SCIENCE AND SURVEILLANCE IN THE VISCERAL LEISHMANIASIS ELIMINATION PROGRAMME IN INDIA

NATALIE J. DIAL
MSc, MIPM

Thesis submitted in accordance with the requirements for the degree of
Doctor of Public Health

of the
University of London

August 2021

Department of Global Health and Development
Faculty of Public Health and Policy
LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

DECLARATION BY CANDIDATE

I have read and understood the LSHTM definition of plagiarism in the 2020-2021 Research Degrees Handbook. I have acknowledged all results and references from published or unpublished work of others.

This thesis presents original and independent work of the author.

NAME IN FULL: Natalie J. Dial

STUDENT ID NO: 1605001

SIGNED: 

DATE: 02 August 2021

ABSTRACT

Early case detection is a pillar of India's strategy to eliminate visceral leishmaniasis (VL) as a public health problem by 2030. To identify and treat the several thousand VL cases remaining within a population of 150 million people, surveillance must be continuously refined and reinforced. In Bihar, India's most endemic state, strategising efficient and long-term surveillance requires understanding current and projected costs of active- and passive-case detection (ACD and PCD) alongside the degree to which policy-relevant research is able to inform and adjust elimination activities.

This thesis is separated into two research themes. First, the impact of economic analyses on surveillance is reviewed and findings are presented on the costs and outcomes of ACD and PCD activities in Bihar. Bottom-up micro-costing and top-down expenditure analyses compare programme costs, cost per case detected, and the cost to scale-up activities across a heterogeneous landscape of incidence. Districts with medium- or high-incidence might be sufficiently addressed through passive case detection accompanied by less costly index case-based active detection, whereas low-incidence districts might require higher cost house-to-house active surveillance to reduce the risk of resurgence.

The second theme explores the extent to which VL modelling research is practically applied within India's elimination programme. In-depth interviews with decision makers, programme managers, and researchers examine the use and perceived value of incidence predictions, the likelihood of reaching elimination targets, and projected effects of different interventions for informing programme strategy. Decision makers and researchers reported that knowledge utilisation may be impeded by assumptions that 1) models accurately reflect transmission dynamics, 2) modellers apply their analyses to specific programme operations, and 3) there is

accountability in the process of translating knowledge to policy. Engaging decision makers in the later stages of the modelling process, especially interpretation, may be crucial to garnering the political support needed to translate knowledge into programme activities.

Modelling and economics are critical research disciplines for projecting incidence and programme costs throughout the process of neglected tropical disease elimination. This DrPH thesis examines and contributes to actionable research and its use in policy through the lens of strategising case detection to eliminate VL as a public health problem in India.

DOCTOR OF PUBLIC HEALTH (DrPH) SUMMARY STATEMENT

The Doctor of Public Health (DrPH) degree at the London School of Hygiene and Tropical Medicine (LSHTM) is a practice- and research-based doctoral level qualification intended to equip graduates with the knowledge and experience to understand and apply scientific knowledge to achieve public health gains. The DrPH programme is organised into three sequential and compulsory components:

I. Two taught modules in Evidence-Based Public Health Policy & Practice and Understanding Leadership, Management, & Organisation
II. A professional research attachment, or Organisational Policy Analysis (OPA), carried out over six- to twelve-months in a public health organisation
III. A research project carried out over 18-months that leads to the production of a thesis

Continuing from a background in public health policy with research experience in population-level interventions, the DrPH programme aligned with my ambition to develop and hone policy-relevant research skills. I enrolled in September 2017 and completed two requisite modules that reinforced my capacity to design research intended for policy, improved my ability to communicate and collaborate with diverse actors, and advanced my understanding of the dynamics between and within public health organisations. In early 2018, I began a part-time 18-month research assistant position within the LSHTM-based consortium SPEAK India (Setting the Post-Elimination agenda for Kala-Azar in India), where my interest in visceral leishmaniasis developed. This led to the completion of my professional attachment (OPA) with the New Delhi branch of the consortium KalaCORE, where I carried out a retrospective analysis of how the organisation rolled out and maintained

an improved VL treatment programme from 2014-2018. The product of this research component was a programme analysis composed explicitly for KalaCORE and published internally at LSHTM.

While evaluating India's VL treatment programme during the OPA, I was motivated to formulate a thesis that would address: 1) how and at what cost VL cases are first detected prior to treatment, and 2) how decision makers in India value and use research insights relating to case detection strategies. The former question would allow me to develop fundamental skills in economic analysis, while the latter would facilitate a real-world examination of research actionability in policy. This thesis proposal was presented to the Public Health Policy faculty, examined by Dr Emma Harding-Esch and Dr Sedona Sweeney of LSHTM, and accepted in June 2019.

During the past several years at LSHTM I also engaged in teaching as a Seminar Leader on two master's level courses: Applied Communicable Disease Control and Health Policy, Process & Power. Guiding students through these modules allowed me to revisit and communicate public health literature, theories, and case studies from a new perspective, which enhanced the breadth of my DrPH experience.

ACKNOWLEDGEMENTS

I have infinite appreciation for the patience, wisdom, and generosity of my main supervisor, Graham Medley. Despite our initially minimal overlap in disciplines, and especially during a more pressing role to advise the UK government during the pandemic, you provided steadfast support for a rigorous and rewarding doctoral experience. Thank you for expanding my work opportunities and funding; challenging my capacity to write, read, and develop research; and validating the power of science in policy.

A tremendous thanks to my second supervisor, Fern Terris-Prestholt, for encouraging and facilitating my understanding of economics. You are a fantastic female role model in public health, and I am grateful to have learned the importance and accessibility of costing through your tutelage and example.

To the inimitable Simon Croft, my third supervisor, thank you for postponing full retirement to share your depth of knowledge, read my many drafts, and support my academic growth with much wisdom, kindness, and a great sense of humour. Admittedly, I am still figuring out the present participle and why not to use it.

I appreciate my Dad for instilling a love of biology and travel early in my youth. You read E.O. Wilson's The Diversity of Life with me, brought me to Tanzania when I was a teen—and always have binoculars and a birding book somewhere on your person. Your example kept science joyous and grounded during this (and the never-ending) pursuit of knowledge.

My older brother, Terry—thank you for helping me see the doctoral-forest for the trees. Our many phone calls, distain for the respective weather in Providence and London, and plans to ski over holiday breaks kept me sane and self-assured throughout this programme.

I am grateful to my Mom for her daily (I kid not) reminder to embody Rihanna's hit song and 'Shine Bright Like a Diamond'. You are a beacon of generosity, encouragement, and superior womanly strength in my life.

I treasure the camaraderie and kindness of my entire DrPH cohort—I learned as much from my classmates as I did from my professors. If you are any indication, the future of global health is indeed in compassionate and competent hands. Jordan, my best DrPH buddy, I am especially indebted to your support, comedy, and myriad Spotify playlists exchanged throughout this degree.

To my best friend and partner, Harry: I appreciate you finally conceding that we were in love as my impetus to move to London and start this programme. Thank you for cooking every meal I ever requested—the brainpower behind this thesis was largely fuelled by your spicy prawn pasta, bone marrow burgers, nigiri platters, and six-figure-Scoville-scale hot sauce. Thank you for rolling your eyes in exasperation during my self-doubting moments. I love you deeply.

DEDICATION

For Ella, Ruth, Jewel, & Mama

i stand
on the sacrifices
of a million women before me
thinking
what can I do
to make this mountain taller
so the women after me
can see farther

Legacy – Rupi Kaur

Kaur, Rupi. Legacy. *The Sun and Her Flowers.* 2017. Andrews McMeel Publishing. P 213.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACRONYMS & ABBREVIATIONS

ACD	Active case detection
AmBisome	Liposomal amphotericin B
ASHA	Accredited social health activist
BCC	Behaviour change communication
BMGF	Bill and Melinda Gates Foundation
CHC	Community Health Centre
COVID-19	Coronavirus disease 2019 (SARS-CoV-2)
DALY	Disability-adjusted life year
DDT	Dichlorodiphenyltrichloroethane
DFID	Department for International Development
DND*i*	Drugs for Neglected Diseases Initiative
DrPH	Doctor of Public Health
EOT	Elimination (interruption) of transmission
EPHP	Elimination as a public health problem
EVIPNet	Evidence-informed policy network
FIND	Foundation for Innovative Diagnostics
FOI	Force of infection
GATES-RC	Bill and Melinda Gates Foundation Reference Case
GDP	Gross Domestic Product
GHCC	Global Health Cost Consortium
GN	Global Network
HPSR	Health policy and systems research
ICMR	Indian Council of Medical Research
IDB	Inter-American Development Bank
IDM	Innovative and intensified disease management
IDM-NTDs	Innovative and intensified disease management-neglected tropical diseases
ISC	Indian Subcontinent
IRS	Indoor residual spraying
KA	Kala-azar
KAMIS	Kala-Azar Management Information System
KEP	Kala-Azar Elimination Programme
KT	Knowledge Translation
KTA	Knowledge-to-Action
LAC	Latin American Country
LLIN	Long-lasting insecticidal nets
LMIC	Low- and middle-income countries
LDNTD	London Declaration on NTDs
LSHTM	London School of Hygiene and Tropical Medicine
MDA	Mass drug administration
MDG	Millennium Development Goal
NGO	Non-governmental organisation
NICE	National Institute for Health Care Excellence
NTD	Neglected tropical disease
NVBDCP	National Vector Borne Disease Control Programme
OOP	Out-of-pocket
PAHO	Pan American Health Organization
PCD	Passive case detection
PC-NTDs	Preventive chemotherapy-neglected tropical diseases

PCT	Preventive chemotherapy and transmission control
PHC	Primary health centre
PKDL	Post-kala-azar dermal leishmaniasis
QALY	Quality-adjusted life year
R_0	Basic reproduction number
RTAG	Regional Technical Advisory Group
SEARO	South East Asia Regional Office
SPEAK	Setting the Post-Elimination Agenda for Kala-Azar
SSG	Sodium stibogluconate
STH	Soil-transmitted helminth
TB	Tuberculosis
UCNTD	Uniting to Combat NTDs
URP	Uncertified rural practitioner
USD	United States Dollar
VEM	Vector ecology and management
VL	Visceral leishmaniasis
WASH	Water, sanitation, and hygiene
WHO	World Health Organization
YLD	Years lived with disability
YLL	Years of life lost

GLOSSARY OF TERMS

acquired immunity
An immune system response to a foreign substance or microorganism in which a person elicits or receives antibodies from another source and thereby develops immunity. There are two subtypes: 1) adaptive immunity, which occurs in response to being infected with or vaccinated against a particular microorganism when the body mounts an immune response that can prevent or reduce future infection; and 2) passive immunity, which occurs when a person receives antibodies to a disease or toxin rather than making them through their own immune system

active case detection (ACD)
A type of surveillance or case finding approach in which health care workers systematically search for and clinically verify infected patients who have not visited a health facility for treatment. Active case detection requires substantially more time and resources than passive case detection, but is more complete and methodical

basic reproduction number (R_0)
Denoted as R_0, this metric is used to quantify the transmission potential of an infectious disease in a particular environment by calculating the average number of secondary infections produced by an initial case of infection in a population where everyone is susceptible during the period of infectiousness. If $R_0 > 1$ the number of cases will increase; if $R_0 = 1$ the number of cases is constant; and if $R_0 < 1$ the number of cases will decrease

control
The mean reduction of disease incidence, prevalence, morbidity, and/or mortality to a locally acceptable level as a result of deliberate efforts or intervention measures

cost analysis
Uses both costs and outcomes to estimate the total cost of implementing a programme or intervention. Useful to decision makers for budgeting, performance monitoring, and resource allocation

cost-effectiveness analysis
An evaluation to compare the costs of interventions against their adverse and beneficial health consequences, usually measured by a natural unit such as cases-averted

cost-minimisation analysis
A form of comparative economic analysis that compares the cost of two or more interventions (or policy alternatives) that are assumed to have equivalent health outcomes

deterministic model (of infectious disease)
A model which describes the average (mean) behaviour of the infection dynamics in a population and does not incorporate the effects of chance. It usually applies to population-based models

disease benchmark
An achievable, quantifiable target relating to disease incidence, prevalence, morbidity, and/or mortality that is used to measure progress of deliberate efforts towards control, elimination,

or eradication in a defined geographical area. These are most often defined and validated by the World Health Organization

dynamic model (of infectious disease)
A model which describes changes in given quantities (typically state variables) over time, frequently used to describe the transmission dynamics of an infectious agent by capturing the processes that lead to transmission, infection, recovery, and/or acquisition/waning immunity, as well as host demographic processes, with the purpose of understanding how these processes impact the incidence and prevalence in the host population

economic cost
Costs that capture the full value of resources, including the monetary value for opportunity foregone of donated goods, volunteer time, or where otherwise no market prices are available

elimination of transmission (EOT)
Commonly referred to as interruption of transmission, this is defined as achieving a mean reduction to zero of the incidence of infection caused by a specific pathogen in a defined geographic area as a result of deliberate intervention efforts, with minimal risk of resurgence and/or reintroduction

elimination as a public health problem (EPHP)
A term related to both infection and disease (morbidity associated with the infection), which is defined by achievement of measurable global targets set by WHO in relation to a specific disease. When targets are reached, continued action is required to maintain targets and/or to advance towards elimination (interruption) of transmission

endemic
A disease or condition regularly found among particular population groups, populations, or in a certain area, by which the number of cases varies around an average determined by transmission conditions. The level of endemicity can be measured by determining how common an infection is, or by determining the change in rates of infection over time

eradication
The global and permanent reduction of incidence to zero of a specific pathogen as a result of deliberate efforts, with no risk of reintroduction

exposure
Having come into contact with a cause of, or possessing a characteristic that is determinant of, a particular public health problem

financial cost
Costs that characterise resources paid for and those planned to be spent, usually from the perspective of a specific payer, programme, or organisation

force of infection (FOI)
The rate at which a susceptible individual becomes infected per unit time

health policy and systems research
An interdisciplinary and emerging field that seeks to understand and improve how societies organise themselves in achieving collective health goals, and how different actors interact in the policy and implementation processes to actualise policy outcomes

incidence
The occurrence of new cases of disease in a population over a specified period of time

incubation period
The time interval from exposure to an infectious agent to the onset of symptoms of an infectious disease

individual-based model
A model that works bottom-up to describe population-level behaviour that emerges from interactions between autonomous individuals and their environment. The history of every individual is used to create a network structure based on a unique set of attributes and state variables

infection
Invasion of the body tissues of a host by an infectious agent, whether or not it causes disease

innovative and intensified disease management (IDM)
A category of disease intervention used when cost-effective control tools do not exist and where large-scale use of tools is limited. The goal is to manage diseases within primary healthcare systems and eliminate those diseases as public health problems

morbidity
Disease; any departure, subjective or objective, from a state of physiological or psychological health and well-being

mortality
Death; in infectious disease models mortality rates enter as background death rates and/or excess mortality rates due to the infection

natural history of disease
The course, development, and/or progression of a communicable disease over a period of time in a person who is not receiving treatment. The stages of natural history are often marked as exposure, infection (symptomatic or asymptomatic), and outcome (either recovery, chronicity, or death)

neglected tropical diseases (NTDs)
An umbrella term used to describe, in contrast with malaria, TB, and HIV, a group of over 20 communicable diseases, conditions, and toxins that affect over 1.7 billion people globally and which perpetuate a cycle of poverty. They are grouped together as a result of similarities in the marginalized populations they affect, the methods of diagnosis and treatment, their disease and economic burdens, and lower levels of investment in diagnostic and therapeutic tools that contribute to their neglect

outcome
Any or all possible results that can stem from exposure to a causal factor or from preventive or therapeutic interventions; all identified changes in health status that result from the handling of a health problem

passive case detection (PCT)
A type of surveillance system in which disease cases and data are generated and reported from a health facility where a symptomatic patient is diagnosed. This is the most common type of surveillance and is typically coordinated through hospitals and clinics governed by one organization or entity

post-kala-azar dermal leishmaniasis (PKDL)
A complication of visceral leishmaniasis characterised by a macular, maculopapular, and nodular rash in a patient who has recovered from VL and is otherwise well. It occurs in 5-15% of successfully treated VL cases, and has been shown to contribute to transmission of VL through the bite of a sandfly vector

prevalence
The proportion of a defined population found to be affected by a disease or medical condition at a specific point in time

preventive chemotherapy/preventive chemotherapy and transmission control (PCT)
A category of disease intervention that focuses on the availability of safe and effective drugs, which make it feasible to implement large-scale preventive chemotherapy (such as mass drug administration). In NTDs it is also referred to as preventive chemotherapy and transmission control (PCT), whereby the term ‘preventive’ refers not only to the prevention of infection but to the prevention of morbidity by tackling the load of infection stages that lead to disease sequelae and transmission. It is typically preceded by rapid epidemiological assessment methods that help determine the endemicity of the infection/disease in a particular area such that individual diagnosis (screening) is not necessary before deploying PCD strategies

resurgence
Disease resurgence is defined as the reappearance of new infections in significant numbers after a disease has subsided, owing to the measures applied to reduce or interrupt its transmission. Resurgence may be a result of societal factors, political dynamics, programmatic factors such as premature cessation of intervention efforts, and/or biological factors such as drug and vector resistance

static model
A model that does not account for changes in given quantities over time, and which does not explicitly describe contact (and therefore disease transmission) between individuals. The force of infection is a fixed value; therefore, a static model may not adequately assess the impact of interventions that reduce incidence or the prevalence of infection

stochastic model
A model that incorporates the effects of chance and randomness, and/or the effects of population size and structure (demographic stochasticity) when determining the number of individuals that become infected, infectious, and recover per unit time. Ranges of (rather than fixed) parameter values can also be considered such that the model runs produce different

outputs when sampling from parameter space. Individual-based models are typically stochastic models

structured model
A model that includes compartmentalisation, usually reflecting various health and disease states. Other characteristics can also be structured, such as age, sex, and other relevant variables

transmission (of infection)
Any mode or mechanism by which an infectious agent is spread to a susceptible host

CHAPTER 1. INTRODUCTION

1.1 Overview and scope of thesis

This DrPH thesis aims to inform visceral leishmaniasis (VL), or kala-azar, elimination strategies in India by contributing to and evaluating the use of policy-relevant research. VL is targeted for elimination as a public health problem (EPHP) in India, which will require long-term surveillance and response. In an effort to inform and support EPHP strategies, this work focuses on case detection activities coordinated by the national Kala-Azar Elimination Programme (KEP). Aligning with the DrPH aim to engage both in research and its use to achieve public health gains, the scope of this thesis is interdisciplinary and includes both quantitative and qualitative methods.

First, this thesis explores research disciplines that are compelling and influential to the design of surveillance programmes around the point of elimination. For VL in India, the science behind resource allocation and the cost of surveillance activities lacks political support and is therefore underdeveloped. This thesis directly addresses a gap in actionable research by presenting a cost analysis and comparison of several active- and passive- case detection (ACD and PCD) activities across varying degrees of VL incidence in India's most endemic state, Bihar. The results of this study inform how and why each case detection method could be more strategically implemented across space and time.

Second, this thesis explores how and whether policy-relevant research is used to inform VL surveillance strategies in India's KEP. Timely and actionable evidence is increasingly generated in the field of mathematical modelling for VL in India, but the extent to which it is valued and applied to elimination activities is unknown. The second research component

investigates the perceived value and use of VL mathematical modelling to decision makers in India involved in programme design and implementation. Opportunities to integrate economics and modelling to generate more robust and comprehensive evidence for policy are also explored.

Presented in a paper-style format, this thesis includes seven chapters that revolve around two central research components: a cost analysis of VL case detection strategies in India, and a qualitative study examining the value and use of VL transmission modelling in India's KEP. The chapters preceding each research component support and substantiate the outlined objectives by presenting theories, literature, gaps in knowledge, and justification of the methodology used for investigation.

1.2 Thesis aim and objectives

Aim: This DrPH thesis aims to inform VL surveillance strategies in India by evaluating the cost of current case detection activities and examining the value and use of mathematical modelling in policy. Three thesis objectives are identified and outlined below, including specific study questions, with two central research components presented as papers R1 and R2:

Objective 1—Literature Reviews

Purpose: To identify policy-relevant research disciplines for informing VL surveillance strategies in India

1. What are examples of timely and policy-relevant research used to inform surveillance and elimination programmes?
2. For VL in India, what is the availability of economic and modelling research to inform surveillance and elimination programmes?

a. What gaps exist in the presence and production of actionable research for VL elimination in India?
b. Where actionable research exists, is there evidence of how it is used and applied in the KEP?

Objective 2—Paper R1

Purpose: To evaluate the costs and outcomes of VL active- and passive case detection activities in India

1. What are the current surveillance activities that support early VL case detection in India?
2. What are the programme and unit costs for detecting additional VL cases in India?
3. Do the costs and outcomes of case detection vary across low, medium, and high VL incidence in India?
4. What are the costs of scaling up current VL case detection strategies in India?

Objective 3—Paper R2

Purpose: To examine how mathematical modelling is valued and used to inform surveillance in India's Kala-Azar Elimination Programme

1. Has mathematical modelling research contributed to informing transmission dynamics and case detection strategies for VL in India?
2. How do decision makers and programme managers in the KEP understand, value, and use VL mathematical modelling research?
3. What are the barriers to translating knowledge produced by VL modelling research into policy in the KEP?

1.3 Outline of chapters

Chapter 1 introduces the scope, objectives, and structure of the work presented in this thesis, detailing specific research questions and a brief synopsis of neglected tropical disease (NTD) control and elimination. Chapter 2, the background, provides a broad overview of VL in India, including disease characteristics, epidemiology, the history of regional elimination

programmes in the Indian Subcontinent (ISC), and current pillars and partners of India's KEP. A review of policy-relevant research disciplines is then presented as they relate more broadly to NTDs around the point of elimination. Several disciplines are identified for their ability to inform elimination programmes: economic evaluations to substantiate resource allocation, and mathematical modelling to project and strategise the feasibility of achieving elimination benchmarks across space and time.

The literature review in Chapter 3 explores the value of economic evaluations for informing the design, implementation, and longevity of surveillance activities during elimination. This chapter details economic analyses conducted for VL in India throughout the past decade and identifies gaps in knowledge addressed in paper R1. Chapter 4 is the first research paper (R1), which presents programme and unit costs of two VL active case detection strategies (index case-based and house-to-house) alongside passive case detection, and compares the outcomes of each programme across low, medium, and high incidence areas.

Where compelling evidence for informing VL case detection strategies already exists, in the case of mathematical modelling, the final aim of this thesis is to identify how actionable research is valued and used in KEP policy. Chapter 5 presents an overview of mathematical models, their actionability within other NTD elimination programmes, and a review of modelling literature specific to VL in India produced over the past decade. The second part of Chapter 5 then reviews literature surrounding theories of Knowledge Translation (KT) and Knowledge to Action (KTA) to substantiate a framework for investigating how knowledge generated from VL modelling is, or could be, applied to surveillance and elimination policies in India. Chapter 6 presents a second research paper (R2) that uses qualitative interviewing to

examine the value and actionability of VL modelling in the KEP from the perspective of decision makers, programme managers, and researchers in India.

The outcomes and implications of the literature reviews and research papers are synthesised in Chapter 7, the discussion, with a focus on contributions and implications of papers R1 and R2 to surveillance and elimination in the KEP. The potential to integrate economic analyses into mathematical models for VL, and its relevance to policy and decision making, is also examined. Lastly, a reflection on the advantages and disadvantages of examining case detection strategies from an interdisciplinary perspective is considered.

Figure 1-1 displays the thematic organisation of the two central research themes and their corresponding literature reviews.

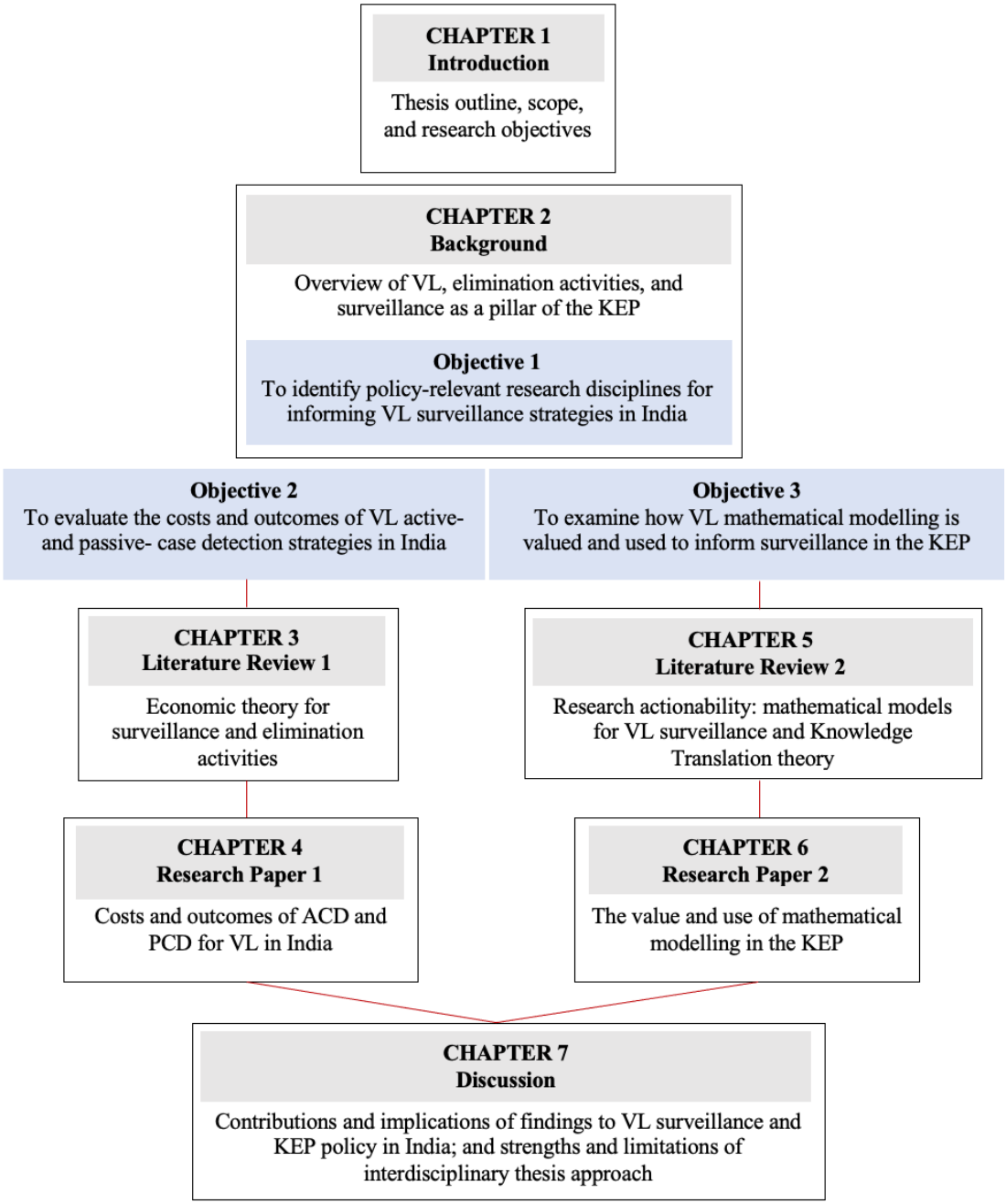


Figure 1-1. Flow-diagram of thesis chapters and objectives

1.4 Neglected Tropical Disease control and elimination

Global NTD burden

Nearly one third of the global population is either living with or at risk of acquiring a neglected tropical disease (NTD) [1]. A collective of over 20 conditions, the vast majority of NTDs are chronic bacterial, parasitic, and viral infections that often cause life-long disfigurement and disability [2]. The joint classification of NTDs was created shortly after the Millennium Development Goals (MDGs) were adopted in 2000 because of stark similarities in their geographical overlap, co-infections, risk factors, and potential synergistic strategies for diagnosis, treatment, and prevention [3]. The World Health Organization (WHO) currently prioritises 22 NTDs for eradication, elimination, or control, recognising that their combined disease burden is comparable to that of malaria, TB, and HIV [4]. Eradication signifies a global and permanent reduction of incidence to zero for a specific pathogen, without risk of reintroduction [5]. Elimination either refers to interruption *of transmission* (elimination of transmission—EOT—defined as a reduction to zero of the incidence of infection in a defined geographical area), or *as a public health problem* (elimination of a public health problem—EPHP—defined by achievement of measurable targets set by the WHO, where continued control actions are required to maintain targets) [5]. Lastly, control is the mean reduction of disease incidence, prevalence, morbidity, or mortality to a locally acceptable level as a result of deliberate and continued intervention measures [5].

As their name suggests, NTDs have been historically overlooked relative to the political voice, research, and funding of higher profile diseases [6]. Their relatively low mortality (measured in years of life lost—YLL) but high morbidity (measured in years lived with disability—YLD) generates substantial economic and societal burdens that are heightened by associations with HIV/AIDS, malaria, tuberculosis, non-communicable diseases, and a

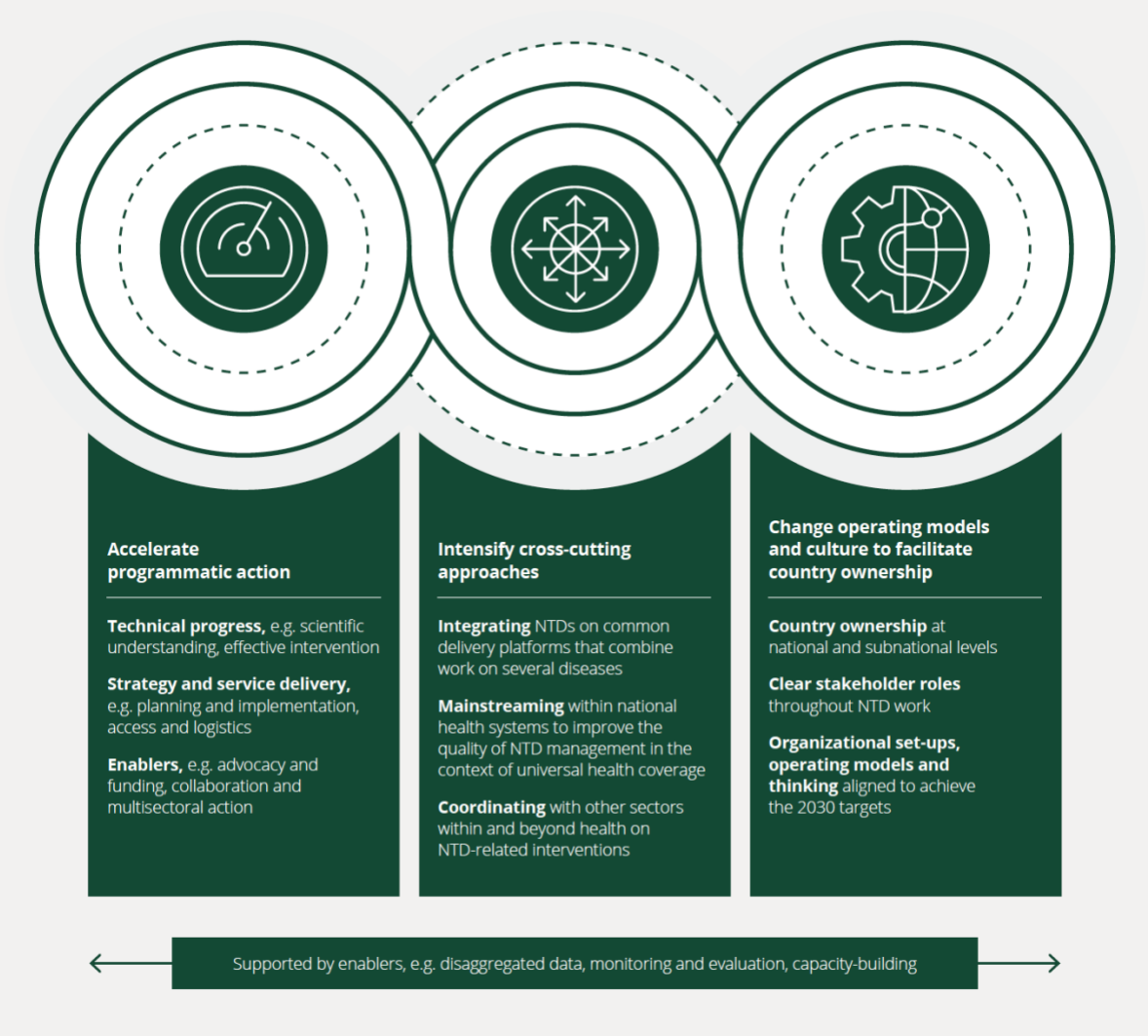
disproportionate impact on women and girls [7]. NTDs consistently afflict rural and impoverished communities through detrimental cycles of malnutrition, lower economic productivity, and physical disability; and although the predisposition of vulnerable populations is not well understood, persistent poverty is shown to be associated with NTD transmission and re-emergence [8–11].

NTD Roadmaps: Historical and current

Over the past two decades, significant political and financial support has developed around international and national agendas to control, eliminate, and eradicate NTDs [12]. WHO, Drugs for Neglected Diseases Initiative (DNDi), and the Foundation for Innovative Diagnostics (FIND) set the stage for elevating NTDs to an international platform in which consolidated targets, guidelines, and partnerships could be acted upon [2]. In 2012, WHO published a *Roadmap for NTD Implementation* to accelerate international efforts by setting seemingly achievable, disease-specific targets [13]. Simultaneously, the London Declaration on NTDs (LDNTDs) was written and endorsed by pharmaceutical companies, research institutions, and several public and private partnerships to eventually form the Uniting to Combat NTDs (UCNTDs) coalition [14]. Five progress reports have since been published by UCNTDs on achievements towards NTD control and elimination, the most recent of which details over one billion people were treated for at least one NTD in 2018, 1.7 billion treatments were donated by the pharmaceutical industry in 2018, and 33 countries have eliminated at least one NTD since 2012 [15–19].

Despite enormous progress and commitment, the goal to control, eliminate, and eradicate NTDs has been retargeted for 2030 [20]. WHO published a new NTD roadmap for 2021-2030 informed by disease experts, modellers, donors, partners, and Member States, which

revolves around three pillars to: 1) accelerate programmatic action, 2) intensify cross-cutting approaches, and 3) change operating models and culture to facilitate country ownership (Figure 1-2) [4]. The three pillars are organised into criterion that require concerted action through research, monitoring and evaluation, and capacity-building, under which each NTD is assessed in terms of requirements to meet the 2030 targets (Figure 1-2).



Source: WHO. Ending the neglect to attain the Sustainable Development Goals: A roadmap for neglected tropical diseases 2021-2030. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

Figure 1-2. Three pillars of the WHO NTD roadmap for 2021-2030, and subcategories that require concerted action through research, monitoring and evaluation, and capacity-building.

These pillars are referenced and adapted throughout this thesis to examine ways in which science can inform surveillance activities in alignment with an internationally endorsed framework for elimination. The WHO NTD roadmap for 2021-2030 also designates updated disease-specific targets for the control, elimination, and eradication of NTDs, which are outlined in Appendix 1.

Tool-readiness for NTD control and elimination

Interventions for NTDs are often categorised according to the availability of instruments for control, in that they are either 'tool-ready' or 'tool-deficient' [21]. Tool-ready diseases are those with inexpensive and scalable strategies such as preventive chemotherapy and transmission control (PCT, or PC-NTDs), in which mass drug administration (MDA) is a commonly employed approach [22]. These diseases include dracunculiasis, leprosy, lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis, and trachoma. Where effective control tools exist for PC-NTDs, emphasis is on capacity strengthening, advocating coordinated approaches, and scaling-up existing programmes to support national preventive chemotherapy programmes [23].

Tool-deficient NTDs are those with comparatively costly strategies for control that require innovative and intensified disease management (IDM, or IDM-NTDs), where early case detection and treatment are usually prioritised [24]. IDM-NTDs include Buruli ulcer, Chagas disease, human African trypanosomiasis, leishmaniases, and yaws. Many IDM-NTD-endemic populations live in remote rural areas with limited access to diagnosis and treatment. There is relatively lower investment in research and development for IDM-NTDs, therefore rapid development and implementation of improved control tools is prioritised alongside health service expansion in affected areas [25]. The remainder of the NTD control strategies

are addressed through vector ecology and management (VEM) or water, sanitation, and hygiene (WASH) practices [26, 27].

Elimination as a public health problem (EPHP)

Tool-readiness is only one facet that informs targets for NTD control, elimination, and eradication. Although many diseases were initially targeted for elimination through interrupted transmission to reach and sustain less than one case per 10,000 population per year, the presence of asymptomatic infections and other elusive drivers of transmission rendered this goal unachievable and counterproductive for some (Appendix 1) [28, 29]. In this, elimination as a public health problem (EPHP) was coined to define measurable targets specific to infection, disease, demographics, or geography that require long-lasting control measures [29]. EPHP has improved the feasibility of targets for Chagas disease, lymphatic filariasis, schistosomiasis, soil-transmitted helminthiases, trachoma, and visceral leishmaniasis, but tools and definitions used for this 'attack' phase may differ from those requisite for long-term control and surveillance [30, 31]. For EPHP diseases, it is essential that financial, political, and research momentum be continuously reinforced to strategise long-term control activities that prevent resurgence [32].

Political and financial support for NTDs

Progress towards NTD benchmarks over the past two decades has been largely dependent on international donors, public-private partnerships, and technical advisory that are projected to continue in support of the WHO 2030 targets [33]. To date, the Bill and Melinda Gates Foundation (BMGF) has donated over $1 billion USD to support organisations working in NTD MDA, surveillance, and vector control, much of which has been earmarked towards research [34, 35]. Twelve pharmaceutical companies have pledged to donate treatment

through 2025 for 14 NTDs, where distribution, monitoring, and evaluation are intended to be coordinated at the national level [4]. Vertical NTD programmes are also being targeted for horizontal integration through joint interventions based on similarities in disease treatment or diagnosis [4, 36–39]. Lastly, cross-coordination within national health systems is currently prioritised to leverage resources and capacity across sectors of vector control, mental health, disability and inclusion, women's and child health, eye health, and nutrition [4, 40–43].

National ownership of NTD programming is increasingly encouraged, especially as evidence suggests its horizontal integration strengthens health systems and increases the stability of finances and resource allocation in the long-term [44–48]. Reliance on international donors and partners complicates the path of transitioning responsibility and accountability to the national level, where roles of international advisory versus national implementation must be critically defined [49–52]. International partners often assume roles to streamline supply chains, develop control tools, and incentivise political mobilisation, whereas surveillance systems to monitor NTD burden, geographical distribution, and populations at risk naturally rely on national ministries of health [53].

Science and surveillance for NTD elimination

As NTD incidence declines, resources to identify and report cases become difficult to sustain [40, 54, 55]. WHO emphasises that evaluation and monitoring of surveillance systems will become increasingly critical and costly for all NTDs, which most national NTD programmes have yet to mobilise at adequate and sustainable levels [45]. Much of the official NTD data reported by health ministries is fragmented and incomplete, where national surveillance systems must be strengthened to not only monitor incidence but also create evidence-based and context-specific decisions for future activities [56, 57].

In a capacity-building study to sustain NTD programmes and progress, 34 country participants identified a need for improved surveillance to monitor disease burden, distribution, morbidity, and programme costs [51]. Support for surveillance is also necessary to evaluate control and elimination indicators outlined in Appendix 1, most of which revolve around transmission levels. Six research priorities have been identified to strengthen national-level surveillance for NTD elimination programmes: 1) dynamic mapping of transmission, 2) near real-time capture of population dynamics, 3) modelling based on a minimum essential database, 4) implementation of mobile health and sensitive diagnostics, 5) design of effective response packages tailored to different transmission settings and levels, and 6) validation of approaches and response packages [58]. A more critical and constructive evaluation of surveillance systems could be achieved through supportive research that focuses on case identification and management, programme evaluation, and transmission dynamics over space and time [59].

Interdisciplinary research for NTD surveillance

To promote comprehensive evidence for NTD elimination strategies, national programme integration, and context-specific programming, surveillance research could be enhanced through cross-collaboration between research disciplines. There has been an over-reliance on unidimensional solutions that often lacks insight into political and environmental contexts, financial feasibility over time, and social compliance and adherence in endemic populations [60]. Interdisciplinary NTD elimination research is key to transition from evaluating solely the effectiveness of an intervention towards its effectiveness in a specific landscape, population, and political context [61]. Addressing this gap requires implementation sciences

that incorporate researchers, policy makers, programme managers, and endemic communities themselves, which many NTD programmes have reported a lack of synergy across [62, 63].

For NTD interventions that involve researchers and implementers interfacing directly with endemic communities, social sciences are key to engendering trust, tailoring programmes to local conditions, promoting broader effects of vertical programmes, and addressing issues of misinformation and non-compliance [64]. The practicality of long-term surveillance also relies on policy makers collaborating with health economists to understand disease burden from the societal perspective, financial planning from the provider perspective, and projected savings of investing in elimination [65]. Health systems research is required for both vertical surveillance and the prospect of integrating NTD surveillance horizontally to assess cost-effectiveness of programmes, multi-sectoral financial coordination, and resource distribution [66]. Environmental sciences show climate change poses challenges to NTD surveillance through increased migration, altered patterns of geographic transmission, and the population biology of parasites, vectors, and hosts [67–69]. COVID-19 research might also provide a platform to improve surveillance through lessons learned on mathematical modelling, contact tracing, smartphone case-identification, and the effects of interrupted NTD programmes [59].

Surveillance-response research is a fundamental pillar to monitoring and achieving NTD elimination targets, especially for diseases targeted for EPHP that require long-term control measures [56]. It can, and should, be used to strengthen national health programme data collection, empower country-level ownership, and facilitate ingenuity and resourcefulness for targeted interventions [4]. Comprehensive surveillance research necessitates interdisciplinary and context-specific assessments that bring a diversity of perspectives to the table, including NTD-endemic populations themselves [63].

1.5 Roles and responsibilities

Table 1-1 outlines the roles and responsibilities of design, data collection, analysis, and presentation of this thesis, and Table 1-2 categorises the intention of each chapter for either publication or thesis only.

Table 1-1. Roles, responsibilities, and additional input of thesis activities.

COMPONENT	ACTIVITY	RESPONSIBILITY	ADDITIONAL INPUT
PREPARATORY WORK	Development of project objectives and work plan	ND, GM	FTP, SC
	Site selection	ND, GM	FTP, SC
	Ethics submission	ND	GM, FTP
	Local authority permissions	ND	GM, SC
DEVELOPMENT OF DATA COLLECTION TOOLS	Costing frameworks and spreadsheets	ND, FTP	GHCC
	Knowledge utilisation interview guide	ND	GM, SC, AF
DATA COLLECTION AND ANALYSIS	R1:		
	Field work with CARE	ND	FTP, GM, SC
	Field work with KalaCORE	ND	FTP, GM, SC
	Site visits to PHC	ND	FTP, GM, SC
	Cost analysis	ND, FTP	GM, SC
	R2:		
	Key informant identification	ND	SC, LC, GM
	Interviews	ND	
	Transcription	ND	
	Coding and analysis	ND	
RESEARCH PAPERS	Paper R1: Costs and outcomes of active and passive case detection for visceral leishmaniasis (kala-azar) to inform elimination strategies in Bihar, India	ND	FTP, GM, SC, TM, SS, BS, KP, LP
	Paper R2: The value and actionability of mathematical modelling in India's Kala-Azar (visceral leishmaniasis) Elimination Programme	ND	GM, FTP, SC, AF, LC
SUPERVISION	Overall DrPH and thesis	GM, FTP, SC	AF

ND: Natalie Dial; GM: Graham Medley (Primary Supervisor); FTP: Fern Terris-Prestholt (Secondary Supervisor); SC: Simon Croft (Tertiary Supervisor); AF: Alec Fraser (External Advisory Member); GHCC: Global Health Cost Consortium; LC: Lloyd Chapman; TM: Tanmay Mahapatra; SS: Sridhar Srikantiah; BS: Bikas Sinha; KP: Khushbu Priyamvada; LP: Lucy Palmer.

Table 1-2. Intention of chapters for publication or thesis only.

Chapter	Title	Submission status
1	Introduction	Unpublished, for thesis only
2	Background	Unpublished, for thesis only
3	Literature review 1: Economic evaluations for surveillance during elimination	Unpublished, for thesis only
4	Paper R1: Costs and outcomes of active and passive case detection for visceral leishmaniasis (Kala-Azar) to inform elimination strategies in Bihar, India	Published in PLOS Neglected Tropical Diseases 03 February 2021
5	Literature review 2: Surveillance, mathematical modelling, and knowledge translation theory	Unpublished, for thesis only
6	Paper R2: The value and actionability of mathematical modelling in India's Kala-Azar (visceral leishmaniasis) Elimination Programme	Prepared for submission to Health Policy and Planning
7	Discussion	Unpublished, for thesis only

References

1. World Health Organization. Control of Neglected Tropical Diseases [Internet]. Geneva 2021. Available from: https://www.who.int/teams/control-of-neglected-tropical-diseases.
2. Fürst T, Salari P, Llamas LM, Steinmann P, Fitzpatrick C, Tediosi F. Global health policy and neglected tropical diseases: Then, now, and in the years to come. PLoS Negl Trop Dis. 2017 11(9): e0005759.
3. Molyneux DH, Malecela MN. Neglected tropical diseases and the Millenium Development Goals--why the "other diseases" matter: reality versus rhetoric. Parasit Vectors. 2011 4: 234.
4. World Health Organization. Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021-2030 [Internet]. Geneva. 2020. Available from: https://www.who.int/publications/i/item/9789240010352.
5. World Health Organization. Generic framework for control, elimination and eradication of Neglected Tropical Diseases [Internet]. Geneva 2015. Available from: https://www.who.int/neglected_diseases/resources/NTD_Generic_Framework_2015.pdf.
6. Hotez PJ. The neglected tropical diseases and the neglected infections of poverty: Overview of their common features, global disease burden and distribution, new control tools, and prospects for disease elimination. In: The Causes and Impacts of Neglected Tropical and Zoonotic Diseases: Opportunities for Integrated Intervention Strategies. Washington DC: National Acadamies Press (USA) 2011.
7. Hotez PJ. V.2.0: 'Blue Marble Health'--Neglected tropical disease control and elimination in a shifting health policy landscape. PLoS Negl Trop Dis. 2013 7(11): e2570.
8. Hotez PJ. The global fight to develop antipoverty vaccines in the anti-vaccine era. Hum Vaccines Immunother. 2018 14(9): 2128-2131.
9. Samuels F, Pose RR. Why neglected tropical diseases matter in reducing poverty [Internet]. Development Progress Working Paper. 2013. Available from: https://unitingtocombatntds.org/wp-content/uploads/2017/11/why_ntds_matter_in_reducing_poverty.pdf.
10. Manderson L, Aagaard-Hansen J, Allotey P, Gyapong M, Sommerfeld J. Social research on neglected diseases of poverty: Continuing and emerging themes. PLoS Negl Trop Dis. 2009; 3(2): e332.
11. Alvarez-Hernandez DA, Rivero-Zambrano L, Martinez-Juarez LA, Garcia-Rodriguez-Arana R. Overcoming the global burden of neglected tropical diseases. Ther Adv Infect Dis. 2020; 7(1): 2049936120966449.
12. Berkley S, Bobadilla J, Hecht R, Hill K, Jamison D, Murray C, et al. World Development Report 1993: Investing in Health [Internet]. World Development Indicators. Washington DC; 1993. Available from: https://openknowledge.worldbank.org/handle/10986/5976. License: CC BY 3.0 IGO.
13. World Health Organization. Accelerating work to overcome the global impact of neglected tropical diseases: A roadmap for implementation [Internet]. Geneva; 2012. Available from: https://www.who.int/neglected_diseases/NTD_RoadMap_2012_Fullversion.pdf.
14. UCNTD. London Declaration on Neglected Tropical Diseases [Internet]. London, UK; 2012. Available from: https://www.who.int/neglected_diseases/London_Declaration_NTDs.pdf?ua=1.
15. Uniting to Combat NTDs. From promises to progress: The first annual report on the

London Declaration on NTDs [Internet]. London, UK; 2013. Available from: https://unitingtocombatntds.org/wp-content/uploads/2017/11/1st_progress_report.pdf.
16. Uniting to Combat NTDs. Delivering on promises and driving progress: The second progress report of the London Declaration on NTDs [Internet]. London, UK; 2014. Available from: https://unitingtocombatntds.org/wp-content/uploads/2017/11/2nd_progress_report_english.pdf.
17. Uniting to Combat NTDs. Reaching the unreached: The fourth progress report of the London Declaration on NTDs. London, UK; 2015.
18. Uniting to Combat NTDs. Reaching a billion. Ending neglected tropical diseases-- A gateway to Universal Health Coverage: The fifth progress report of the London Declaration on NTDs [Internet]. London, UK; 2016. Available from: https://unitingtocombatntds.org/wp-content/themes/tetloose/app/staticPages/fifthReport/files/fifth_progress_report_english.pdf.
19. Uniting to Combat NTDs. Country leadership and collaboration on neglected tropical diseases: The third progress report of the London Declaration on NTDs [Internet]. London, UK; 2014. Available from: https://unitingtocombatntds.org/wp-content/uploads/2017/11/3rd_progress_report_english.pdf.
20. World Health Organization. Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021-2030 [Internet]. Geneva; 2020. Available from: https://www.who.int/publications/i/item/9789240010352.
21. Rosenberg M, Utzinger J, Addiss DG. Preventive Chemotherapy Versus Innovative and Intensified Disease Management in Neglected Tropical Diseases: A Distinction Whose Shelf Life Has Expired. PLoS Negl Trop Dis. 2016; 10(4): e0004521.
22. World Health Organization. Neglected tropical diseases: Preventive chemotherapy and transmission control (PCT) [Internet]. Geneva; 2021. Available from: https://www.who.int/teams/control-of-neglected-tropical-diseases/preventive-chemotherapy.
23. Mitra AK, Mawson AR. Neglected tropical diseases: Epidemiology and global burden. Trop Med Infect Dis. 2017; 2(3): 36.
24. World Health Organization. Neglected tropical diseases: Innovative and intensified disease management (IDM) [Internet]. Geneva; 2021. Available from: https://www.who.int/teams/control-of-neglected-tropical-diseases/intensified-disease-management.
25. Reimer LJ, Adams ER, Paine MJ, Ranson H, Coleman M, Thomsen EK, et al. Fit for purpose: do we have the right tools to sustain NTD elimination? BMC Proc. 2015; 9(10): S5.
26. World Health Organization. Neglected tropical diseases: Vector ecology and management (VEM) [Internet]. Geneva; 2021. Available from: https://www.who.int/teams/control-of-neglected-tropical-diseases/vector-ecology-and-management.
27. World Health Organization. Neglected tropical diseases: Water, sanitation, and hygiene [Internet]. Geneva; 2021. Available from: https://www.who.int/teams/environment-climate-change-and-health/water-sanitation-and-health/burden-of-disease/wash-and-neglected-tropical-diseases
28. Bodimeade C, Marks M, Mabey D. Neglected tropical diseases: elimination and eradication. Clin Med. 2019; 19(2): 157-160.
29. World Health Organization. Generic framework for control, elimination, and eradication of neglected tropical diseases [Internet]. Geneva; 2015. Available from: https://www.who.int/neglected_diseases/resources/NTD_Generic_Framework_2015.p

df.
30. Dowdle WR. The principles of disease elimination and eradication. Bull World Health Organ. 1998; 76(2): 22-25.
31. Heymann DL. Control, elimination, eradication and re-emergence of infectious diseases: Getting the message right. Bull World Health Organ. 2006; 84(2): 82.
32. Engels D, Zhou X. Neglected tropical diseases: an effective global response to local poverty-related disease priorities. Infect Dis Poverty. 2020; 9(1): 10.
33. Fitzpatrick C, Nwankwo U, Lenk E, de Vlas S, Bundy D. An investment case for ending neglected tropical diseases. In: Holmes K, Bertozzi S, Bloom B, editors. Major Infectious Diseases. Third Edit. Washington DC; 2017.
34. Bill and Melinda Gates Foundation. Private and Public Partners Unite to Combat 10 Neglected Tropical Diseases by 2020 [Internet]. Uniting to Combat NTDs. 2014. Available from: https://www.gatesfoundation.org/ideas/media-center/press-releases/2012/01/private-and-public-partners-unite-to-combat-10-neglected-tropical-diseases-by-2020.
35. Bill and Melinda Gates Foundation. Neglected tropical diseases: Strategy overview [Internet]. Seattle, USA; 2021. Available from: https://www.gatesfoundation.org/our-work/programs/global-health/neglected-tropical-diseases.
36. Kabatereine NB, Malecela M, Lado M, Zaramba S, Amiel O, Kolaczinski JH. How to (or not to) integrate vertical programmes for the control of major neglected tropical diseases in Sub-Saharan Africa. PLoS Negl Trop Dis. 2010; 4(6): e755.
37. Linehan M, Hanson C, Weaver A, Baker M, Kabore A, Zoerhoff KL, et al. Integrated implementation of programs targeting neglected tropical diseases through preventive chemotherapy proving the feasibility at national-scale. In: The Causes and Impacts of Neglected Tropical and Zoonotic Diseases: Opportunities for Integrated Intervention Strategies. Washington DC: National Acadamies Press (US); 2011.
38. Tristao I, Cali J. It can be done: An integrated approach for controlling and eliminating neglected tropical diseases [Internet]. 2014. Available from: https://publications.iadb.org/publications/english/document/It-Can-Be-Done-An-Integrated-Approach-for-Controlling-and-Eliminating-Neglected-Tropical-Diseases.pdf.
39. Means AR, Jacobson J, Mosher AW, Walson JL. Integrated healthcare delivery: A qualitative research approach to identifying and harmonizing perspectives of integrated neglected tropical disease programs. PLoS Negl Trop Dis. 2016; 10(10): e0005085.
40. Ortu G, Williams O. Neglected tropical diseases: exploring long term practical approaches to achieve sustainable disease elimination and beyond. Infect Dis Poverty. 2017; 6(1): 147.
41. Golding N, Wilson AL, Moyes CL, Cano J, Pigott DM, Velayudhan R, et al. Integrating vector control across diseases. BMC Med. 2015; 13(249): https://doi.org/10.1186/s12916-015-0491-4.
42. Chanda E, Govere JM, Macdonald MB, Lako RL, Haque U, Baba SP, et al. Integrated vector management: A critical strategy for combating vector-borne diseases in South Sudan. Malar J. 2013; 12(369): DOI: 10.1186/1475-2875-12-369.
43. Bailey F, Eaton J, Jidda M, van Brakel WH, Addiss DG, Molyneux DH. Neglected tropical diseases and mental health: Progress, partnerships, and integration. Trends Parasitol. 2018; 35(1): 23-31.
44. Marchal B, Van Dormael M, Pirard M, Cavalli A, Kegels G, Polman K. Neglected tropical disease (NTD) control in health systems: The interface between programmes and general health services. Acta Trop. 2011; 120(1): 177–185.
45. World Health Organization. Integrating neglected tropical diseases into global health

and development: Fourth report on neglected tropical diseases [Internet]. Geneva; 2017. Available from: https://apps.who.int/iris/handle/10665/255011.
46. Mensah EO, Aikins MK, Gyapong M, Anto F, Bockarie MJ, Gyapong JO. Extent of integration of priority interventions into general health systems: A case study of neglected tropical diseases programme in the western region of Ghana. PLoS Negl Trop Dis. 2016; 10(5): DOI: 10.1371/journal.pntd.0004725..
47. Standley C, Boyce MR, Klineberg A, Essix G, Katz R. Organization of oversight for integrated control of neglected tropical diseases within Ministries of Health. PLoS Negl Trop Dis. 2018; 12(11): e0006929.
48. Dyke E, McKay B, Ly M, Peeling R. Evaluation of the WHO Neglected Tropical Disease Programme: Volume 1 Report [Internet]. Ottawa, Ontario; 2019. Available from: https://www.who.int/docs/default-source/documents/evaluation/evaluation-ntd-report.pdf?sfvrsn=351a363f_2.
49. Lammie P, Solomon A, Secor E, Peeling R. Diagnostic needs for NTD programs. In: The Causes and Impacts of Neglected Tropical and Zoonotic Diseases: Opportunities for Integrated Intervention Strategies. Washington DC: National Acadamies Press (US); 2011.
50. Kollie K, Siakeh A, Zawolo G, Wickenden A, Theobald S, Rogers E, et al. Donor reliance and the impact on neglected tropical disease programme delivery: reflections and solutions for change from programme management perspectives. Int Health. 2021; 13(4): 376–8.
51. Sodahlon Y, Ross DA, McPhillips-Tangum C, Lawrence J, Taylor R, McFarland DA, et al. Building country capacity to sustain NTD programs and progress: A call to action. PLoS Negl Trop Dis. 2020; 14(10): e0008565.
52. Jesudason T. New WHO road map for NTD recovery post COVID-19. Lancet Infect Dis. 2020; 20(8): DOI: https://doi.org/10.1016/S1473-3099(20)30566-1.
53. World Health Organization. WHO Information System to Control/Eliminate Neglected Tropical Diseases [Internet]. Geneva; 2020. Available from: https://www.who.int/neglected_diseases/disease_management/wiscentds/en/.
54. Manyeh AK, Chirwa T, Ramaswamy R, Baiden F, Ibisomi L. Evaluating context-specific evidence-based quality improvement intervention on lymphatic filariasis mass drug administration in Northern Ghana using the RE-AIM framework. Trop Med Health. 2021; 49(16): DOI: https://doi.org/10.1186/s41182-021-00305-3.
55. Bardosh KL. Towards a science of global health delivery: A socio-anthropological framework to improve the effectiveness of neglected tropical disease interventions. PLoS Negl Trop Dis. 2018; 12(7): e0006537.
56. Tambo E, Ai L, Zhou X, Chen J, Hu W, Bergquist R, et al. Surveillance-response systems: the key to elimination of tropical diseases. Infect Dis Poverty. 2014; 3(17): DOI: https://doi.org/10.1186/2049-9957-3-17.
57. Ng'etich AKS, Voyi K, Mutero CM. Assessment of surveillance core and support functions regarding neglected tropical diseases in Kenya. BMC Public Health. 2021; 21(142): DOI: https://doi.org/10.1186/s12889-021-10185-1.
58. Zhou XN, Bergquist R, Tanner M. Elimination of tropical diseases through surveillance and response. Infect Dis Poverty. 2013; 2(1): DOI: https://doi.org/10.1186/2049-9957-2-1.
59. de Souza DK, Picado A, Bieler S, Nogaro S, Ndung'u JM. Diagnosis of neglected tropical diseases during and after the COVID-19 pandemic. PLoS Negl Trop Dis. 2020; 14(8): e0008587.
60. Spiegel JM, Dharamsi S, Wasan KM, Yassi A, Singer B, Hotez PJ, et al. Which new approaches to tackling neglected tropical diseases show promise? PLoS Med. 2010;

7(5): e100025.
61. Hotez PJ, Pecoul B, Rijal S, Boehme C, Aksoy S, Malecela M, et al. Eliminating the neglected tropical diseases: Translational science and new technologies. PLoS Negl Trop Dis. 2016; 10(3): e0003895.
62. Allotey P, Reidpath DD, Pokhrel S. Social sciences research in neglected tropical diseases 1: The ongoing neglect in the neglected tropical diseases. Heal Res Policy Syst. 2010; 8(32): DOI: https://doi.org/10.1186/1478-4505-8-32.
63. Krentel A, Gyapong M, Ogundahunsi O, Amuyunzu-Nyamongo M, McFarland DA. Ensuring no one is left behind: Urgent action required to address implementation challenges for NTD control and elimination. PLoS Negl Trop Dis. 2018; 12(6): e0006426.
64. Krentel A, Fischer PU, Weil GJ. A review of factors that influence individual compliance with mass drug administration for elimination of lymphatic filariasis. PLoS Negl Trop Dis. 2013; 7(11): e2447.
65. World Health Organization. Investing to overcome the global impact of neglected tropical diseases: Third WHO report on neglected diseases 2015 [Internet]. Geneva; 2015. Available from: https://www.who.int/neglected_diseases/9789241564861/en/.
66. Harding-Esch EM, Brady MA, Angeles CAC, Fleming FM, Martin DL, McPherson S, et al. Lessons from the field: Integrated survey methodologies for neglected tropical diseases. Trans R Soc Trop Med Hyg. 2020; 115(2): 124-126.
67. Gazzinelli A, Correa-Oliveira R, Yang GJ, Boatin BA, Kloos H. A research agenda for helminth diseases of humans: Social ecology, environmental determinants, and health systems. PLoS Negl Trop Dis. 2012; 6(4): e1603.
68. Amon JJ. The impact of climate change and population mobility on neglected tropical disease elimination. Int J Infect Dis. 2016; 53(12): DOI: https://doi.org/10.1016/j.ijid.2016.11.034.
69. Booth M. Climate change and the neglected tropical diseases. Adv Parasitol. 2018; 100(1): 1–89.

