematic review and meta-analysis of insecticide-treated nets, curtains and screening against vector-borne diseases

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	52
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	52
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	53-54
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	53-54
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	54-55
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	54
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 3.1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	54
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	55
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix 3.3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data	57, Appendix 3.5

		synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	55-56
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	55-56
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	57, Figure 3.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 3.7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix 3.8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	58-59, 64-66, Table 3.1 - 3.4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	58-59, 64-66, Figure 3.2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	66-69
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	69-70
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	71
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	xiii

Appendix 3.5: Risk of bias assessment form utilised to assess risk of bias in studies of insecticide-treated nets, curtains and screening against vector-borne diseases included in systematic review

Criterion	Type of bias	Explanation		
		Low risk of bias	High risk of bias	Unclear
GENERAL CONSIDERATIONS				
Sequence generation	Selection bias	Randomised study and random nature of sequence generation well described OR rotational design study where each individual / house has received every intervention at least once .	Study is non-randomised OR non-random method of sequence generation used OR rotational design study where each individual / house has not received every intervention at least once.	No or unclear information reported (e.g. paper states study is randomised but method of sequence generation is not described).
Allocation concealment	Selection bias	Patients and investigators could not foresee assignment.	Inadequate concealment of allocations prior to assignment.	No or unclear information reported.
Blinding (performance)	Performance bias	Participants and personnel were not aware of which intervention they were allocated to during the study.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	No or unclear information reported.
Contamination	-	It is unlikely that the control group received the intervention.	Control group may have inadvertently received the intervention (e.g. proximity of control and intervention areas or insufficient washout period during crossover or rotational design study).	No or unclear information reported.
Selective outcome reporting	Reporting bias	Outcomes of interest clearly stated and all pre-specified outcomes are reported.	Not all pre-specified outcomes are reported, or additional outcomes are reported.	Unclear or NA (Outcomes not pre-specified in a published protocol).
Incorrect analysis	-	Correct analysis technique utilised (e.g. clustering taken into account in analysis for cluster-randomised trials or appropriate technique used for repeated measures).	Incorrect analysis technique utilised. (e.g. clustering not taken into account in analysis for cluster-randomised trials or inappropriate technique used for repeated measures).	No or unclear information reported.
CLINICAL OUTCOMES				
Baseline characteristics	Selection bias	Baseline characteristics reported to be similar in control and intervention areas.	Significant differences in baseline characteristics between control and intervention areas.	No or unclear information reported.
Blinding (Detection)	Detection bias	Outcome assessors blinded to intervention allocation.	Detection bias due to knowledge of the allocated interventions by outcome assessors.	No or unclear information reported.

Criterion	Type of bias	Explanation		
		Low risk of bias	**High risk of bias**	**Unclear**
Incomplete outcome data	Attrition bias	No or low missing data (<20%), reason for missing data is unlikely to be related to the true outcome, or missing data is balanced across groups.	High missing data (>20%), missing data is likely to be related to the true outcome, or missing data is unbalanced across groups.	No or unclear information reported.
Recruitment bias	Recruitment bias	No change in size or number of clusters after randomisation	Possible change in size or number of clusters after randomisation	No or unclear information reported
Other biases (confounding)	-	Non randomised studies: no evidence of confounding (selection bias)	Non randomised studies: evidence of confounding (selection bias)	
ENTOMOLOGICAL OUTCOMES				
Baseline characteristics	Selection bias	Pre-post design or randomised controlled trial: Baseline entomological data available for previous transmission season (seasonal transmission) or at least 3-6 months (year round transmission)	Pre-post design or randomised controlled trial: No baseline entomological data OR baseline entomological data available for short time period only (less than one transmission season – seasonal transmission or <3-6 months – year round transmission).	No or unclear information reported
		Rotational design: Each individual / house receives every intervention at least once.	Rotational design: Each individual / house has not received every intervention at least once.	
Blinding (Detection)	Detection bias	Investigators / data collectors blinded to intervention allocation OR Objective measurement technique (e.g. CDC light trap, odour-baited trap, sticky trap) utilised for data collection	Non-standardised measurement technique (human landing catches, aspirator & knock down catches) utilised for data collection. OR Efficiency of sampling technique likely to vary between study arms (e.g. CDC light trap collection – bednet versus no bednet)	No or unclear information reported
Random selection of sites for entomological monitoring	Detection bias	Units for entomological sampling selected randomly and random nature of sequence generation well described OR entomological sampling done in all units	Units for entomological sampling not selected randomly	No or unclear information reported

Appendix 3.6: Study quality assessment form utilised to assess risk of bias in studies of insecticide-treated nets, curtains and screening against vector-borne diseases included in systematic review

