

Effectiveness and efficiency of integrating delivery of neglected tropical disease programs

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Abstract

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Background: Neglected tropical diseases (NTDs) affect over one billion people globally, resulting in severe disability and disfigurement. With recent calls to eliminate or control many of the NTDs, experts and policy makers recommend integrating NTD programs in co-endemic areas to achieve greater health impact and efficiency. While some evidence supports the beneficial effects of integrating NTD programs to optimize coverage and reduce costs in research settings, there is minimal information regarding when or how to effectively operationalize program integration. The lack of systematic analyses of integration experiences and of integration processes may act as an impediment to achieving more effective NTD programming. We aimed to learn about the experiences of a range of NTD stakeholders and their perceptions of integration (Chapter 2), evaluate the effectiveness and synergy of multisectorial approaches to NTD control (Chapter 3), and determine the costs and cost drivers of a sub-national integrated NTD program operating at scale (Chapter 4).

Methodology: We used a multi-disciplined approach to study how NTD integration is implemented and the effects of integration in terms of the key programmatic outcomes of effectiveness and efficiency. Chapter 2: We evaluated differences in the definitions, roles,

perceived effectiveness, and implementation experiences of integrated NTD programs among a variety of NTD stakeholder groups, including multilateral organizations, funding partners, implementation partners, national Ministry of Health (MOH) teams, district MOH teams, volunteer rural health workers, and community members participating in NTD campaigns. Semi-structured key informant interviews were conducted. Coding of themes involved a mix of applying in-vivo open coding and *a priori* thematic coding from a start list. Chapter 3: We conducted a cohort study nested within a randomized trial of empiric deworming of HIV-infected adults in Kenya to evaluate the potential synergistic influence of dual access to deworming medications and water, sanitation, and hygiene (WASH) resources. Helminth infections, including soil transmitted helminths (STH) and schistosomiasis, and infection intensity were diagnosed using semi-quantitative real-time PCR. We conducted a manual forward stepwise model building approach to identify the package of interventions most protective against a helminth infection of any species (combined outcome) and each helminth species individually. We conducted secondary analyses relevant only to individuals with no exposure to antihelminthics and used interaction terms to test for intervention synergy. Chapter 4: We utilized a bottom-up microcosting approach to identify all financial and economic costs associated with implementing an integrated NTD program at scale in two Nigerian States: Abia State and Cross River State. We used an established costing tool, the Tool for Integrated Planning and Costing, to collect costs and evaluate tool functionality. We used societal and provider (government) perspectives. We conducted a series of univariate sensitivity analyses to identify cost drivers within and across States and changes in unit costs associated with increasingly comprehensive program integration. We also conducted scenario analyses to identify the affordability of the NTD program under circumstances in which governments assume all program costs without the assistance of non-governmental organizations or in which governments assume all drug purchasing costs.

Findings: Chapter 2: In total, 41 interviews were conducted. Salient themes varied by stakeholder, however dominant themes on integration included: significant variations in definitions, differential effectiveness of specific integrated NTD activities, community member perceptions of NTD programs, the influence of funders, perceived facilitators, perceived barriers, and the effects of integration on health system strength. In general, stakeholder groups provided unique perspectives, rather than contrarian points of view, on the same topics. The stakeholders identified more advantages to integration than disadvantages, however there are a number of both unique facilitators and challenges to integration from the perspective of each stakeholder group. Chapter 3: Approximately 22% of the 701 stool samples provided were helminth-infected, most of which were of low to moderate intensity. The odds of infection with any STH species were lower for individuals who were treated with albendazole (adjusted odds ratio, aOR: 0.11, 95%CI: 0.05, 0.20, $p<0.001$). Although most WASH interventions demonstrated minimal additional benefit in reducing the probability of infection with any STH species, access to safe flooring did appear to offer some additional protection (aOR:0.34, 95%CI: 0.20, 0.56, $p<0.001$). Only treatment with praziquantel was protective for schistosomiasis (aOR:0.30 95%CI: 0.14, 0.60, $p=0.001$). Amongst individuals who were not treated with albendazole or praziquantel, the most protective intervention package to reduce probability of STH infections included safe flooring (aOR:0.34, 95%CI: 0.20, 0.59, $p<0.001$) and latrine access (aOR:0.59, 95%CI: 0.35, 0.99, $p=0.05$). Across all species, there was no evidence of synergy or antagonism between anthelmintic chemotherapy with albendazole or praziquantel and WASH interventions. Chapter 4: From the provider (MOH, not inclusive of NGO costs) perspective, the average financial cost per treatment delivered was \$0.42 and \$0.34 in Abia and Cross River States, respectively. From the societal perspective, the average financial cost per treatment delivered in Abia State was \$0.46 while in Cross River State it was \$0.64. Economic unit costs accounting for programmatic and community-level opportunity costs were \$4.73 and \$4.04 per treatment delivered while total costs per treatment delivered were

\$5.09 and \$4.68 in Abia and Cross River States, respectively. Total costs per case averted were \$14.10 and \$10.85. In sensitivity analyses, variations in lymphatic filariasis (LF) treatment coverage exhibited the strongest influence on potential reductions in the average financial cost per treatment delivered, with up to a 39% reduction in costs. Variations in the cost of ivermectin tablets for onchocerciasis control had a large potential effect on average total costs per treatment delivered, with the potential to increase costs by up to 81%. Changes to baseline estimated disease prevalence, particularly onchocerciasis, also had a large effect on average total cost per case averted in each State, where the lower the disease prevalence the higher the average unit cost. Integration of activities that minimize the time CDDs spent on training and MDA delivery activities did not have a large influence on average total unit costs per person treated or per case averted. However ensuring that programs are fully integrated for community members could reduce total unit costs per person treated and cases averted up to 12%. Under a variety of scenarios and using several relevant benchmarks of affordability, it is evident that programs are not affordable for State governments without substantial support from NGOs (at least 25% of program costs) and donated drugs.

Conclusions: This dissertation indicates that integration of NTD programs is an anecdotally promising policy for increasing the effectiveness and efficiency of NTD programs in pursuit of global elimination goals, but there is mixed evidence regarding what aspects of the programs to integrate, how to operationalize integration, and what outcomes may realistically be expected.

Chapter 2: Qualitative data suggest several structural, process, and technical opportunities that could be addressed to promote more effective and efficient integrated NTD elimination programs. We highlight a set of ten recommendations that may address stakeholder concerns and perceptions regarding these key opportunities. For example, public health stakeholders should embrace a broader perspective of community-based health needs, including and beyond NTDs, and available platforms for addressing those needs. Chapter 3: Deworming is highly

effective in reducing the probability of helminth infections amongst HIV-infected adults. With the exception of safe flooring, WASH interventions offer minimal additional benefit in our study. However, WASH does appear to significantly reduce infection prevalence in adults who are not treated with deworming medications. These findings suggest that multisectoral integration of deworming and WASH is difficult to measure and may not result in synergies. However there may be political or strategic rationale for pursuing multisectoral integration, and appropriate outcome metrics should be identified accordingly without assumptions regarding heightened health impact. Chapter 4: The average total cost per treatment delivered were far more expensive in this study than most estimates currently available in the literature due to the inclusion of opportunity costs for volunteer drug distributors, community members, and donated drugs. This demonstrates the need for future studies to engage in a more nuanced and comprehensive approach to NTD program costing to understand the totality of integrated NTD program costs. To increase the efficiency of programs, local governments should focus on increasing treatment coverage (i.e. economies of scale) and ensuring that activities are maximally integrated for volunteers and program beneficiaries, without compromises to program quality.

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DEDICATION

For my son, Linden Rubin Means. We did this together.

CHAPTER 1: Introduction to integrated programming and neglected tropical diseases

A core tenant of the drive for Universal Health Coverage (UHC) and the 2030 Sustainable Development Goals (SDGs) is that all individuals should have access to high-quality, affordable, and comprehensive healthcare. To ensure that health systems address the multi-faceted needs of a population, many global health leaders promote the integration of vertical programs into a shared delivery infrastructure (1, 2). The goal of integrated programs is to make more efficient use of human, financial, and material resources while promoting equitable and expansive health improvements.

In the context of UHC, it is important to understand how existing integrated activities function and the influence of integration on program outputs and outcomes. Due to their significant degree of co-endemicity and similar intervention strategies, the neglected tropical diseases (NTDs) are an example of a group of diseases in which synergistic integration may be possible. According to the World Health Organization (WHO), “integrating NTD services has the potential to accelerate progress towards UHC while advancing the broader Sustainable Development Goals for 2030” (3). Improved understanding of how and what, or what not, to integrate within the NTDs is necessary for optimizing NTD programs, as well as for generating useful information for cross-disease integration strategies to attain UHC targets.

NTDs overview

NTDs are chronic, disabling, and disfiguring conditions that affect the world’s most marginalized and impoverished populations. The NTDs are typically associated with low mortality, but result in severe morbidities associated with income loss and chronic poverty in low income countries (4). The NTDs are also spatially congruent, with extensive co-endemicity at the national level (Figure 1). Five of the world’s most prevalent NTDs are generally considered “tool ready” and are controlled through a method called mass drug administration (MDA), including: lymphatic filariasis

(LF), onchocerciasis, schistosomiasis, soil-transmitted helminths (STH), and trachoma. MDA is the presumptive treatment of all at-risk individuals living in an endemic area regardless of an individual's disease status. Annual MDA, also referred to as preventative chemotherapy, has been successful in reducing disease prevalence over time and, in some locations, disrupting disease transmission (5). However over 1 billion people worldwide remain in need of MDA treatment for one or more NTD infections (6). This dissertation focuses specifically on the five NTDs for which MDA is the standard of care. More information on these NTDs and their associated treatment regimens can be found in Table 1.

In January of 2012 a wide array of partners endorsed the WHO NTD Roadmap and launched the London Declaration, a commitment to pursuing control or focal elimination of select NTDs by 2020. A major outcome of the London Declaration is that large pharmaceutical companies committed to donating the drugs necessary to deliver MDA and achieve London Declaration targets. Other goals of the London Declaration include promoting “clean water, basic sanitation, improved living conditions, vector control, health education, and stronger health systems in endemic areas” (7). Thus the Declaration sparked a global concerted effort to identify effective and cost-efficient strategies for achieving the 2020 goals. Integration of NTD programs is considered to be one of the most promising approaches for achieving the London Declaration goals, and integrating NTD programs has been endorsed and recommended by the WHO for all NTD-endemic countries (8).

NTDs integration overview

In 2005 the WHO Department of NTDs was established, in 2006 the Global Network of NTDs was created, and in 2007 the United States Congress made its first budgetary earmark for integrated NTD development assistance (9). Simultaneously, a major paradigm shift occurred in NTD policy that led to increased prioritization of integrated programs. According to the former director of NTDs at the WHO, this shift was the result of a long intellectual process that included: “(1)

the generation and acquisition of the necessary scientific knowledge, (2) the promotion and dissemination of the intervention strategies to decision makers in endemic countries, and (3) the building of the consensus among the potential partners as a way to secure the financial and in-kind resources” (10). In April of 2013, the WHO formally identified integration of NTDs programs as the strategic approach for accelerating global scale up of MDA-based interventions in pursuit of the London Declaration 2020 targets (8). In May of 2013 the World Health Assembly adopted resolution WHA66.12, calling for the expansion of NTD interventions and integration of NTD programs to optimize program implementation. During her address to the Assembly, WHO Director-General Dr. Margaret Chan stated, “The tremendous success in controlling the neglected tropical diseases clearly tells us that integrated strategies can stretch the impact of health investments. They can stretch the value of development dollars”(11).

Integration refers to the creation of linkages among existing or newly introduced programs to improve the delivery of health interventions given existing commitments and resources (12). There are a number of activities that can be integrated between NTD programs. NTDs that are co-endemic in the same geographic area can integrate activities such as mapping, vector control, community sensitization and education, health worker training, MDA drug delivery, surveillance, monitoring and evaluation, and disability management. Integration of these activities across NTD programs provides an opportunity to build upon existing capacity and to leverage the human and physical infrastructure of established programs (8). While there is some evidence of beneficial effects of integration on NTD program coverage (13) and costs (14) in research settings, there is minimal information regarding how to effectively operationalize integration. The lack of systematic analyses of integration processes and outcomes may be a significant impediment to the quality delivery of integrated and non-integrated programs alike (12). In **Chapter 2** of this dissertation we use qualitative research methods to identify barriers and facilitators to effective integration from a

variety of stakeholder perspectives as well as strategies that can be used to optimize integrated NTD activities moving forward.

Integration also involves multilateral approaches to disease control. Current global helminth control guidelines focus on regular deworming of targeted populations using MDA campaigns for morbidity control but water, sanitation, and hygiene (WASH) interventions may also be important for preventing post-treatment reinfections and reducing helminth transmission (15). Notably, a single WASH intervention can impact multiple NTDs, in addition to other waterborne illnesses (Table 2). Although highly promoted, currently there is very little research exploring the impact of coordinated approaches to NTD control utilizing both deworming and WASH strategies (16). In **Chapter 3** of this dissertation we evaluate the impact of different packages of interventions including repeated treatment with albendazole and praziquantel with and without WASH interventions on the prevalence of helminth infections.

One of the primary impetuses of integrating NTD programs is improved efficiency of typically underfunded programs. An analysis of top-down NTD program costs globally estimated that \$0.49 USD per person per year is required to treat all five MDA-indicated NTDs (17). However, as integrated programs are scaled-up to reach 2020 London Declaration goals it is increasingly important to understand how integration affects program costs and affordability. In a recent review of NTD economic analyses researchers found no information regarding drivers of variation in costs among and within countries, or how these drivers have differential effects on NTD program costs at scale. The review also highlighted a lack of information regarding the cost implications of integrated approaches to NTD control (18). In **Chapter 4** of this dissertation we perform a sub-national cost analysis of the Nigerian integrated NTD program to identify drivers of program costs and affordability in two the integrated NTD programs of two Nigerian States operating at scale.

With increased global discourse on achieving UHC, it is important to understand how compatibilities between programs can enhance the efficient and effective delivery of health services (19). Policy makers assert that integrated NTD activities are one pathway for pursuing UHC in that the programs increase healthcare access to previously unreached populations, increase access to services not previously offered, and reduce direct payment costs overall (20, 21). Given that integrated NTD programs are now encouraged in all NTD endemic countries, we have the opportunity to learn from stakeholders and programs as they engage in and scale-up integrated approaches to NTD program delivery. This body of work offers important insights for health systems more broadly by serving as an opportunity to understand how and when to promote inclusive frameworks for cross-program coordination.

This dissertation provides a multi-disciplinary perspective on integrated approaches to healthcare delivery, through the lens of the NTDs. Despite an increase in recommendations to integrate health services, there is minimal information regarding how to purposefully integrate programs and what the potential benefits or drawbacks of integration might be in terms of programmatic efficiency and public health effectiveness. This project aims to fill the gap between policy and practice by generating evidence necessary for national and international-level decision making.

Figure 1: NTD co-endemicity by country (6)

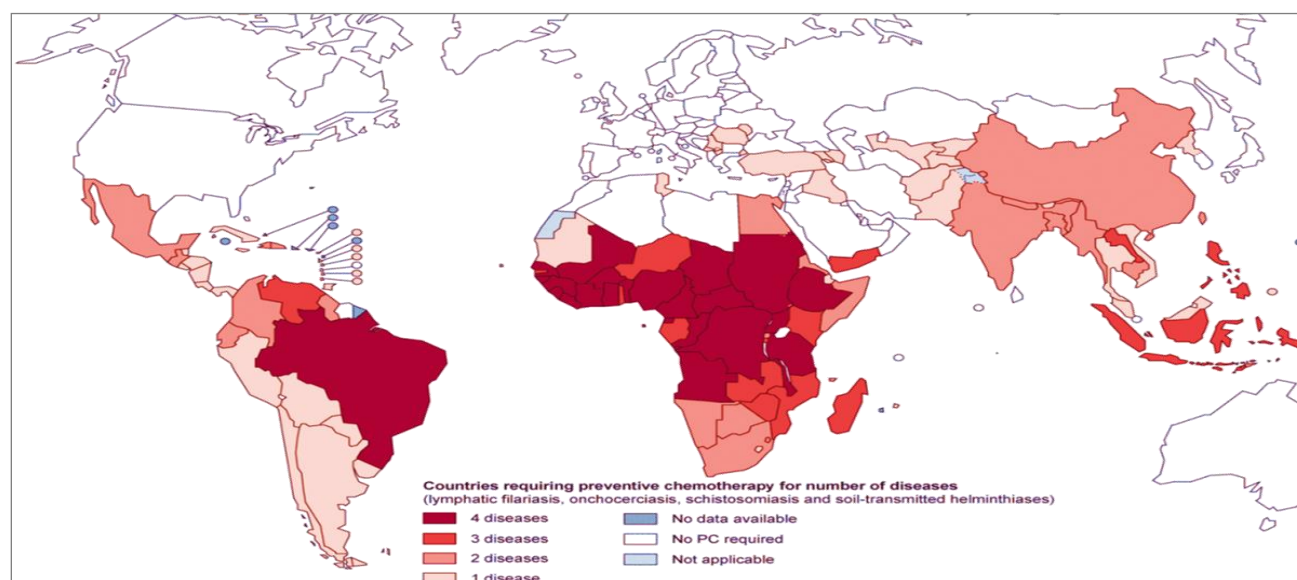


Table 1: Overview of NTD drugs and treatment schedules

Disease	Drugs used in MDA	Global target population size (millions) ¹	Treatment frequency		
			Children <5	Children 5-14	Adults
Lymphatic Filariasis	Ivermectin or diethylcarbamazine and albendazole	1,410	1/year	1/year	1/year
Onchocerciasis	Ivermectin	127	1-2/year	1-2/year	1-2/year
Schistosomiasis	Praziquantel	243	-	1/year	1/year ²
Soil transmitted helminths	Albendazole or mebendazole	873	1-2/year	1-2/year	1/year ²
Trachoma	Azithromycin	302	1/year	1/year	1/year

¹ Note: This reflects the number of people in need of treatment, not the number of people infected

² In high prevalence areas only (prevalence $\geq 50\%$)

Table 2: Influence of WASH on NTDs (22)

Intervention	Specific intervention	NTDs impacted
Water	Increasing access to sufficient amounts of safe water for personal hygienic purposes (ex. Washing hands; bathing; laundry)	LF, schistosomiasis, trachoma, and STH
	Increasing access to sufficient amounts of safe water for environmental sanitation (ex. Cleaning latrines)	STH, schistosomiasis, trachoma
	Increasing access to safe water for drinking/food preparation	STH
	Monitoring impact of water resource development and waste water management on vector breeding	LF, schistosomiasis
Sanitation	Reducing open defecation	STH, schistosomiasis, trachoma
	Disposing of infant/child feces properly	STH, schistosomiasis, trachoma
	Increasing improved sanitation coverage	STH, schistosomiasis, trachoma
	Promoting maintenance and cleaning of latrines	STH, schistosomiasis, trachoma

CHAPTER 2: A Qualitative Research Approach to Identifying and Harmonizing Perspectives of Integrated Neglected Tropical Disease Programs

Introduction

A major challenge facing health systems in low-resource settings is the often ad-hoc and vertically silo-ed approach to organizational structure. Many global health leaders are promoting the integration of vertical programs into a shared delivery infrastructure to strengthen the efficiency, effectiveness, and sustainability of health systems and to optimize resources with the goal of promoting equitable and synergistic health improvements (1, 23, 24). However, the term *integration* is not consistently defined and often incorporates a variety of ideas, including continuity of care, inter-organizational relationships, disease management, and others (25). In addition, a variety of external and internal factors, including local and national politics and complex institutional pressures are also important drivers of, and barriers to, successful integration (26). Understanding facilitators and barriers of integration within existing integrated programs offers the opportunity to improve public health integration efforts globally.