CHAPTER 2. BACKGROUND

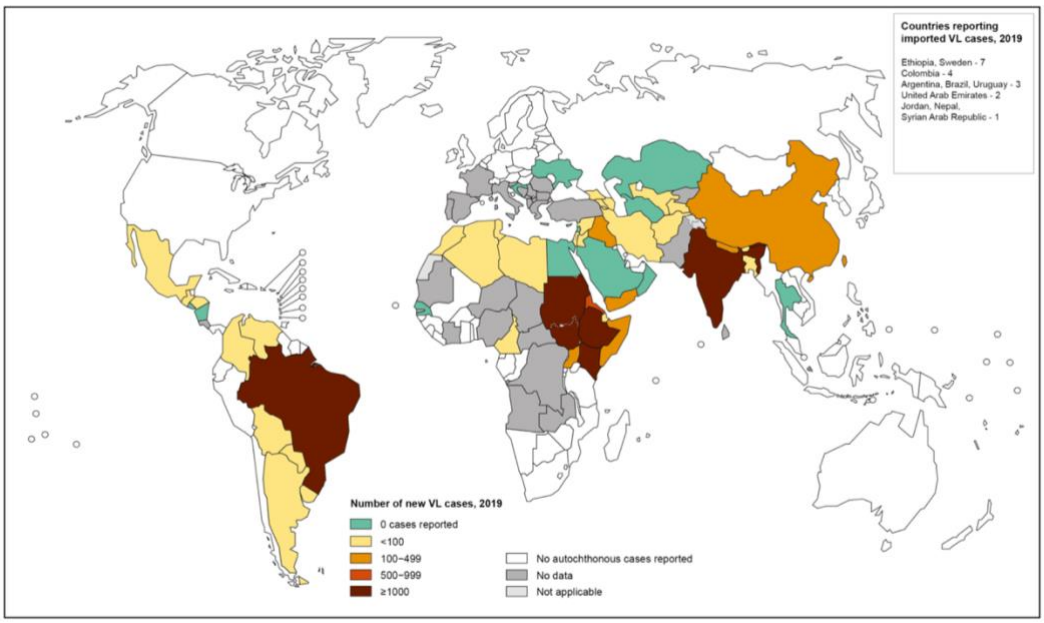
This chapter begins with a broad overview of the epidemiology, geographical distribution, burden, and management of visceral leishmaniasis (VL) globally. It then describes the context-specific history of control and elimination in the Indian Subcontinent, with a focus on programmatic gaps in India. Contextual and demographic characteristics are included to frame socio-economic indicators and health sector fragmentation that influence VL transmission and surveillance. Both epidemiological and operational challenges to eliminating VL as a public health problem are highlighted alongside areas of policy-relevant research. Lastly, the potential for interdisciplinary research—specifically, economics, modelling, and policy evaluations—to inform the design, methods, and long-term requirements of surveillance activities is examined.

2.1 Visceral leishmaniasis disease characteristics and epidemiology

Clinical forms of leishmaniases

The leishmaniases are a group of parasitic protozoan neglected tropical diseases (NTDs) transmitted to humans through the bite of an infective phlebotomine sandfly vector [1, 2]. More than one billion people live in leishmaniases-endemic areas, with risk of disease acquisition associated with poverty, malnutrition, displacement, poor housing, and compromised immunity [3]. Over 20 species of *Leishmania* cause three main forms of the disease: 1) cutaneous leishmaniasis (CL), the most common form; 2) mucocutaneous leishmaniasis (MCL), the most disabling form; and 3) visceral leishmaniasis (VL), the most severe form [1]. CL is characterised by ulcers on exposed skin of the face, arms, and legs of an infected individual [1]. With over one million annual cases, CL is targeted by WHO for control at the country level [1]. MCL is also characterised by lesions, but those on the mucous membranes of the nose, mouth, and throat cavities, which result in social burden and stigma [1]. The development of MCL is not well understood, but often occurs simultaneously with, or subsequent to, CL infection [4].

VL remains one of the top parasitic diseases with outbreak and mortality potential, with an estimated 50-90,000 new cases per year [5]. VL also accounts for 20-30,000 deaths annually and is the second-most fatal disease caused by a parasite globally, after malaria [1]. Severe clinical VL infections (also referred to as kala-azar) are characterised by fever, weight loss, enlargement of the spleen and liver, and a 95% fatality rate if left untreated [1]. Two hundred million people are at risk for VL in over 70 countries, yet 90% of cases are found in only eight: Brazil, Eritrea, Ethiopia, India, Kenya, Somalia, South Sudan, and Sudan (Figure 2-1) [6, 7]. The remainder of this thesis focuses on VL; in particular, science that informs transmission and progress towards its elimination in the context of India.



Source: WHO Global Health Observatory. Map: Control of Neglected Tropical Diseases (NTDs). 2021. World Health Organization. Geneva. [7]

Figure 2-1. Status of global visceral leishmaniasis endemicity (2019).

Taxonomy and geography of VL parasite and vector

Species of the *Leishmania* genus are unicellular parasitic flagellate trypanosomes from the class Kinetoplastida [8]. Transmission and natural history vary according to *Leishmania* species, which also impacts control strategies in different geographical contexts [9]. In Asia, VL transmission is anthroponotic, with humans as the main vertebrate host infected by *Leishmania donovani* [10]. Conversely, VL transmission in Latin America and the Mediterranean is zoonotic, with *Leishmania infantum* causing the majority of infections and the domestic dog serving as the main reservoir host [11].

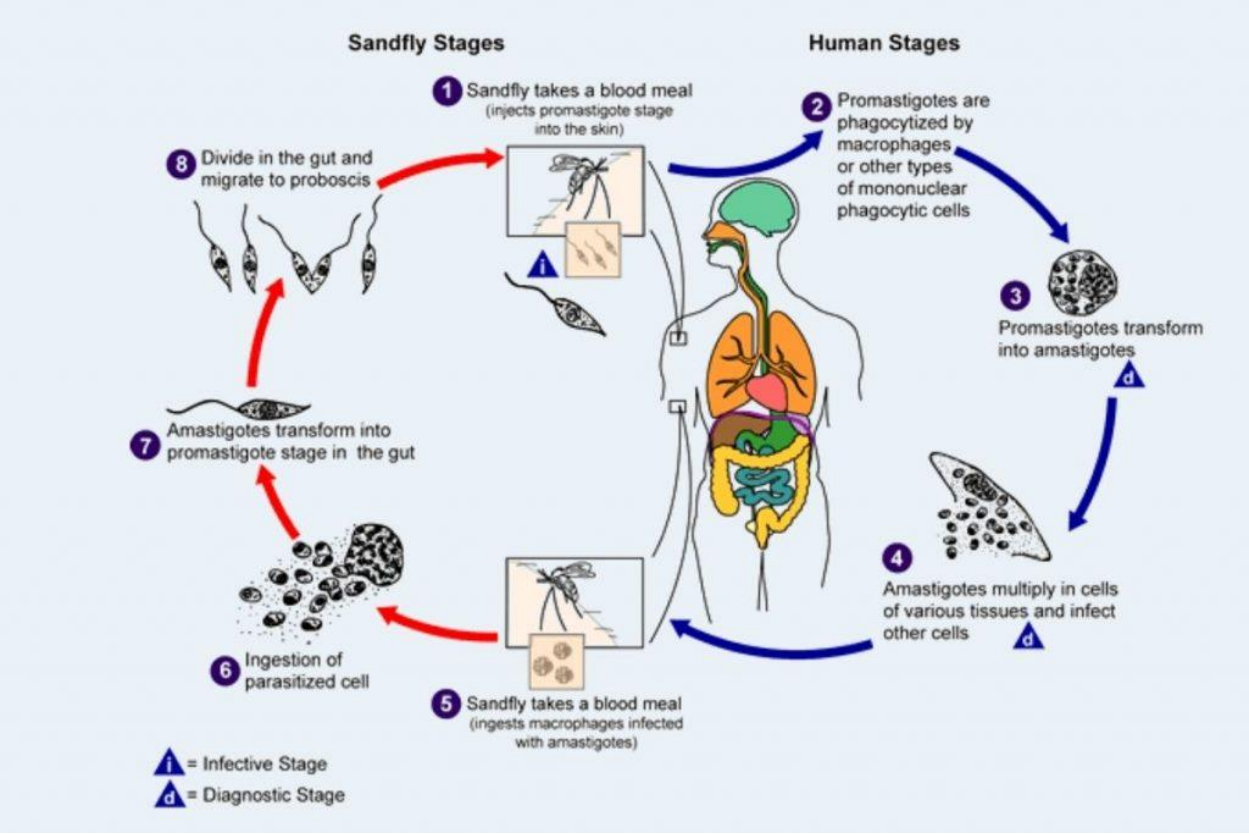
As VL infection is specific to *L. donovani* and *L. infantum*, the parasite species are also specific to sandfly vectors of the subfamily Phlebotominae. Phlebotomine sandflies are

arthropod insects (Diptera: Psychodidae) that average 1.5-3.5 mm in length, with stilt-like legs that mimic those of a mosquito [12]. In the New World, zoonotic VL is transmitted by sandfly species of the genus *Lutzomyia*, while in the Old World anthroponotic VL is transmitted by sandfly species of the genus *Phlebotomus*. *L. donovani* is transmitted exclusively by *Phebotomus argentipes*; and although *Phlebotomus papatsi* species exist as human-biting sandflies in the region, they lack vector competence for *L. donovani* in these settings [13].

Lifecycle of VL parasite

L. donovani parasites require both a human (definitive) host and a sandfly (intermediate) host to complete their lifecycle (Figure 2-2). An infective sandfly transmits the parasite to humans during a bloodmeal by injecting the promastigote stage into the skin [14]. Promastigotes then enter the bloodstream and migrate to the spleen, liver, and bone marrow. Unlike other parasitic protists, *L. donovani* is unable to directly penetrate host cells and instead depends upon phagocytosis by macrophages, or other mononuclear phagocytic cells, within the first 24 hours [14]. Phagocytosed promastigotes then undergo transformation into amastigotes, the unflagellated and unciliated parasitic stage aimed to disseminate infection, over 24-72 hours [15]. Amastigotes multiply in cells of various host tissues, with as many as 50-200 in a fully congested cell [15]. The host cell then ruptures, releasing amastigotes into tissue cavities and back into the blood stream. When a sandfly takes a blood meal, it ingests both free and phatocytosed amastigotes circulating in the peripheral blood. Amastigotes then transform into flagellated promastigotes in the sandfly gut within 1-3 days, becoming larger and considerably elongated [16]. Promastigotes divide by simple binary fission and migrate to the proboscis of the sandfly within 6-9 days to repeat the cycle of infection during the next blood meal [16]. A distinct morphological feature of parasites in this class is a kinetoplast: an

organelle containing a mass of mitochondrial DNA, present in both promastigote and amastigote forms, that can be used for identification in microscopy [17].



Source: Centers for Disease Control and Prevention. DPDx Laboratory Identification of Parasites of Public Health Concern. 2021. CDC. Atlanta.

Figure 2-2. Lifecycle stages of *L. donovani* parasite in human (definitive) and sandfly (intermediate) hosts.

Vector characteristics

Sandflies undergo complete metamorphosis through four life stages: egg, larva, pupa, and adult. The immature stages require warm and moist environments, although they do not rely on standing water (as mosquitoes do) to complete development [18]. Sandfly eggs are laid by female adults in suitable habitats of high organic content, like soil or anima excreta, to provide emerging larvae with shelter, moisture, and nutrition. Time-to-hatch depends largely on environmental temperature and ranges between 6-17 days [18]. Larvae move very little

distance from their hatching site and develop in four larval stages (instars) that mark an increase from 0.55mm to 3.2mm in size [12]. After around three weeks of larval development, the pupa stage denotes shedding of the exoskeleton over 7-10 days, similar to a small butterfly chrysalis [18]. Adult sandfly morphology includes dense 'hair' coverage, wings, large eyes, antennae, long legs, and dagger-shaped mouthparts [12]. The sandfly thorax is distinctively humped, which makes their head appear lower than the upper body surface [19].

Although both male and female sandflies obtain nutrients from plant matter and juices, females require a mammalian blood meal in order to complete egg development [19]. In the Indian Sub-Continent (ISC), both bovines and humans are the typical bloodmeal source of sandflies, which means sandfly breeding and resting sites are located around cowsheds and human dwellings [20]. Host preference varies; as some studies show an affinity for bovine bloodmeals while others document indiscriminate feeding behaviour on either host in the immediate vicinity [21, 22]. Sandflies are largely nocturnal as a result of vulnerability to dehydration during the day, with highest biting activity around midnight [20]. They seek protective habitat during rest hours, such as animal burrows, tree buttresses, holes, and human habitations [23–25]. With an average flight range of 300m, sandflies are considered weak fliers and instead fly close to the ground in short hops [18]. This restricted mobility results in adult sandflies remaining close to the vicinity of their larval development site for the remainder of their life, which averages 9-11 days for females [19, 26].

VL diagnosis, treatment, and sequelae

The incubation period from initial infection to gross inflammatory response can range from two weeks to 18 months, but clinical symptoms may take years to appear [27]. VL can be

diagnosed in several ways: through clinical presentation of fever, splenomegaly, and suppressed immunity; laboratory tests such as microscopy, liver and spleen biopsy, or bone marrow aspiration; or with a rapid diagnostic rK39 antibody test to confirm active infection if a patient presents with clinical symptoms [28]. Liver biopsy, spleen biopsy, and bone marrow aspiration can be used to detect active VL infection via microscopy. VL amastigotes can be identified intracellularly (if phagocytosed by a macrophage) or extracellularly through distinct morphological features of the parasite, such as its kinetoplast [29]. In addition to quantifying parasite load, biopsy and aspiration can detect the presence and abundance of immune response cells, such as lymphocytes, eosinophils, and macrophages [30]. However, some studies have documented parasite presence in either spleen, liver, or bone marrow; therefore, aspiration or biopsy may be required from at least two sites to verify parasite presence [31]. Further, although biopsy and aspiration are highly sensitive methods of diagnosis, the procedures carry risk of fatal haemorrhage in inexperienced medical staff and are therefore not the first-line diagnostic method [14].

The rapid rK39 antibody test is the gold standard for diagnosis in India, as it has high sensitivity (98%) when combined with presentation of clinical symptoms [32]. This immunochromatographic strip test detects the presence of immunoglobulin G (IgG) antibody in response to a recombinant K39 antigen expressed by *Leishmania* species that cause VL [33]. Although antibody tests only verify past and present immune response rather than active parasite infection, they are reliable, non-invasive, cost-effective, and easily administered in rural settings [34]. Specificity for rK39 rapid tests is relatively low, and an improved diagnostic that differentiates infection versus exposure will be essential to reach elimination in the ISC [35]. Another diagnostic challenge exists on the village level, as patients are commonly misdiagnosed and treated for a number of febrile illnesses mistaken for VL. Initial

clinical VL features are shared with other common diseases such as malaria, typhoid, and tuberculosis, which often complicates and postpones correct diagnosis [36]. VL also acts as an opportunistic infection associated with HIV, resulting in mutually reinforcing disease progression and compounded immunosuppression that has been identified as a rising disease threat by WHO [37].

No universal treatment option exists for VL, as drug efficacy varies according to *Leishmania* species and geographical population [38]. In 2014, liposomal amphotericin B (AmBisome) was documented to cure VL in South Asia as a single-dose injection with high efficacy and low toxicity, where a patient could be successfully treated the same day as diagnosis [39, 40]. AmBisome's mechanism of action targets an infected macrophage and disrupts the parasite membrane, causing cell death [41]. Studies in the ISC confirm AmBisome has the highest cure- and recovery rate of any available treatment, reducing over 99% of an individual's parasite load by day 30 post-treatment [42]. The second-line therapy in South Asia is a combination of paromomycin and miltefosine, which respectively involve three-weeks of often painful injections and four-weeks of oral drugs with several toxic effects [43]. In East Africa, pentavalent antimonials (sodium stibogluconate, or SSG) are administered in combination with paromomycin and involve serious risks of cardiotoxicity [44]. Of those successfully treated for VL, the secondary skin condition post-kala-azar dermal leishmaniasis (PKDL) appears in 5-15% of patients [45]. Recent studies have confirmed PKDL infections perpetuate VL transmission through sandfly vectors [46, 47]. Early identification and treatment of PKDL are included as primary objectives in the *WHO Roadmap for NTDs 2021-2030* [48].

Natural history of VL

The progression of VL includes four disease states: susceptible, asymptomatic infection, symptomatic infection, and recovered or dormant (Figure 2-3). The mean duration of asymptomatic infection is 147 days, with 14.7% progressing to symptomatic disease [49]. Onset of symptoms is normally marked by prolonged fever for more than 14 days, which a patient or community healthcare worker may mistake for a number of febrile illnesses such as typhoid, malaria, TB, or typhus [50]. Once an infected individual develops hepatomegaly and splenomegaly, the risk of mortality increases exponentially without treatment [50]. The mean duration of symptomatic VL is around 140 days, but a 98% recovery rate has been documented in patients in the ISC treated with AmBisome [49]. The recovered, or dormant, stage of natural immunity is around 1,110 days (about three years) [49]. PKDL can be considered a fifth disease stage in which individuals develop a secondary skin sequelae within six months to three years, which recent studies confirm contributes to VL transmission [45, 47]. Some PKDL infections clear without intervention, but others require Miltefosine or AmBisome treatment [51].

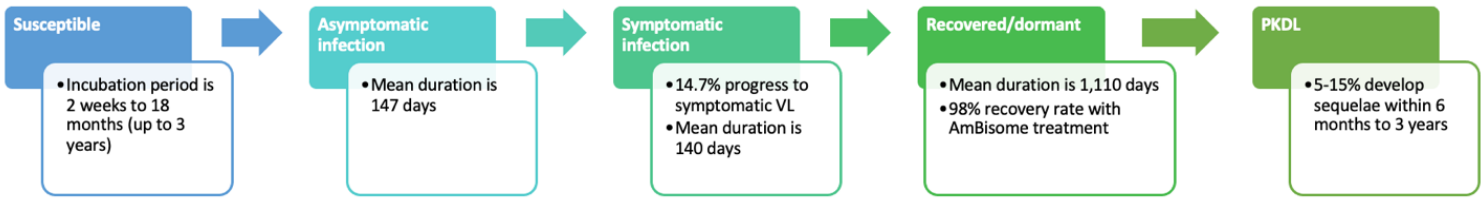


Figure 2-3. Natural history of VL disease stages.

Little is known about the role and duration of acquired immunity after infection, as well as the infectiveness during different disease stages towards the sandfly [52]. Similarly, the underlying immune mechanism that results in infections remaining asymptomatic or

developing into clinical disease is not well understood [53]. Some studies suggest that progression to clinical disease is influenced by parasite dose and inoculation route, but the majority of knowledge concerning immunity is limited to mouse models that exhibit a different compartmentalised immune response than humans [54]. Innate immune response to VL infection may be influenced by nutritional status, as both VL patients and their family members are often underweight and relatively anaemic [55]. Malnutrition is linked to the severity and progression of other parasitic infections, yet a recent Cochrane Review concluded that no studies, completed or ongoing, address the effects of nutritional supplements in patients being treated for VL [56].

2.2 VL in the Indian Subcontinent (ISC)

Geographically considered the Indian Subcontinent (ISC), India, Nepal, and Bangladesh are the last remaining VL-endemic countries in South Asia (Figure 2-4) [57]. In 2003, the region jointly established a regional alliance called the Kala-Azar Elimination Programme (KEP) aimed at lowering VL incidence to a level no longer considered a public health problem [58]. The target of this goal is formally coined elimination as a public health problem (EPHP) by WHO, which relates to both infection and disease [59]. EPHP is a benchmark for diseases that may not be feasibly eliminated through interruption of transmission, which requires reduction to zero of the incidence of infection caused by a specific pathogen in a defined geographic area [59]. EPHP targets are disease- and country-specific, and may refer to: 1) reducing incidence to less than one case per 10,000 population per year, 2) reducing transmission below a certain threshold, 3) reducing the proportion of heavy intensity infections, or 4) reducing case-fatality rates to less than 1%, as is the target for VL in the ISC [60]. A crucial difference between elimination of transmission (EOT) and EPHP is the long-term surveillance efforts required for the latter. Due to the large proportion of asymptomatic

individuals that may not require treatment but do contribute to transmission, it is essential that control measures remain in place after EPHP targets are met in order to maintain identification of and responsiveness to new cases and prevent resurgence or re-introduction [60].

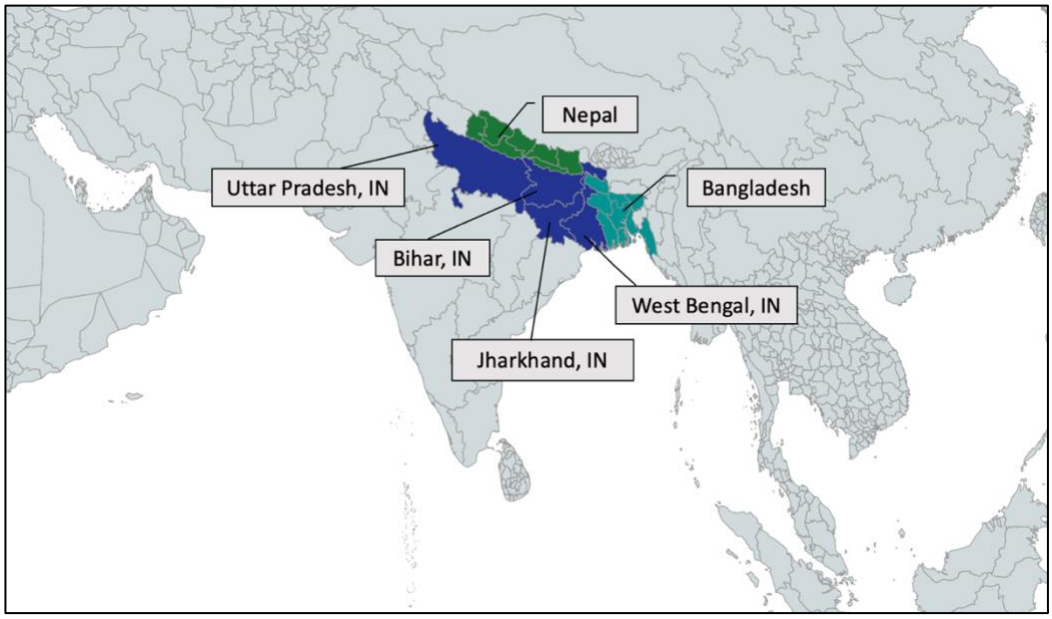


Figure 2-4. Geographical distribution of VL in Nepal (green), Bangladesh (teal), and India's four endemic states (dark blue).

Nepal and Bangladesh claim to have reached VL benchmarks of less than one case per 10,000 population per year at the sub-district level and are undergoing validation by WHO [61, 62]. The process of validation is disease- and country-specific; in the case of VL in the ISC, countries must sustain less than one case per 10,000 population at the sub-district level for three consecutive years [59]. India not only has the highest VL prevalence in South Asia, but also accounts for 25% of all global cases [63]. VL remains endemic in India's four north-eastern states of Bihar, Jharkhand, Uttar Pradesh, and West Bengal (Figure 2-4) [5]. The term *endemic* refers to a disease that is common in a particular geographical area, but may be interpreted as occurring at a particular frequency [64]. Although VL infections are certainly

persistent and localised in India, the remainder of this thesis will reference case numbers in terms of *incidence* rather than level of *endemicity* to avoid confusion.

India: health sector context and demographic indicators

Of India's 1.3 billion population, 12.4% are estimated to be living in poverty [65]. The country's total expenditure on health is 4.7% of their gross domestic product (GDP), one of the lowest in the world, and life expectancy is between 67-70 years from birth [65]. India has one of the lowest health workforce densities, with seven physicians (compared to the global average of 14) per 10,000 population [66]. Only 40% of India's health workforce serve rural communities where over 70% of the population resides [67]. Agricultural labour accounts most of the work in rural India, where 85% of households have access to clean drinking water, 55% of households have access to electricity, and only 17% of households have access to toilets [68]. Malnutrition continues to be India's highest risk factor driving combined death and disability, with rates among children two- and five- times higher than those in Sub-Saharan Africa and China, respectively [69–71]. Several types of malnutrition and micronutrient deficiencies have been associated with increased susceptibility to infectious diseases in the region, especially for rural populations [71].

Healthcare in India is largely divided between public and private sectors. Less than 40% of India's hospitals are government-funded, where much of the population seeks private healthcare at high out-of-pocket (OOP) expenditures [72]. As of 2019, 47% of India was estimated to have achieved Universal Health Coverage, however, the responsibility to fund, govern, and deliver national health services is fragmented between central and state governments [73, 74]. Traditional healers, or uncertified rural practitioners (URPs), are

common in rural communities, of which 40% have received a graduate- or technical- degree beyond secondary school [67].

Heterogeneity of VL and administrative units in India

Since KEP operations rolled out in 2005, the ISC region has reduced VL incidence from 50,000 cases to fewer than 3,000 in 2019, 93% of which are reported from India [75]. Incidence is defined as the number of new or relapsed VL cases reported within a calendar year [76]. VL distribution is vastly heterogeneous across India's four endemic states, with incidence ranging from less than one case to over 600 in a given district (Figure 2-5) [77]. Variation in VL incidence is related to population density and geographical dimensions in each district. In Bihar, India's most VL-endemic state, district-level population varies from over 7 million to just under 800,000 [78]. Therefore, EPHP benchmarks are targeted to a smaller geographical sub-district, or block, level. Bihar's 38 districts contain a total of 534 blocks, and each block may have between 20-130 villages. Village-level population density also varies, with between 500-15,000 residents per village [78]. Although village-level EPHP benchmarks would lead to more accurate and precise operational targets, rigorous data collection and follow-up are difficult to implement and sustain on a granular level. Therefore, VL surveillance data is accumulated for each block, and incidence is measured and compared per 10,000 population per year [76].

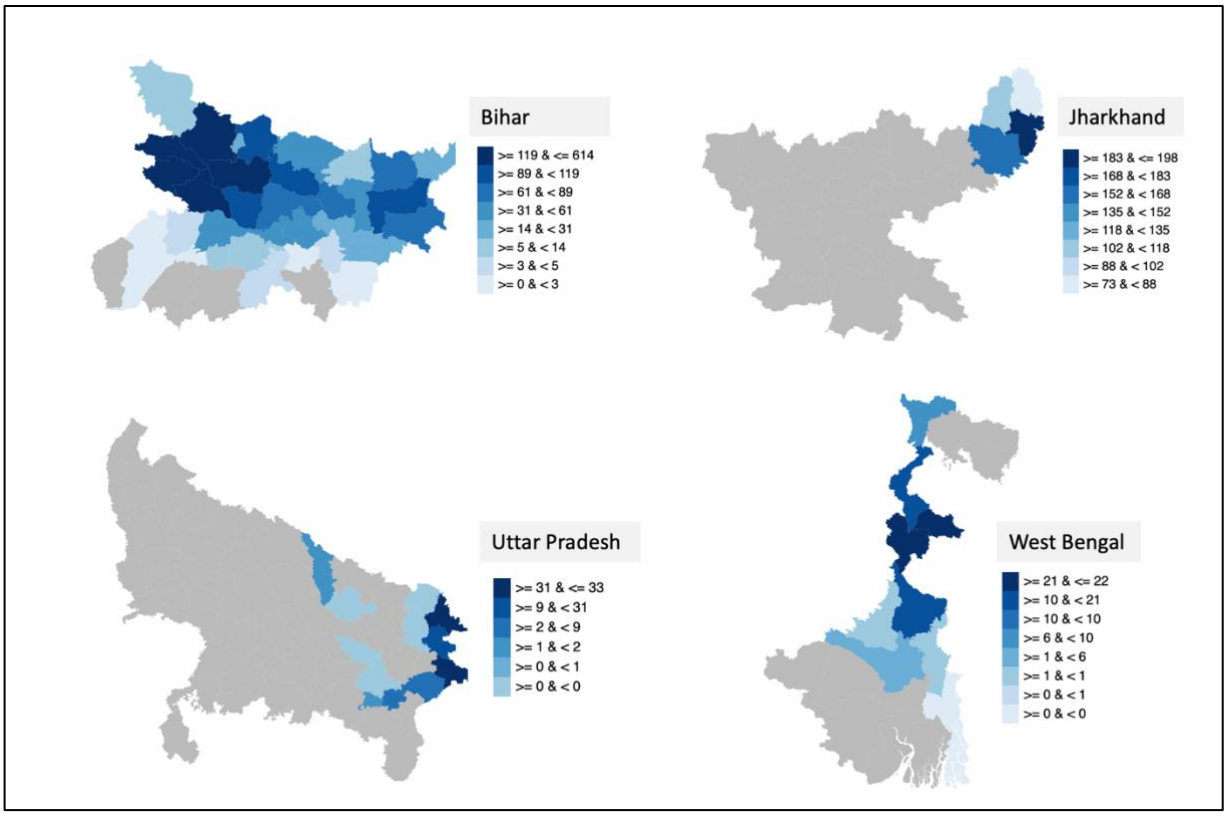


Figure 2-5. District-level heterogeneity of VL incidence per block during 2019 in India's four endemic states: Bihar, Jharkhand, Uttar Pradesh, and West Bengal.

The KEP is technically coordinated through the National Vector Borne Disease Control Programme (NVBDCP), under India's Ministry of Health and Family Welfare, and operationally run at the state level [79]. District- and block-level hospitals are referred to as Community- and Primary- Health Centres (CHCs and PHCs), which serve as government-funded health foci for several villages. PHCs, on average, cover a 120 km radius of approximately 25 villages, or 30,000 people, in rural regions [80]. Each CHC and PHC unit is required to document new and relapse VL cases through several recording tools such as patient treatment cards, laboratory registers, and Kala-Azar registers [81]. Kala-Azar registers are collated at the district level, and new VL cases reported are organised according to block. District-level VL case reports are then analysed and interpreted at the state-level every three months, where operational and management activities are coordinated [81]. The NVBDCP compiles monthly VL reports from each state, and a review of the elimination programme is

conducted every six months for individual states and once per year for the entire country [81].

2.3 Regional Kala-Azar Elimination Programme history and current pillars

During its inception, the KEP was originally operated through state and district Malaria Control Offices and the primary health system with an agenda to roll out government-sponsored drugs and insecticides to reduce VL morbidity [82]. The inertia created by WHO, LDNTD, and UCNTD in 2012 prompted drug procurement pathways and technical advisory to actualise the goal to reduce annual VL incidence to less than one per 10,000 population at the block level [83].

As studies confirming liposomal amphotericin-B (AmBisome) efficacy developed, 2014 marked the beginning of a pivotal four-year programme funded through the UK's Department for International Development (DFID) [84]. Amongst other operational support, DFID and WHO created the consortium KalaCORE to establish AmBisome training and distribution in over 120 PHCs in India [85]. Roll-out of this single-day treatment drastically improved compliance and adherence to VL treatment, as patients were able to complete the drug course directly after diagnosis [86]. Both diagnosis and treatment for VL are currently provided at no-cost in designated CHCs and PHCs through a partnership between WHO and the KEP [87].

In 2017, the KEP published an *Accelerated Plan for Kala-Azar Elimination* that included an operational framework for elimination through: 1) early case detection and complete case management, 2) integrated vector management and surveillance, 3) monitoring and surveillance evaluation, 4) strengthening capacity of human resources, 5) advocacy,

communication and social mobilisation for behavioural impact, and 6) programme management [87]. A national surveillance database, the Kala-Azar Management Information System (KAMIS), was then established to combine case management and surveillance in a single platform [88]. KAMIS is managed by the non-governmental organisation (NGO) CARE India, who are responsible for training medical providers and programme managers to properly document diagnosis, treatment, and follow-up VL patients through the digital- and app-based line-list registry system [89].

The KEP vector control strategy has predominantly employed bi-annual indoor residual spraying (IRS) with synthetic pyrethroids to interrupt human-sandfly transmission [90, 91]. Where people are at risk of transmission of vector-borne diseases, IRS involves spraying insecticide chemicals on the interior walls of houses, animal dwellings, and other public structures. IRS in India was originally implemented in the 1940's to target malaria using dichlorodiphenyltrichloroethane (DDT), which had a secondary benefit to VL control [92]. By 2013, however, vector resistance to DDT was documented in both mosquitoes and sandflies, which prompted the NVBDCP to rely on pyrethroid insecticides instead [93].

Although transmission models suggest IRS is capable of reaching VL EPHP targets in the ISC if sandfly abundance were to be reduced by 67%, spraying approaches have been confronted by issues in quality control of the insecticide and accurate targeting of terrestrial sandfly larvae sites, which have undermined evidence of reducing vector populations [93, 94]. A recent IRS study documented reduction of sandfly populations by using improved quality and dose of the insecticide alongside increased coverage of houses (>80%) in a specified geographical area [92]. Whether the NVBDCP is able to improve insecticide quality and coverage is dependent on operational and funding capacity at the national level [91].

Another study suggested that IRS strategies may require targeting exophagic *P. argentipes* that have adapted their feeding behaviour to take blood meals outside of houses, structures, and dwellings [95]. A vaccine would be the best overall preventive tool, but complexities in host immune response prove challenging and are more often studied for *L. infantum* in zoonotic regions [96–98].

As of 2020 in India, VL is confined to 54 districts within Bihar, Jharkhand, Uttar Pradesh, and West Bengal, with approximately 140 million people at risk of infection [99]. It is important to recognise that full elimination of VL transmission is difficult to achieve and document, as not every infection leads to detectable and symptomatic clinical disease [100]. The NVBDCP currently aims to reach and sustain VL EPHP by prioritising early case detection and prompt treatment, which will require sustained surveillance to maintain reduced incidence [76]. Accordingly, the WHO NTD roadmap for 2021-2030 targets have been updated to achieve less than 1% case fatality rate due to primary VL and to detect 100% of PKDL cases in order to reach EPHP [60].

2.4 Challenges to eliminating VL as a public health problem in India

To review the functionality and challenges of current KEP strategies, an *Independent Assessment of the KEP* was conducted in 2019 by WHO, NVBDCP, state-level programme managers, and international researchers [99]. Threats to achieving elimination targets were identified in high incidence 'hot-spots', low socio-economic castes, gaps in surveillance, and inadequate access to government-sponsored treatment centres [99]. To address focal outbreaks, increased relapse rates, high proportions of HIV-VL co-infection, and high burdens of PKDL, the independent assessment recommended that the KEP [99]:

1) Intensify case-based surveillance activities and later sustain them through a syndromic approach (fever and skin lesions) at the health facility level for VL and PKDL;
2) Systematically introduce a registry and monitoring system of suspected cases;
3) Improve services for the lowest socio-economic castes;
4) Enforce VL as a notifiable disease across public, private, endemic, and non-endemic settings; and
5) Create a National Task Force for governance and accountability between stakeholders and implementers.

Given VL heterogeneity and the presence of asymptomatic infections in India, long-term surveillance and monitoring of suspected cases to reach EPHP will require research that goes beyond epidemiological characteristics of the pathogen [101, 102]. India's confluence of existing environmental, socio-economic, and demographic factors increases its risk for infectious disease outbreaks, with eight emerging and re-emerging diseases documented in recent years [103]. To combat disease recrudescence in India, WHO prioritises surveillance-response research to address the need for and effects of targeted control strategies [104].

Timely and context-specific surveillance research is needed to reinforce political and financial momentum and avoid relaxing control measures too quickly [105]. Other NTD programmes that have achieved low disease incidence have documented threats associated with relaxed control measures around the point of elimination. Barriers to polio eradication include uncertain funding, waning political will, and persistence of silent infections [106, 107]. In India, studies show that leprosy re-emergence may have resulted from the

government's premature enthusiasm to declare elimination, which has in turn undermined accurate reporting of new cases [108].

VL resurgence is also plausible due to cyclical trends that characteristically occur every 15 years in association with maximum and average temperatures prior to peak sandfly periods [109]. Challenges to sustain VL EPHP efforts in Bangladesh were identified as equally scientific and political, where optimising surveillance is prioritised with a focus on operational and technical capacity [110]. Researchers are also studying the impact of the COVID-19 pandemic on delayed surveillance and control efforts for VL in India, projecting increased rates of underlying infection in high-transmission areas that may delay elimination up to nine years [111–113]. VL resurgence is possible, and indeed likely, in India if surveillance is not reinforced through political, financial, and research commitments that substantiate long-term control strategies to reach and maintain EPHP.

2.5 What research is needed to guide and inform VL surveillance in India?

Chapter 1 introduces the three pillars of the WHO NTD roadmap for 2021-2030 to highlight areas where concerted action is needed in the short-, mid-, and long-term to reach disease-specific targets (Figure 2-6) [48]. Pillar 1 refers to programmatic action in the short-term that must be accelerated to continue progress towards disease-specific targets, whereas pillars 2 and 3 aim to mobilise programme integration and country ownership over the mid- and long-term. Where accelerating programmatic action is essential in the immediate, the roadmap assesses each NTD according to technical aspects, strategy and service delivery, and enablers required to address operational gaps. For VL, WHO acknowledges that critical action through research, monitoring and evaluation, and capacity building is required in every sub-category, denoted by orange and red squares in Figure 2-6.

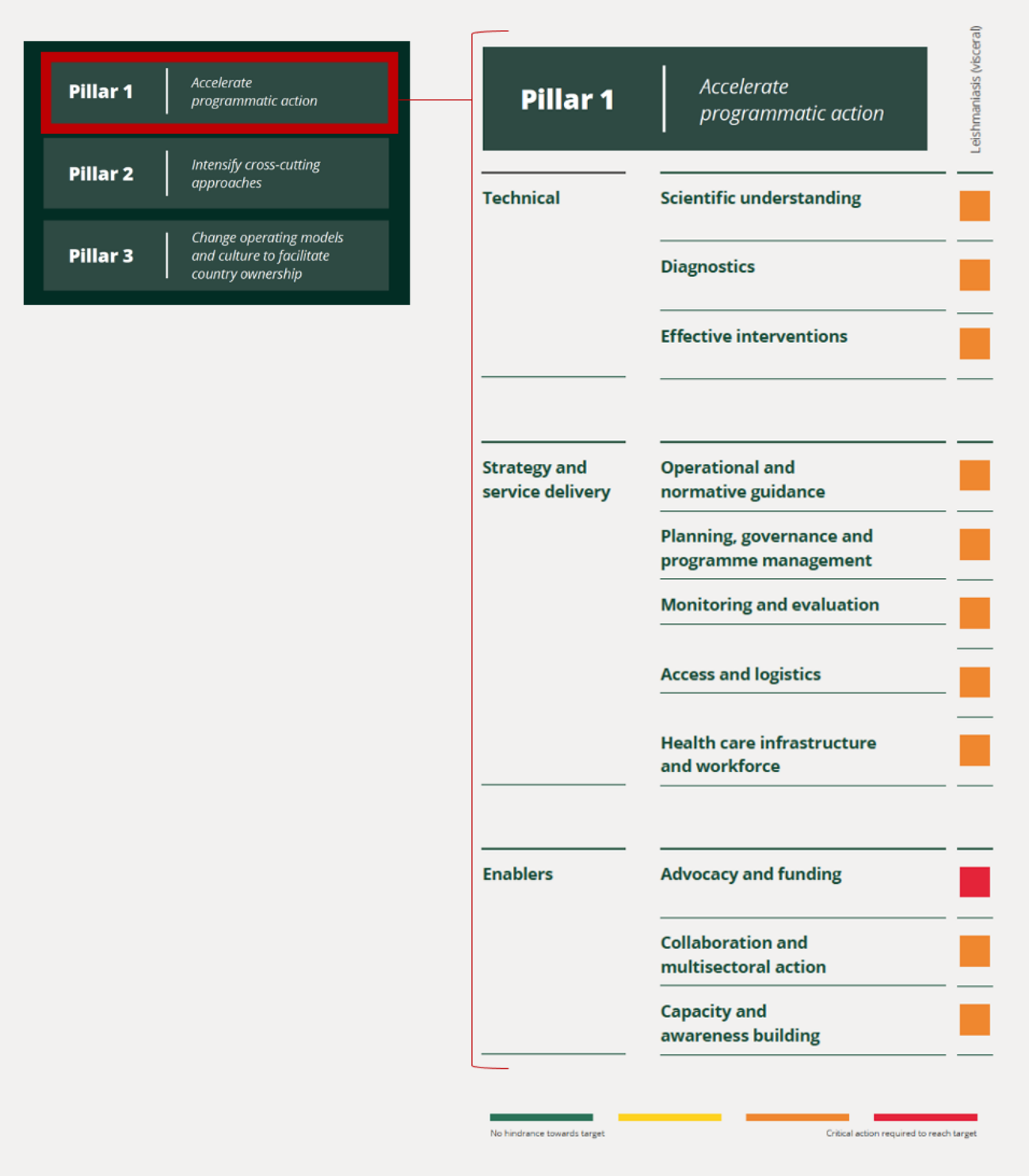


Figure 2-6. Gap assessment for VL according to the WHO NTD roadmap for 2021-2030, identifying support required for Pillar I to *Accelerate Programmatic Action*.

It can be inferred from both the WHO NTD roadmap and the *Independent Assessment of the KEP* that the majority of programmatic action for VL in India revolves around surveillance-response strategies. Surveillance-response strategies are crucial final steps to achieving efficient and effective control measures for diseases approaching elimination and require substantial coordination and support at the national level [114]. Between surveillance and response are core functions of case detection, registration, confirmation, and reporting; data analysis and interpretation; intervention preparedness; and control and response legislation [115]. Surveillance also relies on a functioning network of researchers, implementers, stakeholders, and policy makers, a dynamic in which much less research is focused [115].

Substantiating long-term VL surveillance in India requires an understanding of 1) the technical elements of surveillance (scientific understanding and interventions), 2) strategy and service delivery (operations, governance, logistics, and infrastructure), and 3) what will enable long-term surveillance to reach and sustain EPHP (advocacy, funding, collaboration, and capacity-building). This section explores research disciplines relevant to informing VL surveillance activities, or programmatic action, in alignment with pillar 1 of the WHO NTD roadmap for 2021-2030.

1) Technical elements of surveillance: interventions

WHO classifies three basic systems of passive, sentinel, and active surveillance [116]. Passive surveillance is the regular reporting of disease data by all institutions that see patients for diagnosis and treatment and is usually the least costly method. Sentinel surveillance is used when high-quality data is missing and required for a particular disease, where selected reporting units likely to see cases (typically large hospitals with laboratory facilities) are called upon to collect data within a specified community. Active surveillance, the most

resource-intensive, often involves case searches within communities when diseases are targeted for elimination or eradication and every possible case must be found and investigated.

VL surveillance, or case detection, is carried out both actively and passively in India. An individual either becomes symptomatic and seeks care at a PHC or CHC, referred to as passive case detection (PCD), or is identified through systematic village-level surveillance conducted by health officials, referred to as active case detection (ACD). Three ACD methods have been used in the past decade to identify VL cases at the village level: 1) blanket ACD, which involves house-to-house screening for symptoms, 2) camp ACD, where a temporary diagnostic centre is set up between one to three villages, and 3) index case-based ACD, where mobile ACD officers travel to the village of a recently diagnosed VL case to screen neighbours for symptoms.

Currently, the KEP relies mainly on index case-based ACD, which may be limited in both thoroughness and geographical scope in practice [99]. As ACD requires substantial human resources, two evaluations were recently published in an aim to contribute towards targeting approaches to improve feasibility to reach and sustain EPHP. Bindroo et al. identified that the trade-off between the number of villages targeted and ACD yield depends on operational efficiencies, and that improving sensitivity and comprehensiveness of ACD will be crucial to preventing VL resurgence [117]. Dubey et al. found that ACD strategies are an essential supplement to PCD for reducing the time between VL infection and diagnosis, and therefore risk of transmission, and may be required perpetually even after EPHP is achieved [118]. From 2014-2018, the KEP also employed an intervention that combined blanket and camp ACD in high incidence areas [119–121].

The 2019 WHO independent assessment reported that data was unavailable for many ACD activities, implementers were unclear of ACD guidelines, and the overall approach in Bihar was unsystematic [99]. Lack of a border surveillance mechanism makes identification of sporadic VL infections difficult, particularly in villages with no previous cases [99]. Similarly, although Accredited Social Health Activists (ASHAs) are trained and incentivised to refer suspected VL cases to hospitals for diagnosis, the degree to which this referral system works is not well documented as a standardised record system does not exist at the village level [122, 123]. More rigorous reporting and data collection mechanisms will be necessary at the village-level to monitor suspected cases, treated cases, and population movement across borders.

2) Strategy and service delivery: operations, governance, and logistics

As VL cases become increasingly difficult and important to identify, surveillance must expand beyond a sole reporting system to being hypothesis-driven and aim for preventive, rather than reactionary, responses [124]. Research priorities to improve the design of NTD surveillance systems revolve largely around evaluating transmission, population dynamics, mobile- and active case detection, tailored responses for different transmission settings and levels, and intervention activities [114]. A major challenge for VL surveillance-response is addressing heterogeneity at the sub-district, or block, level where EPHP targets are focused. Control measures must be tailored for both low incidence areas and hotspots, each of which are associated with different indicators of poverty, waning immunity, and seasonal migration [125–127]. Understanding transmission is essential for addressing heterogeneity, as other NTD studies have documented vastly improved efficiency and efficacy in tailoring control activities to spatial correlates [128].

Evaluating VL transmission dynamics is also critical to assess the likelihood of reaching 2030 EPHP targets. Predicting incidence and the impact of interventions across space and time has become standard for many NTD surveillance-response systems during elimination [129]. Where immediate policy responses were required throughout the COVID-19 pandemic, many health systems relied on simulations of the virus across various interventions and demographics to create decisions and recommendations [130–132].

A compelling research tool for emerging and endemic diseases alike is mathematical modelling, which can simulate transmission dynamics across a diversity of epidemiological, environmental, demographic, political, social, and economic indicators to predict potential outbreaks [133]. Modelling for VL in India has gained much traction over the past decade, largely due to international research facilitated by the Bill and Melinda Gates Foundation (BMGF) [134–136]. This modelling has focused on the drivers of VL transmission, effects of delayed health-seeking behaviour, likelihood of reaching EPHP, and forecasts of incidence across future time periods [46, 49, 137–149].

The extent to which this growing body of modelling literature for VL has influenced or informed surveillance in India is not well documented. Policy recommendations have been presented from the perspective of some modellers, as has the need for more investments in surveillance modelling to stop VL transmission [150, 151]. Studies on the development of surveillance systems for COVID-19 identified that experts in computational epidemiology, public health policy, and human behaviour must work in unison to create an effective policy response [152]. A gap in knowledge surrounding VL surveillance in India is not necessarily

in the availability of modelling research to inform its design, but rather in the transfer and application of knowledge into policy.

3) Enablers for long-term surveillance: advocacy, funding, and capacity-building

Lastly, surveillance research must explore not only the technical capacity required to reach EPHP, but also the political, economic, and social contexts in which effectiveness relies on [153, 154]. Health economics has the capacity to inform both political and village-level communities in that it can inform top-down resource allocation for government spending as well as socio-economic benefits and poverty reduction on the individual level [155–157]. Much of the early process to prioritise NTD control and elimination revolved around financial incentives to leverage international funders, drug donations, and policy moments within national agendas [158]. Continuing to mobilise political, donor, and financial support for long-term NTD surveillance will require characterising the cost-effectiveness of current interventions and the investment required to reach elimination [159, 160].

The current costs and investment required for long term surveillance have been identified as unmet challenges in other NTD programmes [161–165]. There is mounting evidence for the cost-effectiveness of mass drug administrations for PC-NTDs [166–169], but economic assessments of case detection and programme integration are sparse [170–172]. An essential step to establish and sustain VL surveillance and control measures in India, and eventually integrate them horizontally into other vector-borne and febrile disease programmes, requires research to understand current and projected costs of surveillance activities [99, 173, 174].

Similar to forecasting incidence across space and time, economic indicators can also be modelled to project the resources and capacity required to reach EPHP [175, 176]. Only three

studies have been conducted on the cost of VL surveillance in India, which were published nearly a decade ago when incidence and control activities differed substantially [119–121]. The effectiveness and efficiency of surveillance could be improved by economic research that informs the cost of different interventions across disease heterogeneity, resource allocation for diagnostic and treatment stockpiles, human capacity necessary for vertical versus horizontal programming, and the potential costs saved by investing in and achieving elimination.

Gaps in knowledge for VL surveillance in India

This chapter explores how interdisciplinary research can inform surveillance and elimination activities for VL in India. Chapters 3 and 4 examine the value of economic evaluations to surveillance-response strategies, where a gap in knowledge exists around the availability of such research for VL in India. Chapters 5 and 6 explore VL modelling research, which is relatively more abundant, and its value to decision makers in the KEP. In the future, it may be important to synthesise interdisciplinary indicators and methods of investigation comprehensively, which is explored in Chapter 7, the discussion. The WHO NTD roadmap for 2021-2030 will continue to be referenced throughout this thesis to frame how research can improve surveillance and facilitate national ownership over design, implementation, and horizontal integration of activities.

