Strengthening the collection, interpretation and use of data to target expansion and integration of case detection and management interventions against neglected tropical diseases

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Thesis submitted in accordance with the requirements for the degree of

Doctor of Philosophy
of the
University of London

July 2023

Department of Disease Control

Faculty of Infectious Tropical Diseases

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

No funding received

Research group affiliation(s): London Applied and Spatial Research Group (LASER)

Declaration of Own Work

I Hope Nancy Simpson, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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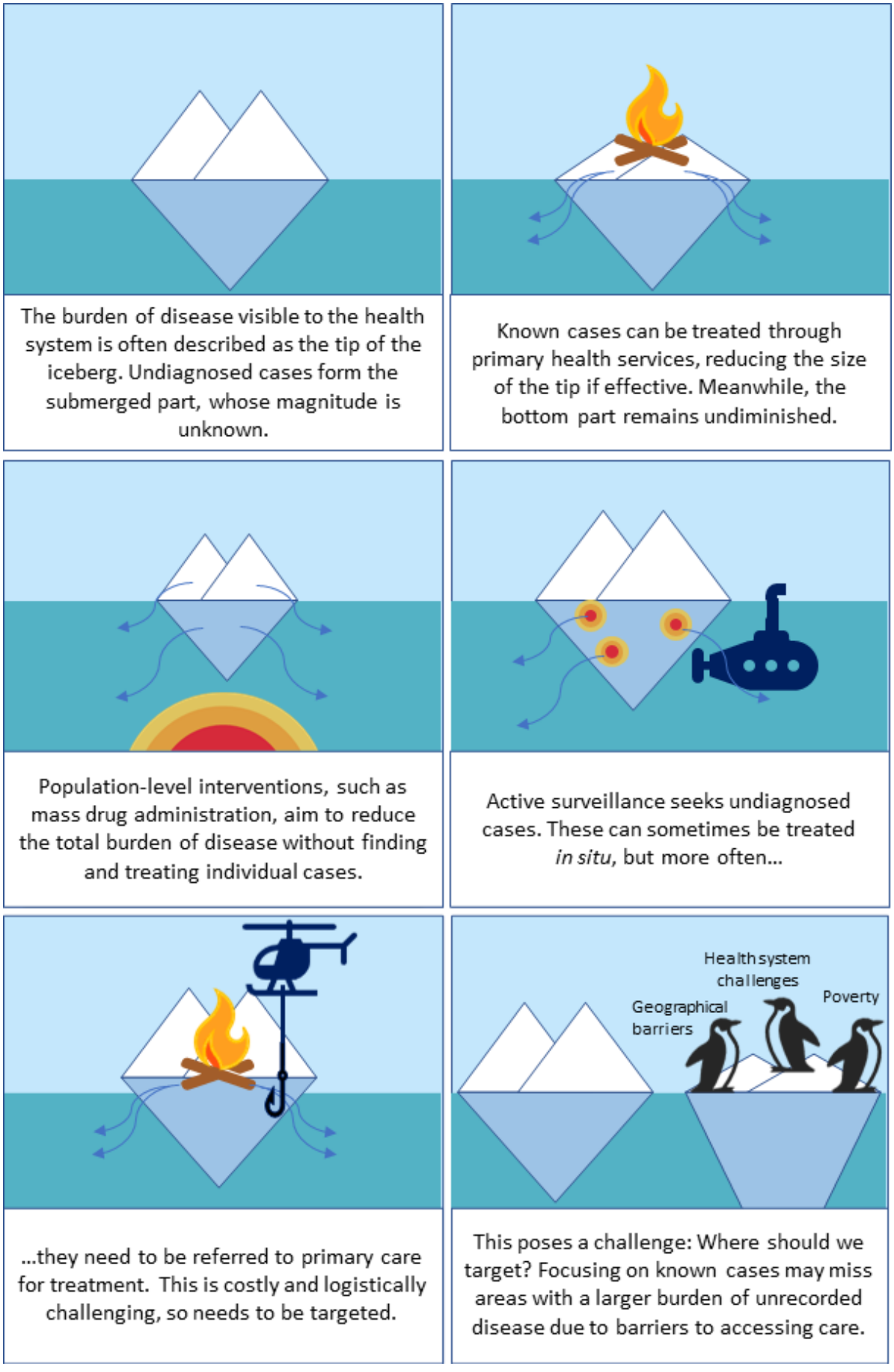
1. Abstract

Neglected tropical diseases (NTDs) cause a large burden of morbidity, primarily affecting disadvantaged communities. They are variously targeted for control, elimination, and eradication, which will require primary health system strengthening and public health interventions. Certain NTDs are controlled through mass drug administration (MDA) to reduce transmission and limit progression of infections to morbidity; others (grouped as 'case management NTDs') by early identification and treatment of individual cases, which can be enhanced through active case searches. To maximise efficiency, interventions should be targeted to high prevalence or incidence areas, and integrated across co-endemic NTDs. Targeting and integration of case detection and management interventions are challenging, however, as existing data on case management NTDs originate mainly from routine health facility notifications, which are both under-representative and biased due to uneven service coverage and accessibility.

This portfolio comprises five research papers exploring these issues, and approaches to strengthen surveillance for NTDs. The first used remote georeferencing to map routinely detected cases of NTD morbidity in Ghana, and investigated epidemiological indicators by health facility accessibility. The second is a systematic literature review of the global distribution of Buruli ulcer. The third used environmental niche modelling to predict suitability for Buruli ulcer in Africa. The fourth integrated multiple decision criteria to target a survey for podoconiosis in India. The fifth describes a prevalence survey for lymphatic filariasis morbidity to evaluate a community-based screening method.

This work advocates for a broader perspective on the targeting of NTD case detection and management interventions, specifically acknowledging potential biases in routine surveillance data, and for further integration of interventions across diseases and within primary health systems. Financial support, development of information and surveillance systems, and further engagement and support of community health staff are critical. This is intended to support more equitable programmes and progress towards universal health coverage.

Figure 1: Graphical abstract



2. Acknowledgements

I am grateful to many people who have supported me over the course of this work.
Firstly I have to acknowledge my supervisors: Dr Rachel Pullan, Dr Katie Gass, and Prof Ben Koudou.

Rachel has provided invaluable support both in terms of leading the projects I have worked on, and in helping me to consolidate this portfolio. Our detailed discussions throughout my registration period enabled me to conceive and express the ideas linking this research together, and her thorough reviews have strengthened this work enormously. She is an inspirational and motivating PI and her supervision has taught me to strive for meaningful research goals. Katie's extensive experience in operational research on neglected tropical diseases was extremely helpful in the development of this summary. She brought important insights on the design and implementation of NTD surveys and challenged me to think more deeply and critically about the work. Ben was co-PI of the project in Cote d'Ivoire, and hosted me there within his research team between January and May 2021. There was no problem he could not solve in the field and he was generous with his time. This experience was foundational to my development as a researcher and Ben continues to be a supportive mentor in ongoing projects. I am also grateful to Dr Daniele Konan and Dr Jeanne d'Arc Koffi who were part of his team. They were not only co-field coordinators (as well as interpreters for my franglais), but became close friends during the time we lived and worked together.

Several others have been essential to this work. Dr Jorge Cano supervised my Masters project in 2015, starting me off on the path I've followed since. Papers 1-3 were all produced under Jorge's expert guidance, particularly Paper 3, which used adaptations of code he had written for earlier projects. Jorge was a patient and generous mentor and his support was foundational to my academic journey. Paper 4 was part of the Global Atlas of Podoconiosis project, led by Dr Kebede Deribe. Kebede's dedication to child health and NTD control is truly inspirational, and his project management skills are unsurpassed. Dr Joe Timothy was co-PI on the project covering Paper 5 and provided extensive supervision covering planning, logistics, field activities and analysis, as well as reminding me to enjoy the experience provided by this unique fieldwork opportunity. I think Joe is the most rigorous epidemiologist I have worked with and I have learnt so much from him. I would also like to thank Dr Kate Halliday and Prof Gail Davey who have been supportive managers and brilliant mentors whilst I have worked on this portfolio, and played important roles in my academic development.

As part of the LASER group and LSHTM more widely, as well as Brighton and Sussex Medical School, I have formed close connections with colleagues which have made work more enjoyable and interesting. Although there are too many to name, I do want to thank Will, Hugo, Kallista, Kim, Stella, Stefan, Georgia and Rowa (in addition to the above) for making collaborations and work trips so fun and fulfilling, as well as for the day-to-day interactions which spark ideas and brighten up the office.

I have been supported by several different funders over my seven years at LSHTM, including the Bill and Melinda Gates Foundation, Unlimit Health, and the NIHR, but the most important to note is the AIM Initiative (part of the American Leprosy Mission). Most of the research in this portfolio was supported by the AIM Initiative, either financially or through technical collaboration.

This section would not be complete without expressing enormous gratitude to my family. The unfailing support of my parents, grandparents, sisters, and partner (who kindly proofread this document) has kept me motivated throughout the course of my work.

3. Introduction

In this section I provide a perspective on the state of the field when I began working on this portfolio, including references up to 2016. More recent developments will be covered in subsequent sections.

Neglected tropical diseases (NTDs) are a medically diverse set of conditions caused by a wide range of pathogens and environmental and animal exposures [1, 2]. They are grouped on the basis that they disproportionately affect the most marginalised, remote, and economically disadvantaged populations, and are under-resourced relative to burden they impart [3, 4]. More than a billion people worldwide are affected by or at risk of NTDs, and while it is difficult to quantify the number who suffer morbidity due to these diseases, the total is estimated to reach into the hundreds of millions [5, 6]. NTDs can cause physical and cognitive impairments, pain, disfigurement, stunting and decreased fitness, and put affected people at risk of stigma and poor mental health outcomes. The extreme burden of NTDs prevents affected populations from enjoying 'the highest attainable standard of health… one of the fundamental rights of every human being '[7]. This is largely preventable, since most cases of NTD morbidity can be averted by preventive chemotherapy (PC)- the strategic delivery of medicines to populations considered at risk [8]- or prompt case management (CM) of individual cases.

3.1. NTD Spatial Distributions

Since NTDs share poverty-related risk factors, their spatial distributions often overlap, resulting in co-endemicity. However, their distributions vary in extent and focality, reflecting differences in their epidemiology and transmission pathways. Some NTDs have strong environmental drivers: lymphatic filariasis (LF), onchocerciasis, trachoma and schistosomiasis are limited to areas suitable for their vectors [9-12], and podoconiosis is restricted to areas of particular soil types [13]. Buruli ulcer (BU) and mycetoma are caused by environmental pathogens, and occur in environments suitable for these organisms, and where humans come into contact with them [14, 15]. The soil transmitted helminthiases (STH) are widespread, but most prevalent in populations with low access to improved water and sanitation, and where environmental conditions favour the survival of their eggs and larvae in the soil [16]. Yaws, which is spread by person to person transmission, may be associated with environmental or climatic factors [17], while other diseases spread by direct contact (such as leprosy and scabies), show spatial heterogeneity most likely driven by socio-economic factors, human population density and contact patterns [18-20].

3.2. NTD Control

Five NTDs are already controlled through large-scale PC programmes, which use mass drug administration (MDA) to treat entire populations in endemic areas, aiming to limit transmission and/or

progression of infections to morbidity [4]. The five PC-NTDs are LF, onchocerciasis, trachoma, schistosomiasis, and STH. Other NTDs, including BU and leprosy, are controlled by early detection (for example, through community education and active case searches) and prompt case management [4]. Although effective treatments are available for many NTDs, they can be difficult to access: health facilities may be too far or too expensive to travel to, or diagnosis/ treatment may not be available. In many instances, untreated infections can progress to chronic cases, which require morbidity management and disability prevention (MMDP) interventions to improve patient quality of life and reduce the risk of further deterioration. While NTDs are often grouped according to their main form of control (PC or CM), chronic manifestations of PC NTDs can also require substantial CM [21].

In 2012, the WHO published a roadmap for accelerating work to overcome the impact of NTDs, setting targets to control, eliminate, or eradicate eleven NTDs by 2020 [4]. The roadmap set out five groups of interventions against target diseases: PC; case detection and management; vector control; veterinary public health; and water, sanitation and hygiene. Health systems strengthening was positioned as a cross-cutting intervention. In the same year, a partnership including representatives of endemic countries, non-governmental organisations, funding bodies, and pharmaceutical companies signed the London Declaration on Neglected Tropical Diseases, committing to support control efforts aligned to the WHO Roadmap [22]. Signatories pledged to expand programmes for the delivery of PC, and pharmaceutical companies committed to donate medicines for MDA, making this a highly cost-effective and scalable intervention, particularly when delivery could be integrated across programmes [23].

For CM-NTDs, the 2012 Roadmap identified an urgent need to reduce the time between initial symptom presentation and diagnosis, and recommended capacity building within NTD programmes, including in case management and monitoring and evaluation, in order to facilitate integrated control. Specific guidance on the integration of activities for CM-NTDs was lacking in the 2012 Roadmap, but the WHO Regional Strategic Plan for NTDs in the African Region 2014–2020 [24], published one year later, recommended integrated case-finding for BU, leprosy, and other NTDs in co-endemic areas. Guidelines on MMDP for LF in 2013 also recommended integration of activities for LF with leprosy and BU [25]. A 2015 paper [26] recommended integrated control for BU and leprosy, particularly in the areas of promoting early diagnosis, confirmatory testing, prevention of disability, and surgeries. It was recognised that integration of these aspects would be more operationally challenging and more costly than integration of MDA, requiring adaptation of training programmes for staff cadres including community health staff, health facility staff, and laboratory personnel. It would also pose a challenge for donor-funded activities by requiring them to include diseases outside of their target remit.

3.3. NTDs and Universal Health Coverage

The United Nations made NTD control part of the Sustainable Development Agenda in 2015, with the third goal (SDG3) - to 'ensure healthy lives and promote wellbeing for all at all ages' - including a target to 'end the epidemic' of NTDs by 2030 [27]. Another target of SDG3 was Universal Health Coverage (UHC), aiming to enable all individuals to receive required health services without incurring financial hardship. In recognition of the fact that populations in need of interventions against NTDs typically have lower access to quality health services, and that UHC is defined by an equitable distribution of health services, NTD control was positioned as a 'litmus test for UHC' and a 'tracer of equity' [28]. In their first monitoring report on UHC, the WHO and World Bank included the proportion of people who received PC out of those requiring it for at least one NTD as one of eight indicators of UHC in health promotion and prevention [29]. The monitoring of this indicator was seemingly straightforward, as Ministries of Health (MoH) in endemic countries are required to report on the number of people targeted for PC and the number receiving it annually, providing a readily available data source.

3.4. Remaining Challenges to NTD Control

While MDA programmes have been vastly scaled up since 2000, access to case detection and management interventions has not increased by the same scale, and remains a global public health challenge [30]. A large part of this challenge is that the delivery of case detection and management interventions requires trained healthcare workers, health services accessible to the population, and reliable supplies of diagnostic tests, medicines, medical materials and equipment, and accredited laboratories with qualified technicians. As such, these interventions are much more costly per person treated compared to MDA, especially for patients who require a continuum of care to manage chronic conditions [31, 32]. Due to the extremely limited funding available for NTD case detection and management, these interventions are under-implemented, and are generally not mainstreamed into primary healthcare, but supported by external partners. This can lead to siloed operational structures, impinge upon country ownership of control programmes, and may jeopardise the long-term sustainability of these interventions [28].