Study design	Lower if:	Quality score
Randomised controlled trial (score +10)	Sample size calculation: 0 sample size calculation performed or significant effect of intervention shown (beneficial or otherwise) -1 sample size calculation not performed and no significant effect of intervention shown (beneficial or otherwise)	≥ 7 high quality ≥4 < 7 medium quality <4 low quality
Cross over or rotational study (score +7)	Sample size calculation (entomological outcomes): 0 sample size calculation performed -0.5 not performed -1 < 10 sampling sites per arm	
Pre-post study (score +4)	Length of follow up period for entomological outcomes: 0 > 1 year or transmission season -0.5 > 1 year or transmission season but limited repeat measures during this time -1 < 1 year or transmission season	
	Risk of bias -0.5 medium -1 high	

Appendix 3.7: Characteristics of studies of insecticide-treated nets, curtains and screening against vector-borne diseases included in systematic review

Characteristics of cutaneous leishmaniasis studies

Author and date	Study Type	No. of subjects / areas	Country	Intervention	Insecticide resistance	1° outcome	2°outcome
Alexander 1995 [1]	Rotational design	3 study houses – treatments and collectors rotated	Colombia	Deltamethrin impregnated bednets (26 mg a.i./m^2. and mesh size 64 per cm^2). Deltamethrin impregnated curtains (26 mg a.i./m^2. and mesh size 64 per cm^2). Impregnated curtains were suspended across the doorways and windows of rooms.	Bioassay: 1 min exposure = 35% knock down within 1h / 66% mortality within 24h. 2 min exposure = 69% knock down within 1h / 100% mortality within 24h.	Sandfly density	-
Alten 2003 [2]	Non-randomised controlled pre-post study	4 clusters (2 control, 2 ITN). Population = 3761 ITN and 5636 Control	Turkey	Deltamethrin impregnated bednets (25 mg a.i./m^2 and mesh size 156 per cm^2, 100 denier). Re-impregnated every 6 months by the field team.	Not reported / assessed.	Incidence of cutaneous leishmaniasis (questionnaire only, no mention of diagnostic test / clinical examination)	Sandfly density
Emami 2009 [3]	Cluster-RCT	12 sectors across 2 cities. Total population = 8,620 Total households = 3000	Iran	Olyset® LLIN (polyethylene net impregnated with 2% permethrin)	Not reported / assessed.	Incidence of cutaneous leishmaniasis (questionnaire, clinical examination, hospital record check)	Sandfly density
Kroeger 2002 [4]	Cluster-RCT	14 sectors (7 intervention / 7 control). Between 53	Venezuela	Lambdacyhalothrin impregnated curtains (12.5 mg/m^2, mesh size = 0.05 mm. Curtains were fitted to the windows of houses and were	Not reported / assessed.	Incidence of cutaneous leishmaniasis (questionnaire, clinical examination, hospital	Sandfly density

		and 509 participants per sector. Total participants = 2913 from 569 houses		re-impregnated after six months.		record check)	
Majori 1989 [5]	Controlled, pre-post crossover study (analysed as if pre-post study)	2 houses – impregnated curtains rotated between houses (3 total, also non impregnated curtains)	Burkina Faso	Permethrin impregnated curtains (1g/m^2, 0.5cm mesh). Curtains installed inside doorways and under the eaves.	Not reported / assessed.	Sandfly density	-
Nadim 1995 [6]	Cluster-RCT	2 clusters/ areas Total population = 2,414	Iran	Deltamethrin impregnated bednets (25mg per m^2)	Not reported / assessed for vector species (bioassay using *Anopheles stephensi* only).	Incidence of cutaneous leishmaniasis (questionnaire and clinical examination)	Sandfly density (data not extractable)
Noazin 2013 [7]	Non-randomised controlled pre-post study	2 clusters/ areas Intervention = 6546 houses (~23,000 pop.) Control = 22,355 houses (61,224 pop.)	Iran	Deltamethrin impregnated screens and curtains (25mg per m^2, polyester fabric 156 holes/in^2). Covered all windows with treated screens and entrances to the interior of the house with treated curtains.	Not reported / assessed.	Incidence of cutaneous leishmaniasis (Microscopic examination of scraping from skin lesion)	-
Reyburn 2000 [8]	Cluster-RCT	Clusters of 10 households each Population = 1195 ITN and 1759 control	Afghanistan	Permethrin impregnated bednets (0.5 g/m^2, 100-denier, 156 holes/mesh per in^2)	Not reported / assessed.	Incidence of cutaneous leishmaniasis (clinical examination)	-
Rojas 2006	Cluster-RCT	20 clusters	Colombia	Deltamethrin impregnated	Not reported /	Incidence of cutaneous	-

[9]		(villages) Population = 1791 ITN and 1,840 control		bednets (K-Othrine E-25® (deltamethrin and 35 holes per cm^2) and two bars of repellents (20 % DEET + 5% permethrin) and tree trunks painted with white wash and educational program. Bednets re-impregnated every 3 months. N.B. Use of repellent (by last survey only 5% of participants were using it every day) and white washing of tree trunks declined rapidly so can attribute effects mainly to bednets.	assessed.	leishmaniasis (clinical examination and leishmanin skin test)	