References

1. World Health Organization. Leishmaniasis Factsheet [Internet]. World Health Organization. Geneva; 2020 [cited 2021 Feb 24]. Available from: https://www.who.int/en/news-room/fact-sheets/detail/leishmaniasis.
2. Hotez P, Herricks J. One million deaths by parasites [Internet]. PLoS Blogs. 2015. Available from: https://speakingofmedicine.plos.org/2015/01/16/one-million-deaths-parasites/
3. World Health Organization. Visceral Leishmaniasis Factsheet [Internet]. World Health Organization. 2020 [cited 2018 Jan 8]. Available from: https://www.who.int/news-room/fact-sheets/detail/leishmaniasis.
4. David CV, Craft N. Cutaneous and mucocutaneous leishmaniasis. Dermatol Ther. 2009; 22(1): 491–502.
5. World Health Organization. Number of cases of visceral leishmaniasis reported by country [Internet]. Geneva; 2021. Available from: https://apps.who.int/gho/data/node.main.NTDLEISHVNUM?lang=en.
6. World Health Organization. World Health Data Platform: Leishmaniasis [Internet]. Global Health Observatory. 2021 [cited 2021 Feb 24]. Available from: https://www.who.int/data/gho/data/themes/topics/gho-ntd-leishmaniasis.
7. World Health Organization. Status of endemicity of visceral leishmaniasis worldwide, 2019 [Internet]. Geneva; 2021. Available from: https://www.who.int/data/gho/data/themes/topics/topic-details/GHO/leishmaniasis.
8. Akhoundi M, Kuhls K, Cannet A, Votypka J, Marty P, Delaunay P, et al. A historical overview of the classification, evolution, and dispersion of Leishmania parasites and sandflies. PLoS Negl Trop Dis. 2016; 10(3): e0004349.
9. Ready PD. Epidemiology of visceral leishmaniasis. Clin Epidemiol. 2014; 6(1): 147–154.
10. Zamir M, Zaman G, Alshomrani AS. Control strategies and sensitivity analysis of anthroponotic visceral leishmaniasis model. J Biol Dyn. 2017; 11(1): 323-338.
11. Ben Helel K, Ben Rejeb M, Habboul Z, Khattat N, Mejaouel H, Said-Latiri H, et al. Risk factors for mortality of children with zoonotic visceral leishmaniasis in Central Tunisia. PLoS ONE. 2017; 12(12): e0189725.
12. Killick-Kendrick R. The biology and control of Phlebotomine sand flies. Clin Dermatol. 1999; 17(3): 279–289.
13. Garlapati R, Iniguiz E, Serafim TD, Mishra PK, Rooj B, Sinha B, et al. Towards a sustainable vector-control strategy in the post-kala-azar elimination era. Front Cell Infect Microbiol. 2021; 11(1): DOI: 10.3389/fcimb/2021/641632.
14. Centers of Disease Control. DPDx Laboratory identification of parasites of public health concern: Leishmaniasis [Internet]. Centers for Disease Control and Prevention. 2021 [cited 2021 Nov 22]. Available from: https://www.cdc.gov/dpdx/index.html
15. Kima PE. The amastigote forms of Leishmania are experts at exploiting host cell processes to establish infection and persist. Int J Parasitol. 2008; 37(10): 1087–1096.
16. Gossage SM, Rogers ME, Bates PA. Two separate growth phases during the development of Leishmania in sand flies: implications for understanding the life cycle. Int J Parasitol. 2003; 33(10): 1027–1034.
17. Sunter J, Gull K. Shape, form, function and Leishmania pathogenicity: From textbook descriptions to biological understanding. Open Biol. 2017; 7(9): DOI: https://doi.org/10.1098/rsob.17065.
18. Halada P, Hlavackova K, Dvorak V, Volf P. Identification of immature stages of phlebotomine sand flies using MALDI-TOF MS and mapping of mass spectra during

sand fly life cycle. Insect Biochem Mol Biol. 2018; 93(1): 47–56.
19. Volf P, Volfova V. Establishment and maintenance of sand fly colonies. J Vector Ecol. 2011; 36(1): S1–9.
20. Chowdhury R, Kumar V, Mondal D, Das ML, Das P, Dash AP, et al. Implication of vector characteristics of Phlebotomus argentipes in the kala-azar elimination programme in the Indian sub-continent. Pathog Glob Health. 2016; 110(3): 87–96.
21. Addy M, Mitra AK, Ghosh KK, Hati AK. Host preference of Phlebotomus argentipes in different biotypes. Trop Geogr Med. 1983; 35(4): 343–345.
22. Mukhopadhyay A, Chakravarty A. Bloodmeal preference of Phlebotomus argentipes and P. papatsi of north Bihar, India. Indian J Med Res. 1987; 86(1): 475–480.
23. Dinesh DS, Bhattacharya SK, Das P. Peridomestic breeding and resting sites of sandflies (Diptera: Psychodidae) in Bihar, India. Entomology. 2009; 120(1): 496–501.
24. Feliciangeli M. Natural breeding places of phlebotomine sandflies. Med Vet Entomol. 2004; 18(1): 71–80.
25. Singh R, Lal S, Saxena VK. Breeding ecology of visceral leishmaniasis vector sandfly in Bihar state of India. Acta Trop. 2008; 107(1): 117–20.
26. Wijerathna T, Gunathilaka N, Gunawardena K. Establishment of a colony of Phlebotomus argentipes under laboratory conditions and morphometric variation between wild-caught and laboratory-reared populations. J Trop Med. 2020;2020(1).
27. Centers for Disease Control. Leishmaniasis [Internet]. Resources for Health Professionals. 2021 [cited 2021 Feb 24]. Available from: https://www.cdc.gov/parasites/leishmaniasis/index.html.
28. Aronson N, Herwaldt BL, Libman M, Pearson R, Lopez-Velez R, Weina P, et al. Diagnosis and treatment of leishmaniasis: clinical practical guidelines by the Infectious Diseases Society of America (ISDA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Clin Infect Dis. 2016; 63(12): 1539–1557.
29. Dhingra KK, Gupta P, Saroha V, Setia N, Khurana N, Singh T. Morphological findings in bone marrow biopsy and aspirate smears of visceral kala azar: A review. Indian J Parasitol Microbiol. 2010; 53(1): 96–100.
30. Salam M, Ahmed I, Ali M, Hossain S, Begum S. Microscopic detection of L.D. bodies in splenic aspirates at Rajshahi Medical College Hospital. J Teach Assoc Rajshahi Med Coll Hosp. 2003; 16(1): DOI: 10.3329/taj.v16i1.3898.
31. Jetley S, Rana S, Khan S, Zeeba JS, Hassan MJ, Kapoor P. Bone marrow negative visceral leishmaniasis in an adolescent male. Iran J Parasitol. 2013; 8(1): 182–185.
32. Boelaert M, Verdonck K, Menten J, Sunyoto T, van Griensven J, Chappuis F, et al. Rapid tests for the diagnosis of visceral leishmaniasis in patients with suspected disease. Cochrane Database Syst Rev. 2014; 2014(6): DOI: 10.1002/14651858.
33. Sundar S, Maurya R, Singh RK, Bharti K, Chakravarty J, Parekh A, et al. Rapid, noninvasive diagnosis of visceral leishmaniasis in India: Comparison of two immunochromatographic strip tests for detection of anti-K39 antibody. J Clin Microbiol. 2020; 44(1): DOI: 10.1128/JCM.44.1.251-253.2006.
34. Goswami RP, Bairagi B, Kundu PK. K39 strip test: Easy, reliable and cost-effective field diagnosis for visceral leishmaniasis in India. J Assoc Physicians India. 2003; 51(1): 759–761.
35. de Ruiter CM, van der Veer C, Leeflang MMG, Deborggraeve S, Lucas C, Adams ER. Molecular tools for diagnosis of visceral leishmaniasis: systematic review and meta-analysis of diagnostic accuracy. J Clin Microbiol. 2014; 52(9): 3147–3155.
36. Sundar S, Rai M. Laboratory diagnosis of visceral leishmaniasis. Clin Vaccine Immunol. 2002; 9(5): DOI: 10.1128/cdli.9.5.951-958.2002.
37. World Health Organization. Leishmaniasis and HIV coinfection [Internet]. Geneva;

2020. Available from: https://www.who.int/news-room/fact-sheets/detail/leishmaniasis.
38. Chappuis F, Sundar S, Hailu A, Ghalib H, Rijal S, Peeling R, et al. Visceral leishmaniasis: what are the needs for diagnosis, treatment and control? Nat Rev Microbiol. 2007; 5(11): 873-882.
39. Sundar S, Singh A, Rai M, Chakravarty J. Single-dose indigenous liposomal amphotericin B in the treatment of Indian visceral leishmaniasis: A Phase 2 study. Am J Trop Med Hyg. 2015; 92(3): 513-517.
40. Mondal D, Alvar J, Hasnain G, Hossain S, Ghosh D, Huda M, et al. Efficacy and safety of single-dose liposomal amphotericin B for visceral leishmaniasis in a rural public hospital in Bangladesh: A feasibility study. Lancet Glob Heal. 2014; 2(1): e51-57.
41. Sundar S, Chakravarty J. Liposomal Amphotericin B and Leishmaniasis: Dose and response. J Glob Infect Dis. 2010; 2(2): 159–66.
42. Sudarshan M, Weirather JL, Wilson ME, Sundar S. Study of parasite kinetics with antileishmanial drugs using real-time quantitative PCR in Indian visceral leishmaniasis. J Antimicrob Chemother. 2011; 66(8): 1751–1755.
43. Alves F, Bilbe G, Blesson S, Goyal V, Monnerat S, Mowbray C, et al. Recent development of visceral leishmaniasis treatments: Successes, pitfalls, and perspectives. Clin Microbiol Rev. 2018; 31(4): 1–27.
44. Drugs for Neglected Diseases initiative. Visceral leishmaniasis: Symptoms, transmission, and current treatments [Internet]. Drugs for Neglected Diseases initiative. 2020 [cited 2021 Feb 24]. Available from: https://dndi.org/diseases/visceral-leishmaniasis/.
45. Zijlstra E, Alvar J. The post-kala-azar dermal leishmaniasis (PKDL) atlas: A manual for health workers [Internet]. Geneva; 2012. Available from: https://apps.who.int/iris/bitstream/handle/10665/101164/9789241504102_eng.pdf
46. Mondal D, Bern C, Ghosh D, Rashid M, Molina R, Chowdhury R, et al. Quantifying the infectiousness of post-Kala-Azar dermal leishmaniasis toward sand flies. Clin Infect Dis. 2019; 69(2): 251-258.
47. Le Rutte EA, Zijlstra EE, de Vlas SJ. Post-kala-azar dermal leishmaniasis as a reservoir for visceral leishmaniasis transmission. Trends Parasitol. 2019; 35(8): 590-592.
48. World Health Organization. Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021-2030 [Internet]. Geneva; 2020. Available from: file:///Users/nataliedial/Downloads/9789240010352-eng.pdf
49. Chapman LAC, Dyson L, Courtenay O, Chowdhury R, Bern C, Medley GF, et al. Quantification of the natural history of visceral leishmaniasis and consequences for control. Parasit Vectors. 2015; 8(521): DOI: https://doi.org/10.1186/s13071-015-1136-3.
50. Jervis S, Chapman LAC, Dwivedi S, Das A, Le Rutte E, Courtenay O, et al. Variations in visceral leishmaniasis burden, mortality and the pathway to care within Bihar, India. Parasites and Vectors. 2017; 10(601): DOI: https://doi.org/10.1186/s13071-017-2530-9.
51. Saurabh S, Roy P, Pandey DK, Ray D, Tarak S, Pandey R, et al. Changing clinico-epidemiology of post-kala-azar dermal leishmaniasis (PKDL) in India: Results of a survey in four endemic states. J Vector Borne Dis. 2020; 57(2): 161–169.
52. Le Rutte EA, Coffeng LE, Bontje DM, Hasker EC, Postigo JAR, Argaw D, et al. Feasibility of eliminating visceral leishmaniasis from the Indian subcontinent : explorations with a set of deterministic age-structured transmission models. Parasit

Vectors. 2016; 9(24): 1–14.
53. Kumar R, Nylen S. Immunobiology of visceral leishmaniasis. Front Immunol. 2012; 3(251): DOI: 10.3389/fimmu.2012.00251.
54. Rodrigues V, Cordeiro-da-Silva A, Laforage M, Silvestre R, Estaquier J. Regulation of immunity during visceral Leishmania infection. Parasites and Vectors. 2016;9(118).
55. Feleke B. Nutritional status of visceral leishmaniasis patients: A comparative cross-sectional study. Clin Nutr. 2019; 33(1): 139–142.
56. Custodio E, Lopez-Alcalde J, Herrero M, Bouza C, Jimenez C, Bonsmann S, et al. Nutritional supplements for patients being treated for active visceral leishmaniasis. Cochrane Database Syst Rev. 2018; 3(1): CD012261.
57. World Health Organization. Status of endemicity of visceral leishmaniasis by country [Internet]. Geneva; 2021. Available from: https://www.who.int/data/gho/indicator-metadata-registry/imr-details/3762.
58. National Vector Borne Disease Control Programme. National Vector Borne Disease Control Programme Road Map for Kala Azar Elimination [Internet]. Delhi, India; 2014. Available from: https://nvbdcp.gov.in/Doc/Road-map-KA_2014.pdf.
59. World Health Organization. Generic framework for control, elimination, and eradication of neglected tropical diseases [Internet]. Geneva; 2015. Available from: https://www.who.int/neglected_diseases/resources/NTD_Generic_Framework_2015.pdf
60. World Health Organization. Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021-2030 [Internet]. Geneva; 2020. Available from: https://www.who.int/publications/i/item/9789240010352.
61. Banjara MR, Joshi AB. Evidence for visceral leishmaniasis elimination in Nepal. Lancet. 2020; 8(1): e161-e162.
62. World Health Organization. Visceral leishmaniasis: WHO publishes validation document as countries approach elimination [Internet]. New Delhi and Geneva; 2016. Available from: https://www.who.int/neglected_diseases/news/Visceral_leishmaniasis_WHO_publishes_validation_document/en/.
63. World Healthh Organization. Global Health Observatory: Number of cases of visceral leishmaniasis reported [Internet]. Geneva; 2020. Available from: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/number-of-cases-of-visceral-leishmaniasis-reported.
64. Merriam-Webster. Endemic (definition) [Internet]. Dictionary. 2021 [cited 2021 Dec 2]. Available from: https://www.merriam-webster.com/dictionary/endemic.
65. World Bank. India Country Profile [Internet]. World Bank Data Report. 2021 [cited 2021 Feb 26]. Available from: https://data.worldbank.org/country/india.
66. Narain JP. Public health challenges in India: Seizing the opportunities. Indian J Community Med. 2016; 41(2): 85-88.
67. Anand S, Fan V. The health workforce in India [Internet]. Geneva; 2016. Available from: https://www.who.int/hrh/resources/16058health_workforce_India.pdf
68. Kumar VV, Reddy AS, Sathish K. Comparison between rural and urban socio-economic indicators in India. Int J Eng Sci Comput. 2019; 9(5): 21863.
69. World Health Organization. Child malnutrition estimates by WHO Child Growth Standards [Internet]. Geneva; 2020. Available from: https://www.who.int/teams/nutrition-and-food-safety/databases/nutgrowthdb.
70. World Bank. Helping India combat persistently high rates of malnutrition [Internet]. 2013. Available from: https://www.worldbank.org/en/news/feature/2013/05/13/helping-india-combat-

persistently-high-rates-of-malnutrition#:~:text=The Government of India has,under three years of age.
71. India State-Level Disease Burden Initiative Malnutrition Collaborators. The burden of child and maternal malnutrition and trends in its indicators in the states of India: The Global Burden of Disease Study 1990-2017. Lancet Child Adolesc Heal. 2019; 3(12).
72. Khetrapal S, Acharya A, Mills A. Assessment of the public-private-partnerships model of a national health insurance scheme in India. Soc Sci Med. 2019; 243(1): 112634.
73. Global Burden of Disease 2019 Universal Health Coverage Collaborators. Measuring universal health coverage based on an index of effective coverage of health services in 2014 countries and territories, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020; 396(1).
74. Gupta I, Patel N, Tikkanen R, Osborn R, Mossialos E, Djordjevic A, et al. International Health Care System Profiles: India [Internet]. New Delhi, India; 2020. Available from: https://www.commonwealthfund.org/international-health-policy-center/countries/india.
75. Rijal S. Eliminating visceral leishmaniasis in South Asia: The road ahead. BMJ. 2019; 364(1): DOI: 10.1136/bmj.k5224.
76. World Health Organization South East Asia Regional Office. Process of validation of elimination of kala-azar as a public health problem in South-East Asia [Internet]. New Delhi, India; 2016. Available from: https://apps.who.int/iris/handle/10665/331974.
77. Bulstra CA, Le Rutte EA, Malaviya P, Coffeng LE, Singh O. Visceral leishmaniasis: Spatiotemporal heterogeneity and drivers underlying the hotspots in Muzaffarpur, Bihar, India. PLoS Negl Trop Dis. 2018; 12(12): e0006888.
78. State of Bihar. Bihar, India Census Report 2011-2020 [Internet]. New Delhi, India; 2020. Available from: https://www.census2011.co.in/census/state/bihar.html.
79. National Vector Borne Disease Control Programme. National Kala-Azar Elimination Programme [Internet]. New Delhi, India; 2021 [cited 2021 Mar 4]. Available from: https://nvbdcp.gov.in/index4.php?lang=1&level=0&linkid=469&lid=3752#:~:text=Concerned with the increasing problem,endemic states in 1990-91.&text=The National Health Policy-2002,which was revised to 2015.
80. Ministry of Health and Family Welfare. Rural Health Statistics [Internet]. New Delhi, India; 2016. Available from: https://main.mohfw.gov.in/sites/default/files/Final RHS 2018-19_0.pdf.
81. National Vector Borne Disease Control Programme. Operational Guidelines on Kala-Azar (Visceral Leishmaniasis) Elimination in India [Internet]. New Delhi, India; 2015. Available from: https://www.who.int/leishmaniasis/burden/Operational_guidelines_on_kala_azar_elimination_in_India.pdf.
82. National Vector Borne Disease Control Programme. National Kala-Azar Elimination Programme [Internet]. New Delhi, India; 2005. Available from: https://nvbdcp.gov.in/index4.php?lang=1&level=0&linkid=469&lid=3752#:~:text=Concerned with the increasing problem,endemic states in 1990-91.&text=The National Health Policy-2002,which was revised to 2015.
83. London Declaration on NTDs. From Promises to Progress: The first annual report on the London Declaration on NTDs [Internet]. London, UK; 2013. Available from: https://unitingtocombatntds.org/reports/1st-report/
84. Drugs for Neglected Diseases initiative. UK Department for International Development (DFID) Commits 30 million GBP to DNDi [Internet]. Geneva; 2013. Available from: https://dndi.org/wp-content/uploads/2009/03/DNDi_Modelpaper_2013.pdf.

85. Reithinger R. Visceral leishmaniasis: operational focus needed. Lancet Glob Heal. 2015; 3(4): e194.
86. Goyal V, Mahajan R, Pandey K, Singh SN, Singh RS, Strub-Wourgaft N, et al. Field safety and effectiveness of new visceral leishmaniasis treatment regimens within public health facilities in Bihar, India. PLoS Negl Trop Dis. 2018; 12(10): e0006830.
87. National Vector Borne Disease Control Programme. Accelerated plan for Kala-Azar elimination [Internet]. New Delhi, India; 2017. Available from: https://www.who.int/leishmaniasis/resources/Accelerated-Plan-Kala-azar1-Feb2017_light.pdf.
88. National Vector Borne Disease Control Programme. Kala-Azar Management Information System (KAMIS) [Internet]. 2021 [cited 2021 Feb 26]. Available from: https://ka-mis.org/kamisLoginPage.html.
89. CARE India. Kala-Azar Elimination Programme: Kala-Azar Management Information System (KAMIS) [Internet]. Patna, India; 2019. Available from: https://www.careindia.org/bihar/pdf/case_studies/Kala_Azar_Management_Information_System.pdf
90. Chowdhury R, Chowdhury V, Faria S, Islam S, Maheswary N, Akhter S, et al. Indoor residual spraying for kala-azar vector control in Bangladesh: A continuing challenge. PLoS Negl Trop Dis. 2018; 12(10): e0006846.
91. Mandal R, Kumar V, Kesari S, Das P. Assessing the combined effects of household type and insecticide effectiveness for kala-azar vector control using indoor residual spraying: a case study from North Bihar, India. Parasit Vectors. 2019; 12(409): DOI: https://doi.org/10.1186/s13071-091-3670-x.
92. Deb R, Singh RP, Mishra PK, Hitchins L, Reid E, Barwa AM, et al. Impact of IRS: Four-years of entomological surveillance of the Indian Visceral Leishmaniasis elimination programme. PLoS Negl Trop Dis. 2021; 15(8): e0009101.
93. Coleman M, Foster GM, Deb R, Singh RP, Ismail HM, Shivam P, et al. DDT-based indoor residual spraying suboptimal for visceral leishmaniasis elimination in India. Proc Natl Acad Sci U S A. 2015; 112(28): 8573–8578.
94. Hirve S, Kroeger A, Matlashewski G, Mondal D, Banjara M, Das P, et al. Towards elimination of visceral leishmaniasis in the Indian subcontinent—Translating research to practice to public health. PLoS Negl Trop Dis. 2017; 11(10): e0005889.
95. Poché DM, Garlapati RB, Mukherjee S, Torres-Poché Z, Hasker E, Rahman T, et al. Bionomics of *Phlebotomus argentipes* in villages in Bihar, India with insights into efficacy of IRS-based control measures. PLoS Negl Trop Dis. 2018; 12(1): e0006168.
96. Jain K, Jain NK. Vaccines for visceral leishmaniasis: A review. J Immunol Methhods. 2015; 422(1): 1–12.
97. Moafi M, Rezvan H, Sherkat R, Taleban R. Leishmania vaccines entered in clinical trials: A review of literature. Int J Prev Med. 2019; 10(95): DOI: 10.4103/ijpvm.IJPVM_116_18.
98. Lage DP, Ribeiro PAF, Dias DS, Mendonca D, Ramos F, Carvalho L, et al. A candidate vaccine for human visceral leishmaniasis based on a specific T cell epitope-containing chhimeric progein protects mice against Leishmania infantum infection. Nat Partn Journals Vaccines. 2020; 5(75): DOI: https://doi.org/10.1038/s41541-020-00224-0.
99. Alvar J, den Boer M, Jain S, Pandey D, Salunke S. Independent assessment of the Kala-Azar elimination programme, India [Internet]. Geneva; 2020. Available from: https://cdn.who.int/media/docs/default-source/searo/evaluation-reports/independent-assessment-of-kala-azar-elimination-programme-in-india.pdf?sfvrsn=fa0d8baa_2.
100. Singh OP, Hasker E, Boelaert M, Sundar S. Elimination of visceral leishmaniasis on

the Indian Subcontinent: Critical knowledege gaps to be answered to get us there. Lancet Infect Dis. 2016; 16(12): e304-e309.
101. Molia S, Saillard J, Dellagi K, Cliquet F, Bart J-M, Rotureau B, et al. Practices in research, surveillance, and control of neglected tropical diseases by One Health approaches: A survey targeting scientists from French-speaking countries. PLoS Negl Trop Dis. 2021; 15(3): e0009246.
102. Mastin AJ, Bosch F, Gottwald TR, Chavez V, Parnell SR. A method of determining where to target surveillance efforts in heterogeneous epidemiological systems. PLOS Comput Biol. 2017; 13(8): e1005712.
103. Dikid T, Jain SK, Sharma A, Kumar A, Narain JP. Emerging and re-emerging infections in India: An overview. Indian J Med Res. 2013; 138(1): 19-31.
104. Nsubuga P, White M, Thacker S, Anderson M, Blount S, Broome C, et al. Public health surveillance: A tool for targeting and monitoring interventions. In: Jamison D, Breman J, Measham A, editors. Disease Control Priorities in Developing Countries. 2nd Editio. Washington DC: Oxford University Press; 2006.
105. Longbottom J, Wamboga C, Bessell PR, Torr SJ, Stanton MC. Optimising passive surveillance of a neglected tropical disease in the era of elimination: A modelling study. PLoS Negl Trop Dis. 2021; 15(3): e0008599.
106. Tajaldin B, Almilaji K, Langton P, Sparrow A. Defining Polio: Closing the gap in global surveillance. Ann Glob Heal. 2015; 81(3): 386-395.
107. Larson HJ, Ghinai I. Lessons from polio eradication. Nature. 2011; 473(1): 446-447.
108. Rao PN, Suneetha S. Current situation of Leprosy in India and its future implications. Indian Dermatol Online J. 2018; 9(2): 83-89.
109. Deb RM, Stanton MC, Foster GM, Gupta RKD, Roy N, Das P, et al. Visceral leishmaniasis cyclical trends in Bihar, India--Implications for the elimination programme. Gates Open Res. 2018; 2(10): DOI: 10.12688/gatesopenres.12793.1.
110. Fitzpatrick A, Al-Kobaisi NSMS, Maya J, Chung Y, Duhan S, Elbegdorj E, et al. Sustaining visceral leishmaniasis elimination in Bangladesh--Could a policy brief help? PLoS Negl Trop Dis. 2017; 11(12): e0006081.
111. Le Rutte EA, Coffeng LE, Munoz J, de Vlas SJ. Modelling the impact of COVID-19-related programme interruptions on visceral leishmaniasis in India. Trans R Soc Trop Med Hyg. 2021;115 (3): 229–235.
112. Toor J, Adams ER, Aliee M, Amoah B, Anderson RM, et al. Predicted impact of COVID-19 on Neglected Tropical Disease Programs and the Opportunity for Innovation. Clin Infect Dis. 2020; 72(8): 1463–1466.
113. Carvalho SFG, Vieira TM, Moura AP, Andrade MPV, et al. Should an intersection between visceral leishmaniasis endemicity and the COVID-19 pandemic be considered? Med Hypotheses. 2020; 144(1): DOI: 10.1016/j.mehy.2020.110289.
114. Tambo E, Ai L, Zhou X, Chen J, Hu W, Bergquist R, et al. Surveillance-response systems: the key to elimination of tropical diseases. Infect Dis Poverty. 2014; 3(17): DOI: https://doi.org/10.1186/2049-9957-3-17.
115. World Health Organization. Communicable disease surveillance and response systems: A guide to monitoring and evaluating [Internet]. Geneva; 2006. Available from: https://www.who.int/csr/resources/publications/surveillance/WHO_CDS_EPR_LYO_2006_2.pdf.
116. World Health Organization. Making disease surveillance work: Training for mid-level managers [Internet]. Geneva; 2008. Available from: https://apps.who.int/iris/handle/10665/337067.
117. Bindroo J, Priyamvada K, Chapman LAC, Mahapatra T, Sinha B, Banerjee I, et al. Optimizing village-level targeting of active case detection to support visceral

leishmaniasis elimination in India. Front Cell Infect Microbiol. 2021; 11(1): DOI: https://doi.org/10.3389/fcimb.2021.648847.
118. Dubey P, Das A, Priyamvada K, Bindroo J, Mahapatra T, Mishra P, et al. Development and evaluation of active case detection methods to support visceral leishmaniasis elimination in India. Front Cell Infect Microbiol. Development and evaluation of active case detection methods to support visceral leishmaniasis elimination in India. 2021; 11(1): DOI: 10.3389/fcimb.2021/648903.
119. Singh SP, Hirve S, Huda MM, Banjara MR, Kumar N, Mondal D, et al. Options for Active Case Detection of Visceral Leishmaniasis in Endemic Districts of India, Nepal and Bangladesh, Comparing Yield, Feasibility and Costs. PLoS Negl Trop Dis. 2011; 5(2): e960.
120. Hirve S, Singh SP, Kumar N, Banjara MR, Das P, Sundar S, et al. Effectiveness and Feasibility of Active and Passive Case Detection in the Visceral. Am J Trop Med Hyg. 2010; 83(3): 507–511.
121. Huda MM, Hirve S, Siddiqui NA, Malaviya P, Banjara M, Das P, et al. Active case detection in national visceral leishmaniasis elimination programs in Bangladesh, India, and Nepal: Feasibility, performance and costs. BMC Public Health. 2012; 12(1): DOI: https://doi.org/10.1186/1471-2458-12-1001.
122. Das VNR, Pandey RN, Pandey K, Singh V, Kumar V, Matlashewski G, et al. Impact of ASHA training on active case detection of visceral leishmaniasis in Bihar, India. PLoS Negl Trop Dis. 2014; 8(5): e2774.
123. Das VNR, Pandey RN, Kumar V, Pandey K, Siddiqui N, Verma R, et al. Repeated training of accredited social health activists (ASHAs) for improved detection of visceral leishmaniasis cases in Bihar, India. Pathog Glob Health. 2016; 110(1): 33-35.
124. Lussier M-T, Richard C, Bennett T-L, Williamson T, Nagpurkar A. Surveillance or research: what's in a name? Sentin Eye. 2012; 58(1): 117.
125. Kumar A, Saurabh S, Jamil S, Kumar V. Intensely clustered outbreak of visceral leishmaniasis (kala-azar) in a setting of seasonal migration in a village of Bihar, India. BMC Infect Dis. 2020; 20(10): DOI: https//doi.org/10.1186/s12879-019-4719-3.
126. Bulstra CA, Le Rutte EA, Malaviya P, Hasker EC, Coffeng LE, Picado A, et al. Visceral leishmaniasis: Spatiotemporal heterogeneity and drivers underlying the hotspots in Muzaffarpur, Bihar, India. PLoS Negl Trop Dis. 2018; 12(12): e0006888.
127. Priyamvada K, Bindroo J, Sharma MP, Chapman LAC, Dubey P, Mahapatra T, et al. Visceral leishmaniasis outbreaks in Bihar: community-level investigations in the context of elimination of kala-azar as a public health problem. Parasit Vectors. 2021; 14(52): DOI: https://doi.org/10.1186/s13071-020-04551-y.
128. Fronterre C, Amoah B, Giorgi E, Stanton MC, Diggle PJ. Design and analysis of elimination surveys for neglected tropical diseases. J Infect Dis. 2020; 221(5): 554–560.
129. Zhou X, Yap P, Tanner M, Bergquist R, Utzinger J, Zhou X-N. Surveillance and response systems for elimination of tropical diseases: Summary of a thematic series in Infectious Diseases of Poverty. Infect Dis Poverty. 2016; 5(49): DOI: 10.1186/s40249-016-0144-7.
130. Adam D. Special report: The simulations driving the world's response to COVID-19. Nature. 2020; 580(1): 316–318.
131. Becker AD, Grantz KH, Hedge ST, Berube S, Cummings DAT, Wesolowski A. Development and dissemination of infectious disease dynamic transmission models during the COVID-19 pandemic: what can we learn from other pathogens and how can we move forward? Lancet Digit Heal. 2021; 3(1): e41-e50.
132. Jia Z, Lu Z. Modelling COVID-19 transmission: from data to intervention. Lancet

Infect Dis. 2020; 20(7): 757-758.
133. Siettos CI, Russo L. Mathematical modeling of infectious disease dynamics. Virulence. 2013; 4(4): 295-306.
134. NTD Modelling Consortium. Insights from mathematical modelling and quantitative analysis on the proposed WHO 2030 targets for visceral leishmaniasis on the Indian subcontinent. Gates Open Research; 2020.
135. Bill and Melinda Gates Foundation. Foundation for Research in Health Systems Grant [Internet]. Bengaluru, Karnataka; 2019. Available from: https://www.gatesfoundation.org/How-We-Work/Quick-Links/Grants-Database/Grants/2019/11/INV-003883.
136. Bill and Melinda Gates Foundation. Global Health Strategies Grant [Internet]. New York, NY; 2019. Available from: https://www.gatesfoundation.org/How-We-Work/Quick-Links/Grants-Database/Grants/2019/11/INV-003883.
137. Hirve S, Boelaert M, Matlashewski G, Mondal D, Arana B, Kroeger A, et al. Transmission Dynamics of Visceral Leishmaniasis in the Indian Subcontinent – A Systematic Literature Review. PLoS Negl Trop Dis. 2016; 10(8): e0004896.
138. Das VNR, Pandey RN, Siddiqui NA, Chapman LAC, Kumar V, Pandey K, et al. Longitudinal study of transmission in households with visceral leishmaniasis, asymptomatic infections and PKDL in highly endemic villages in Bihar, India. PLoS Negl Trop Dis. 2016; 10(12): e0005196.
139. Chapman LAC, Jewell CP, Spencer SEF, Pellis L, Datta S, Chowdhury R, et al. The role of case proximity in transmission of visceral leishmaniasis in a highly endemic village in Bangladesh. PLoS Negl Trop Dis. 2018; 12(10): e0006453.
140. Chapman LAC, Morgan ALK, Adams ER, Bern C, Medley GF, Hollingsworth TD. Age trends in asymptomatic and symptomatic Leishmania donovani infection in the Indian subcontinent : A review and analysis of data from diagnostic and epidemiological studies. PLoS Negl Trop Dis. 2018; 12(12): e0006803.
141. Chapman LAC, Spencer SEF, Pollington TM, Jewell CP, Mondal D, Cameron M, et al. Inferring transmission trees to guide targeting of interventions against visceral leishmaniasis and post – kala-azar dermal leishmaniasis. Proc Natl Acad Sci U S A. 2020; 117(41): 25742-25750.
142. Le Rutte EA, Chapman LAC, Coffeng LE, Jervis S, Hasker EC, Dwivedi S, et al. Elimination of visceral leishmaniasis in the Indian subcontinent: a comparison of predictions from three transmission models. Epidemics. 2017;18 (1): 67–80.
143. Stauch A, Duerr H-P, Dujardin J-C, Vanaerschot M, Sundar S, Eichner M. Treatment of Visceral Leishmaniasis : Model-Based Analyses on the Spread of Antimony-Resistant L . donovani in Bihar , India. PLoS Negl Trop Dis. 2015; 6(12): e1973.
144. Stauch A, Duerr H-P, Picado A, Ostyn B, Sundar S, Rijal S, et al. Model-Based Investigations of Different Vector-Related Intervention Strategies to Eliminate Visceral Leishmaniasis on the Indian Subcontinent. PLoS Negl Trop Dis. 2014; 8(4): e2810.
145. Stauch A, Sarkar RR, Picado A, Ostyn B, Sundar S, Rijal S, et al. Visceral Leishmaniasis in the Indian Subcontinent: Modelling Epidemiology and Control. PLoS Negl Trop Dis. 2011; 5(11): e1405.
146. Rock KS, Le Rutte EA, de Vlas SJ, Adams ER, Medley GF, Hollingsworth TD. Uniting mathematics and biology for control of visceral leishmaniasis. Cell Press. 2015; 31(6): 251-259.
147. Rock KS, Medley GF, Quinnell RJ, Courtenay O. Progress in the Mathematical Modelling of Visceral Leishmaniasis. Adv Parasitol. 2016; 94(1): 49–131.
148. Nightingale ES, Chapman LAC, Srikantiah S, Subramanian S, Jambulingam P,

Bracher J, et al. A spatio-temporal approach to short-term prediction of visceral leishmaniasis diagnoses in India. PLoS Negl Trop Dis. 2020; 14(7): e0008422.
149. Medley GF, Hollingsworth TD, Olliaro PL, Adams ER. Health-seeking behaviour, diagnostics and transmission dynamics in the control of visceral leishmaniasis in the Indian subcontinent. Nature. 2015; 528(7580): 102–108.
150. Le Rutte EA, Chapman LAC, Coffeng LE, Ruiz-postigo JR, Olliaro PL, Adams ER, et al. Policy Recommendations From Transmission Modeling for the Elimination of Visceral Leishmaniasis in the Indian Subcontinent. Clin Infect Dis. 2018; 66(4): 301–308.
151. Olliaro PL, Shamsuzzaman TAKM, Marasini B, Dhariwal AC, Be-Nazir A, Mondal D. Investments in Research and Surveillance Are Needed to Go Beyond Elimination and Stop Transmission of Leishmania in the Indian Subcontinent. PLoS Negl Trop Dis. 2017; 11(1): e0005190.
152. Nature. Developing infectious disease surveillance systems. Nat Commun [Internet]. 2020; 11(4962). Available from: https://www.nature.com/articles/s41467-020-18798-7.
153. Krentel A, Gyapong M, Ogundahunsi O, Amuyunzu-Nyamongo M, McFarland D. Ensuring no one is left behind: Urgent action required to address implementation challenges for NTD control and elimination. PLoS Negl Trop Dis. 2018; 12(6): e0006426.
154. Reidpath DD, Allotey P, Pokhrel S. Social sciences research in neglected tropical diseases 2: A bibliographic analysis. Heal Res Policy Syst. 2011; 9(1): DOI: https://doi.org/10.1186/1478-4505-9-1.
155. Drummond M, Sculpher M, Claxton K, Stoddart G, Torrance G. Methods for the Economic Evaluation of Health Care Programmes. Fourth Edi. Oxford, UK: Oxford University Press; 2015.
156. Parker M, Allen T. De-politicizing parasites: Reflections on attempts to control the control of neglected tropical diseases. Med Anthropol. 2014; 33(3): 223-239.
157. Engels D, Zhou X-N. Neglected tropical diseases: an effective global response to local poverty-related disease priorities. Infect Dis Poverty. 2020; 9(10): DOI: 10.1186/s40249-020-0630-9.
158. Pastrana N, Beran D, Sommerville C, Heller O, Correia JC, Suggs LS. The process of building the priority of neglected tropical diseases: A global policy analysis. PLoS Negl Trop Dis. 2020; 14(8): e0008498.
159. Kaiser Family Foundation Global Health Policy. The U.S. Government and global neglected tropical disease efforts [Internet]. 2020. Available from: https://www.kff.org/global-health-policy/fact-sheet/the-u-s-government-and-global-neglected-tropical-diseases/.
160. Wainwright E, Evans D, Rotondo L, Pou B, Yevstigneyeva V, Zoerhoff KL, et al. The elimination of neglected tropical diseases: A case study exemplifying how foreign assistance funding can be catalytic in reducing the burden of major global health conditions. Clin Infect Dis. 2020; 70(5): 958-964.
161. Fitzpatrick C, Nwankwo U, Lenk E, de Vlas S, Bundy D. Chapter 17: An investment case for ending Neglected Tropical Diseases. In: Holmes K, Bertozzi S, Bloom B, editors. Major Infectious Diseases. Third Edit. Washington DC; 2017.
162. Ortu G, Williams O. Neglected tropical diseases: exploring long term practical approaches to achieve sustainable disease elimination and beyond. Infect Dis Poverty. 2017; 6(1): 147.
163. Turner HC, Toor J, Hollingsworth TD, Anderson RM. Economic evaluations of mass drug administration: The importance of economies of scale and scope. Clin Infect Dis.

2018; 66(8): 1298-1303.
164. Gedge LM, Bettis AA, Bradley MH, Hollingsworth T, Turner H. Economic evaluations of lymphatic filariasis interventions: A systematic review and research needs. Parasit Vectors. 2018; 11(75): DOI: https://doi.org/10.1186/s13071-018-2616-z.
165. Lammie PJ, Miss DM, Goodhew EB, Hamlin K, Krolewiecki A, West SK, et al. Development of a new platform for neglected tropical disease surveillance. Int J Parasitol. 2012; 42(9): 797-800.
166. Fitzpatrick C, Fleming FM, Madin-Warburton M, Schneider T, Meheus F, Asiedu K, et al. Benchmarking the cost per person of mass treatment for selected neglected tropical diseases: An approach based on literature review and meta-regression with web-based software application. PLoS Negl Trop Dis. 2016; 10(12): e0005037.
167. Leslie J, Garba A, Boubacar K, Yaye Y, Sebongou H, Barkire A, et al. Neglected tropical diseases: comparison of the costs of integrated and vertical preventive chemotherapy treatment in Niger. Int Health. 2013; 5(1): 78-84.
168. Stelmach R, Flueckiger R, Shutt J, Davide-Smith M, Solomon A, Rotondo L, et al. The costs of monitoring trachoma elimination: Impact, surveillance, and trachomatus trichiasis (TT)-only surveys. PLoS Negl Trop Dis. 2019; 13(9): e0007605.
169. Turner HC, Truscott JE, Fleming FM, Hollingsworth TD, Brooker SJ, Anderson RM. Cost-effectiveness of scaling up mass drug administration for the control of soil-transmitted helminths: a comparison of cost function and constant cost analyses. Lancet Infect Dis. 2016; 16(7): 838-846.
170. Lenk EJ, Redekop WK, Luyendijk M, Fitzpatrick C, Niessen L, Stolk WA, et al. Socioeconomic benefit to individuals of achieving 2020 targets for four neglected tropical diseases controlled/eliminated bby innovative and intensified disease management: Human African trypanosomiasis, leprosy, visceral leishmaniasis, Chagas disease. PLoS Negl Trop Dis. 2018; 12(3): e0006250.
171. Conteh L, Engels T, Molyneux DH. Socioeconomic aspects of neglected tropical diseases. Lancet. 2010; 375(1): 239-247.
172. Woode ME, Khan JAM, Thomson R, Niessen LW, The Countdown Consortium. Equity and efficiency in the scaled-up implementation of integrated neglected tropical disease control: The health economics protocol of the COUNTDOWN multicountry observational study in Ghana, Cameroon and Liberia. BMJ Open. 2018; 8(1).
173. Marchal B, Van Dormael M, Pirard M, Cavalli A, Kegels G, Polman K. Negelcted tropical disease (NTD) control in health systems: The interface between programmes and general health services. Acta Trop. 2011; 120(1): 177–185.
174. Buyon L, Slaven R, Emerson P, King J, Debrah O, Aboe A, et al. Achieving the endgame: Integrated NTD case searches. PLoS Negl Trop Dis. 2018; 12(12): e0006623.
175. Maude RJ, Lubell Y, Socheat D, Yeung S, Saralamba S, Pongtavornpinyo P, et al. The role of mathematical modelling in guiding the science and economics of malaria elimination. Int Health. 2010; 2(4): 239-246.
176. National Academies of Science, Engineering, and Mathematics. The economics and modeling of emerging infectious diseases and biological risks. In: Understanding the Economics of Microbial Threats: Proceedings of a Workshop. 1st Editio. Washington DC: National Academies of Science, Engineering, and Mathematics; 2018.

CHAPTER 3. *LITERATURE REVIEW I:* HOW CAN ECONOMIC EVALUATIONS CONTRIBUTE TO SURVIELLANCE AND PRIORITY SETTING DURING DISEASE ELIMINATION?

This chapter aims to outline theories and literature surrounding economic evaluations of disease surveillance and elimination programmes to support the design, methods, and gaps in knowledge addressed in paper R1 (Chapter 4). A brief overview of core methods and guidelines for economic evaluation in healthcare is first presented. Literature is then reviewed to outline facets of elimination and surveillance programmes that are amenable to economic evaluation, with a focus on addressing heterogeneity, programme integration, and long-term resource requirements. Lastly, an overview of economic evaluations in India's VL elimination programme is outlined, followed by policy-relevant gaps in knowledge.

3.1 Economic evaluation in healthcare: methods and guidelines

Economic evaluation is a research discipline used to assess resources that are often scarce—people, time, facilities, equipment, knowledge, and the impact of difference courses of action—to inform alternatives, perspectives, and accountability for decision making [1]. In healthcare, it can inform policy and programme design by comparing interventions in terms of their costs and consequences, and can be achieved by considering different contexts, outputs, and techniques for analysis [1]. From the perspective of individual recipients of healthcare, healthcare providers, or society generally, economic evaluations are carried out through various methods and measurements depending on the intended application [1–6].

Methods of analysis

Methods of evaluation are determined by assessing the appropriateness to the intended user, characteristics of the intervention, and relative generalisability, transferability, and comparability of measurements [7]. Cost analysis is an approach to estimate the total cost of implementing a programme or intervention, and is useful to decision makers for budgeting, performance monitoring, and resource allocation [8]. Although both costs and outcomes are assessed, cost analyses are often not considered true economic evaluations as they do not directly compare relative consequences to relative costs [1]. The most common method of economic evaluation is cost-effectiveness analysis, which compares costs of interventions against their adverse and beneficial health consequences as measured by a natural unit, such as cases averted [9]. Cost-utility analysis is a subset of cost-effectiveness analysis where outcomes are presented as utilities, comparing costs to changes in quality and length of life, usually measured by quality-adjusted life years (QALYs) gained or disability-adjusted life years (DALYs) averted. These generic health outcomes allow for comparison of interventions across health conditions [5]. Cost-benefit analysis aims to maximise welfare,

rather than health effects, by comparing costs and health outcomes both presented in monetary terms. This allows for comparisons across broader outcomes such as education or infrastructure investments [4].

Measurements for analysis

The average cost of an intervention, service, or output is expressed as a *unit cost,* where specific terminology is important to define both units and costs. Units are generally the outputs of health services and might refer to interventions, direct or supporting services, activities, or resources [7]. A health outcome should be generalisable, appropriate for the decision problem, and capture positive and negative effects [10]. Common measures to assess quality and quantity of life are DALYs averted or QALYs gained, although other monetary, utility, or interventions measures can be used [11]. Non-disease specific health outcomes encompassed by DALYs and QALYs are encouraged to give decision makers the opportunity to compare trade-offs between competing investments [10].

Costs can be defined in terms of financial and economic, fixed and variable, and incremental and marginal [7]. Financial costs characterise resources paid for and those planned to be spent, usually from the perspective of a specific payer, programme, or organisation. These can generally be found in the providers' accounts. Economic costs capture the full value of resources including estimating a monetary value for opportunity foregone of donated goods, volunteer time, or otherwise where no market prices are available. Fixed costs are inputs that stay constant as the level of service provision increases, whereas variable costs change as the volume of service increases. Average cost functions reflect both fixed and variable costs and are used to describe how unit costs vary as the level of service increases. Marginal cost is the cost of producing one additional unit of output as service levels increase, whereas

incremental cost is the difference in cost between two or more interventions or programmes and can be used to compare the changes of service scale.

Methods of costing can be distinguished between *top-down* and *bottom-up*, which are sometimes interchangeably referred to as *gross-* or *micro-costing,* respectively. Micro-costing includes granular and disaggregated inputs by the activity or patient level, such as counting the quantity of resources used and multiplying by their respective prices, whereas gross-costing characterises overall programme costs and expenditures from the service level [7]. Both top-down and bottom-up methods can be used in tandem to provide comprehensive estimates of interventions and services. Evaluations must be of sufficient duration, or time horizon, to capture all relevant costs and effects, and consider appropriately discounted costs and effects to characterise present values. In reporting the methodology behind economic evaluations, transparency is paramount and must include the uncertainty associated with both internal and external validity [12].

Guidelines and frameworks

Guidelines for economic evaluation have become essential for promoting quality standards across diseases, settings, methods of analysis, and transparent reporting, where the WHO and UK National Institute for Health Care Excellence (NICE) provide comprehensive and open-access resources to support priority setting [13–16]. To encourage the production of quality economic evaluations for low- and middle-income countries (LMICs), BMGF commissioned a reference case (Gates-RC) in 2013 that outlines a systematic approach for standardised metrics and methods in countries with both technical and political constrains [10, 17, 18]. As of 2016, over 230 economic evaluations were published annually specific to LMICs [19].

3.2 Economic evaluation in elimination programmes

As diseases approach elimination and new cases become more difficult to identify, the resources and investment needed for surveillance can increase significantly per outcome achieved [20]. It may be for this reason that many economic analyses produced for LMICs targeting disease elimination focus on the incentives and social benefits of achieving elimination rather than the costs and alternatives to reaching targets [21]. Evaluating the cost of intensifying activities to reach elimination is crucial to maintain political and financial commitments, especially as the investment required to sustain surveillance may dwindle against competing disease priorities [22].

Elimination and its benefits are conceptually simple, but strategising surveillance to achieve incidence targets reveals several time-driven operational challenges [23]. Evaluations to intensify surveillance are more often compared to health outcomes and behaviour change than the resources demanded for such activities, which can complicate implementation and long-term investment for elimination [24]. Surveillance-response activities are particularly difficult to design in heterogenous landscapes of incidence and must be informed by trade-offs between alternative approaches as measured by the cost of early case detection (through economics) and transmission dynamics of the pathogen (through epidemiology and modelling) [25, 26]. This is also true for evaluating trade-offs of investing in efficiency versus equity of scaling up interventions, as elimination often targets diseases that affect poor and vulnerable groups and may require greater resources to access hard-to-reach populations [27].

Although traditional economic evaluation encourages resources to be allocated efficiently, the decision-making process during disease elimination may revolve less around efficiency

and more around ensuring heterogeneity and equity are addressed [28]. There is increasing evidence that incorporating socio-demographics into dynamic transmission modelling is key for addressing both heterogeneity and equity of elimination activities [29–34]. The methodological approaches and reporting practices between modelling and economics are not always immediately synergistic, and early collaboration is required to agree on the comparability and availability of data, patterns of disease, intended and relevant outcomes, and concepts of equity [28]. Including decision makers in economic research is also essential, as many programmes in LMIC experience health system constrains on finances, capacity, and coordination that must be factored in to generate pragmatic recommendations [35].

3.3 Economic evaluation for surveillance during elimination

Surveillance systems typically employ six core activities: case detection, registration, reporting, confirmation, analysis, and feedback, which can be evaluated in terms of efficiency, effectiveness, and integration [36]. The aim of evaluating surveillance-response systems is to predict and contain disease outbreaks, identify high-risk populations, monitor impact and progress towards disease targets, and identify areas in which performance is poor so corrective measures can be taken [37]. Around the point of elimination, programmes and policies can be directly informed by costs and effectiveness of surveillance in terms of: 1) technical requirements, 2) strategy and service delivery, 3) enablers to reach and sustain a post-elimination agenda, and 4) opportunities for shared resources and programme integration [38, 39].

Technical requirements of surveillance

Tools and technology for surveillance refer broadly to databases and information sharing for case management, laboratory and field-based diagnostics, mobile and mapping devices for

disease tracking, vector control instruments, and medicines [40]. The use of these tools depends on human, financial, and political capacity to carry out surveillance-response procedures [41]. To deploy surveillance tools and capacity in a timely, targeted, and efficient manner, economic research is key to evaluating the effectiveness and completeness of operational activities [42].

Strategy and service delivery

Economic evaluation is also essential for substantiating methods of when, how, and to whom surveillance should be targeted to reduce sources of infection and improve case management [43]. Determining the scale and scope of surveillance requires an understanding of how passive-, sentinel-, and active- case detection activities are viable in terms of costs and outcomes over space and time [44, 45]. In this dimension of surveillance research, economic evaluations must be informed by, or compatible with, epidemiological and operational sciences that characterise disease transmission dynamics and implementation activities [43, 46, 47]. Addressing disease heterogeneity and the role of asymptomatic infections are also essential in evaluating the cost and likelihood of identifying cases through different surveillance methods [48, 49].

Enablers for long-term surveillance and the post-elimination agenda

A major challenge in economic evaluations for elimination programmes is determining the reliability and sustainability of resources given funding from both national and international levels. In malaria elimination, complexities of international aid and supranational priority setting influence the financial stability of programmes, but have not been studied extensively [50]. Economic evaluations are key to informing and guiding the action required for long-

term surveillance to reach and sustain post-elimination benchmarks, as well as mobilising the willingness and capacity of national governments to assume financial ownership [51, 52].

Shared resources and programme integration

Opportunities for programme integration are widely promoted across NTDs that employ similar surveillance strategies, especially those eligible for treatment through MDAs [53–56]. Programme integration can also be accomplished by synthesising different activities for the same disease, such as community-level surveillance and IRS for vector control [57, 58]. Integration challenges seen in NTD and malaria surveillance programmes include aligning definitions of suspected cases, clarifying roles, responsibilities, and training requirements for implementers, and synergising support of NGOs and other local sectors [59, 60]. Assessing the resource requirements and benefits of integration requires economic evaluation of programme management, implementation, and monitoring and evaluation [59]. As NTD programmes are promoted for national-level ownership, evaluating the financial requirements to transition and integrate surveillance activities into ministries of health is increasingly essential during the period of elimination [61–63].

3.4 Economic evaluation for VL in the ISC

Costing VL burden

Some economic evaluations have been conducted for VL on the ISC, the majority of which assess socio-economic burden on the individual or household level. A study in Nepal reported the majority of VL patients preferred to consult local faith healers or private services rather than public health facilities, which accounted for 75% of costs prior to receiving allopathic diagnosis and treatment [64]. This and another study also reported most patients sold assets, such as land and livestock, to cover costs of care [64, 65]. Although national

governments in the ISC provide VL treatment at no-cost, the considerable direct and indirect costs of delayed diagnosis often propel households deeper into poverty [66–68]. As it relates to inequity, a 2009 study found that 83% of households in communities with high VL incidence belonged to the two lowest quintiles of wealth distribution [69]. A decade later, patient costs of VL illness in India are decreasing due to shorter treatment regimens and better access to care. However, there remains a dearth of knowledge on current cost estimates to inform elimination strategies and priority setting [70].

Costing vector control activities

Vector control is a prioritised control activity for VL in India using IRS. A 2008 cost analysis found that VL ecological vector management (EVM) activities were not cost-effective at the household-level, but recommended the use of long-lasting insecticidal nets (LLIN) and IRS in various combinations according to geographical incidence [71]. However, the effectiveness of IRS coverage and insecticide quality continues to be questioned, where evaluating the costs and outcomes of IRS programming may provide insight into barriers to effective programme implementation [72–76]. There may be an opportunity to explore the effects of interrupted IRS activities in India due to COVID-19, which could inform future resource allocation, priority setting, and programme integration during elimination and post-elimination phases [77].

Costing case detection

ACD has been shown to contribute to early VL detection that facilitates prompt treatment and transmission declines in India [78–82]. House-to-house (blanket) case detection has historically yielded the highest number of previously unidentified VL cases, but literature on the costs and outcomes of ACD is limited to three studies conducted from 2009-2012 when

VL incidence and control activities differed substantially [79, 81]. Table 3-1 summarises the results of previous ACD cost analyses in India, converted to $USD in 2021, alongside estimated VL incidence at the time of evaluation. In each study, PCD was excluded as an integrated public health service in India.

Table 3-1. Previous cost analyses for ACD in India, reported in 2021 $USD alongside VL incidence during the year of publication.

STUDY	YEAR	ACD COST PER NEW VL CASE DETECTED (IN 2021 $USD)	NATIONAL VL INCIDENCE IN INDIA AT TIME OF STUDY (WHO)
SINGH ET AL.	2010	Blanket: $135 - $758 Camp: $25 - $797 Index case-based: $168 - $241 Incentive-based: $60 - $654	30,000
HIRVE ET AL.	2010	Blanket: $60 - $128	30,000
HUDA ET AL.	2012	Camp: $386	24,000

The costs of blanket and camp ACD approaches vary within and between each study, which could be a result of a number of factors including VL incidence levels, geographical distribution and population size, programme management and staffing, length of programme, and the diagnostic methods employed.

Complementary versus redundant case detection methods

PCD is a fundamental surveillance system for communicable diseases that is typically universally employed for data collection on routine health information [83]. Although PCD is an integrated healthcare reporting platform, analysis is often limited by data quality, timeliness, and uniformity between different institutions [83]. For diseases and conditions where surveillance must be met with timely response and interventions, ACD may be implemented in tandem to PCD as a complementary case detection method. Supplementing

PCD with ACD not only improves the likelihood of identifying cases and connecting individuals to treatment, but also bolsters timely and robust data collection for designing appropriate response activities [37].

There is potential for redundancy between different methods of ACD. For example, the four most common methods of ACD (blanket, camp, index case-based, and incentive-based) would not necessarily be implemented together, other than for: 1) a comparison study to document outcomes of different methods, or 2) a targeted or intensified approach for an at-risk population, geographical area, or time of year where/when cases and transmission are notably higher [84]. Although their costs would be additive, the opportunity for ACD methods to complement one another can be evaluated, especially for centralised diagnostic camps in the vicinity of more rigorous suspected case identification activities [85]. For diseases transitioning from control to EOT or EPHP, it may be prudent to regard multiple case detection methods as complementary, rather than redundant, across space and time as a means to identify the critical remaining cases [86].

3.5 Gaps in economic evaluation of VL surveillance in India

To reach and sustain elimination of VL as a public health problem in India, research is needed to substantiate the investment required and strategy behind long-term surveillance activities across a heterogeneous landscape of incidence. Economic evaluations are key to addressing several unknowns in VL surveillance as they relate to pillars of the WHO NTD framework for 2021-2030, including:

1) The projected cost and likelihood of reaching EPHP using current surveillance tools and capacity;

2) How surveillance activities can be effectively tailored to address heterogeneity and equity;
3) Opportunities and trade-offs of integrating surveillance into other disease programmes; and
4) The international- and national-level investments needed to reach elimination benchmarks, and if national ownership is feasible for long-term control and a post-elimination agenda.

Requisite to each of these unknowns is understanding the cost and outcomes of current surveillance activities, particularly in terms of comparing the investment required to identify one additional VL case. Incidence has decreased ten-fold since the three previous cost-analyses were published for VL ACD activities in India between 2010 and 2012 [87]. 2018 is the most recent year in which several case detection activities were carried out simultaneously, including PCD, index case-based ACD, and a combination of blanket and camp ACD. Evaluating the costs and outcomes of VL surveillance activities could provide policy-relevant information on their effects across different geographical incidence levels, mobilise further economic analyses on programme intensification and integration, and might also be applied to transmission modelling to comprehensively inform elimination targets and strategies. Figure 3-1 displays how these research questions connect to the three pillars of the WHO NTD framework for 2021-2030 and could inform both short- and long-term surveillance strategies for VL EPHP in India.

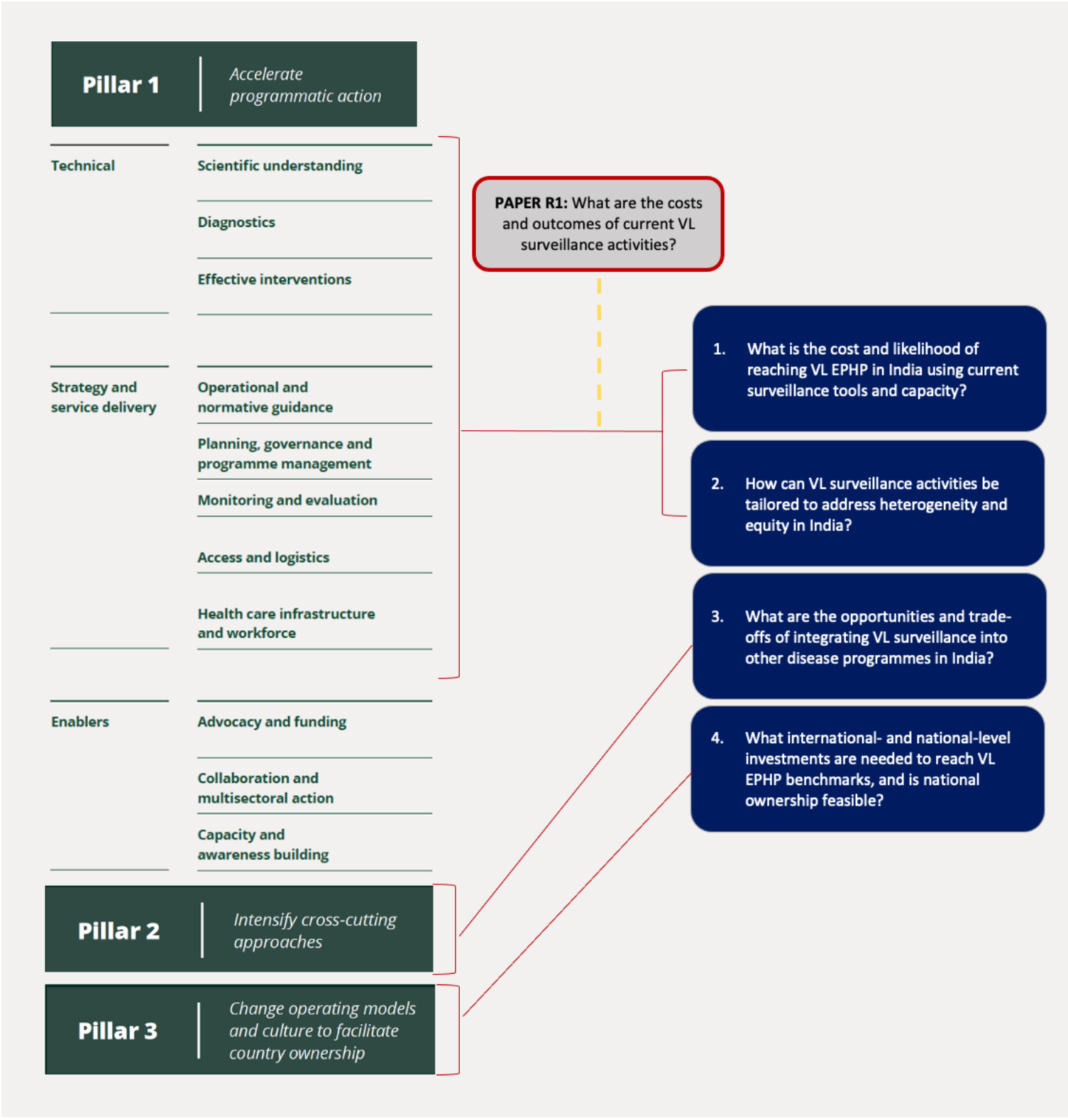


Figure 3-1. Gaps in economic evaluations for VL in India as they relate to surveillance activities and the three pillars of the WHO NTD framework for 2021-2030.

Informing surveillance and priority setting in the KEP

Action taken to manage, intervene, or monitor elimination activities is often coordinated at the state- and district levels, where surveillance data is also synthesised and reported [88, 89]. Although an evaluation of VL case detection activities may have the potential to inform district- and state-level operational activities, it would likely be most relevant to budgeting and resource allocation at the national level where KEP directives are generated. Assuming both human and financial resources are limited, identifying and comparing the cost of surveillance activities to find an additional VL case would be useful to prioritise activities in the short- and medium-term during this phase of elimination in India.

Priority setting requires rational, explicit, and transparent evidence to influence design and implementation of surveillance activities, which a singular study would not accomplish [90]. WHO promotes the iterative analysis of surveillance plans, metrics for programme evaluation, and characterisation of disease dynamics, where contributing partners likely require a platform for collaboration and priority setting. Such a platform does exist for VL in India; Chapters 5 and 6 explore this alongside the relationship between researchers, decision makers, and implementers.

3.6 Framing study design and methods for paper R1

Guidelines for costing surveillance

Paper R1 (Chapter 4) presents a cost analysis of VL ACD and PCD activities in India, with an aim to compare provider-level costs per VL case detected across varying levels of incidence. As disease- and context-specific costing resources for VL in India do not exist, the design of paper R1 relied on several methodological principles guided by the Global Health Cost Consortium Reference Case (GHCC-RC), WHO-CHOICE framework, and a toolkit for

evaluating the cost-effectiveness of syphilis screening [7, 10, 13, 91, 92]. Literature also guided methods to cost intervention activities in terms of the likelihood of reaching elimination benchmarks in a geographical setting by comparing the total cost, average cost per outcome (e.g., new cases detected), and cost of scaling up activities [93–95].

Paper R1 is submitted in published form under word-count limitations, therefore Appendix 2 includes a table and description of specific parameters of design, methods, and analysis as guided by GHCC-RC methodological principles. Appendix 3 details example data collection forms used for the cost analysis in paper R1.

Implications for thesis

As Chapter 2 identifies a specific KEP objective to intensify VL surveillance, this chapter explores how economic research can inform its design, implementation, and long-term requirements to reach and sustain elimination targets. For VL in India, the scale and scope of surveillance must be iteratively updated to encourage efficient use of resources as cases become more difficult to find. Although ACD is promoted as a surveillance strategy in India, the costs per additional VL case detected have not been evaluated in recent years or compared to PCD as an integrated public health service. This chapter identifies the relevance of evaluating and comparing costs and outcomes of VL surveillance activities across varying geographical incidence, which is carried out in paper R1 (Chapter 4). The applicability of economic evaluations to policy and other research disciplines is examined in both Chapter 5, a literature review on mathematical modelling, and Chapter 7, the discussion.