Due to the low levels of access to diagnostic and treatment services for NTDs, many people requiring CM interventions are un-diagnosed, or untreated following loss to follow-up after initial identification [33, 34]. Furthermore, since cases from remote and marginalised populations- those most at risk of NTDs- are less able to access quality health services, they are even less likely to be diagnosed and reported, and travel times have been reported as a major cause of treatment default [35]. As a result, routine surveillance data are not only under-representative of NTD burdens, they are likely to show a biased representation of disease distribution, with rates apparently higher in areas where cases have

the best chance of reaching health services. This presents a major challenge to NTD programmes in deciding where to implement interventions to promote early case detection and improve case management. Routine surveillance data are generally the only information readily available to identify endemic communities, and so are often used to target interventions and inform supply chains [36]. However, restricting case detection activities to areas with higher numbers of recorded cases risks exacerbating health inequalities reflected in routine surveillance data, and neglecting those most in need.

3.5. Overarching Objectives of this PhD

1. To review the use of surveillance and monitoring data and model predictions for the geographical targeting of interventions against NTDs.
2. To explore opportunities for integration of routine surveillance data on NTDs controlled through case management, and make recommendations for future surveillance to inform integrated interventions.
3. To describe biases affecting data on NTDs and their potential impact on global understanding of disease distributions.
4. To use environmental modelling to predict the distribution of Buruli ulcer in Africa.
5. To demonstrate the integration of multiple data sources and decision criteria for targeting podoconiosis case finding activities.
6. To evaluate the reliability and equity of routine NTD surveillance and make recommendations for strengthening of community-based surveillance.

The first objective will be elaborated through a narrative review drawing on the literature and programmatic experience of elimination programmes for NTDs. Objectives 2-6 will be covered by publications within this portfolio.

4. Literature Review: Geographical targeting of NTD interventions

Objective: *To review the use of surveillance and monitoring data and modelling predictions for the geographical targeting of interventions against NTDs*

In this chapter, I present a narrative review describing how data collection, analysis, and modelling have been applied to inform geographically targeted interventions against NTDs. Public health interventions are deliberate measures intended to improve population health, providing complementary services to facility-based care. Interventions are necessary for the control and elimination of NTDs (and other infectious diseases) when routine services for diagnosis, treatment, and case management are insufficient, or when people affected do not or cannot access them [37]. Interventions for NTDs include mass drug administration (MDA), active case finding, and improving access to diagnostic and treatment services. To improve cost-efficiency and limit unnecessary implementation and treatment, these interventions can be targeted to populations at risk or to geographical areas with high prevalence or incidence. Spatial targeting depends on defining areas where incidence or prevalence is concentrated. I describe different approaches to data collection and analysis to inform spatially targeted interventions, considering how this relates to control at different levels, disease epidemiology, and the need for treatment and management of individual cases.

4.1. Mass drug administration

Since 2000, MDA to control five NTDs has expanded widely across the African continent [38]. A top-down approach to programming and decision making, with oversight by large disease-specific or integrated programmes enabled rapid implementation and scale-up of operations, and impressive progress in the surveillance and monitoring of PC-NTDs [38]. The need for MDA to control transmission or morbidity within defined units of population (implementation units [IUs]) is determined by infection prevalence, measured in 'mapping surveys', which apply simple diagnostic tests for infection or clinical screening for signs of disease. As MDA is a population-level intervention, individual cases are not treated on the basis of infection or disease status. Rather, entire communities or risk-groups (including school-aged children, women of reproductive age, and people whose livelihoods place them at higher risk) receive treatment in areas where prevalence exceeds a given threshold. The impact of MDA on disease transmission is monitored through surveillance, usually in sentinel sites, which are purposively selected on the basis of high baseline prevalence and/or ecological characteristics [39]. If surveillance indicates reduction in prevalence to below a given level, impact assessments are conducted following a predetermined number of MDA rounds, and the results are used to evaluate the need for ongoing MDA or changes to the programme. Since mapping surveys and impact assessments often target the same population groups and use similar diagnostics, (e.g.

stool samples for intestinal schistosomiasis and soil transmitted helminths [40] and clinical signs for onchocerciasis and trachoma [41]), they can be integrated within co-endemic regions to enable cost sharing and efficiency [40].

An important feature of MDA mapping surveys is that they are designed to estimate relatively high prevalence of target diseases. Baseline surveys designed to determine MDA requirements are powered to detect prevalence of around 1% for LF [42], 10% for schistosomiasis and trachoma [43, 44], and 20% for STH [39]. To obtain estimates to a reasonable degree of accuracy at these prevalence levels (often around 20% of the estimate), the WHO recommends testing 50-100 people per site in at least 1 site for LF; 50 children per site in at least 5 sites per ecological zone for schistosomiasis and STH; and around 50 children in 20-30 villages per district for trachoma [40]. These designs generally result in sample sizes ranging from 200- 1,500 per IU [45].

As control and elimination for PC-NTDs have progressed however, emerging evidence has suggested that more granular prevalence estimation will be required for monitoring and to ensure interventions are well targeted. For example, fine-scale surveys have revealed that schistosomiasis prevalence has not declined substantially in some villages within districts that have achieved high coverage of MDA for several years [46]. These persistent hotspots may not be identifiable from district-level prevalence surveys, and may require focused, intensified interventions. As such, micro-targeting of schistosomiasis MDA to sub-district level was recommended in the WHO 2030 Roadmap [47]. The Kenyan MoH recently implemented precision mapping to guide MDA for schistosomiasis and STH at the level of wards, a unit below sub-counties, which were the initial units of implementation. Results showed that the sub-county treatment strategy would have led to overtreatment in some wards, and undertreatment in a lower number, such that the total number of drugs needed would be lower with micro-targeting [48]. For LF, transmission assessment surveys (TAS) are conducted to validate elimination as a public health problem following at least five years of MDA, and when prevalence of microfilaremia in sentinel sites is less than 1% (or when prevalence by antigen testing is less than 2%) [49]. Evidence from some settings suggests that persistent LF transmission may be restricted to focal areas within districts which fail TAS [50], and that even districts passing TAS may contain residual transmission foci [51].

Authors have recommended that impact surveys (such as TAS) could be made more efficient by using geostatistical approaches to analyse survey data, accounting explicitly for geographical variation in risk within evaluation units [52]. Risk models for diseases with strong environmental drivers can be made more precise by including variables representing environmental, accounting for otherwise unexplained variation in prevalence. The expansion in the availability and accessibility of spatial datasets derived

from satellite imagery has vastly increased opportunities to develop such models in recent years [53]. Model-based geostatistics have been applied to prevalence analyses for a wide range of NTDs including (but not limited to) LF, loaiasis, onchocerciasis and STH [10, 52, 54-56].

4.2. Case detection and management interventions

Although LF and trachoma are classified as PC-NTDs, elimination strategies for both diseases also include case management elements. For LF, elimination as a public health problem depends on documentation of the number of lymphedema and hydrocele cases and provision of management services for these conditions in endemic and previously endemic districts [57]. There is no standard WHO guidance on approaches to estimate the number of lymphedema and hydrocele cases, but screening through community health workers (CHWs) is commonly used [58]. For trachoma, elimination requires reduction of late stage trachoma (trachomatous trichiasis; TT) unknown to the health system to below 0.2% prevalence in those aged 15 years and older, and evidence that incident cases can be managed through the primary healthcare system [59]. Trachoma baseline and impact evaluation surveys often measure the prevalence of active trachoma (trachoma follicular; TF) and TT simultaneously, but are powered to estimate the prevalence of TF and generally accept a lower precision in estimation of TT prevalence, which usually affects a lower proportion of the population [60]. In certain circumstances however, such as when TF prevalence does not meet the threshold for MDA but TT prevalence appears to be above the elimination threshold, TT-only surveys are used to evaluate the impact of surgical interventions and to estimate the backlog of cases requiring surgery. The WHO has provided specific guidance on the design of such surveys [60].

The success of NTD mapping and its integration across diseases by PC programmes has galvanised interest in the mapping of CM-NTDs, but surveys for these have been implemented much less extensively. Nonetheless, there are some successful examples of integrated NTD morbidity surveys. In Ethiopia, collaboration between teams including the Ethiopian Public Health Institute and academic partners enabled integration of nationwide surveys for LF morbidity and podoconiosis, which had been planned as standalone activities [61]. In this example, 129,959 individuals in 1,315 communities were surveyed for lymphedema over three months, and integration resulted in a reduction of costs to approximately half the combined budget estimates for the standalone surveys. The survey estimated a total podoconiosis prevalence of 4.04%, with marked geographical variation between regions. Results were presented to MoH stakeholders and informed the 2016 NTD Master Plan, which notably included recommendations for integrated MMDP for LF and podoconiosis [62]. The Ethiopia NTD Master Plan 2021 noted that the data-driven approach adopted by the previous plan had been successful in

reducing morbidity due to these two diseases, with MMDP services implemented in 150 of 345 districts targeted for podoconiosis and in all districts endemic for LF [63].

Subsequent statistical modelling of relationships between podoconiosis occurrence and environmental covariates allowed for estimation of risk across the entire country [64], and geostatistical modelling provided estimates of the total disease burden [65]. The environmental suitability model was also projected to predict risk in Cameroon, and predictions were used to inform a nationwide podoconiosis survey with cluster selection stratified by predicted suitability [66]. This survey identified higher prevalence of podoconiosis in clusters predicted suitable, implying a gain in survey efficiency compared to random sampling.

While the integrated survey for podoconiosis and LF morbidity provided important estimates of population burden of these diseases, it was not powered to evaluate fine-scale variation in their distributions. Buruli ulcer shows a highly focal distribution in endemic areas, apparently reflecting suitability for its causative agent, *Mycobacterium ulcerans* [14]. Active transmission foci may be targets for active case finding to promote early detection and management, or educational campaigns to raise awareness of the disease. On this basis, WHO recommends micro-mapping of BU, but specific guidance on the operationalisation of this approach is lacking [4]. A key challenge is identifying areas for targeting, which is difficult given the low prevalence of and focality of BU. Large sample sizes are required for precise estimation of the prevalence of rare diseases, and are further increased by disease focality, as individuals within primary sampling units (clusters) have similar levels of risk relative to the population. This is quantified as the intra-cluster correlation coefficient (ICC), and higher ICC values increase the sample size needed for precise prevalence estimation, meaning that cluster-based survey designs generally become unfeasible for low-prevalence and focal diseases. As a result, control programmes currently depend on routine surveillance data as the primary information source for targeting active case finding [36].

A recent survey in Liberia was designed to evaluate fine-scale variation in the geographical distribution of BU, LF morbidity, leprosy and yaws in a district co-endemic for these diseases. A total of 56,825 individuals were screened, identifying 0.9 cases of BU, 4.4 of leprosy, 2.6 of yaws, 17.5 LF lymphoedema and 8.5 of hydrocele per 10,000 people at district level [67]. All of these diseases were underrepresented by routine surveillance data from facility-based recording. However, the authors concluded that the costs of accurately mapping disease focality may outweigh the benefits of micro-targeting disease-specific interventions in settings such as this [67]. This finding raises the question of how programmes should implement the WHO Roadmap recommendation for BU micro-mapping, given the high costs of population-based surveys.

For leprosy, the high burden of cases who remain undiagnosed, untreated, or lost to follow-up is a major challenge to elimination, and evidence suggests that an active approach to case detection will be required to meet global targets [68]. Innovative case-finding approaches to increase early case finding have also been recommended by the WHO [69]. When global elimination of leprosy was declared in the year 2000, investment in active case detection was scaled back considerably. This is considered to be the main reason for the dramatic fall in leprosy notifications since 2000 [74], supported by evidence of untreated cases identified in surveys in high-burden settings [82, 83].

There are a few examples of spatial targeting of active case finding for leprosy based on notified cases within high-incidence regions [37]. In the municipality of Mossoró in Brazil, which had a new case detection rate of 6.16 per 10,000 population in 2004, active case finding was targeted using a density map of patients' homes [70]. This identified 115 new leprosy cases, almost the same number as was diagnosed in the entire municipality in the previous year. With a total cost of £1,500, this targeted approach appeared cost-effective compared to a municipality-wide campaign in 2002, which had a total cost of £7,500, and identified 28 new patients. However, the initial notifications on which the campaigns were targeted may have been subject to bias resulting from geographical or sociodemographic differences in subpopulations' ability to reach a facility for diagnosis. The authors noted that the total annual notification rate had varied year on year with the number of primary health centres, training of health teams, the number of dermatologists, and the application of screening campaigns, all of which may have varied within the municipality.

4.3.The role of the primary healthcare system

A key difference between surveys conducted in the context of MDA and those for case management interventions is that in the former, cases are not treated at individual level, while in the latter, they require individual assessment, treatment and management, driving up the costs and complexity of surveys. For most NTDs controlled through case detection and management, treatment must be delivered by formally trained health workers in a health facility. Mapping surveys for NTDs are usually implemented by teams external to local facilities, making referrals challenging, and even when this is possible, facilities may not be able to provide the continuum of care required for chronic cases. In districts endemic for trachoma and LF, the surgical capacity of local health systems is often insufficient to address the burden of TT and hydrocele, so surgeries are often delivered through periodic community-based camps [71]. For trachoma this often necessitates exhaustive screening by CHWs to ensure that all cases are identified and linked to treatment [72], at a further cost to programmes. Successful treatment of BU and leprosy requires early treatment of infections, with ongoing disease management required for individual patients [73]. In the case of the targeted case finding activities in

Mossoró, Brazil, the authors noted that this activity was feasible in the targeted areas since they contained local health facilities [70], highlighting the challenges of implementing this approach in communities without health facilities.

When implemented with broader goals of health system strengthening, case detection and management interventions can support local treatment capacity. The study in Mossoró delivered in-service training to facility doctors, which allowed 93% of the 104 cases found to be treated at primary health centres, compared to just 25% before the campaigns were implemented [70]. For a lasting impact however, continued investment into routine primary healthcare and refresher training beyond the timeframe of the research project would be required. Primary health system strengthening is also required for the sustainable control of PC-NTDs. For example, existing MDA schemes for schistosomiasis do not include children under five years old, and often use school-based administration to reach children aged five and older. These schemes have been said to leave a "double gap" comprising untreated pre-school age children and school-age children not in school. The infection puts these children at risk of stunting, wasting and early-onset morbidity due to the disease, and schistosomiasis morbidity management is lacking in many endemic countries [74]. The integration of treatment for PC-NTDs into local health services has also been recommended as a way to increase the equity of NTD treatment and to ensure access to treatment when MDA is scaled back or stopped [75].

4.4. The practicalities of using spatially-referenced data for decision making

The use of data for decision making relies on decision makers being able to access, interpret, and trust epidemiological data. The national-level organisation and integration of PC programmes provides a central point for the reporting of baseline, intervention coverage, and monitoring data [39]. Under the WHO Regional Office for Africa (AFRO), the Expanded Special Project for Elimination of Neglected Tropical Diseases (ESPEN) was established as a framework to provide technical support and advice to Ministries of Health responsible for driving PC programmes [38]. Programmes are required to report annually to ESPEN on intervention coverage (measured as the proportion of the target population who received MDA in each round), with requests for medicines for MDA linked to these reports.

One objective of ESPEN was to improve the use of data for decision making in PC programmes. The project established an integrated regional database to collate epidemiological and intervention coverage data collected by national programmes. The ESPEN database now hosts a vast database of data on NTD prevalence, representing pre- and post-control settings, as well as surveillance sites where prevalence is monitored to assess changes in disease epidemiology. The platform allows programmes and partners to visualise and manipulate these data, intended to support decision

making around MDA by allowing programmes to identify where delivery strategies require modification or intensification, or where PC can be scaled back.