Characteristics of visceral leishmaniasis studies

Author and date	Study Type	No. of subjects / areas	Country	Intervention	Insecticide resistance	1° outcome	2°outcome
Elnaiem 1999 [10]	Rotational design	Single site – collectors rotated round	Sudan	Lambda-cyhalothrin (ICON®) impregnated bednets (10mg a.i./m^2, 100 denier, 156 mesh), hand treated	Bioassay: 30 sec exposure = 100% mortality of *P. orientalis* within 1h	Sandfly (*P. orientalis*) density	-
Joshi 2009 [11]	Cluster-RCT	In each of the 4 study sites: Bangladesh (one), India (one) and Nepal (two) six clusters were randomly assigned to each of the study interventions. Each cluster = 50 – 100 houses	Bangladesh, India and Nepal	PermaNet® LLIN (Vestergaard-Frandsen Company, Lausanne, Switzerland) with small mesh (156 holes/in^2), polyester, resin coating containing deltamethrin (55 mg/m^2)	Bioassay of wild caught *P. argentipes*: 3 min exposure = > 80% mortality within 24h in all sites	Sandfly density	-
Picado 2010 [12, 13]	Cluster-RCT	26 clusters Population = 10,563 LLIN and 10,704 control	India and Nepal	PermaNet® 2.0 LLIN (75 denier, 25 holes/cm^2, with deltamethrin (55 mg/m^2) coated fibres)	Bioassay of wild caught *P. argentipes:*60 min exposure = >95% mortality within 24h in both sites [14]	Number of incident *L. donovani* infections (seroconversion using direct agglutination test)	Number of incident cases of visceral leishmaniasis (clinical examination and rapid diagnostic test) Density of sandflies (*P. argentipes*)

Characteristics of lymphatic filariasis studies

Author and date	Study Type	No. of subjects / areas	Country	Intervention	Insecticide resistance	1° outcome	2°outcome
Bøgh 1998 [15]	Cluster-RCT	12 villages – populations ranged from 375 to 1151 inhabitants.	Kenya	Permethrin impregnated bednets (100 denier, mesh 156, 500 mg/m^2 permethrin). Nets were re-impregnated every six months.	Not reported / assessed.	Mosquito density (indoor and outdoor resting, split by species)	-
Charlwood 1987 [16]	Rotational design	3 study houses - treatments and collectors rotated	Papua New Guinea	Permethrin impregnated bednets (0.5g/m^2)	Not reported / assessed.	Mosquito density (indoor resting)	-
Poopathi 1995 [17]	Non-randomised controlled pre-post study	12 huts with high indoor resting density of mosquitoes selected: 8 with impregnated curtains, 2 with untreated curtains, 2 with nothing.	India	Deltamethrin impregnated curtains (50 mg/m^2, hessian fabric, mesh size of 5.5 x 5.5 mm). Curtains hung in the eaves and doorways.	Bioassay: 3 min exposure to freshly treated curtains = 100% mortality of both lab reared *An.stephensi* and *Cx. quinquefasciatus* females after 24h. 3 min exposure 10-16 wks post treatment = <50% mortality after 24h	Mosquito density (indoor resting and man biting)	-

Characteristics of dengue studies

Author and date	Study Type	No. of subjects / areas	Country	Intervention	Insecticide resistance	1° outcome	2°outcome
Kroeger 2006 [18]	Cluster- RCT	Total participants = 4743 inhabitants (1095 houses) in Veracruz	Mexico (Veracruz site)	Lambdacyhalothrin impregnated curtains (15 mg/m^2 netting, treated by hand). Curtains were hung loosely at the windows (mean 2.8 curtains per household). N.B. Intervention also included water treatment with pyriproxyfen chips. However, people didn't accept or use the pyriproxyfen chips, so changes can be attributed to curtains mainly.	Not reported / assessed.	Breteau index, house index, pupae per person	-
Lenhart 2008 [19]	Cluster-RCT	Total study area = 1017 houses, divided into 18 sectors (clusters) with approximately equal number of houses in each sector.	Haiti	Olyset® LLIN (2% permethrin)	Bioassay using lab reared *A. aegypti:* 2 min exposure to new bednets = 50% knock down after 60 min, 30% mortality after 24h. 2 min exposure to 5 mth (or 10mth) old bednets = 80% (37%) knock down after 60 mins, 34% (15%) mortality after 24h.	House index, container index, Breteau index, pupae per person, ovitrap positivity	IgM serostatus (but no control data so not extractable)
Lenhart 2013 [20]	Cluster RCT	Total of 2,037 houses in 26 clusters	Thailand	Deltamethrin impregnated window curtains (55 mg/m^2, made from PermaNet® polyester LLIN netting, factory treated with long-lasting deltamethrin formulation). Sufficient number of curtains were provided to each house	WHO standard bioassay using mosquitoes reared from eggs collected in oviposition traps: 6 mth timepoint = 84% mortality in ITC and 90% in control clusters, 9 mth timepoint = 92% mortality in ITC and	House index, container index, Breteau index, pupae per person, oviposition rates	-