References

1. Drummond M, Sculpher M, Claxton K, Stoddart G, Torrance G. Introduction to economic evaluation. In: Methods for the Economic Evaluation of Health Care Programmes. Fourth Edi. Oxford, UK; 2015.
2. Robinson R. Costs and cost-minimisation analysis. BMJ. 1993; 307(6906): 726-728.
3. Robinson R. Cost-effectiveness analysis. BMJ. 1993; 307(6907): 793-795.
4. Robinson R. Cost-benefit analysis. BMJ. 1993; 307(6909): 924-926.
5. Robinson R. Cost-utility analysis. BMJ. 1993; 307(6908): 859-862.
6. Drummond M, McGuire A. Theoretical concepts in the economic evaluation of health hcare. In: Economic Evaluation in Health Care: Merging theory with practice. Oxford, UK: Oxford University Press; 2001.
7. Vassall A, Sweeney S, Kahn J, Gomez G, Bollinger L, Marseille E, et al. Global Health Cost Consortium Reference Case for Estimating the Costs of Global Health Services and Interventions [Internet]. London, UK; 2017. Available from: https://ghcosting.org/pages/standards/reference_case
8. Centers for Disease Control. POLARIS Economic Evaluation [Internet]. Atlanta; 2019. Available from: https://www.cdc.gov/policy/polaris/economics/index.html.
9. Levin H, McEwan P. Cost-Effectiveness Analysis. In: Cost-Effectiveness Analysis: Methods and Applications. Second Edi. Thousand Oaks, CA; 2001.
10. Claxton K, Revill P, Sculpher M, Wilkinson T, Cairns J, Briggs A. Methods for Economic Evaluation Project (MEEP): The Gates Reference Case [Internet]. Seattle, USA; 2013. Available from: https://www.idsihealth.org/wp-content/uploads/2015/01/MEEP-report.pdf.
11. Drummond M, Sculpher M, Claxton K, Stoddart G, Torrance G. Measuring and valuing effects: health gain. In: Methods for the Economic Evaluation of Health Care Programmes. Fourth Edi. Oxford, UK; 2015. p. 123–70.
12. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ. 2013; 346(1): DOI: https://doi.org/10.1136/bmj.f1049.
13. Edejer T, Baltussen R, Adam T, Hutubessy R, Acharya A, Evans D, et al. Making choices in health: WHO guide to cost-effectiveness analysis [Internet]. Geneva; 2003. Available from: https://www.who.int/choice/publications/p_2003_generalised_cea.pdf.
14. Wilkinson T, Chalkidou K. Improving the quality of economic evaluation in health in low- and middle-income countries: Where are we now? J Comp Eff Res. 2019; 8(13): DOI: https://doi.org/10.227/cer-2019-0119.
15. Rawlins M. National Institute for Clinical Excellence: NICE works. J R Soc Med. 2015; 108(6): 211-219.
16. NICE. Improving health and social care through evidence-based guidance [Internet]. National Institute for Health and Care Excellence. 2021 [cited 2021 Mar 11]. Available from: https://www.nice.org.uk/
17. Wilkinson T, Sculpher MJ, Claxton K, Revill P, Briggs A, Cairns JA, et al. The International Decision Support Initiative Reference Case for Economic Evaluation: An aid to thought. Value Heal. 2016; 19(1): 921-928.
18. iSDI and BMGF. Guide to Economic Analysis and Research (GEAR) [Internet]. Seattle, USA; 2021. Available from: http://www.gear4health.com/gear.
19. Pitt C, Goodman C, Hanson K. Economic evaluation in global perspective: A bibliometric analysis of the recent literature. Health Econ. 2016; 25(1): 9-28.
20. Fitzpatrick C, Sankara DP, Agua JF, Jonnalagedda L, Rumi F, Weiss A, et al. The cost-effectiveness of an eradication programme in the end game: Evidence from

guinea worm disease. PLoS Negl Trop Dis. 2017; 11(10): e0005922.
21. Sicuri E, Evans DB, Tediosi F. Can economic analysis contribute to disease elimination and eradication? A systematic review. PLoS One. 2015; 10(6): e0130603.
22. World Health Organization. Global Polio Eradication Initiative investment case 2019-2023 [Internet]. Geneva; 2019. Available from: https://polioeradication.org/wp-content/uploads/2019/08/Polio-InvestmentCase-Report-20190819.pdf.
23. Dowdle WR. The principles of disease elimination and eradication. Centers Dis Control Prev. 1999; 48(SU01): 22-25.
24. Hoomans T, Severens JL. Economic evaluation of implementation strategies in health care. Implement Sci. 2014; 9(168): DOI: https://doi.org/10.1186/s13012-014-0168-y.
25. Mastin AJ, van den Bosch F, van den Berg F, Parnell SR. Quantifying the hidden costs of imperfect detection for early detection surveillance. Philos Trans R Soc. 2019; 374(1776): https://doi.org/10.1098/rstb.2018.0261.
26. Epanchin-Niell RS, Haight RG, Berec L, Kean JM, Liebhold AM. Optimal surveillance and eradication of invasive species in heterogenous landscapes. Ecol Lett. 2012; 15(1): 803-812.
27. Mangham LJ, Hanson K. Scaling up in international health: what are the key issues? Health Policy Plan. 2010; 25(2): 85-96.
28. iSDI. Equity, economic evaluation, and disease transmission modelling [Internet]. London, UK; 2018. Available from: http://tb-mac.org/wp-content/uploads/2018/09/EquityTransmissionModelling_meetingMarch2018_final-report.pdf.
29. Klepac P, Funk S, Hollingsworth TD, Metcalk CJE, Hampson K. Six challenges in the eradication of infectious diseases. Epidemics. 2015; 10(1): 97–101.
30. Maude RJ, Lubell Y, Socheat D, Yeung S, Saralamba S, Pontavornpinyo W, et al. The role of mathematical modelling in guiding the science and economics of malaria elimination. Int Health. 2010; 2(4): 239-246.
31. Sterner RT, Smith GC. Modelling wildlife rabies: Transmission, economics, and conservation. Biol Conserv. 2006; 131(2): 163-179.
32. Turner HC, Bettis AA, Dunn JC, Whitton JM, Hollingsworth TD, Fleming FM, et al. Economic considerations for moving beyond the Kato-Katz technique for diagnosing intestinal parasites as we move towards elimination. Trends Parasitol. 2017; 33(6): 435-443.
33. Sutherland C, Yukich J, Coeree R, Tediosi F. A literature review of economic evaluations for a neglected tropical disease: Human African Trypanosomiasis ("Sleeping Sickness"). PLoS Negl Trop Dis. 2015; 9(2): e0003397.
34. Cookson R, Mirelman AJ, Griffin S, Asaria M, Dawkins B, Norheim OF, et al. Using cost-effectiveness analysis to address health equity concerns. Value Heal. 2017; 20(2): 206–12.
35. Pitt C, Vassall A, Teerawattananon Y, Griffiths UK, Guinness L, Walker D, et al. Foreward: Health economic evaluations in low- and middle-income countries: Methodological issues and challenges for priority setting. Health Econ. 2016; 25(1): 1-5.
36. McNabb SJN, Chungong S, Ruan M, Wuhib T, Nsubuga P, Alemu W, et al. Conceptual framework of public health surveillance and its application in health sector reform. BMC Public Health. 2002; 2(2): DOI: 10.1186/1471-2458-2-2.
37. World Health Organization. Making disease surveillance work: Training for mid-level managers [Internet]. Geneva; 2008. Available from: https://apps.who.int/iris/handle/10665/337067.
38. World Health Organization. Communicable disease surveillance and response systems:

Guide to monitoring and evaluating [Internet]. Geneva; 2006. Available from: https://www.who.int/csr/resources/publications/surveillance/WHO_CDS_EPR_LYO_2006_2.pdf.
39. World Health Organization. Evaluating the costs and benefits of national surveillance and response systems: Methodologies and options [Internet]. Geneva; 2005. Available from: http://apps.who.int/iris/bitstream/handle/10665/69335/WHO_CDS_EPR_LYO_2005_25_eng.pdf?sequence=1.
40. Hamilton JJ, Hopkins RS. Using technologies for data collection and management [Internet]. The CDC Field Epidemiology Manual. Atlanta; 2018. Available from: https://www.cdc.gov/eis/field-epi-manual/chapters/data-collection-management.html.
41. World Health Organization. Disease surveillance for malaria control [Internet]. Geneval; 2012. Available from: https://apps.who.int/iris/bitstream/handle/10665/44851/9789241503341_eng.pdf?sequence=1.
42. Hemingway J, Shretta R, Wells TNC, Bell D, Djimde AA, Achee N, et al. Tools and strategies for malaria control and elimination: What do we need to achieve a grand convergence in malaria? PLoS Biol. 2016; 14(3): e1002380.
43. Toor J, Coffeng LE, Hamley JID, Fronterre C, Prada JM, Castaño MS, et al. When, Who, and How to Sample: Designing Practical Surveillance for 7 Neglected Tropical Diseases as We Approach Elimination. J Infect Dis. 2020; 221(5): 499–502.
44. Marston L, Kelly GC , Hale E, Clements A, Hodge A, Jimenez-Soto E. Cost analysis of the development and implementation of a spatial decision support system for malaria elimination in Solomon Islands. Malar J. 2014; 13(325): DOI: https://doi.org/10.1186/1475-2875-13-325.
45. Stelmach R, Flueckiger R, Shutt J, Davide-Smith M, Solomon A, Rotondo L, et al. The costs of monitoring trachoma elimination: Impact, surveillance, and trachomatous trichiasis (TT)-only surveys. PLoS Negl Trop Dis. 2019; 13(9): e0007605.
46. Drake TL, Devine A, Yeung S, Day NPJ, White LJ, Lubell Y. Dynamic transmission economic evaluations of infectious disease interventions in low- and middle-income countries: A systematic literature review. Health Econ. 2016; 25(1): 124-139.
47. Pitman R, Fisman D, Zaric GS, Postma M, Kretzschmar M, Edmunds J, et al. Dynamic transmission modeling: A report of the ISPOR-SMDM Modeling Good Research Practices Task Force-5. Value Heal. 2012; 15(6): 712-721.
48. Sturrock HJW, Hsiang MS, Cohen JM, Smith DL, Greenhouse B, Bousema T, et al. Targeting asymptomatic malaria infections: Active surveillance in control and elimination. PLoS Med. 2013; 10(6): e1001467.
49. Stresman G, Sepulveda N, Fornace K, Grignard L, Mwesigwa J, Achan J. Association between the proportion of Plasmodium falciparum and Plasmodium vivax infections detected by passive surveillance and the magnitude of the asymptomatic reservoir in the community: A pooled analysis of paired health facility and community data. Lancet Infect Dis. 2020; 20(8): DOI: 10.1016/S1473-3099(20)30059-1.
50. Drake TL, Lubell Y. Malaria and economic evaluation methods: Challenges and opportunities. Appl Health Econ Health Policy. 2017; 15(3): 291-297.
51. Herida M, Dervaux B, Desenclos J-C. Economic evaluations of public health surveillance systems: A systematic review. Eur J Public Health. 2016; 26(4): 674-680.
52. Kim YE, Sicuri E, Tediosi F. Financial and economic costs of the elimination and eradication of onchocerciasis (River Blindness) in Africa. PLoS Negl Trop Dis. 2015; 9(9): e0004056.
53. Lammie PJ, Fenwich A, Utzinger J. A blueprint for success: integration of neglected

tropical disease control programmes. Trends Parasitol. 2006; 22(7): 313-321.
54. Solomon AW, Engels D, Bailey RL, Blake IM, Brooker S, Chen J-X, et al. A diagnostics platform for the integrated mapping, monitoring, and surveillance of neglected tropical diseases: rationale and target product profiles. PLoS Negl Trop Dis. 2012; 6(7): e1746.
55. Deribe K, Meribo K, Gebre T, Hailu A, Ali A, Aseffa A, et al. The burden of neglected tropical diseases in Ethiopia, and opportunities for integrated control and elimination. Parasit Vectors. 2012; 5(240): DOI: https://doi.org/10.1186/1756-3305-5-240.
56. Gedge LM, Bettis AA, Bradley MH, Hollingsworth TD, Turner H. Economic evaluations of lymphatic filariasis interventions: A systematic review and research needs. Parasit Vectors. 2018; 11(75): DOI: https://doi.org/10.1186/s13071-018-2616-z.
57. Banjara MR, Das ML, Gurung CK, Singh VK, Joshi AB, Matlashewski G, et al. Integrating case detection of visceral leishmaniasis and other febrile illness with vector control in the post-elimination phase in Nepal. Am J Trop Med Hyg. 2019; 100(1): 108-114.
58. Sutherland CS, Stone CM, Steinmann P, Tanner M, Tediosi F. Seeing beyond 2020: An economic evaluation of contemporary and emerging strategies for elimination of Trypanosoma brucei gambiense. Lancet Glob Heal. 2016; 5(1): e69-e79.
59. Tristao I, Cali J. It can be done: An integrated approach for controlling and eliminating neglected tropical diseases [Internet]. 2014. Available from: https://publications.iadb.org/publications/english/document/It-Can-Be-Done-An-Integrated-Approach-for-Controlling-and-Eliminating-Neglected-Tropical-Diseases.pdf.
60. Perry HN, McDonnell SM, Alemu W, Nsubuga P, Chungong S, Otten M, et al. Planning an integrated disease surveillance and response system: a matrix of skills and activities. BMC Med. 2007; 5(24): DOI: https://doi.org/10.1186/1741-7015-5-24.
61. Phalkey R, Shukla S, Shardul S, Ashtekar N, Valsa S, Awate P, et al. Assessment of the core and support functions of the Integrated Disease Surveillance system in Maharashtra, India. BMC Public Health. 2013; 13(575): DOI: 10.1186/1471-2458-13-575.
62. World Health Organization. Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021-2030 [Internet]. Geneva; 2020. Available from: file:///Users/nataliedial/Downloads/9789240010352-eng.pdf.
63. Standley C, Boyce MR, Klineberg A, Essix G, Katz R. Organization of oversight for integrated control of neglected tropical diseases within Ministries of Health. PLoS Negl Trop Dis. 2018; 12(11): e0006929.
64. Rijal S, Koirala S, Van der Stuyft P, Boelaert M. The economic burden of visceral leishmaniasis for households in Nepal. Trans R Soc Trop Med Hyg. 2006; 100(9): 838-841.
65. Okwor I, Uzonna J. Social and economic burden of human leishmaniasis. Am J Trop Med Hyg. 2016; 94(3): 489-493.
66. Boelaert M, Meheus F, Robays J, Lutumba P. Socio-economic aspects of neglected diseases: Sleeping sickness and visceral leishmaniasis. Ann Trop Med Parasitol. 2010; 104(7): 535-542.
67. Sarnoff R, Desai J, Desjeux P, Mittal A, Topno R, Siddiqui NA, et al. The economic impact of visceral leishmaniasis on rural households in one endemic district of Bihar, India. Trop Med Int Heal. 2010; 15(2): 42-49.
68. Alvar J, Yactayo S, Bern C. Leishmaniasis and poverty. Trends Parasitol. 2006; 22(12): 552-557.

69. Boelaert M, Meheus F, Sanchez A, Singh SP, Vanlerberghe V, Picado A, et al. The poorest of the poor: a poverty appraisal of households affected by visceral leishmaniasis in Bihar, India. Trop Med Int Heal. 2009; 14(6): 639-644.
70. Sunyoto T, Boelaert M, Meheus F. Understanding the economic impact of leishmaniasis on households in endemic countries: a systematic review. Expert Rev Anti Infect Ther. 2019; 17(1): 57-69.
71. Das M, Banjara M, Chowdhury R, Kumar V, Rijal S, Joshi A, et al. Visceral leishmaniasis on the Indian sub-continent: a multi-centre study of the costs of three interventions for the control of the sandfly vector, Phlebotomus argentipes. Ann Trop Med Parasitol. 2008; 102(8): 729-741.
72. Chowdhury R, Chowdhury V, Faria S, Islam S, Maheswary NP, Akhter S, et al. Indoor residual spraying for kala-azar vector control in Bangladesh: A continuing challenge. PLoS Negl Trop Dis. 2018; 12(10): e0006846.
73. Coleman M, Foster GM, Deb R, Singh RP, Ismail HM, Shivam P, et al. DDT-based indoor residual spraying suboptimal for visceral leishmaniasis elimination in India. Proc Natl Acad Sci U S A. 2015; 112(28): 8573–8578.
74. Le Rutte E, Coffeng L, Bontje D, Hasker E, Postigo J, Argaw D, et al. Feasibility of eliminating visceral leishmaniasis from the Indian subcontinent: explorations with a set of deterministic age-structured transmission models. Parasit Vectors. 2016; 9(24): DOI: 10.1186/s13071-061-1292-0.
75. Huda MM, Mondal D, Kumar V, Das P, Sharma SN, Das ML, et al. Toolkit for monitoring and evaluation of indoor residual spraying for visceral leishmaniasis control in the Indian Subcontinent: Application and results. J Trop Med. 2011; 2011(1): DOI: 10.1155/2011/876742.
76. Mandal R, Kumar V, Kesari S, Das P. Assessing the combined effects of household type and insecticide effectiveness for kala-azar vector control using indoor residual spraying: a case study from North Bihar, India. Parasit Vectors. 2019; 12(409): DOI: https://doi.org/10.1186/s13071-019-3670-x.
77. Le Rutte EA, Coffeng LE, Munoz J, de Vlas SJ. Modelling the impact of COVID-19-related programme interruptions on visceral leishmaniasis in India. Trans R Soc Trop Med Hyg. 2021; 115(3): 229–235.
78. Hirve S, Kroeger A, Matlashewski G, Mondal D, Banjara MR, Das P, et al. Towards elimination of visceral leishmaniasis in the Indian subcontinent—Translating research to practice to public health. PLoS Negl Trop Dis. 2017; 11(10): 1–25.
79. Huda MM, Hirve S, Siddiqui NA, Malaviya P, Banjara MR, Das P, et al. Active case detection in national visceral leishmaniasis elimination programs in Bangladesh, India, and Nepal: Feasibility, performance and costs. BMC Public Health. 2012; 12(1): DOI: hhttps://doi.org/10.1186/1471-2458-12-1001.
80. Khatun J, Huda MM, Hossain S, Presber W, Ghosh D, Kroeger A, et al. Accelerated Active Case Detection of Visceral Leishmaniasis Patients in Endemic Villages of Bangladesh. PLoS One. 2015; 9(8): DOI: https://doi.org/10.1371/journal.pone.0103678.
81. Hirve S, Singh SP, Kumar N, Banjara MR, Das P, Sundar S, et al. Effectiveness and Feasibility of Active and Passive Case Detection in the Visceral. Am J Trop Med Hyg. 2010; 83(3): 507–511.
82. Singh OP, Hasker E, Boelaert M, Sundar S. Elimination of visceral leishmaniasis on the Indian Subcontinent: critical knowledge gaps to be answered to get us there. Lancet Infect Dis. 2017; 16(12):e304-e309.
83. Nsubuga P, White M, Thacker S, Anderson M, Blount S, Broome C, et al. Public health surveillance: A tool for targeting and monitoring interventions. In: Jamison D,

Breman J, Measham A, editors. Disease Control Priorities in Developing Countries. 2nd Editio. Washington DC: Oxford University Press; 2006.
84. Aye S, Majumdar SS, Oo MM, Tripathy JP, Satyanarayana S, Kyaw NTT, et al. Evaluation of a tuberculosis active case finding project in peri-urban areas, Myanmar: 2014-2016. Int J Infect Dis. 2018; 70(1): 93–100.
85. Biermann O, Tran PB, Viney K, Caws M, Lonnroth K, Annerstedt K. Active case-finding policy development, implemetation and scale-up in high-burden countries: A mixed-methhods survey with National Tuberculosis Programme mangers and document review. PLoS One. 2020; 15(10): e0240696.
86. Dubey P, Das A, Priyamvada K, Bindroo J, Mahapatra T, Mishra PK, et al. Development and evaluation of active case detection methods to support visceral leishmaniasis elimination in India. Front Cell Infect Microbiol. 2021; 11(1): 648903.
87. World Health Organization. Number of cases of visceral leishmaniasis reported by country [Internet]. Geneva; 2021. Available from: https://apps.who.int/gho/data/node.main.NTDLEISHVNUM?lang=en
88. John TJ, Samuel R, Balraj V, John R. Disease surveillance at district level: a model for developing countries. Lancet. 1998; 352(9121): 58-61.
89. Chowdhury R, Mondal D, Chowdury V, Faria S, Alvar J, Nabi SG, et al. How far are we from visceral leishmaniasis elimination in Bangladesh? An assessment of epidemiological surveillance data. PLoS Negl Trop Dis. 2014; 8(8): e3020.
90. World Health Organization. Setting priorities in communicable disease surveillance [Internet]. Geneva; 2006. Available from: https://www.who.int/csr/resources/publications/surveillance/WHO_CDS_EPR_LYO_2006_3.pdf.
91. Terris-Prestholt F, Santos A, Sweeney S, Kumaranayake L. The Rapid Syphilis Test Toolkit. Implementation 1: Guidelines for Cost Effectiveness Analysis of Syphilis Screening Strategies [Internet]. London, UK; 2011. Available from: https://media.tghn.org/articles/IMPLEMENTATION_1.pdf
92. Calba C, Goutard FL, Hoinville L, Hendrikx P, Lindberg A, Saegerman C, et al. Surveillance systems evaluation: a systematic review of the existing approaches. BMC Public Health. 2015; 15(448): DOI: https://doi.org/10.1186/s12889-015-1791-5.
93. Terris-Prestholt F, Kumaranayake L, Obasi AIN, Cleophas-Mazige B, Makokhha M, Todd J, et al. From trial intervention to scale-up: Costs of an adolescent sexual health program in Mwanza, Tanzania. Sex Transm Dis. 2006; 33(10): S133-139.
94. Maccario R, Rouhani S, Drake T, Nagy A, Bamadio M, Diarra S, et al. Cost analysis of a school-based comprehensive malaria program in primary schools in Sikasso region, Mali. BMC Public Health. 2017; 17(572): DOI: https://doi.org/10.1186/s12889-017-4490-6.
95. Jo Y, Mirzoeva F, Chry M, Qin ZZ, Codlin A, Bobokhojaev O, et al. Standardized framework for evaluating costs of active case finding programs: An analysis of two programs in Cambodia and Tajikistan. PLoS One. 2020; 15(1): e0228216.

CHAPTER 4. *PAPER R1:* COSTS AND OUTCOMES OF ACTIVE AND PASSIVE CASE DETECTION FOR VISCERAL LEISHMANIASIS (KALA-AZAR) TO INFORM ELIMINATION STRATEGIES IN BIHAR, INDIA

The need for interdisciplinary research to substantiate the design, implementation, and longevity of VL surveillance in India is reviewed in Chapters 2 and 3. Economic research is particularly compelling alongside epidemiological and operational assessments and could provide policy-relevant information in a number of valuable ways—including evaluations of surveillance tools and capacity, scale and scope of activities, opportunities for integration, and resources required for long-term control measures. An apparent gap in knowledge exists surrounding the costs and outcomes of VL surveillance activities from the perspective of India's Ministry of Health.

This research paper presents a cost analysis of VL ACD and PCD activities in India's most VL-endemic state, Bihar, and compares the outcomes of each programme across district-level incidence. Two ACD methods are included: index case-based ACD, and a combination of blanket (house-to-house) and diagnostic camp ACD, which were last implemented in tandem during 2018. Paper R1 fulfils the methodological Objective 2 outlined in Chapter 1: to determine programme and unit costs for detecting additional VL cases in India, to assess how costs and outcomes vary according to VL incidence, and to evaluate the costs of scaling up case detection activities. Implications to this thesis are discussed and presented following the reference list.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1605001	**Title**	Ms.
First Name(s)	Natalie		
Surname/Family Name	Dial		
Thesis Title	SCIENCE AND SURVEILLANCE IN THE VISCERAL LEISHMANIASIS ELIMINATION PROGRAMME IN INDIA		
Primary Supervisor	Graham Medley		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PLOS Neglected Tropical Diseases		
When was the work published?	03 February 2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	ND led conceptualisation, data curation, investigation, formal analysis, visualisation, original draft writing, review and editing.

SECTION E

Student Signature	[redacted]
Date	16 July 2021

Supervisor Signature	[redacted]
Date	29 July 2021

Costs and outcomes of active and passive case detection for visceral leishmaniasis (Kala-Azar) to inform elimination strategies in Bihar, India

Natalie J. Dial[1*], Graham F. Medley[1], Simon L. Croft[2], Tanmay Mahapatra[3], Khushbu Priyamvada[3], Bikas Sinha[3], Lucy Palmer[4], Fern Terris-Prestholt[1]

[1] Department of Global Health and Development, Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom

[2] Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

[3] CARE India Solutions for Sustainable Development, Patna, Bihar, India

[4] Mott MacDonald, London, United Kingdom

*natalie.dial@lshtm.ac.uk (ND)

Abstract

Background: Effective case identification strategies are fundamental to capturing the remaining visceral leishmaniasis (VL) cases in India. To inform government strategies to reach and sustain elimination benchmarks, this study presents costs of active- and passive-case detection (ACD and PCD) strategies used in India's most VL-endemic state, Bihar, with a focus on programme outcomes stratified by district-level incidence.

Methods: Expenditure analysis was complemented by onsite micro-costing to compare the cost of PCD in hospitals alongside index case-based ACD and a combination of blanket (house-to-house) and camp ACD from January to December 2018. From the provider's perspective, a cost analysis evaluated the overall programme cost of each activity, the cost per case detected, and the cost of scaling up ACD.

Results: During 2018, index case-based ACD, blanket and camp ACD, and PCD reported 1,497, 131, and 1,983 VL-positive cases at a unit cost of $522.81, $4,186.81, and $246.79, respectively. In high endemic districts, more VL cases were identified through PCD while in meso- and low-endemic districts more cases were identified through ACD. The cost of scaling up ACD to identify 3,000 additional cases ranged from $1.6-4 million, depending on the extent to which blanket and camp ACD was relied upon.

Conclusion: Cost per VL test conducted (rather than VL-positive case identified) may be a better metric estimating unit costs to scale up ACD in Bihar. As more VL cases were identified in meso-and low-endemic districts through ACD than PCD, health authorities in India should consider bolstering ACD in these areas. Blanket and camp ACD identified fewer cases at a higher unit cost than index case-based ACD. However, the value of detecting

additional VL cases early outweighs long-term costs for reaching and sustaining VL elimination benchmarks in India.

Author summary

Visceral leishmaniasis (VL) is targeted for elimination in India by 2020, where early identification and prompt treatment are essential measures for reaching and sustaining incidence benchmarks. Both active- and passive- case detection (ACD and PCD) strategies have been employed in recent years, and evaluating the cost and outputs of each is now important for sustaining funding and political momentum. This study presents overall and unit costs for PCD, index case-based ACD (where neighbours in the vicinity of a recent VL case are screened), and a combination of blanket and camp ACD (involving house-to-house case searching and weekly diagnostic camps) in Bihar, India during 2018. Results of this study indicate that a larger proportion of VL cases were found through PCD in high incidence districts, which may be related to increased interaction with ACD officers. ACD can be bolstered in meso- and low-incidence districts where educational exposure to VL is low and risk of resurgence is high. Although blanket and camp ACD unit costs were at least four times higher than index case-based ACD, the number of VL cases identified through this approach may warrant the investment to achieve VL elimination. Cost and outcomes of VL case finding approaches need to be continuously evaluated until elimination benchmarks are reached and integrated into sustained surveillance programmes.

Introduction

The Kala-Azar Elimination Programme (KEP)

Visceral leishmaniasis (also known as Kala-Azar) is a parasitic Neglected Tropical Disease (NTD) endemic in 83 countries worldwide, with reported global incidence just over 17,000 in 2018 [1]. Transmitted by the female phlebotomine sandfly, VL is characterised by prolonged fever, enlarged spleen and liver, anaemia, substantial weight loss, and a 95% fatality rate if left untreated [2]. International elimination efforts alongside increased availability of rapid diagnostic tests and improved treatment have contributed to a substantial decline in VL cases over the past decade, particularly in the Indian Subcontinent (ISC) [1,3]. Due to elusive transmission dynamics confounded by asymptomatic carriers and the sequela post-Kala-Azar dermal leishmaniasis (PKDL), VL is currently targeted for elimination as a public health problem (EPHP), signifying sustained control activities are essential for reaching and maintaining incidence targets to prevent disease resurgence [4].

Over 25% of the global VL burden exists in India, where 85% of cases are reported in the state of Bihar. In 2005, a regional Kala-Azar Elimination Programme (KEP) developed within the ISC to mobilise national programming, international financial support, and drug donations; this has helped facilitate Nepal and Bangladesh achieve EPHP benchmarks [5]. Early case detection is a prioritized measure for reducing transmission in India, which relies on effective surveillance to support accurate diagnosis and complete treatment at the hospital level [6,7].

However, institutional and socio-economic barriers challenge the integration of rural populations into India's health system, where patients may consult uncertified rural practitioners (URPs), lack accessibility to and trust in government health facilities, or not

seek medical support [8-10]. To expedite identification and referral of potential VL cases, the KEP has supported village-level active case detection (ACD) over the past decade.

Active and passive case detection (ACD & PCD) in the KEP

Prompt diagnosis and treatment of VL serves two purposes: to prevent death, and to reduce transmission. Through the systematic screening of populations in endemic areas by health staff to find cases, ACD has been shown to contribute to early VL detection in India [6,8,11]. Four distinct, but not mutually exclusive, approaches to ACD exist: blanket (house-to-house screening), camp (mobile diagnostic teams visiting targeted villages), index case-based (searching for new cases in the vicinity of confirmed cases) and incentives-based (village health workers paid to find suspected cases) [6]. Although ACD activities are conducted at the village level, suspected cases are then reported at the block level (a sub-district region where elimination targets are measured) as well as within Bihar's 33 endemic districts.

In Bihar, a range of ACD strategies have been managed by two different organisations: CARE and KalaCORE. Since 2017, the non-profit organisation CARE has worked with the state government to lead index case-based ACD in support of the KEP. Their programme relies on Kala-Azar Block Coordinators (KBCs) conducting snowball-surveillance in the vicinity of recent VL patients at one-, six- and 12- months post-treatment. Fortnightly ACD is then conducted in each village for 12 months after its last reported VL case. Additionally, key informants such as family members, school teachers, and shop keepers, as well as Accredited Social Health Activists (ASHAs), are trained to report potential VL cases to KBCs by telephone. Separately, KalaCORE (a consortium funded by UK Aid) operated from 2015-2019 employing a combination of blanket and camp ACD. KalaCORE recruited and trained KBCs, local medical staff, and other ACD officers to conduct blanket (house-to-house)

surveillance in villages with high VL incidence, followed by weekly diagnostic camps to confirm VL infections and refer cases to treatment facilities.

Without active intervention, VL cases are presumed to be found through Passive Case Detection (PCD), that is, symptomatic individuals presenting at a static hospital or Primary Health Centre (PHC) with no prior interaction with a KBC or ACD officer. In 2014, as part of India's KEP, over 120 VL treatment centres were strategically established within PHCs in close proximity to high endemic villages (with more than five cases per 10,000 population per year) [12]. These treatment centres offer free rK-39 rapid VL diagnostics and single-dose AmBisome treatment through the Government of India's National Vector Borne Disease Control Programme (NVBDCP), and are designated referral sites for all suspected cases [13].

Informing and updating EPHP strategies

To achieve Bihar's EPHP target of less than one VL case per 10,000 population per block per year by 2020, policy-relevant research is needed to assess current VL surveillance strategies [13,14]. Economic evaluation compares resources required, cases identified, and costs of parallel surveillance programmes for informing priority setting across elimination strategies. Three economic analyses of ACD on the ISC were conducted between 2010-2012, where the cost per case detected through blanket and camp ACD varied between $21-$629 and PCD was excluded as it was considered an integrated public health service [6,8,11]. As VL incidence was five-fold higher during that time[1], it is important now to re-evaluate the cost and investment in ACD during a period when numbers of VL cases are low and the elimination target is close.

Importantly, as disease cases decrease often so does financial and political support to maintain control activities given competing disease priorities in lower-middle income countries (LMIC) [15,16]. Donor-funded VL programmes in India are especially vulnerable at the point around EPHP, where viability, value, and longevity of current programmes must be evaluated to adapt and advocate financial support [17]. Methods for assessing disease screening during EPHP often compare programme costs to the likelihood of reaching elimination benchmarks as a means to provide translatable evidence for decision makers [18-21]. Therefore, the aim of this study was to conduct a cost-minimisation analysis of current VL case detection programmes to determine the least costly approach to achieving EPHP in the endemic state of Bihar.

Results of this study should extend insight into how the health officials could scale-up and modify ACD strategies to reach EPHP efficiently, which may provide generalizable lessons for VL globally as well as other NTDs approaching elimination [22,23]. This evaluation may also provide information for the eventual integration of VL case detection horizontally into other febrile illness programmes after elimination benchmarks are achieved.

Methods

Ethics statement

Ethical approval was obtained from the London School of Hygiene and Tropical Medicine in November 2019 (Reference Number 17763), and permission to collect data from CARE and KalaCORE was subsequently confirmed (Appendices 4-6).

Cost model

National guidelines for economic analysis in India are not available, where this study followed the Global Health Cost Consortium Reference Case alongside costing literature for disease surveillance in low- and middle-income contexts [24-27].

Fig 4-1 illustrates the basic activities, communication, and patient flow of each programme: PCD, blanket and camp ACD, and index case-based ACD. This study involved both primary and secondary data collection from three organisations and two government facilities involved in ACD and PCD in Bihar, India. Using a top-down approach (including facility-level financial data) supplemented by bottom-up micro-costing (relying on observation and interviewing), programme inputs, costs, and outputs were estimated to generate a cost model from the provider's perspective (Bihar Ministry of Health and Family Welfare). Given VL seasonality and occurrence of overlapping ACD activities, a full year (January-December 2018) was used to capture transmission dynamics, start-up, and project costs at a standard discount rate of 3%. Costs of treatment were excluded from this study under the assumption that all VL cases are eventually confirmed in hospital and treated same day for all approaches. Although PKDL case finding is integral to the KEP, it was excluded due to lack of comparable data across ACD and PCD programmes.

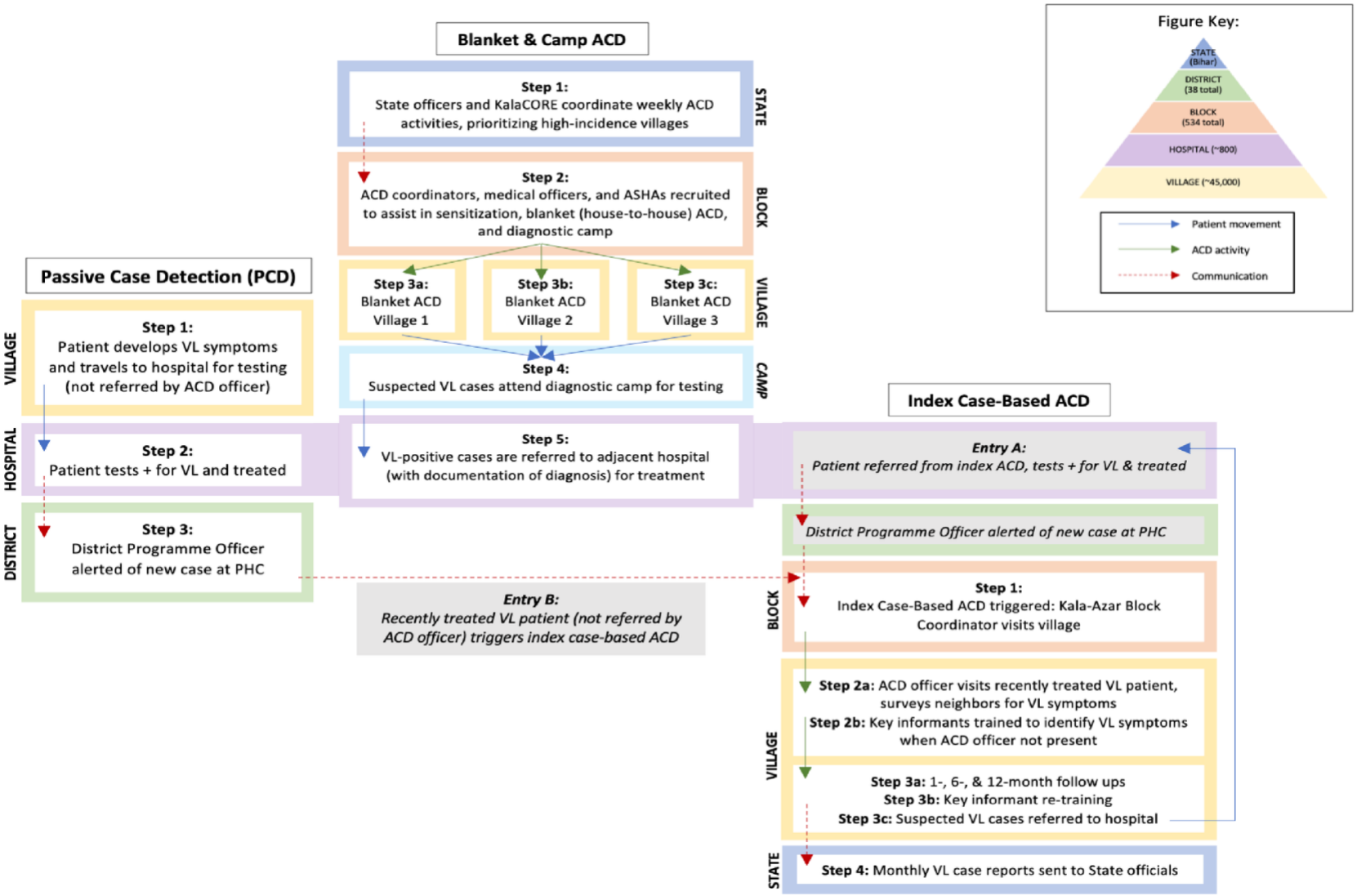


Fig 4-1. Diagram of VL active and passive case detection in Bihar. Activities, communication, and patient flow involved in PCD, blanket and camp ACD, and index case-based ACD for visceral leishmaniasis in Bihar, India during 2018.

Study area

With a population of 104 million, the north-eastern state of Bihar is India's fifth most impoverished municipality [28]. As Bihar is 89% rural, over 60% of the workforce engages in agricultural and farming activities [28,29]. One third of the state reportedly lives below the poverty line, accounting for the second highest malnutrition rates in India [29]. Less than 25% of Bihar residents have completed secondary education, where females exhibit the lowest national levels of both educational attainment and labour force participation [29].

Data sources

ACD. Data was collected from CARE regarding index case-based ACD, and from KalaCORE regarding blanket (house-to-house surveillance) and diagnostic camp ACD. Project accounts and expenditure reports from 2018 were collated to determine start-up costs (training, materials, per diems), capital costs (buildings, equipment, vehicles), and recurrent costs (salaries, medical supplies, travel). Economic costs were estimated for donated goods, indirectly purchased equipment, and training. Interviews with financial officers, programme managers, KBCs, and District Programme Officers then triangulated programme reports by examining programme structure, length of activities, and missing costs associated with ACD. Some inputs were also estimated from other VL costing studies in the literature, manufacturer costs for vehicles, rental rates for equivalent office space in Bihar, and market prices of relevant supplies (see Appendix 7 for sources of each input).

Outputs were reported individually by CARE and KalaCORE, detailing the number of suspected, tested, and VL-positive cases identified at the district level through respective ACD programmes during 2018.

PCD. The cost of PCD was calculated at the PHC level, designating 2015 as the 'start-up' period when VL treatment centres were established in Bihar that included updated diagnostic and treatment protocol. The start-up (training, staff, materials) and capital costs (cold-chain storage, buildings, vehicles) were estimated from programme asset registers and interviews. Recurrent costs to screen and test individual patients were estimated through direct observation and interviews with medical officers to determine staff time for clinical examination, laboratory costs, and prices to stock, maintain and use VL diagnostics in Bihar. Costs and time associated with medical officers' absence from normal duties to attending training were included.

Outputs included number of patients tested and identified as VL-positive through PCD, which were estimated from incidence reported by the Kala-Azar Management Information System (KAMIS) and Ministry of Health Management and Information System (HMIS) databases. PCD-specific outputs were estimated by subtracting the number of cases identified through ACD from overall VL incidence reported by KAMIS in Bihar during 2018.

Cost Analysis

The annual incremental economic costs of each programme were estimated for the base year 2018. All resources were accounted for, including donated goods and opportunity costs of unpaid time to attend trainings. Start-up, capital, and recurrent costs were analysed by categorising each line item by input type. The start-up period was defined as all costs incurred during project conception and training prior to implementation (first patient screened). Where provider costs were shared across hospital units (overheads, staff time, laboratory equipment), allocation factors were estimated from direct observation,

interviewing, and referencing hospital-based costing literature specific to Northern India [30,31].

Unit costs were calculated in Excel by dividing each programme's total cost by the total number of cases suspected, tests conducted, and VL-positive cases identified. All costs were reported in local currency, Indian Rupee (INR), and converted to 2018 $USD using central bank exchange rates [32]. The least costly approach of ACD and PCD was evaluated by comparing total and unit programme costs as well as the cost of scaling up ACD to identify further unreported VL cases. Outcomes of each programme were stratified by district-level (high >200 cases, meso 50-200 cases, and low <50 cases) VL incidence in Bihar to evaluate areas where bolstering ACD may have a greater epidemiological advantage.

Sensitivity Analysis

A sensitivity analysis was conducted to determine the robustness of assumptions used in the cost analysis (see Appendix 7 for list of assumptions). To determine the extent to which variation in values, unmeasured variables, and altering key assumptions led to different interpretations or conclusions, a univariate sensitivity analyses varied vehicle life years (+/- 5 years), operation (+/- 10%), discount rate (+/- 3%), central cost allocation factors (+/- 5%), personnel salaries (+/- 10%), and economic life years of start-up, training, and other capital costs (+/- 2 years).

A scenario analysis also explored the impact on variability of the observed intervention, such as personnel time allocation (+/- 5%), number of VL tests conducted (+/- 10%), and price of rK-39 tests (+/- 50%). A multivariate sensitivity analysis illustrated best- and worst-case scenarios according to variation in the univariate parameters.

Modelling and scale-up

Marginal costs of scaling up each ACD strategy were estimated through variable costs required to detect one additional VL case or conduct one additional test. The cost of scaling up each ACD programme to varying degrees was compared by calculating marginal cost to conduct an additional 25,000 tests (which would identify an additional 3,000 VL cases). Finally, outcomes of each programme were compared by district-level incidence in Bihar, as reported by the KAMIS database during 2018, to understand how costs were likely to be influenced by incidence.

Results

Cost summary

Programme outputs. Of the 3,611 VL cases reported in Bihar during 2018, 45% were identified through ACD. PCD, blanket and camp ACD, and index case-based ACD respectively conducted 31,000, 1,945, and 12,261 VL tests and found 1,983, 131, and 1,497 VL-positives during this timeframe (Table 4-1). The percentage of VL-positives identified relative to tests conducted ranged from 7% in both PCD and blanket and camp ACD to 12% in index case-based ACD.

Table 4-1. Cost Summary and Outputs of PCD, Blanket & Camp ACD, and Index Case-Based ACD for VL during 2018.

Cost Category	PCD		Blanket & Camp ACD		Index Case-Based ACD	
	$USD	%	$USD	%	$USD	%
Start-up						
Training	$22,304.51	4.56%	$1,565.54	0.29%	$7,699.88	0.98%
Other Start-up	--	--	$1,058.48	0.19%	$767.07	0.10%
Total Start-up	$22,304.51	4.56%	$2,624.02	0.48%	$8,466.95	1.08%
Capital Costs						
Building & Storage	$8,961.77	1.83%	$1,311.27	0.24%	$591.90	0.08%
Equipment	$11,611.70	2.37%	$4,350.14	0.79%	$4,157.75	0.53%
Vehicles	$837.97	0.17%	$2,399.51	0.44%	$13,574.20	1.73%
Other Capital Costs	$1,121.69	0.23%	$1,128.25	0.21%	--	--
Total Capital Costs	$22,533.13	4.60%	$9,189.17%	1.68%	$18,323.85	2.34%
Recurrent Costs						
Personnel	$200,781.30	41.03%	$347,630	63.38%	$536,650.78	68.57%
Supplies	$177,295.91	36.23%	$20,972.75	3.82%	$4,774.75	0.61%
Vehicle Operation & Maintenance	$2,793.04	0.57%	$21,885	3.99%	$181,025	23.13%
Building Operation & Maintenance	$51,151.70	10.45%	$430.23	0.08%	$373.88	0.05%
Recurrent Training	$12,525.23	2.56%	$1,555.52	0.28%	$33,038.30	4.22%
Diagnostic Camps	--	--	$144,185	26.29%	--	--
Total Recurrent Costs	$444,547.18	90.84%	$536,658.50	97.85%	$755,862.71	96.58%
TOTAL ANNUAL COSTS	$489,384.82	100%	$548,471.69	100%	$782,653.51	100%
Total Costs without Start-up	$467,080.31	95.4%	$545,847.67	99.52%	$774,186.56	98.8%
Units & Costs	N	Cost per ($USD)	N	Cost per ($USD)	N	Cost per ($USD)
Suspected or Screened VL Case	225,000	$2.18	2,212	$247.95	16,459	$47.55
VL Tests	31,100	$15.74	1,945	$281.99	12,261	$63.83
VL Positives	1,983	$246.79	131	$4,186.81	1,497	$522.81
VL Tests (Recurrent costs only)		$14.29		$275.92		$61.65
VL Positives (Recurrent costs only)		$224.18		$4,096.63		$504.92

Start-up, capital, recurrent, and total annual costs of PCD, blanket and camp ACD, and index-case based ACD in Bihar during 2018, presented in $USD and as a percentage of total programme cost. Cost per suspected or screened VL case, VL tests conducted, and VL-positive case identified in each programme are included.

Total programme costs. Total programme cost calculations included both financial and economic costs, where index case-based ACD was the highest at $782,653.51, and blanket and camp ACD and PCD were similar at $548,471.69 and $489,384.82, respectively. Financial costs for index case-based ACD, blanket and camp ACD, and PCD were $559,019.33, $525,996.80, and $279,260.99. Over 90% of costs were recurrent in all programmes, the majority of which were attributed to personnel salary. Vehicle operation, supplies, and the cost of diagnostic camps within blanket ACD were the second highest overall program expenditures.

Unit costs. At $4,186.81 per VL-positive case identified, blanket and camp ACD was eight times higher than index case-based ACD at $522.81. However, blanket and camp ACD was only four times higher than index case-based ACD per VL test conducted, at $281.99 versus $63.83. PCD was $246.79 per VL-positive identified and $15.74 per test conducted. Within each ACD programme, the cost per suspected case and cost per test conducted were similar, indicating accuracy in their respective screening strategies.

Sensitivity analysis

Sensitivity analyses conducted for each of the three programmes are shown, where Figs 4-2 through 4-4 represent variations in cost per VL test conducted and Figs 4-5 through 4-7 represent cost per VL-positive case identified.

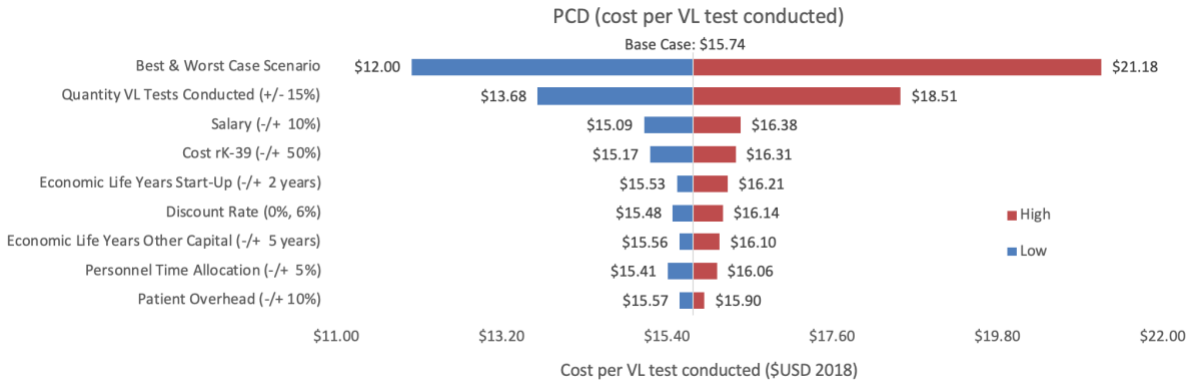


Fig 4-2. Sensitivity analysis of PCD costs per VL test conducted. Variations in PCD cost per VL test conducted in Bihar during 2018.

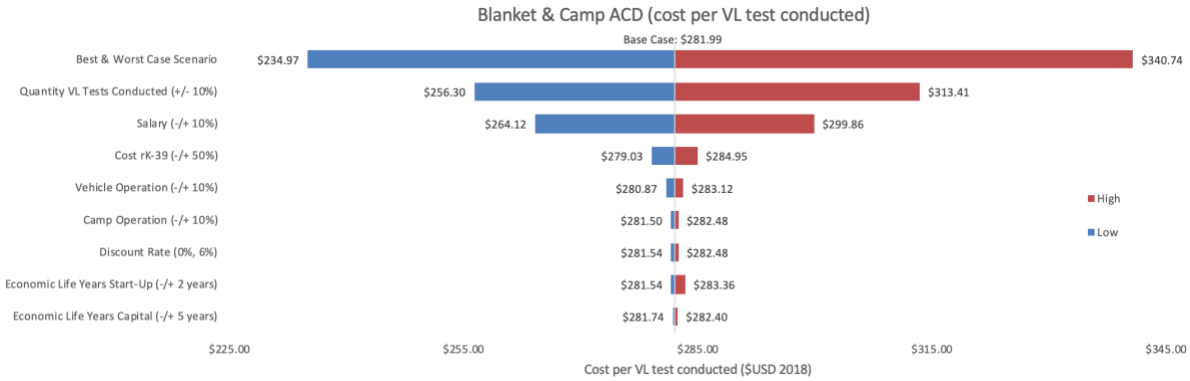


Fig 4-3. Sensitivity analysis of blanket & camp ACD per VL test conducted. Variations in blanket & camp ACD cost per VL test conducted in Bihar during 2018.

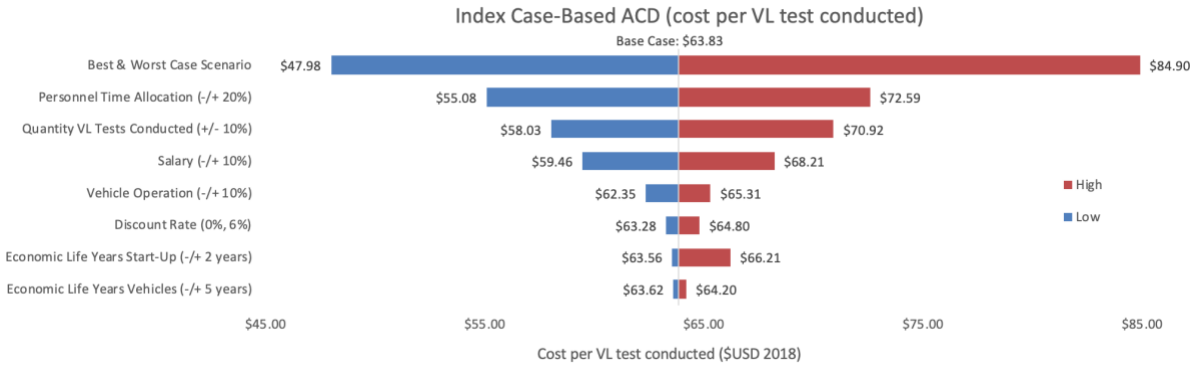


Fig 4-4. Sensitivity analysis of index case-based ACD per VL test conducted. Variations in index case-based ACD cost per VL test conducted in Bihar during 2018.

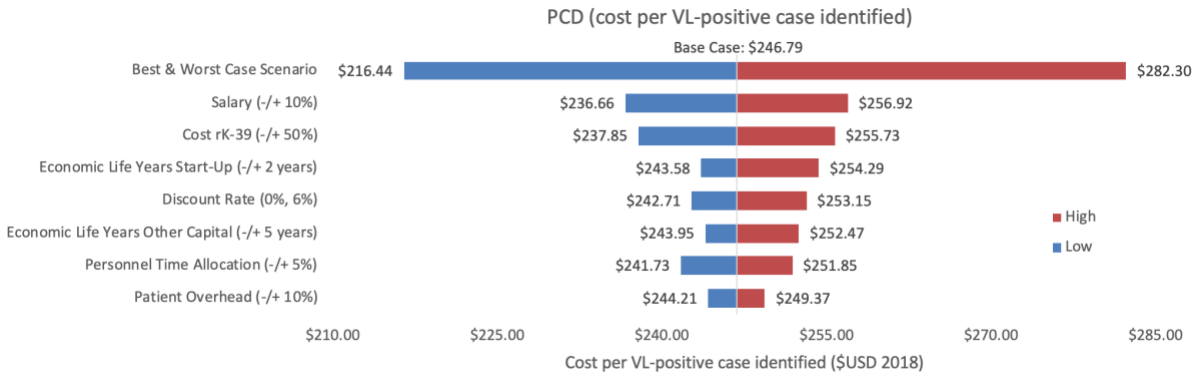


Fig 4-5. Sensitivity analysis of PCD costs per VL-positive case identified. Variations in PCD cost per VL-positive case identified in Bihar during 2018.

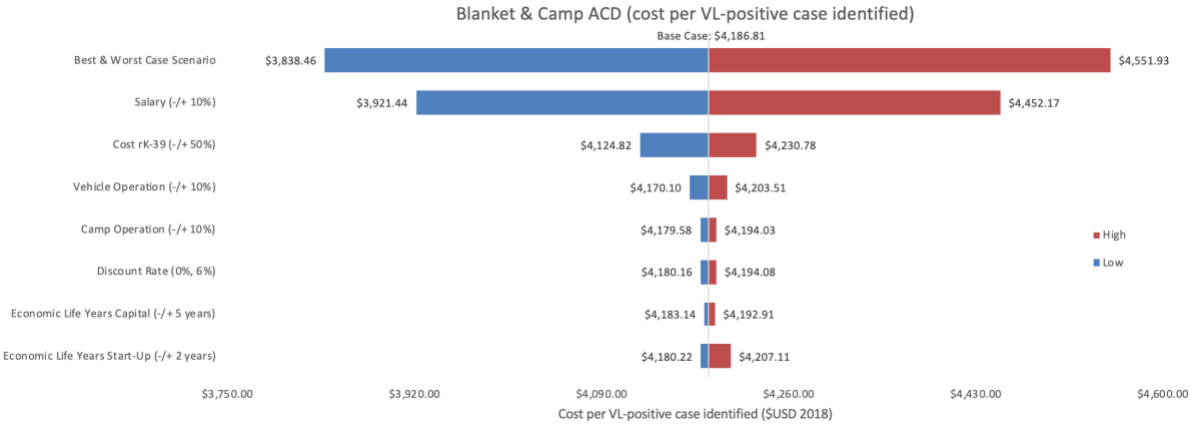


Fig 4-6. Sensitivity analysis of blanket & camp ACD per VL-positive case identified. Variations in blanket & camp ACD cost per VL-positive case identified in Bihar during 2018.

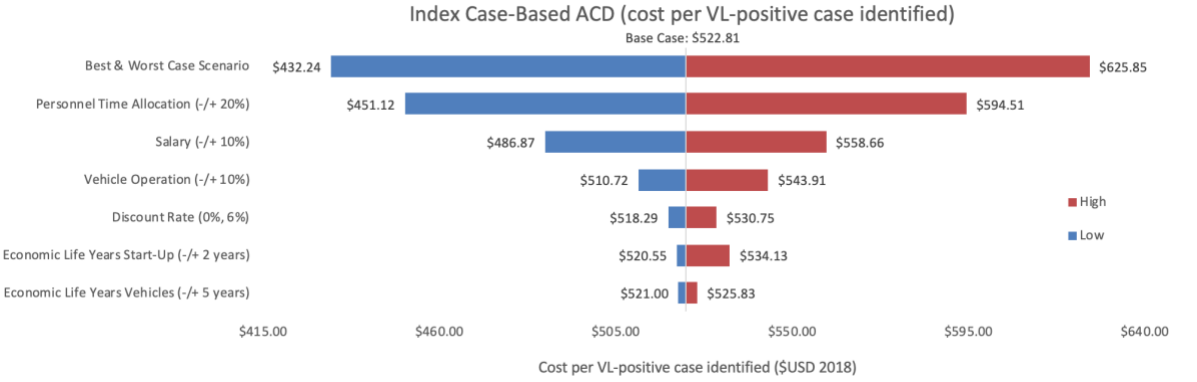


Fig 4-7. Sensitivity analysis of index case-based ACD per VL-positive case identified. Variations in index case-based ACD cost per VL-positive case identified in Bihar during 2018.

Cost per VL test conducted. As an alternative scenario, quantity of tests conducted (+/-10%) yielded the largest unit change in cost per test for blanket and camp ACD (ranging from $256.30 to $313.41) and PCD (ranging from $13.68 to $18.51). For index case-based ACD (Fig 4-4 and Fig 4-7), increasing or decreasing personnel time allocated to ACD activities contributed the largest unit cost range (from $55.08 to $72.59).

Cost per VL-positive identified. As an assumptions test, variations in personnel time and salary produced the greatest influence on cost per case detected in each of the three programmes. Altering staff salaries by 10% would increase or decrease cost per VL case detected between 5-12%.

District-level incidence

Within Bihar's 33 VL-endemic districts, incidence ranged from over 800 to less than 10 cases in 2018. Fig 4-8 displays the number of district-level VL-positive cases identified within each programme stratified by incidence. PCD identified more VL-positive cases in high incidence districts, while both ACD programmes collectively identified more VL-positive cases across districts reporting less than 200 cases. Blanket and camp ACD mostly targeted 'hot spots' and high-incidence villages, but also contributed to detecting some cases in low-incidence districts.

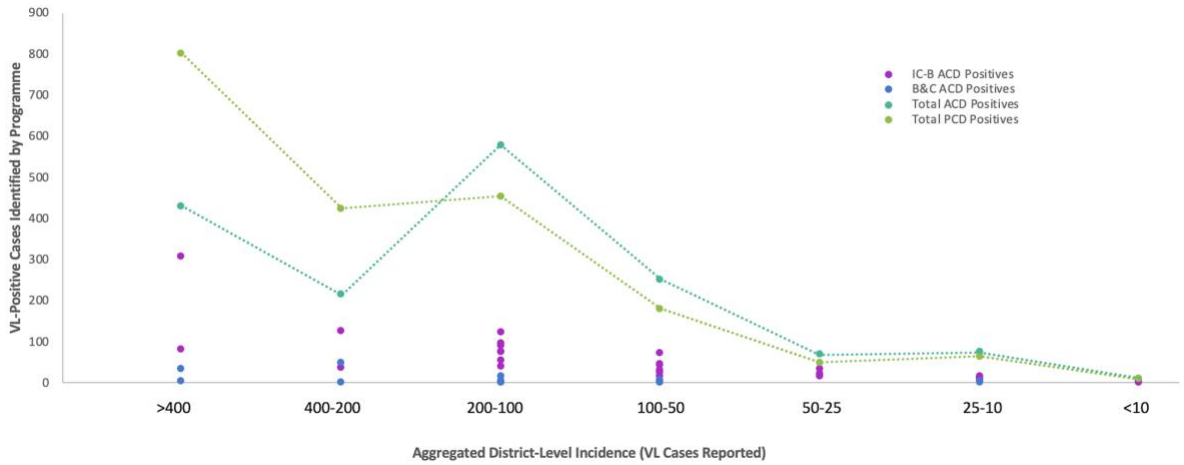


Fig 4-8. VL-positive cases identified through ACD and PCD stratified by district-level incidence. Number of VL-positive cases identified according to district-level incidence through index case-based ACD (IC-B) (pink), blanket & camp ACD (B&C) (blue), total ACD (index case-based ACD and blanket & camp ACD together) (teal), and PCD (green) in Bihar during 2018.

Cost of scaling up ACD

ACD has the potential to be scaled up to find additional cases, whereas PCD is integrated in the health system without the opportunity to expand existing services. Decision makers may be interested in the costs and outputs of detecting additional VL cases by investing differently in each ACD strategy. To project outcomes of scaling up ACD in Bihar, programme costs of both ACD methods were pooled together as if hypothetically allocated or coordinated through one entity, such as NVBDCP.

Ninety percent of VL cases identified through ACD in 2018 were detected using the index case-based strategy. WHO declares around one-half of global VL cases are actually reported, therefore Fig 4-9 displays the cost of scaling up ACD to identify an additional 3,000 VL cases in Bihar [2]. Fig 4-10 illustrates the additional cost of investing from 0-50% in blanket and camp ACD to conduct 25,000 more VL tests. In each scenario, the overall programme cost would increase from approximately $1,600,000 USD to around $4,000,000 USD if blanket and camp ACD were increasingly relied on.

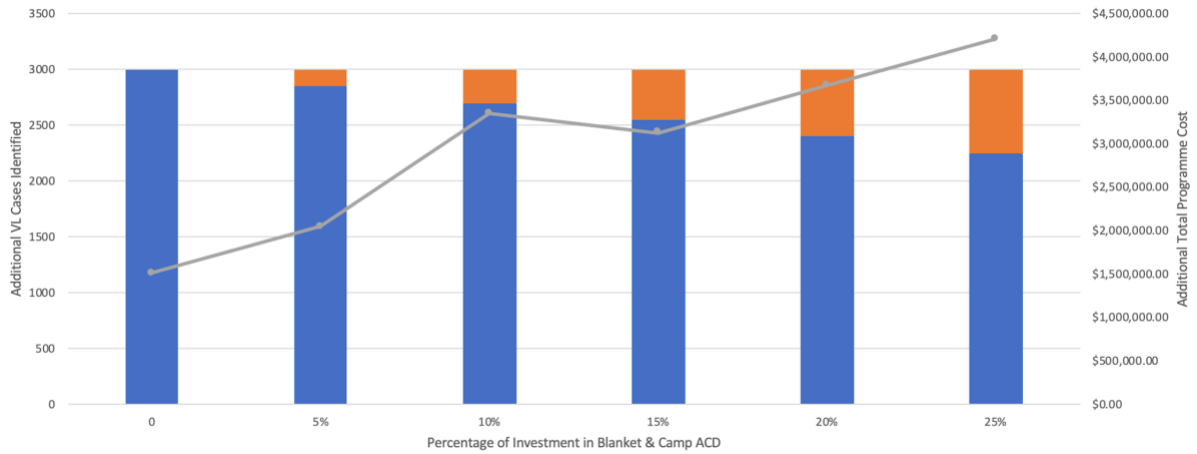


Fig 4-9. Cost of scaling up ACD to identify additional cases. Cost of scaling up index case-based (IC-B) and blanket & camp (B&C) ACD to identify 3,000 additional VL cases. Total programme cost includes both IC-B and B&C together, as if managed by a single funder.