The neglected tropical diseases (NTDs) are an example of a group of 17 diseases in which synergistic integration may be ideal given their high degree of geographic and population overlap. Furthermore, five of the world's most prevalent NTDs are generally considered "tool ready" and are primarily controlled through mass drug administration (MDA), including: lymphatic filariasis (LF), onchocerciasis, schistosomiasis, soil transmitted helminths (STH), and trachoma (6). Schistosomiasis and STH MDA programs are typically delivered to pre-school and school-age children via school-based delivery platforms. LF, onchocerciasis, and trachoma programs, on the other hand, are typically delivered via community-based delivery platforms. LF and onchocerciasis MDA programs are uniquely delivered using community directed intervention (CDI) strategies.

Triple drug administration (TDA) is one option for integrated treatment through the simultaneous provision of albendazole, ivermectin, and praziquantel or azithromycin. Studies suggest that TDA is clinically effective and cost-efficient, and the WHO recommends TDA of albendazole, ivermectin and praziquantel in areas that have had one to two previous rounds of treatment (5). However, TDA is not widely utilized in co-endemic countries, even those with established integrated NTD programs. In addition to preventative treatment strategies such as MDA there are a number of other activities that can potentially be integrated between NTD programs. NTDs that are co-endemic in the same geographic area can integrate activities such as mapping, vector control, community sensitization and education, health worker training, surveillance, monitoring and evaluation, and disability management.

In January 2012 an array of partners gathered to endorse the World Health Organization (WHO) NTD Roadmap and launch the London Declaration, a commitment to pursuing control or focal elimination of select NTDs by 2020 (7). Integration of NTD programs is considered to be one of the most promising approaches for achieving the London Declaration goals, and integrated NTD programming has been endorsed and recommended by the WHO for NTD endemic countries to optimize program implementation (11, 27). However, while there is evidence suggesting beneficial effects of integration on NTD program coverage (13) and costs (14), there is minimal information regarding how to effectively operationalize integration or any potential detrimental impacts. The lack of a systematic analysis of integration experiences limits the ability of programs to optimize NTD program implementation in co-endemic areas (12). Given that integrated NTD programs are now encouraged in endemic countries, there is currently a unique opportunity to learn from stakeholders as they engage in integrated programming.

In this study we aimed to identify how perceptions regarding the role, effectiveness, and implementation of integrated NTD programs differ among various NTD stakeholders. We also aimed to describe program integration and best practices for implementing integrated programs

from each stakeholder's perspective. We focus specifically on the NTDs for which MDA is the standard of care due to geographic and interventional congruencies, as well as to limit the scope of this analysis.

Methods

Study design and conceptual model

We conducted a qualitative cross-sectional study to identify and harmonize NTD stakeholder approaches to integrated program delivery. We identified seven primary stakeholder groups involved in and affected by integrated programming of NTDs, including partners at multilateral organizations, funding partners, implementation partners, national Ministry of Health (MOH) teams, districts MOH teams, volunteer rural health workers (known as community drug distributors, CDDs), and community members participating in MDA campaigns. The conceptual model in Figure 1 outlines the stakeholders involved in integrated NTD programs as well as simplified descriptions of their driving interests and influences on NTD integration.

Sampling frame and recruitment strategy

The sampling methodology utilized the NTD stakeholder group (N=7) as the unit of analysis, as determined through a maximum variation approach. An overarching tenet of maximum variation is the understanding that each stakeholder group must be considered separately, and thus a distinct sampling frame and sampling strategy was identified for each group.

The sampling frame for stakeholders working in multilateral organizations and funder organizations was individuals deemed as subject matter experts (i.e. key informants). In this study, subject matter experts are defined as influential individuals recognized in the NTD domain

as thought-leaders or policy-influencers, who often present and publish in the field. Subject matter experts must have been working in the field of NTDs for ten or more years.

The sampling frame for the implementation partners and national MOH workers was limited to subject matter experts working in five highly co-endemic countries (i.e. endemic to all five MDA-indicated NTDs) and thus these stakeholders work in a variety of NTD-endemic countries throughout sub-Saharan Africa and Asia. The sampling frame for district and rural MOH workers was even further limited to one country of in-depth focus. The country of in-depth focus was selected because it is endemic for all five NTDs for which MDA is the standard of care, noted above. It is located in sub-Saharan Africa, and the population is largely rural. The name of the country cannot be provided, in accordance with Institutional Review Board (IRB) stipulations.

The recruitment strategy used to identify all stakeholders—with the exception of community members— was purposive quota sampling of mutually exclusive key informant groups (28). The strategy was deemed appropriate as this research aims to capture and equally value the range of NTD stakeholder perspectives, from influential key informants at the global level to program implementers at the local level. Only individuals working on two or more of the five NTDs for which MDA is the standard of care were recruited.

For community members, the sampling strategy was random purposive sampling (29). During four community-based MDA campaigns in the country of focus, community members gathered to receive NTD health education and treatment at schools and health posts. Education was provided prior to treatment, and then treatment was delivered to community members throughout the day. During the campaigns, a translator or CDD made an announcement that community members may be approached and invited to participate in interviews regarding their experiences with NTD programs. The translator or CDD was instructed to approach every 5th woman who participated in MDA treatment, starting with the first woman treated. This probabilistic sampling strategy for

community members was used as this group is much larger than the other stakeholder groups and we aimed to capture a more representative sample of these NTD stakeholders.

Due to the large number of individual stakeholders in each stakeholder group, it was not possible to ensure complete data saturation.

Interview structure

Semi-structured key informant interviews with a mix of respondent and informant style questions were used. Participants were asked both to describe the process through which they engage in integrated programs as well as their recommendations to others regarding how integration should be pursued. They were asked to explain their rationale for these recommendations, describe factors that facilitate success, and describe barriers that challenge successful integration. Many of the questions were similar across stakeholders in order to compare and contrast answers. However, questions were also specific to the experiences and roles of the particular stakeholder.

Ethics

All interviews were audio recorded and participants were required to provide verbal consent prior to the commencement of the interview. This methodological approach was granted exemption status from the University of Washington IRB committee under a minimal risk determination status. Exemption was granted with the understanding that no country names or personal identifiers of interviewees would be available.

Data Management and Analysis

Transcripts were uploaded to the software program Atlas ti. (V.7 2012). Coding of key themes involved a mix of applying in-vivo open coding and *a priori* thematic coding from a start list (30).

After the first round of coding was completed, a second round was conducted using an adaptation of the constant comparative coding method. Constant comparative methods help conceptualize and describe the variety of responses in the data (31). This set of codes and memos were used to identify themes that highlight commonalities and differences between stakeholder group responses (30). In qualitative research, themes are recurrent unifying concepts or statements about the topic of inquiry (32). By undertaking this two stage analysis process we utilized a mix of case-oriented and variable-oriented analytical strategies (33).

Results

Study participants

A total of 41 interviews were conducted with stakeholders: 2 from multilateral organizations, 2 from funding partner agencies, 4 implementation partners, 5 national MOH health workers, 6 MOH district health workers, 8 CDDs, and 14 community members. Salient themes varied by stakeholder however dominant themes arising during analysis were relevant to (1) variations in definitions of “integration”, (2) differential effectiveness of integration according to the specific NTD activities integrated (3) community perceptions of integrated NTD programs, (4) the influence of funders on NTD integration, (5) perceived facilitators of integration, (6) perceived barriers to integration, and (7) the effect of integration on health system strength. Within each of these themes, we identified where feedback was similar, differed, or was unique to each stakeholder group. In the section that follows these themes are discussed in greater detail, with a selection of supportive quotes provided in context.

Theme 1: There are variations in definitions of the term “integration”

All participants, with the exception of community members, were asked to provide a definition of the term “integration” within the context of NTD programs. In general, definitions were broad, even

within stakeholder groups, and participants often provided rationales for integration rather than a working definition. Health workers, particularly CDDs, described integration of specific activities while individuals at multilateral, funder, and implementing organizations focused on definitions of integration relevant to upstream planning and measurement.

Integration is doing several activities at one time in one day. For example, distribution of Mectizan together with the salt testing for iodine. We can also be measuring the growth of under 5 children at the same time, giving us more efficiency – CDD 5

The idea of integration is not to have a disease focused approach but to think about the program outcomes to accomplish, what must be done, and how and for whom [necessary activities] overlap – Multilateral 1

A number of participants noted the lack of an existing definition but cautioned against being too definitive, citing the need to maintain flexibility in applications of the term.

Seeing some of the conversations people *don't* have, I don't think there's a standard [definition]. On some of these things, the minute we define them or put parameters around it, you restrict yourself instantly. And that's a problem – Funder 1

Conversely, several stakeholders noted the danger of having such ubiquitous, vague terminology.

I think integration, you know, has got this buzz. "Integration!", but it means different things to different people at different times in different ways and to really define it, we have to be very, very specific. It becomes a buzz word and then people didn't want to hear it anymore for a while. "Don't say integration. Say coordination". It's hard, but I think we just need to be much more defined about what we mean here – Implementation Partner (IMP) 4

The lack of consensus regarding the definition of integration was evident in the many ways stakeholders used the term to describe various clinical, political, and organizational processes. However, the most common definition of integration across stakeholders was the act of coordinating specific activities and interventions when mutually relevant to two or more health programs. Some stakeholders also identified integration as a way to transfer knowledge between programs, particularly for diseases at different stages of elimination.

Theme 2: Integration is differentially desirable and effective, depending upon the specific NTD activities under consideration

Multiple stakeholders argued that there was a common misconception that integrating NTD programs for the five MDA-indicated diseases simply requires co-delivering all designated drugs. Rather, there are a number of activities involved in NTD control in addition to drug delivery (Fig 2). These activities can be integrated with one another or with complementary co-interventions such as safe water, sanitation, or nutritional interventions. But stakeholders unanimously noted that not all of these activities are contextually or scientifically appropriate for integration across NTDs.

It depends on the activities which can be integrated... There are some activities which you can totally not integrate. So we shouldn't force matters, to say, "Let's integrate. Let's integrate," but let's look at the activities. Can we integrate these activities? Can we co-implement these products? – MOH National 2

It's not integration for its own sake. It's smart program implementation and management – Funder 1

All of the specific program activities mentioned by stakeholders during interviews are discussed below.

Baseline mapping. Most MOH and implementation stakeholders were skeptical regarding the efficiency of integrated mapping efforts due to the need to modify existing mapping technologies and methodologies. Implementation stakeholders in particular noted that there are a number of approaches to developing integrated sampling strategies for mapping and subsequent surveillance, all of which would need to be considered carefully from both epidemiological and operational perspectives.

I think you could integrate everything together on the same [mapping] survey if you get all the right people together and they all agree on the sampling framework and collection methods. But I'm more concerned about whether the field teams can actually do that... what is the capacity of the team and how much time, extra time, they would spend out in the field to collect additional specimens during integrated surveys? – IMP3

Program planning. Stakeholder feedback indicated that integrated planning is a crucial and often overlooked aspect of integrated programming. Stakeholders mentioned that often integrated programs are launched without careful epidemiological mapping, considering disease specific targets, program maturity, integration history, or thinking through the specific activities that should be integrated or remain vertical across programs.

...we need to get our plan straight about how we are going to do this and we need to make sure that we know what we want and get consensus within our community...otherwise it can get really complex really quickly...it can stifle progress for a while –IMP4

Each country is in a different stage of absorbing [integration] and taking it on. And I think one of the mistakes that people make is you say okay, we write up a national

plan and we say we're going to integrate... It does not happen overnight. And it phases in, and I don't think people have thought about that – Funder1

During discussions on planning, most stakeholders mentioned NTD Steering Committees. Implementation partners in particular notes that a critical aspect of planning is empowering an NTD Steering Committee that serves as an entity for harmonizing partner and MOH interests into a broad and long-term country-specific implementation strategy.

If [partners] are not coordinated well before implementation you create huge tensions between partners in the field and that is not good, that's not helpful to any program. It is really important for partners to have those conversations to work out how are we going to work together, how are we going to support the ministry, and then go in with a well-coordinated integrated strategy – IMP3

Supply chains. National MOH stakeholders highlighted supply chain integration as an important activity in successfully integrated programs. If supply chains are not appropriately coordinated it can delay co-distribution of drugs to the community. Various MOH stakeholders reported that these delays can undermine long-term program credibility and community desire to engage in integrated programming if drug delivery is repeatedly postponed. However, multilateral partners noted difficulties with integrating supply chains due to the different ways in which drugs are shipped and managed.

Another challenge with integration is supply chains...Ivermectin is already in the country, ready for MDA but they just put it by the doors waiting to go to the community because albendazole is not yet here – MOH District 6

Health worker training. Health worker training was one of the activities that national MOH stakeholders were most enthusiastic to integrate. They noted that the degree to which

trainings should be integrated depends upon which level of health provider is targeted (for example, CDDs versus district-level environmental health technicians). For CDDs, some MOH stakeholders cautioned against consolidating two disease-specific trainings into one integrated training. Rather they recommended that the same number of integrated trainings take place whereby individual CDDs learn about the same diseases multiple times. No recommendations were made regarding specific training tools for integrated trainings. In contrast, CDDs recommended that they participate in fewer vertical trainings overall, particularly trainings that are repetitive and uncompensated.

Community sensitization. Most MOH stakeholders said that integrated community sensitization activities have the benefit of presenting a coherent message to community members, both across NTD programs and other community-based delivery programs. The MOH stakeholders reported that integration of community member education is less controversial relative to CDD education, because the messages are simpler and effectiveness is highly influenced by consistency.

If we use those resources together and get whatever is our target population together, possibly the effectiveness will be much – I want to believe much, much higher than it could if we wanted to do them independently. And the other disadvantages of doing that independently is that when you go into the community, you find that you may be telling them the same information, but from just a slightly different angle. They're going to say, "But this, we have already heard this thing. Why are they coming again like this?" – MOH National 2

Drug delivery. Drug delivery was one of the most contentious activities to integrate, with stakeholders exhibiting particular hesitancy around potential programmatic transitions to triple drug administration TDA-based MDA programs. Several MOH stakeholders in favor of TDA were of the opinion that drug co-delivery would facilitate greater community participation in MDA

activities. Some CDDs also explained that co-delivery regimens such as TDA would give them more time for farming, from which they generate more income than they currently do from the allocated program incentives.

I think more people would participate when you are using one stop to kill several bits. They would come in large numbers because we will not bother them a lot. We just go to the community and say, “Okay. This year we’re going to do MDAs for schisto, for LF, for oncho, for STH at one go.’ After doing that, we are done with them. Otherwise, they get tired of the participation – MOH District 6

We are needing to go into the fields, so if those drugs were together we would have only one day to treat two types of diseases so it saves time we can spend outside in the fields – CDD2

A number of stakeholders mentioned that co-delivery of drugs or TDA in particular will only be feasible with improved community sensitization efforts and political will. A number of additional challenges associated with TDA are described in sections below.

Supervision. MOH stakeholders described that there are multiple layers of supervision required in NTD programs: national MOH workers supervise district workers, district workers supervise local health workers and community activities, etc. District MOH workers reported that integrated supervision of community activities is extremely effective. Integrated supervision saves them time and two district workers reported that it also improves their relationship with the communities in which they work.

Doing supervision of the community should be integrated. If you go and come back for all these things, each time separately, people say that, “this person doesn’t know how to leave. She comes here quite often just to check on one thing and she goes –

the thing you are interested in is something else, other than the job you are doing."

So if you integrate you go and you check all the disease registers, you discuss everything and then you come back so you give time to those people to reflect on other things – MOH District 5

Reporting. Individuals across stakeholder groups said that MOH reporting activities are not typically integrated. MOH health workers often found this paradoxical given that they are at times completing disease-specific reporting forms for integrated activities targeting multiple NTDs simultaneously. MOH stakeholders discussed complex disease reporting procedures as an impediment to conducting integrated data quality assurance, monitoring, and evaluation.

Implementation and multilateral partners pointed to recent efforts to develop integrated reporting forms to address these issues. However, a number of MOH stakeholders highlighted that these forms are not yet user friendly. Additionally, multilateral stakeholders pointed out that some rich disease-specific information is lost in integrated reporting forms.

Depending on the country, you see very complex forms that try to integrate everything together. Who is filling these out? It's mostly farmers who don't have a lot of education and we're not making it easy for them. And so if that's the key entry for data and it's already being entered incorrectly and then it's just being aggregated up, what kind of quality data are we getting? - IMP3

Integrating forms adds efficiency in reporting by creating one form but by trying to improve the efficiency we may have decreased quality...There is less information now for expert panels to review and give advice on. It dilutes the quality of [disease-specific] guidance that can be provided. At the same time without it, we couldn't see the whole country as a whole picture - Multilateral 2

Morbidity management. Morbidity management of individuals with advanced NTD sequelae was an activity that the majority of stakeholders reported should remain vertical. They cited that while the identification of individuals in need of morbidity management may easily be integrated into MDA or mapping activities, the overlap in target populations requiring surgery for specific diseases may not be extensive. One stakeholder described how there are two models for integrating morbidity management with other program activities. In one model, programs attain cost-effectiveness by integrating resource intensive activities such as identifying people in need of surgery, seconding experts from other areas, and transporting patients to specialty treatment areas. In another less efficient model, these activities are referred to as integrated, but are actually conducted serially, one after the other. None of the stakeholders discussed integrating morbidity management into the health system more broadly.

Research. Implementation partners and funders similarly noted that integrated research drives integrated implementation. However several of the implementation partners highlighted that preemptive vertical priority setting is a necessary step to avoid compromising scientific rigor when trying to integrate research efforts, such as developing integrated sampling methodologies or new diagnostics; thus disease specific end points can at times drive integrated methodological innovations. Additionally they described how research that promotes standardized integrated NTD metrics, methods, and delivery systems across NTDs as well as other diseases is crucial for building the evidence base necessary for achieving comprehensive universal health coverage.

Research is very complex because each NTD has...its own life cycle, its own specific dynamics, ecological dynamics and transmission dynamics, etc. So sometimes one size will fit all and sometimes it won't and we have to figure out when it does fit all and when it doesn't, when it makes sense and when it doesn't. Having more people at the table with more perspectives is good. You develop more innovative and creative

methods. But sometimes it's hard, too, because it takes longer to get there and you have to compromise to satisfy more parties – IMP4

Standardized [data] collection methods are essential to create opportunities for an integrated approach whether it's the immediate NTDs that we're focused on or new opportunities – IMP3

Theme 3: Community members have favorable perceptions of NTD programs, but few explicit opinions regarding integration

Community members had unique feedback regarding the acceptability and feasibility of integrated NTD programs. Amongst those interviewed there was unanimous fear of NTD-associated morbidities, particularly elephantitis and visible worms in stool. This fear translated to strong community demand for MDA programs.

When those volunteers come with those medicines, we receive it with a green light because we know that those medicine which they are coming with, they are one, for free. Two, they give hope for life. Once you have been attacked by these diseases, you cannot even dress well because the leg swells so badly – Community Member (CM) 15

There were three points of constructive feedback from community members regarding MDA in general. First, during pre-treatment community sensitization and education it is often not clear which diseases are being treated simultaneously or during different MDA treatment rounds. Second, MDA programs can demand considerable time from community members to participate in all education, registration, and treatment activities. Depending upon the treatment schedule, these NTD activities can occur several times per year and are likely one of many community-based health campaigns in which community members are asked to participate. Lastly, some

community members desired more treatments, particularly expanding praziquantel treatment to adults in schistosomiasis endemic areas. These points of feedback were echoed by volunteer CDDs.