Challenges affecting the usability of these data for decision making have been identified. For example, the quality of treatment register data, collected by community drug distributors (CDDs) is limited by the fact that CDDs use paper forms for recording treatment numbers and have to collect large amounts of data, for which they may be insufficiently trained and supervised, and are often underpaid [76]. The low accuracy of treatment register data is recognised by NTD programme managers, and erodes programmes' ability to monitor progress in control and their readiness to use these data to inform targeted strategies. It also brings into question the use of MDA coverage rates as a tracer of health equity by the World Bank [29].

Another challenge to the use of data for decision making is the existence of disparate data management systems [76]. Increasing the interoperability of NTD databases and health information systems, with inbuilt analysis and visualisation functions, would enable more effective evaluation of data for decision making. With many countries adopting the DHIS2 system for routine surveillance of infectious diseases, and in some cases for monitoring health service delivery [77], this is likely to offer a suitable platform for integration and monitoring of NTD data in many countries. There are also examples of bespoke systems used by other disease control programmes. For example, malaria elimination programmes in several countries have used spatial decision support systems (SDSS), which integrate data sources and expert knowledge and automate incidence and risk modelling [78-80]. These systems offer a practical way for decision makers to access and use data and other information sources to guide strategic action at different levels. In Bhutan, the SDSS was used to support long-lasting insecticidal net distribution, indoor residual spraying, and reactive case detection in two of the seven malaria-endemic districts [79]. An evaluation showed that while the system did not appear to improve intervention coverage, officials felt that the system facilitated reactive case detection activities and could support more accurate and timely public health responses, monitoring, and future planning and budgeting [79].

The skills and epidemiological support to interrogate, manipulate, visualise, and interpret surveillance data at the level of decision-making are equally important. Capacity building to strengthen these skills within NTD programmes is already a key priority for ESPEN and related WHO programmes [81], and could be expanded to include material relevant to targeting case finding and management interventions. For locally responsive interventions, it is important that capacity for data collection, analysis, and interpretation is built at local as well as national level, and that local decision makers have autonomy to design and implement public health strategies [82].

Unlike the data used for PC-programming, collected through population-level surveys and control activities, routine data on CM-NTDs are mostly collected at health facility level and recorded in paper or electronic patient registers. Usually, data are summarised before reporting, and summaries are used to calculate monitoring and evaluation metrics to measure progress towards control programme goals. However, as data in this form do not indicate where the case was likely to have been infected, these summaries may mask or distort spatial heterogeneity in disease burdens, particularly when facility catchments are large. This may also emerge as an issue for the PC-NTDs as MDA is scaled back and programmes transition towards facility-based test and treat strategies. To identify groups at higher risk of disease, resurgence, access challenges, and loss to follow-up, case-level data including patients' home and treatment locations and sociodemographic variables would need to be integrated within local health databases and analysed at fine-scale. These variables would include individual identifiers, which can help with patient and contact tracing, but are important to safeguard for confidentiality [76].

4.5. Conclusions

These examples of using data to target NTD interventions emphasise different approaches available and appropriate for different diseases. Determinant factors include the epidemiology of target diseases, the type of control implemented, the capacity of local primary care facilities, and resource availability. For diseases which are relatively common and treated at population level (notably the PC-NTDs), cross-sectional surveys provide data to estimate disease burden and target treatment to areas of highest prevalence. Cross-sectional surveys are more costly for CM-NTDs due to their low prevalence and focality, and the need to target interventions at finer scales. As such, their surveillance relies mostly on passive case detection. Since passive surveillance is prone to under-detection, active case detection activities can be necessary for elimination or control, but decisions about where to implement these activities are challenging. Nonetheless, the planning, monitoring and evaluation of MDA programmes provides principles that may be applied to inform the integration, scale-up, and targeting of case detection and management.

While prevalence surveys on the scale implemented for PC-NTDs are not feasible for mapping most CM-NTDs, sub-nationally representative prevalence surveys are useful in specific contexts, especially in the evaluation of routine surveillance data. Prevalence estimates can be compared to the rate of new cases detected through routine surveillance to indicate the rate of under-detection and identify facilities or zones which are under-performing. In such contexts, integrated surveys for CM-NTDs could improve efficiency, and as with integrated surveys for PC-NTDs, this is optimised when there is a common platform for diagnosis [67, 83, 84]. For diseases with strong environmental drivers, modelling

predictions may help to improve survey efficiency, or indicate areas suitable for the disease but without known patients, which may harbour unidentified cases.

Evidence-based decision-making relies on the availability of quality data accessible to decision makers, so will require strengthening of facility-based recording of NTD indicators, and their inclusion in national health information systems [76, 85]. However, interpretation of epidemiological data should be made cautiously and with reference to existing control activities and indicators of health service coverage. Further, the monitoring of access to CM-interventions by demography, geography, and socioeconomic characteristics could provide a useful metric of health equity [86]. This contextual information would help to ensure that decisions on where to intensify, adapt, or scale-down interventions and surveillance do not exacerbate existing health inequalities reflected by routine data, and inform more inclusive and equitable interventions. I explore these issues and potential solutions further in the next section, through a critical account of the publications within this portfolio.

5. Critical Account of Published Works

This portfolio of five research papers, published between 2018 and 2022, addresses ways in which routine surveillance data and complementary information sources can be used to inform equitable expansion and integration of case detection and management interventions against NTDs.

5.1. Describing data routinely available in Ghana

Portfolio publication: Simpson, H., Quao, B., Van Der Grinten, E., Saunderson, P., Ampadu, E., Kwakye-Maclean, C., Odoom, S., Biritwum, N.K., Pullan, R. and Cano, J., 2018. Routine surveillance data as a resource for planning integration of NTD case management. *Leprosy Review*, 89(3), pp.178-196.

In 2016, American Leprosy Missions launched the AIM (Accelerating Integrated Management) Initiative, a special programme focusing on partnerships with ministries of health [87]. It aimed to build capacity for data visualisation and use, integrate strategies and systems, target resources, and improve access to care for people affected by NTD morbidity [87]. The AIM Initiative supported this study, which was conducted in collaboration with their partners from the Ghana MoH.

Recognising the need for compilation of surveillance data as a first step to planning integration of MMDP for skin-NTDs, I worked with NTD control programme managers in Ghana to collate their surveillance data into a single electronic database, with skin-NTD morbidity summarised at community- and heath facility-levels. I interviewed programme staff to understand the recording and reporting processes and the flow of data through the surveillance systems. This collaboration provided an insight into programmatic priorities and the challenges they faced in collating, storing, and managing surveillance data. I aimed to map the geographical distribution of skin-NTD morbidity to identify suitable health facilities for the piloting of integrated MMDP, and then investigated rates of reported disease and the risk of more severe morbidity within and beyond 5km from primary healthcare facilities.

The epidemiological data were collected by national NTD control programmes as part of their routine surveillance and control activities. These included passive detection (for leprosy & BU), active case search in known hotspots (for BU), and exhaustive screening by CDDs during MDA for LF morbidity. After compiling the data into a single database, I georeferenced reported cases to community level using online tools. I obtained a list of georeferenced health facilities in Ghana [88] and measured the distance from each recorded and georeferenced case to the nearest health facility. I defined zones of higher and lower geographical accessibility using buffers of 5km radius around each mapped health facility, and estimated rates of recorded disease and more severe morbidity within these zones.

Overlap of skin-NTD morbidity was identified at many health facilities in the Upper West Region and in parts of Greater Accra (containing the capital city). However, I was concerned that the mapped morbidity reflected differences in case detection and recording, especially given the higher level of

morbidity overlap in and around the main city. This was supported by the observation that rates of reported disease were higher in the population within 5km of a PHC facility, suggesting under-detection from populations with lower geographical access to health facilities. However, this relationship was reversed for leprosy and BU when non-georeferenced cases were assumed to occur in zones of low accessibility, suggesting that the association may have been due to bias in geo-location data, which was likely to have been less complete for remote locations. I also found that zones of lower accessibility had a higher proportion of leprosy cases with disability at diagnosis, suggesting more advanced disease, although this association was not observed for BU cases.

The completeness of disability grading data for leprosy cases was also lower in zones of low accessibility, further suggesting a burden of unrecorded morbidity in populations further from health facilities. This introduces a problematic bias for decisions around where to implement integrated MMDP services: targeting to known cases risks exacerbating health inequalities related to service accessibility. While cases known to the health system may be a good starting point for piloting of integrated MMDP, this work emphasises the need for strengthened case finding activities, especially in areas of lower accessibility, to inform an equitable MMDP strategy.

When this paper was published, I wrote that it would be 'critical to update these maps with current data' as surveillance and control activities continued. I anticipated that the mapping could be repeated each year by control programme staff within Ghana, following training in GIS. However, I now believe that it would be most appropriate for this mapping step to be automated within a health management information system. Working on the Skin Health Africa Research Project (SHARP), I learnt that the GHS has recently piloted and is in the process of rolling out a national patient information management system for electronic recording and reporting of health data. Supporting the functionality of this system, and its suitability for use at lower levels of the health system will be essential for its utility as a tool to support decision making.

How this paper has contributed to the field

This work was presented by Dr Paul Saunderson in 2015 in a breakout session on MMDP at the annual meeting of the Coalition for Operation Research on NTDs (COR-NTD). This meeting provides a forum through which researchers, the WHO, programme managers, implementers and donors meet to discuss current issues and research priorities in the field of NTDs. This paper appears to have helped shape the research agenda of the Global Partnership for Zero Leprosy (GPZL), established in 2018 and aligned to the WHO global leprosy programme and other large stakeholders and collaborations. A commentary describing the agenda of the GPZL in *Infectious Diseases of Poverty* [89] cited this paper as an example of implementation research strengthening the quality of leprosy data. Further papers

from GPZL sub-groups reference this work as an example of the use of GIS to link geography to health metrics [90, 91]. The report from the Subgroup on Epidemiologic Modelling and Socioeconomic Research recognises that the mapped data 'may not adequately reflect the true burden of disease because of the variable quality of case-finding', and raises the need for research to optimise surveillance methods to better capture the true burden of leprosy.

This paper has also been used as a reference for the distribution of skin-NTD cases in Ghana in papers on molecular biology and health services [92, 93]. Another paper cited this work as an example of using reported cases to identify potential hotspots for targeted post-exposure prophylaxis for leprosy, although this work did not acknowledge the potential bias introduced by variation in case detection methods [94].

Following the experience I gained from this work, I contributed to the AIM Initiative protocol for integrated mapping of NTDs, their data visualisation guidelines, and to strategic plans for integrated MMDP in Ghana and Ethiopia. I also delivered training in GIS to NTD programme staff in Nigeria and Myanmar, and produced interactive web-maps of reported cases skin-NTDs in Cameroon, Nigeria, and Myanmar.

5.2. Synthesising epidemiological data into evidence

Portfolio publication: Simpson, H., Deribe, K., Tabah, E.N., Peters, A., Maman, I., Frimpong, M., Ampadu, E., Phillips, R., Saunderson, P., Pullan, R.L. and Cano, J., 2019. Mapping the global distribution of Buruli ulcer: a systematic review with evidence consensus. *The Lancet Global Health*, 7(7), pp.e912-e922..

After my work mapping reported CM-NTDs in Ghana, I was interested in further exploring the impact of health system and surveillance factors on epidemiological indicators of disease occurrence. I was motivated to focus specifically on BU not only because it is typically under-diagnosed, but also because my reading of the literature revealed substantial outstanding questions around its epidemiology, including its reservoirs, transmission route, and environmental drivers [14]. Recognising that available data on BU provides at best, an under-representation of the occurrence of this disease, and at worst, a biased representation, I wanted to explore whether factors relating to under-detection and reporting could be used to evaluate the evidence for disease absence in areas with no cases known to the health system. Following the use of evidence-based consensus approaches to compile and grade evidence for the endemicity of diseases including dengue and the leishmaniases [95, 96], I developed a similar framework. Alongside data from literature review and surveillance data from countries I had worked with through the AIM Initiative, I additionally incorporated indicators of health system strength, and the endemicity of diseases sharing clinical features with BU, which might mask incident BU due to misdiagnosis.

Through this evidence consensus framework, each country was assigned a score representing evidence of BU presence or absence. The evidence consensus score consisted of three components: 1) endemicity status according to the WHO and GIDEON (the Global Infectious Diseases and Epidemiology Network); 2) a data quality score, representing the contemporariness of case detection and specificity of diagnostic techniques used; and 3) the total number of cases from the literature review and surveillance data. Each of these components was represented by a numerical score with higher positive numbers representing stronger evidence. Consensus presence was assigned if cases had been reported to WHO between 2002 and 2018; BU had been reported through GIDEON; at least one laboratory confirmed case had been recorded in peer-reviewed literature or by the national programme (for countries which had contributed surveillance data); and if a threshold number had been reported from all sources. I also applied a sub-national evidence consensus, grading the strength of evidence for BU in upper sub-national administrative areas in which the disease had been reported.

To represent evidence for absence, I planned to include an indicator of health system strength, and another representing the likelihood of BU cases being misdiagnosed as another endemic condition with similar clinical features to BU. For the first, I used a proxy measure: average per capita national

health expenditure from 2011- 2015 from all financing sources, reported by the WHO [97]. This had been used as a proxy for surveillance strength in an evidence consensus exercise to refine the global limits of dengue [95]. The indicator of potential for misdiagnosis was based on the endemicity of skin diseases sharing common features with BU (nodules, plaques, oedema and ulcers). The misdiagnosis score was adjusted by the health system score to represent a lower likelihood of misdiagnosis in countries with higher health expenditure, assuming a higher diagnostic capacity. Consensus absence was assigned to countries with no evidence of BU cases reported through WHO or GIDEON, or in peer-reviewed literature, no evidence of endemicity of the potential confounding diseases considered, and high health expenditure.

As well as defining countries and sub-national areas with strong evidence of BU cases, including 12 countries with consensus presence, the results highlighted countries where there was weaker evidence- perhaps with sporadic or historical cases. It also represented those with indeterminate evidence of BU- including Burkina Faso, Ethiopia, Honduras, Indonesia, Malawi, Malaysia, and Suriname, and those with weak evidence of absence- notably Niger, Eritrea, The Gambia, and Mauritania. These countries have lower health system strength and are endemic for diseases which present similarly to BU. Additionally, most were located near countries with evidence of BU. Taken together, this evidence suggests potential undiagnosed or misdiagnosed cases of BU. These countries could be targets for further investigation to determine BU endemicity. Suitable approaches might include a review of cases of skin diseases by an expert dermatologist from a BU-endemic country, or an integrated skin survey targeting other diseases but with support to test cases suspect for BU.

I explored several strategies to combine and weight evidence for BU endemicity and potential causes of under-detection, but ultimately presented results only for the final framework. A more transparent approach could have included a range of weights for different components of the framework, and mapped the variation in the evidence consensus scores generated. This would have allowed me to explore and express the influence of the various assumptions made, including potentially unreliable proxies such as the use of health expenditure to represent health system and surveillance strength. Additionally, integrating expert opinion from dermatologists with experience of working in the potentially endemic countries would also have added further nuance to the results presented.

How this paper has contributed to the field

This publication has become a contemporary reference paper on the distribution of BU, cited by over 40 diverse articles from the fields of epidemiology [98-100], genetics [101-104], immunology [103, 105-113], clinical medicine [114-116] and bioinformatics [117-119]. These contributions are

anticipated to support the development of new treatments for and vaccines against BU, and improved understanding of disease transmission and risk factors.

Through this work I also compiled large geographical datasets of observations of BU and its causative agent, *M. ulcerans*, reported in the literature, and made these datasets available via the LSHTM Data Compass [120]. Comparable datasets exist for the leishmaniases [121] but not for other CM-NTDS, making this a relatively unique contribution. These data have so far been downloaded 84 times. The article was also shared widely on Twitter to reach a large audience.