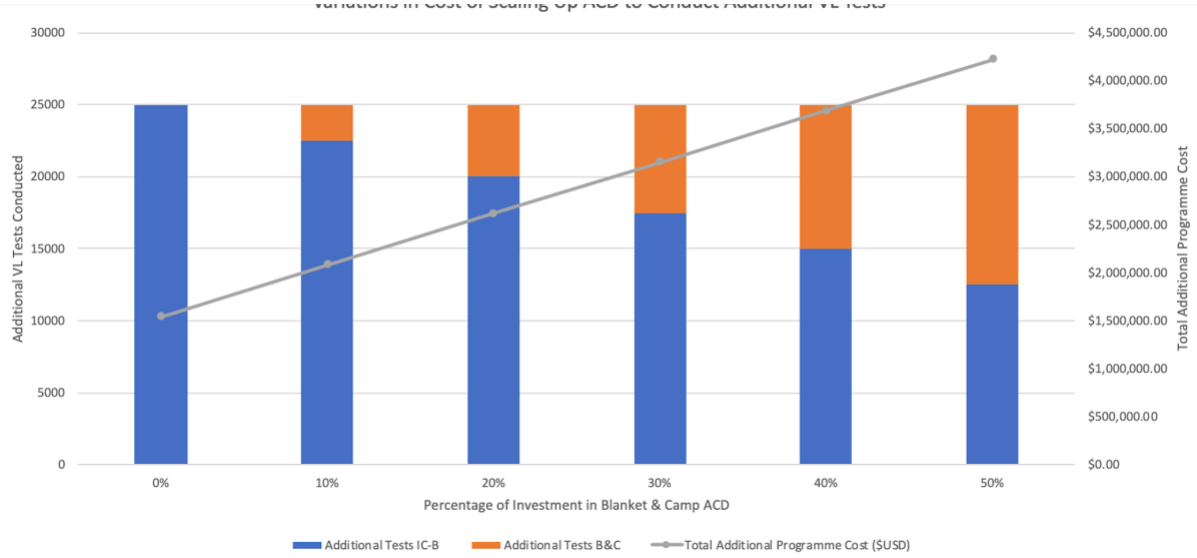


Fig 4-10. Cost of scaling up ACD to conduct additional tests. Cost of scaling up index case-based (IC-B) and blanket & camp (B&C) ACD to conduct 25,000 additional VL tests. Total programme cost includes both IC-B and B&C together, as if managed by a single funder.

From the average cost per test conducted of index case-based ($63.83) and blanket and camp ACD ($281.99), the marginal cost per test of scaling up to detect 3,000 additional cases was $61.65 and $275.92, respectively. In both strategies, the marginal cost of scaling up testing was only slightly less than the average cost and continued to decrease minimally with up to 70,000 additional tests conducted.

Discussion

In addition to evaluating programme and unit costs during 2018, this study revealed that more VL cases were identified through PCD in high-incidence areas and through ACD in meso- and low-incidence areas. This pattern aligns with previous studies on high-incidence areas in the ISC, although there is a lack of literature examining the effects of ACD in meso- and low-incidence populations [6,8,11]. The lowest cost for scaling up ACD would solely involve the index case-based strategy given high unit costs of blanket and camp ACD. However, the blanket and camp approach accounted for 8% of VL cases identified through ACD, which may rationalise high unit costs to achieve and sustain EPHP.

Alongside overall and unit costs, evaluating the tactical strengths and weaknesses of each ACD programme informs where to re-direct VL resources in Bihar to reach EPHP. Index case-based ACD is likely more advantageous over time and blanket and camp ACD over space. Effects of index case-based ACD are longer-term as a product of educating key informants to identify and refer potential cases when ACD officers are not present. Blanket and camp ACD is more robust and systematic in a given geographic area, yet house-to-house surveillance is limited by absence of disease symptoms at a given point in time.

Strengthening educational reach of index case-based ACD

Results of this cost analysis indicate an opportunity to bolster ACD in districts with less than 200 cases, where individuals may have less physical, but also educational, exposure to VL. As the frequency and magnitude of index case-based ACD mirrors VL incidence in each area, high-incidence populations presumably have more interaction with ACD officers and

trained key informants. Therefore, these populations might be more likely to recognise VL symptoms early and seek care than lower-incidence populations.

Similarly, a 2009 study in the ISC found a lower percentage of VL cases were detected through ACD than PCD in areas with increased educational activities from NGOs [33]. VL populations already have higher poverty levels and lower educational attainment and literacy compared to India's national average [6,8,34], therefore sustaining vigilant disease identification is especially challenging and crucial in neglected areas. Even where VL cases are infrequent in meso- and low-incidence areas, reinforcing educational aspects of index case-based ACD might facilitate longer-term diagnosis through PCD.

Blanket & camp ACD in low-incidence districts

Clustered outbreaks have been recently documented in previously low-incidence settings in Bihar, possibly in part due to decreased host competence in areas with few VL infections [35]. In these populations, a greater proportion show decreased immunity over time and are disproportionately susceptible to transmission from acute VL infections [36,37]. Other studies show a correlation in time and space between outbreaks in previously non-endemic areas adjacent to endemic areas, especially in highly impoverished populations [38,39]. Curtailing such outbreaks may require more robust ACD tactics, where drivers of transmission are related to lack of previous VL exposure, high poverty, and risk-related proximity to new cases [40].

In this, blanket and camp ACD may be best utilised as a deployable intervention in low-incidence areas at risk of VL outbreaks. Although blanket and camp ACD unit costs were eight times higher than index case-based ACD, it remains a valid strategy for two reasons: 1)

it targeted high-incidence areas and may actually be more beneficial for low-incidence areas, and 2) the value of detecting additional cases early may be significant enough to support the high initial investment necessary for reaching EPHP.

Focusing house-to-house surveillance on districts with less than 200 cases per year could be more valuable than presuming it will capture a high number of cases in high-incidence areas. Detecting few cases in low-endemic areas would likely yield the same high unit cost but at a greater epidemiological advantage. Blanket ACD might also be strategically implemented around months of the year when VL transmission is greatest.

Horizontal programme integration

To date, VL treatment and prevention programmes have been predominantly vertical in India. Given the importance of continued surveillance, yet the high cost of identifying cases at the village level, it will be prudent to eventually integrate VL ACD horizontally with other infectious disease programmes. VL blanket and camp ACD tactics align with other skin- and fever-related disease surveillance strategies, both of which are ongoing in the ISC. Several recent studies document feasibility of integrating VL into ACD for febrile illnesses such as malaria, tuberculosis, and leprosy, particularly using the camp approach [41,42].

Additionally, historical data trends show a spike in VL transmission often occurs every 15-17 years, which will likely be exacerbated by relaxed control measures as incidence is lowered [43,44]. Even when EPHP benchmarks are reached, it will be important to sustain VL surveillance in some form to avoid and prepare for potential transmission resurgence. The appropriate stage for integration, additional resources required, and potential risk of neglecting cases due to decreased concentration on VL should be explored.

To support ACD scale-up in the immediate, it may be best to focus on the cost of additional tests conducted rather than additional cases detected. Figs 4-9 and 4-10 show the same investment is needed when relying on the blanket and camp strategy for 50% of additional tests conducted but only 25% of additional VL-positive cases detected. Although blanket and camp ACD is undeniably more costly, a diversified case-finding strategy may be critical around this period of EPHP. ACD scale-up should ideally be strategised and coordinated by one entity, such as NVBDCP. As VL incidence further declines, it will become necessary to document all ACD outputs at the block and village level, which the index case-based programme must adopt.

Costs and outcomes reported in this study may be applicable to VL strategies on the ISC, or other diseases aiming toward elimination where active case finding is increasingly relied on. It is imperative that ACD tactics, outputs, and barriers be readily shared between programmes in India to continue supporting a timeline and best strategy for achieving EPHP thresholds. Future research on the investment needed to reach VL EPHP should include expenditures and outcomes of other control activities such as indoor residual spraying (IRS) for sandfly vector control, treatment to remove the threat of PKDL as a reservoir, and antigen diagnostic tests.

Conclusion

The characterisation and projection of VL case detection costs are fundamental to India's elimination strategy. As VL cases become both more difficult and critical to find, this study provides insight into how PCD and index case-based ACD might be enhanced by targeting blanket and camp ACD in areas with lower incidence. This analysis should be built upon in future economic studies, particularly where horizontal ACD programme integration is

considered. Blanket and camp ACD must be investigated for its additional value to addressing PKDL, co-infections, and marginalised groups. Economic evaluations should also be integrated into complementary disciplines that forecast the impact of case finding strategies alongside the likelihood of reaching elimination, such as mathematical modelling. Cost analyses provide compelling information for decision makers to strategise resource allocation and programme activities and must be encouraged and expanded as NTD-endemic countries approach disease elimination.

Limitations

This study includes several limitations. First, it is possible that some cases reported in each distinct ACD or PCD activity overlap between programmes. No patient identifiers were collected in this study, where future research may consider tracing suspected cases from village-level identification to confirmed treatment.

Uncertainty may also exist in the generalisation of costs across different populations, given varying VL endemicity and the potential for co-infection with other diseases. This study was limited in availability of block- and village-level data, which would have more accurately informed programme outputs within specific incidence levels.

Bias may be present in reported expenditures of each programme, especially under- or over-estimation of inputs and time spent on activities. To address this, staff-time and input allocation was estimated through micro-costing the hours, resources, and frequency of activities in each strategy. Determining micro-costing parameters relied on interviews and direct observation, and therefore may include bias of self-reporting by staff or in generalising observed activities across other facilities. However, the diversity of data sources, lack of

missing data, and sensitivity analyses should provide a best estimate regarding overall inputs, costs, and outputs of each strategy.

This study did not include costs of treatment of VL cases in India, under the assumption that all VL cases identified at the PHC-level are treated the same day. There may have been loss to follow up between VL-positives identified through ACD and those cases confirmed at PHCs. Loss to follow-up in index case-based ACD was addressed by documenting and tracing potential cases between ACD officers, doctors at adjacent PHCs, and NVBDCP. In a similar attempt to minimize loss to follow-up, confirmed cases found through blanket and camp ACD were given formal documentation of their VL-positive test result, allowing them to proceed directly to treatment at the PHC.

Acknowledgements

The authors would like to thank CARE, KalaCORE, IPE Global, and all participants for contributing data and insight to this study. ND would also like to acknowledge the SPEAK India research consortium for providing feedback and support. ND is grateful to Saritha Nair and the Indian Council of Medical Research for valuable discussions on the logistics and feasibility of economic analysis in India's KEP.

References

1. WHO, “Global Health Observatory: Number of cases of visceral leishmaniasis reported,” 2020.
2. WHO, “Visceral Leishmaniasis Factsheet,” *World Health Organization*, 2018. .
3. LDNTD, “Uniting to Combat NTDs: Fourth progress report of the London Declaration,” London, UK, 2015.
4. P. Olliaro, T. Shamsuzzaman, B. Marasini, A. Dhariwal, A. Be-Nazir, and D. Mondal, “Investments in Research and Surveillance Are Needed to Go Beyond Elimination and Stop Transmission of Leishmania in the Indian Subcontinent,” *PLoS Negl. Trop. Dis.*, vol. 11, no. 1, 2017.
5. NVBDCP, “Directorate of National Road Map for Kala Azar Elimination,” Delhi, India, 2014.
6. S. Singh *et al.*, “Options for Active Case Detection of Visceral Leishmaniasis in Endemic Districts of India, Nepal and Bangladesh, Comparing Yield, Feasibility and Costs,” *PLoS Negl. Trop. Dis.*, vol. 5, no. 2, 2011.
7. WHO, “World Health Organization Visceral Leishmaniasis Factsheet,” *World Health Organisation*, 2018. [Online]. Available: http://www.who.int/leishmaniasis/disease/en/.
8. S. Hirve *et al.*, “Effectiveness and Feasibility of Active and Passive Case Detection in the Visceral,” vol. 83, no. 3, pp. 507–511, 2010.
9. D. Lim, M. Banjara, V. Singh, A. Joshi, C. Gurung, and E. Al., “Barriers of Visceral Leishmaniasis reporting and surveillance in Nepal: comparison of governmental VL-program districts with non-program districts,” *Trop Med Int Heal.*, vol. 24, no. 2, pp. 192–204, 2019.
10. E. McArthur, S. Bali, and A. Khan, “Socio-cultural and Knowledge-Based Barriers to Tuberculosis Diagnosis for Women in Bhopal, India,” *Indian J Community Med*, vol. 41, no. 1, pp. 62–64, 2016.
11. M. M. Huda *et al.*, “Active case detection in national visceral leishmaniasis elimination programs in Bangladesh , India , and Nepal : feasibility , performance and costs,” *BMC Public Health*, vol. 12, no. 1, p. 1, 2012.
12. S. Burza, K. Misra, and V. Aggarwal, “Evidence based planning to maximise coverage of treatment services for Kala-Azar in resource constraint settings in India,” New Delhi, India, 2018.
13. NVBDCP, “Accelerated Plan for Kala Azar Elimination,” Delhi, India, 2017.
14. S. Sundar, O. Singh, and J. Chakravarty, “Visceral leishmaniasis elimination targets in India, strategies for preventing resurgence,” *Expert Reve Anti Infect Ther*, vol. 16, no. 11, pp. 805–812, 2018.
15. WHO, “Investing to overcome the global impact of neglected tropical diseases: third WHO report on neglected diseases 2015,” 2015.
16. A. Krentel, M. Gyapong, O. Ogundahunsi, M. Amuyunzu-Nyamongo, and D. McFarland, “Ensuring no one is left behind: Urgent action required to address implementation challenges for NTD control and elimination,” *PLoS Negl. Trop. Dis.*, vol. 12, no. 6, 2018.
17. Y. Zhang, C. MacArthur, L. Mubila, and S. Baker, “Control of neglected tropical diseases needs a long-term commitment,” *BMC Med.*, vol. 8, no. 67, 2010.
18. N. Menzies, G. Gomez, F. Bozzani, S. Chatterjee, N. Foster, and I. Baena, “Cost-effectiveness and resource implications of aggressive action on tuberculosis in China, India, and South Africa: a combined analysis of nine models,” *Lancet Glob. Heal.*, vol. 4, no. 11, 2016.

19. G. Smit *et al.*, “Cost-effectiveness of screening for active cases of tuberculosis in Flanders, Belgium,” *WHO Res.*, 2016.
20. B. Larson *et al.*, “A framework for evaluating the costs of malaria elimination interventions: an application to reactive case detection in Southern Province of Zambia, 2014,” *Malar. J.*, vol. 15, no. 1, 2016.
21. P. Winskill, P. Walker, R. Cibulskis, and A. Ghani, “Prioritizing the scale-up of interventions for malaria control and elimination,” *Malar. J.*, vol. 18, no. 122, 2019.
22. S. Kumar, A. Williams, and J. Sandy, “How do we evaluate the economies of health care?,” *Eur. J. Orthod.*, vol. 28, no. 6, 2006.
23. E. McIntosh and R. Luengo-Fernandez, “Economic evaluation. Part 2: Frameworks for combining costs and benefits in health care,” *J. Fam. Plan. Reprod. Heal. Care*, vol. 32, no. 3, 2006.
24. A. Vassall *et al.*, “Reference Case for Estimating the Costs of Global Health Services and Interventions,” London, UK, 2017.
25. A. Vassal, L. Mangham-Jefferies, G. Gomez, C. Pitt, and N. Foster, “Incorporating demand and supply constraints into economic evaluation in low-income and middle-income countries,” *Health Econ.*, vol. 25, no. 1, pp. 95–115, 2016.
26. F. Terris-Prestholt, A. Santos, S. Sweeney, and L. Kumaranayake, “The Rapid Syphils Test Toolkit. Implementation 1: Guidelines for Cost Effectiveness Analysis of Syphilis Screening Strategies,” London, UK, 2011.
27. L. Mwenge *et al.*, “Costs of facility-based HIV testing in Malawi, Zambia and Zimbabwe,” *PLoS One*, vol. 12, no. 10, 2017.
28. GoI, “Cencus Report 2011: Districts of Bihar, India,” 2012.
29. World Bank Group, “Bihar - Poverty, growth, health, education and inequality brief,” 2016.
30. M. Boelaert, L. Lynen, P. Desjeux, and P. Van der Stuyft, “Cost-effectiveness of competing diagnostic-therapertic strategies for visceral leishmaniasis,” *Bull World Heal. Organ*, vol. 77, no. 8, pp. 667–674, 1999.
31. S. Chatterjee, C. Levin, and R. Laxminarayan, “Unit cost of medical services at different hospitals in India,” *PLoS One*, vol. 8, no. 7, 2013.
32. OANDA, “OANDA Currency Converter and Historical Exchange Rates,” 2020. [Online]. Available: https://www1.oanda.com/currency/converter/.
33. D. Mondal *et al.*, “Visceral Leishmaniasis Elimination Programme in India, Bangladesh, and Nepal: Reshaping the Case Finding/Case Management Strategy,” *PLoS Negl. Trop. Dis.*, vol. 3, no. 1, 2009.
34. WHO, “Education is key to controlling visceral leishmaniasis,” *Bull World Heal. Organ*, vol. 88, no. 1, pp. 11–12, 2010.
35. A. Kumar, S. Saurabh, S. Jamil, and V. Kumar, “Intensely clustered outbreak of visceral leishmaniasis (kala-azar) in a setting of seasonal migration in a village of Bihar, India,” *BMC Infect. Dis.*, vol. 20, no. 10, 2020.
36. E. Le Rutte *et al.*, “Policy Recommendations From Transmission Modeling for the Elimination of Visceral Leishmaniasis in the Indian Subcontinent,” *Clin. Infect. Dis.*, vol. 66, no. S4, 2018.
37. G. Medley, T. Hollingsworth, P. Olliaro, and E. Adams, “Health-seeking behaviour, diagnostics and transmission dynamics in the control of visceral leishmaniasis in the Indian subcontinent,” *Nature*, vol. 528, 2015.
38. C. Bulstra *et al.*, “Visceral leishmaniasis: Spatiotemporal heterogeneity and drivers underlying the hotspots in Muzaffarpur, Bihar, India,” *PLoS Negl. Trop. Dis.*, 2018.
39. R. Mandal, S. Kesari, V. Kumar, and P. Das, “Trends in spatio-temporal dynamics of visceral leishmaniasis cases in a highly-endemic focus of Bihar, India: an investigation

based on GIS tools," *Parasit. Vectors*, vol. 11, no. 220, 2018.
40. V. Das *et al.*, "Longitudinal study of transmission in households with visceral leishmaniasis, asymptomatic infections and PKDL in highly endemic villages in Bihar, India," *PLoS Negl. Trop. Dis.*, vol. 10, no. 12, 2016.
41. M. Banjara *et al.*, "Feasibility of a combined camp approach for vector control together with active case detection of visceral leishmaniasis, post kala-azar dermal leishmaniasis, tuberculosis, leprosy and malaria in Bangladesh, India and Nepal: an exploratory study," *Trans. R. Soc. Trop. Med. Hyg.*, vol. 109, no. 6, pp. 408–415, 2015.
42. M. Banjara *et al.*, "Integrating Case Detection of Visceral Leishmaniasis and Other Febrile Illnesses with Vector Control in the Post-Elimination Phase in Nepal," *Am J Trop Med Hyg*, vol. 100, no. 1, pp. 108–114, 2018.
43. R. Deb *et al.*, "Visceral leishmaniasis cyclical trends in Bihar, India--implications for the elimination programme," *Gates Open Res.*, vol. 2, no. 10, 2018.
44. D. Bora, "Epidemiology of visceral leishmaniasis in India," *Natl Med J India*, vol. 12, no. 2, pp. 62–68, 1999.

Implications for thesis

This chapter contributes new and relevant information for both political and research realms by presenting the costs and outcomes of VL case detection activities in India across varying levels of incidence. Although a singular cost analysis does not necessarily merit policy change, the results of this study could facilitate and contribute towards future surveillance-response research as discussed in Chapters 2 and 3. These findings could also inform resource allocation and budgeting within the KEP and operational partners, as it expands what was known on the scope and scale of ACD within a heterogeneous landscape of incidence.

There is potential to integrate the costs identified in this study into transmission models to forecast the costs and likelihood of reaching elimination benchmarks using different combinations of ACD and PCD, which is discussed in Chapter 5. There is also potential to examine the costs of long-term control measures and opportunities to integrate VL ACD horizontally into other surveillance programmes, which will become increasingly relevant as VL incidence continues to decline.

CHAPTER 5. *LITERATURE REVIEW II:* EXAMINING RESEARCH ACTIONABILITY IN THE KEP THROUGH MATHEMATICAL MODELLING AND KNOWLEDGE TRANSLATION THEORY

This chapter presents literature and theories to support the study design and gaps in knowledge addressed in paper R2 (Chapter 6). The value and use of research to decision makers in India is examined through the lens of mathematical modelling due to its relevance and volume of studies aligned with VL surveillance in India. An overview of modelling in policy is examined across NTD programmes, followed by modelling literature specific to VL in India according to its applicability to surveillance and elimination activities.

The theory of Knowledge Translation is then reviewed to structure the design and conceptual framework used in paper R2. Elements of the Knowledge-to-Action (KTA) cycle are examined, where the theory of Knowledge Utilisation is identified for its categorical dimensions of knowledge exchange between producers (researchers) and users (decision makers). As paper R2 is included with word count limitations, this section aims to provide additional support for the background and methods of Chapter 6.

5.1 Mathematical modelling for surveillance and elimination programmes

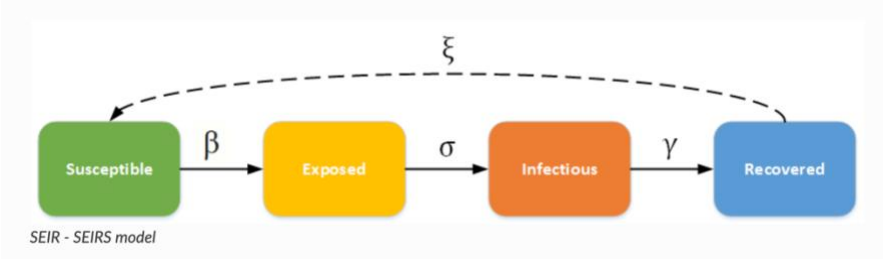
Modelling origins and theory

Some of the first mathematical models were produced in the 18th century to simulate the epidemiology behind smallpox and cholera outbreaks [1]. In characterising increased life expectancy by eliminating diseases, or their transmission, the value of modelling grew rapidly in the late 19th and early 20th century amongst public health physicians in collaboration with statisticians [2, 3]. Modern mathematical epidemiology today is largely a product of compartmental models developed throughout these decades, which argued that disease transmission depends on the number of susceptible and infectious individuals in a population [4]. The concept of a *basic reproduction number*, R_0, was also coined during this time to define the average number of secondary infections resulting from an infectious person in a fully susceptible population during the duration of infectiousness. R_0 denotes a threshold condition between an infection dying out (when $R_0<1$) or the onset of an epidemic (when $R_0>1$) [2, 5].

Mathematical modelling for public health allows for simplified representations of complex phenomena in real-world populations, infectious diseases, and vectors. They are built to describe dynamics, behaviour, and parameters that can be expressed as symbols linked to mathematical formulae and are usually analysed using computers. In the circumstance of a particular disease—VL, for example—the dynamics of infection are categorised into different states: 1) pre-infectious or latent, as the time from infection to when a host is able to transmit to another host, 2) incubation, as the time from infection to onset of clinical symptoms, and 3) infectious, as the period of time until a host is no longer able to transmit the infection to others [6]. There are also different stages of immunity that may result after a host is infected: 1) solid immunity, when an individual cannot become infected again, 2) susceptible, when an

individual recovers from infection but remains vulnerable to some extent to further infection, and 3) no immunity, when an individual develops little or no immunity after recovering from infection [6].

Compartmental models commonly display the dynamics of infection between those susceptible, exposed, infectious, and recovered (SEIR), with the possibility of becoming susceptible once again after recovered (SEIRS) (Figure 5-1) [7, 8]. In Figure 5-1, the infectious rate, β, represents the rate of transmitting the infection between an infectious individual and a susceptible individual (and therefore includes the contact rate and the probability of transmission upon contact); the incubation rate, σ, is the rate at which latent individuals becoming infectious; the recovery rate, γ, is determined by the average duration of infection (i.e. its reciprocal), and ξ is the rate at which recovered individuals lose immunity and return to a susceptible state. The average duration of incubation is 1/σ, and the recovery rate is γ = 1/D (where D is the average duration of infection).



Source: Institute of Disease Modelling (IDM). 2021. Bill and Melinda Gates Foundation.

Figure 5-1. Compartmental model of susceptible, exposed, infectious, recovered (SEIR) and again susceptible (SEIRS) individuals.

Generally, the total population size (N) will be the sum of S + E + I + R. In a closed population with no births or deaths, the reproduction number R_0 = β/γ. In a compartmental model that captures vital dynamics (births and deaths) and the introduction of new

susceptible individuals that may sustain an epidemic, μ and ν represent birth and death rates and are assumed to be equal to maintain a constant population size. In the SEIRS model, ξ represents the rate of waning immunity, whereby individuals remain immune for a certain period of time followed by an exponential distribution when immunity diminishes (at constant rate ξ). Compartmental models may be represented using difference equations that describe the change (increase and decrease) in the number of susceptible, exposed, infectious, and recovered individuals over a discrete time period (Δt), or using differential equations that describe the rate of change with respect to time *t* in the number of susceptible, exposed, infectious, and recovered individuals (i.e. taking time to be infinitesimally small, denoting rates of change) [9].

Model characteristics

Mathematical models are used to understand the situation of an infection in the absence or presence of control interventions; for simulation when the cost of collecting some data may not be feasible but epidemiological projections may be required, or when there is a large number of experimental conditions to test, so that models can be used to test potential hypotheses [10]. A variety of methods have been developed to approach modelling objectives and problem-solving from different perspectives. There are three general categories of methods that encompass mathematical modelling of infectious diseases: 1) statistical methods for epidemic surveillance, outbreaks, and identification of spatial patterns; 2) mathematical and mechanistic state-space models that forecast the evolution of hypothetical spread in dynamic systems; and 3) machine learning approaches that use web-based data mining and surveillance networks to forecast the evolution of on-going epidemic spread [10]. Choosing the appropriate model structure relies on considerations of the natural history of infection, the

accuracy and time period over which model predictions are required, and the research question.

Types of models can be further specified into categories of deterministic or stochastic, static or dynamic, and individual or structured. Deterministic models use pre-determined input parameters that describe what happens on average in a population; for example, using a fixed rate of disease onset and rate of recovery [9]. Stochastic models account for chance and randomness, where the number and rate of people who progress between different disease states may vary [9]. If the risk or force of infection is predetermined and population contact is not explicitly described, a static model will be used [9]. If the risk or force of infection depends on the number of infectious individuals in a population, and will therefore change over time, a dynamic transmission model will be used [9]. Compartmental SEIR models are a type of structured model that categorises health and disease states, and may be further partitioned by age, sex, and other relevant characteristics [11]. Individual-based models are more complex to formulate, as they construct bottom-up population-level networks by identifying interactions and behaviours of autonomous individuals in their environment [11].

Models can also be tailored to the complexities of endemic, epidemic, or vector-borne diseases, and populations with heterogeneous, spatiotemporal, or age-specific indicators [12]. In a given population, R_0 can be used to indicate a theoretical target for an intervention programme to achieve, usually in terms of a vaccine or case detection activities. However, application of this concept is complicated for diseases with long incubation periods between infection and the onset of symptoms, as well as for diseases that require individual level case detection and treatment [13]. This is the case for VL, where the next section details a compartmental SEIR model specific to the pathway of disease progression alongside sandfly

infectivity. Although modelling may be limited in its capacity to provide policy-relevant results for more complex diseases, it remains an important tool for synthesising both quantitative data and qualitative assumptions to examine the impact of different interventions on interrupting transmission [13].

Modelling NTD control and elimination programmes

The application of modelling to inform policy came into widespread use throughout the 20th century, with notable advances to HIV/AIDS, SARS, influenza A, smallpox, tuberculosis, and malaria control programmes [14]. A substantial amount of current infectious disease modelling is aimed at providing support to elimination and eradication efforts by examining population- and host- level dynamics alongside the simulated impact of interventions [15]. Mathematical models have played a pivotal role in guiding programmes and policy making for NTD control and elimination, especially over the past decade [16]. Several research groups have emerged over this time, namely the NTD Modelling Consortium and the London Centre for Neglected Tropical Disease Research (LCNTDR), in efforts to 1) evaluate the effectiveness of current interventions for achieving WHO benchmarks, and 2) to investigate how to best implement new and complementary strategies in the case of insufficient WHO strategies [17, 18].

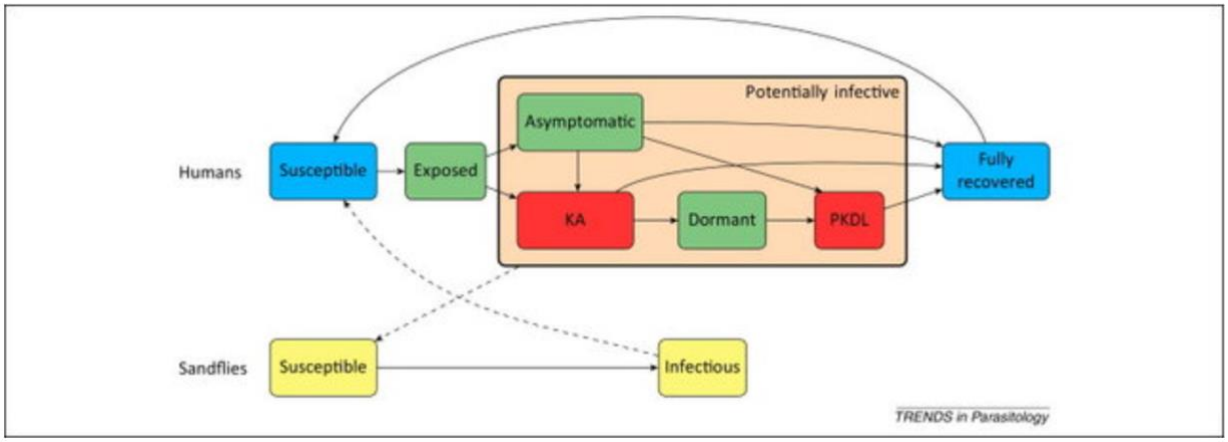
In 2015, the NTD Modelling Consortium published a thematic collection of papers to highlight recent work and advances of modelling for disease-specific NTD control and elimination [19]. Chapter 1 of this thesis describes why NTDs are often categorised according to their tool-readiness as PC-NTDs or IDM-NTDs, under which control- and elimination strategies are also designated. The NTD Modelling Consortium's 2015 publications categorise their developments and insights according to PC-NTDs and IDM-

NTDs. For PC-NTDs eligible for population-level treatment, the intensity and frequency of mass drug administration (MDA) rounds have been successfully modelled to inform elimination strategies, including how to securely scale-down resources without the risk of resurgence [20–24]. Where IDM-NTDs are not suitable for population-level treatment, modelling is instead focused on the effects of surveillance and vector control strategies. For human African trypanosomiasis, Chagas disease, and VL, modelling has consistently identified the risk of hot-spots, heterogeneity, long incubation periods, and insufficient intervention coverage as likely barriers to achieving elimination or EPHP benchmarks [25–28].

5.2 Mathematical modelling for VL

VL model characteristics

The majority of VL modelling in the ISC explores the pathway in which a human host passes through various disease stages at certain rates. These models are constructed using assumptions that rely on the current understanding of biology and natural history of the disease and its vector, or otherwise fitting each model to the best available data. Figure 5-2, cited from a 2015 publication by Rock et al., illustrates a flow diagram of VL disease states and how the sandfly vector may interface with each stage [29]. The coloured boxes correlate to various stages of infection: 1) blue denotes no current infection, 2) green denotes non-symptomatic but infected individuals, 3) red denotes infected and symptomatic individuals, and 4) yellow denotes sandflies with and without infection. The orange box indicates infected human stages that are also infective to sandflies. The dotted lines illustrate the pathway of transmission between humans and sandflies, whereas solid lines illustrate potential paths of progression through various disease stages.



Source: Rock K, Le Rutte E, de Vlas S, Adams E, Medley G. Uniting mathematics and biology for control of visceral leishmaniasis. 2015. **Trends in Parasitology.** 31(6) p 254.

Figure 5-2. SEIR model for visceral leishmaniasis, illustrating pathway of disease states in humans and pathways of transmission with sandfly vectors.

For a parasite or pathogen with multiple host species, cross-species transmission is determined by the force of infection (FOI), which is the rate at which susceptible individuals become infected per unit time [30]. In indirectly transmitted zoonotic diseases with a single reservoir and single target, as is the case of anthroponotic VL's intermediate sandfly vector and definitive human host, FOI is calculated as the product of the prevalence in the reservoir, the reservoir-human contact rate (via the vector contact rate), and the probability of infection given contact [31]. However, the measure of parasite infection in sandflies and incidence in humans is nonlinear, which complicates models and their underlying assumptions [31].

Characterising the prevalence of infection in a vector population is usually accomplished using insect light traps and examining parasite presence in sandflies through microscopy and PCR [32]. A xenodiagnoses study found that infectiousness in VL patients increased with severity of disease—patients with less than 10 parasites per mL blood transmitted to fewer than one in 200 blood-fed flies, while patients with severe clinical disease transmitted to one in five blood-fed flies [33]. Models must also consider the human biting rate and vector density, which may vary according to how temperature and humidity change throughout the

year [34]. There are few studies that estimate sandfly biting rates, and those that exist may not include standardised methods that are sufficiently robust to inform modelling [35, 36]. Sandfly bites elicit a strong antibody response in humans that is specific to the sandfly salivary proteins, which drops 30 days after exposure if the host is not re-exposed [37]. This biomarker provides the best indicator of sandfly biting rates, but is limited by the cross-reactivity observed against saliva of other human-biting sandflies [38, 39].

VL models are further complicated by PKDL sequelae in 5-15% of patients successfully treated for VL, which can take over two years to develop [40]. An individual with PDKL is nearly equally as infectious as a VL patient and is therefore a key component of VL transmission modelling [41]. As PKDL infectiousness was only documented in recent years, its inclusion in models is also relatively recent [42]. However, the emphasis on PKDL transmission in modelling has had a direct impact on updated VL EPHP targets within the WHO 2021-2030 NTD roadmap [43].

VL modelling in the ISC

Since 2015, over two dozen modelling studies have been published specific to VL in India (or the ISC) in an aim to inform national elimination strategies. Chapter 6 (paper R2) of this thesis presents a qualitative study on the perceived value and use of VL modelling to decision makers in India for informing elimination strategies. Although an overview of VL modelling literature is presented in Chapter 6, this section provides further detail on the models and their development over time. The central thematic objectives of this literature revolve around VL transmission, the effects of interventions, and the likelihood of reaching elimination targets, which are explored descriptively below. Table 5-1 then outlines the model type, objectives, outcomes, and gaps identified in each study. The models referenced in this section

aim to provide a comprehensive overview of VL modelling studies in the context of India over the past decade, but are not necessarily exhaustive.

Transmission

Initial modelling of VL in India focused on addressing unknowns of individual-level disease progression, infectivity, and demographic indicators. Modelling the natural history of VL helped to characterise the likelihood of asymptomatic individuals developing VL and the risk of increasing infectivity with progression to clinical symptoms [28, 44, 45]. Where longitudinal data is important but missing, age has been used as a proxy for time but requires more data to uncover infectivity in relation to disease progression [45, 46]. For asymptomatic infections, modelling has shown that age patterns vary considerably over space and time and that acquired immunity may increase with age [47].

The majority of recent VL models have aimed to estimate who contributes to transmission and to what extent, the effects of declining VL incidence, and the accuracy with which future cases can be predicted. Modelling studies have suggested that PKDL presents a major barrier to achieving elimination through *status quo* intervention activities [48]. While earlier modelling studies suggested that asymptomatic individuals were the main drivers of transmission [48, 49], a more recent detailed spatio-temporal analysis incorporating data from xenodiagnoses studies suggests that the relative contribution of asymptomatic individuals is small, and that VL and PKDL cases drive transmission [40, 50–53]. Analyses have shown that as VL incidence decreases in a population, the contribution of PKDL to transmission and the pool of immunologically naïve individuals may increase, creating the potential for new outbreaks [44, 50, 54, 55]. Most recently, modellers have been able to forecast incidence at the sub-district level with meaningful accuracy over a one- to four- month time horizon [56].

Interventions

Interventions have also been evaluated according to their current and projected contribution towards elimination targets. One study modelled the likelihood of achieving elimination by reducing delays in detection or by increasing population coverage for ACD [57]. Another showed that reducing the time from health-seeking behaviour to diagnosis could significantly reduce transmission and incidence, but would require novel diagnostic tests with high specificity to avoid false positives [58]. The role of case proximity in transmission has also been modelled to assess the potential impact of spatiotemporally targeted interventions, which would need to cover a radius up to 500 metres around a new VL case within a short timeframe of their onset in order to reduce transmission risk [50, 59].

Some VL models have analysed scenarios in which the intervention or its effects are more theoretical. The role of a potential vaccine, for instance, has been modelled despite the absence of a vaccine for human VL, as has the potential to control sandfly density by treating cattle with fipronil drugs, which kill both blood-feeding adults and faecal-feeding larval sandflies [60–62]. Vector control models suggest elimination could be possible if sandfly density is reduced by increased efficacy and coverage of IRS or by destroying breeding sites, but there is a lack of evidence that IRS reduces VL incidence and scepticism surrounding the quality of current synthetic pyrethroid used [48, 63–66].

Elimination targets

As elimination targets have been re-defined for 2030, the Bill and Melinda Gates Foundation (BMGF)-funded NTD Modelling Consortium (NTDMC) VL Group reviewed recent models and reported that the current target is suitable for sub-districts with mid-level incidence (up to

five cases per 10,000 population), but additional interventions may be required for high incidence settings and hot spots [67]. NTDMC advised that PKDL must be included in the new targets and that an unintended structural incentive may exist for the KEP to not report cases and prematurely claim elimination [67]. Additionally, a 2017 review suggested VL elimination in India has yet to be achieved because models fail to capture relevant local socio-economic risk factors such as community awareness, access to care, adherence to treatment and follow up, and cost-effectiveness of interventions and policies [68].

Table 5-1. Outline of VL modelling studies in India by model type, objectives, assumptions, outcomes, and gaps identified.

Model [Ref]	Model type, objectives, & assumptions	Outcomes & gaps identified
Stauch et al. 2011 [49]	Deterministic compartmental model Parameters estimated for *L. donovani* transmission and optimising EPHP by comparing treatment-based or vector-based interventions	- Simulation showed that asymptomatic individuals ineligible for treatment primarily drive transmission - Treatment can reduce prevalence of symptomatic disease, but incidence remains unchanged due to intensity of transmission - Vector-related interventions can reduce prevalence of asymptomatic infections, but must be combined with treatment (especially for active PDKL infections)
Stauch et al. 2014 [64]	Transmission model Investigated transmission thresholds dependent on reduction of sandfly density through IRS, LLIN, or destroying breeding sites	- Simulations suggest that EPHP is possible if sandfly density is reduced by 67% by killing sandflies, or if breeding sites can be reduced by 79% through environmental management - Reduction of vector's life expectancy is more effective than reduction of breeding site capacity
Chapman et al. 2015 [28]	Multi-state Markov (compartmental) model Using data collected over a 4-year timeframe, key epidemiological parameters were estimated to simulate the duration of asymptomatic infection and the proportion of individuals that develop clinical symptoms	- Probability of progressing to clinical disease was associated with initial seropositivity and seroconversion - Estimated duration of asymptomatic infection was 147 days, and symptomatic infection was 140 days, with 14.7% of asymptomatic individuals developing clinical disease - The extended period of asymptomatic infection is important to transmission, and future interventions must aim to reduce time from onset of symptoms to diagnosis and treatment
Medley et al. 2015 [58]	A) Disease progression and health-seeking behaviour model Modelled progression of disease from symptoms to diagnosis, and progression of health-seeking behaviour B) Transmission model Modelled incidence of infection, delay between infection and onset of symptoms, duration of latent stage, and compared intervention that reduces time to diagnosis	- Shortening time from healthcare-seeking to diagnosis is likely to reduce VL incidence dramatically - Maintaining population and health system awareness are key as incidence declines - Diagnosing patients early in the fever stage could reduce incidence, even using a moderately-sensitive test - Improving diagnostic specificity is crucial to detecting early stages of active infection

	to intervention targeting undifferentiated fever stage	
Das et al. 2016 [44]	Statistical model Examined VL transmission and seroconversion in households with VL, PKDL, and asymptomatic infections	- VL infections are the major reservoir for transmission - PKDL and asymptomatic individuals do not exhibit higher transmission than VL - Early identification and treatment must be priority interventions for reaching EPHP
Hirve et al. 2016 [63]	Systematic review Examining role of asymptomatic infection, VL treatment relapse, and PKDL in VL transmission	- Prevalence of asymptomatic infections was 4-17 times higher than VL infections - Infectiveness of PKDL was 32-53%, meaning infections do contribute to VL transmission - VL relapse is highest in HIV-VL coinfected patients - Modelling outcomes varied, predicting that elimination is unlikely; asymptomatic individuals may account for up to 82% of transmission; VL cases are the main drivers of transmission; or sandfly density and breeding sites must be reduced by 67-79% to reach EPHP
Poché et al. 2016 [61]	Individual-based, stochastic, life-stage-structured model Simulated the impact of interventions on sandfly vector populations based on fipronil-based drugs for cattle	- Simulation indicated fipronil-based drugs are effective in reducing sandfly abundance, depending on timing of administration relative to seasonality of sandfly lifecycle - For cost-effectiveness, model suggested administration between April-August (3 times per year) - Sandfly density could be reduced between 83-97%
Rock et al. 2016 [45]	Systematic review Examined biology and data behind VL models, realistic predictions, effectiveness of interventions, and key issues	- Better documentation and understanding of the natural history of disease, immunity, and stages of infection are key for future modelling - The role of asymptomatic and symptomatic infections to contributing to transmission must be considered alongside parasite-sandfly-vector interaction - Gaps in knowledge around current biological understanding and the impact of diagnosis, treatment, and vector control undermine model capacity, and will be crucial for the next generation of VL modelling
Le Rutte et al. 2016 [48]	Deterministic, age-structured transmission model 3 models with different main reservoirs of infection (asymptomatic, reactivation after initial infection, and PKDL) were developed. Assumptions about the duration of immunity, exposure to sandflies, and optimal versus sub-optimal IRS effectiveness were fitted to the data for different levels of VL endemicity	- Predicted impact of IRS varied substantially between each model - Reaching EPHP targets in the ISC depends on assumptions regarding the main reservoir of infection - The model assuming asymptomatic infections are main drivers of transmission is likely the most realistic based on model fit to data - Reaching EPHP targets is most likely feasible in areas with low- and medium- endemicity and optimal IRS - In highly endemic settings with sub-optimal IRS efficacy, additional interventions (such as ACD) will be required
Le Rutte et al. 2017 [60]	Transmission model: population-based, deterministic, age-structured Compared 3 models assuming different contributors to transmission: symptomatic individuals, asymptomatic individuals, and asymptomatic individuals with vector population dynamics	- EPHP targets are likely to be met in blocks with <10 VL cases per 10,000 population per year using ACD and IRS tools - In blocks with <5 VL cases per 10,000 population per year, increasing the scope and effectiveness of IRS could lead to elimination 1-3 years earlier - All models suggest VL transmission will continue after EPHP targets are met, and surveillance and control must remain until interruption of transmission is achieved
Hollingsworth et al. 2018 [46]	Systematic Review Modelling literature is reviewed for 9 NTDs to examine progress towards 2020 goals.	- Models have contributed to the knowledge base in terms of natural history, duration and progress of disease states, and drivers of transmission

	For VL, knowledge garnered from statistical, probabilistic, and deterministic age-structured, and transmission models is extrapolated to identify progress and gaps	- More recent models compare and predict the impact of different interventions on reaching EPHP targets - Policy implications can be generated from the body of modelling during this period, especially for improving access to diagnosis and improving efficacy of IRS - Most models suggest asymptomatic individuals contribute significantly to transmission - The relative infectivity of different disease stages is not well-understood, but must be examined to better define assumptions relating to transmission
Le Rutte et al. 2018 [54]	Transmission models Policy-relevant conclusions are synthesised from recent transmission modelling. A model is generated to predictions VL incidence relating WHO-recommended interventions	- Model suggests that WHO guidelines should be sufficient to reach EPHP targets in areas with medium VL endemicity (up to 5 cases per 10,000 population per year) - Additional interventions may be required in high-incidence regions, but the efficacy of interventions depends on the relative infectiousness at different disease stages - Asymptomatic and PKDL infections pose threats to reaching EPHP - As incidence decreases, the pool of immunologically naïve individuals (and potential for new outbreaks) will increase
Chapman et al. 2018 [47]	Statistical and catalytic models Diagnostic tests were compared to prevalence of infection and age groups to assess trends. Infection prevalence age distribution data was modelled using reverse catalytic model to determine seroconversion rates and immunological responses over different timescales	- The age-independent catalytic model provided the best fit to infection prevalence data - Model suggests infection rates may increase with age - Age patterns in asymptomatic infection vary significantly in the ISC - Infection prevalence increased with age, but acquired immunity may also increase with age - Young children may have lower exposure to sandflies - There is poor standardisation of serological tests, which makes data comparison difficult between studies
Chapman et al. 2018 [59]	Spatiotemporal transmission model Key parameters were determined by fitting a transmission model to geo-located epidemiological data in high VL endemic villages. Bayesian inference framework was developed to account for unknown infection times, missing symptom onset, and recovery times	- Parameter estimates suggest that in high endemic settings, VL risk decreases in relation to distance from a case - At 90m from an infective individual, the risk of developing VL is reduced by half - VL cases contribute significantly more to transmission than asymptomatic individuals - Spatially targeted interventions may be key to reducing VL transmission - Interventions must target a radius >300m around a new case to reduce risk of VL transmission
Barley et al. 2019 [55]	Transmission model Model is developed to quantify risk of VL infection in India and Sudan, relying on prevalence level and control reproductive number	- Value of reproductive number is found to be 60% higher in India than in Sudan - Reproductive number is also found to be most sensitive to the average sandfly biting rate, regardless of regional difference - Treatment rate is found to be most sensitive parameter to VL prevalence - Risk factors associated with vector are identified as more critical to transmission dynamics than factors relating to humans
Chapman et al. 2020 [50]	Spatiotemporal transmission model This study combined xenodiagnoses data with geo-located incidence data to detail the changing roles of VL, PKDL, asymptomatic infection, immunity, and transmission	- Model suggests that while VL cases drive transmission in high incidence areas, the contribution of PKDL increases significantly as VL declines - VL transmission is highly focal: 85% of secondary cases occur <300m from inferred infector

		- Average time from infector to secondary cases was <4 months for 88% of cases - Time from PKDL infector to secondary VL infection can be up to 2.9 years - Estimated secondary cases per VL and PKDL case varied from 0 to 6, and depended on infector's duration of symptoms - Prevention of PKDL could reduce VL incidence 25% - Prompt detection and treatment of PKDL is crucial to reaching EPHP
Coffeng et al. 2020 [57]	Transmission model Study aimed to understand how changes in detection delay and population coverage of improved detection impact VL incidence and mortality. Predicted impact of reduced detection delays and increased population coverage	- Improved case detection, either by higher population coverage or by reduced time in detecting symptomatic cases, would cause an initial rise in observed VL incidence followed by a reduction in incidence - Similarly, relaxed detection efforts would lead to an apparent (temporary) one-year reduction of VL incidence followed by resurgence - Duration of symptoms is highly associated with detection effort - Effectiveness of case detection activities cannot be based solely on VL incidence - Duration of symptoms in detected cases must be used as an additional indicator of programme performance
Nightingale et al. 2020 [56]	Spatiotemporal statistical model Models were developed for monthly VL case counts at block level to evaluate fit and one-month-ahead predictive power	- Model captured 94% of observed case counts during a 24-month test period - One-, three-, and four-month ahead forecasts demonstrated strong predictive performance - For models informed by routinely collected surveillance data, predictions are sufficiently accurate and precise - Forecasts could be used to guide stock requirements of RDTs and drugs, or target ACD strategies over space and time
NTDMC 2020 [67]	Systematic review To assist the WHO in formulating new guidelines for 2021-2030 NTD roadmap, NTDMC reviewed modelling objectives and outcomes over past decade	- Current EPHP target is feasible for settings with low to medium endemicities - Additional control measures are required for high incidence areas - PKDL must be added to targets, as models simulate PKDL contributes to VL transmission and will pose a barrier to reaching EPHP - VL is highly focal, and hotspots must be prioritised for increased control measures - 2020 target may incentivise countries to not detect and report cases as incidence declines and benchmarks are approached - Future modelling may focus on the risk of recrudescence when interventions are relaxed after EPHP targets are achieved

Of the 19 published studies included in this table, four are systematic reviews, three are statistical models, one is an individual-based model, and eleven are transmission dynamics models. A reliance on transmission modelling is common across NTDs and vector-borne diseases, as the state variables and parameters used help to characterise and address

underlying biological mechanisms of disease spread, issues of data availability, and political strategies for control and elimination [31, 46, 69]. Although VL required additional time, funding, and momentum to build a modelling base that could inform EPHP and elimination strategies, this decade-long cross-collaboration between disciplines, countries, and modelling partners directly contributed towards the 2021-2030 roadmap for NTDs and was congratulated upon by the WHO [70, 71].

Actionability of VL modelling in the KEP

Mathematical models are increasingly relied on as support tools to estimate risks and generate public health recommendations, but there are no formal guidelines or frameworks to substantiate their professional competencies or translation into policy [72]. In public health, actionability spans: 1) the relevance and completeness of information provided by knowledge producers, 2) the way in which information is communicated to a target audience, and 3) the capacity of decision makers to address barriers and take recommended steps [73]. Several factors may influence the actionability of modelling to inform policy that are both internal and external to models themselves. A study on HIV modelling in Africa attributed its successful policy influence to sustaining partnerships, capacity building, and identifying a champion for promoting the value and use of modelling evidence [74]. For malaria elimination, another study identified that mathematical modelling had greater influence in policy when combined with economic modelling, particularly at the end stages of elimination [75].

Figure 5-3 depicts how published VL modelling literature for the ISC aligns with objectives of pillar 1 within the WHO NTD roadmap for 2021-2030. Framing this literature within the WHO roadmap helps to convey their relational development over time, where the majority of

models address technical and strategic dimensions of VL elimination. The objective of paper R2, which examines ways in which modelling may be enabled to inform policy in India, is outlined in red.

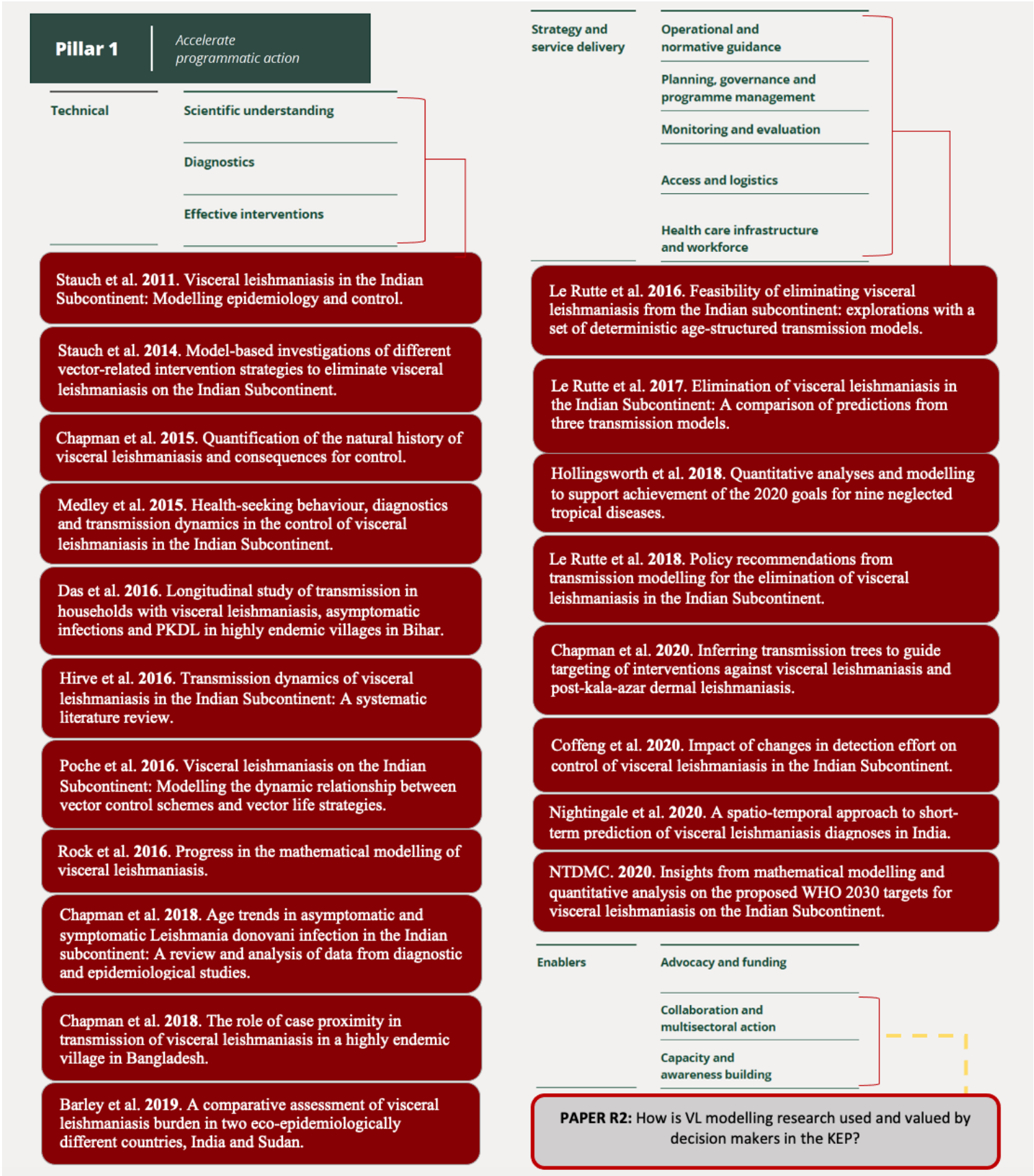


Figure 5-3. Mathematical modelling literature for VL in the ISC framed within Pillar 1 of the WHO NTD framework for 2021-2030.

5.3 Examining the actionability of VL modelling within the KEP

Chapter 6 details the conceptual framework and methodology of knowledge utilisation used to guide paper R2. This section aims to discuss knowledge translation theories and literature for additional context and support.

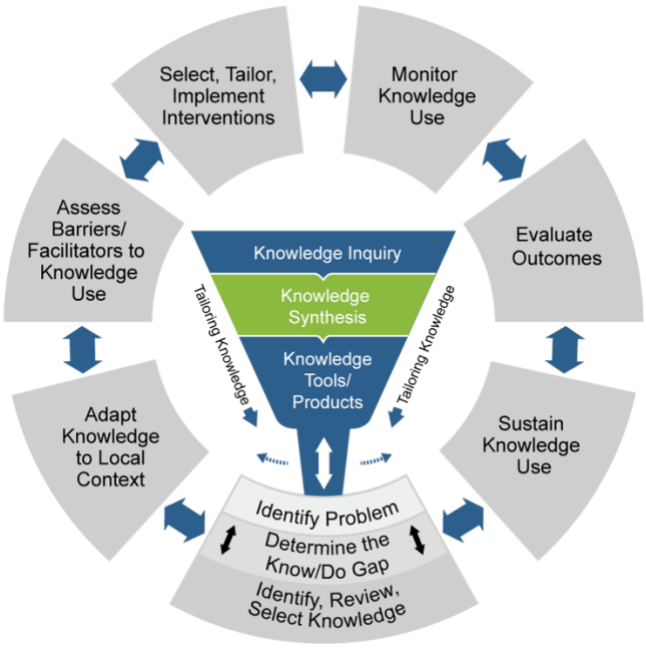
Health policy and systems research (HPSR)

Health policy and systems research (HPSR) is a broad and interdisciplinary field that aims to improve how health systems respond and adapt to health policies, and how health policies can shape broader determinants of health [76]. HPSR is a collection of economics, sociology, political science, and epidemiology that seeks to understand and improve how health goals can be achieved and how actors interact in the policy and implementation process. Although commonplace in high-income country governance, HPSR is not a foundation of many LMIC policy processes, which results in barriers to effectively designing and implementing health services for populations in need [77, 78]. A prevalent issue in HPSR is the inconsistent use of terminology to describe research being conducted: depending on the discipline, multiple definitions of operational-, implementation-, dissemination-, or health systems research exist for often duplicated or overlapping objectives [79]. Defining the appropriate HPSR domain is essential to characterise the focus, users, and utility of the research outputs. Health system research focuses on building blocks and policy within a healthcare system, implementation research focuses on strategies for specific products or services, and operational research focuses on specifics of health programmes on a local level [79].

Knowledge Translation and Knowledge-to-Action theories

Often synonymous with implementation research is the theory of knowledge translation (KT), which aims to explore gaps in decision making, improve knowledge synthesis and

distillation, enhance determinants of knowledge uptake, and determine the effectiveness and sustainability of different KT approaches [80]. KT involves examining the 'know-do' gap between knowledge producers (researchers) and knowledge users (decision makers). A commonly applied KT model is the knowledge-to-action (KTA) framework, which provides an iterative and dynamic approach to investigating complexities of the KTA cycle (Figure 5-4).



Source: Straus S, Tetroe J, Graham I. Chapter 1: Knowledge Translation in Health Care: Moving from Evidence to Practice. 2013. BMJ Publishing Group. 2nd Edition. Oxford, UK.

Figure 5-4. The Knowledge-to-Action cycle.

KTA is used widely in public health research, either in its entirety or in component form, to guide and conceptualise the design, delivery, and evaluation of implementation activities [81]. WHO also embeds the KTA cycle into several international projects, including the GRADE working group, which evaluates the quality of evidence and strength of policy

recommendations, and the evidence-informed policy network (EVIPNet), which promotes the use of health research evidence in policy making within 36 LMIC [82, 83].

To design a study that addresses research actionability of modelling in the KEP, KTA cycle components that are most relevant to the content and context of VL in India must be identified. The KTA framework contains two components: the generation of knowledge to address a public health issue or problem (the central funnel) and its translation into action (the outer cycle). The components and dynamics within the knowledge-generation cycle could be used to examine the processes and barriers of translating mathematical modelling research into policy in India.

Knowledge generation begins with knowledge creation, which typically stems from basic, applied, and action research published in scientific literature [84]. Knowledge diffusion, then, focuses on communication channels and information dissemination between researchers and public health actors. Lastly, knowledge utilisation seeks to measure information pickup, processing, and application from the perspective of decision makers and other public health actors, which denotes an important transfer of power and accountability in the cycle. Knowledge on VL modelling in the KEP has been both created (generated) and diffused (published), therefore the question of whether or not it is or should be applied to policy must be investigated within the component of knowledge utilisation.

5.4 Knowledge utilisation

Knowledge utilisation is not only a component of the KTA cycle, but also an independent model that encompasses many perspectives, contexts, and stages of knowledge application [85]. It can be applied to evaluate programme and policy effectiveness against different types

of knowledge use in certain contexts, or the ways in which knowledge may be used symbolically, rhetorically, or tactically. Several knowledge utilisation models have emerged since the late 1970's, which span different objectives: to address public policy making, problem-, structure-, or process-contingency, as well as different perspectives: towards either the knowledge producer (researcher) or knowledge user (decision maker) [86, 87].