When we do [MDA] in different days what happens is the people may not understand. They're going to think that the drug which has been given at the second day is the same drug which was given in the first, then they will miss out on one of the treatments – CDD5

When we talk of primary healthcare, it's integrating all the health programs together and bringing them to the community. And with that the community then knows and gets used to it. But we have brought everything vertical, everything alone. And now when you come to the community, they will even tell you "I'm confused". Yesterday you came and told me that my nutrition is this, this, and this. And yet today you are coming and saying my nutrition is this – which one now should I follow?" Each program, they want to achieve their own goals with their own messages... So maybe working together we would have also relieved these confusions which we bring to the community – CDD4

Women noted that men in particular are likely to be absent from MDA events when they perceive that the campaigns require a large amount of time throughout the year for each separate program.

It's hard for these male people because they need to find food for the family. So, they can't force themselves to stay there and wait for medicine while at home there is no food. That's why the [CDDs] don't find these males – CM6

In general it was difficult for community members to discuss their preferences regarding integrated activities relative to vertical activities. When asked, one community member shrugged and said,

“This is government decision, when they say to receive drugs, we just accept it, and we don’t have an option.” (CM9). When asked about their potential participation in integrated treatments in the future, some community members feared taking too many tablets at once during integrated campaigns. Additionally, two community members mentioned concerns that further integration would actually make treatment days longer, especially if there are only a few health workers present at each campaign.

If you would say four, five tablets, I say oooh no, four or five tablets at once. That must be too heavy. We’d say no, from fear – CM3

However, the majority of community members independently noted that they are accustomed to taking several medications at once, repeatedly providing the example of malaria treatment regimens and pain killers. Most of those in favor of integrated MDA drug delivery focused on the time savings that would be accrued.

If you take both type of medicines together, you prevent both types of diseases, while if you take one type of medicine, then you might see that other disease... when you take both types of medicine at once, you still have time to do other things. That means your time is your time – CM14

Several district and rural health workers noted that community members are unknowingly already accustomed to integrated NTD programs through co-delivery of schistosomiasis and STH services in schools and LF and onchocerciasis programs in communities. One CDD was surprised that some might consider programs such as LF and onchocerciasis separately in the first place, “From our side, we only call it the oncho program...though I suppose we know the filariasis is there” (CDD 2). Similarly, although several programs have successfully integrated activities in some co-endemic countries, it is clear that integrated programming has led to some confusion on

the part of CDDs and, as a result, community members. One CDD erroneously explained, “We combine treatments because Mectizan is there to prevent disease while albendazole is there to cure worms that are already too much so it’s good to combine them. One is for prevention and the other is for cure for which is already there” (CDD3).

Many community members cited the expanded program on immunizations (EPI) as an example for why integrated community-based programs are acceptable and advisable. Community members noted that “first clinic” (EPI and growth monitoring during child health weeks) was appropriately integrated because all activities shared the common goal of promoting child growth. These community perceptions were echoed by district workers in the same communities.

Let’s take it from the way we evolved from doing child health days. Previously we were giving under-fives so many different programs, but now you find that we’ve brought several other activities together. So that kind of integration – that helps people to get all services under one roof and then it improves the turnout – MOH District 2

Theme 4: There are a number of multi-level factors that stakeholders perceive as integration facilitators

Interview participants identified four main facilitating factors of integration including the need for efficiency with limited resources, strong central leadership, conception and launching of new integrated programs, and continued relevancy post elimination. The need for program efficiency was the most frequently cited driver for and benefit of integration during stakeholder interviews. Specifically, MOH stakeholders at every level described financial and time efficiencies as the primary factors encouraging program integration in low income settings. For example, several national MOH health workers noted that when they don’t have adequate funding to hold a CDD

training on one disease, they will utilize resources earmarked for another disease to provide an integrated training.

Without integration there would only be funding for one training rather than four trainings. So even in delivering drugs, it's a matter of just bringing those drugs in one vehicle and distributing them rather than coming separately for each disease, where, at the end, you are putting much pressure to the [District Health Office]. At the end, we would not be able to assist – MOH District 6

Almost all of the stakeholders interviewed, with the exception of community members, stated that integrated strategies will be most effective if they are first institutionalized at the national level of a health system before being launched at district or local levels.

The LF coordinator comes and says, "Okay. I want the volunteers to do this and this." And off he goes. Next time the onchocerciasis coordinator comes and says, "Okay, I want to meet you guys" and, starts again telling us or teaching us about [onchocerciasis]. Then next time, oh, we get tired...Integration should be started from the national level. With so many coordinators at the national and district level you are trying to create the programs vertically – MOH District 4

Most multilateral, implementation, and MOH stakeholders said integration at the national level is most efficient if there is a single NTD coordinator overseeing disease-specific NTD focal persons. Such a leader can promote cross-disease coordination and improved communication at the national level which, according to MOH stakeholders, will trickle down to the peripheries.

Each disease has its own unique needs and you still need to have someone behind each of those diseases...But, having an individual who can take responsibility for the

larger NTDs, I mean that's desirable in terms of integration, having someone with the big picture, especially when you have specific activities that can be integrated – IMP3

The country should begin by sensitizing the program managers, knowing that like in Africa, the resources, they'll never be enough so they need to come together, sit together as program managers, work together, share. If people in districts see that you are working together, they will work together as well – MOH National 3

Additionally, several multilateral and donor partners remarked that it is easier to launch new integrated programs in a country than it is to integrate extant disease-specific programs due to entrenched institutional identities. One multilateral stakeholder noted that, in this capacity, NTD Steering Committees endowed with decision making power (not simply endorsing entities) are critical in the integration process to ensure that Integrated NTD Master Plans are available with actionable recommendations and integrated activities.

What we are doing is very very simple. Providing the drugs is simple. Record keeping is simple. Of course reaching people can be complex. But newly integrated programs combine efforts and it becomes even more simple... It is very rare that a country with a Steering Committee would decide not to launch programs as integrated. It is just logical – Multilateral 1

Additionally, as countries work towards NTD elimination, some MOH stakeholders noted there are political incentives for national and sub-national health workers to integrate their workloads and programs. Specifically, it allows programs and personnel to have continued relevancy and expertise after single diseases have been locally eliminated.

Theme 5: There are a number of multi-level factors that stakeholders perceive as integration barriers

Stakeholders identified four primary barriers to effective NTD program integration: (1) a fear amongst MOH workers that they will lose their jobs or recognition of their work, (2) external timelines or funder pressures that do not allow for a lengthy integration processes, (3) tensions between school and community-based delivery proponents, and (4) the fact that some strong or well-funded programs do not see integration as a “win-win”. These barriers are driven by political and administrative factors.

Stakeholders at all levels reported that integration is often not pursued or is inefficiently pursued when stakeholders perceive that they won’t be able to maintain some degree of disease-specific autonomy and recognition of program-specific markers of success.

The other thing that could be a challenge in integration is basically the attitude of those people who manage programs asked to integrate. Attitude, prestige, come in and begin to affect the way we work. Some people want to take all of the glory, all of the success, all of the compliments that come, so they would feel like if they bring in other people, they may lose that kind of a degree of complementarity that goes to them. That now would have to become a shared success – MOH District 2

It has been in the ministry’s interest to have integration, for the sake of time and money, but what I see is it’s maybe us individuals that are the problem...we have been wanting vertical programs because coordinating together, it’s like I’m going to lose my powers – IMP1

While leveraging strong programs to increase the coverage or efficiency of weaker programs is a primary rationale for integration, several stakeholders expressed concern that integrating strong and weak programs could be to the detriment of strong programs. However, when asked, stakeholders could not provide examples of a situation where this phenomena had occurred.

If one program manager is laissez-faire, the laissez-faire will affect the whole integrated thing. Now, this other person that was hardworking would feel like they would lose a little bit success...If somebody's scoring usually 80 percent. You'll find once you've integrated with someone scoring 75, now you're scoring 65 –MOH District 3

Several district level MOH workers and implementing partners also expressed concerns that successful integrated programming might be used as a rationale for minimizing the financial support provided to sub-national disease control teams.

Often one car is used to supply everybody. It's like: "Well our malaria car broke down, but thank God the schistosomiasis car is coming in." Then it's like, "but now you only get one car because malaria and schisto – they're working together." Well, if you were managing things from the perspective of playing off all the vertical programs to get your resources, does that sound like a good deal? It sounds like a good deal for the people who buy the cars – IMP2

MOH stakeholders unanimously noted that vertical funding mechanisms limit the ability for NTD programs to integrate at national and sub-national levels. Some stakeholders recommended that funders and implementation partners take more responsibility for ensuring greater collaboration between disease-focused groups while other stakeholders recommended that governments take more responsibility for ensuring coordination amongst NTD partners working in a country. Funder influence is discussed in greater detail in *Theme 6*.

I think it could be fiefdoms, disease-specific groups who look at the disease-specific track but don't look at how it relates to the other diseases. Some groups come in and say, "we just look at our piece and we're not gonna worry about what the platform is

to get all the diseases moving forward.” And so you kind of just work in your silo –
Funder 1

My advice is to the government because whenever each NGO comes in the country, they have to sign a memorandum of understanding with the government and it is the government which has to assign that NGO to a particular place... And I know that each NGO comes with its own goals and what have you. But the government can still say, “Okay, you are doing part A and we have an NGO which is doing part B. Is it possible that you should work together?” – IMP1

Another identified barrier to achieving more extensive NTD program integration is the operational and political divides between community-based MDA programs (LF, onchocerciasis, and trachoma programs) and school-based MDA programs (schistosomiasis and STH programs). For example, according to several implementation and multilateral stakeholders TDA has not been introduced or scaled-up in any country largely due to the political paradigm shift that would need to take place prior to providing treatments to children in community-based settings.

And I think it has to do with politics. It has to do with the fact that there are school-based people and there are community-based people. And when you start linking everything into community-based, which you have to for triple drug administration, the school-based people are unhappy. So in the great political compromise, it's kept as the status quo: you pay 40% more and things are kept as two distinct rounds [of treatment] so that the school-aged treatment advocates are not threatened – IMP2

Many of the community members recommended that all treatment take place during community campaigns so that parents can supervise their children. Without advocating for one delivery system over another, the majority of implementation partners and MOH stakeholders commented

on the political complexity of choosing either school or community based delivery over the other. Some national stakeholders argued that more school-age children will miss integrated treatments if targeted in the community, while a number of CDDs argued that integrated community-based treatments could expand treatment to children who do not attend school. Several stakeholders noted that shared responsibility between Ministries of Education and Health means that there is an authority vacuum where both entities have a stake but neither claims ownership for the disease program.

When the community-based [treatments] aren't needed anymore, then you just switch over to the school-based...The idea is to find the people who are suited to provide the treatment...A large argument is related to cost. And another large argument is related to sustainability. Not enough is said about penetrance to the poor who may not be able to pay school fees and be there. And gender is a major issue in a lot of places where I work, because girls are less likely to go to school – IMP2

Lastly, many stakeholders highlighted that while integration is necessary and desirable in some locations, stakeholders should still track disease specific outcomes. A lack of disease-specific outcomes limits funder or partner ability to track impact and may diminish their desire to pursue integrated programs. Specifically implementation partners and multilateral stakeholders recommended disease-specific coverage metrics as indicators of integrated program success.

The idea is you go about implementing programs together in a way that results in efficiencies and cost savings but does not compromise the specific objectives of any of the disease-specific programs that are being integrated– IMP2

What are we aiming to do? We aren't aiming to integrate, we are aiming to eliminate a disease. You can quantify how much a program is integrated, but you have to monitor the progress of specific disease indicators – Multilateral 2

Similarly, although stakeholders noted opportunities for NTDs to integrate with other community-based health programs within a comprehensive primary healthcare system, this broad integration is often not undertaken because stronger, well-funded programs often do not see integration with NTDs as a “win-win”.

When discussing integration between NTDs and tuberculosis there was a comment “um, well, we can do that as long as it doesn't affect our program in any way”...and I said, “I mean if you integrate, it's going to change the dynamic and it could have an impact on your [progress and goals], but maybe for a broader good ultimately”. But it was sort of like, I'll integrate, but I don't want any of our programs to be affected in any way and I was like, “okay, maybe then you don't really want to integrate.” – IMP4

Theme 6: Funders have a profound influence on NTD integration activities

Many MOH stakeholders cited that integrated programs would be more effective if funder and partner resources were more easily integrated. A common theme arising in this regard was related to incentives for volunteer CDDs; given that programs rely on a largely volunteer workforce, the sustainability of the programs is compromised by changes in volunteer incentivizing. MOH stakeholders recommended that community volunteer incentive schedules align across NTDs. They also recommended that NTD incentives align with other disease programs, noting that well-funded programs such as HIV may compromise less-funded programs such as NTDs by offering larger incentives to health workers for similar work.

Now in the community you will find organizations giving CDDs incentives which is far much better than what we give. And our job is only done once, maybe twice. So they feel like this is something of less value...And when there is something that is not of good value in terms of appreciating the effort that you're putting in, people feel like it is something that is not to be taken seriously – MOH National 2

You have to look at sustainability. Because if funders just come with a lot of money, they can say \$50.00 a day for CDDs, and they'll be very happy. But after three years, the funder will go and that will be the death of the program. These programs that are there, they have to be assimilated in the government system. The funders, they come and go...When they go, still, the government should function – MOH National 3

And you start looking at all the other programs, not just an integrated NTD program, but you're looking at malaria, you're looking at HIV, you're looking at immunization, nutrition...Some programs provide per diems, others don't, and there are different incentives that are given to volunteers from each program...They don't feel like they're part of anything consistently. And I think we've really sort of failed in that regard at keeping them engaged throughout the year - IMP3

According to the stakeholders interviewed, funders may unintentionally thwart integration due to their desire for limited resources to be spent efficiently, causing different funders to cover different geographies of a country in a piece-meal manner. Additionally, because some funders only provide resources for specific diseases their resources may not be available for integrated programs. As one stakeholder points out, there is a delicate balance that a funding organization must maintain to ensure that it has fidelity to its mission statement while ensuring maximum health impact.

If donors will only work on one disease then there is no hope that integration will take place. Usually donors just take each part of a country to cover and do some different things. While if they really worked together it would be just one intervention that they work together for training, reporting, such things. The donors can be very convincing and have a lot of power over what happens in the community –Multilateral 1

In all fairness to the funders, if they're going in and saying we are supporting trichiasis surgeries, then they just want to have information on trichiasis, not eye health overall. So it's like you know, some flexibility is nice not to be so closed off of those opportunities, but I totally understand to a certain extent, like yeah we could quickly start going in another direction, lose focus, and start spending a lot more money than we wanted – IMP3

However most of the funder, multilateral, and implementation partner stakeholders remarked that funder and implementation partner culture appears to be changing, with increased emphasis on country needs and integrated programming. Newly established NTD coordinating committees might be a facilitating factor.

I think it's starting to change with some of the partners. I appreciate that organizations have disease-specific mandates. But I think new groups coming in need to be brought into that culture that's been developed in the existing community. Yes, you may have a disease-specific focus that your institution requires. But on the ground, if we all work together, maybe we can all leverage more bang for our buck... I have always been really impressed by the flexibility but also the positive, informal nature of the NTD community. – Funder 2

We don't want to duplicate any efforts. So if you go into a country and you say these three groups are in there supporting the Ministry of Health and they covered everything but trachoma, then we might go in to bring the trachoma piece in. And you could say in a more traditional sense, we're just supporting trachoma in that country but we really see it being done within the context of an integrative program – Funder

1

Theme 7: NTD integration affects NTD program strength, but also has broader health system effects

Stakeholders reported that NTD integration can affect NTD delivery systems as well as the health-system more generally. NTD-specific effects include transferring knowledge from successful programs to scaling programs and strengthening the presence of NTDs on the global health agenda. Broader health system effects include general improvements in community based healthcare programs, encouraging a culture of learning from other disease delivery platforms, and progress towards universal primary healthcare coverage.

A number of stakeholders across levels recommended that in order to maintain NTD scale-up success, integration be pursued in a “fluid manner” (IMP3) based on the maturation of different disease programs and disease dynamics at a local level.

Integration helped improve the coverage of the weaker program in [our country] because we relied on the existing strategies of the stronger program to implement the weaker one...LF was the stronger program at the time so onchocerciasis was added on to it logically and financially and LF is still going on as it should – MOH National 5

In this regard, stakeholders repeatedly provided LF and STH as examples of programs for which integration might facilitate a transfer of knowledge within the NTD system; geographies that have

successfully controlled LF and are transitioning to post-MDA surveillance while attempting to scale-up nascent STH programs could integrate activities to avoid losing progress made by LF programs. These disease programs have particular co-dependencies and a natural opportunity for synergy due to the fact that they utilize MDA of the drug albendazole.

Now the really important piece of integration is about transferring...If we've got these programs like trachoma, onchocerciasis, and LF that are going to be shutting down, schistosomiasis and STH are these nascent programs that don't know what they're trying to do...But I'm afraid it may wind up, in the end, with one structure collapsing and another having to be build up again – IMP2

We're ready to scale up [STH programs]...We need to make sure that there's really not a hiatus after LF programs are stopped....because you do have the potential to lose some gains if you drop back to nothing– Donor 2

Several stakeholders also discussed how integration helped NTDs develop a larger presence on global health agendas and include a larger number of stakeholders. Various stakeholders noted that the benefit of integration to NTDs in terms of advocacy and fundraising has been indispensable.

There was some smart rethinking of some major people in the field who looked at the burden and looked at the funding and knew that we had this rapid impact package. We could do a lot for a little bit of money, for less than 50 cents per person at least from a preventive chemotherapy standpoint, and decided to really re-package it and advocate for it in this new framework. So being able to show that the NTDs as a whole has this huge disability...equal to in many cases tuberculosis or malaria or HIV where there's been a lot more funding, you're able to address them at very little cost...I think

that was very smart and it certainly has had many benefits to leveraging more money and funding into the NTD space. We're a larger voice together than we are separate and I think it has been beneficial, but certainly challenging in some ways as well –
IMP4

According to a number of MOH stakeholders, NTD program integration could also result in broad health system improvements if it encourages health worker efficiencies. These efficiencies could improve community participation in community-based healthcare activities generally.

Each of us has demands on our own time. If we become more efficient, everybody in the system will have time for spare...If we're telling the people that we want to meet you at the dissemination and community sensitization on Mectizan, if you bring in the LF, you bring in praziquantel, that could reduce the community's absence in doing their other works, which will possibly increase the attendance for NTDs and also for other health programs rather than saying, 'today you want them for praziquantel and then next week you'd want them for Mectizan. And then the other week we want them for child health days. People, say "Ah, are we not going to be doing our own things?"'
– MOH District 2

Multilateral and implementation partners noted that the act of implementing integrated health programs forces public health workers to learn from what works, to look to programs and platforms that have had success, and to think about what can be learned from them. Several stakeholders argued that a focus on learning from integrated programs will benefit both NTDs and country health systems more broadly.

There's a lot of different platforms out there that are doing great work for other [disease] programs. We're just not aware of all those platforms...And boiling down

complex problems into specific problems, identifying what we really want to understand and test with a platform is not easy but it could likely be worth it – IMP3

A subset of stakeholders across levels also mentioned that establishing an integrated community-based NTD platform affords the opportunity to provide preventative healthcare for NTDs and other conditions outside of formal treatment settings. This is important for achieving universal health coverage of preventative healthcare services and for disease elimination efforts in particular.