				to hang in every window, regardless of the presence or absence of other window coverings.	92% in control clusters.		
Nguyen 1996 / Igarashi 1997 [21, 22]	Non-randomised controlled pre- post study	2 villages – intervention village had 500 houses (unclear how many in control village)	Vietnam	Olyset® net (LLIN) installed as screens fitting windows, entrances and ventilation openings near the ceilings of the houses in the experimental area.	100% knock down after 9-12 min exposure to new nets. This effect remained 100% after 8 months.	House index (HI), density index (adults)	IgM serostatus (IgM-capture ELISA)
Vanlerberghe 2013 [23]	Cluster RCT	22 clusters – intervention (total of 2032 houses) 66 clusters – control (each 10 houses, total approx. 660 houses)	Thailand	Deltamethrin impregnated window and door curtains (55 mg/m^2, made from PermaNet® polyester LLIN netting, factory treated with long-lasting deltamethrin formulation).	WHO tube bioassay on *Aedes* sp. (eggs reared to adults in the insectary): 87% mortality pre- and 84% post-intervention.	House index (HI), Breteau index (BI), pupae per person index	-

Characteristics of Japanese encephalitis studies

Author and date	Study Type	No. of subjects / areas	Country	Intervention	Insecticide resistance	1° outcome	2°outcome
Dutta 2011 [24]	Non-randomised controlled pre- post study	2 localities (clusters) each consisting of 2-3 villages: intervention = 560 ITNs distributed, population / no. of houses unclear.	India	Deltamethrin impregnated bednets [25 mg/m^2, Deltamethrin 2.5% (K-othrine®, Bayer Cropscience India Limited, Gujrat, India) emulsifiable concentrate (EC), 156 holes/in^2]	Not reported / assessed.	Mosquito density (by species). Catches performed in cattle sheds, mosquitoes resting in or around sheds or landing on animals)	IgM serostatus (IgM- capture ELISA)

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Appendix 3.8: Assessment of risk of bias in studies of insecticide-treated nets, curtains and screening against vector-borne diseases included in systematic review

Study	General considerations						Clinical outcomes					Entomological outcomes			**Overall rating**
	Sequence generation	Allocation concealment	Blinding (performance)	Contamination	Outcome reporting	Incorrect analysis	Baseline characteristics	Blinding (Detection)	Incomplete outcome data	Recruitment bias	Other biases (confounding)	Baseline characteristics	Blinding (Detection)	Monitoring site selection	
Cutaneous leishmaniasis															
Alexander 1995	L	NA	H	L	NA	L	-	-	-	-	-	L	H	L	**L**
Alten 2003	U	U	H	L	NA	H	U	H	U	L	NA	H	L	U	**H**
Emami 2009	L	U	H	L	NA	L	H	H	U	L	NA	H	L	U	**L**
Kroeger 2002	L	U	H	L	NA	L	L	H	L	L	NA	L	L	L	**L**
Majori 1989	U	U	H	NA	NA	L	-	-	-	-	-	H	H	L	**H**
Nadim 1995	L	U	H	L	NA	L	L	U	L	L	NA	-	-	-	**L**
Noazin 2013	H	H	H	H	NA	L	H	U	L	L	NA	-	-	-	**H**
Reyburn 2000	U	U	H	L	NA	L	L	L	L	L	NA	-	-	-	**L**
Rojas 2006	L	U	H	L	NA	L	L	U	L	L	NA	-	-	-	**L**
Visceral leishmaniasis															
Elnaiem 1999	L	NA	H	L	NA	L	-	-	-	-	-	L	H	L	**L**
Joshi 2009	U	U	H	L	NA	L	-	-	-	-	-	L	L	U	**L**
Picado 2010	L	L	H	L	NA	L	L	L	L	L	NA	L	L	H	**L**
Lymphatic filariasis															
Bøgh 1998	U	U	H	L	NA	L	-	-	-	-	-	L	H	H	**M**
Charlwood 1987	L	NA	H	L	NA	L	-	-	-	-	-	L	H	L	**L**
Poopathi 1995	U	U	H	L	NA	L	-	-	-	-	-	H	H	L	**M**
Dengue															
Kroeger 2006	L	L	H	H	NA	L	-	-	-	-	-	H	L/H*	L	**L**
Lenhart 2008	L	L	H	L	NA	L	-	-	-	-	-	H	L/H*	L	**L**

Lenhart 2013	L	L	H	L	NA	L	-	-	-	-	-	H	L/H*	L	**L**
Nguyen 1996 / Igarashi 1997	U	U	H	L	NA	L	L	U	U	L	NA	H	H	U	**L**
Vanlerberghe 2013	U	U	H	L	NA	L	-	-	-	-	-	H	H	L	**M**
Japanese encephalitis															
Dutta 2011	U	U	H	L	NA	L	L	U	U	L	NA	U	H	U	**L**
U = unclear, L = low risk of bias, H = high risk of bias, NA = not applicable, M = medium risk of bias, *used both ovitraps (objective measurement technique, L) and larval surveys (non-objective measurement technique, H)															