5.3. Modelling disease suitability using secondary data and evidence consensus

Portfolio publication: Simpson, H., Tabah, E.N., Phillips, R.O., Frimpong, M., Maman, I., Ampadu, E., Timothy, J., Saunderson, P., Pullan, R.L. and Cano, J., 2021. Mapping suitability for Buruli ulcer at fine spatial scales across Africa: a modelling study. *PLoS neglected tropical diseases*, 15(3), p.e0009157.

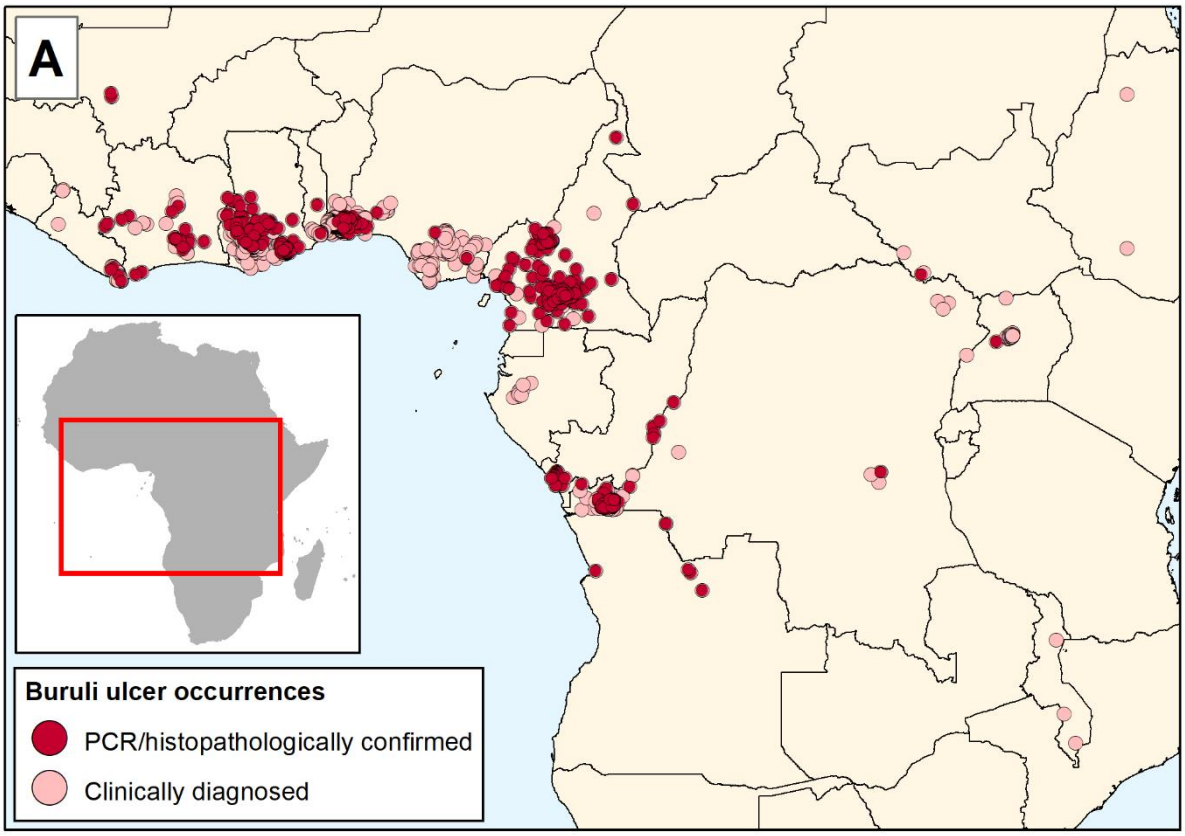
Having identified evidence for BU or its possible under-detection beyond the known endemic range, I wanted to investigate the application of environmental modelling to predict fine-scale suitability for the disease. I used an approach termed Species Distribution Modelling (SDM), or Ecological Niche Modelling (ENM), originally developed to predict the distribution of plant and animal species based on environmental correlates [53], and more recently developed to predict risk or suitability for infectious diseases. Examples of SDM for disease suitability include malaria [122], dengue [95], the leishmaniases [96], LF [9], and Human African Trypanosomiasis [123].

The data I used entailed 3 particular challenges for model development: 1) they were collected over a long period of time (approximately 60 years) and using different methods of confirmation (clinical diagnosis, microbiological confirmation, molecular confirmation); 2) there were very few absence points relative to the dataset size; and 3) they were biased due to geographical differences in surveillance and data collection activities. Such challenges are common to datasets compiled through non-standardised approaches, and particular approaches within the SDM framework are available to account for these issues. However, decisions about how these approaches are implemented can impact the accuracy of SDMs to varying extents [124]. A final challenge was the selection of candidate model predictors, especially given uncertainty about the precise transmission routes of BU. In this section I discuss the development and refinement of the BU suitability models with reference to these four challenges.

1. Variation in date of case detection and confirmation methods

In the evidence consensus work, I had considered how historical cases, and those without laboratory confirmation contributed relatively lower evidence of BU, and had assigned ‘data quality ’scores based year of detection and method of confirmation (highest for PCR-confirmed cases, slightly lower for those confirmed by other methods, and lowest for those diagnosed on clinical grounds only; Figure 2).

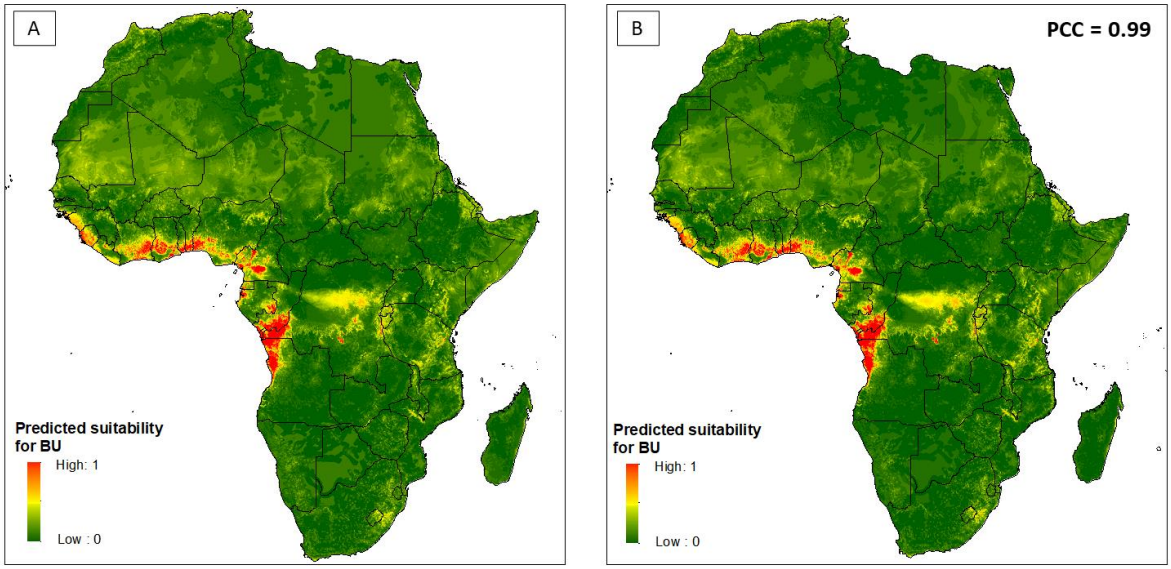
Figure 2: Distribution of Buruli ulcer cases in Africa by method of diagnosis.



Country boundaries from the Database of Global Administrative Areas (GADM) [125]

I used these scores to weight data points included in the main model, so that older and non-PCR confirmed records had relatively less influence. I compared an initial model with cases weighted using this scheme to one in which all points had equal influence, and found that the relative weighting of occurrence points had a very small effect on the model (Figure 3).

Figure 3: Comparison of BU suitability models A) with occurrences weighted by the date and method of diagnosis; B) with occurrences weighted equally.



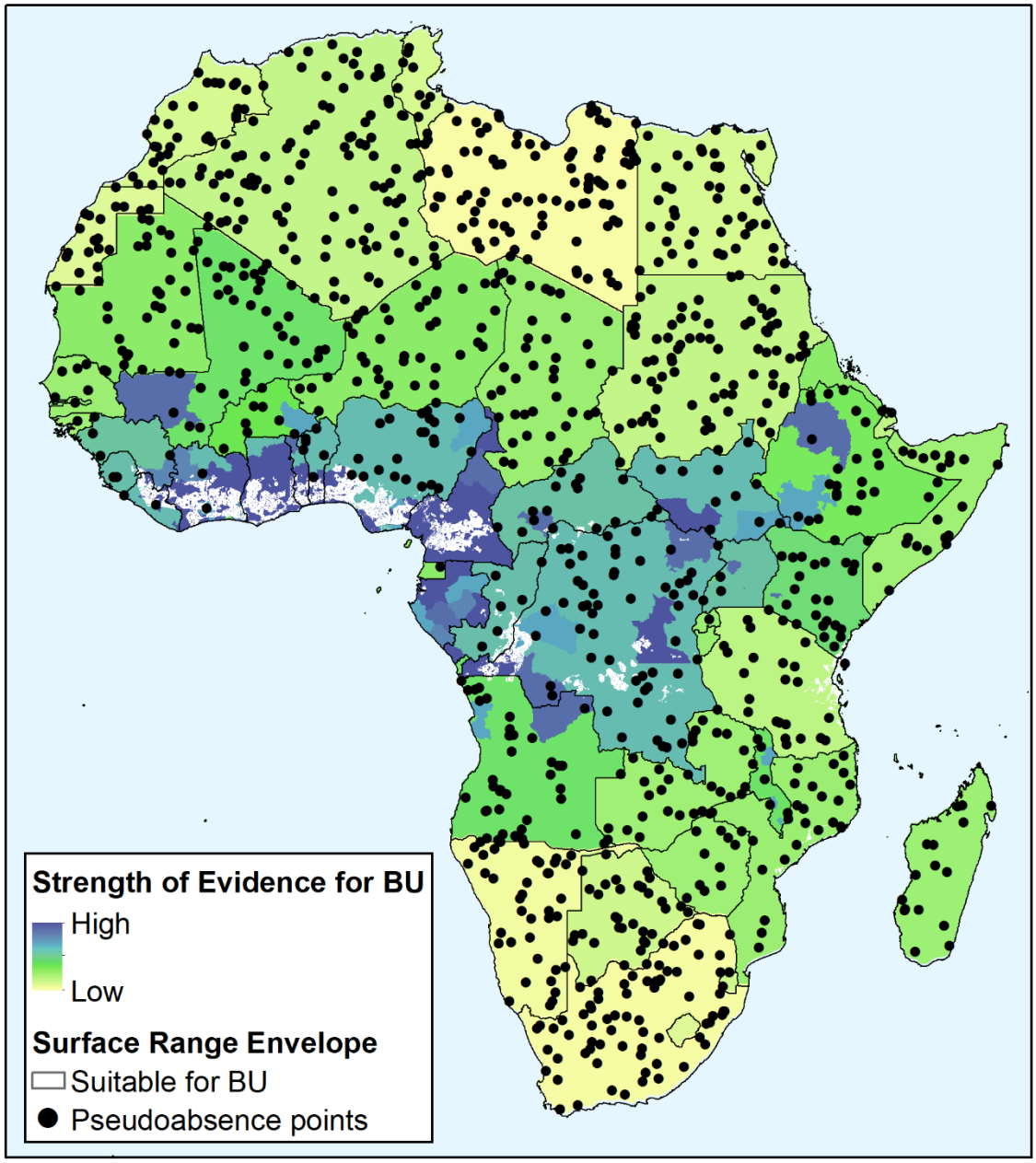
Country boundaries from the Database of Global Administrative Areas (GADM) [125]

2. Accounting for the lack of absence data

Since true absence of a disease or species from a study area is difficult to demonstrate with certainty, SDM often incorporate 'pseudoabsence points': datapoints systematically generated prior to model development and used as a comparator class. Different approaches are available to select pseudoabsences - at random; within a limited distance from presence points (spatial restriction); or based on environmental conditions (environmental restriction) [124]. Environmental restriction may be according to known limiting conditions [9] or simple environmental profiling methods [126]. The most suitable approach depends on the number of occurrence points, the size of the study area, and the modelling approach used [124, 127]. Authors often use the term 'pseudoabsence' interchangeably with 'background' to mean model negatives which either characterise the environment in areas where the disease or species is unlikely to occur, or capture available conditions across the study area [124]. I see a useful distinction between these definitions, so use 'pseudoabsence' to refer to model negatives intended to represent absence of the target disease or organism, and 'background' when no assumption is made about presence or suitability.

I used environmental restriction to limit the selection of pseudoabsence points to areas outside of the potentially suitable area for BU. I extracted the values of the selected predictor variables at occurrence locations and used the *biomod2* package [128] to produce a surface range envelope, delineating the area containing values between the 2.5th and 97.5th percentiles of these predictors. I then used the results of the evidence consensus [120] to bias selection of pseudoabsences towards areas with lower evidence for BU (Figure 4).

Figure 4: Pseudoabsence selection using environmental restriction and evidence consensus

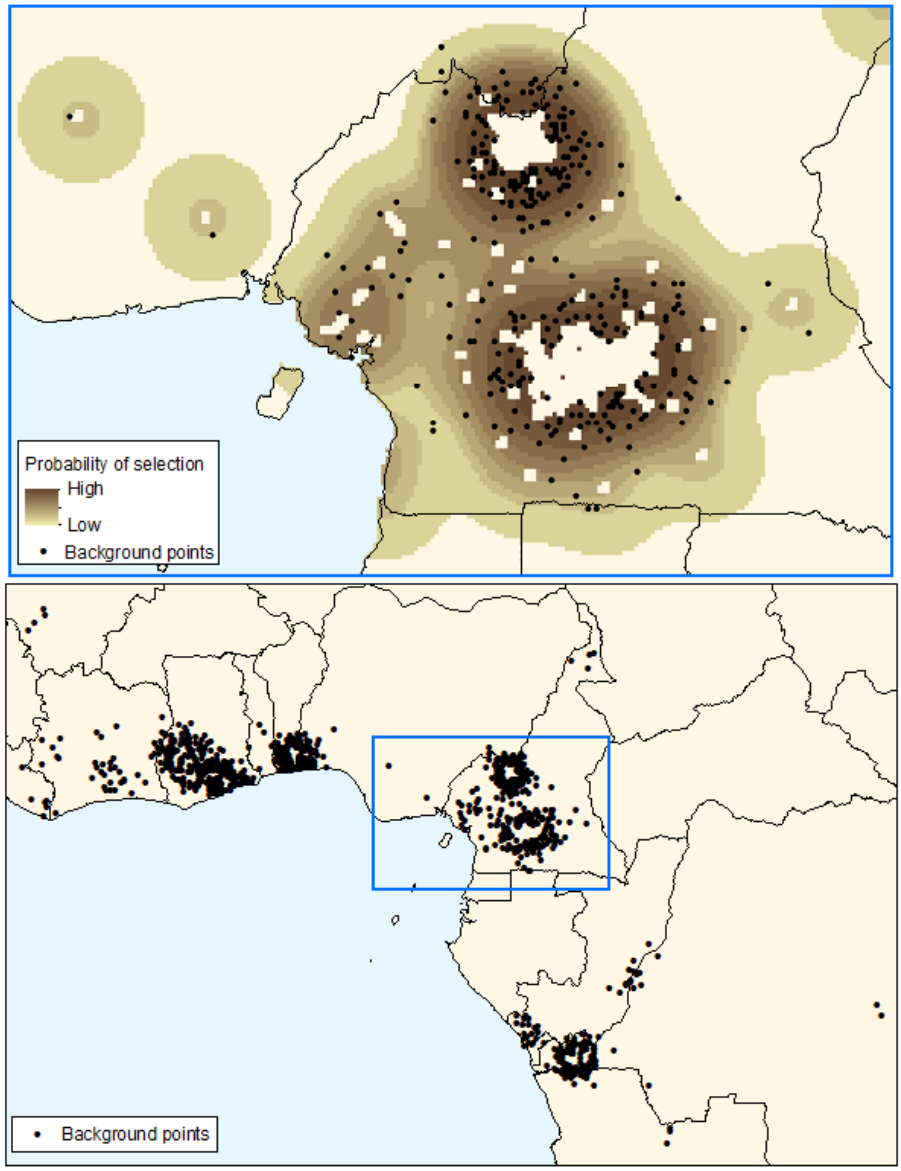


Country boundaries from the Database of Global Administrative Areas (GADM) [125]

3. Biased distribution of occurrence points

I sought to address the biased distribution of occurrence points by generating background points with the same geographical bias as occurrence points, using a kernel density surface around occurrences (Figure 5). To prevent contamination with presence locations, I restricted selection to at least 5km from occurrence points, and up to 150km. I believe I developed this method independently, but between initial submission of this paper and peer review, a similar approach was used by another group and termed 'background thickening' [129].