Take Ebola for example. When people talk about a health system, they're talking about the ability to have outreach. And outreach using community-based approaches is part of the health system...They've activated a part of the healthcare system that's a very important part...So what we have to learn from NTDs is how to get out of the healthcare system and find people who are not "sick" yet – IMP2

So often [community-based] campaigns strengthen the larger health system... You can't just sit back and say, well, the primary healthcare system's gonna figure this all out. By having these opportunities and platforms from a community-based elimination program you do strengthen the capacity of the health system at a very local level, outside of the health units, to do disease surveillance, to do specific activities that I think the primary healthcare system fails at. We're more developed in healthcare delivery, and we often fail in primary healthcare outcomes because of that – IMP3

Now all the NTDs are enmeshed, because we're working together in a lot of ways and we're dependent on each other now. If we reach these elimination benchmarks in this integrated way it will be a proof of principle...It's a whole new paradigm for how you can potentially eliminate in this bundled integrated fashion – IMP4

Discussion

In this qualitative study conducted among NTD stakeholder groups, seven main themes emerged regarding integration. These themes reveal a number of perceptions, facilitating factors, and barriers to integrating NTD programs. In general, MDA programs provide a well-accepted platform for reaching at-risk community members with preventative health services in low-income communities. The primary rationale provided for integrating NTD programs was to build upon existing program strengths for the benefit of one or more programs, achieving financial and human resource efficiencies in the process. However, as highlighted by varying stakeholder definitions of “integration”, the term has often been simplified to mean co-implementation and stakeholders unanimously highlighted that co-implementation only makes sense for certain advantageous activities. Activities that most multilateral, funder, implementation partners, and MOH partners highlighted as particularly advantageous to integrate included planning, health worker trainings, supply chain management, drug delivery, and community outreach. Quotes and opinions provided by stakeholders must be considered within the context of stakeholder positionality within the NTD community. For example, many of the remarks from implementation partners regarded understanding and meeting expectations of target communities and funders.

Stakeholders identified a number of factors facilitating or challenging NTD integration, a summary of which can be found in Table 1. These factors build upon important themes such as community perceptions of integrated NTD programs and funder influences on programs. Stakeholders identified integration barriers similar to those identified in research on integrated primary healthcare in high income countries, including vague visions of change and the absence of guiding operational definitions, amongst others (34). Another commonality with findings from healthcare programs in higher income settings include that stakeholders in this study acknowledged the essentiality of relationships, trust, buy-in, cooperation and communication for successful program integration (35). Lastly, a prevailing health systems message was that as

NTD elimination goals are met in some countries it is important to leverage the established community-based infrastructure for other NTDs or broader preventative healthcare programs.

Based on these findings, we suggest a need for three types of integration to be considered separately and transparently: structural integration, process integration, and technical integration. Structural integration refers to coordination of organizational and human resource arrangements across disease programs. Process integration refers to co-implementation of existing programmatic activities and procedures. Technical integration refers to methodological innovations that can take place across disease programs to introduce or improve co-delivery of services. We also propose a set of ten specific recommendations for improving the efficiency, effectiveness, or acceptability of integrated NTD programs, a summary of which can be found in Table 2. Many of these recommendations echo actions that are already considered best practices in NTD programs, but draw attention to the need to fully enact or strengthen these actions for the purposes of successful and effective integrated implementation.

Structural integration recommendations

Recommendation 1: Countries may wish to establish a single NTD Coordinator for all NTDs for which MDA is the standard of care. Stakeholders recommended that this NTD coordinator could oversee disease-specific program managers and resource allocation, with frequent communication with the NTD Steering Committee. A leader with an integrated perspective and relevant competencies appears critical in contexts with changing vocabulary and foci, and can help facilitate alignment amongst stakeholders within a given health system (36).

Recommendation 2: Country-level NTD Steering Committees should be established or strengthened where already present. Weak committees should be strengthened by increasing decision making capacity and requiring implementation partners to present to the Committee prior

to program launchings. In this way Steering Committees could also help coordinate donor funding or support MOH program managers working with multiple donors. Stakeholder theory suggests that meeting the multiple needs of stakeholders on Steering Committees would maximize overall systems effectiveness. Steering Committees should help develop or review long-term integrated Master Plans that must include detailed planning regarding specific activities that will be integrated, how they will be integrated, and how integrated activities may be uniquely assessed for impact. According to study stakeholders, most existing integrated Master Plans do not meet these criteria.

Process integration recommendations

Recommendation 3: Healthcare integration in resource-limited settings is facing a similar definitional challenge that integrated care implementers have faced in higher income countries for decades (25). Thus the NTD Steering Committee in each country should establish contextual definitions and rationales for integration. Rationales for integration should include evidence or hypotheses relevant to (1) scientific rationales for integration, (2) administrative rationales for integration, and (3) health system rationales for integration. According to strategic change management theory, articulating a shared need for change with consideration of diverse stakeholder roles positively influences implementation effectiveness and structural change efforts (35). This process will provide a standardized manner for the Steering Committee to consider why they are pursuing integration and any potential unintended consequences. These rationales should be shared with all other levels of the MOH and Ministries of Education, where relevant.

Recommendation 4: Funders and implementation partners should empower and work with NTD Steering Committees by coordinating closely with the Committee and ensuring that MOH priorities are paramount (37). Evidence suggests that funder conditions can hamper resource allocation decisions following strategic planning or produce additional workload for health workers in the

field (38). Thus partners must also ensure that they are working closely with other institutions and organizations to ensure funds and activities are complementary. Contributing to a single integrated Master Plan may be a way to promote inter-organizational coordination from the onset.

Recommendation 5: NTD integration is complicated and, given that many of the challenges to effective integration are procedural and behavioral rather than scientifically based, change management activities should be undertaken at the national level and used to clearly communicate integration definitions, rationales, and Master Plan strategies to peripheral district and local MOH offices. While evidence from other studies found topdown management of NTD programs to result in negative feedback from peripheral levels (37), according to district-level stakeholders in this study, a strong core management structure is necessary to promote sustainable consensus on integrated NTD programming. There is a general understanding amongst stakeholders that effective integration is facilitated by having a collective vision, shared strategies, and common culture (39). A number of change management strategies such as promoting a shared mental model of integrated care, for example, would create an inter-organizational and inter-professional environment necessary for delivery of integrated care (35).

Recommendation 6: Many community members cited EPI as an appropriately integrated program because all distinct health interventions clearly share the common goal of promoting child health. This suggests that, in order to promote program acceptability, it is up to NTD public health practitioners to ensure that integrated programs have a clearly expressed unified goal and that this goal is being communicated to the public. In communicating this unified message, community members should be made fully aware of what diseases they are receiving treatment for and why. This may involve changing the structure of current CDD training curriculum and prioritizing community sensitization efforts.

Technical integration recommendations

Recommendation 7: The “justification for integrated delivery systems is to meet patients’ needs rather than providers” (40). Public health stakeholders should embrace a broader perspective of community-based health needs and available platforms for addressing those needs. For example, most district health workers recommended that child health weeks, which are well attended and accepted, be expanded to include other community-based healthcare delivery activities, including MDA delivery. This will necessitate some technical adjustments to standard clinical procedures. Other evaluations of community-based programs such as EPI have also concluded that shared platforms may have broad health system benefits (41). Ultimately multisectoral integration between activities such as nutritional intervention, water, sanitation, and MDA will result in more effective programs and thus shorter necessary durations of treatment (42). However, broader approaches to community-based delivery must be designed carefully in fragile health systems so as not to induce operational problems affecting program quality (37).

Recommendation 8: Where appropriate, MOHs should incorporate TDA into drug delivery schedules. Most community members described the implementation method as hypothetically acceptable and other health programs, such as polio immunization initiatives, have similarly identified community dissatisfaction when the number of intervention rounds are high (43). Yet many health workers do not know that TDA of albendazole, ivermectin, and praziquantel is approved by the WHO for the simultaneous treatment of onchocerciasis, LF, STH, and schistosomiasis (27). According to stakeholders, promoting TDA will require more specific guidelines from the WHO as well as more deliberate attempts to bridge the political divide between school and community-based treatment approaches. These efforts will require multi-year advanced planning to sync previously vertical NTD programs within an integrated platform.

Recommendation 9: Incentives and support systems for community volunteers and health workers should be aligned across NTDs and other community-based disease programs. This will require cooperation by multiple funding partners. By integrating approaches to volunteer

recruitment and maintenance there may be greater sustained engagement overall. Such necessary activities would also align with the WHO-endorsed Joint Commitment to Harmonized Partner Action for Community Health Workers and Frontline Health Workers (44). This recommendation could also be considered a part of process integration.

Recommendation 10: Stakeholders should standardize and redesign subnational reporting systems to capture information regarding which NTD program activities are integrated with other activities. Stakeholders reported that current data collection methods are confusing for health workers and supervisors working on integrated programs, and aggregated field data do not provide information regarding the effectiveness of specific integrated activities. Such data are necessary for linking particular integrated interventions to programmatic outcomes or health impacts in non-experimental settings. These data must be shared promptly and transparently with the WHO to ensure global disease control benchmarks are accurately monitored.

Limitations

One limitation of this analysis is that on one-on-one interviews of community members and health workers took place in private rooms within clinics or in places of work. Responses may have been biased if interviewed individuals felt that their feedback may reach employers or community leaders. A second limitation is that the data analysis did not involve multiple coders and thus intercoder reliability was not possible to establish. Lastly, the stakeholders' views and opinions reflect a subset of the NTD community and are not representative of all stakeholders. While patterns emerged, complete data saturation by stakeholder group was not sought, nor achieved. Further geographically-specific research should be conducted prior to the introduction of any relevant policy changes.

Conclusion

Application of a social science approach allowed us to provide a theoretical understanding of a number of similarities and differences between different stakeholder perceptions of the complex process of NTD integration. In general, there was greater variation between groups than within and stakeholder groups provided unique perspectives, rather than contrarian points of view, on the same topics. The stakeholders identified more advantages to integration than disadvantages, however there are a number of both unique facilitators and challenges to integration from the perspective of each stakeholder group. These findings provide both explanatory as well as meditative information to NTD integration stakeholders. The ten recommendations provided draw from the qualitative data to highlight structural, process, and technical opportunities to maximize stakeholder interests while promoting more effective and efficient integrated NTD elimination programs.

Table 1: Summary of facilitators and barriers to effective NTD integration, as reported by study participants

Stakeholder	Integration Facilitators	Integration Barriers
All stakeholders	• Efficiencies in time and human resources • Increased uptake in services through integrated programming • Ability to share elimination lessons learned across disease initiatives • Leadership structures that promote communication between disease focal persons	• Vague and varying “integration” terminology • External timelines or funder pressures that don’t allow for a lengthy integration process • Some strong or well-funded programs do not see integration as a “win-win” • Political encampments of stakeholders who work on school-based versus community-based NTD programming
Multilateral partners	• Communication between disease-specific working groups	• Loss of important disease-specific data resulting from integrating and simplifying data collection forms
Funders	• Disease specific outcomes that can be quantitatively improved following integration	• Difficulty in measuring progress of integrated investments • Concern for maintained effectiveness of stronger programs if integrating with weaker programs
Implementation partners	• Launching newly integrated programs as opposed to supporting existing disease specific programs	• Difficulty in integrating efforts with other partners • Absence of some integrated tools and methods, limiting ability to perform some technical integrated activities (ex. mapping)
MOH-national	• Need to maintain relevancy after disease-specific elimination goals are met • Efficiency with minimal financial resources • Strong NTD Steering Committees with decision making capacity • Detailed NTD Master Plans with specific actionable integrated activities	• Human resource challenges/ fear of unemployment or loss of recognition • Vertical funding which prohibits integrated activities • Vertical supply chains that can delay treatment • Fear of reducing effectiveness of a successful program following integration
MOH-district	• Human resource efficiencies • Desire to promote streamlined community-based activities • Integrated leadership at the national level	• Vertical direction and supervision at the national level • Fear of losing funding/resources following integration
Volunteer rural health workers	• Efficiencies in income generating time expenditure • Coordinated trainings that promote unified messaging • Perceived increase in community participation	• Incentives that discourage concentrated NTD labor inputs relative to other disease programs • Confusion in NTD knowledge base
Community members	• Efficiencies in income generating time expenditure • Presence and acceptability of integrated community programs such as EPI • Demand for MDA services that don’t consume excess time • Unified NTD messages during community sensitization	• Confusion during community sensitization activities • Fear amongst some of taking large amounts of medication simultaneously

Table 2: Ten integration recommendations

	Recommendation	Rationale provided by stakeholders
<i>Structural integration recommendations</i>		
1	Establish a single NTD Coordinator for all NTDs for which MDA is the standard of care.	The NTD coordinator could efficiently oversee disease-specific program managers, with an integrated perspective and necessary competencies.
2	Country-level NTD Steering Committees should be established or strengthened where already present.	Steering Committees should review long-term integrated Master Plans that must include detailed planning regarding specific activities that will be integrated and how they may be uniquely assessed for impact.
<i>Process integration recommendations</i>		
3	The NTD Steering Committee in each country should establish contextual definitions and rationales for integration.	Rationales for integration should include evidence or hypotheses that will build scientific and administrative consensus and promote a harmonized approach to program delivery.
4	Funders and implementation partners should empower NTD Steering Committees.	Partners must ensure that they are working closely with government institutions and Steering Committees to ensure funds and activities are complementary.
5	Integrated activities and systems should start at the national level of the MOH.	Integrated activities must be institutionalized at the national level to promote the necessary multi-level inter-organizational and inter-professional environment at district and local levels.
6	NTD public health practitioners should ensure that integrated programs communicate clear unified goal to community members	Community members should be made fully aware of what diseases they are receiving treatment for and why. This may involve changing the structure of current CDD training curriculum.
<i>Technical integration recommendations</i>		
7	Public health stakeholders should embrace a broader perspective of community-based health needs.	There is much to learn and gain from coordinating with other disease platforms. Additionally, platforms such as EPI, water and sanitation programs, and nutritional interventions provide complementary opportunities for providing preventative primary healthcare.

8	MOHs should incorporate TDA into drug delivery schedules.	TDA may result in greater coverage, time, and resource efficiencies. Promoting TDA will require more specific guidelines and bridging the political divide between school and community-based treatment approaches.
9	Incentives and support systems for community volunteers should be aligned across community-based disease programs.	Integrated approaches to volunteer recruitment and maintenance may results in greater sustained engagement overall.
10	Subnational reporting frameworks should be standardized or redesigned to capture information regarding which NTD program activities are integrated with other activities.	Current data collections methods are confusing for health workers and supervisors working on integrated programs, and aggregated field data do not provide information regarding the effectiveness of specific integrated activities.

Figure 1: Theoretical model of NTD integration stakeholders, simplified stakeholder interest drivers, and influence on integrated delivery

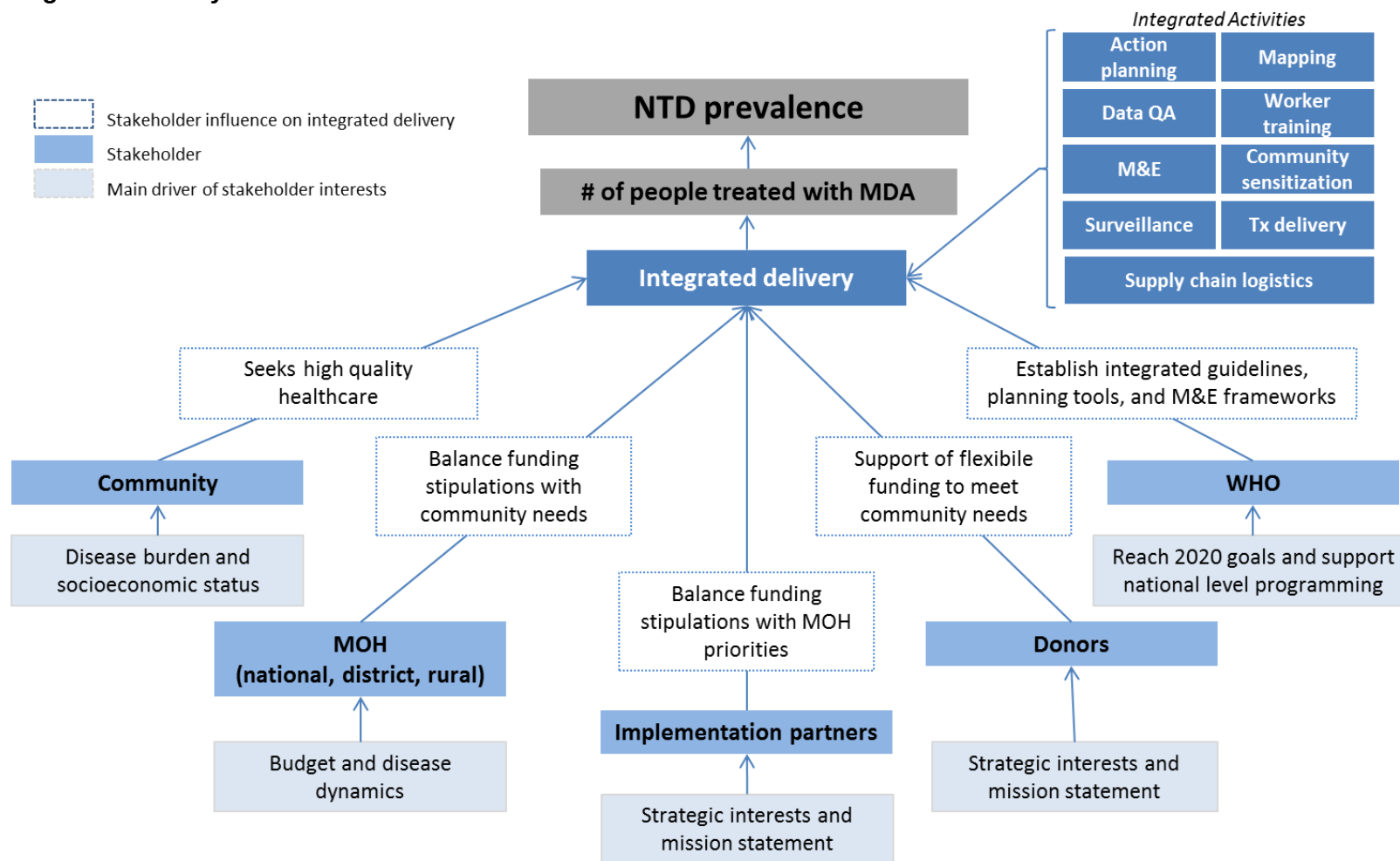
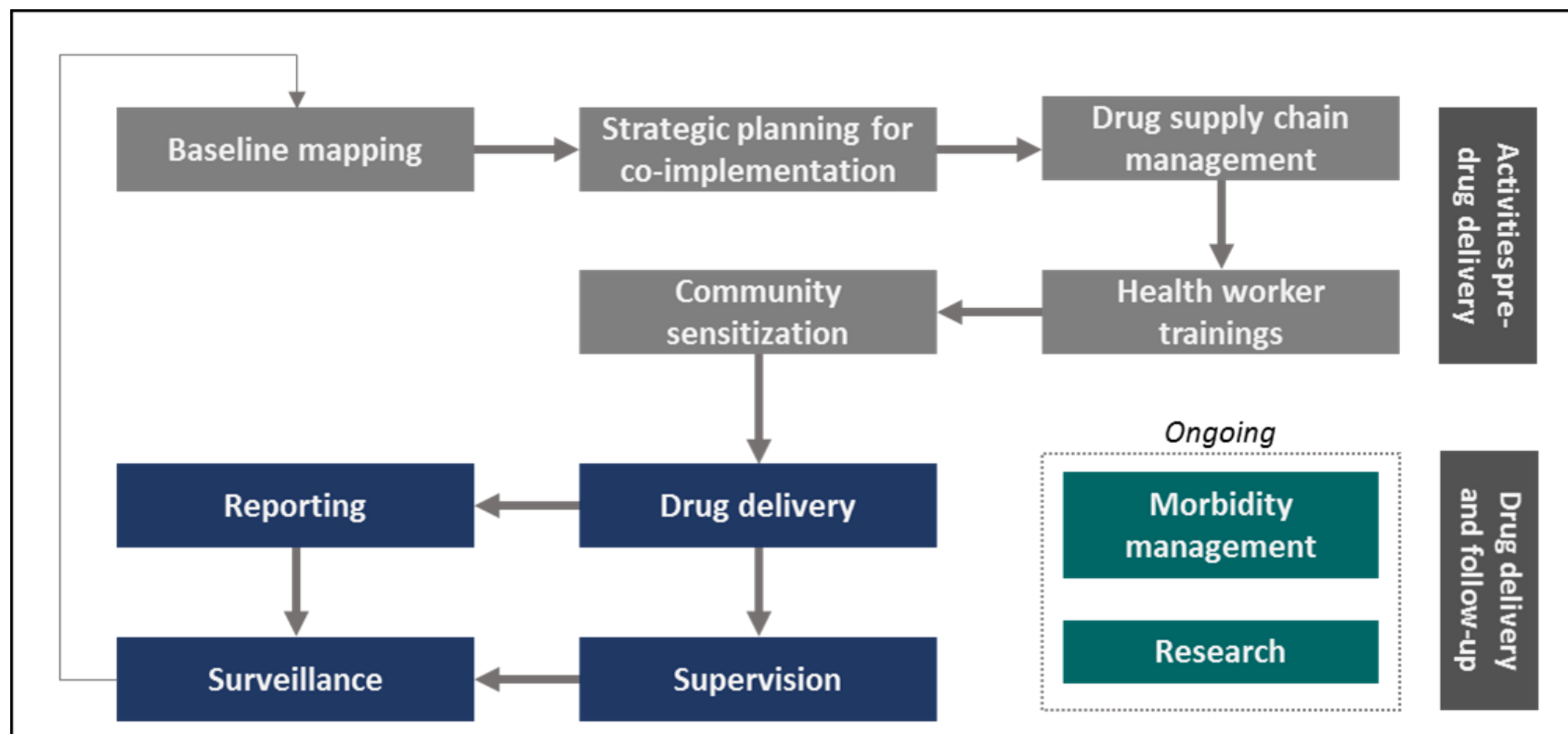