Appendix 3.9: Assessment of study quality of studies of insecticide-treated nets, curtains and screening against vector-borne diseases included in systematic review

Study	Study design	Sample size calculation (overall / clinical)	Sample size calculation (entomological outcomes)	Length of follow up period	Risk of bias	Overall score	Study quality
	RCT (+10), crossover / rotational study (+7), pre post study (+4)	Not performed and no sig. effect shown (-1)	Not performed (-0.5), <10 sampling sites/ arm (-1)	-0.5 > 1 year/season but limited repeat measures < 1 year/ transmission season (-1)	Medium (-0.5) High (-1)		≥ 7 high, ≥4 < 7 medium, <4 low
Cutaneous leishmaniasis							
Alexander 1995	Crossover (+7)	NA	< 10/arm (-1)	< 1 year (-1)	Low (0)	5	Medium
Alten 2003	Non-randomised pre post (+4)	Sig. effect shown (0)	Not done (10/arm) (-0.5)	> 1 year (0)	High (-1)	2.5	Low
Emami 2009	RCT (+10)	Sig. effect shown (0)	Not done (30 sticky + 20 LT) (-0.5)	1 year (0)	Low (0)	9.5	High
Kroeger 2002	Matched RCT (+10)	Not done and no sig. effect shown (-1)	Not done (565 LT total) (-0.5)	< 1 year (-1)[1]	Low (0)	7.5	High
Majori 1989	Non-randomised pre post (+4)*	NA	< 10/arm (-1)	< 1 year (-1)	High (-1)	1	Low
Nadim 1995	RCT (+10)	Not done and no sig. effect shown (-1)	NA	1 year (0)	Low (0)	9	High
Noazin 2013	Non-randomised pre post (+4)	Sig. effect shown (0)	NA	> 1 year (0)	High (-1)	3	Low
Reyburn 2000	RCT (+10)	Done (0)	NA	> 1 year	Low (0)	10	High
Rojas 2006	RCT (+10)	Sig. effect shown (0)	NA	1 year (0)	Low (0)	10	High
Visceral leishmaniasis							
Elnaiem 1999	Crossover (+7)	NA	< 10/arm (-1)	< 1 year (-1)	Low (0)	5	Medium
Joshi 2009	RCT (+10)	NA	Not done (-0.5)	< 1 year (-1)	Low (0)	8.5	High
Picado 2010	RCT (+10)	Done (0)	Not done (≥ 10/arm) (-0.5)	> 1 year (0)	Low (0)	9.5	High

Lymphatic filariasis							
Bøgh 1998	RCT (+10)	NA	Not done (12/arm) (-0.5)	> 1 year but limited repeat measures (-0.5)	Medium (-0.5)	8.5	High
Charlwood 1987	Crossover (+7)	NA	< 10/arm (-1)	< 1 year (-1)	Low (0)	5	Medium
Poopathi 1995	Non-randomised pre post (+4)	NA	< 10/arm (-1)	< 1 year (-1)	Medium (-0.5)	1.5	Low
Dengue							
Kroeger 2006	RCT (+10)	NA	Not done (> 10/arm) (-0.5)	> 1 year (0)	Low (0)	9.5	High
Lenhart 2008	RCT (+10)	NA	Not done (> 10/arm) (-0.5)	> 1 year (0)	Low (0)	9.5	High
Lenhart 2013	RCT (+10)	NA	Not done (> 10/arm) (-0.5)	Season (0)	Low (0)	9.5	High
Nguyen 1996 / Igarashi 1997	Non-randomised pre post (+4)	Sig. effect shown (0)	Not done (> 10/arm) (-0.5)	Season (0)	Low (0)	3.5	Low
Vanlerberghe 2013	RCT (+10)	Done (0)	Not done (>10 arm) (-0.5)	> 1 year but limited repeat measures (-0.5)	Medium (-0.5)	8.5	High
Japanese encephalitis							
Dutta 2011	Non-randomised pre post (+4)	Sig. effect shown (0)	< 10/arm (-1)	> 1 year (0)	Low (0)	3	Low

* study is controlled, pre-post crossover design (analysed as if pre-post study), [1] follow up period differed for clinical and ento outcomes - was < 1 year for entomological outcomes.