Figure 5: Selection of background points representing geographical bias of occurrence points

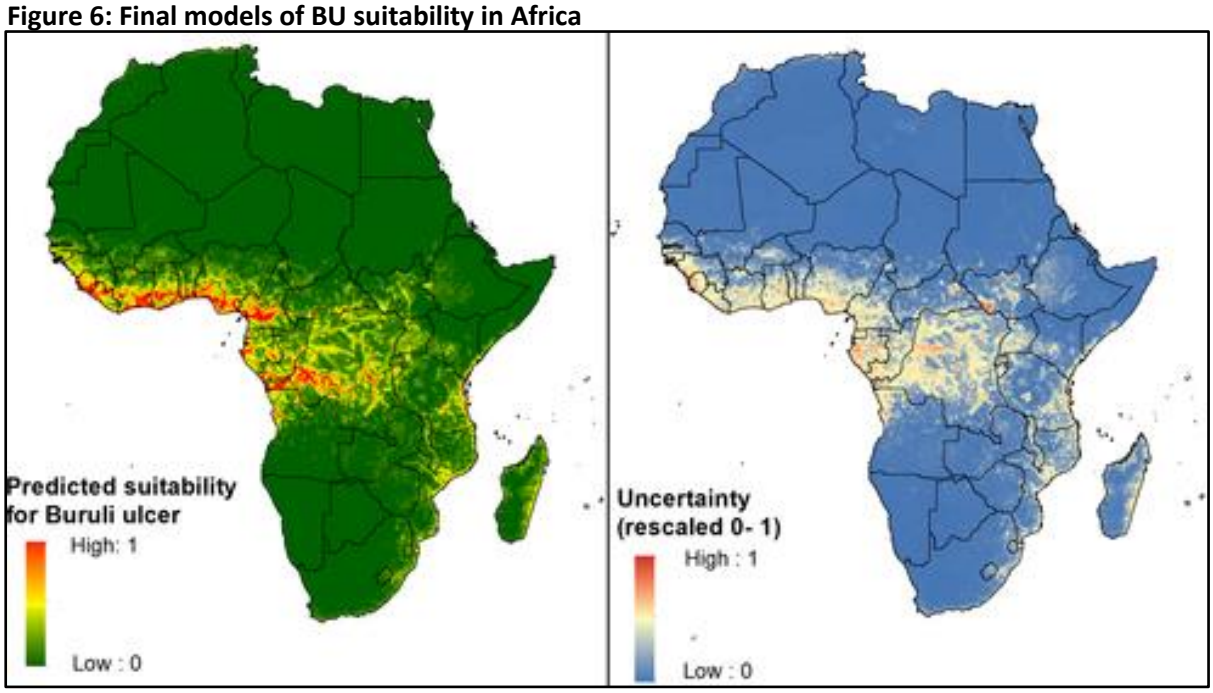


Country boundaries from the Database of Global Administrative Areas (GADM) [125]

4. Covariate selection

In the initial models I ran, I used a wide set of candidate predictors representing climatic, topographical and hydrological conditions, human influence, and the modelled distributions of hemipteran families purported to act as reservoirs for *M. ulcerans* [130]. Peer reviewers suggested it would be more appropriate to limit covariates to those considered most relevant to the ecological niche of the bacterium or disease, so for the final models (Figure 6) I reselected 14 variables with reference to existing literature.

Figure 6: Final models of BU suitability in Africa



Country boundaries from the Database of Global Administrative Areas (GADM) [125]

The process of refining these models reinforced my appreciation of how methodological decisions at various stages of model development can result in remarkably different predictions from the same epidemiological dataset. Many of the models I produced performed well according to internal validation statistics, often the only indicators of performance published alongside model predictions. While there has been quite extensive (mostly theoretical) discussion of methods for selection of background/pseudoabsence data [124], ENM/SDM analyses often use automated background selection [131-133], without reporting how different comparator datasets impact results. I recognise that the model presented here is only one of a range of possible outcomes of an SDM approach to predicting BU suitability. The uncertainty shown in the results represents only the relative uncertainty imparted by variation in the results of different models included within the ensemble. In reality, there are numerous sources of uncertainty and error not captured by this measure. Firstly, the majority of records were geolocated remotely, introducing imprecision [134]. Most cases were georeferenced to their nearest mapped community, which is unlikely to represent their exact location. Even for precisely geolocated cases, these coordinates may not represent the location at which they were infected. Error was also introduced by the covariate datasets used, partly because of errors in remotely sensed or modelled covariates, and also because they may not align temporally with the dates of case occurrence. For example, the bioclimatic variables [135] represent average conditions between 1970 and 2000, which may have changed systematically since then. Additionally, the variable representing distance to the nearest dam was constructed based on dams recorded on OpenStreetMap in 2018. Cases may have occurred in a location where a dam was later constructed, and so be erroneously associated with this covariate.

How this paper has contributed to the field

I presented this work, alongside findings from Paper 2, at the annual meetings for COR-NTD and the American Society for Tropical Medicine and Hygiene in 2019. This paper has been referenced in studies of the transmission and prevalence of BU [67, 100] and a book chapter on BU surveillance [136]. After this work, I supervised a PhD student to develop national-level SDM of mycetoma suitability in Sudan [137], and contributed to a paper modelling suitability for podoconiosis in Africa [138].

I consider this paper complementary to Paper 2, providing a more refined representation of potential BU occurrence, and suggesting suitability in some countries with no previous cases of PCR-confirmed BU, including Sierra Leone and Equatorial Guinea. These results could be used to target case searches to areas where suitable conditions for BU are met, ideally prioritising the validation of areas predicted suitable but where cases are currently not reported. Using the predicted risk surfaces could potentially reduce costs compared to random surveys, as was achieved in a nationwide survey for podoconiosis [66].

5.4. National-level evidence consensus to target case finding activities

Portfolio publication: Simpson, H., Panicker, K.N., George, L.S., Cano, J., Newport, M.J., Davey, G. and Deribe, K., 2020. Developing consensus of evidence to target case finding surveys for podoconiosis: a potentially forgotten disease in India. *Transactions of The Royal Society of Tropical Medicine and Hygiene*, 114(12), pp.908-915.

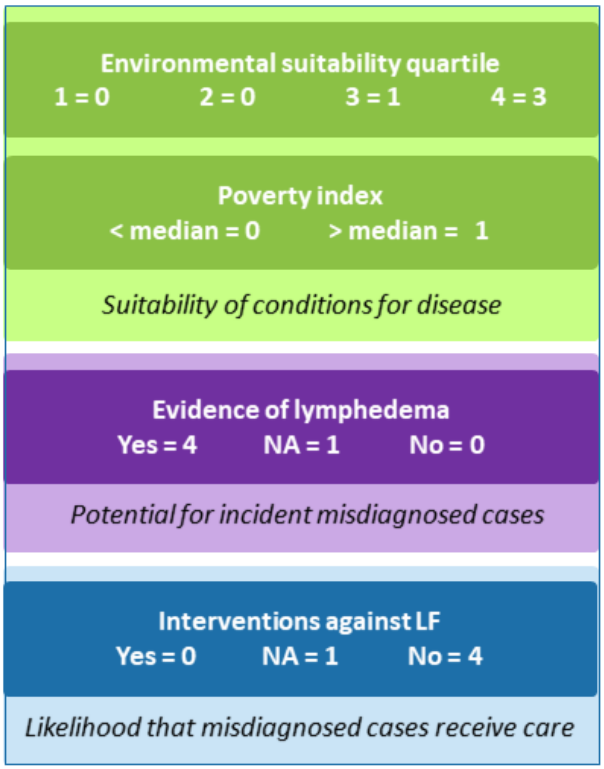
Podoconiosis is a non-infectious tropical lymphedema, which presents similarly to filarial lymphedema but is caused by exposure to barefoot exposure to mineral particles in genetically susceptible populations [13]. In 2018 I started working with collaborators on the Global Atlas of Podoconiosis (GAP) project, based at Brighton and Sussex Medical School. This provided opportunity to further explore how surveillance data, disease suitability models, and other information could be used to target active case finding. The GAP included population-based surveys to estimate the burden and distribution of podoconiosis, and the data generated through these activities were used to develop SDM, building upon the one I developed for BU. Another aim of the GAP was to confirm endemicity status in countries where evidence for the disease was indeterminate, including India, where there was historical evidence of clusters of lymphedema in areas non-endemic for LF [139], but no active reporting [140]. There is a high burden of lymphedema in India as the country is endemic for LF, and we posited that incident cases of podoconiosis there might be misdiagnosed as filarial lymphedema.

Based on my experience of using evidence consensus to synthesise global evidence for BU occurrence, I considered this a suitable framework to combine evidence on suitability for the disease, the incidence of lymphedema, and the implementation of MMDP services. As the survey was planned to be led by researchers in India, and potentially scaled-up to a national programme for podoconiosis control if cases were confirmed, public health experts in India were engaged at an early stage. Clinicians and researchers in community medicine and public health from each of the 36 states and union territories in India were invited to a workshop at the Amrita Institute for Medical Sciences. At this workshop, I gave a presentation on risk factors for podoconiosis, and showed the results of extrapolating the environmental suitability model (based on surveys in Africa [138]) to India. We discussed the caveats and limitations of this model, including the fact that we could not be certain that the environmental associations of podoconiosis in Africa could be applied in India. We also discussed how environmental suitability would not necessarily equate to endemicity for a variety of reasons, focusing on the social determinants of the disease such as poverty, agricultural practices, and lack of shoe-wearing.

I then led a session in which representatives discussed the possibility of podoconiosis in districts within their states, based on environmental and social factors, the incidence of lymphedema, and the

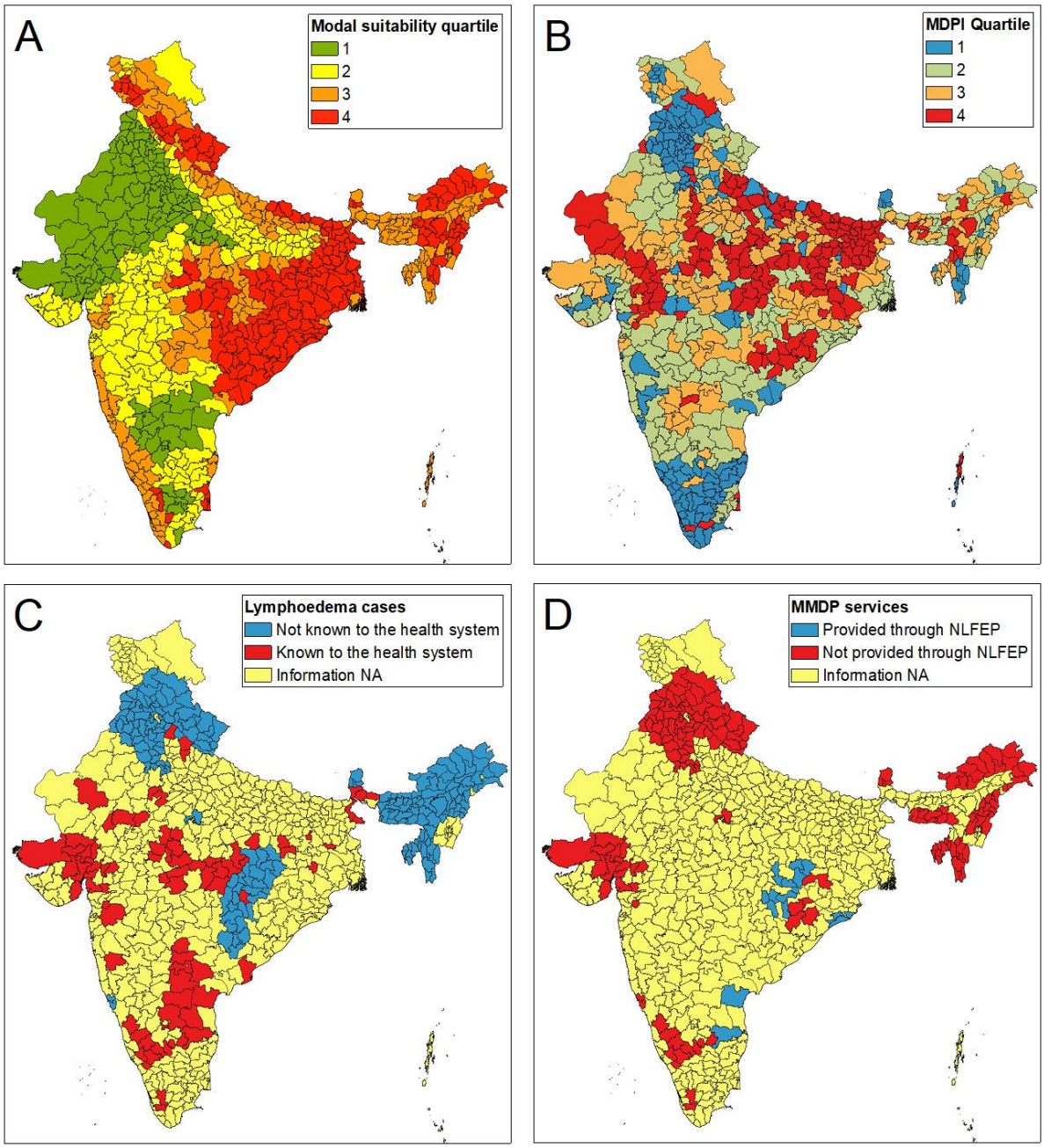
implementation of MMDP for LF. Through discussions at the workshop, I developed a district-level evidence consensus framework to combine and score four relevant sources of information (Figure 7).

Figure 7: Component scores used in the evidence consensus framework to prioritise the podoconiosis survey



Through the evidence consensus framework, districts were assigned four component scores, reflecting A) environmental suitability (based on the extrapolated model), B) social determinants (using a multi-dimensional indicator of poverty from a secondary source [141]), C) cases of lymphedema known to the health system and D) implementation of interventions against LF (Figure 8). Unfortunately, there were substantial missing data on the distribution of cases known to the health system and the implementation of LF MMDP services. Service provision indicators might have been obtainable if we had collaborated with the National Vector Borne Disease Control Programme (NVBDCP), which is a consideration for similar approaches in the future.