Figure 2: Summary of activities required for delivery of mass drug administration campaigns



CHAPTER 3: Combined effectiveness of anthelmintic chemotherapy and WASH interventions among HIV-infected adults

Introduction

The neglected tropical diseases (NTDs) are a group of viral, parasitic and bacterial infections that are associated with substantial global disease and disability, particularly in low income communities. Among the NTDs, helminth infections including schistosomiasis and the soil transmitted helminths (STH) are highly prevalent, infecting over two billion people (45). Mass drug administration (MDA), or the presumptive treatment of all at risk individuals with preventive chemotherapy, is used to control helminth associated morbidity in endemic areas. In 2001 the World Health Organization (WHO) endorsed MDA as the recommended strategy for controlling STH and schistosomiasis, with a goal of reaching at least 75% of at risk populations and up to 100% of school-aged children (27, 46).

The effectiveness of MDA as a control strategy is influenced by the treatment coverage of affected populations, the prevalence of different helminth species, drug susceptibility and socio-behavioral patterns that influence infection and re-infection rates (47). In addition, while MDA reduces morbidity by decreasing parasite burden, treatment offers only temporary benefit, as individuals remain at risk of reinfection following treatment. Other strategies, including water, sanitation, and hygiene (WASH) interventions may be needed to reduce the risk of reinfection and ultimately to break transmission of schistosomiasis and STH (48-50). The presence or absence of WASH, in addition to other social and economic factors, may influence the success of helminth control programs as the intensity of transmission (as estimated by the reproductive number, R_0) is influenced by the survival of free living helminth stages in the surrounding environment (51).

Recent modeling efforts highlight the potential importance of WASH in controlling helminth infections, particularly in high prevalence areas (52, 53). Data from a meta-analysis of water and

hygiene protective measures suggest that drinking treated water, soap use, and wearing shoes were associated with approximately 45-60% lower odds of infection (54). Access to and utilization of sanitation facilities is also associated with significant reductions in the prevalence of all three major STH infections; *A. lumbricoides* (OR: 0.54, 95% CI: 0.43–0.69), *T. trichiura* (OR: 0.58, 95% CI: 0.45–0.75), and hookworm species (OR: 0.60, 95% CI: 0.48–0.75) (55).

Despite these associations, data from randomized trials evaluating the impact of WASH interventions have demonstrated minimal or no benefit in reducing STH prevalence or intensity in children (56, 57). However, evaluations of the impact of school-based deworming programs indicate that treatment programs have a larger impact on reducing helminth prevalence in areas with improved sanitation facilities, as compared to areas with unimproved or no sanitation (58). Integrating WASH and MDA strategies may be a promising approach to eliminating disease transmission, however data are limited (16, 59). One cluster-randomized trial in Kenya found a 44% reduction in the odds of *A. lumbricoides* infection (but not in other STH species) among children receiving both WASH and MDA, as compared to MDA alone (60). However, another randomized participatory hygiene and sanitation behavior change intervention trial found no significant difference in helminth infection between the group receiving both WASH and deworming, as compared those receiving deworming alone (61).

Using data from a randomized controlled trial of deworming among HIV infected adults in Kenya, we evaluated associations between WASH access and utilization and helminth prevalence following repeated rounds of treatment with albendazole and praziquantel.

Methods

Study design and population

We conducted a retrospective cohort study nested within the Helminth Eradication to delay ART Trial (HEAT) (62). HEAT was a randomized trial of single-dose albendazole (400 mg) provided every 3 months plus single dose praziquantel (25 mg/kg) provided annually for 2 years to HIV-infected adults. Participants were recruited from HIV clinics at three sites in Kenya (Kisii Provincial Hospital, Kisumu District Hospital, and Kilifi District Hospital) between February 6, 2008, and June 28, 2010. Individuals were eligible for inclusion if they were 18 years of age or older, were HIV seropositive, were not pregnant at the time of enrollment, and did not meet current criteria for ART initiation (on the basis of documented WHO disease stage and CD4+ cell count within the previous 3 months and a clinical assessment at enrollment). Participants were followed every 3 months for 24 months after enrollment.

A single stool sample was obtained from participants after 24 months of follow up. All stool samples were initially examined with a combination of direct microscopy techniques, Kato-Katz and formol-ether concentration by trained laboratory technologists at each of the study sites. Stool aliquots of approximately 1 gram were placed in cryotubes and frozen at -80°C for subsequent DNA extraction and examination at the Leiden University Medical Center (the Netherlands). For this analysis, intensity of helminth infections was assessed by PCR only.

Following a bead-beating step, DNA was isolated using DNeasy 96 Blood & Tissue Kit spin columns in accordance with the manufacturer's instructions (Qiagen, Hilden, Germany) (63, 64). Phocin herpes virus-1 (PhHV-1) was added to the lysis buffer in each sample as an internal control and virus-specific primers and detecting probe were included in each reaction mixture. Two different multiplex real-time PCR detection panels were used for parasite specific DNA detection of STH and *Schistosoma*: (i) *Ancylostoma spp* (i.e. detecting both *A. duodenale* and *A. ceylanicum*), *Necator americanus*, *Ascaris lumbricoides*, and *Strongyloides stercoralis*, and (ii) *Schistosoma spp* (i.e. detecting both *S. mansoni* and *S. haematobium* DNA without differentiation) and *Trichuris trichiura* (63). For the DNA isolation and setup of the PCR reactions a custom-made

Hamilton robot platform was used, while amplification, detection and analysis were performed using the CFX real-time detection system (Bio-Rad Laboratories, USA). Negative and positive control samples for each parasite species were included in each PCR run. Fifty PCR amplification cycles were run per sample, with the output expressed as a cycle threshold (Ct). Ct reflects the amplification cycle in which the level of fluorescent signal exceeds background fluorescence and thus species-specific DNA loads in stool samples. For each parasite-specific target, DNA loads were arbitrarily categorized into the following intensity groups, according to previous publications: low ($35 \leq Ct < 50$), moderate ($30 \leq Ct < 35$) and high ($Ct < 30$) (65).

In addition to deworming history, four WASH interventions were assessed; access to safe water via purchasing of purified water or treating water independently (filtration, chlorination, boiling, etc), access to a flush latrine or pit latrine in a house or on compound premises, consistent hand washing after using the latrine, and residence in a household in which the floors of the house are made of cement, iron, stone, or timber (i.e. not earthen). Access to these protective WASH interventions were ascertained during longitudinal HEAT surveys. If any of the responses regarding access to WASH resources varied over follow-up, we utilized a participant's response from the end of the study (when stool samples were collected), or from the preceding three months if not available at study conclusion. Study teams were able to validate reported access to latrines and safe flooring during household visits. Hand washing and safe water access were self-reported by study participants.

The primary outcome of interest was the detection of any STH species infection after 24 months follow-up. As numerous studies have found differential effects of both WASH and deworming by specific helminth species, secondary outcomes of interest included the detection of specific species of helminths (60). Intensity of infection was examined but could not be assessed due to a lack of statistical power and precision.

We conducted a manual forward stepwise model building approach to identify the package of interventions most protective against a helminth infection of any STH species (combined outcome). Individual sex and age were included as covariates in the forward stepwise model building process due to their hypothesized role as potential confounders in the relationship between WASH access and helminth infection. We did not further adjust for SES as the specific WASH resources of interest lie on the causal pathway between SES and helminth infections and access to these WASH resources is a modifiable characteristic that may influence susceptibility to helminth infections.

Multiple imputation using the chained equations (MICE) method was used to address missing values for four of the exposure variables; water treatment status (22% missing), hand washing status (22% missing), safe latrine status (2% missing), and safe flooring status (2% missing). Among individuals not asked about water treatment and hand washing status during surveys, missingness was assumed to be random. Logistic regression was used to impute missing values with ten imputations. Derived estimates from each imputation were combined using Rubin's methods (66). We also performed a sensitivity analysis including only complete cases. Estimates from the complete case analysis did not differ qualitatively from those produced with multiple imputation. Therefore, only the effect estimates, 95% confidence intervals (CIs), and p-values derived through imputation are presented.

We used logistic regression and a cutoff threshold of $p \leq 0.1$ on the Wald Test as criteria for graduating a variable into the next stepwise model (i.e. branching), or as criteria for removing a variable from a model (i.e. pruning). We started with univariate models that included each independent variable and the outcome. We branched variables that met the cutoff threshold in univariate models into a single multivariate model. After pruning back any variables that did not meet the cutoff threshold, we introduced interaction terms for all independent variable combinations. The purpose of the interaction terms was to identify any potential synergy

associated with access to more than one intervention (i.e. a larger protective effect than would be possible with access to one intervention alone). We pruned back any higher level interaction terms that did not meet the cutoff threshold. We then inspected the lower order interaction terms, and pruned back terms that did not meet the cutoff threshold. The branching and pruning stopped once all remaining terms met the cutoff threshold (i.e. equilibrium). Odds ratios (ORs) and their 95% CIs are reported, with significance determined at the $\alpha=0.05$ level.

We also utilized the manual forward stepwise model building method to identify the optimal package of interventions relevant to each helminth species. This process was undertaken separately for *A. lumbricoides*, hookworm species (all identified infections were *N. americanus*), *T. trichiura*, *S. stercoralis* and *Schistosoma spp.* Finally, we evaluated the package of WASH interventions most protective against helminth infections in HIV-infected adults without access to anthelmintic treatment (the HEAT placebo group) using the manual forward stepwise model building method described above.

Results

Of the 740 individuals who participated in HEAT, stool samples were available from 701 individuals. These individuals were predominately young, 44% were 25-34 years old, female (78%) and socio-economically disadvantaged (42% earned less than 2000 Kenyan shillings per month (approximately \$20 U.S. dollars). Individuals enrolled in the HEAT study were relatively immunocompetent; median CD4+ cell count was 517 cells/mm³ (interquartile range, IQR: 430-700 cells/mm³) and median viral load was 4.2 log₁₀ copies (IQR: 3.5-4.8 log₁₀ copies) (Table 1).

Exactly half (50% (n=348)) of the participants received albendazole and praziquantel in the 6 months preceding stool collection and half (n=353) received placebo. Nearly 60% (n=418) of the participants reported access to safe or treated drinking water and 56% (n=393)

reported consistent handwashing after using the latrine. Latrines were accessible in the homes or on the compounds of 66% (n=480) of study participants and 46% (n=325) lived in homes with safe, non-earthen flooring. Some of the participants (n=59, 8%) had access to treatment and all of the protective WASH interventions. Only 6 individuals (0.9%) of the participants reported no protective WASH access of any kind.

In total, 152 helminth infections were detected amongst 137 infected individuals using real-time PCR, including: 21 *A. lumbricoides*, 60 *N. americanus*, 43 *Schistosoma* spp., 8 *S. stercoralis*, and 20 *T. trichiura* infections. There were 96 STH infections detected, none of which were *Ancylostoma* spp. (Table 2). When evaluating intensity of infection by qPCR, the majority of hookworm, *A. lumbricoides*, and *T. trichiura* infections were of moderate infection intensity while the majority of *S. stercoralis* and *Schistosoma* infections were of low intensity. *S. stercoralis* had the highest percentage of high intensity infections of any of the helminth species (25%), while *T. trichiura* had the lowest percentage of high intensity infections (5%) (Table 3).

During the stepwise model building process pruning and branching steps were undertaken to derive the package of interventions most protective against any STH infection (combined outcome). Only two of the protective interventions remained in the final model: deworming treatment and safe flooring. The odds of infection with any STH species was lower for individuals who were treated relative to those who were not (aOR: 0.11, 95% CI: 0.05, 0.20, $p < 0.001$). The odds of infections with any STH species was also lower for individuals with access to safe flooring relative to those without (aOR: 0.34, 95% CI: 0.20, 0.56, $p < 0.001$) (Table 4). All interaction terms were pruned out of the model, indicating no statistical synergy (or antagonism) across interventions.

The same process was undertaken to derive the most protective package of interventions for each helminth species individually. Treatment (aOR: 0.03, 95% CI: 0.01, 0.11, $p<0.001$), safe flooring (aOR: 0.27, 95% CI: 0.14, 0.52, $p<0.001$) and latrine access (aOR: 0.51, 95% CI: 0.29, 0.92, $p=0.03$) interventions were included in the *N. americanus* intervention package (Table 4). Only treatment was associated with reduced probability of infection with *A. lumbricoides* (aOR: 0.32, 95% CI: 0.11, 0.88, $p=0.03$), *T. trichiura* (aOR: 0.11, 95% CI: 0.02, 0.46, $p=0.003$) and *Schistosoma sp.* (aOR: 0.30, 95% CI 0.14, 0.60, $p=0.001$). Interestingly, handwashing was associated with an elevated probability of *Schistosoma sp.* infection (aOR: 3.14, 95% CI: 0.83, 11.85, $p=0.09$). No interventions appeared associated with reductions in *S. stercoralis* infection.

In the absence of anthelmintic treatment, the most protective intervention package for any STH infection included safe flooring (aOR: 0.34, 95% CI: 0.20, 0.59, $p<0.001$) and latrine access (aOR: 0.59, 95% CI: 0.35, 0.99, $p=0.05$) (Table 5). For the specific outcome of *N. americanus*, safe flooring (aOR: 0.25, 95% CI: 0.13, 0.50, $p<0.001$) and latrine access (aOR: 0.47, 95% CI: 0.26, 0.86, $p=0.01$) appeared most protective. For *A. lumbricoides*, the most protective package not including anthelmintics contained safe water only (OR: 0.37, 95% CI: 0.12, 1.12, $p=0.08$). No intervention was effective at reducing the probability of *T. trichiura* infection in the absence of anthelmintics. Consistent handwashing was associated with an increased risk of *Schistosoma sp.* infection in the absence of anthelmintic therapy (OR: 3.62, 95% CI: 0.78, 16.92, $p=0.10$). Finally, latrine access appeared to reduce the probability of infection with *S. stercoralis* in the absence of treatment (OR: 0.13, 95% CI: 0.01, 1.15, $p=0.07$). Across all species, interaction terms were pruned out of the models, indicating no statistical synergy (or antagonism) across interventions.

We assessed the pairwise correlation between the independent variables in order to understand if multicollinearity was affecting the variance in the models, and thus causing some independent variables to appear statistically insignificant and drop out of the stepwise model building process.

Correlation appeared to be mild, ranging from -0.05 (treatment and safe water) to 0.17 (safe flooring and toilet access). We also performed a sensitivity analysis including only complete cases. Estimates from the complete case analysis did not differ qualitatively from those produced with multiple imputation. Therefore, only the effect estimates, 95% CIs, and p-values derived through imputation are presented

Discussion

Given recent calls for the elimination of several NTDs by 2020, evaluation of multilateral approaches to morbidity control and interruption of disease transmission through combination interventions including MDA and WASH programs is critically important. In this analysis, both treatment with albendazole and praziquantel and access to some WASH interventions demonstrated benefit in reducing the probability of STH and schistosomiasis infections. Despite this, there was no evidence of multiplicative benefit (synergy) associated with access to more than one WASH intervention when combined with chemotherapy. However, access to several WASH interventions did appear to demonstrate benefit in reducing STH prevalence and intensity in adults who did not receive albendazole or praziquantel.

Treatment with albendazole and praziquantel was effective in preventing all helminth infections with the exception of *S. stercoralis*. This is consistent with previous studies documenting high treatment efficacy of albendazole for *A. lumbricoides* (cure rate of 88%) and hookworm species (cure rate of 72%), and of praziquantel for schistosomiasis (cure rate of 76%). It is also consistent with the documented poor treatment efficacy of albendazole for *S. stercoralis*.⁽⁶⁷⁾ The finding of consistent benefit of albendazole for *T. Trichiura* was somewhat surprising given previous data suggesting relatively poor treatment efficacy for this organism (28%), and may be due to the fact that individuals in this study were treated with albendazole repeatedly over 24 months (47, 68).

In this study, 60% and 69% of participants had access to safe drinking water and improved latrine facilities, respectively. However, among individuals who received deworming medications, access to safe water did not appear to provide additional benefit in reducing helminth infections and access to latrines only appeared to reduce infection with hookworm species. The apparent contradiction between these findings and understood mechanisms of helminth exposure are echoed in previous studies (57, 69), including a three year cluster randomized trial with over 50,000 participants in India that found no association between increased latrine coverage and reductions in helminth infection or intensity (56). These findings suggest that the additional benefit of reducing exposure in individuals receiving repeated rounds of chemotherapy may be limited. In addition, access to safe water and latrines is not equivalent to consistent or effective uptake of the interventions, and cultural norms regarding use of these resources greatly influence helminth exposure.