Appendix 4.1: PRISMA checklist for systematic review and meta-analysis of studies of topical repellents against malaria

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	72
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	72
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	73-74
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	74
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	74-75
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	74
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 4.2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	74
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	75
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	75
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	76

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	75-76
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	75-76
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	76, Figure 4.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	77-78, Additional File 3 (original manuscript)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix 4.4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	78, Table 4.1 and 4.2
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency	80, Figure 4.2 and 4.3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	81-83
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	83
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	83-84
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	xiii

Appendix 4.2: Search terms used to identify studies of topical repellent against malaria

Date of search	Database	Search terms
17th Jan 2014 28th July 2014	Medline	exp Malaria/ AND [exp Insect Repellents/ DEET/ "Insect Bites and Stings"/ repellent.mp. / Permethrin/]
	Embase	exp malaria/ AND [permethrin/ or diethyltoluamide/ or exp insect repellent/ or insect bite/ or repellent.mp.]
	Web of Science	TOPIC: (malaria) AND TOPIC: (repellent)

Appendix 4.3: Characteristics of studies of topical repellents against malaria included in systematic review

Study	Study type	Year study conducted	Location	Study population	Intervention	Compliance	Control	Outcomes	Measurement
Chen-Hussey *et al*. [1]	Double blind, household randomised, placebo-controlled trial	2009-10	Lao PDR	1,597 households recruited from agricultural communities. Up to 25% of households per village recruited. Participants aged 6-60 years and 55% were female.	15% DEET lotion + LLINs	Compliance measured by self-reporting, observed volume of lotion used and random infrequent sniff checks. 58% of participants used lotions >90% of the time.	Placebo lotion + LLINs	Incidence of *P. falciparum* and *P. vivax* infection (confirmed using RDT)	Monthly active detection (5-8 month follow up period, average 6.3 months).
Dadzie *et al*. [2]	Non-randomised, two village, controlled study	2010-11	Ghana	2 villages (study pop. unclear but 200-350 people recruited for malaria parasite prevalence survey).	NO MAS mosquito repellent (active ingredient not stated)	Self-reported compliance at 3 months = 96%	No repellent	Prevalence of *P. falciparum* infection (confirmed using RDT)	Cross sectional survey at 8 month timepoint.
Deressa *et al*. [3]	Cluster-randomised controlled trial	2008	Ethiopia	16 rural villages with 1,235 households 3,078	Buzz-Off® petroleum jelly and essential oil blend + LLINs	Not reported	LLINs only	Prevalence of *P. falciparum* and *P. vivax* infection (confirmed	Cross sectional surveys at 1 and 2 month timepoints.

				individuals in intervention and 3,004 in control group				using microscopy)	
Dutta *et al*. [4]	Non-randomised cluster allocated factorial trial	2003-6	India	Intervention: 306 households with pop of 1,836; Control: 294 households with a pop. of 1764.	12% N,N-diethylbenzamide w/w. cream-base tubes (25 mg) (Odomos)	Compliance assessed by unannounced 'sniff checks'. Figures not reported	No repellent	Malaria (*P. falciparum*) incidence (confirmed using microscopy)	Weekly active case detection (2 year follow up period)
Hill *et al*. [5]	Double blind, randomised, controlled trial	2003	Bolivia	4,008 individuals in 860 households in rural villages/peri-urban districts Participants aged >10 years and 45% were female	*Eucalyptus maculata citriodon* with a PMD concentration of 30% + ITN	Measured by questionnaires, observed volume of lotion used and random sniff checks. 99% of participants used lotions >90% of the time	0.1% clove oil + ITN	Incidence of *P. falciparum* or *P. vivax* infection - with or without fever (*P. falciparum* confirmed by RDT and *P. vivax* confirmed by blood slide at local clinic)	Monthly active detection for *P. falciparum*. Passive detection for *P. vivax*. 4 month follow up period.
Kroeger *et al*. [6]	Matched cluster randomised controlled trial	1991-2	Ecuador and Peru	18 rural communities	Repellent soap containing 20% DEET and 0.5% permethrin	50-70% when soap was distributed free, 6% when soap was sold	No repellent	Self-reported malaria incidence (period prevalence of attacks)	Single survey for recall of malaria attacks in previous 4 months.

								Parasites species not determined: manuscript reports that Ecuador = 86% *P. falciparum* and Peru = 100% *P. vivax*	
McGready *et al*. [7]	Double blind, individually randomised, placebo controlled trial	1995-6	Thailand	897 women 3-7 mths pregnant recruited from Karen refugee camps in western Thailand	Repellent lotion containing 20% DEET and thanaka (*Limonia acidissima*)	Compliance self-reported at 91% and actively detected at 85%	A placebo formulation containing thanaka	Incidence of *P. falciparum* and *P. vivax* infection ('patent parasitaemic episode' confirmed by microscopy)	Weekly active detection (median follow-up of 18 weeks, range 0-32 weeks)
Sangoro *et al*. [8]	Cluster-randomised, placebo-controlled trial	2009-10	Tanzania	937 households recruited from a rural village. 50% of households in a village were recruited. Participants were aged >6 mths and 55.3% of	15% DEET lotion + LLINs	Compliance measured by self-reporting and compliance with repellent reported at 89% and placebo 68%	Placebo lotion + LLINs	Malaria (*P. falciparum*) incidence (confirmed using RDT)	Passive case detection (14 month follow-up period)