For VL modelling in the KEP, knowledge utilisation requires the perspective of decision makers and programme managers as knowledge users, the identification of specific knowledge transfer events, and a way in which the value and application of modelling could be examined. In 1980, Knott and Wildavsky coined 'seven standards of knowledge utilisation' to untangle specific dimensions of knowledge transfer that capture experiences, perceptions, and insight of policy makers [88]. These seven dimensions of knowledge utilisation include: reception, cognition, reference, effort, adoption, implementation, and impact, and are employed in the conceptual framework used in Chapter 6 (paper R2) to study the value and use of VL modelling to decision makers in India.

5.5 How can HPSR inform modelling actionability in India?

WHO advocates that HPSR must be embedded into the process of decision making, rather than existing as an end in itself, which requires global, regional, and country-level collaboration [89]. A systematic review found that HPSR was particularly influential to policy in LMIC when embedded within one or more building blocks of: health service delivery, medical products, information systems, health workforce, financing, or government leadership [90]. The institutional embeddedness of research in the health sector also relies on sufficient research capacity, reputation, and the quantity and quality connections between institutions and decision makers [91].

Policy implementation in the context of India is complex, whereby some decision makers and stakeholders are thought to have less power than front-line providers, managers, and citizens [92]. However, healthcare directives and programme funding are coordinated at the national level, with operations run by individual states. For a disease such as VL with low incidence and relatively limited political attention, it is likely that state, district, and block-level programme managers will have different insight into barriers, gaps, and successes of KEP activities than policy makers at the national level. VL modelling has the potential to inform KEP activities and health system building blocks on a variety of echelons, and it is important to examine its value and use to a diversity of actors involved in the knowledge-use process. In this, the participants in paper R2 span different institutions, geographic locations, educational and training backgrounds, and proximities to working with research in an effort to understand how research is embedded and how its use could be improved in the policy process.

Implications for thesis

This chapter reviews the current VL modelling literature specific to the context of India, and frames how this body of work addresses technical and strategic objectives outlined in pillar 1 of the WHO NTD roadmap for 2021-2030. A gap is identified in the mobilisation VL modelling research to inform policy. Although its relevance to policy is evident, the extent to which decision makers understand, value, and use modelling to inform surveillance strategies is documented or understood. The second half of this chapter identifies how research actionability can be studied through the theory of KT, or more specifically the knowledge utilisation framework. Events of knowledge reception, cognition, and application from researchers to decision makers are emphasised in this model and employed within the

qualitative study presented in Chapter 6 (paper R2). The importance of embedding HPSR into research and decision-making processes is also highlighted and discussed further in Chapter 7, the discussion.

References

1. Brauer F, Castillo-Chavez C, Feng Z. Mathematical models in epidemiology. First Edit. Bloch A, Epstein C, Goreily A, Greengard L, editors. New York: Springer Nature; 2019.
2. Ross R. The Prevention of Malaria. 2nd ed. Murray J, editor. London; 1911.
3. En'ko P. On the course of epidemics of some infectious diseases. J Epidemiol. 1889; 18(1): 749–55.
4. Hamer W. Epidemic disease in England - the evidence of variability and of persistance. Lancet. 1906; 167(1): 733–8.
5. MacDonald G. The Epidemiology and Control of Malaria. Oxford, UK: Oxford University Press; 1957.
6. Vynnycky E, White R. An Introduction to Infectious Disease Modelling. In: An Introduction to Infectious Disease Modelling. First Edit. Oxford, UK: Oxford University Press; 2010.
7. IDM. SEIR and SEIRS models [Internet]. Institute for Disease Modelling: Bill and Melinda Gates Foundation. 2021 [cited 2021 Mar 23]. Available from: https://docs.idmod.org/projects/emod-hiv/en/latest/model-seir.html
8. Kermack W, McKendrick A. Contributions to the mathematical theory of epidemics--I. 1927. Bull Math Biol. 1990; 53(1): 1-2.
9. Vynnycky E, White R. How are models set up? An introduction to difference equations. In: An Introduction to Infectious Disease Modelling. First Edit. Oxford, UK: Oxford University Press; 2010. p. 13–40.
10. Siettos C, Russo L. Mathematical modeling of infectious disease dynamics. Virulence. 2013; 4(4): 295-306.
11. Willem L, Verelst F, Bilcke J, Hens N, Beutels P. Lessons from a decade of individual-based models for infectious disease transmission: A systematic review (2006-2015). BMC Infect Dis. 2017; 17(612): DOI: https://doi.org/10.1186/s12879-017-2699-8.
12. Brauer F, Castillo-Chavez C, Feng Z. Mathematical Models in Epidemiology. First. Bloch A, Epstein C, Goreily A, Greengard L, editors. New York, NY: Springer Nature; 2019.
13. Vynnycky E, White R. Special topics in infectious disease modelling. In: An Introduction to Infectious Disease Modelling. First Edit. Oxford, UK: Oxford University Press; 2010.
14. Kretzschmar M, Wallinga J. Mathematical models in infectious disease epidemiology. Mod Infect Dis Epidemiol. 2010; 12(1): 209–21.
15. Institute for Disease Modelling. Research [Internet]. Institute for Disease Modelling: Bill and Melinda Gates Foundation. 2021 [cited 2021 Mar 23]. Available from: https://idmod.org/research
16. Basáñez M-G, Anderson R. Mathematical Models for Neglected Tropical Diseases: Essential Tools for Control and Elimination, Part B. In: Advances in Parasitology [Internet]. First Edit. London, UK: Elsevier; 2016. Available from: https://www.elsevier.com/books/mathematical-models-for-neglected-tropical-diseases-essential-tools-for-control-and-elimination-part-b/anderson/978-0-12-809971-1
17. NTD Modelling Consortium. NTD Modelling Consortium [Internet]. 2021 [cited 2021 Mar 23]. Available from: http://www.ntdmodelling.org/
18. London Centre for NTD Research. London Centre for Neglected Tropical Disease Research [Internet]. 2021 [cited 2021 Mar 23]. Available from: https://www.londonntd.org/

19. NTD Modelling Consortium. Quantitative analysis of strategies to achieve the 2020 goals for neglected tropical diseases: where are we now? Parasit Vectors. 2015; 8(1): DOI: https://doi.org/10.1186/s13071-015-1235-1.
20. Stolk WA, Walker M, Coffeng LE, Basáñez M-G, de Vlas SJ. Required duration of mass ivermectin treatment for onchocerciasis elimination in Africa: a comparative modelling analysis. Parasites and Vectors. 2015; 8(552): DOI: 10.1186/s1307-015-1159-9.
21. Irvine MA, Reimer LJ, Njenga SM, Gunawardena S, Kelly-Hope L, Bockarie M, et al. Modelling strategies to break transmission of lymphatic filariasis - aggregation, adherence and vector competence greatly alter elimination. Parasites and Vectors. 2015; 8(547): DOI: https://doi.org/10.1186/s13071-015-1152-3.
22. Jambulingam P, Subramanian S, de Vlas S, Vinubala C, Stolk W. Mathematical modelling of lymphatic filariasis elimination programmes in India: required duration of mass drug administration and post-treatment level of infection indicators. Parasites and Vectors. 2016; 9(501): DOI: https://doi.org/10.1186/s13071-016-1768-y.
23. Coffeng LE, Bakker R, Montresor A, de Vlas S. Feasibility of controlling hookworm infection through preventive chemotherapy: a simulation study using the individual-based WORMSIM modelling framework. Parasites and Vectors. 2015; 8(541): DOI: https://doi.org/10.1186/s13071-015-1151-4.
24. Gurarie D, Yoon N, Li E, Ndeffo-Mbah M, Durham D, Phillips A, et al. Modelling control of Schistosoma haematobium infection: predictions of the long-term impact of mass drug administration in Africa. Parasites and Vectors. 2015; 8(529): DOI: https://doi.org/10.1186/s13071-015-1144-3.
25. Rock KS, Torr SJ, Lumbala C, Keeling M. Quantitative evaluation of the strategy to eliminate human African trypanosomiasis in the Democratic Republic of Congo. Parasites and Vectors. 2015; 8(532): DOI: https://doi.org/10.1186/s13071-015-1131-8.
26. Cucunubá Z, Nouvellet P, Conteh L, Vera M, Angulo V, Dib J, et al. Modelling historical changes in the force-of-infection of Chagas disease to inform control and elimination programmes: application in Colombia. BMJ Glob Heal. 2017; 2(3): e000345.
27. Rock KS, Torr SJ, Lumbala C, Keeling MJ. Predicting the impact of intervention strategies for sleeping sickness in two high-endemicity health zones of the Democratic Republic of Congo. PLoS Negl Trop Dis. 2017; 11(1): e0005162.
28. Chapman LAC, Dyson L, Courtenay O, Chowdhury R, Bern C, Medley GF, et al. Quantification of the natural history of visceral leishmaniasis and consequences for control. Parasit Vectors. 2015; 8(521): DOI: https://doi.org/10.1186/s13071-015-1136-3.
29. Rock KS, Le Rutte EA, de Vlas SJ, Adams ER, Medley GF, Hollingsworth TD. Uniting mathematics and biology for control of visceral leishmaniasis. Cell Press. 2015; 31(6): 251-259.
30. Kilpatrick A. Disease ecology. Nat Educ Knowl. 2010; 3(10): 55.
31. Hollingsworth TD, Pulliam JRC, Funk S, Truscott JE, Isham V, Lloyd AL. Seven challenges for modelling indirect transmission: Vector-borne diseases, macroparasites and neglected tropical diseases. Epidemics. 2015; 10(1): 16–20.
32. Poché DM, Poché RM, Mukherjee S, Franckowiak GA, Briley LN, Somers DJ, et al. Phlebotomine sandfly ecology on the Indian subcontinent: does village vegetation play a role in sandfly distribution in Bihar, India? Med Vet Entomol. 2017; 31(2): 207–213.
33. Singh OP, Tiwary P, Kushwaha AK, Singh SK, Singh DK, Lawyer P, et al. Xenodiagnosis to evaluate the infectiousness of humans to sandflies in an area endemic for visceral leishmaniasis in Bihar, India: a transmission-dynamics study.

Lancet Microbe. 2021; 2(1): e23-e31.
34. Cameron MM, Acosta-Serrano A, Bern C, Boelaert M, Den Boer M, Burza S, et al. Understanding the transmission dynamics of Leishmania donovani to provide robust evidence for interventions to eliminate visceral leishmaniasis in Bihar, India the LCNTDR Collection: Advances in scientific research for NTD control. Parasites and Vectors. 2016; 9(25): DOI: https://doi.org/10.1186/s13071-016-1309-8.
35. Ready P. Biology of phlebotomine sand flies as vectors of disease agents. Annu Rev Entomol. 2013; 58(1): 227–250.
36. Bates PA, Depaquit J, Galati EA, Kamhawi S, Maroli M, McDowell M, et al. Recent advances in phlebotomine sand fly research related to leishmaniasis control. Parasites and Vectors. 2015; 8(131): DOI: https://doi.org/10.1186/13071-015-0712-x.
37. Andrade BB, Teixeira CR. Biomarkers for exposure to sand fly bites as tools to aid control of leishmaniasis. Front Immunol. 2012; 3(121): DOI: https://doi.org/10.3389/fimmu.2012.00121.
38. Clements MF, Gidwani K, Kumar R, Hostomska J, Dinesh DS, Kumar V, et al. Measurement of recent exposure to Phlebotomus argentipes, the vector of Indian visceral leishmaniasis, by using human antibody responses to sand fly saliva. Am J Trop Med Hyg. 2010; 82(1): 801–807.
39. Gidwani K, Picado A, Rijal S, Singh SP, Roy L, Volfova V, et al. Serological markers of sand fly exposure to evaluate insecticidal nets against visceral leishmaniasis in India and Nepal: A cluster-randomized trial. PLoS Negl Trop Dis. 2011; 5(9): e1296.
40. Mondal D, Bern C, Ghosh D, Rashid M, Molkina R, Chowdury R, et al. Quantifying the infectiousness of post-kala-azar dermal leishmaniasis towards sandflies. Clin Infect Dis. 2019; 69(2): 251-258.
41. Das V. Clinical epidemiologic profile of a cohort of post-kala-azar dermal leishmaniasis patients in Bihar, India. Am J Trop Med Hyg. 2012; 86(1): 959–961.
42. Le Rutte EA, Zijlstra EE, de Vlas SJ. Post-Kala-Azar dermal leishmaniasis as a reservoir for visceral leishmaniasis transmission. Trends Parasitol. 2019; 35(8): 590–592.
43. World Health Organization. Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021-2030 [Internet]. Geneva; 2020. Available from: https://www.who.int/publications/i/item/9789240010352
44. Das VNR, Pandey RN, Siddiqui NA, Chapman LAC, Kumar V, Pandey K, et al. Longitudinal study of transmission in households with visceral leishmaniasis, asymptomatic infections and PKDL in highly endemic villages in Bihar, India. PLoS Negl Trop Dis. 2016; 10(12): e0005196.
45. Rock KS, Medley GF, Quinnell RJ, Courtenay O. Progress in the Mathematical Modelling of Visceral Leishmaniasis. Adv Parasitol. 2016; 94(1): 49–131.
46. Hollingsworth TD, Adams ER, Anderson RM, Atkins K, Bartsch S, Basáñez M, et al. Quantitative analyses and modelling to support achievement of the 2020 goals for nine neglected tropical diseases. Parasit Vectors. 2015; 8(630): DOI: https://doi.org/10.1186/s13071-015-1235-1.
47. Chapman LAC, Morgan ALK, Adams ER, Bern C, Medley GF, Hollingsworth TD. Age trends in asymptomatic and symptomatic Leishmania donovani infection in the Indian subcontinent : A review and analysis of data from diagnostic and epidemiological studies. PLoS Negl Trop Dis. 2018; 12(12): e0006803.
48. Le Rutte EA, Coffeng LE, Bontje DM, Hasker EC, Postigo JAR, Argaw D, et al. Feasibility of eliminating visceral leishmaniasis from the Indian subcontinent : explorations with a set of deterministic age-structured transmission models. Parasit Vectors. 2016; 9(24): DOI: 10.1186/s13071-016-1292-0.

49. Stauch A, Sarkar RR, Picado A, Ostyn B, Sundar S, Rijal S, et al. Visceral Leishmaniasis in the Indian Subcontinent: Modelling Epidemiology and Control. PLoS Negl Trop Dis. 2011; 5(11): e1405.
50. Chapman LAC, Spencer SEF, Pollington TM, Jewell CP, Mondal D, Cameron M, et al. Inferring transmission trees to guide targeting of interventions against visceral leishmaniasis and post – kala-azar dermal leishmaniasis. Proc Natl Acad Sci U S A. 2020; 117(41): 25742-25750.
51. Napier LE, Smith ROA, Das Gupta CR, Mukerji, S. The infection of *phlebotomus argentipes* from Dermal Leishmanial lesions. Indian J Med Res. 1933; 21(1): 173-177.
52. Addy M, Nandy A. Ten years of kala-azar in west Bengal, Part 1. Did post-kala-azar dermal leishmaniasis initiate the outbreak in 24-Parganas? Bull World Health Organ. 1992; 70(3): 341-346.
53. Molina R, Ghosh D, Carrillo E, Monnerat S, Bern C, Mondal D, et al. Infectivity of post-kala-azar dermal leishmaniasis patients to sand flies: Revisiting a proof of concept in the context of the Kala-Azar Elimination Program in the Indian Subcontinent. Clin Infect Dis. 2017; 65(1): 150-153.
54. Le Rutte EA, Chapman LAC, Coffeng LE, Ruiz-Postigo JA, Olliaro PL, Adams ER, et al. Policy Recommendations From Transmission Modeling for the Elimination of Visceral Leishmaniasis in the Indian Subcontinent. Clin Infect Dis. 2018; 66(4): 301–308.
55. Barley K, Mubayi A, Safan M, Castillo-chavez C. A Comparative Assessment of Visceral Leishmaniasis Burden in Two Eco-Epidemiologically Different Countries, India and Sudan. Biology (Basel). 2019; DOI: https://doi.org/10.1101/592220.
56. Nightingale ES, Chapman LAC, Srikantiah S, Subramanian S, Jambulingam P, Bracher J, et al. A spatio-temporal approach to short-term prediction of visceral leishmaniasis diagnoses in India. PLoS Negl Trop Dis. 2020; 14(7): e0008422.
57. Coffeng LE, Le Rutte EA, Muñoz J, Adams ER, Prada JM, de Vlas SJ, et al. Impact of Changes in Detection Effort on Control of Visceral Leishmaniasis in the Indian Subcontinent. J Infect Dis. 2020; 221(Supplement 5): S546-S553.
58. Medley GF, Hollingsworth TD, Olliaro PL, Adams ER. Health-seeking behaviour, diagnostics and transmission dynamics in the control of visceral leishmaniasis in the Indian subcontinent. Nature. 2015; 528(7580): 102–108.
59. Chapman LAC, Jewell CP, Spencer SEF, Pellis L, Datta S, Chowdhury R, et al. The role of case proximity in transmission of visceral leishmaniasis in a highly endemic village in Bangladesh. PLoS Negl Trop Dis. 2018; 12(10): e0006453.
60. Le Rutte EA, Chapman LAC, Coffeng LE, Jervis S, Hasker EC, Dwivedi S, et al. Elimination of visceral leishmaniasis in the Indian subcontinent: a comparison of predictions from three transmission models. Epidemics. 2017; 18(1): 67–80.
61. Poché DM, Grant WE, Wang H-H. Visceral Leishmaniasis on the Indian Subcontinent: Modelling the dynamic relationship between vector control schemes and vectorlLife cycles. PLoS Negl Trop Dis. 2016; 10(8): e0004868.
62. Poché DM, Wang H-H, Grant WE. Visceral leishmaniasis on the Indian Subcontinent: Efficacy of fipronil-based cattle treatment in controlling sand fly populations is dependent on specific aspects of sand fly ecology. PLoS Negl Trop Dis. 2020; 14(2): e0008011.
63. Hirve S, Boelaert M, Matlashewski G, Mondal D, Arana B, Kroeger A, et al. Transmission Dynamics of Visceral Leishmaniasis in the Indian Subcontinent – A Systematic Literature Review. PLoS Negl Trop Dis. 2016; 10(8): e0004896.
64. Stauch A, Duerr H-P, Picado A, Ostyn B, Sundar S, Rijal S, et al. Model-Based Investigations of Different Vector-Related Intervention Strategies to Eliminate

Visceral Leishmaniasis on the Indian Subcontinent. PLoS Negl Trop Dis. 2014; 8(4): e2810.
65. Poché DM, Garlapati RB, Mukherjee S, Torres-Poché Z, Hasker E, Rahman T, et al. Bionomics of Phlebotomus argentipes in villages in Bihar, India with insights into efficacy of IRS-based control measures. PLoS Negl Trop Dis. 2018; 12(1): e0006168.
66. Picado A, Dash AP, Bhattacharaya S, Boelaert M. Vector control interventions for visceral leishmaniasis elimination initiative in South Asia, 2005-2010. Indian J Med Res. 2012; 136(1): 22-31.
67. NTD Modelling Consortium. Insights from mathematical modelling and quantitative analysis on the proposed WHO 2030 targets for visceral leishmaniasis on the Indian subcontinent. Gates Open Research; 2020.
68. DebRoy S, Prosper O, Mishoe A, Mubayi A. Challenges in modeling complexity of neglected tropical diseases: a review of dynamics of visceral leishmaniasis in resource limited settings. Emerg Theme Epidemiol. 2017; 14(10): DOI: https://doi.org/10.1186/s12982-017-0065-3.
69. Hollingsworth TD. Counting down the 2020 goals for 9 neglected tropical diseases: What have we learned from quantitative analysis and transmission modelling? Clin Infect Dis. 2018; 66(4): 237–44.
70. NTD Modelling Consortium. Modelling study widens viewpoints for new roadmap for neglected tropical diseases. Roadmap to 2030. 2019. Available from: https://www.ntdmodelling.org/news/modelling-provides-fresh-perspective-to-who-s-new-roadmap-for-neglected-tropical-diseases.
71. World Health Organization. Thirteenth meeting of the Strategic and Technical Advisory Group for neglected tropical diseases. Geneva; 2020. Available from: https://www.who.int/news-room/events/detail/2020/09/15/default-calendar/13th-meeting-of-the-strategic-and-technical-advisory-group-for-neglected-tropical-diseases.
72. Boden LA, McKendrick IJ. Model-based policymaking: A framework to promote ethical “good practice” in mathematical modeling for public health policymaking. Front Public Heal. 2017; 5(68): DOI: 10.3389/fpubh.2017.00068.
73. World Health Organization. Communicating for health: Principle of Actionability [Internet]. World Health Organization. 2021 [cited 2021 Jun 10]. Available from: https://www.who.int/about/communications/actionable.
74. Njeuhmeli E, Schnure M, Vazzano A, Gold E, Stegman P, Kripke K, et al. Using mathematical modeling to inform health policy: A case study from voluntary medical male circumcision scale-up in eastern and southern Africa and proposed framework for success. PLoS One. 2019; 14(3): e0213605.
75. Maude RJ, Lubell Y, Socheat D, Yeung S, Saralamba S, Pongtavornpinyo W, et al. The role of mathematical modelling in guiding the science and economics of malaria elimination. Int Health. 2010; 2(4-6): 239-246.
76. World Health Organization. What is Health Policy and Systems Research (HPSR) and why does it matter? [Internet]. Geneva; 2007. Available from: https://ahpsr.who.int/what-we-do/what-is-health-policy-and-systems-research-(hpsr)
77. Fryatt R, Mills A, Nordstrom A. Financing of health systems to achieve the health Millenium Development Goals in low-income countries. Lancet. 2010; 375(9712): p419-426.
78. Madon T, Hofman KJ, Kupfer L, Glass RI. Public health implementation science. Science. 2007; 318(5857): 1728-1729.
79. Remme JHF, Adam T, Becerra-Posada F, D’Arcangues C, Devlin M, Gardner C, et al. Defining research to improve health systems. PLoS Med. 2010; 7(11): e1001000.
80. Straus SE, Tetroe J, Graham I. Knowledge translation: What it is and what it isn’t. In:

Knowledge Translation in Health Care: Moving from Evidence to Practice. 2nd ed. Oxford, UK: John Wiley & Sons; 2013. p. 1–14.
81. Field B, Booth A, Ilott I, Gerrish K. Using the Knowledge to Action Framework in practice: A citation analysis and systematic review. Implement Sci. 2014; 9(172): DOI: https://doi.org/10.1186/s13012-014-0172-2.
82. World Health Organization. EVIPNet in Action: Evidence- Informed Policy Network [Internet]. Geneva; 2016. Available from: https://www.who.int/initiatives/evidence-informed-policy-network.
83. World Health Organization. Knowledge-to-Action (KTA) Framework [Internet]. Geneva; 2021. Available from: https://www.who.int/reproductivehealth/topics/best_practices/greatproject_KTAframework/en/.
84. Edwards L. Chapter II: Knowledge utilization: A historical and conceptual overview. In: Using Knowledge and Technology to Improve the Quality of Life of People who have Disabilities. Union Institute; 1991.
85. Blake SC, Ottoson JM. Knowledge utilization: Implications for evaluation. New Dir Eval. 2009; 2009(124): 21-34.
86. Weiss C. The many meanings of research utilization. Public Adm Rev. 1979;39(5).
87. Edwards L. Chapter VI: Models of Knowledge Utilization. In: Using Knowledge and Technology to Improve the Quality of Life of People who have Disabilities. Union Institute; 1991.
88. Knott J, Wildavsky A. If dissemination is the solution, what is the problem? In: Knowledge: Creation, Diffusion, Utilisation. 1980. p. 537–78.
89. World Health Organization. Alliance for Health Policy and Systems Research 2019 Annual Report [Internet]. Geneva; 2020. Available from: https://www.who.int/alliance-hpsr/resources/publications/2019-annual-report/en/.
90. Koon AD, Rao KD, Tran NT, Ghaffar A. Embedding health policy and systems research into decision-making processes in low- and middle-income countries. Heal Res Policy Syst. 2013; 11(30): DOI: 10.1186/1478-4505-11-30.
91. Koon AD, Nambiar D, Rao KD. Embedding of research into decision-making processes in low- and middle-income countries. Heal Res Policy Syst. 2012; 8(11): 1-27.
92. Gupta A. Red Tape: Bureaucracy, Structural Violence, and Poverty in India. Duke University Press; 2012.

CHAPTER 6. *PAPER R2:* VISCERAL LEISHMANIASIS ELIMINATION IN INDIA: WHY DO POLITICAL DECISION MAKERS STRUGGLE TO ACT UPON MATHEMATICAL MODELLING EVIDENCE?

Mathematical modelling of infectious diseases is a practical and progressive tool in policy making, particularly for informing NTD surveillance and elimination programmes. This chapter presents paper R2, a qualitative examination of the perceived value and actionability of VL modelling to decision makers in the KEP. Chapter 5 details VL modelling literature published over the past decade as it relates to informing transmission dynamics, the impact of interventions, and the likelihood of reaching EPHP targets in India. The theory of knowledge utilisation is also described in the previous chapter to frame its relevance towards specific events of knowledge transfer between producers (researchers) and users (decision makers). This chapter aims to explore research actionability through the lens of VL modelling in India given its substantial evidence base and relevance to surveillance-response activities. Ways in which modelling and decision-making processes could be improved are discussed within this chapter, whereas broader implications towards VL surveillance and interdisciplinary research are explored in Chapter 7, the discussion.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1605001	**Title**	Ms.
First Name(s)	Natalie		
Surname/Family Name	Dial		
Thesis Title	SCIENCE AND SURVEILLANCE IN THE VISCERAL LEISHMANIASIS ELIMINATION PROGRAMME IN INDIA		
Primary Supervisor	Graham Medley		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	PLOS Global Public Health
Please list the paper's authors in the intended authorship order:	Natalie J. Dial, Simon L. Croft, Lloyd A. C. Chapman, Fern Terris-Prestholt, Graham F. Medley
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	ND led conceptualisation, data curation, investigation, formal analysis, visualisation, original draft writing, review and editing.

SECTION E

Student Signature	[redacted]
Date	16 July 2021

Supervisor Signature	[redacted]
Date	29 July 2021

Visceral leishmaniasis elimination in India: Why do political decision makers struggle to act upon mathematical modelling evidence?

Natalie J. Dial[1*], Simon L. Croft[2], Lloyd A.C. Chapman[1], Fern Terris-Prestholt[1] Graham F. Medley[1]

[1] Department of Global Health and Development, Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom

[2] Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

*natalie.dial@lshtm.ac.uk (ND)

ABSTRACT

As India comes closer to eliminating visceral leishmaniasis (VL) as a public health problem, surveillance efforts and elimination targets must be continuously revised and strengthened to identify the estimated 3,000 remaining cases. Mathematical modelling is a compelling research discipline for informing policy and programme design in its capacity to project incidence across space and time, the likelihood of achieving benchmarks, and the impact of different interventions. To gauge the extent to which modelling informs policy in India, this qualitative analysis explores how and whether decision makers understand, value, and reference recently produced VL modelling research. Sixteen semi-structured interviews were carried out with both users and producers of VL modelling research, guided by a knowledge utilisation framework grounded in knowledge translation theory. Participants reported that barriers to knowledge utilisation often relate to assumptions that 1) models accurately reflect transmission dynamics, 2) modellers apply their analyses to specific programme operations, and 3) there is accountability in the process of translating knowledge to policy. Employing communication intermediaries may be crucial to garnering the political trust and support needed to translate knowledge into programme activities.

BACKGROUND

Neglected Tropical Disease Elimination

Substantial progress has been made globally over the past decade to interrupt and drive down transmission across the collective of now 20 neglected tropical diseases (NTDs) [1]. The World Health Organization (WHO) roadmap for control, elimination, and eradication has now been restructured for 2030 [1], reflecting the fact that reaching and sustaining low-incidence becomes increasingly challenging and costly as targets are approached. Political, financial, and research momentum must be reinforced to find NTD cases transparently, substantiate and secure resource allocation, and streamline the evidence to policy process [2, 3]. As the COVID-19 pandemic has additionally postponed fundamental programmes and activities, actionable research is essential for informing the scale, scope, and intensity of intervention strategies required to reach elimination targets and mitigate NTD resurgence [4].

Visceral Leishmaniasis Elimination in India

Visceral leishmaniasis (VL), also known as kala-azar, is a NTD with the second highest fatality rate of any parasitic disease, where India accounts for 25% of the global burden [5]. Transmitted by the female phlebotomine sandfly, VL is characterised by fever, anaemia, enlargement of the spleen and liver, and a 95% fatality rate in those untreated [5]. Cases of post-kala-azar dermal leishmaniasis (PKDL), a secondary skin condition of VL, also contribute to transmission [6–8]. Therefore, VL in India is targeted for elimination as a public health problem (EPHP) and will require long-term surveillance to sustain low-incidence and quell the risk of both outbreaks and resurgence.

Since its inception in 2005, India's national Kala-Azar Elimination Programme (KEP) has achieved substantial declines in VL incidence, but an estimated 3,000 cases remain amongst

an at-risk population of approximately 150 million within India's four VL-endemic north-eastern states [5]. With difficulty actualising the previous elimination goal of less than one VL case per 10,000 population at the sub-district (or block) level, the revised WHO target aims to achieve less than 1% case fatality rate due to primary VL and to detect 100% of PKDL cases in India by 2030 [1, 9]. Early diagnosis, treatment and vector control are pillars of India's KEP, which are carried out through a combination of active and passive case detection activities alongside indoor residual spraying (IRS) of synthetic pyrethroids [1, 10].

Modelling to inform elimination strategies

Strategising the scale and scope of elimination activities requires iterative research to identify drivers and dynamics of VL transmission, which is best characterised by rigorous reporting and evaluation of surveillance activities [4]. As ubiquitous and complete disease-specific surveillance is impossible, case detection during pre-elimination must be prudently designed and implemented to minimise uncertainty in reported incidence. However, as disease incidence decreases, so do sample numbers that generate statistical power necessary for programme evaluation [11].

With its capacity to capture and reproduce important features of the real world through simplified structures, mathematical modelling is a compelling research tool for characterising dynamics between those susceptible, exposed, infectious, and recovered from a disease [12, 13]. Modelling has played an integral role in mitigating modes of disease transmission across populations at risk by projecting the dynamics of pathogens, vectors, and hosts, the potential impact of different interventions, and herd immunity thresholds requisite for achieving and sustaining elimination targets [12, 14].

The direct application of modelling to policy, however, is not only context- and disease-specific but also influenced by factors internal and external to the models [15]. For malaria and NTDs eligible for population-level treatment through mass drug administration (MDA), the application of modelling to inform policy and programme design is relatively straightforward through evaluating the intensity and longevity of interventions necessary to reach elimination targets [14, 16–19]. Other NTDs, like VL, require individualised case finding through 'innovative and intensified disease management' (IDM) due to non-specific symptoms, transmission, and involved treatment, which in some cases complicates how modelling extends to strategising surveillance, interventions, and elimination targets [20–24]. Partnerships and stakeholders within and between modelling and policy realms also affect their translatability [25], as does the inclusion or exclusion of economic, social, and political indicators [15].

Insights from VL modelling in India

Over the past seven years, a marked increase in VL modelling has been sought and accomplished to contribute towards India's national elimination strategy [26–28]. This body of modelling has spanned various objectives to characterise transmission, the effects of interventions, and the likelihood of reaching elimination, including the improvement of data collection to better inform models themselves.

Much of the early modelling on individual-level disease progression, infectivity, and demographic indicators improved knowledge surrounding the natural history of VL [6, 14, 29–31]. More recent transmission models have contributed knowledge that 1) VL and PKDL cases are the main drivers of transmission, 2) the pool of immunologically naïve individuals increases alongside declining incidence, and 3) VL incidence can be accurately forecasted up

to 4-months over space and time [6, 32–36]. Interventions, particularly those that reduce the time from infection to diagnosis, have also been modelled and compared to the prospect of reaching elimination targets [35, 37–39]. Lastly, the geographical scope and timeline of WHO elimination targets have been modelled to evaluate their feasibility given current strategies and a dynamic landscape of incidence [40].

Although these VL models did not include, or necessarily warrant, explicit policy recommendations or responses, they have contributed sufficient knowledge towards drivers of transmission, the potential impact of interventions, and whether elimination targets are achievable. The ability of VL modelling to inform surveillance-response activities in India will become increasingly relevant throughout this stage of elimination, especially as cases become more difficult to find and require resources be allocated efficiently across a heterogenous landscape of incidence [41, 42]. Policy-relevant knowledge garnered from modelling should be examined to support political momentum for reaching EPHP targets against competing disease priorities [43, 44].

The use of modelling in KEP policy

Given the volume of VL modelling research now available within the context of India, it is timely to consider the extent to which these individual and collective findings have or could influence the design and implementation of KEP elimination activities. As models are only as robust as the data they rely on, so too are they only as influential as their actionability and perceived relevance to decision makers. A divergence has been observed between the goals of researchers and decision makers throughout the development of models for communicable diseases, where the objective of broad epidemiological understanding verses practical management must be addressed and resolved [13].

Modellers recognise the significance of carefully presenting assumptions and comparisons within their evolving evidence base to garner trust and support of policy makers [4]. The NTD Modelling Consortium recently published a guideline of Policy-Relevant Items for Reporting Models in Epidemiology (PRIME) to improve 1) stakeholder engagement, 2) complete model documentation, 3) complete description of data used, 4) communication of uncertainty, and 5) testable model outcomes [45]. Although these PRIME guidelines offer actions that modellers may take, what is crucially missing is the perspective of decision makers and the degree to which policy and its actors must be engaged throughout research formulation, data collection, analysis and interpretation of results.

Knowledge utilisation to examine modelling in the KEP

This study aims to explore whether, and how, VL modelling research has informed or influenced KEP strategies in India and the ways in which its actionability could be improved. Characterising barriers between information generated from research and what is done in practice requires investigating the 'know-do' gap, where this study employs the theory of knowledge utilisation to explore the transfer, exchange, diffusion, and implementation of VL modelling research into KEP policy [46–48]. Barriers to the operationalisation of VL modelling are identified from the perspective of those designing, interpreting, and implementing policy related to VL elimination research in India. Exploring decision makers' perceived value and use of VL modelling will assist researchers in the next iteration of models and politicians in the next iteration of elimination guidelines, which should likewise extend to other NTDs and broader geographical contexts.

METHODS

Conceptual Framework

Knowledge translation (KT) is a dynamic and iterative process that includes the synthesis, dissemination, exchange, and ethically sound application of knowledge to improve health, provide more effective health services, and strengthen healthcare systems [49]. It requires collaboration between researchers, clinicians, decision makers, and communities, and can extend to the design, implementation, or evaluation of public health programmes. There remains an important distinction between information (objective, contextualised facts), knowledge (empirical analyses), and evidence (replicable, hypothesis-driven propositions) in the way scientific results should be packaged and portrayed for policy [50]. VL modelling research in this study is categorised as knowledge, in that it represents individual, and not necessarily comprehensive, studies specific to VL elimination and surveillance programmes in India. However, this body of VL modelling work might also be considered a collection of state-of-the-art frameworks that represent the transmission dynamics and impact of VL interventions according to updated evidence, assumptions, and data.

A review of KT, knowledge-to-action (KTA), and diffusion of innovations theories was carried out to identify a framework that would systematically approach the relationship between knowledge producers and users, as well as examine barriers to the transfer of VL modelling to policy in India [48, 51–53]. The conceptual framework of knowledge utilisation, developed by Knott and Wildavsky, was employed for its identification of explicit stages of KT between producer to user [54]. These stages of knowledge utilisation guided development of a semi-structured interview questionnaire to explore seven dimensions of the theory's framework, outlined in Table 6-1.

Table 6-1. The seven dimensions of the knowledge utilisation framework

Knowledge Utilisation Dimension	Description
Reception	How relevant information was received
Cognition	How information was read, digested, and understood
Reference	If and how information changed the views, preferences, or understanding of the magnitude or probabilities of the impact
Effort	The process by which information influences action
Adoption	How information is put into policy
Implementation	How information is implemented into policy or the programme
Impact	How and whether a change in policy can influence desired results

Data Collection

Ethical approval was obtained from the London School of Hygiene and Tropical Medicine in November 2019 (Reference Number 17763), and data collection was conducted from August to October 2020 (Appendix 4).

Participant selection and characteristics

This study targeted international-, national-, and state-level decision makers, programme managers, and researchers involved in designing and implementing VL elimination in India. As VL prevalence is low compared to other infectious diseases, the number of senior decision makers and programme managers was expected to be relatively limited. Purposive sampling drove participant selection for inclusion in the study, which was subsequently expanded by snowball sampling. In-person meetings were not feasible due to the COVID-19 pandemic; therefore, all interviews took place over private and secure video conference calls.

Interviews

Twenty-eight decision makers, programme managers, and researchers with knowledge, insight or experience regarding mathematical modelling for VL in India were initially contacted by email to request participation in the study. Of these, 16 key informants

(affiliated with the organisations detailed in Table 6-2) agreed to participate in an in-depth, semi-structured interview.

Table 6-2. Organisation and location of key informants included in the study.

Organisation (Abbreviation)	Location (City or State, Country)	Number of Participants
CARE India	Bihar, India	2
Banaras Hindu University (BHU)	Uttar Pradesh, India	1
Institute of Post-Graduate Medical Education and Research	Kolkata, India	1
Médicines Sans Frontières (MSF)	Amsterdam, Netherlands	1
World Health Organization Headquarters (WHO HQ)	Geneva, Switzerland	2
World Health Organization South-East Asia Regional Office (WHO SEARO)	Uttar Pradesh, India	1
Indian Council of Medical Research (ICMR) / Vector Control Research Centre (VCRC)	Uttar Pradesh, India	1
Drugs for Neglected Diseases Initiative (DND*i*)	Uttar Pradesh, India	1
Institute of Tropical Medicine (ITM)	Antwerp, Belgium	1
PATH	Bihar, India	1
Bill and Melinda Gates Foundation (BMGF)	Uttar Pradesh, India	1
Rajendra Memorial Research Institute (RMRI)	Bihar, India	1
Bangladesh Ministry of Health and Family Welfare	Dhaka, Bangladesh	1
National Vector Borne Disease Control Programme (NVBDCP)	Uttar Pradesh, India	1

Consent to participate in the study was confirmed prior to initiating interviews, each of which lasted between 35-80 minutes (Appendices 8 and 9). The interview guide was iteratively updated based on key informant responses, especially as new themes emerged surrounding modelling and the policy process in India (Appendix 10). Interviews were audio-recorded, transcribed verbatim, and corroborated by notes taken during interviews. Key informants were assigned a unique identifier to ensure anonymity, where interview excerpts and

references denote each participant's overarching affiliation within either 'research' (R-) or 'policy' (P-) followed by a number.

Coding and Analysis

Interview transcriptions were analysed using the qualitative software NVIVO 12.6.0 (released in November 2019) by QSR International using a mixed-methods deductive (grounded in knowledge utilisation theory) and inductive (generation of new theories) approach [55]. Codes were organised and compared within each of the seven dimensions of knowledge utilisation and analysed according to converging and diverging views on perceived value and usefulness of VL modelling research to decision makers. With the aim to highlight and address specific barriers to knowledge utilisation, flexibility was retained in analysis to explore shifts in key informant responses regarding linear, relational, and systems-based dynamics of knowledge producers and users [56]. Participant responses are organised in the results section in alignment with the seven dimensions of knowledge utilisation and examined analytically through thematic comparison within the discussion.

RESULTS

Themes are presented within each of the seven dimensions of knowledge utilisation, supported by direct quotes or in-text paraphrasing, and referenced by each participant's unique identifier. Although the knowledge utilisation framework suggests a linear path between information reception and its eventual impact via policy, this study considers each dimension impartially without implicit correlation between former and subsequent categories.

Reception. The majority of participants received information regarding past and ongoing modelling studies at international meetings involving multiple organisations and institutions, in which modelling was one of several foci. Those engaged in modelling itself received new information from either research collaborations or published literature (R1, R4, R6). Each of the 16 participants affirmed that the best timeframe for modellers to formally engage with decision makers is at least once per year, either virtually or in-person. Meetings between researchers and policy makers should focus on discussing and deciding whether modelling results have the potential to update the programme (P4).

Modelling presented alongside other research fields helped to contextualise its purpose and contribution towards VL elimination, and sparked interest in broadening interdisciplinary collaborations between biologists, economists, social scientists, and modellers (R8). One key informant suggested a liaison between researchers and decision makers would aid effective communication:

> 'You can't be a jack of all trades; you can't be a modeller and also a public health communicator. Sometimes you need individuals who are experts in public health who can actually be that bridge between modellers and policy makers. Often people who are good communicators are not good modellers, and vice versa. We need public health individuals as part of the modelling group who are similar to human resources division who can communicate with the policy makers.' (R8)

Cognition. Participants expressed varying degrees of understanding modelling research. Within specific study components, the objectives of modelling were most easily digested and comprehended by decision makers. However, a disconnect was reported in objectives prioritised between modellers and decision makers:

> 'Sometimes politicians are interested in something different than what we as modellers think is important; sometimes they want us to answer a question that cannot be addressed through modelling. They don't always understand what the models can and can't do, and we have to tell them we are limited in what our models can be used for.' (R6)

Specific equations, parameters, and processes of the models themselves were understood least by decision makers, as well as by researchers without specific training in modelling (R5 & R8). Decision makers felt comfortable to ask questions and seek clarification directly with researchers to improve their understanding of study outcomes (P7). However, where actionable policy recommendations were not regularly communicated as part of modelling research, or perhaps not warranted, the perceived relevance of modelling to decision makers diminished:

> 'Generally, the decision makers think that a model is made because something has to be done as an academic exercise and based on that modellers come up with results that only they understand which doesn't have any practical ground-level reality. My recommendation is for each and every researcher to learn how to describe our processes clearly, comprehensively and intuitively, which is possible. [Modelling] can be explained in a language that is more practical and pragmatic, and it can be interpreted in a way which is actionable giving us estimates or predicted values that are scalable and later on sustainable.' (R4)

To increase political support and ownership through comprehensive engagement, decision makers should be involved in the modelling process from the beginning stage of identifying knowledge gaps and objectives (R2, R4, R8, P2, and P4).

> '[We should] create a training programme where people from NVBDCP or [the Indian Council of Medical Research] come together for a 2- to 3-week intensive modelling training, and everyone uses their own data, and everything is basic. Like, put in these 5 inputs and produce this; something elementary enough that the programme might see effects of increasing their IRS coverage. I think the programme could feel that modelling is a tool for them to use with their own data and knowhow. But because a training like that hasn't happened, modelling results are always an

> outsider coming in with a fully baked model that is always mysterious, and they wonder *how did they get there? Especially because I haven't given them my data*. If it were done more hand-in-hand with the programme from a capacity-building angle, modelling might have more influence on the programme.' (P5)

Reference. Where different modelling outcomes could influence the magnitude and probability of policy change, key informants expressed resounding interest in case predictions and forecasts at the village level (R1, R2, R3, R5, R6, P3, P4, and P8). Village-level case predictions were perceived as desirable for decision makers to 1) inform a more targeted, coordinated, and actionable response:

> 'From the case-level and village-level data, a very valuable thing I would like to know is which are the villages in which I am sure to get a VL case, or at least the highest probability. Some models give me a number of how many blocks might have cases based on looking at the whole of the previous year, but we need to go as micro-level as possible so that we can have a point of action. We need to be able to plan pro-actively and go there well-prepared. If I know that in a block there will be 10 villages with VL cases based on the previous year, then I can pay attention to that block. I would want to prove that modeller wrong by intensifying my ACD. That type of research would help for planning.' (R1)

and 2) improve surveillance for other sources of VL-related transmission:

> 'If modelling shows us outbreak predictions for a certain number of cases and we end up seeing in reality that 20-30% of those cases are missing and undiagnosed, then we can plan to improve the surveillance part. This is the major role I see for modelling predictions is on programme implementation. The foremost thing is for us to find cases at the earliest and not permit a case of VL, PKDL, or HIV-VL so that ultimately, we stop transmission. Once we have that, then diagnostics and treatment are both available so there is not much issue financially for the programme. Surveillance activities need to be improved based on the models.' (P8)

The next most anticipated modelling outcome was to re-evaluate and substantiate VL elimination targets in India. Key informants referenced one modelling study, in particular, that was 'used extensively by the programme' as it 'gave insight into how realistic it is to reach a target' (P7):

> 'The definition of elimination is based on an annual incidence of VL per lowest administrative unit, the block or subdistrict, below a certain target. One model showed that even with very low transmission, there will always be by coincidence a block or other administrative unit that will in one year exceed that limit. This means the disease is no longer eliminated, which makes it very difficult to evaluate and maintain elimination. If you always have these small pockets that pop up and go away again,

> that in itself is not a problem if the higher incidence in that specific year is just a coincidence. But it still means you have to send outbreak teams to that area for further investigation and if necessary, do control activities. So that is an important activity for post-elimination control and sustainability, because it will require quite big investments to sustain elimination.' (P1)

Effort. Key informants largely viewed researchers, not politicians, as responsible for the provision of information that compels policy change (P2, R4, P4, and P8). When research objectives, methods, results, and limitations were not clearly communicated by researchers, key informants identified that disinterest or distrust arose in decision makers:

> 'We need trust from the fraternity of people using modelling results, and that trust will help decision makers to be informed. This is thoroughly missing, and what has happened now is that the difference between a prediction, forecast, and speculation is not clear to anyone. So, programme managers and general people think much of modelling as an educated guess. Every statistic is an educated guess, but that education is informing the randomness that's taken into account in the systematic results. That structured common sense is required to be explained in a language so that people will stop thinking about modelling as assumption-based speculations.' (R4)

Modelling assumptions have in part been a result of unknowns in transmission dynamics, for which modelling has mobilised improved data collection. Therefore, on the other hand, some key informants conveyed the value of modelling despite its inherent unknowns:

> 'I think despite the unknowns about VL transmission, modelling is still valuable. The data is increasingly solid that asymptomatic carriers are not contributing to transmission but PKDL is. The beauty of a model to me is, you can assume with one symptomatic person there are 10 asymptomatic people that contribute 0% versus 5% to transmission, and you can model different scenarios to understand at what point would we need to intervene. You can have sensitivity analyses that say *we don't know everything, but what if it were this or that and what would the impacts be?* If you knew absolutely every variable then obviously you could model that, but right now what's appealing is that you can have a set of equations in which you can plug in different variable estimates and get different answers and impacts.' (P5)

Adoption. Key informants identified differences between VL and other NTDs in the way modelling is able to explore ongoing intervention strategies and thereby be adopted into policy.

> ‘For some diseases, modelling is much more direct in that it simulates interventions that you can quickly translate to policy. I think that’s the case to a much lesser extent for VL. Much of the modelling work has been on gaining insight into transmission and the unknowns, like how important is this duration of immunity that we don’t know about? What could be the role of asymptomatics, and if they do play a role then what is their impact? These are higher-level questions and not necessarily informing an ASHA or an IRS spray-man of what to do tomorrow.’ (R6)

To increase the likelihood of adopting modelling outcomes into policy, key informants stated modelling should leverage economic indicators and provide comprehensive projections of programme impact alongside long-term costs (P5 & R8). The importance for models to explore novel strategies, especially during this stage of peri-elimination, was also encouraged:

> ‘People should not think that innovation and operational research ends now. I think it is important now because when you have a reduced number of cases it becomes more difficult to bring cases further down because of the lack of evidence and knowledge. This is where innovation and research should be supported, and we continue to advocate for this. Otherwise, there is a tendency to think that further research is not required because we’re on the verge of elimination. It took 20 years to reach this space, and if we lose out everything in the next 5 years it will be difficult to restart such activities.’ (R5)

Implementation. In order for modelling outcomes to be implementable within the KEP, the majority of key informants reported that modellers should improve their understanding of ongoing programme activities, capacity, and infrastructure.

> ‘Modellers absolutely need to know more about operational activities on the ground. I don’t think modellers personally visit those places. It is very important to look at operations in the field and understand the context, then adjust the data to those realities.’ (P6)

Beyond refining research objectives and contextualizing results for policy, key informants reported that directly observing operational activities was also essential to combat unreliable data and discrepancies in reported coverage of activities (P2 & P4).

> ‘Once you predict the areas where the elimination programme needs to be, the modellers need to know what is in those areas physically on the ground. If they knew what was on the ground, they would have a better idea of how to come up with a solution. They need to visit the areas where the programme is going on—they need to see the system and what is lacking at the ground level. Being a researcher, sitting at a

> big institution either in India or in London, it is difficult to compare this to what is going on in the national programme and being delivered.' (R7)

Impact. The bureaucracy, policy process, and relationship between WHO and the KEP complicate the observed impact of modelling through policy change.

> 'The way in which elimination work is done in India, in particular, is that WHO has a guideline, and you do A, B, C and all the programmes follow A, B, C. Modellers might come in and say *you know, if you did A twice, skipped B and jumped to C, you could see a better impact*. The problem is even if the programme fully believes and trusts this information, they feel their hands are tied because of the way WHO controls policy. So, it's difficult to see a model have direct programmatic impact.' (P5)

Key informants acknowledged that even if a policy change were to be achieved, barriers to enforcement may undermine actual impact.

> 'This is the main frustration with working at WHO is that when you gather the experts and those on top of the knowledge to make reports, recommendations, and research questions, it's often just a paper that remains on a shelf or in a PDF on a website because those with the power and money decide not to support it.' (P2)

DISCUSSION

The value and use of VL modelling research examined in this study was largely perceived as instrumental and conceptual, in that it had identified and addressed unsolved problems relating to VL elimination but had not legitimised concrete policy solutions for the KEP. Participants believed that researchers should improve their communication of models and understanding of operational activities, but that accountability and enforcement between the WHO and KEP remain institutional barriers to policy change. Political trust might be heightened by either engaging decision makers in model interpretation to enhance ownership and understanding of research, or by employing a communication intermediary.

Assumptions undermine knowledge utilisation

Assumptions were identified as barriers to knowledge utilisation in the way models themselves are designed and presented, but also in how modellers assume programme operations occur and in assumed ownership over knowledge translation in the policy process.

1) Model assumptions and uncertainty

As models are an abstraction of reality, their application to programmes and policy can be limited by variability in parameters that leads to different assumptions, especially across space and time [30]. In this, decision makers expressed confusion and distrust surrounding model assumptions and uncertainties, in that they undermined the substance of results by rendering them speculative. Assumptions and uncertainties are inherent elements of modelling and, although they may be mitigated or reduced by optimising model structure, parameters, and fit, the ways in which they are presented and negotiated for end-users hold equal importance [57–59]. From the research perspective, modellers must identify, quantify, and communicate model outcomes in a way that delineates *risk* from *uncertainty* [60].

Uncertainty may exist in the model structure, parameters, or natural variability of temporal and spatial elements, which might be leveraged by identifying how improved data collection and surveillance could minimise uncertainties for future research [61]. From the policy perspective, decision uncertainty might relate to the risk of choosing one alternative course of action over another, for example, in terms of financial or epidemiological risk [62]. There is an opportunity to negotiate the perceived usefulness of models from objective beliefs about their quality towards how they function within broader research, societal, and political environments [59].

Much of the VL modelling accomplished over the last seven years required modellers to first address gaps in the collective understanding of transmission, natural history, and immunity. When less was understood about the drivers and parameters of VL transmission, model assumptions may have dissuaded decision makers from acknowledging their potential usefulness. As VL modelling is increasingly intended for and potentially warrants a policy response, its limitations may need to be addressed by encouraging decision makers and researchers to explicitly discuss the meaning and confines of assumptions, how to test them, and what data to collect.

Improving political trust of VL models may necessitate a new role altogether by employing a communication intermediary, or liaison, between researchers and decision makers. Communication intermediaries must have expertise in the relevant research field to be able to communicate and endorse research, but also have insight into the policy process and actors in the relevant context to identify routes and opportunities for change [63]. Such a role might be stipulated and supported by funders and jointly recruited by researchers and decision makers.

2) Modellers' assumptions of on-the-ground operations

Participants recognised that a strength of modelling is its power to hypothesise a variety of scenarios on a scale to help inform decision making, but many indicated that VL modelling must be improved through its design around and for operationalisation. Successful modelling in other NTD programmes, especially those reliant on MDA, demonstrates that existing processes are easier to refine and improve than roles, resources and activities that are not in place [17–19, 64, 65]. Participants identified that models should not only address ongoing interventions such as ACD and IRS, but that modellers must also observe these activities on-the-ground to determine operational gaps, central roles, and scalable activities. Further, participants indicated that without witnessing on-the-ground operations, national programme data lends itself to skewed interpretation and less-realistic analyses. It is important that VL modellers exhibit an understanding of activities, roles, and hierarchies within the KEP and more directly gauge their work towards a policy response.

3) Assumptions of ownership over knowledge translation

The process of translating knowledge into policy between researchers, the KEP, and WHO in India poses challenges to enforcement. Some participants were discouraged in the prospect of translating modelling into actionable policy due to confusion in assumed power of implementation between the KEP and WHO. Although the KEP ultimately coordinates and enforces activities, they rely on formal technical support and guidance from WHO frameworks that are not always promptly realised into action. Further, WHO frameworks may be too broad and infrequent to align with the timely and policy-relevant results that modelling intends to produce.

An independent assessment was published by researchers, decision makers, and programme managers through WHO in 2020, which suggested modellers publish objectives early and often to improve their usefulness to decision makers [66]. This study, conversely, found that the majority of decision makers are currently, and prefer to be, briefed on modelling through in-person partnership meetings. Therefore, it may be beneficial to capitalise on existing platforms and relationships between modellers and decision makers to encourage research actionability in the KEP. Modelling might be more effectively operationalised incrementally through informal routes of policy change by leveraging influence and discussion during partnership meetings.

Eliciting a top-down national- or state-level KEP response may not be feasible or justified from existing VL modelling research, but a bottom-up approach could be useful to inform and evaluate the impact of village- or block-level programme activities. For example, as some participants suggested, a pilot programme to heighten ACD in a village or block where incidence is forecasted to be higher in subsequent months could be feasibly trialled on a small scale. In this, models themselves can be considered a tool to communicate current and prospective policy-relevant research opportunities primed for implementation or scale-up. Knowledge utilisation literature also indicates that research is used in different ways over time by different groups, and the dynamics between knowledge producers, users, and translation can be adjusted during periods of static response [52].

Co-production of modelling objectives and interpretation

Researchers and politicians are often viewed separately as ‘two communities’ in public health, and barriers to the translation of research into policy are regularly traced back to the production and communication of scientific knowledge [46]. As producers of knowledge

with accountability over analysis and scientific integrity of modelling results, researchers in this study were assumed to hold more influence than decision makers in determining the relevance of models to policy; and although decision makers in the KEP readily support modelling objectives and data collection, they are not consistently included in analysis, interpretation, and therefore application of modelling for policy.

Co-production of research between scientists and decision makers can improve accountability in translating knowledge to policy [67, 68]. Especially as participants identified deficiencies in modellers' understanding of on-the-ground operations, and researchers likewise identified unrealistic goals or requests from decision makers, co-production of research embeds and is embedded in a more realistic discussion around normative operational practices and analytic techniques [69, 70]. It may be important that all stakeholders aim to reach consensus of modelling results in order to effectively translate research into policy [25].

The fidelity of co-production, however, is often limited by increased time commitment, financial and reputational costs, and power struggles [71]. Co-production should be approached cautiously, as it requires agreement to responsibilities, outputs, and authority that may be unrealistic or even damaging to established partnerships [72]. As an exercise of co-production, participants proposed a modelling workshop giving decision makers the opportunity to formulate, analyse, and interpret models themselves to improve their ownership and understanding of results. This aligns with some findings that co-production is best adopted as an exploratory social practice to shift, but not mandate, conventional dynamics of engagement, credibility, and productivity between researchers and policy makers [73].

The NTD and policy interface

Barriers to knowledge utilisation identified in this study are reflected in other NTD programmes globally, particularly in contextual governing dynamics and research communication [45, 74]. The process of informing elimination strategies through modelling not only relies on aligning research objectives and national agendas but also then translation to and observation of WHO guidelines. Other NTD programmes supported by international donors found that silo-ed funding poses additional challenges to implementation and policy influence, which strengthens the case for national-level programme integration and financial ownership [75]. As modelling continues to drive forward innovative and policy-relevant elimination research for NTDs, its application might best be encouraged through informal policy platforms, workshops, and communication intermediaries. Future qualitative studies are necessary to continue identifying context-specific barriers to translating knowledge into policy.

CONCLUSION

With its capacity to employ diverse variables, illuminate trends and drivers of transmission, and project the likelihood and resources required for reaching elimination, mathematical modelling is an increasingly applicable field for informing VL elimination in India. Through the framework of knowledge utilisation, key informants gauged their reception, understanding, and prioritisation of VL modelling outputs aimed at informing the KEP and identified barriers to action within the policy process. Overarchingly, participants assigned value to the knowledge mathematical modelling has contributed to VL transmission and elimination targets in India, but with reservation surrounding its direct application to ongoing activities. Where objectives, outcomes, and limitations are not effectively communicated, the capacity of modelling to influence policy is undermined. Results of this study suggest

knowledge utilisation may be impeded specifically within the process of interpreting and operationalising modelling findings. Political trust and endorsement of modelling might be improved by employing communication intermediaries and engaging decision makers in interpretation of results.

LIMITATIONS

This study aimed to gauge the value and practicality of VL modelling for decision makers in India, which may have resulted in participation, researcher, and sampling biases. Although a strength of qualitative research is its ability to identify complexities and subtleties of issues in depth and detail, it is often subject to issues of rigor, transparency, reliability, and validity compared to quantitative research. Validity, as it relates to the honesty and genuineness of data collected, was addressed by relying on a substantiated and commonly used theoretical framework of knowledge utilisation. Reliability, as it relates to the reproducibility and stability of data, was addressed by including a diversity of actors and presenting coinciding and conflicting responses. Further, the framework of knowledge utilisation allows for reproducibility and transparency of future research conducted in this field.

Although the study was grounded in the theoretical framework of knowledge utilisation, qualitative interviewing is inherently subjective due to the presence and training of the interviewer. The interviewer did not have prior involvement with the modelling work in question, which strengthened the objectivity and neutrality of their perspective. The influence researchers may exert on their findings is a common concern throughout qualitative research and was also addressed by considering reflexivity throughout the process of study design, data collection and analysis.

The number of participants may have resulted in sampling bias. The limited number of decision makers and programme managers working in VL in India was identified prior to conducting interviews but was reduced further by lack of participant availability throughout the COVID-19 pandemic. Sampling bias was addressed by including participants from diverse organisations, countries, and positions in research, programme implementation, and policy, as well as recruiting additional participants through snowball sampling. Participant bias was also addressed by transparently reporting the interviewer's position, affiliation, and research aims prior to conducting interviews, as well as through framing open-ended and neutral questions.

Participation bias is likely present in that key informants' perspectives, insight, and experience were influenced by their current job position, organisational affiliation, and field of expertise. Some participants had more technical experience with modelling while others had more technical experience with the policy process and its actors in India. Both perspectives were important to compare and contrast in this study and should provide a more comprehensive understanding of the working relationship between VL researchers, decision makers, and programme managers in India. This qualitative analysis could be strengthened and expanded by further investigating the relationship between modellers and researchers through direct observation during partnership meetings, analysing documents of the KEP and WHO policy processes in India, and through case studies following the influence of a particular modelling study from inception to reception by policy makers.