Despite the inconsistent benefit of WASH demonstrated in this study, reducing exposure through primary transmission routes may be particularly important in populations not targeted by global guidelines for routine deworming, including adults. Amongst adults who did not receive albendazole or praziquantel, the impact of WASH interventions in reducing STH infection was more pronounced. In untreated participants, access to latrines reduced the probability of infection of both hookworm and *S. stercoralis* and access to safe water reduced the probability of *A. lumbricoides* infection. This finding is consistent with previous evidence suggesting that untreated individuals without access to improved latrines have an increased odds of infection with skin penetrating helminths such as hookworm and *S. stercoralis* (combined aOR 3.9, 95% CI: 2.6-5.9) and that unimproved drinking water is associated with increased odds of infection with orally-ingested helminths such as *A. lumbricoides* and *T. trichiura* (combined aOR = 2.2; 95% CI: 1.3-3.7) (70).

In many settings, handwashing has also been associated with prevention of intestinal parasitic infections (71-75). However, predictive models from the data presented here suggest that consistent handwashing may not provide benefit and, in fact, may be associated with an increased probability of *Schistosoma* infection. This may be due to self-reporting bias that misrepresents the true number of people practicing consistent hand washing. Alternatively, this observation may be due to a practice of handwashing with water from *Schistosoma* contaminated water sources. Individuals who live in close proximity to water sources may be more likely to practice handwashing and also more likely to be exposed to infective cercariae. Handwashing with soap is recommended when washing hands with fresh water in endemic areas in order to reduce the infectivity of cercariae, and soap use was not observed in this study (76).

In this analysis, the WASH intervention that appeared to have the largest and most consistently protective effect was residence in a household with non-earthen floors. Earthen floor have been shown to be a significant risk factor for hookworm infection, responsible for as much as 86% of all hookworm infections in West Africa (77). Given that 44% of helminth infections in this cohort were hookworm species (as expected in an adult population), it is likely that safe flooring was particularly important for preventing infection in this group. Although we did not measure shoe wearing practices, consistent use of footwear has also been shown to lower the odds of hookworm infection (60, 78).

While biologic rationale would seem to indicate that integration of deworming and WASH interventions would have a synergistic effect on helminth prevalence through dual removal of extant infections and sources of exposure, there was no indication of such synergy in our study. These observations are in contrast to findings from a randomized trial that identified a significant reduction in *A. lumbricoides* infections amongst school children who received a school-based WASH program plus albendazole as compared to children who received albendazole alone (60). Other studies have also found that health education, latrine construction, and deworming

significantly reduce STH prevalence (79), and a systematic review concluded that combined sanitation, education, and deworming reduced STH prevalence by more than 60% relative to sanitation and education alone (80). New efforts are underway to understand the influence of integrated WASH activities and mass deworming of entire communities using a cluster randomized trial design (81).

There are several notable strengths of this analysis. These data were rigorously collected as part of a randomized trial of deworming interventions and highly sensitive molecular diagnostic tools were used to detect helminth infections. Given the poor sensitivity of microscopic techniques in low prevalence areas (82), and the fact that 39% of infections in this cohort were low intensity, it is likely that we detected infections that would have gone undetected using standard microscopic methods. However, there were also several limitations associated with this retrospective cohort study. First, we were unable to document true WASH usage, adherence, and behavior patterns and using WASH access as a surrogate for WASH usage may be problematic (83). In addition, our data do not provide insight into food preparation or shoe wearing practices, which could also influence helminth exposure and infection estimates. Although individuals did report whether they had access to latrines, we did not assess whether or not the latrines were improved or unimproved or if they were well maintained. Additionally, it is possible that repeat surveys regarding WASH access affected participant behavior, such that the final survey was not necessarily a representative index of risk throughout follow-up. Finally, because the study was conducted in HIV-infected adults, the generalizability of our findings may be limited. However, there is some evidence that HIV infected adults may benefit from deworming and the potential additive role of WASH in this population warrants further investigation (84).

Conclusion

Access to WASH is unequivocally essential, it is a human rights necessity and a hallmark of the Sustainable Development Goals. However evidence supporting the additive benefit of integrated deworming and WASH strategies has been mixed, in part due to the logistical and ethical challenges surrounding the design and implementation of large randomized WASH studies (85). In this study, anthelmintic treatment was shown to be highly effective in reducing the probability of helminth infections. WASH interventions, with the exception of safe flooring, did not appear to provide substantial synergistic benefit to chemotherapy. However, among individuals not receiving chemotherapy, there was clear benefit of WASH in reducing the probability of helminth infections. Given the complexity of integrating multisectorial approaches to disease control (86), researchers and NTD programs should carefully consider if and how pursuing integrated chemotherapeutic and WASH strategies may influence capacity to deliver high quality interventions and achieve targeted outcomes.

Table 1: Participant (N=701) characteristics (non-imputed)

Characteristic	N	%
Female	548	78.2
Avg. (std. dev.) people per household	4.6	2.3
Age		
18-24	94	13.4
25-34	307	43.8
35-44	194	27.7
45-54	69	9.8
55+	37	5.3
Location		
Kilifi	212	29.2
Kisii	257	35.5
Kisumu	256	35.3
Self-reported monthly income (Kenyan shilling)		
<2000	297	43.7
2000-4999	209	30.7
5000-9999	100	14.7
≥10000	74	10.9
Missing	21	3.0
Occupation		
Business/self-employed	217	31.7
None	143	20.9
Farmer	137	20.0
Casual laborer	75	11.0
Business/employed by other	57	8.0
Professional (i.e. teacher/lawyer)	55	8.0
Missing	17	2.0
Median (IQR) endpoint CD4+ cell count (cells/mm3)	517	430-700
Median (IQR) endpoint log ₁₀ copies viral load	4.2	3.5-4.8
Received deworming medications in past 6 months as part of trial intervention	348	49.6
Missing	3	0.43
Access to treated or piped water (most recent report)	418	59.6
Missing	155	22.1
Access to a latrine	480	68.5
Missing	17	2.4
Consistent hand washing (most recent report)	393	56.1
Missing	155	22.1
Access to safe flooring (i.e. non earthen floors)	325	46.4
Missing	17	2.4

Table 2: Prevalent infections

Species	n (N=152)	% of helminth infections	% of total population
Ascaris lumbricoides	21	14%	3%
Hookworm			
Necator americanus	60	40%	9%
Ancylostoma spp.*	0	0%	0%
Trichuris trichiura	20	13%	3%
Strongyloides stercoralis	8	5%	1%
Schistosoma spp.	43	28%	6%

Table 3: Intensity of prevalent infections (percent of infections)

Species	High (Ct <30)	Moderate (Ct 30-35)	Low (Ct >35)
Ascaris lumbricoides	10%	67%	23%
Hookworm			
Necator americanus	13%	45%	42%
Ancylostoma spp.*	NA	NA	NA
Trichuris trichiura	5%	50%	45%
Strongyloides stercoralis	25%	25%	50%
Schistosoma spp.	14%	40%	47%

Table 4: Optimal interventions identified through stepwise model building, by species (adjusted for sex and age)¹

Species	Treatment (aOR, 95% CI)	Safe floors (aOR, 95% CI)	Latrine (aOR, 95% CI)	Handwashing (aOR, 95% CI)	Safe water (aOR, 95% CI)
Any STH species (combined)	0.10 (0.05, 0.20)	0.34 (0.20, 0.56)			
Ascaris lumbricoides	0.32 (0.11, 0.88)				
Hookworm	0.03 (0.006, 0.11)	0.27 (0.14, 0.52)	0.51 (0.29, 0.92)		
Strongyloides stercoralis					
Trichuris trichiura	0.11 (0.02, 0.46)				
Schistosoma spp	0.30 (0.14, 0.60)			3.14 (0.83, 11.85)	

¹ Grey boxes indicated that variables did not graduate into the final species-specific model based on $p \leq 0.1$ cutoff

²Any STH species includes *Ancylostoma spp*, *Ascaris lumbricoides*, *Necator americanus*, *Strongyloides stercoralis*, *Trichuris trichiura*. *stercoralis* and *T. trichiura*

Table 5: Optimal interventions in adults without access to treatment identified through stepwise model building, by species (adjusted for sex and age)¹

Species	Safe floors (aOR, 95% CI)	Latrine (aOR, 95% CI)	Handwashing (aOR, 95% CI)	Safe water (aOR, 95% CI)
Any STH species (combined)	0.10 (0.05, 0.20)	0.34 (0.20, 0.56)		
Ascaris lumbricoides	0.32 (0.11, 0.88)			
Hookworm	0.03 (0.006, 0.11)	0.27 (0.14, 0.52)	0.51 (0.29, 0.92)	
Strongyloides stercoralis				
Trichuris trichiura	0.11 (0.02, 0.46)*			
Schistosoma spp	0.30 (0.14, 0.60)			3.14 (0.83, 11.85)

¹ Grey boxes indicated that variables did not graduate into the final species-specific model based on $p \leq 0.1$ cutoff

²Any STH species includes *Ancylostoma spp*, *Ascaris lumbricoides*, *Necator americanus*, *Strongyloides stercoralis*, *Trichuris trichiura*. *stercoralis* and *T. trichiura*

CHAPTER 4: Evaluating the costs and affordability of integrated neglected tropical disease programs at a sub-national level: More costly than we may think

Introduction

Neglected tropical disease (NTD) programs are among some of the largest public health platforms in the world. For five NTDs—lymphatic filariasis (LF), onchocerciasis, schistosomiasis, soil-transmitted helminths (STH) and trachoma—the primary control or elimination strategy is predicated upon mass drug administration (MDA) during which all at-risk individuals in a given geographic area are presumptively treated using safe and efficacious drugs. In 2015, nearly one billion preventive chemotherapy treatments were delivered by NTD MDA programs globally (87). MDA is an effective strategy for reducing disease prevalence and community-level force of infection and is deemed highly cost-effective, particularly in high prevalence areas (50, 88).

Because NTDs are often co-endemic and utilize similar intervention platforms such as MDA, NTD experts suggest that NTD programs integrate with one another to achieve greater coverage and efficiency (89). Integration refers to the creation of linkages among programs to improve the delivery of health interventions given existing commitments and resources (12). The World Health Organization (WHO) recommends integration of NTD programs in co-endemic areas, and over 70 countries have launched integrated NTD Master Plans as a result (90). One of the primary rationale for integration is potential time savings for both volunteer workforces and community member beneficiaries given that the number of times that they need to engage in program preparation or delivery may decrease with further integration (86). However, the precise manner and degree to which NTD programs are integrated can be inconsistent and vague, and it may even be possible for some integrated activities such as program coordination to incur higher costs (86, 91).

An analysis of global top-down MDA-based NTD program costs estimated that \$0.49 USD per person per year is required to treat all five MDA-indicated NTDs, and advocacy materials typically

cite a unit cost of \$0.50 per treatment delivered (17, 90, 92, 93). NTD programs appear to be very inexpensive because pharmaceutical companies have committed to donating drugs to MDA programs in endemic countries and the programs are delivered by largely non-remunerated workforces of teachers and volunteer community drug distributors (CDDs) (94). However, as integrated NTD programs are scaled-up to reach global control and elimination targets, it is increasingly important to understand the more nuanced costs of these large public health platforms, both in terms of total programmatic opportunity costs as well as implications for program affordability at more granular geographic levels. A recent review of NTD economic analyses found no information regarding drivers of variation in costs among and within countries, or how these drivers have differential effects on NTD program costs at scale. The review also highlighted a lack of information regarding the cost implications of integrated approaches to routine NTD program delivery (18).

Evidence from research studies and pilot projects suggest that integrated MDA programs will make more efficient use of the limited financial and human resources so often present in NTD endemic countries (89). In two Nigerian states, MDA program costs decreased by 41% when delivering integrated MDA treatments (i.e. triple drug administration) during a research study compared to delivering vertical MDA treatments. It was noted during this study that cost-savings were incurred in areas with larger populations due to economies of scale (14). In six districts in Niger, integration of programmatic activities was associated with savings of 21%, accounting for MOH salaries and some economic costs (95). More information is needed regarding the costs of routine, integrated MDA programs operating at scale.

When similar and transparent methods for measuring and valuing resources are used, cost analyses can compare the cost profiles of an intervention across similar entities, such as comparable but distinct geographical areas. It can reasonably be assumed that similar geographic entities (i.e. units of analysis) would have similar cost profiles, and major differences in cost

profiles can guide investigations into strategies for improving intervention efficiencies (96). We utilized the United States Agency for International Development (USAID)-developed Tool for Integrated Planning and Costing (TIPAC) to collect data at a sub-national level in Nigeria and conduct a cost analysis across two Nigerian States. Nigeria has one of the highest burdens of NTDs in sub-Saharan Africa (97), and scrutiny of program delivery at a sub-national level is important in large, decentralized countries like Nigeria (98). The purpose of this analysis was to generate evidence on costs and affordability of sub-national integrated NTD programs that can be used to drive decision making and guide the refinement of integrated NTD costing tools moving forward.

Methods

The primary research aims of this study include: (1) To describe the financial and economic costs associated with implementing integrated NTD programs in two Nigerian States, (2) to identify modifiable, programmatic variables (ex. treatment coverage) that are drivers of costs, and (3) to examine the affordability of the integrated NTD program in Nigeria in terms of the potential long-term costs shifted to the MOH from donors and non-governmental organizations (NGOs).

Locations of study

In 2015 twelve Nigerian States were trained by the RTI International ENVISION Project to complete the TIPAC tool at a State-level. Based on their comparable disease profiles and performance in the training, we used judgement sampling to select Abia and Cross River States to participate in this study to provide practical case studies of sub-national NTD costing and output data in Nigeria.

Data sources

Financial, or direct, costs reflect actual expenditures incurred while economic costs capture the opportunity cost of all resources, whether or not they incur a financial cost [2]. The TIPAC provides

a source for budgeted financial costs on behalf of both the MOH and other implementing partners and donors, acting as an approximation for actual expended financial costs.

The USAID NTD Control Program developed the TIPAC as a versatile planning and costing instrument to be used by members of a NTD program at the national level or, in decentralized systems, at a sub-national level. The TIPAC includes four main phases: (1) input of background data such as demographic and epidemiologic data, (2) data entry, including integration opportunities across diseases, (3) finalization and approval by NTD programs, and (4) application of results, via advocacy, fundraising, drug procurement, etc (99).

The TIPAC tool has 11 pre-set activity categories and 32 sub-activity categories to capture financial costs. The tool does not explicitly capture cost input categories. For the purposes of this exercise, select changes were made to standardized TIPAC cost categories to add specificity *a priori*. For example, the TIPAC tool categorized fuel costs in the sub-activity category of “other”, and for this analysis, we categorized it as “transportation”, and the additional category of “travel/per diems/ allowances” was added to the tool. Additionally, we also reclassified some costs during a week-long TIPAC review meeting conducted by an external research team. All changes were made in full consultation with both participating States and national-level supervisors. For example, a number of data inputs for one State were changed from the activity of “advocacy” to “social mobilization” once the specific activity was discussed with the State NTD Program Manager (in this case, producing information sheets for local distribution to community members).

It is important to account for economic costs in NTD program evaluations given the critical role played by volunteers and integration with already funded government programs to deliver services. The economic cost of using volunteers is the forgone income volunteers could have earned if they had not been volunteering with MDA campaigns. Because the TIPAC is not designed to collect these costs, we provided supplementary Excel-based surveys to State NTD Program Managers to assemble information on volunteer labor costs by collecting information on

the number of days worked by volunteer CDDs per campaign (vertical or integrated) in each local government area (LGA), the duration of training activities by LGA, and the duration of campaigns by LGA. Other economic costs include shared government costs provided by the state level departments supporting NTD control. Therefore, the survey was also used to collect information regarding the annual cost of maintaining State-level NTD office space. Building costs were assumed to be spread across all endemic diseases

Perspective

The choice of perspective for a cost analysis is important because it determines what costs and outcomes to account for and how to value them (100). We employ a societal perspective, which considers all aspects of an intervention regardless of who experiences the costs. We use this perspective to examine program costs (all costs associated with delivering a specific intervention) as well as non-program community costs (costs associated with community member participation in programs). We also use a provider (i.e. government) perspective to capture the financial costs incurred by the Nigerian government (not accounting for costs incurred by NGOs) in providing integrated NTD programs, which can be used to understand the long-term sustainability of the program.

Financial cost classification

Micro-costing, or bottom-up costing, of specific financial costs was conducted during which State NTD Program Managers, Deputies Program Managers, and Finance Managers participated in completion all of the TIPAC modules. Sub-activity costs were organized according to the general activity or function for which the resources were used, including: administration, advocacy, the program office, drug logistics, MDA registration, MDA service delivery, monitoring and evaluation, social mobilization, strategic planning, training, morbidity management, and vector control (Table 1). Activity costs were further classified according to resource inputs categories containing

elements with similar characteristics, including: contracted services, equipment, overhead, personnel, program supplies, transportation, and travel/per diem/allowances (Table 1).

Costs were also distinguished by whether they were capital costs or recurrent costs. Capital costs refer to resources that last longer than one year and depreciate over time. Recurrent costs refer to resources that are used up in the course of a year and purchased regularly (96). We assumed the useful life of large equipment such as vehicles and motorcycles to be five years, of smaller items such as computer accessories to be two years, and of stationaries and office supplies to be one year. Any start-up costs such as previous trainings or planning activities that were not implemented in 2015 were not captured in the TIPAC, however given the annual nature of MDA programs this was not a major concern.

Salary costs and per diems of NTD program personnel were provided by Program Managers directly in the TIPAC. This includes the salary costs of full-time personnel as well as the salary contributions for personnel who only expend a proportion of their time on the NTD Program (i.e. District level supervisors). Because the TIPAC does not apportion personnel costs to specific activities, a supplemental survey was provided to NTD Program Managers and their National NTD Supervisor in which they allocated percentages of different health worker cadres time to each aforementioned activity group. At a minimum, all cadres spent at least 5% of their time on administrative duties.

Financial costs were distinguished according to whether they were NGO or MOH sourced, as indicated by Program Manager inputs into the TIPAC. Costs were also identified by analysts as either fixed costs (i.e. remain the same regardless of output produced) or variable costs (i.e. dependent on output). An inflation rate of 1.3% was applied to all costs.

Economic cost classification

Programmatic economic costs include the value of quantified opportunities costs of donated goods and services, including those provided by volunteer CDDs. These costs were classified according to the same activity and input categories as financial costs (Table 1). To account for the potential opportunity costs (i.e. lost wages) incurred by CDDs in exchange for participating in NTD trainings and MDA, we identified the number of MDA campaigns and training days per LGA in 2015 via the aforementioned supplemental surveys. “CDD work days” were converted to 8-hour work day equivalents and multiplied by the Nigerian minimum wage in 2015 (approximately 18,000 Naira, or \$57.17 2015 USD per month, equivalent to about \$1.91 USD per day). Per diems were provided to volunteer CDDs and are generally considered an additional proxy for value of time. Per diems provided by the NTD program were subtracted from monetized CDD opportunity costs so as not to overestimate total lost wages.

There are a number of community-level economic costs that could be accounted for in a costing analysis, including costs associated with long-term NTD disability or care seeking. However because minimal information is available regarding NTD-associated productivity losses, we focused on the main category of associated economic costs: opportunity costs associated with adult community member beneficiaries receiving treatment or prevention in NTD programs through MDA campaigns. These economic costs were calculated as lost wages by identifying the number of MDA “campaign days” delivered to adults in a LGA in 2015 and the number of adults who attended the campaigns, based upon MOH reports of the number of people treated and TIPAC inputs regarding the proportion of the population that is categorized as an adult 15 years of age or older. “Campaign days” were converted to 8-hour work day equivalents and multiplied by the Nigerian minimum wage.