Figure 8 A-D: data sources used in the evidence consensus to target podoconiosis survey in India.



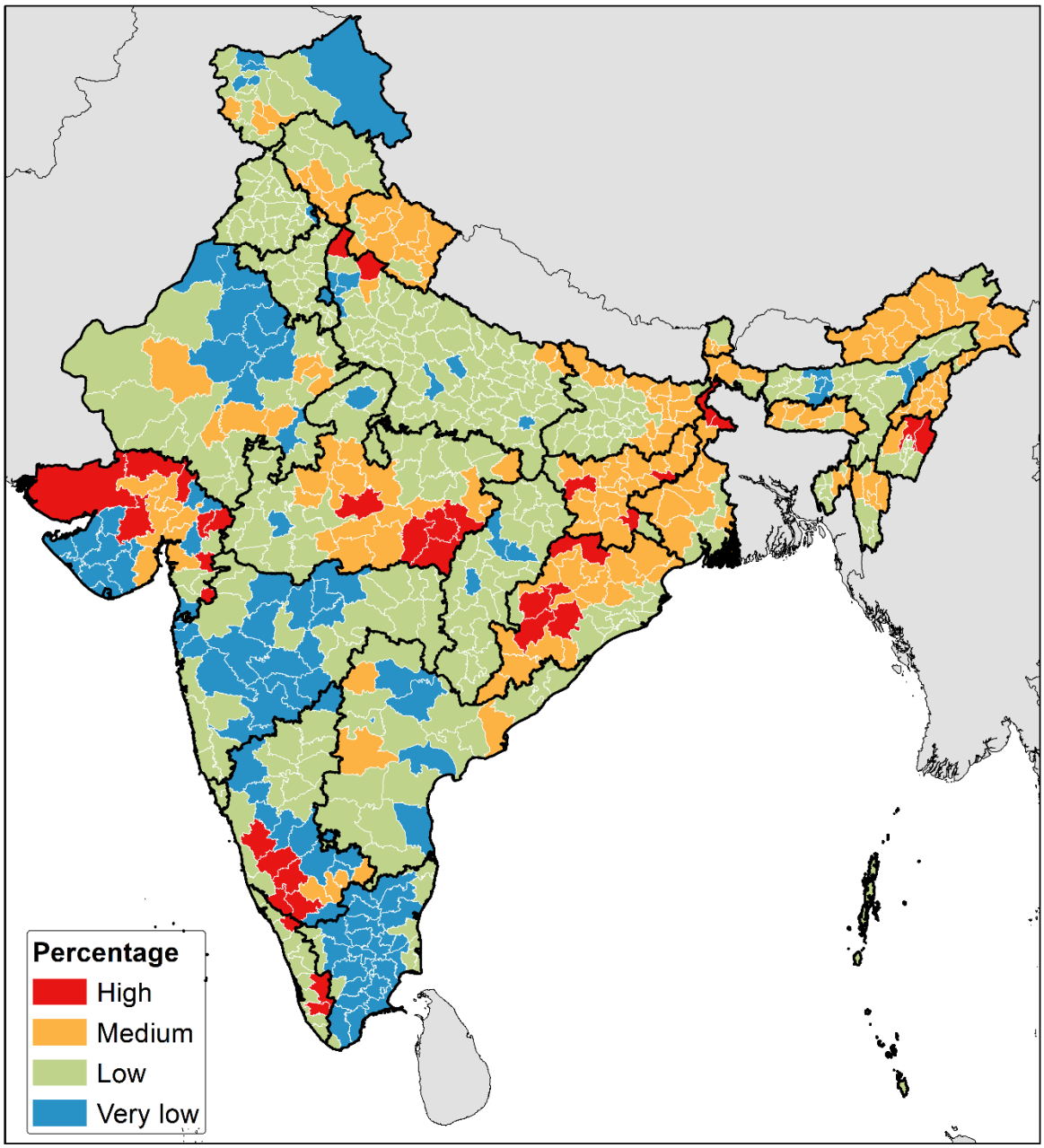
District boundaries from the Database of Global Administrative Areas (GADM) [142]

The four component scores were summed to give an overall prioritisation score, and districts were then classified as high, medium, low, or very low priority for case search activities (Figure 9).

How this paper has contributed to the field

This study informed the selection of a district in south India for a podoconiosis survey which was implemented through the GAP project. No cases of podoconiosis were identified, providing strong evidence that the district is non-endemic for podoconiosis. However, other priority districts need to be investigated before the country can be considered non-endemic.

Figure 9: Categorisation of districts in India by priority for pilot surveys for podoconiosis.



District boundaries from the Database of Global Administrative Areas (GADM) [142]

This exercise demonstrated how primary and secondary data and expert opinion can be translated into evidence for strategic prioritisation of public health control activities. The participation of national public health experts throughout this project was key to ensuring engagement and leadership within the country. This is certainly an approach I would use again to engage local experts and encourage the use of data to inform decision making in public health programmes.

5.5. Development & evaluation of community-based surveillance tools

Portfolio publication: 5. Simpson H, Konan DO, Brahima K, Koffi Jd, Kashindi S, Edmiston M, et al. (2022) Effectiveness of community-based burden estimation to achieve elimination of lymphatic filariasis: A comparative cross-sectional investigation in Côte d'Ivoire. *PLOS Glob Public Health* 2(8): e0000760. https://doi.org/10.1371/journal.pgph.0000760

Having previously undertaken research using secondary data, this project provided an opportunity for direct involvement with a programmatic case finding activity, and practical experience of primary data collection. Along with LSHTM supervisors, I worked with the Cote d'Ivoire NTD Programme (NTDP), sociologists at the Centre Suisse de Recherches Scientifiques en Côte d'Ivoire (CSRS), and the AIM Initiative. The aims were to evaluate the cost, coverage, equity, and reliability of community-based screening (CBS) for LF morbidity in Côte d'Ivoire.

As part of their LF elimination plan, the Ivorian NTDP had recently started implementing CBS, with CHWs and CDDs screening for leg swellings and scrotal swellings during MDA. We strengthened the existing approach by improving training materials, supervision, and recording forms, and decoupling it from MDA to reduce the task-load on enumerators. We evaluated the reliability and equity of this strengthened CBS strategy using a population-based prevalence survey employing eighteen purpose-trained local nurses.

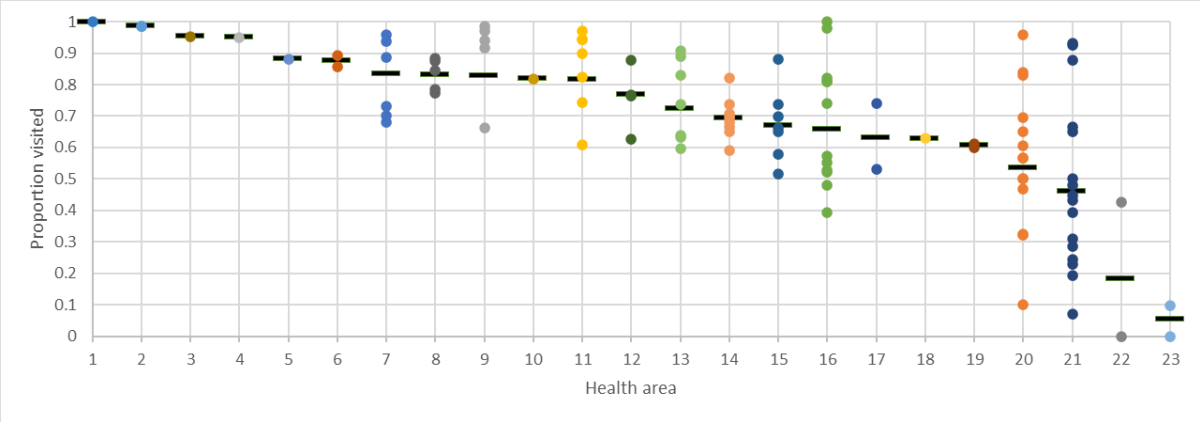
I developed training materials, paper-based recording forms and a two-stage training cascade to train 24 health area supervisors (stage 1) who then trained 220 CHWs and CDDs in their areas (stage 2) to implement CBS. Importantly, the first stage of the cascade included detailed and practical training on LF morbidity diagnosis and management, to ensure appropriate local care for cases identified through the screen. I designed electronic data collection forms for entry of data from the paper-based CDD recording forms and for mobile-based data collection during the survey. I also selected the clusters for the population-based prevalence survey, following the design of the WHO protocol for trachomatous trichiasis surveys [60]. During the data collection activities, I acted as field coordinator along with two CSRS sociologists, troubleshooting issues with the protocol, questionnaire forms, and diagnostic process. I also monitored and analysed the data.

The survey confirmed reliable prevalence estimation of lymphedema by CDDs, with a prevalence ratio (PR) of CDD-identified leg swellings to confirmed filarial lymphedema of 1.13 (95% confidence interval [CI] 0.97- 1.31). CDDs overestimated hydrocele prevalence (PR of 2.93 [95% CI 2.46- 3.55]), explained at least in part by the fact that the screening was not intended to distinguish hydrocele from hernia. The PR of scrotal swellings identified in CBS to those confirmed in the survey was 1.06 (95% CI 0.93- 1.21) indicating reliable estimation with reference to the case definition used. Based on re-examination of CDD-identified cases by nurses, we estimated 77.5% (95% CI 69.0- 84.6%) of leg

swellings identified by CDDs were due to filarial lymphedema; 34.0% (95% CI 27.3- 41.2%) of scrotal swellings identified by CDDs were due to filarial hydrocele; and 93.7% (95% CI 89.3- 96.7%) were confirmed to have scrotal swelling.

Household coverage by CDDs during CBS was 64.3% (95% CI 63.2–65.3%), which we considered a positive result with reference to the WHO target for effective coverage of LF MDA (65%) [49]. However, this level of coverage would not be sufficient for comprehensive case detection, suggesting that additional case identification activities may be required in areas shown to have higher prevalence. Household coverage varied substantially by health area (from 5.3% [95% CI 1.7-9.8%]- 100% [95% CI 95.0-100%]), being driven by variation between CDDs within these areas (Figure 10). The health areas with the highest proportions of households visited were small zones with a low number of CDDs. There were two outlying health areas in which the mean proportion of households visited was less than 20%. My personal interpretation of these low coverage rates is that they reflect a lower quality of supervision of CDDs: in one of these areas, the supervisory health worker was away during the enumeration activity, and in another, the supervisory health worker was newly recruited and relatively inexperienced.

Figure 10: Proportion of households visited by CDDs (as reported by household heads) during community-based screening for lymphatic filariasis morbidity in Bongouanou, Cote d'Ivoire, at health area and CDD-zone level.



Black bars show the mean proportion of households reporting visitation by CDDs within health areas, coloured points show the proportion of households reporting visitation by CDDs within CDD zones.

We found some evidence that households of certain minority languages and of lower socioeconomic status were less likely to have been visited, indicating potential to improve equity with adjustments to the approach. The overall direct financial cost of CBS was $26,678.36 USD, the cost per case confirmed was $69.62, and that per person targeted was $0.17. With comparison to the costs of other NTD control activities, this appears scalable: the cost per person screened was comparable to the cost per person treated through MDA in African countries [143], and substantially lower than the cost per

person examined in the global trachoma mapping project ($4.20 in Côte d'Ivoire in 2015) [144]. The cost per case found was also low with reference to published estimates from CBS for leprosy, ranging from $72 (in Mali, 1999)- $313 (in Nigeria, 2002) [145].

Designing, implementing, and analysing data from a population-based prevalence survey provided useful experience which I have since applied to other research projects in Ghana and Uganda. It also gave me an appreciation of the utility of this approach for the validation of routine surveillance data, balanced with the need to rationalise the implementation of such resource intensive activities. Although prevalence surveys do not provide externally representative prevalence data, they should be expected to provide evidence generalisable to other (similar) settings; for example by indicating whether an existing routine surveillance approach is suitable or requires modification. In design, the evaluation survey was analogous to MDA coverage surveys, which are expected to be undertaken by NTD programmes implementing MDA. As such, similar evaluations of CBS could be delivered by programmes for the monitoring and evaluation of LF MMDP activities.

How this paper has contributed to the field

Following this study, I engaged with the NTDP to support the scale-up of the CBS exercise to a national activity. This included presenting the findings and recommendations at two meetings with the programme, and contribution to reports on CBS activities. I hope the materials available online will support other programmes to implement CBS based on the recommendations emerging from this work [146]. As the activity is scaled up, we might expect a reduction in CBS coverage and the reliability of case identification without the involvement of an on-site field team for supervision. This question could be explored through a process evaluation at-scale. Scale-up will also require the development of a routine surveillance system for reporting of the data collected, which could be a further element to investigate through process evaluation.

This collaboration gave me an insight into how research embedded within national programmes can both support programmatic aims and be strengthened by expertise from within them. NTDP collaborators reviewed, edited and piloted training and data collection materials, delivered training to supervisors, and helped to supervise CDD training and CBS, ensuring that CBS was wholly delivered as a programmatic activity. Their involvement ensured an excellent level of engagement from the district health team, who selected fieldworkers for the project, ensured that personnel were replaced if they were unable to work, and provided advice on the implementation timeline. I feel this is a good model for collaborative research, and will carry this perspective forward into future projects.

6. Discussion

The current WHO Roadmap for Implementation, published in 2021, builds upon global experiences in NTD control since the 2020 Roadmap. It is founded on three pillars: i) to accelerate programmatic action; ii) to intensify cross-cutting approaches; and iii) to change operating models and culture to facilitate country ownership [147]. It cites two main conclusions from the decade of NTD control to 2020: that PC represents one of the 'best buys' in global public health, and that NTDs are 'critical tracers of equity in access to health services and progress towards UHC' [147]. In this final chapter, I discuss four factors which I consider to have enabled the high cost-effectiveness and the wide reach of MDA: evidence for action; financial support; engagement of community-health staff; and integration of planning and implementation. I consider the relevance of these factors and additional requirements for the next decade of control, particularly in relation to the scale-up of case detection and management interventions necessary to meet WHO Roadmap Goals by 2030.

6.1. Evidence for action

Control through MDA is delivered on the basis of evidence for disease endemicity from mapping surveys, with clear criteria for intervention when prevalence exceeds a certain threshold. The wide implementation of mapping surveys across the WHO African Region provided strong evidence for the burden of PC-NTDs and intervention requirements. Part of the reason for the underfunding of NTD case detection and management interventions is the paucity of data on the prevalence of NTD morbidity, which means the burden of disease is underestimated by existing data sources [34, 148, 149]. According to the WHO Roadmap, critical action on monitoring and evaluation is required to meet targets for nearly all diseases and disease groups. It is noted that 'the need for monitoring and evaluation is greater for diseases targeted for control, for which investment has been limited, particularly for mapping and understanding their burden' [4].

To demonstrate the need for further resource allocation, disease mapping has been described as a pressing issue for skin-NTD control, and integrated skin-NTD surveys have been recommended as a way to spread the costs of prevalence surveys for rare outcomes [147, 148]. An integrated survey for BU, leprosy, yaws, and lymphatic filariasis morbidity in Maryland County of Liberia showed that each of these diseases had a higher burden than indicated by routine data, but that out of all cases of skin disease identified, 91% were diagnosed with a non-skin NTD condition [67]. This is an important consideration for countries initiating integrated programmes with case finding activities, as the existing health system may not have capacity to treat and manage the full burden of disease identified. With this risk in mind, other authors have recommended strengthening of primary healthcare and NTD management as a starting point for integration [150]. These dual needs for

burden estimates to justify service expansion, and for guaranteed provision of immediate and potentially ongoing care for newly identified cases, represent a paradox facing programmes at the earliest stage of implementation of MMDP strategies.