ACKNOWLEDGEMENTS

The authors appreciate the time, expertise, and insight provided by all participants of this study, especially throughout the height of the COVID-19 pandemic. ND is grateful for

direction and feedback given by Alec Fraser on the design, conceptual framework, and presentation of this paper.

REFERENCES

1. World Health Organization. Accelerating work to overcome the global impact of NTDs: 2011-2020 Progress dashboard [Internet]. Geneva; 2020. Available from: https://apps.who.int/iris/handle/10665/70809.
2. Uniting to Combat NTDs. Reaching a billion. Ending Neglected Tropical Diseases: A gateway to Universal Health Coverage. Fifth progress report on the London Declaration on NTDs [Internet]. London, UK; 2016. Available from: https://unitingtocombatntds.org/wp-content/themes/tetloose/app/staticPages/fifthReport/files/fifth_progress_report_english.pdf.
3. Krentel A, Gyapong M, Ogundahunsi O, Amuyunzu-Nyamongo M, McFarland D. Ensuring no one is left behind: Urgent action required to address implementation challenges for NTD control and elimination. PLoS Negl Trop Dis. 2018; 12(6): e0006426.
4. Toor J, Coffeng EL, Hamley J, Fronterre C, Prada JM, Castaño MS, et al. When, Who, and How to Sample: Designing Practical Surveillance for 7 Neglected Tropical Diseases as We Approach Elimination. J Infect Dis. 2020; 221(5): 499–502.
5. World Health Organization. WHO Visceral Leishmaniasis Factsheet [Internet]. Geneva; 2020. Available from: https://www.who.int/news-room/fact-sheets/detail/leishmaniasis.
6. Das VNR, Pandey RN, Siddiqui NA, Chapman LAC, Kumar V, Pandey K, et al. Longitudinal study of transmission in households with visceral leishmaniasis, asymptomatic infections and PKDL in highly endemic villages in Bihar, India. PLoS Negl Trop Dis. 2016; 10(12): e0005196.
7. Mondal D, Bern C, Ghosh D, Rashid M, Molina R, Chowdhury R, et al. Quantifying the infectiousness of post-Kala-Azar dermal leishmaniasis toward sand flies. Clin Infect Dis. 2019; 69(2): 251-258.
8. Singh OP, Tiwary P, Kushwaha AK, Singh SK, Singh DK, Lawyer P, et al. Xenodiagnosis to evaluate the infectiousness of humans to sandflies in an area endemic for visceral leishmaniasis in Bihar, India: a transmission-dynamics study. Lancet Microbe. 2021; 2(1): e23-e31.
9. National Vector Borne Disease Control Programme. National Vector Borne Disease Control Programme Road Map for Kala Azar Elimination [Internet]. Delhi, India; 2014. Available from: https://nvbdcp.gov.in/Doc/Road-map-KA_2014.pdf.
10. National Vector Borne Disease Control Programme. National Vector Borne Disease Control Programme Accelerated Plan for Kala Azar Elimination [Internet]. New Delhi, India; 2017. Available from: https://www.who.int/leishmaniasis/resources/Accelerated-Plan-Kala-azar1-Feb2017_light.pdf.
11. Fronterre C, Amoah B, Giorgi E, Stanton MC, Diggle PJ. Design and analysis of elimination surveys for neglected tropical diseases. J Infect Dis. 2020; 221(5): 554–60.
12. Vynnycky E, White R. An Introduction to Infectious Disease Modelling. In: An Introduction to Infectious Disease Modelling. First Edit. Oxford, UK: Oxford University Press; 2010.
13. Brauer F, Castillo-Chavez C, Feng Z. Mathematical models in epidemiology. First Edit. Bloch A, Epstein C, Goreily A, Greengard L, editors. New York: Springer Nature; 2019.
14. Hollingsworth TD, Adams ER, Anderson RM, Atkins K, Bartsch S, Basáñez M-G, et al. Quantitative analyses and modelling to support achievement of the 2020 goals for

nine neglected tropical diseases. Parasit Vectors. 2015; 8(630): DOI: https://doi.org/10.1186/s13071-015-1235-1.
15. Maude RJ, Lubell Y, Socheat D, Yeung S, Saralamba S, Pongtavornpinyo P, et al. The role of mathematical modelling in guiding the science and economics of malaria elimination. Int Health. 2010; 2(4): 239-246.
16. Okell L, Slater H, Ghani A, Pemberton-Ross P, Smith T, Chitnis N, et al. Consensus modelling evidence to support the design of mass drug administration programmes [Internet]. Geneva; 2015. Available from: https://www.who.int/malaria/mpac/mpac-sept2015-consensus-modelling-mda.pdf?ua=1.
17. Jambulingam P, Subramanian S, de Vlas SJ, Vinubala C, Stolk W. Mathematical modelling of lymphatic filariasis elimination programmes in India: required duration of mass drug administration and post-treatment level of infection indicators. Parasites and Vectors. 2016; 9(501): DOI: https://doi.org/10.1186/s13071-016-1768-y.
18. Coffeng LE, Bakker R, Montresor A, de Vlas SJ. Feasibility of controlling hookworm infection through preventive chemotherapy: a simulation study using the individual-based WORMSIM modelling framework. Parasites and Vectors. 2015; 8(541): DOI: https://doi.org/10.1186/s13071-015-1151-4.
19. Gurarie D, Yoon N, Li E, Ndeffo-Mbah M, Durham D, Phillips A, et al. Modelling control of Schistosoma haematobium infection: predictions of the long-term impact of mass drug administration in Africa. Parasites and Vectors. 2015; 8(529): DOI: https://doi.org/10.1186/13071-015-1144-3.
20. Brook CE, Beauclair R, Ngwenya O, Worden L, Ndeffo-Mbah M, Leitman T, et al. Spatial heterogeneity in projected leprosy trends in India. Parasites and Vectors. 2015; 8(542): DOI: https://doi.org/10.1186/s13071-015-1124-7.
21. Rock KS, Torr SJ, Lumbala C, Keeling M. Quantitative evaluation of the strategy to eliminate human African trypanosomiasis in the Democratic Republic of Congo. Parasites and Vectors. 2015; 8(532): DOI: https://doi.org/10.1186/s13071-015-1131-8.
22. Pandey A, Atkins KE, Bucheton B, Camara M, Aksoy S, Galvani A, et al. Evaluating long-term effectiveness of sleeping sickness control measures in Guinea. Parasites and Vectors. 2015; 8(550): DOI: https://doi.org/10.1186/s13071-015-1121-x.
23. Peterson JK, Bartsch SM, Lee BY, Dobson A. Broad patterns in domestic vector-borne Trypanosoma cruzi transmission dynamics: synanthropic animals and vector control. Parasites and Vectors. 2015; 8(537): DOI: https://doi.org/10.1186/s13071-015-1146-1.
24. Rosenberg M, Utzinger J, Addiss DG. Preventive Chemotheraphy Versus Innovative and Intensified Disease Management in Neglected Tropical Diseases: A Distinction Whose Shelf Life Has Expired. PLoS Negl Trop Dis. 2016; 10(4): e0004521.
25. Njeuhmeli E, Schnure M, Vazzano A, Gold E, Stegman P, Kripke K, et al. Using mathematical modeling to inform health policy: A case study from voluntary medical male circumcision scale-up in eastern and southern Africa and proposed framework for success. PLoS One. 2019; 14(3): e0213605.
26. Bergquist R, Yang G-J, Knopp S, Utzinger J, Tanner M. Surveillance and response: Tools and approaches for the elimination stage of neglected tropical diseases. Acta Trop. 2015; 141(B): 229–34.
27. Matlashewski G, Arana B, Kroeger A, Be-Nazir A, Mondal D, Nabi S, et al. Research priorities for elimination of visceral leishmaniasis. Lancet Glob Heal. 2015; 2(12): e683–684.
28. Bi K, Chen Y, Zhao S, Kuang Y, Wu C-H. Current visceral leishmaniasis research: A research review to inspire future study. Biomed Res Int. 2018; 5(1): 1–13.
29. Chapman LAC, Dyson L, Courtenay O, Chowdhury R, Bern C, Medley GF, et al. Quantification of the natural history of visceral leishmaniasis and consequences for

control. Parasit Vectors. 2015; 8(521): DOI: https://doi.org/10.1186/s13071-015-1136-3.
30. Rock KS, Medley GF, Quinnell RJ, Courtenay O. Progress in the Mathematical Modelling of Visceral Leishmaniasis. Adv Parasitol. 2016; 94(1): 49–131.
31. Chapman LAC, Morgan ALK, Adams ER, Bern C, Medley GF, Hollingsworth TD. Age trends in asymptomatic and symptomatic Leishmania donovani infection in the Indian subcontinent : A review and analysis of data from diagnostic and epidemiological studies. PLoS Negl Trop Dis. 2018; 12(12): e0006803.
32. Le Rutte EA, Coffeng LE, Bontje DM, Hasker EC, Postigo JAR, Argaw D, et al. Feasibility of eliminating visceral leishmaniasis from the Indian subcontinent : explorations with a set of deterministic age-structured transmission models. Parasit Vectors. 2016; 9(24): DOI: 10.1186/s13071-016-1292-0.
33. Stauch A, Sarkar RR, Picado A, Ostyn B, Sundar S, Rijal S, et al. Visceral Leishmaniasis in the Indian Subcontinent: Modelling Epidemiology and Control. PLoS Negl Trop Dis. 2011; 5(11): e1405.
34. Barley K, Mubayi A, Safan M, Castillo-Chavez C. A Comparative Assessment of Visceral Leishmaniasis Burden in Two Eco-Epidemiologically Different Countries, India and Sudan. Biology (Basel). 2019; 1(1): DOI: https://doi.org/10.1101/592220.
35. Chapman LAC, Spencer SEF, Pollington TM, Jewell CP, Mondal D, Cameron MM, et al. Inferring transmission trees to guide targeting of interventions against visceral leishmaniasis and post – kala-azar dermal leishmaniasis. Proc Natl Acad Sci U S A. 2020; 117(41): 25742-25750.
36. Nightingale ES, Chapman LAC, Srikantiah S, Subramanian S, Jambulingam P, Bracher J, et al. A spatio-temporal approach to short-term prediction of visceral leishmaniasis diagnoses in India. PLoS Negl Trop Dis. 2020; 14(7): e0008422.
37. Coffeng LE, Le Rutte EA, Muñoz J, Adams ER, Prada JM, de Vlas SJ, et al. Impact of Changes in Detection Effort on Control of Visceral Leishmaniasis in the Indian Subcontinent. J Infect Dis. 2020; 221(Supplement 5): S546-S553.
38. Medley GF, Hollingsworth TD, Olliaro PL, Adams ER. Health-seeking behaviour, diagnostics and transmission dynamics in the control of visceral leishmaniasis in the Indian subcontinent. Nature. 2015; 528(7580): S102–108.
39. Chapman LAC, Jewell CP, Spencer SEF, Pellis L, Datta S, Chowdhury R, et al. The role of case proximity in transmission of visceral leishmaniasis in a highly endemic village in Bangladesh. PLoS Negl Trop Dis. 2018; 12(10): e0006453.
40. NTD Modelling Consortium. Insights from mathematical modelling and quantitative analysis on the proposed WHO 2030 targets for visceral leishmaniasis on the Indian subcontinent. Gates Open Research; 2020; 3(1651): DOI: 10.12688/gatesopenres.13071.1.
41. Boden LA, McKendrick IJ. Model-based policymaking: A framework to promote ethical “good practice” in mathematical modeling for public health policymaking. Front Public Heal. 2017; 5(68): DOI: 10.3389/fpubh.2017.00068.
42. Hollingsworth TD, Langley I, Nokes DJ, Macpherson EE, McGivern G, Adams ER, et al. Infectious disease and health systems modelling for local decision making to control neglected tropical diseases. BMC Proc. 2015; 9(10): S6.
43. Aya Pastrana N, Beran D, Sommerville C, Heller O, Correia JC, Suggs LS. The process of building the priority of neglected tropical diseases: A global policy analysis. PLoS Negl Trop Dis. 2020; 14(8): e0008498.
44. Iltis AS, Matthews KRW. NTD policy priorities: Science, values, and agenda setting. PLoS Negl Trop Dis. 2017; 11(5): e0005431.
45. Behrend MR, Basáñez M-G, Hamley JID, Porco TC, Stolk WA, Walker M, et al.

Modelling for policy: The five principles of the Neglected Tropical Diseases Modelling Consortium. PLoS Negl Trop Dis. 2020; 14(4): e0008033.
46. Caplan N. The two-communities theory and knowledge utilization. Am Behav Sci. 1979; 22(3): DOI: 10.1177/000276427902200308.
47. Weiss CH. The many meanings of research utilization. Public Adm Rev. 1979; 39(5): 426-431.
48. Graham ID, Logan J, Harrison MB, Straus SE, Tetroe J, Caswell W, et al. Lost in knowledge translation: time for a map? J Contin Educ Heal Prof. 2006; 26(1): 13–24.
49. Straus SE, Tetroe J, Graham ID. Knowledge translation: What it is and what it isn't. In: Knowledge Translation in Health Care: Moving from Evidence to Practice. 2nd ed. Oxford, UK: John Wiley & Sons; 2013. p. 1–14.
50. Gudea S. Data, information, knowledge: A healthcare enterprise case study. Perspect Heal Inf Mangement. 2005; 2(8): 1-9.
51. Rogers E. Diffusion of Innovations. Fifth Edit. New York, NY: Simon & Schuster, Inc; 2003. p. 168–218.
52. Boaz A, Nutley S. Using Evidence. In: What Works Now? First Edit. Bristol, UK; 2019. p. 251–77.
53. Estabrooks CA, Thompson DS, Lovely JJE, Hofmeyer A. A guide to knowledge tranlsation theory. J Contin Educ Heal Prof. 2006; 26(1): 25–36.
54. Knott J, Wildavsky A. If dissemination is the solution, what is the problem? In: Knowledge: Creation, Diffusion, Utilisation. 1980. p. 537–78.
55. QSR International Pty Ltd. NVivo 12.6.0 (released in November 2019). 2020.
56. Bazeley P. Analysing qualitative data: more than "identifying themes." Malaysian J Qual Res. 2009; 2(2) 6-23.
57. Shea K, Bjørnstad ON, Krzywinski M, Altman N. Uncertainty and the management of epidemics. Nat Methods. 2020; 17(1): 867–868.
58. Chowell G. Fitting dynamic models to epidemic outbreaks with quantified uncertainty: A primer for parameter uncertainty, identifiability, and forecasts. Infect Dis Model. 2017; 2(3): 379–98.
59. Christley RM, Mort M, Wynne B, Wastling JM, Heathwaite AL, Pickup R, et al. "Wrong, but useful": Negotiating uncertainty in infectious disease modelling. PLoS One. 2013; 8(10): e76277.
60. Loucks DP, van Beek E, Stedinger J, Dijkman J, Villars M. Model sensitivity and uncertainty analysis. In: Water Resources Systems Planning and Management: An Introduction to Methods, Models, and Applications. Second Edi. UNESCO Publishing; 2017. p. 255–87.
61. Lessler J, Edmunds WJ, Halloran ME, Hollingsworth TD, Lloyd AL. Seven challenges for model-driven data collection in experimental and observational studies. Epidemics. 2015; 10(1): 78–82.
62. Briggs AH, Weinstein MC, Fenwick EAL, Karnon J, Sculpher MJ, Paltiel AD. Model parameter estimation and uncertainty analysis: A report of the ISPOR-SMDM Modeling Good Research Practices Task Force Writing Group-6. Med Decis Mak. 2012; 32(5): 722-732.
63. Otten JJ, Dodson EA, Fleischhacker S, Siddiqui S, Quinn EL. Getting research to the policy table: a qualitative study with public health researchers on engaging with policy makers. Public Heal Res Pract Policy. 2015; 12(56): DOI: https://dx.doi.org/10.5888/pcd12.140546.
64. Irvine MA, Reimer LJ, Njenga SM, Gunawardena S, Kelly-Hope L, Bockarie M, et al. Modelling strategies to break transmission of lymphatic filariasis - aggregation, adherence and vector competence greatly alter elimination. Parasites and Vectors.

2015; 8(547): DOI: https://doi.org/10.1186/s13071-051-1152-3.
65. Stolk WA, Walker M, Coffeng LE, Basáñez M-G, de Vlas SJ. Required duration of mass ivermectin treatment for onchocerciasis elimination in Africa: a comparative modelling analysis. Parasites and Vectors. 2015; 8(552): DOI: 10.1186/s13071-015-1159-9.
66. Alvar J, den Boer M, Jain S, Pandey D, Salunke S. Independent assessment of the Kala-Azar elimination programme, India [Internet]. Geneva; 2020. Available from: https://cdn.who.int/media/docs/default-source/searo/evaluation-reports/independent-assessment-of-kala-azar-elimination-programme-in-india.pdf?sfvrsn=fa0d8baa_2
67. Bijker W, Bal R, Hendriks R. The Paradox of Scientific Authority: The Role of Scientific Advice in Democracies. First. Cambridge, Massachusetts: Massachusetts Insitute of Technology; 2009.
68. Guston DH. Boundary organisations in environmental policy and science. Sci Technol Hum Values. 2001; 26(4): DOI: https://doi.org/10.1177/016224390102660040l.
69. Jansanoff S. States of knowledge. First Edit. London: Routledge: Taylor and Francis Group; 2004.
70. Wehrens R. Beyond two communities - from research utilization and knowledge translation to co-production? Public Health. 2014; 128(6): 545-551.
71. Hawkins J, Madden K, Fletcher A, Midgley L, Grant A, Cox G, et al. Development of a framework for the co-production and prototyping of public health interventions. BMC Public Health. 2017; 17(689): DOI: https://doi.org/10.1186/s12889-017-4695-8.
72. Oliver K, Kothari A, Mays N. The dark side of coproduction: do the costs outweigh the benefits for health research? Heal Res Policy Syst. 2019; 17(33): DOI: https://doi.org/10.1186/s12961-019-0432-3.
73. Filipe A, Renedo A, Marston C. The co-production of what? Knowledge, values, and social relations in health care. PLoS Biol. 2017; 15(5): e2001403.
74. Silumbwe A, Zulu JM, Halwindi H, Jacobs C, Zgambo J, Dambe R, et al. A systematic review of factors that shape implementation of mass drug administration of lymphatic filariasis in sub-Saharan Africa. BMC Public Health. 2017; 17(1): 484.
75. Standley C, Boyce MR, Klineberg A, Essix G, Katz R. Organization of oversight for integrated control of neglected tropical diseases within Ministries of Health. PLoS Negl Trop Dis. 2018; 12(11): e0006929.

Implications for thesis

This chapter explores research actionability by examining the perceived value and use of VL modelling to decision makers in India. Modelling was identified as a discipline in which a substantial amount of knowledge has been generated over the past decade, especially for VL in India, but with scarce evidence of its use in policy. Chapter 5 details how modelling has informed surveillance-response activities across other NTDs, especially those eligible for MDA. This chapter offers a new perspective on barriers and challenges to informing and influencing KEP directives through VL modelling. Guided by the theory of knowledge

utilisation, events of knowledge reception, cognition, influence, and impact are examined by collating the insight, experience, and perspective of participants included in this study. To address barriers to knowledge utilisation in the KEP, both researchers and decision makers may need to adjust processes and expectations. This chapter identifies the importance of qualitative research and HPSR to describing complexities, dynamics, and working relationships between researchers, policy makers, and stakeholders. Ways in which HPSR might be encouraged and embedded in future research and decision-making processes are considered in Chapter 7, the discussion.

CHAPTER 7. DISCUSSION

This DrPH thesis set out to examine and contribute to actionable research for VL elimination and surveillance activities in India. From an interdisciplinary perspective, it addresses the science behind VL surveillance strategies by 1) evaluating the costs and outcomes of case detection activities across varying levels of incidence, and 2) examining the value and use of mathematical modelling research to decision makers. This chapter synthesises key findings and contributions of papers R1 and R2, considers strengths and weaknesses of an interdisciplinary approach, and discusses implications to surveillance, integration, and regional VL elimination in South Asia.

7.1 Key findings and contributions to knowledge

In alignment with the objectives outlined in Chapter 1, this section summarises the literature reviewed in Chapters 2, 3, and 5, and discusses key findings and specific contributions of the research presented in Chapters 4 and 6 (papers R1 and R2).

Objective 1: To identify policy-relevant research disciplines for informing VL surveillance strategies in India

To support the research conducted in papers R1 and R2, Objective 1 examines specific challenges behind reaching VL EPHP in India and how policy-relevant research might address gaps identified in the WHO 2021-2030 roadmap. Surveillance-response research will be crucial for reinforcing the political and financial commitment needed to reach and sustain VL EPHP targets throughout pre- and post-elimination phases. Lessons learned from PC-NTDs and other elimination programmes show that epidemiology, economics, and health systems research have a strong influence on the design and implementation of surveillance, especially when approached from an interdisciplinary perspective. Chapter 3 identifies how

economic analyses aid in strategising resource allocation to address heterogeneity and equity, the scale and scope of surveillance, opportunities for programme integration, and long-term funding requirements to reach and sustain elimination. The literature reviewed in Chapter 3 also identifies that economic evaluations from the providers' perspective for VL in India are scare.

Conversely, mathematical models examining the dynamics of VL transmission, potential impact of different interventions, and likelihood of reaching elimination benchmarks in India are relatively abundant. Chapter 5 explores how the field of modelling has contributed to strategising surveillance-response activities in other elimination programmes, highlighting how the actionability of VL modelling is complicated by disease characteristics, transmission, and treatment. As modelling can provide valuable insight on the scale, scope, and intensity of surveillance required to reach VL EPHP targets, it is essential that HPSR be incorporated into future research and policy processes to improve the translation of knowledge to action. This literature review makes a case for examining how VL modelling is valued and used by decision makers in India.

Although not a formal research component of this thesis, Objective 1 (Chapters 2, 3, and 5) frames and supports how actionable research for VL surveillance activities in India can be examined from a dual perspective. Where economic evidence is absent, paper R1 addresses the costs and outcomes of case detection activities; and where modelling evidence is more available, paper R2 addresses its perceived value and usefulness to decision makers.

Objective 2: To evaluate the costs and outcomes of VL active- and passive case detection activities in India

Recent KEP evaluations assert that improved efficiency, sensitivity, and comprehensiveness of ACD will be key to achieving VL EPHP in India [1, 2]. To update and expand the economic perspective of VL surveillance, which has not been explored since 2012, paper R1 compares costs and outcomes of PCD, index case-based ACD, and a combination of blanket & camp ACD when all three methods were employed in 2018 [3–5]. As the most resource-intensive activity, it was expected that blanket and camp ACD would yield the highest cost at $4,186.81 USD per VL positive case detected. Index case-based ACD was one-eighth this cost at $522.81 USD per VL positive case detected, followed by PCD at $246.79 USD. However, if instead considering the number of VL tests conducted, the margin between blanket and camp ACD and index case-based ACD is nearly halved, at $281.99 USD versus $63.83 USD, respectively.

To contextualise the costs of VL surveillance, outcomes of each activity are compared across geographical incidence ranging from over 800 to less than 10 VL cases per district during 2018. Around 45% of all VL cases were detected from cumulative ACD, which identified more VL positive cases in low incidence districts than PCD. It is possible that the larger proportion of VL cases identified through PCD in high incidence districts may have been a result of increased community awareness of VL due to the frequency of index case-based ACD interventions in those areas. A 2018 study found that villages having received behaviour change communication (BCC) for VL were 50% more likely to refer symptomatic community members to visit PHCs for diagnosis and treatment [6]. Future programme evaluations should consider the secondary impact of community education through ACD, which could be valuable for strategising case detection in populations with limited knowledge on VL symptoms and referral sites.

Lastly, this study estimated that between $1.6 to $4 million USD is required to identify an additional 3,000 VL cases, depending on the extent to which blanket and camp ACD is intensified. Blanket and camp ACD was targeted towards high-incidence districts during 2018, which may not be its most effective application. Although blanket and camp ACD requires substantial investment and human capacity, it should not be excluded as an option for future case detection strategies. Several assessments of case detection strategies for malaria have reasoned that index case-based ACD alone is insufficient for reaching elimination, especially in low-incidence regions where patient follow-up is a primary operational challenge [7–10]. The contribution of detecting additional, albeit few, VL cases through blanket and camp ACD may be critical to reaching and sustaining EPHP if it is targeted towards low-incidence or previously non-endemic areas in India.

More economic analyses are needed to inform India's VL surveillance activities in the short-, mid-, and long-term [11–15]. To inform or intensify strategies in the short-term, disease heterogeneity and equity must be factored into design and implementation. In the mid-term, the results of paper R1 can be 1) expanded upon using different methods of economic measurement to inform resource allocation and the impact of different strategies, and 2) integrated into mathematical models to project costs and incidence in future time states. In the long-term, economic analyses will be crucial for examining the trade-offs of integrating VL surveillance horizontally into other disease programmes and identifying the investment needed to sustain EPHP in the post-elimination phase [16–25].

Although intermediary health outcomes, such as number of tests conducted, are not ideal in economic evaluations, they may be relevant to long-term planning in elimination programmes. Malaria elimination programmes highlight a need to determine the cost of

establishing a consistent baseline of surveillance for long-term control methods, which could be reflected in the number of tests conducted [26]. For diseases with low incidence, comparing the probability of success between interventions, rather than the lowest cost intervention, becomes more important in evaluations that aim to address decision uncertainty. A recent NTD study advocated for a new economic framework that considers the implications of switching from an optimal strategy (such as DALYs averted or cases detected) to a strategy with higher likelihood of meeting elimination targets (such as long-term surveillance or integrated case detection) [27]. Justifying and incentivising a baseline number of tests required for annual surveillance might also address the perverse incentive to not report VL cases as incidence declines [28].

Objective 3: To examine how mathematical modelling is valued and used to inform VL case detection in India's KEP

The second research component of this thesis contributes knowledge on the extent to which VL modelling research is valued and used to inform surveillance activities in the KEP, which was previously unexplored [29–34]. A common theme in paper R2 relates to assumptions: 1) within the models themselves, 2) in whether modellers orient their analyses and recommendations towards specific programme operations, and 3) as to whom is responsible for translating knowledge to policy. Participants reported confusion surrounding the meaning and confines of assumptions, which likely resulted in a distrust of modelling results. Similar challenges to resolving assumptions have been identified in modelling of disease outbreaks in Europe, where the impetus for timely policy change and alignment between stakeholders may have been stronger [35].

Paper R2 identifies that a communication intermediary, or liaison, may be necessary to improve trust and confidence between researchers and decision makers in India. Knowledge translation and exchange literature affirm that including members of the research setting in decision-making discussions can contribute to data credibility and implementation [36–40]. Therefore, a communication intermediary position between VL modellers and decision makers should undoubtedly be held by a modeller, or collaborator, in India. Further, a long-term capacity strengthening approach to improve communication, which would also scale up the availability and usefulness of modelling for policy, will likely require a training scheme to ensure scientists in India have the ability to construct and interpret their own models independently [41–43].

A dedicated position or role for communicating between researchers and decision makers is not widely employed in elimination programmes, but its value has been considered [44]. More often, the opportunity for co-production between modellers and decision makers is promoted to develop mutual understanding of programme operations, political restrains, and the analytic capacity of models to inform policy [45]. As most participants received information about past, current, and proposed modelling during VL partnership meetings, there may be an opportunity to engage decision makers in the process of analysing and interpreting models to improve their understanding of results and relevance to policy. A workshop could allow researchers to train decision makers in the process of design, analysis, and interpretation of modelling, which might present an opportunity to trial the value of a communication intermediary.

Participants also questioned the direct relevance and application of modelling to ongoing programme activities. It will be important for researchers to design and interpret future

models around specific programme operations by observing ACD, IRS, and data collection activities in-person. Although most disease control and elimination programmes are coordinated at the national level, implementation is highly dependent on local context and often requires bottom-up consideration of operations on the frontline [46]. Several participants requested that modelling results be piloted on the village-level, especially where incidence can be forecasted several months in advance to inform the resources and capacity required for ACD activities. The significance of forecasting incidence is recognised for other NTDs, but a framework is likely required to improve the rigor and utility of predictions for use in policy [47].

The emergence of modelling consortia and ensembles are expected to improve interactions between necessary stakeholders considerably in the foreseeable future, especially for modellers and decision makers [48]. The Regional Technical Advisory Group (RTAG) on VL is a platform in which research consortia, funders, and governing bodies can jointly evaluate science, policy, and barriers to EPHP for endemic Member States of the South Asia region [49]. Despite its existence for over a decade, paper R2 identified confusion surrounding who is ultimately accountable for mobilising knowledge into policy. Modelling consortiums for tuberculosis (TB) and HIV have seen improved translation of knowledge to policy through long-term relationships between stakeholders. One way mutual trust was established in these consortiums was by iteratively re-evaluating models that decision makers were familiar with as new data and parameters became relevant [45].

The governing dynamics of VL surveillance in India are complicated, as WHO ultimately guides and validates elimination but does not perform an implementation role. The KEP directs and enforces activities according to WHO guidelines that are based in scientific

evidence but often time-consuming and challenging to revise. A study investigating policy development and scale-up of ACD for TB found that 56% of programme managers relied on WHO guidelines to inform decision making, while only 13% used scientific evidence [50]. As modellers work closely with decision makers in the KEP, there may be an opportunity to leverage informal routes of policy change by piloting activities on a small-scale. Overarchingly, barriers to translating knowledge into policy identified in paper R2 align with existing literature that calls for improved engagement in and capacity for HPSR research in developing countries [51–53].

7.2 Limitations and strengths of thesis approach

Chapters 4 and 6 discuss limitations to internal and external validity of the methods, analysis, and generalisability within papers R1 and R2. In this section, limitations and strengths are considered in terms of the thesis approach and how interdisciplinary research fulfils and confines DrPH programme objectives and practical public health solutions.

7.2.1 Limitations

Cost analysis: units of measurement and generalisability

The units of measurement used to compare ACD and PCD costs and outcomes in paper R1 may be limited in their generalisability and longevity, as they do not encompass generic health outcomes that allow for comparison of interventions across health conditions [54]. Although the cost per new VL case detected has relevance to the KEP in the short term, it may require re-evaluation in the future as cases decline and heterogeneity increases in India [55–58]. One of the intended applications of these unit costs is within mathematical models to examine the validity and viability of surveillance activities over time. This opportunity is discussed in the research findings but the overlap between economic and modelling

disciplines is not well-established for VL in India. Paper R1 was not designed or analysed for application to a specific or ongoing mathematical model, which may undermine its applicability. It may be important to conduct future economic analyses in direct collaboration with modellers to build appropriate parameters and indicators into the design, data collection, and analysis [59, 60].

Paper R1 presents costs and outcomes of ACD and PCD specific to the endemic state of Bihar, which may not be directly generalisable to operational activities and governance in Jharkhand, Uttar Pradesh, and West Bengal. For example, 70% of Jharkhand is considered rural and 30% of populations are tribal communities [61]. Rates of education and knowledge of infectious diseases are lower in Jharkhand, which negatively impacts trust in medical professionals and health-seeking behaviour [62]. However, VL surveillance is also carried out on the KAMIS platform in Jharkhand, and the state shares similar KEP governance, funding, and implementation to Bihar [1]. The application of paper R1 to remaining VL-endemic states would require additional analysis of context-specific operations and disease heterogeneity in these areas.

Research actionability and dissemination

Paper R2 includes recommendations and opportunities to improve the actionability of VL modelling research to policy in India, but is likely limited in its exposure, language, and accessibility to relevant decision makers and programme managers. Although this study is written for publication in a scientific journal, it aims to inform a broader audience than solely researchers. This is a limitation of evaluating and disseminating research without a programmatic platform to encourage its visibility to other stakeholders [63, 64]. There may also be a limitation in the relevance of the knowledge utilisation framework, where its

usefulness depends on whether and how it can be embedded into future research and policy evaluations [65–67]. To improve the exposure of this study and encourage knowledge translation assessments in the future, these research findings should be shared with a diversity of relevant policy, programme, and research actors. Evidence-to-policy initiatives may appear relevant to only researchers and decision makers, but programme designers, implementers, and managers should all be included in future policy studies for their influence and insight [68].

Interdisciplinary approach

A DrPH thesis is relatively reduced in content compared to a PhD and challenged to fulfil both breadth and depth of its research objectives. Mounting a practical public health contribution can become further complicated by engaging in multiple research disciplines [69]. Although the importance of interdisciplinary research is a key theme in the literature referenced throughout this work, neither paper R1 nor R2 combine multiple disciplines into a single study. There may also have been a missed opportunity to contribute knowledge and develop skills within a single discipline, which was substituted for the objective of engaging in practical and diverse public health research.

7.2.2 Strengths

Methodology and participant inclusion

Papers R1 and R2 highlight an advantage of assessing issues at multiple scales by including different echelons of programme implementers, management, and governance [70]. Paper R1 not only examined top-down expenditure reports and managers of ACD and PCD programmes, but also compared the reality of activities in the field through observation and micro-costing. The differences in perceived cost and time of ACD activities reveals the

importance of including a diversity of participants in economic analyses of surveillance programmes. Future economic evaluations of VL surveillance activities should include both top-down (national and state governance) and bottom-up (on-the-ground implementation) perspectives for a representative assessment [68]. Similarly, a diversity of participants was sought for inclusion in paper R2 to explore the extent to which programme managers, implementers, and decision makers understand and value VL modelling research. Participants in this study conveyed the importance of considering programme governance from WHO and KEP perspectives in tandem with on-the-ground operational activities to design research intended for a policy response.

Methodological strengths of this thesis approach are also apparent within and across quantitative and qualitative disciplines. Interviews conducted in both papers R1 and R2 revealed subjective insights and experiences that could potentially impact KEP operations. In paper R1, ACD officers claim to have spent more time on case detection than their supervisors reported, which is important to this and future analyses. Paper R2 identified several barriers to knowledge translation that otherwise would not be captured through quantitative programme and process evaluations. To analyse complex biological, political, and social factors in public health programmes, a dual-qualitative and quantitative perspective should be increasingly employed [71].

Interdisciplinary approach

An interdisciplinary approach was advantageous for examining and contributing towards actionable research to inform VL surveillance strategies in India. This thesis was able to explore actionability from a dual perspective: both the availability of research and its use in policy. Where economic analyses for VL surveillance in India are deficient, paper R1

contributes knowledge on the cost and outcomes of surveillance activities. Under the notion that compelling research should inform policy, barriers to knowledge translation could then be studied through the comparatively strong evidence base of mathematical modelling. Challenges and opportunities for translating modelling into policy could foreshadow and inform similar circumstances for economic analyses in the future. Although economics and modelling are independent disciplines, this thesis identifies opportunities to synthesise and explore them comprehensively to improve actionability [55, 72–75].

The importance of HPSR to research actionability also emerged through this interdisciplinary approach [76]. Although this thesis focused largely on the content of policy-relevant research, it identified that barriers exist beyond the availability of evidence and its perceived significance to decision makers. Other NTD elimination programmes may face similar systems-based challenges between researchers, implementers, national governance, and WHO that extend beyond the content of research. This strengthens the case for not only examining barriers to knowledge translation but embedding HPSR broadly into policy making to encourage and maximise opportunities for research actionability [77].

The benefits of an interdisciplinary thesis also relate to the advancement and application of diverse research skills gained under DrPH programme objectives. Paper R1 allowed for the development of skills in designing, analysing, and interpreting economic research with an aim to inform VL surveillance activities in India. Paper R2 allowed for the development of skills in quantitative interviewing, which highlighted the value of examining experiences, insight, and perspectives of those designing and implementing surveillance activities. Maintaining flexibility through quantitative, qualitative, and systems-based research can

contribute to professional competencies across public health directives, academia, and geographical settings.

7.3 Implications of thesis

This section considers the overarching and generalisable implications of this work to VL surveillance, horizontal integration with other disease programmes, and regional elimination.

Research for improving surveillance

Research for IDM-NTDs has been broadly prioritised to improve early case detection, control tools, and health service expansion to reach WHO targets for control and elimination [78, 79]. In comparison to PC-NTDs that readily employ economic and modelling research to elimination activities, IDM-NTDs struggle to both develop and apply actionable research [78]. Beyond the technical aspects of surveillance, NTD elimination research is challenged to address the feasibility of implementation on health system and community levels [80, 81]. Repercussions of the COVID-19 pandemic will likely amplify the need for comprehensive research that is focused on sustaining progress towards elimination and quelling the risk of NTD resurgence [82].

For vertical VL surveillance in India, interdisciplinary research may be the key to resolving technical requirements of surveillance with political and community-based constraints [83]. Although research that focuses on the cost and impact of interventions over time is essential to reaching EPHP in India, the practicality of inciting change from national- to community-levels should also be prioritised [1, 2]. Several studies identify that social and health systems research are neglected elements of NTD elimination programming and have the potential to directly complement biomedical disciplines [84–86].

In paper R1, the greater number of VL cases identified through PCD in high incidence districts may have been an unintended consequence of increased ACD activities in those areas. Integrating such findings into dynamic transmission models could further explore the non-linear effects of VL interventions and their impact on transmission [75]. Financial and logistical constraints of long-term surveillance have been experienced by other elimination programmes, where community-based vigilance is promoted as a cost-effective supplement for improving knowledge and access to resources in [87]. Context-specific community evaluations might provide the KEP with more robust and precise evidence to base programme decisions on, considering incidence varies from over 600 to less than one VL case in endemic districts [88].

Another programmatic challenge in India may be the relative number of public- versus private healthcare facilities and the geographic extent of KEP coverage. The trend of private health sector growth is on the rise in South Asia, where 55% of patients in Nepal and 27% of patients in Bangladesh prefer to access non-governmental sectors [89]. In India, up to 80% of outpatient services are provided by the private facilities, especially in rural areas where distrust in medical professionals is higher [89–91]. A surveillance assessment in Nepal showed the average time from onset of symptoms to diagnosis for VL patients was 20 days in non-programme districts and only three days in KEP-covered districts [92]. To improve trust in KEP-sponsored treatment facilities in India, as well as knowledge of VL symptoms and treatment, community education may be a necessary component of future surveillance activities [93–95].

Opportunities for horizontal integration

Research on programme integration has been largely focused on PC-NTDs that share similar diagnosis or treatment, especially where MDA can be implemented for several diseases at once [96]. A multi-country assessment of PC-NTD programme integration established a 'best practice roll-out package' detailing the value of: 1) conducting leadership and situational analyses, 2) developing a plan for disease mapping and programme scale-up, and 3) creating a central coordinating mechanism [97]. However, dichotomising the 'tool-readiness' of NTDs may contribute to a lack of research, innovation, and development of resources for horizontal integration of IDM-NTDs [98]. For VL, the opportunity to combine the diagnostic application of existing surveillance programmes of skin-related diseases or febrile illnesses must be explored.

As more than half of the 20 NTDs present with skin manifestations, WHO encourages that endemic countries develop an approach to integrating skin-related diseases for community awareness, surveillance and mapping, and monitoring and evaluation [99]. Integrating skin-related disease surveillance programmes could both increase coverage and decrease costs, although operational challenges are anticipated [100]. Many skin-related infections are not painful or disparaging enough to mobilise patients to participate in active surveillance, especially during early stages of clinical presentation [101]. One integration study identified that improving community awareness is essential for combatting stigma and lack of knowledge surrounding treatment for skin-related NTDs [102]. From the operational perspective, synergising fragmented disease programmes requires additional funding and capacity to assess cost-effectiveness and feasibility throughout the integration process [103, 104].

Febrile illnesses such as malaria, typhoid, and TB are more commonly investigated for the prospect of integrated surveillance. Interestingly, the emergence of COVID-19 may promote new opportunities to expand integrated programming to include both emerging and endemic fever-related illnesses, which could include VL [105]. A major challenge for integrating febrile illnesses is in disease heterogeneity, where surveillance mapping is crucial to characterise co-endemicity and develop a targeted approach [106]. Studies also show that increased availability of diagnostic tools is essential for integrated surveillance to correctly identify undifferentiated fevers [107].

To support and inform programme integration, a shift is necessary from disease-specific and unidimensional research to cross-cutting approaches with adjacent disciplines [108]. Although the feasibility and impact of integrating VL diagnostic camps with other activities has been examined in the ISC, economic analyses and transmission models are excluded from existing assessments [20, 109, 110]. Trade-offs of programme integration could be informed by the costs and outcomes of surveillance activities presented in paper R1, but will require interdisciplinary research across other disease programmes to strategise funding and implementation [73, 111, 112]. A comprehensive approach to integrating surveillance should include economics, epidemiology, and policy disciplines supplemented by 1) social sciences to engender trust in communities and tailor surveillance to local levels, 2) environmental sciences to characterise the effects of climate change and migration, and 3) COVID-19 research to understand its ongoing and residual impact on elimination progress in India.

Regional VL elimination efforts in the ISC

The past two decades of prioritising NTDs onto the international stage for action exposed technical-, disease-, and context-specific barriers to control and elimination [113]. The next

decade of action may be challenged to mobilise knowledge gained from other elimination programmes to strengthen surveillance, secure long-term funding, and respond to modern challenges [114–116]. As new VL cases have been recently reported in Bhutan, Thailand, and Sri Lanka, cross-border initiatives will be essential to map and manage regional incidence throughout pre- and post-elimination phases [49, 117]. Open borders and poor national coordination of state-run surveillance are identified as barriers to malaria elimination in India [118].

A principal recommendation from the *Independent assessment of the KEP* was to create a national task force that oversees progress and guides strategic action for VL elimination in India, but strengthening regional advisory may be more beneficial to accelerating outbreak- and targeted responses across countries [119]. Several regional South Asia elimination programmes for malaria and other NTDs have seen success in sharing context-specific surveillance strategies such as community-level incentives for case referral, increasing awareness through educational campaigns, and establishing an inter-country platform for sharing epidemiology and migration data [120–123]. As RTAG functions to provide technical advisory on VL elimination for the region, there may be an opportunity to translate lessons learned from Nepal and Bangladesh to synergise operational guidelines, information sharing, and financial and programme management structures to other countries in South Asia [124].

Lessons learned from Latin American countries (LACs), where VL is also targeted for regional elimination, could be relevant to RTAG's role in South Asia. An analogous partnership structure operates between the Inter-American Development Bank (IDB), Pan American Health Organization (PAHO), and Global Network for NTDs (GN) that provides

community-based technical support measures to eliminate NTDs regionally [125]. Over the past decade, the partnership launched several demonstration projects to show proof of principle of integrated surveillance for trachoma, Chagas disease, leishmaniasis, rabies, onchocerciasis, and soil-transmitted helminths (STHs) [126]. Results from the demonstration projects were translated into a conceptual framework that outlines key components of management, financing, implementation, and monitoring and evaluation of integration on a continuum ranging from linkage to coordination and full merging of programmes [22]. Integrating socio-economic, environmental, and political indicators into geospatial modelling have also been integral to regional NTD integration in LACs and Africa, which strengthens the argument for collaboration between disciplines [126, 127].

Novel strategies to improve VL surveillance for EPHP in India may necessitate cross-collaboration between research disciplines, regional programmes, and diseases eligible for horizontal integration. RTAG, KEP, and NTD modelling consortium are viable platforms to facilitate collaboration but establishing modes of accountability and actionability may require international governance and oversight. In tandem with prioritising comprehensive evidence across disciplines, programmes, and countries, the KEP must embed modes of understanding and facilitating the translation of knowledge into action.

7.4 Recommendations for actionable research in the KEP

In alignment with DrPH objectives to encourage the application of research towards a practical public health response, this thesis includes recommendations to improve research actionability in the KEP. First, the production of economic analyses for VL in India from the provider's perspective must be strengthened to inform the effectiveness of interventions and identify trade-offs of integrating surveillance into other disease programmes. Research on

programme integration with other tool-deficient NTDs as well as febrile and skin-related illnesses should be designed in collaboration with modellers, implementers, and decision makers [128–132].

Second, mathematical modelling should be tailored towards ongoing operational activities and employ a communication intermediary between researchers and decision makers. Opportunities to pilot modelling results on a small-scale should be considered, especially for forecasting incidence as a surveillance-response tool. It will be prudent for modellers and economists to collaborate on the costs and impact of both vertical and horizontal interventions over time to reach EPHP benchmarks. Lastly, HPSR must be embedded into both policy and research processes to better understand how changes to surveillance can be realised on national and community levels.

To orient the objectives and findings of this thesis within NTD targets and KEP directives, the WHO NTD roadmap for 2021-2030 is referenced throughout Chapters 1-6. Figure 7-1 outlines recommendations generated from this thesis as they align with the three pillars to reflect: 1) technical, strategic, and operational challenges of VL surveillance in India, and 2) opportunities for research to inform surveillance strategies, programme integration, and country ownership [133]. Across all three pillars, improvements in economic, modelling, and HPSR research are identified for ways in which they could accelerate programmatic action, intensify cross-cutting approaches, and facilitate country ownership. Papers R1 and R2 are included for their contribution to informing programmatic action, in contrast to the broad and generalisable implications examined in this section.

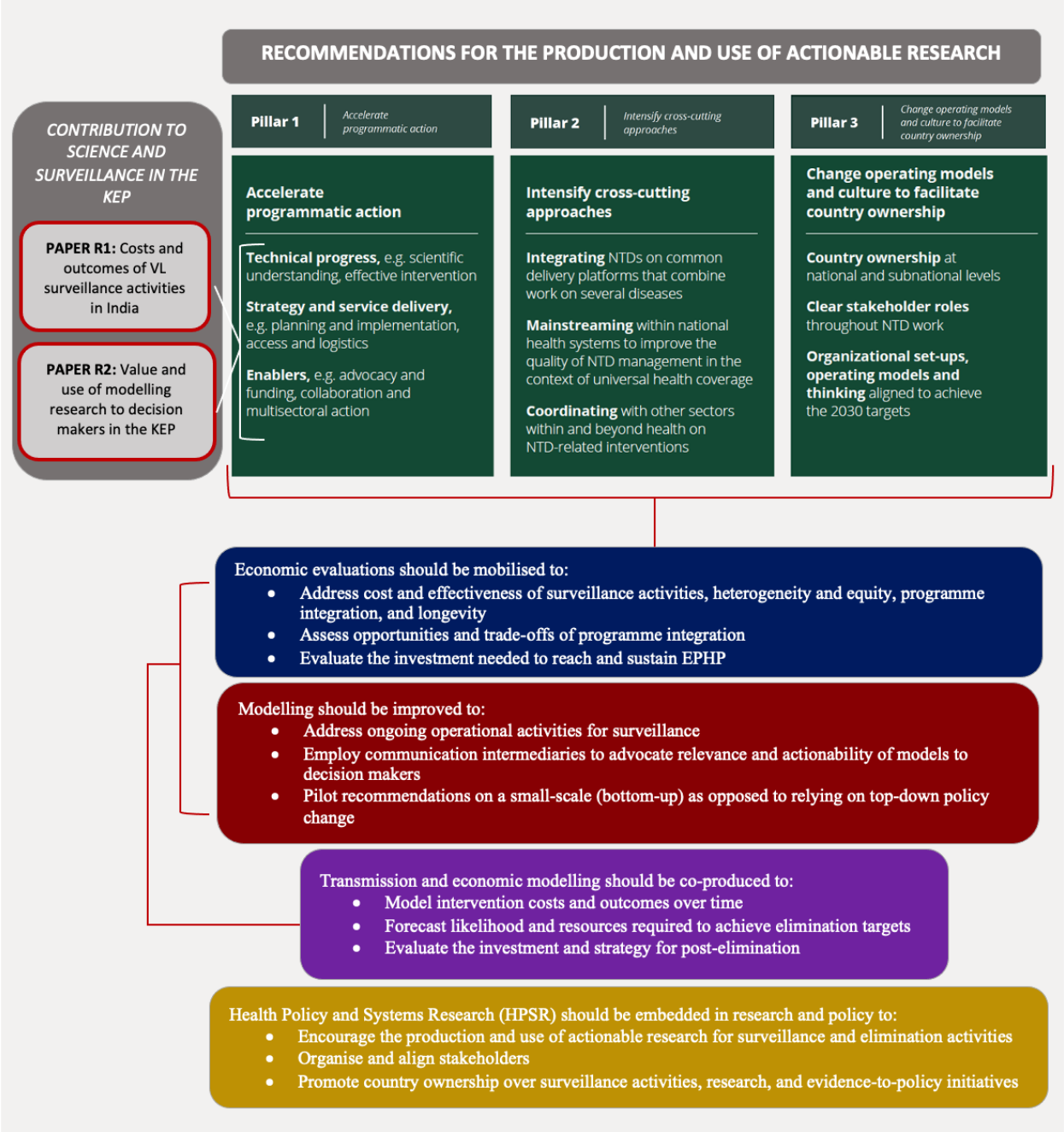


Figure 7-1. Policy and research recommendations framed within pillars of the WHO NTD roadmap for 2021-2030.

CONCLUSION

As VL incidence declines in India, surveillance-response activities must be substantiated by research that addresses transmission dynamics, programme operations, and accountability in decision making. Where economic analyses to inform VL intervention costs and effectiveness are scarce, research actionability is limited by its availability. This thesis contributes knowledge towards the costs and outcomes of index case-based ACD, blanket and camp ACD, and PCD across varying levels of VL incidence in India. While index case-based ACD and PCD are less costly, it may be valuable to employ blanket and camp ACD in areas at risk of VL outbreaks or resurgence. Conversely, where VL modelling literature is readily available, research actionability is limited by communication and governance. Championing the value and relevance of modelling to decision makers may necessitate an intermediary to align research objectives with operational activities and government mobilisation. Modellers should explore opportunities to pilot results on a small scale and assess the value of integrating economic indicators to strengthen comprehensive evidence for decision makers. HPSR must be embedded within research and policy making processes to encourage the production and use of actionable research in the KEP. Throughout remaining pre- and post-EPHP phases in India, VL surveillance strategies should prioritise knowledge generated from, but not limited to, economic, modelling, and policy evaluations to improve programme effectiveness and longevity.

References

1. Dubey P, Das A, Priyamvada K, Bindroo J, Mahapatra T, Mishra PK, et al. Development and evaluation of active case detection methods to support visceral leishmaniasis elimination in India. Front Cell Infect Microbiol. 2021;11(1): DOI: 10.3389/fcimb.2021.648903.
2. Bindroo J, Priyamvada K, Chapman ACL, Mahapatra T, Sinha B, Banerjee I, et al. Optimizing village-level targeting of active case detection to support visceral leishmaniasis elimination in India. Front Cell Infect Microbiol. 2021; 11(1): DOI: 10.3389/fcimb.2021.648847.
3. Hirve S, Singh SP, Kumar N, Banjara MR, Das P, Sundar S, et al. Effectiveness and feasibility of active and passive case detection in the visceral leishmaniasis elimination initiative in India, Bangladesh, and Nepal. Am J Trop Med Hyg. 2010; 83(3): 507–511.
4. Singh SP, Hirve S, Huda MM, Banjara MR, Kumar N, Mondal D, et al. Options for Active Case Detection of Visceral Leishmaniasis in Endemic Districts of India, Nepal and Bangladesh, Comparing Yield, Feasibility and Costs. PLoS Negl Trop Dis. 2011; 5(2): e960.
5. Huda MM, Hirve S, Siddiqui NA, Malaviya P, Banjara M, Das P, et al. Active case detection in national visceral leishmaniasis elimination programs in Bangladesh, India, and Nepal: Feasibility, performance and costs. BMC Public Health. 2012; 12(1): DOI: https://doi.org/10.1186/1471-2458-12-1001.
6. Srinivasan R, Ahmad T, Raghavan V, Kaushhik M, Pathak R. Positive influence of behavior change communication on knowledge, attitudes, and practices for visceral leishmaniasis/kala-azar in India. Glob Heal Sci Pract. 2018; 6(1): 192-209.
7. Searle KM, Hamapumbu H, Lubinda J, Shields TM, Pinchoff J, Kobayashi T, et al. Evaluation of the operational challenges in implementing reactive screen-and-treat and implications of reactive case detection strategies for malaria elimination in a region of low transmission in southern Zambia. Malar J. 2016; 15(1): 412.
8. Gerardin J, Bever CA, Hamainza B, Miller JM, Eckhoff PA, Wenger EA. Optimal population-level infection detection strategies for malaria control and elimination in a spatial model of malaria transmission. PLOS Comput Biol. 2016; 12(1): e1004707.
9. Moonen B, Cohen JM, Snow RW, Slutsker L, Drakeley C, Smith DL. Operational strategies to achieve and maintain malaria elimination. Lancet. 2010; 376(9752): 1592-1603.
10. Aidoo EK, Afrane YA, Machani MG, Chebore W, Lawson B, Atieli H, et al. Reactive case detection of Plasmodium falciparum in western Kenya highlands: effective in identifying additional cases, yet limited effect on transmission. Malar J. 2018; 17(111): DOI: https://doi.org/10.1186/s12936-018-2260-2.
11. Fitzpatrick C, Sankara DP, Agua JF, Jonnalagedda L, Rumi F, Weiss A, et al. The cost-effectiveness of an eradication programme in the end game: Evidence from guinea worm disease. PLoS Negl Trop Dis. 2017; 11(10): e0005922.
12. Sicuri E, Evans DB, Tediosi F. Can economic analysis contribute to disease elimination and eradication? A systematic review. PLoS One. 2015; 10(6): e0130603.
13. World Health Organization. Global Polio Eradication Initiative investment case 2019-2023 [Internet]. Geneva; 2019. Available from: https://polioeradication.org/wp-content/uploads/2019/08/Polio-InvestmentCase-Report-20190819.pdf.
14. Hoomans T, Severens JL. Economic evaluation of implementation strategies in health care. Implement Sci. 2014; 9(168): DOI: https://doi.org/10.1186/s13012-014-0168-y.
15. Mastin AJ, van den Bosch F, van den Berg F, Parnell SR. Quantifying the hidden costs

of imperfect detection for early detection surveillance. Philos Trans R Soc. 2019; 374(1776): DOI: https://doi.org/10.1098/rstb.2018.0261.
16. Lammie PJ, Fenwich A, Utzinger J. A blueprint for success: integration of neglected tropical disease control programmes. Trends Parasitol. 2006 ;22(7): 313-321.
17. Solomon AW, Engels D, Bailey RL, Blake IM, Brooker S, Chen J-X, et al. A diagnostics platform for the integrated mapping, monitoring, and surveillance of neglected tropical diseases: rationale and target product profiles. PLoS Negl Trop Dis. 2012; 6(7): e1746.
18. Deribe K, Meribo K, Gebre T, Hailu A, Ali A, Aseffa A, et al. The burden of neglected tropical diseases in Ethiopia, and opportunities for integrated control and elimination. Parasit Vectors. 2012; 5(240): DOI: https://doi.org/10.1186/1756-3305-5-240.
19. Gedge LM, Bettis AA, Bradley MH, Hollingsworth TD, Turner H. Economic evaluations of lymphatic filariasis interventions: A systematic review and research needs. Parasit Vectors. 2018; 11(75): DOI: https://doi.org/10.1186/s13071-081-2616-z.
20. Banjara MR, Das ML, Gurung CKKK, Singh VK, Joshi AB, Matlashewski G, et al. Integrating case detection of visceral leishmaniasis and other febrile illness with vector control in the post-elimination phase in Nepal. Am J Trop Med Hyg. 2019; 100(1): 108-114.
21. Sutherland CS, Stone CM, Steinmann P, Tanner M, Tediosi F. Seeing beyond 2020: An economic evaluation of contemporary and emerging strategies for elimination of Trypanosoma brucei gambiense. Lancet Glob Heal. 2016; 5(1): E69-E79.
22. Tristao I, Cali J. It can be done: An integrated approach for controlling and eliminating neglected tropical diseases [Internet]. 2014. Available from: https://publications.iadb.org/publications/english/document/It-Can-Be-Done-An-Integrated-Approach-for-Controlling-and-Eliminating-Neglected-Tropical-Diseases.pdf.
23. Perry HN, McDonnell SM, Alemu W, Nsubuga P, Chungong S, Otten M, et al. Planning an integrated disease surveillance and response system: a matrix of skills and activities. BMC Med. 2007; 5(24): DOI: https://doi.org/10.1186/1741-7051-5-24.
24. Phalkey RK, Shukla S, Shardul S, Ashtekar N, Valsa S, Awate P, et al. Assessment of the core and support functions of the Integrated Disease Surveillance system in Maharashtra, India. BMC Public Health. 2013; 13(575): DOI: https://doi.org/10.1186/1471-2458-13-575.
25. Standley C, Boyce MR, Klineberg A, Essix G, Katz R. Organization of oversight for integrated control of neglected tropical diseases within Ministries of Health. PLoS Negl Trop Dis. 2018; 12(11): e0006929.
26. Sabot O, Cohen JM, Hsiang MS, Kahn JG, Basu S, Tang L, et al. Costs and financial feasibility of malaria elimination. Lancet. 2010; 376(9752): 1604-1615.
27. Antillon M, Huang C-I, Rock KS, Tediosi F. Economic evaluation of disease elimination: An extension to the net-benefit framework and application to human African trypanosomiasis. Proc Natl Acad Sci U S A. 2021; 118(50): DOI: https://doi.org/10.1073/pnas.2026797118.
28. Keusch GT, Pappaioanou M, Gonzalez MC. Incentives for disease surveillance, reporting, and response. In: Sustaining Global Surveillance and Response to Emerging Zoonotic Diseases. Washington DC: National Acadamies Press (US); 2009.
29. Stolk WA, Walker M, Coffeng LE, Basáñez M-G, de Vlas SJ. Required duration of mass ivermectin treatment for onchocerciasis elimination in Africa: a comparative modelling analysis. Parasites and Vectors. 2015; 8(552): DOI: 10.1186/s13071-015-1159-9.