Drugs used in MDA programs are, for the most part, donated by pharmaceutical companies. Therefore, while drug procurement is not an expense incurred by national governments, the cost of the drugs must also be considered in the overall economic cost calculation. With the exception

of praziquantel used for schistosomiasis preventive chemotherapy, these costs were available directly from the TIPAC tool, based on State-level drug requests for 2015. The cost of praziquantel was identified from a separate source and added into the TIPAC tool (14).

Outcome measures

The primary cost metric of interest was average financial, economic, and total (financial plus economic) costs per treatment delivered. If a person was reached by an integrated treatment campaign (such as dual delivery of albendazole and ivermectin for LF and onchocerciasis programs), this was considered two “treatments delivered”. The number of treatments delivered in 2015 was provided directly by States, and TIPAC demographic data inputs were used to derive MDA treatment coverage.

The primary cost-outcome of interest was economic cost per case averted from the societal perspective. To estimate this cost-outcome, state-level prevalence was derived by multiplying the estimated prevalence of disease in Nigeria by the number of people at risk of the disease in each state (101). This value was multiplied by reported treatment coverage and treatment efficacy to estimate the number of potential cases averted (47, 102, 103).

Benchmarks

Benchmarking was used to evaluate the affordability of unit costs in this study. Benchmarks identify setting-specific unit costs against which program costs might be compared (91). Affordability refers to unit cost estimates that are appropriate given the characteristics of the health systems and insights from relevant experts. A WHO-led systematic review and meta-regression accounting for 34 NTD studies was used to develop an online application that allows users to identify setting-specific benchmarks based on target population size, treatment coverage, degree of integration, GDP per capita, and population density (91). We used the application to identify unit costs benchmarks specific to both Abia and Cross River State. Based on 2015 data

inputs, financial unit cost benchmarks (i.e. not accounting for economic costs such as donated drugs) were set at \$0.13 (\$0.06-\$0.20) and \$0.14 (\$0.06-\$0.23) per treatment delivered for Abia and Cross River States, respectively.

We also sought to identify financial unit cost benchmarks from the perspective of major program stakeholders: funders and endemic country policy makers. We developed an online survey with 5 discrete and one “other” option asking participants about their preference for average financial unit costs for MDA treatments delivered. Five individuals participated (three donor partners and two endemic country Program Managers). All participants unanimously identified \$0.50 as the benchmark for an NTD MDA-program financial unit cost per person reached with treatment. We compared identified unit costs to these benchmarks in scenario analyses.

As final indications of program affordability and sustainability, we compare the per capita financial costs from the government perspective to the most recently available WHO estimate of per capita government expenditure on health in Nigeria (104). We also identify the proportion of national MOH health expenditure spent on NTD program costs in each State.

Sensitivity analysis

Sensitivity analysis is critical for any cost analysis (105). A series of one-way, or univariate, sensitivity analyses was conducted separately for financial, economic, and total costs. Sensitivity analyses focused on key variables that met the following criteria: variable values are uncertain, are most in the control of policy makers, or are key to explaining different costs or outputs across States. Variables that met inclusion criteria and were accounted for in the sensitivity analyses include: disease prevalence, treatment coverage for each disease in each State, CDD total work days per State, the value of CDD opportunity costs, cost per tablet of drugs, and costs associated with advocacy. Unless otherwise indicated, variables of interest were varied up to a 50% decrease and increase from their base case cost. For variations in treatment coverage it was assumed that coverage could not surpass 100% or, for MDA campaigns that treated more people than were

targeted, could not surpass the observed coverage estimate above 100%. Sensitivity analyses were reported as the percent deviation in unit cost from base case observations.

Sensitivity analyses were also conducted to capture potential changes to costs given varying degrees of integration across compatible programs. LF and onchocerciasis were considered compatible programs as their MDA campaigns are delivered in communities and share co-indicated drugs. Likewise, schistosomiasis and STH were considered compatible programs as their MDA campaigns are delivered in schools. Activities that may be more easily integrated across programs include advocacy, drug supply chains, monitoring and evaluation, training, and social mobilization (106) and thus these activities were included in integration sensitivity analyses. It was assumed that integration may reduce costs to be as low as costs associated with a single disease, specifically the disease with higher costs for the particular activity. And it was assumed that integration may increase costs up to 110% of the total cost of conducting the activity for the two diseases separately (assuming that integration may add additional coordination costs (91)).

Scenario analysis

Scenario analyses were also conducted to assess program sustainability by exploring the relationship between government and NGO expenditure. In these scenarios, the proportion of total costs supported by NGOs and costs of donated drugs were gradually shifted to the Nigerian government to understand the resulting influence on unit costs and affordability from the provider perspective.

Results

Overview of States

Abia and Cross River States are located in southern Nigeria and are endemic to LF, onchocerciasis, schistosomiasis, and STH. Schistosomiasis was unmapped in Abia State at the time of this analysis, and therefore no schistosomiasis treatments were delivered across the

State. Because schistosomiasis and STH programs are often co-delivered (i.e. integrated) in a school-delivery platform, Abia State also chose not to distribute albendazole for STH to school-age children in 2015.

The population sizes of the States are similar: 3,452,952 people are estimated to reside in Abia and 3,603,151 in Cross River State. Not accounting for schistosomiasis or STH amongst school-age children in Abia, in 2015 there were 5.1 million and 4.5 million treatments indicated in Abia and Cross River States, respectively, for targeted endemic diseases. The number of treatments required exceeds the population because many people required treatment for more than one co-endemic disease.

All LGAs in both States were endemic for LF. In Abia State, 74% of the LGAs also required treatment for onchocerciasis and 95% of LGAs also required treatment for STH in children (although this was not delivered in 2015). In Cross River State, 88%, 100%, and 100% of LGAs were LF co-endemic with onchocerciasis, schistosomiasis, and STH, respectively. Each State reported that CDDs spent about half of their time on integrated activities such as integrated trainings or drug delivery (50% in Abia and 46% in Cross River State). The States also reported that 63% and 70% of community member time expended on NTD program involvement was spent on integrated activities in Abia and Cross River States, respectively.

Costs

In 2015, financial costs from the societal perspective (i.e. regardless of who pays) were \$1.3 million and \$2.2 million in Abia and Cross River States, respectively. Financial costs from the provider (i.e. government) perspective were \$1.2 and \$1.1 million and per capita government expenditure on NTD programs was thus \$0.34 and \$0.32 in Abia and Cross River States, respectively. Programmatic economic costs (i.e. excluding community member opportunity costs) were \$11.8 million and \$8.8 million in each State, respectively. Economic costs (program and

community costs) were \$13.2 million and \$13.8 million, and total costs were \$14.3 million and \$16.1 million in Abia and Cross River States, respectively (Table 2).

Financial costs from the societal perspective for State-level integrated NTD programs were \$1.3 million and \$2.2 million in Abia and Cross River States (Table 3). The allocation of costs by program activity varied greatly by State. In Abia the largest percentage of costs (20%) was spent on training activities while in Cross River the largest percentage of costs (23%) was spent on MDA service delivery (Figure 1). Social mobilization (19%) and monitoring and evaluation (16%) were also large activity cost categories in Abia, while training (20%) and MDA registration (14%) were in Cross River. Cross River budgeted for costs specific to morbidity management and vector control activities, while these activities were not implemented in Abia State in 2015 and therefore no funds were allocated (Figure 1).

Financial costs were also organized by relevant resource input. For both Abia and Cross River States, the largest proportion of costs was allocated to the input of personnel (64% and 73%, respectively) (Table 4 and Figure 2). In Abia personnel salaries were approximately \$819,000 while in Cross River they were around \$1.6 million, \$1.04 million of which were provided by NGOs as opposed to the MOH. Per diems and travel costs were the second largest cost input category across States. In Abia \$341,827 was allocated for per diems while \$501,567 was allocated for per diems in Cross River State.

Nearly 95% and 96% of costs were recurrent rather than capital costs in Abia and Cross River States, respectively. Most training, mobilization, and strategic planning activities are recurrent for MDA-based programs, with the exception of the development of materials such as training manuals. The source of funding for activities was quite different across the two States. In Abia, 92% of total financial costs were attributed to the MOH and 8% to NGOs. In contrast, in Cross River State the MOH was responsible for 53% of total financial costs while NGOs were responsible for 47%.

In 2015, economic costs (programmatic and community) for State-level integrated NTD programs were \$13.2 million and \$13.9 million in Abia and Cross River States, respectively (Table 6). In Abia, 90% (\$11.8 million) of economic costs were programmatic costs associated with donated drug costs. In Cross River State, only 63% (\$8.8 million) of costs were associated with donated drugs and 37% were associated with community member opportunity costs (Figure 3). Abia has seven times less the number of CDDs than Cross River State, but reported paying \$80,000 more in CDD per diems due to a higher per diem rate. However, in both States, the costs of CDD per diems paid were greater than the opportunity costs associated with CDD participation in trainings and treatment days, and therefore there were no additional economic costs associated with CDD volunteer labor inputs.

Average cost per output

In Abia State, reported treatment coverage ranged from 0% for schistosomiasis and STH to 158% for onchocerciasis (because LF and onchocerciasis treatment campaigns were integrated, some people who were not indicated for onchocerciasis treatment received it by default). In Cross River State treatment coverage ranged from 27% for schistosomiasis to 87% for onchocerciasis. The average total cost per treatment delivered was \$5.19 and \$4.68 in Abia and Cross River States, respectively. From the societal perspective, the average financial cost per treatment delivered in Abia was \$0.46 while in Cross River it was \$0.64. From the provider (MOH, not inclusive of NGO costs) perspective, the average financial cost per treatment delivered was \$0.42 and \$0.34 in Abia and Cross River States, respectively. Economic unit costs accounting for programmatic and community costs were \$4.73 in Abia and \$4.04 in Cross River States (Table 6).

Average cost per outcome

In Abia State the estimated number of cases averted in 2015 ranged from 0 for schistosomiasis and STH to 776,000 for onchocerciasis. In Cross River State the number of cases averted ranged

from 135,000 for schistosomiasis to 746,000 for STH. From the societal perspective, the average total cost per case averted was \$14.10 in Abia and \$10.85 in Cross River State (Table 6).

Univariate sensitivity analyses

In Abia State, variations in LF treatment coverage exhibited the strongest influence on average societal financial unit costs, ranging from a 45% increase to a 39% reduction in the average financial cost per treatment delivered, when coverage decreased by 50% and increased to 100% respectively. Similarly, in Cross River State, variations in LF treatment coverage exhibited the strongest influence on potential reductions in the average financial cost per treatment delivered, with up to a 32% reduction in costs. Changes in the number of community supervisors resulted in the largest potential increase in costs, up to 47% (Figure 4).

Variations in the cost of ivermectin tablets had a large potential effect on average total costs per treatment delivered in Abia State, with costs ranging from an 81% increase to a 41% reduction when tablet costs increased by twice their value and decreased by 50%, respectively. Similarly in Cross River State, changing the costs of ivermectin tablets resulted in a 53% increase and up to a 27% reduction in average total unit costs (Figure 4).

Changes to baseline estimated disease prevalence had a profound effect on average total cost per case averted in each State, where the lower the disease prevalence the higher the average unit cost. In particular, changes to onchocerciasis prevalence resulted in an increase in average total unit costs up to 60% when prevalence was halved and a reduction up to 44% in Abia State when prevalence increased by 50%. In Cross River State changes to schistosomiasis prevalence had the largest effect on average total unit cost per case averted, with costs ranging from a 53% increase to a 15% decrease (Figure 4).

Abia reported engaging with 835 CDDs in 2015 with an average of 5 days spent per CDD (835 total CDD days on training and 3,340 CDD days on MDA delivery). Cross River reported engaging

with 6,164 CDDs with an average of 10 days spent per CDD (15,578 total CDD days were reported spent on training while 49,950 were spent on MDA delivery). However reductions and increases in CDD days in both States had no effect on unit costs as the amount of per diems paid to the volunteers was greater than the opportunity costs associated with any changes in lost wages due to participation in the programs.

We assumed that integration could reduce financial costs to be as low as costs associated with a single disease, specifically the disease with higher costs for the particular activity. And it was assumed that integration may increase costs up to 110%. These assumptions for activities including advocacy, drug logistics, monitoring and evaluation, training, and social mobilization had relatively minor influences on average financial unit costs per treatment delivered. In Abia State, integration of LF and onchocerciasis training costs resulted in cost increases up to 7% and cost reductions up to 3%. Similarly, in Cross River State, integration of financial training costs (as opposed to economic opportunity costs) across LF and onchocerciasis programs resulted in cost increases up to 6% and cost reductions up to 4% (Figure 5). The TIPAC allows the user to either specify activity costs for each disease, or to equally divide an activity cost across endemic diseases. Both participating States elected to equally distribute costs by disease as costs are often not recorded at a sufficiently granular level to capture disease specific budget or expenditure. Thus estimates of LF and onchocerciasis integration are equivalent to estimates of schistosomiasis and STH integration, where all diseases are co-endemic.

Integration of activities that minimize CDDs time spent on training and MDA delivery activities did not have a large influence on average total unit costs per person treated or per case averted. However ensuring that programs are fully integrated for community members could reduce total unit costs per person treated and cases averted up to 12% (from \$4.68 to \$4.13 per person treated) (Figure 5). These analyses could not be conducted in Abia State, where it was reported that all costs associated with provider and participant time were already maximally integrated.

Scenario analysis

Scenario analyses were conducted to identify how the affordability of the NTD program changes when the proportion of total financial costs paid by the MOH, as opposed to NGOs, gradually increases. In Cross River State, two benchmarks of affordability were applied: \$0.14 per treatment delivered (identified from the online WHO NTD benchmarking application (91)) and \$0.50 (identified from partner survey responses). In comparison to the first benchmark, the NTD program in Cross River State was not affordable unless NGOs supported at least 80% of NTD program costs. In comparison to the second benchmark, the program in Cross River State was not affordable unless NGOs support at least 20% of program costs (Figure 6). In Abia State, where the MOH supported a larger percentage of overall program costs (92%) at baseline, the WHO State-specific benchmark was set at \$0.13 per treatment delivered (91). The NTD program was not affordable unless NGOs supported at least 75% of NTD program costs. However according to the partner's benchmark of \$0.50 per treatment delivered, the Abia NTD program was affordable under any scenario, including if the MOH shoulders all program costs.

Scenario analyses were also conducted to identify how financial unit costs from the provider perspective may change should drugs no longer be donated by pharmaceutical companies. Overall, average financial unit costs paid by State governments could increase as high as \$4.63 in Abia State and \$2.90 in Cross River State. This is largely due to the cost of ivermectin which, at \$1.50/tablet, and would add an additional \$12 million to Abia's required expenditure and \$9 million to Cross River's. If either State had to pay for ivermectin alone or in addition to any other donated drugs, the unit costs would far exceed affordability benchmarks (Figures 7).

Reflections on process of completing TIPAC

The TIPAC tool provided an organized and systematic way of recording NTD program costing data. However the teams responsible for completing the tool in each State encountered several challenges and points of confusion during tool completion. Specifically, the tool does not

necessarily facilitate consistent terminology across geographies, specificity in costed activities, or the opportunity to identify inputs. For example, one State allocated \$2,222 for each endemic disease program for a sub-activity entitled “Secure Needed Logistics” under the transportation activity category. This sub-activity was vague and, upon pressing the State for specificity, it was determined that these funds were necessary for pre-MDA vehicle maintenance, and were clarified as such in the tool. Similar confusion in costing allocation was observed in categorizing costs across resource mobilization and social mobilization. Although cost categorization is complex even for trained financial managers, the TIPAC is intended to be routinely completed by NTD Program Managers, and thus must be easily applied with minimal errors by diverse users.

About 45% of data points initially entered into the TIPAC had to be re-categorized during the review meeting from external researchers to increase specificity or to harmonize terminology across geographies. For example, one State classified “Development/printing of training materials” as relevant to “coordination mechanisms”, while the other State classified similar costs as part of training activities. Without the extensive review that this study entailed, the TIPAC tool may not have provided standardized or representative perspectives of the States’ NTD program activities.

Discussion

Abia and Cross River States have similar population sizes, similar disease profiles and similar financial and economic costs per beneficiary, however the relative proportioning of costs by activity category was different across the integrated NTD programs. Training was the largest activity cost in Abia and MDA service delivery was the largest in Cross River, which is consistent with the main activity cost categories identified in other West African national NTD programs (95). The distribution of resource inputs, in contrast, was consistent across the States with the majority of costs allocated to personnel in each setting. Personnel is often one of the largest resource inputs in cost analyses, not only within the NTDs but across public health programs (107).

From the societal perspective, average financial costs per treatment delivered were \$0.46 and \$0.64 in Abia and Cross River States while the economic cost per beneficiary was \$5.09 and \$4.68, respectively. The difference in financial and economic costs per beneficiary primarily reflects the inclusion of community member time and donated drug costs. The financial costs identified are well-aligned with top-down global estimates of \$0.50 per treatment delivered as well as with a study of the African Programme for Onchocerciasis Control (APOC), which identified a financial cost of \$0.58 per vertical ivermectin treatment delivered (108). However the APOC study found that economic costs doubled to \$1.26 per treatment delivered, while in this study economic costs increased by ten-fold, likely due to the inclusion of community-member opportunity costs, as described below.

The per capita financial cost of NTD programs from the government perspective was \$0.34 and \$0.32 in Abia and Cross River States, respectively. Given the WHO estimate of \$30 per capita health expenditure in Nigeria (104), government contributions to NTD programs in these States are equivalent to 1% of per capita health expenditure. Given an annual government expenditure on health of nearly \$21 billion in Nigeria, each State's NTD-associated financial costs are an estimated 0.006% of total national government health expenditure. Governments have numerous competing funding priorities and Nigeria has the wellbeing of 36 States to consider, however given the low per capita input required, small budget expenditure on NTDs, and extensive public health impact of NTD programs, the associated costs as currently allocated in Nigeria appear relatively quite small.

While the total cost of the Cross River NTD program was more expensive than the Abia program, the economic cost per person treated and per case averted were lower. This is primarily because the program in Cross River State treated more people, resulting in economies of scale, while the Abia State program was not fully functional and a lower number of children in need of treatment for schistosomiasis and STH were reached. Inequalities in who is reached by treatment programs

thus results in inefficiencies, and areas that fail to achieve coverage of at-risk populations may be more expensive to re-initiate in subsequent years due to repeat start-up costs (109). These findings, in addition to other data, also suggest that as MDA-based NTD programs are successful in addressing control and elimination objectives, and thus where the number of treated cases is low, the average total cost per case averted will likely rise (110, 111).

The average financial cost per treatment, that measures all financial costs, regardless of who delivers services, was lower in Abia than in Cross River. However, the estimate of financial cost per treatment from the MOH perspective, reflecting the government's contribution to MDA campaigns, was lower in Cross River because a large proportion of the NTD program was supported by NGOs. Under a variety of scenarios, it is evident that the government would not be able to fully support all NTD program costs in Cross River, and potentially in Abia State as well. However, in Abia State, program managers were not aware of the precise financial contribution of NGOs to the State NTD program, or how to access the budgetary or expenditure data of NGOs operating in the State, suggesting that the contribution of NGOs has been underestimated. This may be one reason why some specific program costs, such as drug logistics, are particularly low in Abia State. This is important for policy makers and donors to consider not only because overlooked NGO activities would alter the overall unit costs observed in Abia State, but also because both government actors and their partners claim to prioritize long term sustainability and government ownership of domestic NTD programs (112). Improving the participation and contribution of NGOs to TIPAC data collection will help estimate more precise costs as the WHO works to incorporate NTDs into the WHO Health Accounts Country Platform to track expenditure on NTDs, compare domestic funding on NTDs with external NTD funding, and compare domestic funding with internal investment targets (90).