				household heads were female					
Rowland *et al*. [9]	Cluster randomised placebo controlled trial	1999-2000	Pakistan	127 households recruited from a refugee camp on Afghan border. 25% of households in camp were enrolled. Participants were aged >5 yrs and 49.2% were female	20% DEET and 0.5% permethrin soap	20 (16%) households interviewed at end of study, 19 (95%) reported using the repellent 'regularly'	Placebo lotion	Incidence of *P. falciparum* and *P. vivax* infection (confirmed by microscopy)	Passive detection (5 month follow-up period)
Vittal *et al*. [10]	Non-randomised, two village controlled study	1976-1978	India	2 rural villages	Insect repellent, proprietary name Enteemosq (active ingredient not stated)	Not estimated	No repellent	Malaria incidence (confirmed by microscopy) Parasite species not determined: according to expert opinion (Dr. Ramesh Dhiman, National Institute of Malaria	Active case detection (2 year follow-up period)

								Research, India) approx. 85% of cases are *P. vivax* in this area	

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Appendix 4.4: Assessment of risk of bias of studies of topical repellent against malaria included in systematic review

Study	Criteria assessed								
	Sequence generation	Allocation concealment	Baseline outcome measurement similar	Baseline characteristics similar	Loss to follow up	Blinding of outcome assessment	Contamination	Selective outcome reporting	Other bias
Chen-Hussey *et al*. [1]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dadzie *et al*. [2]	Unclear	Unclear	High risk	Unclear	Unclear	Unclear	Low risk	Low risk	High risk*
Deressa *et al*. [3]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dutta *et al*. [4]	Unclear	Unclear	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	High risk*
Hill *et al*. [5]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kroeger *et al*. [6]	Unclear	Unclear	Low risk	Unclear	Unclear	High risk (self-reported malaria)	Low risk	Low risk	High risk*
McGready *et al*. [7]	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sangoro *et al*. [8]	Low risk	Low risk	Unclear	High risk	Low risk	Unclear	Low risk	Low risk	Low risk
Rowland *et al*. [9]	Low risk	Unclear	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Vittal *et al*. [10]	Unclear	Unclear	High risk	Unclear	Unclear	Unclear	Low risk	Low risk	High risk*
* Analysis did not take into account clustering									

References for Appendix 4.4

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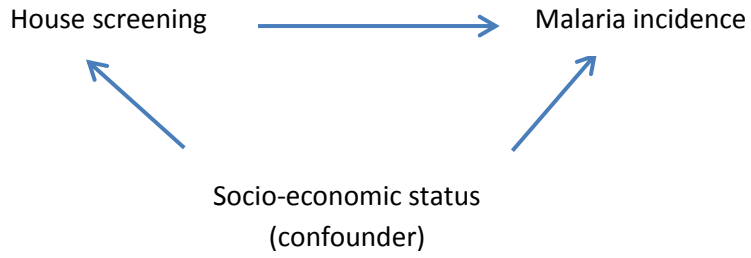
Appendix 5.1: Glossary of key terms relating to efficacy trial design and conduct

Allocation concealment	Refers to keeping the investigator unaware of to which group (i.e., treatment or control) an individual or cluster is assigned. Selection bias can be introduced if the investigator or participant can foresee the assignment; e.g., use of alternation or rotation, assignment envelopes not sealed, not opaque or not sequentially numbered.
Attrition bias	Refers to systematic differences between those individuals or communities that withdraw from the study or those that are lost to follow-up versus those that continue in the study.
Blinding	A procedure used in trials in which participants/investigators/outcome assessors do not know to which group the individual or cluster has been assigned to. Single blind refers to either the participant or investigator/outcome assessor being blinded, while double blind refers to both the participant and investigator/outcome assessor being blinded.
Case-control study	Study in which a group of people with the disease of interest (cases) and a group of people without the disease (controls), but representing the population from which the cases originated are identified. The prevalence of the exposure of interest (e.g., use of protective intervention) is compared between these two groups.
Cohort study	Study in which two groups of disease free people are identified: exposed (using a protective intervention) and unexposed (not using a protective intervention). The groups are then followed over a period of time for the outcome of interest (usually disease or infection). In this study type, the people are not allocated to the intervention of interest.
Confounding bias	According to Porta "confounding occurs when all or part of the apparent association between the exposure and the outcome is in fact accounted for by other variables that affect the outcome and are not themselves affected by exposure" [1]. A variable that is on the causal pathway between the exposure and the outcome is not a confounder. Confounding bias refers to "bias of the estimated effect of an exposure on an outcome due to the presence of common causes of the exposure and the outcome" according to Porta [1]. This is a common type of bias in observational studies and non-randomised trials. For example, in an observational study of the association between house screening and malaria incidence, the relationship is likely to be confounded by socio-economic status since people in superior houses that use screening are likely to be of higher socio-economic status, who may for example have greater access to other protective measures against malaria, such as LLINs. 
Control group	Group of study participants that receive either no intervention, a placebo or the standard of care depending on the study design, which thereby serve as a comparison group when the intervention results are evaluated.
Courtesy bias	A tendency for study participants to give favourable answers out of courtesy to the investigator e.g., incorrect reporting of high