30. Irvine MA, Reimer LJ, Njenga SM, Gunawardena S, Kelly-Hope L, Bockarie M, et al. Modelling strategies to break transmission of lymphatic filariasis - aggregation, adherence and vector competence greatly alter elimination. Parasites and Vectors. 2015; 8(547): DOI: https://doi.org/10.1186/s13071-015-1152-3.
31. Jambulingam P, Subramanian S, de Vlas SJ, Vinubala C, Stolk WA. Mathematical modelling of lymphatic filariasis elimination programmes in India: required duration of mass drug administration and post-treatment level of infection indicators. Parasites and Vectors. 2016; 9(501): DOI: https://doi.org/10.1186/s13071-016-1768-y.
32. Coffeng LE, Bakker R, Montresor A, de Vlas SJ. Feasibility of controlling hookworm infection through preventive chemotherapy: a simulation study using the individual-based WORMSIM modelling framework. Parasites and Vectors. 2015; 8(541): DOI: https://doi.org/10.1186/s13071-015-1151-4.
33. Gurarie D, Yoon N, Li E, Ndeffo-Mbah M, Durham D, Phillips A, et al. Modelling control of Schistosoma haematobium infection: predictions of the long-term impact of mass drug administration in Africa. Parasites and Vectors. 2015; 8(529): DOI: https://doi.org/10.1186/s13071-015-1144-3.
34. Rock KS, Torr SJ, Lumbala C, Keeling M. Quantitative evaluation of the strategy to eliminate human African trypanosomiasis in the Democratic Republic of Congo. Parasites and Vectors. 2015; 8(532): DOI: https://doi.org/10.1186/s13071-015-1131-8.
35. Salajan A, Tsolova S, Ciotti M, Suk JE. To what extent does evidence support decision making during infectious disease outbreaks? A scoping literature review. Evid Policy. 2020; 16(3): DOI: 10.1332/174426420x15808913064302.
36. Hofmeyer A, Scott C, Lagendyk L. Researcher-decision-maker partnerships in health services research: Practical challenges, guiding principles. BMC Health Serv Res. 2012; 12(280): DOI: https://doi.org/10.1186/1472-6963-12-280.
37. Golden-Biddle K, Reay T, Petz S, Witt C, Casebeer A, et al. Toward a communicative perspective of collaborating in research: The case of the researcher-decision-maker partnership. J Heal Serv Res Policy. 2003; 8(2): 20–25.
38. Adler P. Membership roles in field research. In: Qualitative Research Methods. Newbury Park, CA: Sage; 1987: DOI: https://dx.doi.org/10.4135/9781412984973.
39. Hanson E. Issues concerning the familiarity of researchers with the research setting. Adv Nurs. 1994; 20(1): 940–2.
40. Straus SE, Tetroe JM, Graham ID. Knowledge translation is the use of knowledge in health care decision making. J Clin Epidemiol. 2011; 64(1): 6–10.
41. Jacobs JA, Duggan K, Erwin P, Smith C, Borawski E, Compton J, et al. Capacity building for evidence-based decision making in local health departments: Scaling up an effective training approach. Implement Sci. 2014; 9(124): DOI: https://doi.org/10.1186/s13012-014-0124-x.
42. Onwujekwe O, Etiaba E, Mbachu C, Arize I, Nwankwor C, Ezenwaka U, et al. Does improving the skills of researchers and decision-makers in health policy and systems research lead to enhanced evidence-based decision making in Nigeria? A short term evaluation. PLoS One. 2020; 15(9): e0238365.
43. Dussault G, Franceschini MC. Not enough there, too many here: Understanding geographical imbalances in the distribution of the health workforce. Hum Resour Health. 2006; 4(12): DOI: 10.1186/1478-4491-4-12.
44. Morgan O. How decision makers can use quantitative approaches to guide outbreak responses. Philos Trans R Soc. 2019; 374(1776): 20180365.
45. Knight GM, Dharan NJ, Fox GJ, Stennis N, Zwerling A, Khurana R, et al. Bridging the gap between evidence and policy for infectious diseases: How models can aid public health decision-making. Int J Infect Dis. 2016; 42(1): 17-23.

46. Hudson B, Hunter D, Peckham S. Policy failure and the policy-implementation gap: Can policy support programs help? Policy Des Pract. 2019; 2(1): 1-14.
47. Johansson MA, Apfeldorf KM, Dobson S, Devita J, Buczak A, et al. An open challenge to advance probabilistic forecasting for dengue epidemics. Proc Natl Acad Sci U S A. 2019; 116(48): DOI: https://doi.org/10.1073/pnas.1909865116.
48. Baguelin M, Medley GF, Nightingale ES, O'Reilly KM, Rees EM, Waterlow NR, et al. Tooling-up for infectious disease transmission modelling. Epidemics. 2020; 32(1): 100395.
49. World Health Organization. Report of Meeting of the Regional Technical Advisory Group (RTAG) on Visceral Leishmaniasis and the National Visceral Leishmaniasis Programme Managers of endemic Member States [Internet]. New Delhi; 2020. Available from: https://apps.who.int/iris/bitstream/handle/10665/340612/sea-cd-329-eng.pdf?sequence=1&isAllowed=y.
50. Biermann O, Tran PB, Viney K, Caws M, Lönnroth K, Annerstedt K. Active case-finding policy development, implementation and scale-up in high-burden countries: A mixed-methhods survey with National Tuberculosis Programme mangers and document review. PLoS One. 2020; 15(10): e0240696.
51. Ezenwaka U, Mbachu C, Etiaba E, Uzochukwu B, Onwujekwe O. Integrating evidence from research into decision-making for controlling endemic tropical diseases in South East Nigeria: perceptions of producers and users of evidence on barriers and solutions. Heal Res Policy Syst. 2020; 18(4): DOI: https://doi.org/10.1186/s12961-019-0518-y.
52. Feldstein AC, Glasgow RE. A Practical, Robust Implementation and Sustainability Model (PRISM) for integrating research findings into practice. Jt Comm J Qual Patient Saf. 2008; 34(4): 228-243.
53. Henao-Martinez AF, Colborn K, Parra-Henao G. Overcoming research barriers in Chagas disease--designing effective implementation science. Parasitol Res. 2016; 116(1): 35-44.
54. Drummond M, Sculpher M, Claxton K, Stoddart G, Torrance G. Introduction to economic evaluation. In: Methods for the Economic Evaluation of Health Care Programmes. Fourth Edi. Oxford, UK; 2015. DOI: https://dx.doi.org/10.1136/emj.19.3.198.
55. Sutherland CS, Yukich J, Coeree R, Tediosi F. A literature review of economic evaluations for a neglected tropical disease: Human African Trypanosomiasis ("Sleeping Sickness"). PLoS Negl Trop Dis. 2015; 9(2): e0003397.
56. Pitt C, Vassall A, Teerawattananon Y, Griffiths UK, Guinness L, Walker D, et al. Foreward: Health economic evaluations in low- and middle-income countries: Methodological issues and challenges for priority setting. Health Econ. 2016; 25(1): 1-5.
57. World Health Organization. Evaluating the costs and benefits of national surveillance and response systems: Methodologies and options [Internet]. Geneva; 2005. Available from: http://apps.who.int/iris/bitstream/handle/10665/69335/WHO_CDS_EPR_LYO_2005_25_eng.pdf?sequence=1.
58. Toor J, Coffeng LE, Hamley JID, Fronterre C, Prada JM, Castaño M, et al. When, Who, and How to Sample: Designing Practical Surveillance for 7 Neglected Tropical Diseases as We Approach Elimination. J Infect Dis. 2020; 221(5): 499–502.
59. Hirve S, Kroeger A, Matlashewski G, Mondal D, Banjara MR, Das P, et al. Towards elimination of visceral leishmaniasis in the Indian subcontinent—Translating research to practice to public health. PLoS Negl Trop Dis. 2017; 11(10): e0005889.

60. World Health Organization. Setting priorities in communicable disease surveillance [Internet]. Geneva; 2006. Available from: https://www.who.int/csr/resources/publications/surveillance/WHO_CDS_EPR_LYO_2006_3.pdf.
61. Aich P, Banerjee S, Jha T, Aggarwal A, Sinha D. Situation analysis of MTP services: Jharkhand [Internet]. New Delhi, India; 2011. Available from: https://www.researchgate.net/profile/Sushanta-Banerjee-2/publication/260595590_Situation_Analysis_of_MTP_Services_Jharkhand_Situation_Analysis_of_MTP_Services_Jharkhand/links/00b49531b2e444c1a5000000/Situation-Analysis-of-MTP-Services-Jharkhand-Situation-Analysis-of-MTP-Services-Jharkhand.pdf.
62. Jacob I. Health and health seeking behaviour among tribal communities in India: A socio-cultural perspective. J Tribal Intellect Collect India. 2014; 2(1): 1-16.
63. Ross-Hellauer T, Tennant JP, Banelyté V, Gorogh E, Luzi D, Kraker P, et al. Ten simple rules for innovative dissemination of research. PLOS Comput Biol. 2020; 16(4): e1007704.
64. Derman RJ, Jaeger FJ. Overcoming challenges to dissemination and implementation of research findings in under-resourced countries. Reprod Health. 2018; 15(86): DOI: https://doi.org/10.1186/s12978-018-0538-z.
65. World Health Organization. What is Health Policy and Systems Research (HPSR) and why does it matter? [Internet]. Geneva; 2007. Available from: https://ahpsr.who.int/what-we-do/what-is-health-policy-and-systems-research-(hpsr).
66. Koon AD, Nambiar D, Rao KD. Embedding of research into decision-making processes in low- and middle-income countries. Heal Res Policy Syst. 2012; 8(11): 1-27.
67. Koon AD, Rao KD, Tran NT, Ghaffar A. Embedding health policy and systems research into decision-making processes in low- and middle-income countries. Heal Res Policy Syst. 2013; 11(30): DOI: https://doi.org/10.1186/1478-4505-11-30.
68. Kivits J, Ricci L, Minary L. Interdisciplinary research in public health: the “why” and the “how.” J Epidemiol Community Heal. 2019; 73(12): DOI: http://dx/doi.org/10.1136/jech-2019-212511.
69. Lee JM, Furner SE, Yager J, Hoffman D. A review of the status of the doctor of public health degree and identification of future issues. Public Health Rep. 2009; 124(1): 177-183.
70. Galway LP, Parkes MW, Allen D, Takaro TK. Building interdisciplinary research capacity: A key challenge for ecological approaches in public health. AIMS Public Heal. 2016; 3(2): 389-406.
71. Faltermaier T. Why public health research needs qualitative approaches. Eur J Public Health. 1997; 7(4): 357-363.
72. DebRoy S, Prosper O, Mishoe A, Mubayi A. Challenges in modeling complexity of neglected tropical diseases: A review of dynamics of visceral leishmaniasis in resource limited settings. Emerg Themes Epidemiol. 2017; 14(10): DOI: https://doi.org/10.1186/s12982-017-0065-3.
73. Behrend MR, Basáñez M-G, Hamley JID, Porco TC, Stolk WA, Walker M, et al. Modelling for policy: The five principles of the Neglected Tropical Diseases Modelling Consortium. PLoS Negl Trop Dis. 2020; 14(4): e0008033.
74. Garchitorena A, Sokolow SH, Roche B, Ngonghhala CN, Jocque M, Lund A, et al. Disease ecology, health and the environment: a framework to account for ecological and socio-economic drivers in the control of neglected tropical diseases. Philos Trans R Soc. 2017; 372(1722): DOI: 10.1098/rstb.2016.0128.

75. Turner HC, Walker M, French MD, Blake IM, Churner TS, Basáñez M-G. Neglected tools for neglected diseases: Mathematical models in economic evaluations. Trends Parasitol. 2014; 30(12): 562-570.
76. Lach D. Challenges of interdisciplinary research: reconciling qualitative and quantitative methods for understanding human-landscape systems. Environ Manage. 2014; 53(1): 88-93.
77. Gavens L, Holmes J, Bühringer G, McLeod J, Neumann M, Lingford-Hughes A, et al. Interdisciplinary working in public health research: a proposed good practice checklist. J Public Health (Bangkok). 2018; 40(1): 175-182.
78. World Health Organization. Neglected tropical diseases: Innovative and intensified disease management (IDM) [Internet]. Geneva; 2021. Available from: https://www.who.int/teams/control-of-neglected-tropical-diseases/intensified-disease-management.
79. Reimer LJ, Adams ER, Paine MJ, Ranson H, Coleman M, Thomsen E, et al. Fit for purpose: do we have the right tools to sustain NTD elimination? BMC Proc. 2015; 9(10): DOI: https://doi.org/10.1186/1753-6561-9-S10-S5.
80. Ehrenberg JP, Zhou X-N, Fontes G, Rocha EMM, Tanner M, Utzinger J. Strategies supporting the prevention and control of neglected tropical diseases during and beyond the COVID-19 pandemic. Infect Dis Poverty. 2020; 9(86): DOI: 10.1186/s40249-020-00701-7.
81. Hotez PJ, Fenwick A, Molyneux D. The new COVID-19 poor and the neglected tropical diseases resurgence. Infect Dis Poverty. 2021; 10(10): DOI: https://doi.org/10.1186/s40249-020-00784-2.
82. Brooker SJ, Ziumbe K, Negussu N, Crowley S, Hammami M. Neglected tropical disease control in a world with COVID-19: An opportunity and a necessity for innovation. Trans R Soc Trop Med Hyg. 2021; 115(3): 205-207.
83. Hollingsworth TD, Langley I, Nokes DJ, Macpherson EE, McGivern G, Adams ER, et al. Infectious disease and health systems modelling for local decision making to control neglected tropical diseases. BMC Proc. 2015; 9(10): DOI: 10.1186/1753-6561-9-S10-S6.
84. Allotey P, Reidpath DD, Pokhrel S. Social sciences research in neglected tropical diseases 1: The ongoing neglect in the neglected tropical diseases. Heal Res Policy Syst. 2010; 8(32): DOI: https://doi.org/10.1186/1478-4505-8-32.
85. Boatin BA, Basáñez M-G, Prichard RK, Awadzi K, Barakat RM, García HH, et al. A research agenda for helminth diseases of humans: Towards control and elimination. PLoS Negl Trop Dis. 2012; 6(4): e1547.
86. Basáñez M-G, McCarthy JS, French MD, Yang -JG, Walker M, Gambhir M, et al. A research agenda for helminth diseases of humans: Modelling for control and elimination. PLoS Negl Trop Dis. 2012; 6(4): e1548.
87. O'Sullivan M, Kenilorea G, Yamaguchi Y, Bobogare A, Losi L, Atkinson J, et al. Malaria elimination in Isabel Province, Solomon Islands: Establishing a surveillance-response system to prevent introduction and reintroduction of malaria. Malar J. 2011; 10(235): DOI: https://doi.org/10.1186/1475-2875-10-235.
88. National Vector Borne Disease Control Programme. Kala-Azar Management Information System (KAMIS) [Internet]. 2021 [cited 2021 Feb 26]. Available from: https://ka-mis.org/kamisLoginPage.html.
89. Sengupta A, Mukhopadhyaya I, Weerasinghe M, Karki A. The rise of private medicine in South Asia. BMJ. 2017; 16(357): DOI: https://doi.org/10.1136/bmj.j1482.
90. Kane S, Calnan M. Erosion of trust in the medical profession in India: Time for doctors to act. Int J Heal Policy Manag. 2017; 6(1): DOI: 10.15171/IJKPM.2016.143.

91. Naher N, Hoque R, Hassan MS, Balabanova D, Adams A, Ahmed S. The influence of corruption and governance in the delivery of frontline health care services in the public sector: a scoping review of current and future prospects in low and middle-income countries of south and south-east Asia. BMC Public Health. 2020; 20(880): DOI: https://doi.org/10.1186/s12889-020-08975-0.
92. Lim D, Banjara MR, Singh VK, Joshi AB, Gurung CK, Das ML, et al. Barriers of visceral leishmaniasis reporting and surveillance in Nepal: Comparison of governmental VL-program districts with non-program districts. Trop Med Int Heal. 2018; 24(2): 192–204.
93. Madon S, Malecela MN, Mashoto K, Donohue R, Mubyazi G, Michael E. The role of community participation for sustainable integration neglected tropical diseases and water, sanitation and hygiene intervention programs: A pilot study in Tanzania. Soc Sci Med. 2018; 202(1): 28-37.
94. Das JK, Salam RA, Arshad A, Maredia H, Bhutta ZA. Community based interventions for the prevention and control of non-helmintic NTD. Infect Dis Poverty. 2014; 3(24): DOI: 10.1186/2049-9957-3-24.
95. Ahmed BN, Nabi SG, Rahman M, Selim S, Bashar A, Rashid M, et al. Kala-azar (visceral leishmaniasis) elimination in Bangladesh: Successes and challenges. Curr Trop Med Reports. 2014; 1(1):163–169.
96. Ortu G, Williams O. Neglected tropical diseases: exploring long term practical approaches to achieve sustainable disease elimination and beyond. Infect Dis Poverty. 2017; 6(1): DOI: 10.1186/s40249-017-0361-8.
97. Hanson C, Weaver A, Zoerhoff K, Kabore, ALinehan M, Doherty A, Engels D, et al. Integrated implementation of programs targeting neglected tropical diseases through preventive chemotherapy: Identifying best practices to roll out programs at national scale. Am J Trop Med Hyg. 2012; 86(3): DOI: https://doi.org/10.4269/ajtmh.2012.11-1589.
98. Rosenberg M, Utzinger J, Addiss D. Preventive Chemotherapy Versus Innovative and Intensified Disease Management in Neglected Tropical Diseases: A Distinction Whose Shelf Life Has Expired. PLoS Negl Trop Dis. 2016; 10(4): e0004521.
99. World Health Organization. Promoting the integrated approach to skin-related neglected tropical diseases [Internet]. Geneva; 2021. Available from: https://www.who.int/activities/promoting-the-integrated-approach-to-skin-related-neglected-tropical-diseases.
100. Mitjà O, Marks M, Bertran L, Kollie K, Argaw D, Fahal AH, et al. Integrated control and management of neglected tropical skin diseases. PLoS Negl Trop Dis. 2017; 11(1): e0005136.
101. Yotsu RR. Integrated management of skin NTDs--Lessons learned from existing practice and field research. Trop Med Infect Dis. 2018; 3(4): DOI: 10.3390/tropicalmed3040120.
102. Ukwaja KN, Alphonsus C, Eze CC, Lehman L, Ekeke N, Nwafor CC, et al. Investigating barriers and challenges to the integrated management of neglected tropical skin diseases in an endemic setting in Nigeria. PLoS Negl Trop Dis. 2020; 14(4): e0008248.
103. Kabatereine NB, Malecela M, Lado M, Zaramba S, Amiel O, Kolaczinski JH. How to (or not to) integrate vertical programmes for the control of major neglected tropical diseases in Sub-Saharan Africa. PLoS Negl Trop Dis. 2010; 4(6): e755.
104. Gyapong JO, Gyapong M, Yellu N, Anakwah K, Amofah G, Bockarie M, et al. Integration of control of neglected tropical diseases into health-care systems: challenges and opportunities. Lancet. 2010; 375(9709): 160-165.

105. Dittrich S, Lamy M, Acharya S, Thu HK, Datta R, Blacksell SD, et al. Diagnosing malaria and other febrile illnesses during the COVID-19 pandemic. Lancet Glob Heal. 2020; 8(7): E879-E880.
106. Newton PN, Guerin PJ. Febrile illness mapping--much of the world without data and without evidence-based treatments. BMC Med. 2020; 18(287): DOI: https://doi.org/10.1186/s12916-020-01747-y.
107. McDonald CR, Weckman A, Richard-Greenblatt M, Leligdowicz A, Kain K. Integrated fever management: disease severity markers to triage children with malaria and non-malarial febrile illness. Malar J. 2018; 18(353): DOI: https://doi.org/10.1186/s12936-018-2488-x.
108. Laing G, Vigilato MAN, Cleaveland S, Thumbi SM, Blumberg L, Salahuddin N, et al. One Health for neglected tropical diseases. Trans R Soc Trop Med Hyg. 2020; 115(2).: 182-184
109. Huda MM, Ghosh D, Alim A, Almahmud M, Olliaro PL, Matlashewski G, et al. Intervention packages for early visceral leishmaniasis case detection and sandfly control in Bangladesh: A comparative analysis. Am J Trop Med Hyg. 2019; 100(1): 97-107.
110. Banjara MR, Kroeger A, Huda MM, Kumar V, Gurung CK, Das ML, et al. Feasibility of a combined camp approach for vector control together with active case detection of visceral leishmaniasis, post kala azar dermal leishmaniasis, tuberculosis, leprosy, and malaria in Bangladesh, India, and Nepal: An exploratory study. Trans R Soc Trop Med Hyg. 2015; 109(6): 408–415.
111. Bloom D, Kuhn M, Prettner K. Modern infectious diseases: Macroeconomic impacts and policy responses [Internet]. Cambridge, Massachusetts; 2020. Available from: https://www.nber.org/system/files/working_papers/w27757/w27757.pdf.
112. Perrings C, Castillo-Chavez C, Chowell G, Daszak P, Fenichel EP, Finnoff D, et al. Merging economics and epidemiology to improve the prediction and management of infectious disease. Ecohealth. 2014; 11(4): 464-475.
113. Malecela MN. Reflections on the decade of the neglected tropical diseases. Int Health. 2019; 11(5): 338-340.
114. Hotez PJ. NTDs in the 2020s: An epic struggle of effective control tools versus the Anthropocene. PLoS Negl Trop Dis. 2020; 14(9): e0007872.
115. Huang XX, Toure H, Biswas G. Resource tracking for neglected tropical disease programmes: The first step for developing a sustainable financing strategy. Trans R Soc Trop Med Hyg. 2021; 115(2): 179-181.
116. Flueckiger RM, Nikolay B, Gelderblom HC, Smith JL, Haddad D, Tack W, et al. Integrating data and resources on neglected tropical diseases for better planning: The NTD Mapping Tool (NTDmap.org). PLoS Negl Trop Dis. 2015; 9(2): e0003400.
117. Singh OP, Hasker E, Boelaert M, Sundar S. Elimination of visceral leishmaniasis on the Indian Subcontinent: Critical knowledge gaps to be answered to get us there. Lancet Infect Dis. 2016; 16(12): E304–E309.
118. Wangdi K, Gatton ML, Kelly GC, Banwell C, Dev V, Clements ACA. Malaria elimination in India and regional implications. Lancet Infect Dis. 2016; 16(10): E214-E224.
119. Alvar J, den Boer M, Jain S, Pandey D, Salunke S. Independent assessment of the Kala-Azar elimination programme, India [Internet]. Geneva; 2020. Available from: https://cdn.who.int/media/docs/default-source/searo/evaluation-reports/independent-assessment-of-kala-azar-elimination-programme-in-india.pdf?sfvrsn=fa0d8baa_2.
120. Senyonjo L, Downs P, Schmidt E, Bailey R, Blanchet K. Lessons learned for surveillance strategies for trachoma elimination as a public health problem, from the

evaluation of approaches utilised by guinea worm and onchocerciasis programmes: A literature review. PLoS Negl Trop Dis. 2021; 15(1): e0009082.
121. World Health Organization-South East Asia Regional Office. Inter-Country meeting on cross-border collaboration to eliminate malaria in South Asia [Internet]. New Delhi; 2016. Available from: https://apps.who.int/iris/bitstream/handle/10665/272763/sea-mal-283.pdf.
122. Andrus JK, Thapa AB, Withana N, Fitzsimmons JW, Abeykoon P, Aylward B. A new paradigm for international disease control: lessons learned from polio eradication in Southeast Asia. Am J Public Health. 2001; 91(1): 146-150.
123. Acharya KP, Subedi D, Wilson RT. Rabies control in South Asia requires a One Health approach. One Heal. 2021; 12(1): DOI: 10.1016/j.onehlt.2021.100215.
124. Herzog SA, Blaizot S, Hens N. Mathematical models used to inform study design or surveillance systems in infectious disease: A systematic review. BMC Infect Dis. 2017; 17(1): 775.
125. Ault S, Periago M. Regional approaches to neglected tropical disease control in Latin America and the Caribbean. In: The Causes and Impacts of Neglected Tropical and Zoonotic Diseases: Opportunities for Integrated Intervention Strategies. Washington DC: National Academies Press (US); 2011.
126. Colston J. The neglected tropical diseases (NTD) initiative for Latin America and the Caribbean of the Inter-American Development Bank and the role of geospatial analysis in health programmes. Geospat Health. 2012; 6(3): S11-S14.
127. Grant C, Lo Iacono G, Dzingirai V, Bett B, Winnebah T, Atkinson P. Moving interdisciplinary science forward: Integrating participatory modelling with mathematical modelling of zoonotic disease in Africa. Infect Dis Poverty. 2016; 5(17): DOI: https://doi.org/10.1186/s40249-016-0110-4.
128. Lenk EJ, Redekop WK, Luyendijk M, Fitzpatrick C, Niessen L, Stolk WA, et al. Socioeconomic benefit to individuals of achieving 2020 targets for four neglected tropical diseases controlled/eliminated bby innovative and intensified disease management: Human African trypanosomiasis, leprosy, visceral leishmaniasis, Chagas disease. PLoS Negl Trop Dis. 2018; 12(3): e0006250.
129. Conteh L, Engels T, Molyneux DH. Socioeconomic aspects of neglected tropical diseases. Lancet. 2010; 375(9710): 239-247.
130. Woode ME, Khan JAM, Thomson R, Niessen LW, The COUNTDOWN Consortium. Equity and efficiency in the scaled-up implementation of integrated neglected tropical disease control: The health economics protocol of the COUNTDOWN multicountry observational study in Ghana, Cameroon and Liberia. BMJ Open. 2018; 8(6): e020113.
131. Marchal B, Van Dormael M, Pirard M, Cavalli A, Kegels G, Polman K. Neglected tropical disease (NTD) control in health systems: The interface between programmes and general health services. Acta Trop. 2011; 120(1): 177–185.
132. Buyon L, Slaven R, Emerson PM, King J, Debrah O, Aboe A, et al. Achieving the endgame: Integrated NTD case searches. PLoS Negl Trop Dis. 2018; 12(12): e0006623.
133. World Health Organization. Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021-2030 [Internet]. Geneva; 2020. Available from: https://www.who.int/publications/i/item/9789240010352

APPENDICES

Appendix 1. Disease-specific targets and indicators for reaching NTD control, elimination, elimination as a public health problem (EPHP), and eradication by 2030.

Target	Disease	Indicator	2020	2030
Eradication	Dracunculiasis	Number of countries certified free of transmission	187 (96%)	194 (100%)
	Yaws	Number of countries certified free of transmission	1 (1%)	194 (100%)
Elimination (interruption of transmission)	Human African trypanosomiasis (gambiense)	Number of countries verified for interruption free of transmission	0	15 (62%)
	Leprosy	Number of countries with zero new cases	50 (26%)	120 (62%)
	Onchocerciasis	Number of countries verified for interruption of transmission	4 (12%)	12 (31%)
Elimination as a public health problem (EPHP)	Chagas disease	Number of countries achieving interruption of transmission with 75% treatment coverage	0	15 (37%)
	Human African trypanosomiasis (rhodesiense)	Number of countries validated for EPHP (<1 case/10,000 people/year over five years)	0	8 (61%)
	Leishmaniasis (visceral)	Number of countries validated for EPHP (<1% case-fatality rate)	0	64 (85%)
	Lymphatic filariasis	Number of countries validated for EPHP (below transmission threshold four years after stopping MDA)	17 (24%)	58 (81%)
	Rabies	Number of countries having achieved zero human deaths from rabies	80 (47%)	155 (92%)
	Schistosomiasis	Number of countries validated for EPHP	0	78 (100%)
	Soil-transmitted helminthiases	Number of countries validated for EPHP	0	96 (96%)
	Trachoma		10 (15%)	66 (100%)
Control	Buruli ulcer	Proportion of cases in late stage at diagnosis	30%	<10%
	Dengue	Case-fatality rate	0.80%	0%
	Echinococcosis	Number of countries with intensified control	1	17
	Foodborne trematodiases	Number of countries with intensified control	N/A	11 (12%)
	Leishmaniasis (cutaneous)	Number of countries in which 85% of all cases are detected and reported, and 95% of cases treated	N/A	87 (100%)
	Mycetoma, Chromoblastomycosis and other deep mycoses	Number of countries in which diseases is included in national control and surveillance programme	1 (3%)	15 (50%)
	Scabies and other ectoparasites	Number of countries having incorporated scabies management into UHC package of care	0	194 (100%)
	Snakebite envenoming	Number of countries having achieved reduction of mortality by 50%	N/A	132 (100%)
	Taeniasis and cysticercosis	Number of countries with intensified control	2 (3%)	17 (27%)

Adapted from: WHO. Ending the neglect to attain the Sustainable Development Goals: A roadmap for neglected tropical diseases 2021-2030. Geneva: World Health Organization; 2020. License: CC BY-NC-SA 3.0 IGO.

Appendix 2. Methodological principles of the Global Health Cost Consortium Reference Case (GHCC-RC) used to develop the parameters of paper R1.

GHCC REFERENCE CASE OUTLINE	METHODOLOGICAL PRINCIPLE	PAPER R1 PARAMETERS
STUDY DESIGN	1. Purpose, population, and intervention	A) Priority setting for medium-term financial planning B) Facility and community level surveillance implementers C) Index case-based ACD, blanket & camp ACD, and PHC-level PCD
	2. Perspective	Provider (or payer): India Ministry of Health
	3. Type of cost	Economic and financial, real-world costs
	4. Definition of Units	Average cost of intervention per VL case- screened, suspected, or found positive
	5. Time horizon	January-December 2018, when index case-based ACD, blanket & camp ACD, and PCD were ongoing simultaneously
RESOURCE USE MEASUREMENT	6. Scope of costing	All start-up, training, capital, recurring, and opportunity costs were included
	7. Measuring and allocating resource use	Bottom-up micro-costing and top-down expenditure costing were conducted in tandem to capture relevant costs and activities comprehensively
	8. Sampling	Sampling included several months of document-collection prior to a 3-week fieldwork visit, in which index case-based ACD and PCD activities were observed first-hand. Interviews were also conducted with programme managers and directors of each ACD and PCD activity.
	9. Measuring units of outputs	Number of VL cases screened, number of suspected VL cases identified, and number of VL cases diagnosed
	10. Timing of data collection	Recall bias was minimised for index case-based ACD and PCD, as they were ongoing activities during data collection. Blanket and camp ACD activities last conducted in 2018 relied more heavily on expenditure reports, but were supplemented by several interviews with programme managers and implementers
PRICING AND VALUATION	11. Sources of price data	Data reflected relevant prices across settings and were adjusted to the purpose of the study. All costs were converted into $USD during the base year 2018.
	12. Valuing capital inputs	All capital costs were appropriately annuitized and depreciated based on their useful life, opportunity cost, discount rate, and year purchased.
	13. Discount, inflation, and conversion rates	Discount rates in India over the past three years were consistently 3%, which was used in this study. Currency conversion was achieved using OANDA and World Bank exchange rates to adjust prices to the base year.
	14. Shadow prices	Opportunity costs were estimated by referencing products or activities with similar market value, useful life, or salary (for volunteer time). Prices of donated and subsidised goods were included in full, as reported by WHO and DFID.
ANALYSING AND PRESENTING RESULTS	15. Cost functions and heterogeneity	Heterogeneity was considered in terms of VL incidence at the district-level.
	16. Uncertainty	Uni- and multi-dimensional sensitivity analyses were conducted for each calculation of intervention per VL test conducted and found positive.

	17. Transparency	All cost estimates, resources, and assumptions were recorded and published in an open-access data repository.

Study design

Defining the purpose, perspective, costs, units, and time horizon were straightforward in that VL ACD and PCD should be evaluated from the provider's perspective (India's Ministry of Health) during 2018, the most recent year in which two distinct ACD programmes were implemented in tandem with PCD. The outcome of finding one additional case through distinct ACD and PCD activities was determined the best unit of comparison to inform national programme strategy and for potential application to modelling studies. The method of comparison aligned as a cost analysis or cost-minimisation analysis to identify the least-costly method of finding an additional VL case. An inherent limitation of this method is in the exclusion of DALYs averted or QALYs gained as a natural unit of measurement, although separate cost and benefit analyses still provide valuable information.

Resource use measurement

To determine the scope of costing, resource use measurement, sampling techniques, output measurement, and timing of data collection, a toolkit for evaluating the implementation of syphilis screening largely guided data collection. The toolkit outlined specific programme functions relevant to ACD and PCD activities in India, and importantly provided a roadmap synthesising bottom-up micro-costing and top-down expenditure analysis. The toolkit also outlined explicit inputs for each programme to define start-up, training, capital, recurrent, and quality assurance costs that were otherwise generic in other guidelines.

Pricing and valuation

Methods from similar costing literature in surveillance and elimination programmes, especially malaria and tuberculosis, guided the statistical and uncertainty analyses of paper R1. These studies focused on evaluating the cost of two or more activities in terms of the likelihood of reaching elimination benchmarks in a geographic setting by comparing the total cost, average cost per outcome (e.g., new cases detected), and cost of scaling up an activity.

Analysing and presenting results

For this study, it was important to present results and recommendations for not only the national government as a provider, but other supporting organisations that implement operational activities of ACD and the greater scientific community to encourage additional economic analyses.

Appendix 3. Example Costing Worksheets used for data collection in Paper R1.

START UP COSTS:
TRAINING (EXA)

Sources of data: _____ _____ _____ _____

Central costs	Quantity	Days used	Fin. cost	Econ. cost (daily charge for equivalent space)	**Total cost**		**%Allocation** (# project participants / # participants)	Annual programme cost	
					Fin.	Econ.		Fin.	Econ.
Training Venue									
Training rooms									
Lab rooms									
Other space									
Equipment:									
Transport (e.g van use/ hire plus fuel)									
Training supplies	quantity		unit price		**Total cost**		**%Allocation**	**Annual programme cost**	
					Fin.	Econ.		Fin.	Econ.
practice test kits									
gloves									
refreshments									
stationary									
Other costs									
communications									
TOTAL CENTRAL TRAINING COSTS									

* please remember that though some of the inputs are generally considered recurrent, the activity as a whole should have a life of longer than a year, and is therefore annualised and treated in the same way capital costs.

CAPITAL COSTS: BUILDINGS AND STORAGE (EXA)

Sources of data: _____ _____ _____ _____ _____

Buildings/ storage spaces (list)	Annual rent/hire		Furnishing @ 10%	Annual cost		% Allocation cost	Annual programme cost	
	Fin.	Econ.		Fin.	Econ.		Fin.	Econ.
TOTAL								

RECURRENT COSTS: PERSONNEL (EXA)

Sources of data: _____ _____ _____ _____ _____

Category of personnel (list with grade where appropriate)	Gross annual salary		Cost of annual allowance (specify)		Total annual cost		9.% Allocation cost	Annual programme cost	
	Fin.	Econ.	Fin.	Econ.	Fin.	Econ.		Fin.	Econ.
TOTAL									

Appendix 4. LSHTM Ethical Approval for research conducted in papers R1 and R2**.**

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Ms Natalie Dial
LSHTM

6 November 2019

Dear Natalie,

Study Title: Evaluating the cost of active and passive case detection for visceral leishmaniasis (Kala-Azar) to inform post-elimination strategies in India

LSHTM ethics ref: 17763

Thank you for your application for the above research, which has now been considered by the Observational Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	Natalie Dial CV 2019	06/08/2019	1
Investigator CV	Emily Sara Nightingale - CV	30/08/2019	1
Information Sheet	DrPH Cost Analysis Participant Consent Form	30/08/2019	1
Information Sheet	DrPH Cost Analysis Participant Information Sheet	30/08/2019	1
Information Sheet	DrPH Knowledge Utilisation Participant Consent Form	30/08/2019	1
Information Sheet	DrPH Knowledge Utilisation Participant Information Sheet	30/08/2019	1
Advertisements	Cost Analysis Recruitment Email	30/08/2019	1
Advertisements	Knowledge Utilisation Recruitment Email	30/08/2019	1
Protocol / Proposal	DrPH Knowledge Utilisation Interview Guide	30/08/2019	1
Protocol / Proposal	ACD Micro-costing data collection form	30/08/2019	1
Protocol / Proposal	PHC Micro-costing data collection form	30/08/2019	1
Protocol / Proposal	Draft Cost Analysis Spreadsheet and Calculations Framework	30/08/2019	1
Protocol / Proposal	Ethics application study protocol	03/09/2019	1
Local Approval	Permission letter - KalaCORE	26/09/2019	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Yours sincerely,

[redacted]

Professor Jimmy Whitworth
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Appendix 5. KalaCORE permissions letter.

MOTT MACDONALD

Permission to Collect and Use Active Case Detection Data

26 September 2019

To whom it may concern

I hereby confirm that I have given approval to Natalie Dial to collect and use cost data on Active Case Detection of Visceral Leishmaniasis cases that was generated during the KalaCORE programme. She is also granted permission to interview former members of the KalaCORE project team.

Mott MacDonald was the leading managing contractor to the Department for International Development for this programme and I was the Project Principal for the programme.

10 Fleet Place
London EC4M 7RB
United Kingdom

T +44 (0)20 7651 0300
F +44 (0)20 7248 2698
mottmac.com

[redacted]

Lucy Palmer

KalaCORE Project Principal

+44 207 651 0135

Appendix 6. CARE India permissions request and confirmation.

Project title:
Evaluating the cost of active and passive case detection for visceral leishmaniasis (Kala-Azar) to inform post-elimination strategies in India

Investigator
Natalie Dial, MSc, MIPM
DrPH Candidate, LSHTM
Research Assistant, SPEAK India

Supervisors
Graham Medley, LSHTM
Fern Terris-Prestholt, LSHTM
Simon Croft, LSHTM

Project summary

The objective of this doctoral thesis is to evaluate the cost and outcomes of active and passive case detection (ACD & PCD) in areas with different VL endemicity within Bihar, India. By collecting financial and incidence data reported by CARE, KalaCORE and Primary Health Centres from 2017-2018, a cost analysis will be conducted to evaluate:

1) Total cost of ACD and PCD programmes
2) Cost of ACD and PCD per new VL case diagnosed
3) Cost and outcome of scaling up ACD in areas comparing high and low incidence

This cost analysis will then be used to develop a methodology for integrating economic models into ongoing transmission models (with the math modelling team in SPEAK India), to predict incidence and expected costs for reaching elimination benchmarks. Finally, a qualitative study (supervised by Simon Croft) will investigate the relevance of these economic and modelling studies to decision makers in India for strategising VL case detection tactics to reach elimination as a public health problem. The investigator also works within the SPEAK India research consortium at LSHTM, where this project is both supported and supervised by Graham Medley and Simon Croft. The costing component, including all financial data collection and analysis, will be overseen by Fern Terris-Prestholt, an economist at LSHTM.

Outcomes

The overarching goal of the project is to produce results that will inform and support VL case detection strategies.
Results of this project will be included in a thesis submitted to LSHTM, and, where feasible and possible, developed for peer-reviewed publication. The collaboration with CARE India will be acknowledged and co-authorship offered where appropriate.

Data request from CARE

Active Case Detection Programme Reports:

1. Financial Reports

This research project will rely on information, reports, and data regarding costs associated with CARE's ACD programme during 2017-2018. In similar economic studies, costing data includes financial allocation reports, project expenditures, budget line-lists, and interviews with senior programme and financial officers. First, the researcher will request permission to include CARE data in her thesis project. If the organisation agrees to share data, the researcher will enquire on the existence of ACD financial documentation via email with senior CARE programme managers. Once a consensus is reached regarding the availability of data, the researcher will coordinate a fieldwork visit to India in the Fall of 2019 to obtain relevant financial reports and documentation from CARE. Access to such financial information, documentation and reports may require some data-gathering within CARE. Where information and reports require considerable effort to locate or consolidate data, the researcher may be able to assist during a fieldwork trip to India in Fall 2019. Additionally, where financial data may be missing or not documented in CARE programme reports, the researcher requests the ability to interview 2-5 senior programme officers and financial managers. This is to capture important metrics of costs, time, and resources dedicated to ACD during the time period to ensure accuracy in the subsequent economic calculations and analysis.

2. VL Case Detection Data

To determine the number of new VL cases detected through ACD, this project also requires programme data on VL diagnoses within CARE's ACD programme during 2017-2018. This data may already exist within ACD programme reports or as a part of KA-MIS, but will be requested as it best matches and relates to the data available in CARE ACD financial reports. These ACD case detection reports may also be collected as a part of her fieldwork trip in Fall 2019.

3. KA-MIS Database

Finally, the research project will require reference to the KA-MIS database to stratify and tailor the economic analysis to variations in incidence. Emily Nightingale of the SPEAK India mathematical modelling team currently works with the KA-MIS dataset, supervised by Graham Medley, which the researcher requests permission to use and cite for VL endemicity calculations.

Confidentiality

All information, datasets, and programme reports obtained by the researcher will be kept confidential, and only discussed with or shown to her supervisors (listed above) during analysis. Project results will be shared with CARE prior to publication or presentation.

Email confirmation:

From: Sridhar Srikantiah <ssridhar@careindia.org>
Subject: Re: Economics of case detection
Date: 1 October 2019 at 14:29:46 BST
To: Graham Medley <Graham.Medley@lshtm.ac.uk>
Cc: Bikas Sinha <bikas@careindia.org>

Please let Natalie come, I am marking Bikas who will co-ordinate this.

Sridhar

Appendix 7. Cost model assumptions.

VARIABLE	ASSUMPTIONS	SOURCE
All Programmes		
Cost per VL test	350INR or $4.75USD (+/- 50% in the sensitivity analysis)	rK-39 manufacturers (Bio-Rad Laboratories, InBios International Inc, CTK Biotech Inc) and VL literature
Discount Rate	3% (0%, 6% in the sensitivity analysis)	World Bank Discountt Rates
Treatment (excluded)	All patients are eventually diagnosed (or re-confirmed VL-positive) at the hospital (PHC) level and immediately treated with AmBisome. The cost for AmBisome treatment would be consisted in all three programmes, therefore cost of treatment was excluded to focus on cost of diagnosis and case identification.	National Vector Borne Disease Control Programme (NVBDCP) Guidelines (2017)
Index Case-Based ACD		
Economic life years of start-up	3 years was determined the average start-up period to roll out CARE's ACD programme and get the KAMIS database off the ground. Start-up included mostly training and travel costs.	CARE records and staff interviews
Outputs	Total number of patients suspected, tested, and found VL-positive through CARE's ACD programme were recorded by DPOs, KBCs, and lab technicians and ultimately recorded in the KAMIS database. This analysis relied on data reported in KAMIS, but triangulated average monthly patient tests and positives by interviewing DPOs, KBCs and lab technicians.	KAMIS and staff interviews
Training	Conference venue rates included subsistence (650INR or $8.81USD per person), and 18% tax added, plus rental of podium, projector, and microphone CARE estimated all travel costs were included in staff salary for training, therefore this study included travel expenses as economic costs (not declared by the provider)	CARE records and staff interviews
Vehicles	CARE claimed transportation vehicles (motorbikes) of Kala-Azar Block Coordinators as a stipulation of their hiring. Therefore, CARE did not include this expense as a financial cost, and this study included the cost of each motorbike as an economic cost. The cost of an average motorbike was estimated from direct observation and staff interviews. Manufacturer prices were used to calculate vehicle price, where expected useful life of the bike and average discount rate of capital goods were used to evaluate depreciation.	Staff interviews, direct observation, and manufacturer prices
Salaries	1. State Programme manager (SPM) and SPM Jr. (1,200,000INR or $16,271USD per year at 5% allocation) 2. Field Research Officer (960,000INR or $13,017USD per year at 50% allocation) 3. District Programme Officer (696,000INR or $9,437USD per year at 50% allocation) 4. Kala-Azar Block Coordinator (240,000INR or $3,254USD per year at 75% allocation) 5. ASHA (550INR or $7.45USD per year at <5% allocation)	CARE records and staff interviews

Vehicle Operation	Vehicle and motorbike operating costs (fuel, oil, maintenance, registration, etc) were estimated from both staff interviews and local prices for equivalent services. Again, CARE included this cost in the salary of each staff member, where this analysis included vehicle operating costs as economic costs.	Staff interviews, local (Patna, Bihar) prices for fuel, oil, insurance, maintenance, registration, etc
Building Operation	Furnishing, electricity and rent were determined from some CARE records and costs of equivalent office space in Patna and were allocated individually between the three staff members who manage the programme from CARE headquarters (two staff work <5% while another worked 75%).	CARE records and online rental price for equivalent space
Training & recurrent training	Accommodation, travel, salary, and subsistence fees per training session were estimated from staff interviews and occurred an average of once per year for DPOs and KBCs. Quality control (or quality assurance) was considered to be a part of recurrent training, and included in these estimations.	CARE records and staff interviews
Personnel time allocation	Due to discrepancies in staff interviews between supervisors and fieldworkers on personnel allocation, direct observation was used to triangulate minutes spent on each activity (and +/-20% was used in the sensitivity analysis). Supervisors claimed that ACD officers worked 30% of their time on the programme, while the ACD officers themselves claimed to work between 75-95%. Therefore, time and frequency of activities were estimated from direct observation and used to determine KBCs work 75% and DPOs work 50% on ACD activities. The sensitivity analysis varied this allocation by 20% to better capture the large discrepancy.	Staff interviews and direct observation
Supplies	Patient case registers were the main supply expense for each District Programme Officer and Kala-Azar Block Coordinator, with a useful life of one year.	Staff interviews and direct observation
Equipment	Cell phones were the main equipment used by KBCs and DPOs, and the average cost was estimated from the current retail value in 2019 and converted to the base year of 2018.	Staff interviews, direct observation, and manufacturer prices
Waste Management	Not disclosed to investigator and may be negligible	No record in CARE
Blanket & Camp ACD		
Economic life years of start-up	Initial training costs were sourced from KalaCORE's expenses dataset from 2017, detailing costs in the start-up up year of 2015 and lasted 2 years. Costs were annualized and translated into the base year 2018. Transport costs detail flights from Delhi to Patna for Project managers (reported in lump-sum) and local travel for managers within Patna to conduct training. Trainers present and total number of field coordinators and ASHAS (participants) were estimated through interviews and the data expenses spreadsheet. Financial salary costs were reported for FCs to attend this training, which included travel and per diem. Accommodation was detailed separately. Cost of training venue was not reported, therefore the cost of hiring an equivalent venue for three days (reported training time) was estimated in Patna, India and included as an economic cost. The start-up period is defined as the inception period, where one month in 2015 was dedicated to developing training protocol and plans prior to the first ACD round implementation. Management fees (salaries) were estimated from the inception report detailing phase 1 ACD monthly, where project staff were shown to work 1 month before the start of the program. Economic costs of ASHAs taking one day off from normal work to attend training are included.	KalaCORE expenditure reports and staff interviews

Outputs	Project outputs included number of people screened, number of people tested for VL, and total VL positive cases during 2018. No cases are included in the start-up period. Although KalaCORE detailed patient data down to the village level (including district, block, and village where patient was screened, tested, and diagnosed), data was only considered on the district level to match data in the CARE dataset.	KalaCORE programme report
Salary	Both staff salary per grade and allocation factors detailed in KalaCORE expenditure reports	KalaCORE expenditure reports
Vehicle operation	For managerial staff, only one vehicle was purchased for the programme, and the remainder of vehicles were rented vehicles or taxis. These costs were included as a lump sum (specific to staff position) in the travel cost section. Travel costs were triangulated by estimating distance and fuel using Google maps. For fieldworkers, vehicle operation and maintenance costs were detailed in the expenditure spreadsheet as lump sums for fuel, oil, maintenance, registration, and spare parts. These costs reported in KalaCORE's expenditure report were triangulated with staff interviews.	KalaCORE expenditure reports and staff interviews
Capital goods	Building and storage costs were detailed in KalaCORE's assets register from 2015-2018. Office costs were minimal and only included 1 table and 4 chairs. Other capital costs included additional equipment used in the KalaCORE office in Patna (laptop, microwave, refrigerator).	KalaCORE expenditure reports, asset registers, and manufacturer prices
Camp operation	Economic costs of using local health facilities (sub-centres) for diagnostic camps at the end of each week were included, as the centres were dedicated to VL testing rather than normal operations. The sub-centre's normal cost of operation and equipment use was estimated by referring to government reports on construction, size, equipment, electricity, and supplies lists. The allocation factor for use of this space for one day was estimated using information from staff interviews on the utility of each item for the diagnostic camp. The cost of operating a sub-centre for one day was estimated by referring to another costing study conducted in Norther India during 2014 (and costs were translated to the base year of 2018).	KalaCORE expenditure reports, staff interviews, and IPE Global interviews
Retraining	Recurrent training was recorded as a lump sum per staff level (fieldworkers, ASHAs, or additional refresher trainings).	KalaCORE expenditure reports and staff interviews
Waste management	Waste management was estimated by protocol detailed by project managers during interviews, along with medical waste disposal costs reported for Bihar by government facilities. rK-39 test disposal occurred after each camp was held, with waste transferred back to Patna for disposal at a government health facility. Travel costs for waste disposal were included in the staff's 'overall travel costs', but was evaluated as an economic cost as an activity funded by NVBDCP (and not KalaCORE).	Staff interviews and KalaCORE expenditure reports
Recurrent costs	Other recurrent costs included management fees or goods and services taxes, detailed in KalaCORE's expenditure dataset. Management fees are attributable to consultancy from IPE Global, which was confirmed during interviews with KalaCORE project managers.	KalaCORE expenditure reports and staff interviews
Passive Case Detection		
Economic life years of start-up	Although India's Government of Health and Family Welfare was the provider in this programme's cost analysis, KalaCORE was responsible for implementing the new VL treatment programme in PHCs over 2 years, including medical officer	KalaCORE staff interviews and expenditure reports

	training, ice-lined refrigerators for cold chain storage, and rK-39 and AmBisome distribution to each facility. KalaCORE's asset registers, programme expenditures, and interviews with staff detailed the start-up costs for passive case detection, and were recorded as economic costs (not financial) as they were funded by DFID and not the Government of India	
Salaries	Doctor, lab technician, and nurse salaries were estimated from average local salaries published on governmental public records for similar positions in Bihar, which were also triangulated through staff interviews. A generalization was made (based on several interviews) that the average hospital has one medical officer, one auxiliary nurse, and two lab technicians per VL-unit that assist in patient intake and diagnosis. Salaries were varied by 10% in the sensitivity analysis.	Local job forums and staff interviews
Training	Staff trainings were conducted by KalaCORE and MSF during AmBisome rollout (the start-up period). Training costs estimated frequency, participation, and standard operating procedures of initial trainings that targeted doctors, nurses and lab technicians. Training was considered part of their 'continuing medical education' and staff were paid their normal salary, but this study took into account the economic cost of staff not engaging in normal working activities. No additional compensation for travel or subsistence was given. Retraining occurred 1-2 days per year and involved one trainer from MSF or KalaCORE during 2018.	KalaCORE records and interviews with medical staff, lab technicians, and trainers from IPE Global (contracted by KalaCORE)
rK-39 tests	rK-39 costs were estimated using distributor prices online, and included as an economic costs as they are donated goods and not paid for by the provider.	Manufacturer prices (Bio-Rad Laboratories, InBios International Inc, CTK Biotech Inc)
Equipment	Medical equipment costs were drawn from KalaCORE reports detailing cost of ILR, diagnostic tests, and various administrative supplies (desks, chairs, fans, refrigerators). Other capital costs in patient rooms were documented through observation (average room included two beds, desk, fan, ILR, small fridge/freezer, patient registrars, phone, waste disposal) and estimated through distributer prices in Bihar online, and converted to the base year of 2018. A 50% allocation was estimated for diagnostic use of equipment, as the other 50% was excluded as dedicated for treatment (according to staff interviews, direct observation, and standard operating procedures published by NVBDCP).	National Vector Borne Disease Control Programme (NVBDCP) published equipment lists, staff interviews and direct observation
Supplies	Recurrent supplies include rK-39, rK-16 diagnostics, gloves, and other general medical supplies (such as disinfectant, disposable goods, and administrative supplies) were documented through staff interviews, direct observation, and average diagnostic materials for vector-borne disease units published in the literature. Costs were estimated using manufacturer pricing online, alongside KalaCORE expenditure reports. The cost of parasitological diagnosis through bone marrow and spleen aspiration were estimated from a previous costing study (Boelaert 1999) and converted to 2018 base year costs for the 17% of patients that could not be diagnosed with a Rapid Diagnostic antibody test (according to KAMIS database).	Staff interviews, direct observation, standard operating procedures (NVBDCP), and literature (Boelaert 1999)
Building, storage, and patient overhead	Size of patient rooms were estimated through direct observation (3 square meters), collated with government PHC reports of operational capacity, and averaged across all 73 hospitals were ILRs and AmBisome had been distributed as part of the national Kala-Azar Elimination Programme. Annual rent in Bihar was estimated to be 30INR or $0.41USD per square foot during	Direct observation, staff interviews, and costing literature detailing VL patient diagnostic costs within

	2018 according to rental information in equivalent spaces. Patient allocation was estimated to be 50% for diagnosis and 50% for treatment, the former of which was used in the cost model. Waste management was also documented within patient overhead costs.	hospitals in Northern India (Chatterjee 2013)
Economic life years of capital	Life years of capital were estimated from literature specific to Northern India and staff interviews, with an average working life of 20 years for general office equipment. The working life of medical equipment (ILR, lab equipment, and diagnostic tests) was estimated from each individual manufacturer.	Staff interviews and average life span of medical supplies in the literature (specific to Northern India)
Personnel time allocation	Time spent on patient intake and diagnostic activities was self-reported by medical officers and triangulated with standard operating procedures for each rK-39 test, bone marrow aspiration procedure, laboratory activities, and general patient administrative activities.	Staff interviews, direct observation, standard operating procedures, administration, and average outpatient time in hospital from the literature
Quality Control (monitoring)	Two vehicles were dedicated to Monitoring and Evaluation officers who oversaw ILRs, rK-39 stock and use, and medical officer training. Costs of these two M&E officers were considered economic (as funded by KalaCORE and not the provider), where supplies, equipment, salaries and travel costs were included in the overall PCD cost.	KalaCORE expenditure reports and staff interviews
Outputs	Number of VL cases screened, diagnosed, and treated were estimated by the lab technician and patient registry. Number of patients diagnosed in hospitals during 2018 was estimated using the KAMIS database. The number of VL cases documented by HMIS in Bihar during 2018 was 3,659, where KAMIS documented 3,611. The KAMIS database is assumed to be more reliable in this study, but the sensitivity analysis took into account this slight discrepancy by varying the number of tests conducted by +/- 10%.	Patient registries, KAMIS, HMIS database, and staff interviews

Appendix 8. Participant information sheet for paper R2.

Participant Information Sheet

Knowledge Utilisation Study

Date: July 2020

Project Title

Evaluating the use of modelling research in India's Kala-Azar Elimination Programme

Invitation

You are being invited to take part in this research project. Before you decide to do so, it is important you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss concerns with the investigator. Please ask questions if any information or aims remain unclear, or if you would like more information before taking part in this study. You are free to decline answering any questions or taking part all together. Thank you for your time reviewing this document.

What is the project's purpose?

This project aims to study how modelling research is understood, valued, and used by decision makers for strategising elimination of visceral leishmaniasis (VL) as a public health problem in India. The goal is to understand how this research can best contribute to informing KEP strategies for reaching reductions in incidence.

Why have I been chosen?

You have been chosen because of your knowledge and experience relating to VL elimination and programme delivery. The purpose of this interview is to better understand your interpretation and assessment of recent modelling studies, with a goal to increase usefulness and value of this research to the Kala-Azar Elimination Programme for strategising elimination as a public health problem.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be able to keep a copy of this information sheet and will be asked to indicate your agreement with a consent form. You are free to withdraw at any time and are not required to give a reason.

What will happen to me if I take part?

You will be asked a series of questions relating to VL modelling and India's elimination programme. The questions and answers will be recorded on an audio device, to later be transcribed in a confidential and secure file.

What do I have to do?

Please answer the questions honestly, according to your own opinion, and to the best of your recollection. There are no commitments or restrictions associated with participating.

What are the possible benefits of taking part?

There are no immediate benefits for those people participating in the project. The aim of the research is to better understand and strategise VL case detection activities in Bihar as India aims toward elimination as a public health problem.

What if something goes wrong?
If you have any complaints or concerns surrounding the project, in the first instance you can contact the investigator, and further any supervising member of her research team or the London School of Hygiene and Tropical Medicine.

Will my taking part in this project be kept confidential?
All the information collected about you during the course of the research will be kept strictly confidential. You will not be able to be identified or identifiable in any reports or publications. All data collected about you in the interview or supporting documentation will be stored in an encrypted USB drive that is only accessible by the investigator.

What will happen to the results of the research project?
Results of the research will be reported back to participants, key actors involved in VL case detection activities in India, and decision makers with an aim to inform future programming. This study is also intended to be published in scientific literature, to share experiences of the program with the broader scientific community.

Who has ethically reviewed the project?
This project has been ethically approved by the London School of Hygiene and Tropical Medicine's Ethical Review Committee.

Contacts and further information:
Investigator: Natalie Dial
natalie.dial@lshtm.ac.uk
DrPH Candidate, London School of Hygiene and Tropical Medicine
15-17 Tavistock Place, London UK WC1H 9SH

Academic Supervisor: Prof Graham Medley
Professor of Infectious Disease Modelling, London School of Hygiene and Tropical Medicine
graham.medley@lshtm.ac.uk

Fern Terris-Prestholt
Professor of Health Economics, London School of Hygiene and Tropical Medicine
fern.terris-prestholt@lshtm.ac.uk

Prof Simon Croft
Professor of Parasitology, London School of Hygiene and Tropical Medicine
simon.croft@lshtm.ac.uk

Thank you for taking part in this research.

Appendix 9. Participant consent form for paper R2.

Participant Consent Form

Knowledge Utilisation Study

Version: 1
Date: July 2020

Name of Researcher: Natalie Dial (Investigator)

Please Initial Box:

I confirm that I have read and understood the Participant Information Sheet dated July 2020 (version 1). I have had an opportunity to consider the information, asked questions, and have received satisfactory answers:	
I understand that my participation is voluntary and that I am free to withdraw at any time from the interview, without giving any reason:	
I consent to the interview being recorded. I understand that the researcher will not use any specific quotations from this interview in any paper or reports without my explicit permission. I understand that the researcher will contact me to seek permissions and that I am free to decline the use of my quotations in any documents. My quotations in papers or reports will be anonymous and not attributable to me:	

I agree to participate in the study.

Name of Participant Date Signature

Researcher Date Signature

Appendix 10. Interview guide for paper R2.

Interview Guide

Knowledge Utilisation Study

Study title: Evaluating the Cost of Active and Passive Case Detection of Visceral Leishmaniasis (Kala-Azar) to inform a post-elimination strategy in India

Version 2: July 2020

Investigator: Natalie Dial, MSc, MIPM, DrPH Candidate, London School of Hygiene and Tropical Medicine

Target participant population: decision makers and senior-level programme managers involved in VL programme delivery in Bihar, India

Semi-structured in-depth interview questionnaire:

Introductory questions

- What organisations, consortiums, universities do you work with?
- What is your role at your organisation?
    - What diseases do you work on?
    - How long have you been working on VL?
- How long have you been working with modellers or on modelling?

1. **Reception:** *how relevant information was received*
    A. How do you normally hear results of new modelling studies?
    B. How do you receive information on newly-published modelling research?
    C. What is your preferred method for receiving study results?

2. **Cognition:** *how information was read, digested, and understood*
    A. Is the modelling research easy to access, read, and understand?
    B. Do you prefer more or less tables, figures, and graphics?
    C. Do you prefer explicit policy recommendations based on research?
    D. What could be improved?

3. **Reference:** *if and how information changed the views, preferences or understanding of the magnitude or probabilities of the impact*
    A. When does new information change your opinion on design of the current KEP?

4. **Effort:** *how information might influence future actions*
    A. When does new information influence how you strategise/change the KEP in the future?
    B. How so?
    C. Has COVID-19 research influenced or mobilized action in India or in your work?

5. **Adoption:** *how information can influence policy outcomes*
    A. What type of modelling results are most valuable to informing elimination strategies?
        a. Likelihood of achieving elimination
        b. Effect of certain interventions
        c. Include broader indicators like SES and economics of programme?
    B. How often should research inform policy?

6. **Implementation:** *how information can be implemented into the programme*
    A. How feasible is it to translate modelling results into policy and programme implementation?
    B. What is the timeframe that modelling predictions would best inform programme delivery in your work?

7. **Impact:** *how a change in policy would influence desired effects*
    A. How can research be made more valuable and useful for influencing programme strategies?
    B. Has COVID-19 research impacted a programmatic or policy response?
    C. Are there any lessons learned from the COVID-19 research and policy response that apply to VL in India?
    D. How has COVID-19 affected you as a decision maker, manager, or researcher?