A potential solution, or compromise, may be the development of district-level integrated strategies, starting with initial assessments to define implementation units as endemic or non-endemic for target diseases [83]. This is challenging with conventional methods used to define endemicity, namely population-based surveys or passive surveillance data. The former are typically too expensive to implement for rare diseases at district-level, and the latter prone to miss cases [67].

Modelled disease distributions as a source of information

Data available from surveillance and surveys can be used to model expected distributions of NTDs with important environmental drivers, adding a further source of information for implementation unit-level endemicity classifications. If unbiased survey information on disease prevalence were available at representative locations across potentially endemic areas, these data could be used to and quantify the effect of environmental covariates and spatial dependence, and predict prevalence or occurrence. In reality, such datasets are extremely sparse and mostly originate from accessible and known endemic areas, representing only narrow portions of the range of environmental conditions across areas of interest [151]. The fact that 'presence-only' datasets, such as disease notifications in epidemiology, or species occurrence records in ecology, tend to be larger and represent broader geographical regions and environmental conditions has motivated the development and use of presence-only approaches to species distribution modelling .

Representing background conditions

Most presence-only species distribution models rely on synthetic background or pseudoabsence points to supplement occurrence points and identify environmental predictors of occurrence. Background points are usually sampled in high numbers relative to presence points and often at random across the area of interest. They are intended to represent available environmental conditions in the area and do not necessarily represent absence, though are sometimes sampled in a way that means they are more likely to do so [152, 153]. Presence-absence data are often treated as presence-only (discarding absences), used only for model evaluation, or excluded altogether [154, 155]. This simplifies model fitting as it allows a single model of observation to be applied to all available presence data, and overcomes the challenge of imperfect detection in surveys, but results in a loss of information [155].

Presence and background data can be modelled following aggregation to grid cells, which are then treated as presences and absences in spatially implicit regression-based or machine learning models [152]. These assume that spatially structed variation between grid cells is driven by environmental variables rather than spatial dependence between points. Alternatively, presence and background data can be modelled as point processes, which describe spatial variation in intensity of point patterns, with the optional inclusion of covariate data [156].

Challenges of modelling distributions from occurrence records

An important caveat to the use of presence-only data is that while the aim of species distribution modelling is to predict the relative likelihood of presence, occurrence records actually arise as a function of three probabilities: first that the target is present at that location, second that the location was surveyed/monitored, and third that it was detected if surveyed/monitored. Inference from presence-only models relies on assumptions 1) that sampling (or surveillance) is random or representative across the study area and 2) that the probability of detection is constant across the study area [155]. If these assumptions are violated, variation in sampling effort and detection probability cannot be disentangled from variation in suitability for the target of interest.

Approaches used to address spatial sampling bias in the field of ecology

Approaches to address these issues have been developed for species distribution modelling within the field of ecology. One approach is to generate background points with equivalent selection bias to the occurrence points [152]. This can be implemented by sampling background points from grid cells in which other species have been recorded, assuming that sampling bias is the same across species. Under this scheme, inaccessible locations do not contribute to prediction. This approach is termed target-group background selection, and has been shown to improve predictions for individual species distributions compared to random background selection [152]. However, some limitations of this method have been identified. It assumes all species have equal probability of being identified across locations, rather than allowing for preferential sampling of some species [157], and assumes equal sampling effort across accessible regions, rather than allowing this to vary [151]. For background selection, it makes no distinction between locations which are inaccessible versus those in which all species are rare [151] and is influenced by the richness of non-target species, as the probability of a grid cell being assigned as a presence or absence location depends on the number of other species recorded within it [153].

It has been argued that the inclusion of bias covariates can be a more informative way to address sampling bias, as this avoids the creation an artificial pattern of absences which can have a strong influence on predictions. If the spatial distribution of sampling effort is known and can be represented

as covariates, then it can be modelled and controlled for. For example, if sampling intensity is highest near to roads, distance to a road can be fixed within models so that suitability is predicted in less accessible areas, rather than being constrained to locations close to roads [157].

More general issues have been identified with the use of grid-based approaches. Firstly, this requires that the spatial resolution of grid cells is set to a pre-determined value, which ignores fine-scale variation in the intensity of points and covariates within them. Secondly, it ignores the influence of spatial dependence between points, which can influence distributions of both species and diseases. Thirdly, these models are scale-dependent, meaning that their parameters are influenced by the spatial resolution used for modelling. As an alternative, several authors have explored the use of point process models to quantify differences in the relative intensity of point processes [151, 157]. These spatially explicit models still require a background sample for comparisons, but as these are not intended to adjust for sampling bias, they can be generated uniformly across the study area, removing the need for artificial sampling schemes and user decisions about how to implement these [157]. The spatial resolution need not be decided *a priori* but can be determined by identifying the point at which increasing it no longer improves the likelihood of estimates [157]. Further, as long as the number of background points is sufficient for model convergence, point process models are scale-independent, meaning that increasing the number of background points does not affect predictions [153].

Warton *et al* applied point process models to presence-only datasets of 62 plant species, including bias covariates for distance to roads and cities to represent a thinning process driven by sampling bias. They compared predictions to those from target-group background regression, using independent presence-absence datasets for evaluation [157]. The bias covariate point process models outperformed the target group background approach for the majority of species, but the relative improvement was smaller for species with few occurrence records, possibly because data sparsity made variation in sampling effort more difficult to quantify [157]. This approach depends on some knowledge of the nature of sampling bias and ability to represent it with spatial variables, and can be compromised when variation in sampling intensity is associated with the covariates used to predict occurrence, a situation considered to be “the rule rather than the exception” [155, 157].

An extension to this approach is offered by integrated distribution models, which use survey data and presence-only data to estimate and adjust for bias [154]. Integrated models can be fit to single [158] or multiple species [151]. Fithian *et al*. used a joint Poisson process model incorporating presence-only and presence-absence data for several species, enabling adjustment for sampling bias even for species with no presence-absence data available, if sampling bias was assumed to be the same as for other species [151]. It also improved estimates of covariates which were strongly associated with sampling

bias. This method allows sampling intensity to vary between species (sampling effort can be higher for species which are preferentially sampled), but assumes that sampling bias is proportional (in under-sampled areas, the relative proportion of unsampled individuals is the same across species). It is important to note that this approach assumes that presence–absence data are unaffected by bias, and that absence points are true absences, meaning that cases have not been missed or misidentified [151].

Applications for skin NTDs

In recent years, ecological niche models have been developed to predict the potential distribution of skin NTDs including BU, cutaneous leishmaniasis, LF, mycetoma, onchocerciasis and podoconiosis, as well as for their vectors where relevant [132, 137, 159-163]. The most common approach has been grid-based modelling exploiting maximum entropy modelling or ensembles of regression and machine learning approaches. Assumptions about sampling effort intensity are violated to varying extents by datasets across these diseases. For podoconiosis, occurrence data mostly originated from representative surveys conducted in a few countries. In this case, survey absence data were considered true absences, as targeted communities had been exhaustively screened for the disease, and diagnosis confirmed by expert clinicians [163]. Pseudoabsence points with lower weight were additionally generated in un-surveyed countries with low evidence of podoconiosis endemicity, based on a pre-existing evidence consensus exercise [164]. For the onchocerciasis model, survey absences were not treated as true absences due to the low sensitivity of diagnostic methods used. Instead, background points were sampled from polygon units which had not been surveyed, from locations within 100km of an occurrence point, which would have had an additional effect on balancing out sampling bias [162]. This was similar to the approach taken for the models of suitability for Buruli ulcer within this thesis [165].

These examples of ecological niche models for skin NTDs represent large-scale potential disease distributions, and may be most useful for identifying possibly-endemic areas where cases have not yet been identified. From a programmatic perspective, these may inform areas where diagnosis of target diseases should be considered when activities such as integrated case-finding are implemented. However, the limitations of grid-based approaches mean they do not accurately represent actual spatial processes and are restricted to estimation at the resolution used for modelling [166]. There is a risk that these models over-estimate the influence of predictors which vary over large scales, such as climate variables, and underestimate those which are more variable at finer scales. They may over-predict occurrence within climatically-suitable areas, but have limited ability to identify local heterogeneity in disease risk. This impacts their utility for informing interventions delivered at fine-

scales, especially case management interventions, as programmes would risk resource wastage if these were scaled-up throughout areas predicted endemic.

Point process modelling including bias covariates may provide a more informative way to identify fine-scale areas for targeted case-finding. Bias covariates considered for species distribution models, such as distance to roads, are likely to be suitable candidates for distribution models of skin NTDs as well. Distance to the nearest health centre may also be useful in this context, but the impact of this variable is likely to depend on the specific services delivered from different facilities. Strengthened surveillance and care provision in a limited number of health facilities and their catchment areas would lead to spatially biased identification of skin NTDs. It may be possible to represent this bias using spatial covariates such as distance to the nearest clinic offering dedicated skin NTD services, or to communities where case searches have been implemented. For BU, case reporting forms include the referral source and laboratory confirmation results, [167] which would provide information about where CHWs referred cases and where cases were confirmed, which may represent surveillance and detection strength. However, the use of these indicators for modelling depends on this information being compiled and shared by NTD control programmes, and so would not be possible for all endemic countries. Integrated models of survey and occurrence data may provide a means to quantify the impact of potential bias covariates. However, for skin NTDs it is generally less likely (than for trees) that survey absences represent true absence due to the low sensitivity of clinical diagnosis, and so these are a less suitable “gold standard”.

Synthesising evidence from different sources

Combining and weighting of various sources of existing information through evidence consensus approaches may provide a useful strategy to prioritise districts for implementation of integrated skin-NTD strategies. Information sources may include existing data from routine surveillance or surveys, suitability predictions, and local expert opinion. Additional indicators of health system strength, service availability, and population vulnerability would facilitate a ‘pro-poor’ approach to programming, as recommended by the WHO in 2015 [28]. Taking a broader perspective on population health needs (beyond the evidence provided by available epidemiological data) would enable more inclusive and equitable scale up of services by targeting of strategies to areas of highest need.

Analogous to the monitoring of treatment coverage within PC programmes, service coverage evaluation should be a key component of MMDP service implementation. For LF elimination, countries are required to demonstrate that MMDP services are available in one health facility per endemic/ previously-endemic district. While this target should lead to increased service provision, district-level service availability is not sufficient to ensure accessibility, equitability, or quality of MMDP services. If

NTD programmes are to be 'centred on the needs of people and communities' [147], these attributes should be considered for monitoring. Monitoring could evaluate rates of case detection, treatment completion, and patient outcomes to identify potential disparities by characteristics such as gender, geography, and socioeconomic status (at community if not individual level). This would provide evidence that could be used to tailor service provision to improve programme equitability or accessibility. However, as the addition of multiple recording requirements to routine consultations may impose a significant administrative burden on health staff, it would be important to develop the process through piloting prior to wider implementation.

6.2. Financial Support

Following the vast expansion of MDA since 2012, the number of people treated for at least one NTD reached 1 billion people in 2016, and is now declining as areas requiring treatment shrink [168]. This scale of delivery was enabled by donations of medicines from pharmaceutical companies, valued at $17 billion in 2017 [168], and support for implementation from charitable organisations and bilateral donors [75]. As endemicity declines towards elimination targets, some donor organisations will seek to withdraw support for implementation, leaving a funding gap for activities such as surveillance and MMDP which will need to continue after transmission elimination targets are reached. Commitments to maintain these activities are considered important criteria for validation of LF elimination, since 'validation implies a potentially reversible state' [57].

The 'mission millions' of leprosy cases accumulated in the 20 years since global elimination illustrate the risk of large scale reductions in programmatic activities when elimination targets are reached and financial support drops [68]. While WHO recommends ongoing surveillance through transmission assessment surveys (TAS) for four years after reduction of LF prevalence to <1%, mathematical modelling suggests that resurgence may occur outside of this window, further demonstrating the need for continued vigilance to new infections [169]. Surveillance will inevitably need to be integrated as vertical programmes are scaled back, and there have been calls for disease-oriented donors to support integration by contributing to strengthening of primary healthcare systems [150]. Existing large-scale initiatives such as Demographic and Health Surveys may also offer appropriate platforms for integrated sero-surveillance to detect potential resurgence of infections [170]. However, there is limited guidance on appropriate strategies to detect low-prevalence and spatially heterogenous infections.

Resources for NTD case detection and management are extremely limited in comparison to those for MDA. NTDs are often considered low priority by national governments, and thus attract little domestic funding. Case detection and management interventions are often delivered through donor

programmes, which are limited in geographical coverage [171, 172]. In Liberia, government spending accounted for 1% of expenditure on NTDs in 2018- 2019, with the majority of activities financed through donors and in-kind support [171]. In the past, reliance on external funding resulted in fragmentation within the health system, with activities implemented according to donor priorities, and health worker salaries varying between programmes [173]. However, the establishment of a single health pool has given the Liberia MoH greater control over financing decisions for general health programmes since 2009 [171].

The NTD programme in Liberia is fully integrated and implements an Integrated Case Management Programme (ICMP) which consists of case searching, referral, diagnosis and management of skin-NTDs, primarily through Community Health Volunteers and Health Assistants. The ICMP directs donor funding to particular components of the ICMP according to need, supporting the third Roadmap pillar to 'increase country ownership' [4]. In the five counties where this programme was implemented, providing free management of NTDs, there were significant increases in the number of target NTDs diagnosed through the health system [174]. However, patients still faced high costs in accessing these services, reflecting general challenges which were exacerbated by stigma [171].

There is overall consensus that increased domestic financing will be required for sustainable NTD programmes and country ownership, but it is clear that external support remains essential in the short- to medium-term [4, 171, 175]. Strengthening of primary healthcare systems and mainstreaming of NTD services within them has long been recognised as a means to increase service accessibility, equity, and sustainability [176], and remains at the forefront of discussions on NTD policy [75], but will require substantial, systemic, and long term investment. Models such as the ICMP, which increase MoH autonomy and support mainstreaming of NTD services into primary healthcare via the community health system, seem to provide a viable route towards this goal. For the long term, broader investment to improve the quality and accessibility of primary healthcare in NTD-endemic countries will support progress towards UHC.

6.3. Engagement of community-based health staff

Community-based volunteers have been instrumental to the successes of MDA, particularly in enabling access to remote communities [38]. As members of the communities in which they work, and by providing a link to the primary healthcare system, these staff are also well placed to maximise the reach of surveillance and case management activities for NTD elimination. Community-based volunteers are responsible for enumerating suspect cases of LF morbidity during MDA in Burkina Faso, Ghana, Malawi and other countries, providing burden estimates required for validation of LF elimination [177]. Community-based approaches have also been demonstrated to be effective and/or

cost-effective as a means to support self-care for people with lower limb disorder due to LF, podoconiosis or leprosy in a variety of settings including Ethiopia [178], [179], India [180, 181], and Nigeria [182].