	compliance to an intervention.
Cross-sectional study	In an analytical cross-sectional study, information is collected at one point in time on the prevalence of the outcome of interest (e.g., disease or infection) and the exposure (e.g., use of a protective intervention).
Cluster randomisation	Study in which clusters are randomly assigned to either control or intervention groups. Clusters can be geographic areas (e.g., sectors of a large city), communities (e.g., villages), administrative units (e.g., district or region), institutions (e.g., schools), health facilities or households.
Controlled before-and-after study (CBA)	Also known as a pre-post study. A study in which observations are made before and after implementation of an intervention, in both the intervention group and a control group that does not receive the intervention.
Cross-over study	Study in which individuals/clusters receive the intervention or control for a period of time before switching to receive control or intervention. There is usually a washout period in between to avoid carry-over effects.
Detection bias	Refers to systematic differences between groups in how outcomes are determined. For example, clinicians assessing patients may be more or less likely to diagnose a particular disease if they know that a person received a protective intervention in the study. Detection bias can be reduced by ensuring that investigators and outcome assessors are not aware of which intervention participants have received.
Effectiveness study	These studies estimate the effect of an intervention under pragmatic or 'real-life' conditions e.g., intervention delivery under routine conditions so that the relevance of the findings for policy and practice is maximised.
Effect size	This is the magnitude of difference between treatment and control groups e.g., risk or rate ratio, percentage reduction in prevalence etc.
Efficacy trial	These studies estimate the effect of an intervention under highly controlled conditions e.g., maximal coverage of the target population and adherence to the intervention etc.
Experimental study	Study design in which we allocate exposure to study subjects and observe the outcome.
Interrupted time series (ITS)	Study in which the outcome is measured on a number of occasions both prior to and following introduction of an intervention (the 'interruption'). This allows us to see whether an intervention has had an impact greater than any underlying trend in the data. This study design may or may not include a parallel control group.
Observational study	Study design in which we observe the effect of the exposure on the study subjects, but no role is played in assigning the exposure to the participants.
Performance bias	According to Porta refers to "systematic differences in the care provided to members of the different study groups other than the intervention under investigation" [1]. For example, if participants know they are in the control group of a trial of repellents, they may be more likely to use other forms of vector control, such as protective clothing. Alternatively, health care providers may care for patients differently if they are aware of which study group they are in. Performance bias can be reduced by blinding to ensure that participants, health care providers, and researchers are not aware of which intervention participants have received, although this is not always possible.
Randomisation	Individuals or clusters are allocated to intervention and control using a random method. Randomisation consists of two inter-

	related steps, sequence generation and allocation concealment (not to be confused with blinding).
Randomised controlled trial (RCT)	Individuals or clusters (cluster-RCT) are randomly allocated to receive either intervention or control. Intervention and control groups are then followed-up for the outcome of interest.
Recall bias	Refers to systematic differences between groups in the recall of information regarding exposures. It is a particular problem in case-control studies where surveys are used to gather information on past exposures.
Sequence generation	Method of generating allocation sequence. The method can be non-random (e.g., odd or even date of birth, investigator preference) or random (e.g., random number generator, drawling lots, coin tossing).
Selection bias	Refers to "bias in the estimated association or effect of an exposure on an outcome that arises from the procedures used to select individuals into the study or the analysis" according to Porta [1]. Often selection bias refers to systematic differences between the characteristics of the study population and those of other populations, and as such there is a lack of generalisability. Non-randomised studies are particularly susceptible to selection bias although randomised studies can suffer from selection bias if randomisation procedures are not followed correctly. Selection bias can also be introduced into observational studies. For example, in case-control studies, selection bias is introduced if cases are selected which are not representative of all cases within the population or controls are selected that are not representative of the population which produced the cases.
Step-wedge design	Studies in which the intervention is rolled out to clusters in a staged fashion. At the end of the study, all clusters will have received the intervention. The order in which clusters receive the intervention is usually determined at random.
Stratification / stratified randomisation	A technique used to ensure that equal numbers of individuals or clusters with a characteristic thought to affect response to the vector control intervention (e.g., baseline incidence) will be allocated to each study arm. Multiple clusters are grouped to form strata based on a characteristic (e.g., low versus high incidence of disease) and clusters are randomly allocated within the strata such that equal numbers are assigned to intervention and control. Within each strata more than one cluster is assigned to an arm.
Systematic review	According to Porta a systematic review is "a review of the scientific evidence which applies strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on the specific topic" [1]. The Cochrane Collaboration produces 'gold-standard' systematic reviews which are conducted in a highly rigorous fashion.
Time series	Study in which the outcome is measured on a number of occasions following introduction of an intervention. This study design generally has a parallel control group, but may not be randomised.
(adapted from [1-5])	

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