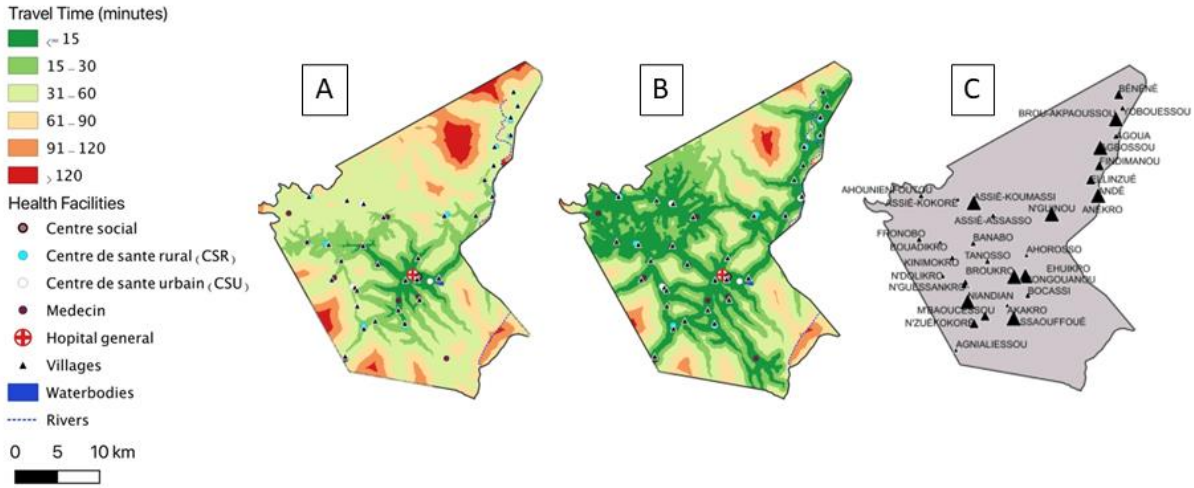
However, programmes seeking to expand surveillance and case management functions through community health systems should consider workforce capacity to support additional roles. Evidence suggests that when included as an extra task on top of drug distribution, LF morbidity enumeration by CHWs tends to underestimate case numbers [183]. Anecdotal reports from CHWs indicate that the workload of these two roles is unmanageable, and that fixed-post strategies, often used for drug distribution from a central point such as a marketplace, are not suitable for registration of morbidity cases (personal communication with CHWs in Côte d'Ivoire). Paper 5 in this portfolio suggests that standalone community-based screening provides more reliable estimates of morbidity burden, which are essential to ensure sufficient funding for service provision [184]. There may be alternative adaptations to improve the efficiency of integrated MDA and screening approaches, such as increasing the number of days allowed per activity, or pairing of distributors and enumerators. Piloting and evaluation of such approaches under programmatic conditions would provide further evidence for reliable and scalable methods of LF morbidity estimation.

The sustainability of community-based approaches is also limited by high staff turnover rates, as community health staff are often informal workers paid via remuneration for specific activities. The formalisation of these cadres, for example by offering fully-paid salaries and pathways for progression, has been recommended to increase the sustainability of NTD control programmes [150], and as a means to improve access to primary health care in pursuit of UHC [185]. Community health workers have a vital role in achieving UHC, and PC coverage has been used as an indicator of health equity [186], helping to position NTDs as tracers of progress towards UHC [147]. There are issues with this indicator, however, including incomplete data, lack of information on individual treatment, and the fact that its availability declines with the scale-back of MDA [75].

Beyond engagement of CHWs, sustainable NTD elimination will also require strengthening of primary healthcare systems [150]. The provision of basic care for affected individuals is already incorporated into WHO targets for two NTDs (LF and trachoma) [147], and it has been proposed that monitoring of inclusion in these activities could provide more insightful measures of health equity than PC receipt, by emphasising more holistic, systemic, and long-term aspects of health care delivery [187]. However, under the minimum scale-up of services required to meet these targets (provision of services at one facility per district), care would remain difficult to access for many communities, and would likely be inequitable across the population in need. Taking the example of Bongouanou, where the study for

Paper 4 was conducted, an analysis by an MSc student I supervised showed that travel times to the district hospital were over 30 minutes (by walking or driving) for the majority of district population (Figure 11A). Under an alternative scenario in which LF services were made available at all health facilities in the district (Figure 11B), the majority of the population would be able to reach these services within 15 minutes' travel time.

Figure 11: Modelled geographical accessibility of services in Bongouanou Health District, Côte d'Ivoire, considering A) delivery from the district hospital or B) all health facilities in the district. C) shows the location of communities in the district.



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A lack of services at primary healthcare level has been demonstrated as a cause of delayed presentation in several settings [188-190]. Decentralisation of diagnosis and treatment to the level of primary health facilities, or where appropriate, communities, could have a great impact on service accessibility and equity. A case study of community-based management of BU in Benin showed that 71% of all BU cases identified could be treated in the community [191], while in Côte d'Ivoire, a trial of community-based wound management (including BU and LF) demonstrated that 40% of wounds could be treated at community level [192]. These studies provide important evidence for the potential effectiveness of decentralisation, and suggest that this would reduce both costs to the health system, and patient costs of treatment. For wider uptake as strategy, however, estimates of cost-effectiveness and the affordability of such models will be required.

6.4. Integration of planning and implementation

The centring of cross-cutting approaches within the 2030 Roadmap demonstrates a paradigm shift in NTD control beyond MDA. Another important development is the grouping of skin-NTDs- including both PC- and CM-NTDs- as a key target for integration, with a cross-cutting target for 40 countries to adopt and implement integrated strategies against skin-NTDs [147]. The term 'skin-NTDs' was coined in 2016, in a paper which recommended integration of activities such as mapping, training, diagnosis and management, and community control [148]. Another published shortly after proposed a framework for integrated district-level strategies against skin-NTDs [83].

Calls for integration of skin-NTD activities have also posited wider potential benefits for skin-health in general, on the basis that patients presenting with skin symptoms in NTD-endemic areas would be more likely to be diagnosed with a common skin condition than an NTD [83]. A 2018 review further elaborated on these benefits, recommending training in general dermatology for health workers in areas endemic for skin-NTDs, while commenting on the scale of this challenge [84]. Dermatological expertise is limited in Africa - excluding North Africa, the rate of dermatologists per capita is currently less than 10 per million, and less than 1 per million in many countries [193]. Specialists are often concentrated, for example, in BU treatment and research facilities in Ghana, Côte d'Ivoire, Togo and Benin. Attrition of disease-specific expertise from within vertical disease control programmes is one perceived risk of integration of skin-NTD control, although with proper coordination and funding, the creation of regional training centres in dermatology could provide an opportunity for cross-border capacity building, curricula development, and collaborative research [83].

At the COR-NTD 2021 annual meeting, I contributed to sessions entitled *How to Develop a Country Integrated Skin-NTD Strategy - Identifying and Filling the Research Gaps*. These were intended to generate solutions to support progress towards the adoption of integrated skin NTD strategies, as targeted by the 2030 Roadmap. As part of the panel, I discussed integrated approaches to mapping disease distributions and overlaps, alongside colleagues who discussed integration of MMDP, integration of MDA, and social sciences respectively. We summarised the outputs of these meetings in a viewpoint paper [194], which included six research priorities to support the development of integrated skin NTD strategies. Among these were evaluations of case detection platforms, integrated surveys, integrated MMDP, and the impact of integration on CHWs. Providing evidence of the cost-effectiveness of integration was considered a priority across all aspects of integration. During the process of peer review, one reviewer commented that research activities can add an extra burden of work to programmes, which is an important consideration for researchers aiming to support programmatic activities. For operational research to be truly beneficial to programmes, projects should aim to include programmatic staff as co-researchers and incorporate their priorities from the inception stage. Programmatic priorities (for example, capacity development for implementation) may deviate from research-focused objectives (such as measuring effect sizes), which may add complexity to research studies, but represents an opportunity for projects to maximise real-world benefits and the potential for future uptake.

The Skin Health Africa Research Project (SHARP) is developing interventions to improve access to care for people living with skin-NTDs. One of these is a district-level package of interventions to improve early diagnosis and affordable care for NTDs in Ghana, in a study district selected on the basis of recorded cases of BU, leprosy, and yaws, and having not been previously targeted for NTD case finding

and management interventions [190]. The intervention was developed through a collaborative process informed by qualitative and quantitative baseline research, and with input from NTD programme directors within the Ghana Health Service (GHS) and district health staff from the study district [195]. Originally intended to improve outcomes for 'severe and stigmatising skin diseases', it was developed into an integrated, decentralised skin strategy, reflecting GHS stakeholder priorities for broader service improvements. Compared to district-level integrated MDA, this package is considerably more complex, with the health facility component alone including clinical training on general dermatological principles and disease-specific pathways for 37 health staff; weekly clinics; provision of medical materials; strengthening of information systems; and supporting patient self-care. The intervention will be delivered through the local health workforce, including the district health team, healthcare workers, and CHWs, and is intended to be manageable for the district to implement without major reliance on externally funded NGOs and research teams. The evaluation of this intervention will include analysis of its impact, equity, cost-effectiveness and affordability, as well as a process evaluation to assess the fidelity of implementation to the planned strategy and views of the target patient groups. This will provide much needed evidence to inform the scale-up of integrated strategies for skin-NTD control, and is also likely to shed light on the technical complexity and financial costs of providing comprehensive, equitable, high quality, and accessible skin-health services through local health systems. However, even if the intervention proves feasible and cost-effective, it may not be scalable to all endemic regions under current resource availability.

6.5. Conclusions

The provision of accessible and equitable case management services for NTDs represents a significant opportunity to reduce the morbidity associated with these diseases and to improve the health of affected people and communities. Scale-up of case management interventions is required for elimination of certain NTDs and would also support attainment of UHC by strengthening primary health systems.

As NTDs requiring case management are often focal, and become increasingly so as their incidence declines, geographical targeting of interventions seems to offer an attractive prospect. At present however, NTD data are too limited to guide equitably targeted implementation, and the costs of reliably mapping their focality may outweigh the benefits [67]. Instead of targeting disease-specific services to fine-scales, strengthening of broader skin-health services would ensure a wider benefit.

Delivery of basic interventions at community level has great potential to increase referral rates, promote early diagnosis before progression to severe disease, and support patients to complete treatment and continue self-care [171, 191, 192, 196]. This potential would be maximised by

formalisation and support of the community health workforce [67]. Such initiatives would need also to be complemented by parallel strengthening of services and capacity building at primary healthcare and district levels to ensure appropriate management of more complex cases.

Further development of information and surveillance systems, and ongoing epidemiological monitoring would help to demonstrate the impact of strengthened service provision on detection rates and patient outcomes, while embedded research could demonstrate the costs and cost-effectiveness of interventions. Such programmes will be costly, however (even if cost-effective), and may not be affordable for many endemic countries given multiple competing health priorities [197]. Increased financial support both from national governments and external partners will therefore be critical for the scale-up of services required.

Ministries of health will also have to make decisions about where skin heath programmes are initially implemented. With this in mind, and given links to UHC, prioritisation rather than targeting may be a more constructive concept for decision makers. Beyond surveillance data, programmes could consider using a wider range of data for decision support to inform initial expansion of services. These may include predicted disease suitability in combination with expert local opinion, information on existing health service provision, and indicators of population vulnerability, to enable targeting to areas of greatest need. I believe this is a just and necessary approach to end the neglect of disadvantaged communities, which persists despite decades of scientific research and programmatic implementation focused on neglected tropical diseases.

Published Works

1. Simpson, H., Quao, B., Van Der Grinten, E., Saunderson, P., Ampadu, E., Kwakye-Maclean, C., Odoom, S., Biritwum, N.K., Pullan, R. and Cano, J., 2018. Routine surveillance data as a resource for planning integration of NTD case management. *Leprosy Review*, *89*(3), pp.178-196.

2. Simpson, H., Deribe, K., Tabah, E.N., Peters, A., Maman, I., Frimpong, M., Ampadu, E., Phillips, R., Saunderson, P., Pullan, R.L. and Cano, J., 2019. Mapping the global distribution of Buruli ulcer: a systematic review with evidence consensus. *The Lancet Global Health*, *7*(7), pp.e912-e922.

3. Simpson, H., Tabah, E.N., Phillips, R.O., Frimpong, M., Maman, I., Ampadu, E., Timothy, J., Saunderson, P., Pullan, R.L. and Cano, J., 2021. Mapping suitability for Buruli ulcer at fine spatial scales across Africa: a modelling study. *PLoS neglected tropical diseases*, *15*(3), p.e0009157.

4. Simpson, H., Panicker, K.N., George, L.S., Cano, J., Newport, M.J., Davey, G. and Deribe, K., 2020. Developing consensus of evidence to target case finding surveys for podoconiosis: a potentially forgotten disease in India. *Transactions of The Royal Society of Tropical Medicine and Hygiene*, *114*(12), pp.908-915.

5. Simpson, H., Konan, D.O., Brahima, K., Koffi, J.D.A., Kashindi, S., Edmiston, M., Weiland, S., Halliday, K., Pullan, R.L., Meite, A. and Koudou, B.G., 2022. Effectiveness of community-based burden estimation to achieve elimination of lymphatic filariasis: a comparative cross-sectional investigation in Côte d'Ivoire. *PLoS global public health, 2*(8), p.e0000760.

Applicant contributions to publications and underlying research within portfolio.

1. **Simpson**, H., Quao, B., Van Der Grinten, E., Saunderson, P., Ampadu, E., Kwakye-MacLean, C., Odoom, S., Biritwum, N.K., Pullan, R. and Cano, J., 2018. Routine surveillance data as a resource for planning integration of NTD case management. *Leprosy Review*, *89*(3), pp.178-196

HS assembled a database of surveillance data from three disease-control programmes, remotely geo-referenced the locations of all recorded cases, planned and implemented analyses, produced figures and tables, and drafted the manuscript.

2. **Simpson**, H., Deribe, K., Tabah, E.N., Peters, A., Maman, I., Frimpong, M., Ampadu, E., Phillips, R., Saunderson, P., Pullan, R.L. and Cano, J., 2019. Mapping the global distribution of Buruli ulcer: a systematic review with evidence consensus. *The Lancet Global Health*, *7*(7), pp.e912-e922

HS planned and conducted all stages of the literature review, designed the evidence consensus framework and synthesised data, produced figures and tables, and drafted the manuscript.

3. **Simpson**, H., Tabah, E.N., Phillips, R.O., Frimpong, M., Maman, I., Ampadu, E., Timothy, J., Saunderson, P., Pullan, R.L. and Cano, J., 2021 Mapping suitability for Buruli ulcer at fine spatial scales across Africa: A modelling study. *PLoS neglected tropical diseases*, *15*(3), p.e0009157

HS implemented the analyses, produced figures and tables and drafted the manuscript.

4. **Simpson**, H., Panicker, K.N., George, L.S., Cano, J., Newport, M.J., Davey, G. and Deribe, K., 2020. Developing consensus of evidence to target case finding surveys for podoconiosis: a potentially forgotten disease in India. *Transactions of The Royal Society of Tropical Medicine and Hygiene*, *114*(12), pp.908-915

HS co-facilitated a workshop through which the evidence consensus framework was developed and through which local experts shared surveillance data and their knowledge of local epidemiology of lymphoedema. HS co-synthesised data through the evidence consensus framework, produced figures and tables and drafted the manuscript.

5. **Simpson**, H., Konan, D., Brahima, K., Koffi, J d'A, Kashindi, S., Rogers, E., Edmiston, M., Weiland, S., Halliday, K., Pullan, R., Meite, A., Guibehi, BK. & Timothy, J. 2022. Evaluation of a scalable, community-based case finding strategy to achieve elimination of lymphatic filariasis as a public health problem in Côte d'Ivoire

HS led the development of data collection tools and training materials, jointly co-ordinated the data collection activities, designed and implemented all analyses, produced figures and tables, and drafted the manuscript.

Signed: Hope Simpson (Applicant) Date: 14/01/2022

Signed: Dr. Rachel Pullan (PI papers 1, 2, 3 & 5) Date: 21/01/2022

Signed: Dr. Kebede Deribe (PI paper 4) Date: 21/01/2022

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