Integration of disease-specific activities exhibiting joint costs may reduce the amount of time it takes to perform the activities, and researchers project that integration of NTD programs in Africa

could result in cost-savings of up to 26-47% (113, 114). In this study, sensitivity analyses that varied the degree of activity integration in Abia and Cross River States resulted in only small changes to average total financial costs (up to 7%) but larger changes to overall economic costs (up to 12%). However some activities in the States were already integrated at baseline.

Integration of CDD activities in sensitivity analyses had a smaller influence on unit costs relative to analyses of community member time because the minimum wage in Nigeria is low, and thus CDD per diems earned were larger than the opportunity costs (i.e. potential wages lost) by individuals earning the country's minimum wage. Thus at a sub-national level, local governments may expect to see increased efficiency associated with activity integration, particularly of health worker training activities, and even larger efficiencies would be observed as communities benefit from time savings accrued from integrated community-based MDA delivery. However it is very important that program quality is not compromised as activities integrate, and quality assessments were not incorporated into this study.

One of the few studies that utilized program expenditures to evaluate the cost of integrated NTD programs observed an average economic cost of \$0.19 per treatment delivered and overall savings of 16–21% relative to vertical programs. Specific integrated activities were limited to program planning, supply chains, training, supervision, and reporting. The study did not account for drug costs, community member opportunity costs, and also compared costs from vertical programs delivered shortly after the NTD program was launched to costs of the integrated program several years later; thus natural improvements to program delivery over time may have affected observed efficiencies (95). Another study in Nigeria evaluated the cost-effectiveness of integrated treatment delivery, and found that a one time delivery of integrated MDA (i.e. triple drug administration) had a financial cost of \$0.10 per treatment delivered and reduced costs by 40% relative to vertical treatments, but also did not account for broader opportunity costs (14). Both of these studies identified lower average unit costs associated with integrated programs than did our

study, but this may be due to the more extensive inclusion of economic costs in our analysis, the scale at which the costs were collected, and the cost collection setting (i.e. routine collection as opposed to collection within a research setting).

Improving tool performance

Comparing microcosts across similar geographic areas was a helpful exercise in identifying programmatic cost drivers as well as in evaluating tool performance and data quality. Both States had similar user feedback regarding challenges encountered, such as in reporting specific integrated costs or in accounting for the salaries of individuals peripherally involved in NTD programs.

The TIPAC provides an opportunity for users to record “integration” in drug supply, such as the number of albendazole treatments indicated in areas that are both STH and LF endemic, and to account for overlapping intervention target groups across NTDs. But the tool does not provide an opportunity to indicate specific activities and sub-activities that are integrated with one another. Thus the tool does not generate the rich data source needed to truly understand the relative advantage of integrating some activities and not others. As a result, the tool serves as a functional budgeting aid but, unlike the name suggests, it is not a sufficient planning aid. Once funds are allocated based on TIPAC budget requests, States have to undertake an additional, immense planning process to identify which diseases and LGAs to allocate sub-activity funds to upon receipt.

The TIPAC would be a superior planning tool if modules are slightly modified and more internal checks are built into the tool. Specifically, we recommend that (1) the TIPAC does not allow costs to be evenly distributed across diseases as a default mechanism but rather only upon confirming that funds are indeed spent on the NTD program generally and not on any disease-specific efforts, (2) in co-endemic LGAs (or equivalent) a checkbox should automatically appear that asks if these activities were disease-specific or delivered for multiple diseases at once, (3) if users indicate that

activities are integrated, they should be prompted to select the diseases that the activity is integrated for, (4) automated boxes should also solicit information regarding the planned duration of activities to better understand some of the economic costs of programs, and (5) automated boxes should solicit information regarding specific personnel who were involved in each activity via pre-set menus modified by baseline personnel inputs. Data resulting from these revisions would not substitute for in-depth expenditure-based research studies, but would provide the routine data at scale needed to accurately cost and compare integrated NTD programs. And, although these additional data points may not be priorities for funders or for informing budget requests from the national level, they may be important for maximizing performance and internal review by NTD Supervisors.

Limitations

This study used judgement sampling to identify the small sample of two States, limiting the broader generalizability of findings. Because information regarding donor contributions in one of the States was of poor quality, it was also not possible to completely distinguish costs by source. Additionally, while States provided estimates of the number of “campaign days” required of adults in each LGA, in practice there will be extensive heterogeneity within and between communities in terms of the time spent by community members who are treated by MDA programs. Information on resource use should ideally be collected in real-time directly from community members involved. Also, while benchmarks are important mechanisms for identifying affordability, many of the studies used to inform the State-specific benchmarks used in this analysis did not account for drug costs and were from peri-urban areas, and may not accurately represent costs associated with delivery in primarily rural areas (90). Lastly, this analysis does not account for the complicated health outcomes associated with NTD cases averted, disability life-years averted, or the important secondary effects of morbidity on caregiver time and productivity (115), and therefore does not provide information regarding the relative cost-effectiveness of different integrated programs.

Conclusion

The Nigerian government's need and commitment to scaling up integrated NTD programs was highlighted in the 2013 release of a five year integrated NTD Master Plan (116). However, there is dearth of information regarding the cost and relative efficiency of integrated programs relative to vertical programs, both within the NTDs and across community-based public health programs more broadly (91, 117). In two Nigerian States, the average financial unit costs of the integrated NTD programs were aligned with a stakeholder-identified benchmark of affordability, however the programs would not be affordable under most scenarios in which governments have to shoulder costs currently supported by NGOs or assume drug purchasing costs. The average total costs per treatment delivered were far more expensive in this study than most estimates currently available in the literature due to the inclusion of donated drugs and opportunity costs for volunteer drug distributors and community members. This demonstrates the need for future studies to engage in a more nuanced and comprehensive approach to NTD program costing. To increase the efficiency of programs, local governments should focus on increasing treatment coverage (i.e. economies of scale) and ensuring that activities are maximally integrated for program beneficiaries, without compromises to program quality.

Accurately capturing integrated NTD program costs in the TIPAC is important, particularly as the WHO plans to build a TIPAC-based module into the WHO's Sector-Wide Costing Tool (59), which will present NTD costs alongside other diseases to facilitate comparative planning and budgeting. However, if the tool is not capturing costs accurately, this could mislead domestic prioritization activities. Thus, comparisons of integrated NTD program costs and outputs at a State level is useful not only for understanding drivers of affordability and sustainability within Nigeria, but also for identifying opportunities for improved cost collection mechanisms in integrated NTD programs more broadly.

Table 1: Definitions of cost classifications

Classification	Cost Category	Definition
Activity	Administration	Personnel time spent on administration and overhead.
Activity	Advocacy	Efforts to encourage district government participation in NTD control and elimination and soliciting funds and support from implementation partners and the national government.
Activity	Program office	Equipment and office supplies in the State NTD office, including building space provided by the national government in-kind.
Activity	Drug logistics	Drug transportation, drug importation, drug repackaging, and drug storage, including the costs of donated drugs.
Activity	MDA registration	Efforts to gather accurate information on the size and eligibility of the target populations.
Activity	MDA service delivery	MDA drug distribution, including opportunity costs to CDDs and community members.
Activity	Monitoring and evaluation	Data quality assurance activities, including spot checks and site surveys.
Activity	Morbidity management	Efforts to identify and manage existing morbidities and prevent further disability.
Activity	Social mobilization	Development and dissemination of information, education, and communication (IEC) materials and messages.
Activity	Strategic planning	Annual review meeting (i.e. high level review meetings), national stakeholders meeting, and technical planning meeting.
Activity	Training	Development/printing of training materials, training of trainers, training of supervisors, training of teacher/health worker (school-based MDA delivery), training of CDDs (community-based MDA delivery), and refresher trainings.
Activity	Vector control	Efforts to reduce or interrupt disease transmission by controlling vectors.
Input	Travel/per diem/allowances	Costs for NTD workers to travel, spend time in the field, attend trainings, or other supplementary activities.
Input	Contracted services	Conduct media air announcements, printing via third parties, and other services contracted out.
Input	Equipment	Purchasing and maintenance of refrigerators or other equipment with a cost of USD \$100 or more.

Input	Overhead	Administrative offices and storage facilities.
Input	Personnel	Supervisors, health workers, administrators, technicians, and other program personnel.
Input	Program supplies	Any purchased drugs, office supplies, and small equipment less than USD \$100.
Input	Transportation: operation and maintenance	Bicycles, motorcycles, vehicles, fuel, maintenance, spare parts for vehicles or transportation reimbursement via other methods.

Table 2: Costs by perspective

	Perspective/Costs	Abia State	Cross River State
Program Costs	Provider (i.e. MOH) Perspective		
	Financial	\$1.2 million	\$1.1 million
	Societal Perspective		
	Financial	\$1.3 million	\$2.2 million
	Economic	\$11.8 million	\$8.8 million
	Total Costs	\$13.3 million	\$11.0 million
Community Costs	Societal Perspective		
	Economic	\$1.4 million	\$5.1 million
Program + community costs	Total Costs	\$14.6 million	\$16.1 million

Table 3: Financial costs by activity category

Activity	Abia		Cross River	
	Total (2015 USD)	Percent	Total (2015 USD)	Percent
Admin	\$ 65,293.74	5.1%	\$ 411,238.00	18.7%
Advocacy	\$ 95,369.44	7.4%	\$ 99,136.55	4.5%
Program office	\$ 77,610.47	6.0%	\$ 4,188.59	0.2%
Drug Logistics	\$ 908.89	0.1%	\$ 71,788.07	3.3%
MDA registration	\$ 75,697.47	5.9%	\$ 303,149.24	13.8%
MDA service delivery	\$ 127,862.02	10.0%	\$ 494,052.51	22.5%
Monitoring and evaluation	\$ 203,100.00	15.8%	\$ 54,741.12	2.5%
Social mobilization	\$ 240,782.22	18.8%	\$ 132,509.50	6.0%
Strategic Planning	\$ 144,975.56	11.3%	\$ 72,247.62	3.3%
Training	\$ 251,661.52	19.6%	\$ 430,883.99	19.6%
Morbidity management			\$ 84,507.04	3.9%
Vector control			\$ 36,446.70	1.7%
TOTAL	\$ 1,283,261.33	100.0%	\$ 2,194,888.93	100.0%

Figure 1: Financial activity costs, by State

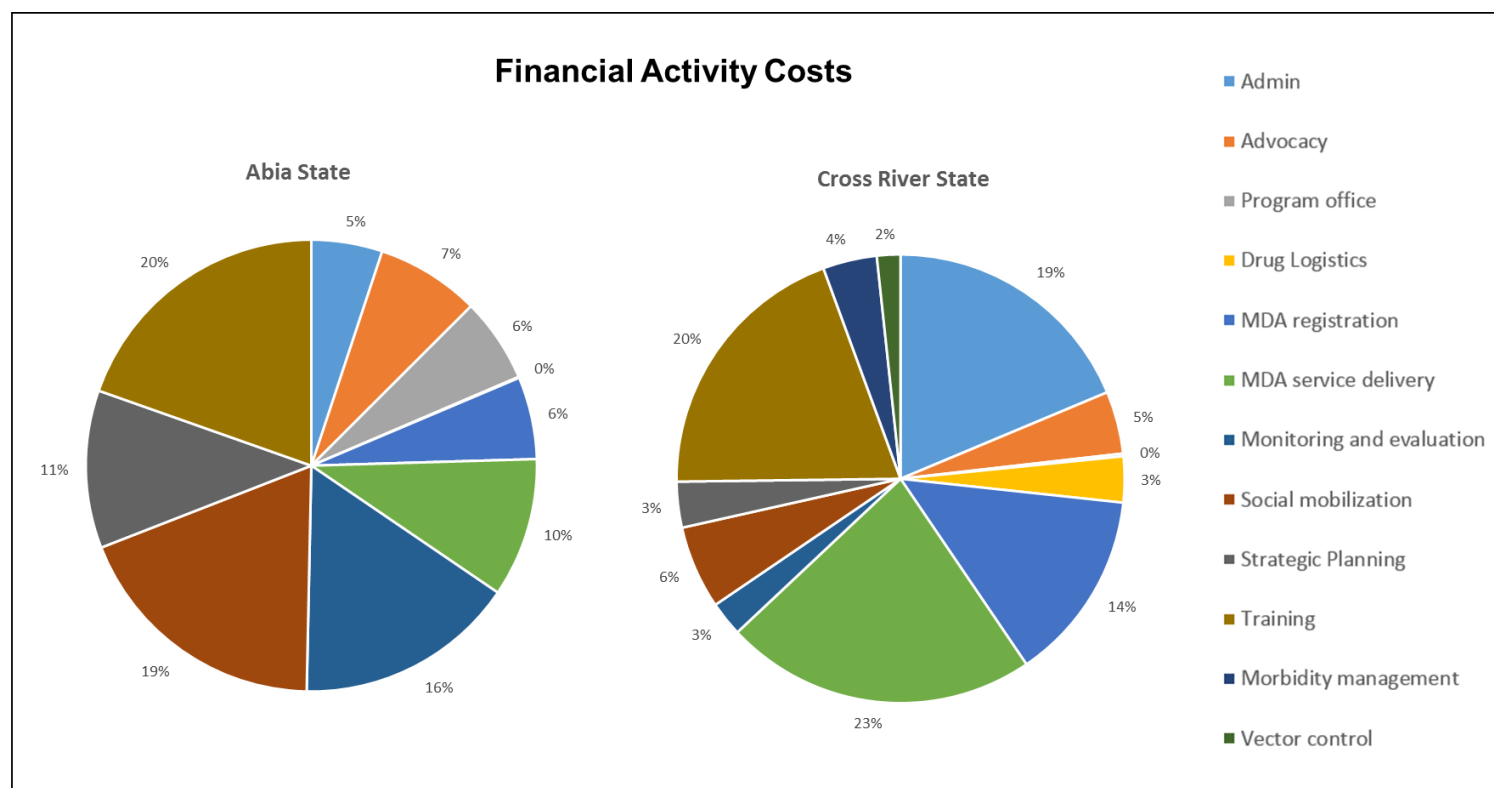


Table 4: Financial costs by input category

Input	Abia		Cross River	
	Total (2015 USD)	Percent	Total (2015 USD)	Percent
Contracted services	\$50,951.11	4.0%	\$1,808.95	0.1%
Equipment	\$25,474.13	2.0%	\$332.53	0.0%
Overhead	\$20,540.78	1.6%	\$5,757.58	0.3%
Personnel	\$819,105.86	63.8%	\$1,609,269.34	73.3%
Program supplies	\$15,413.89	1.2%	\$29,629.20	1.3%
Transportation	\$9,947.78	0.8%	\$46,524.23	2.1%
Travel/per diem/allowances	\$341,827.78	26.6%	\$501,567.11	22.9%
TOTAL	\$1,283,261.33	100.0%	\$2,194,888.93	100.0%

Figure 2: Financial resource inputs, by State

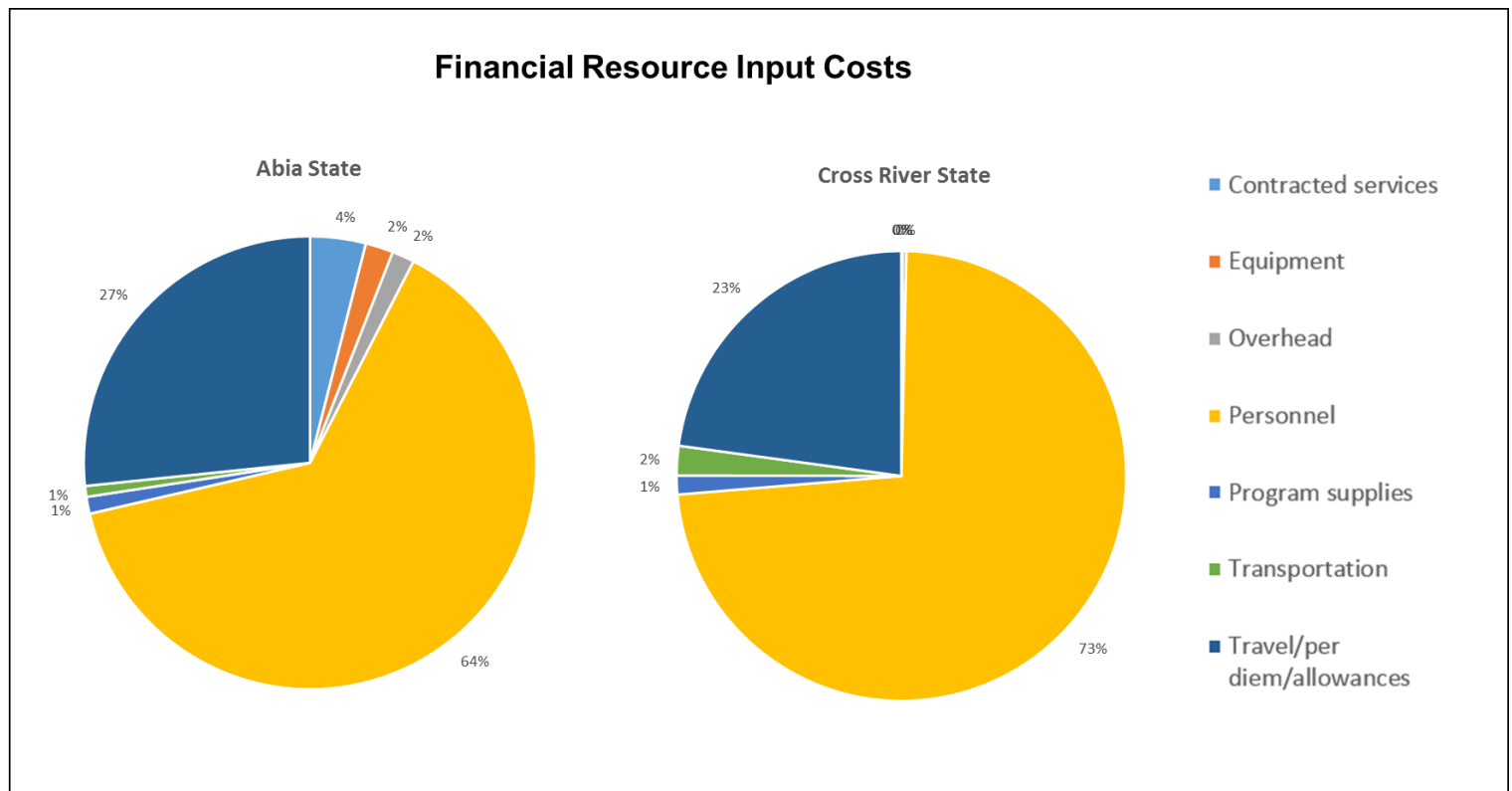


Table 5: Economic activity costs

Input	Abia		Cross River	
	Total (2015 USD)	Percent	Total (2015 USD)	Percent
Program costs: Donated drugs	\$11,793,284.83	89.0%	\$8,804,153.91	63.5%
Community costs: Community member lost income	\$1,453,217.39	11.0%	\$5,070,143.21	36.5%
Total economic costs	\$13,246,502.22	100.0%	\$13,874,297.12	100.0%

Figure 3: Economic activity costs, by State

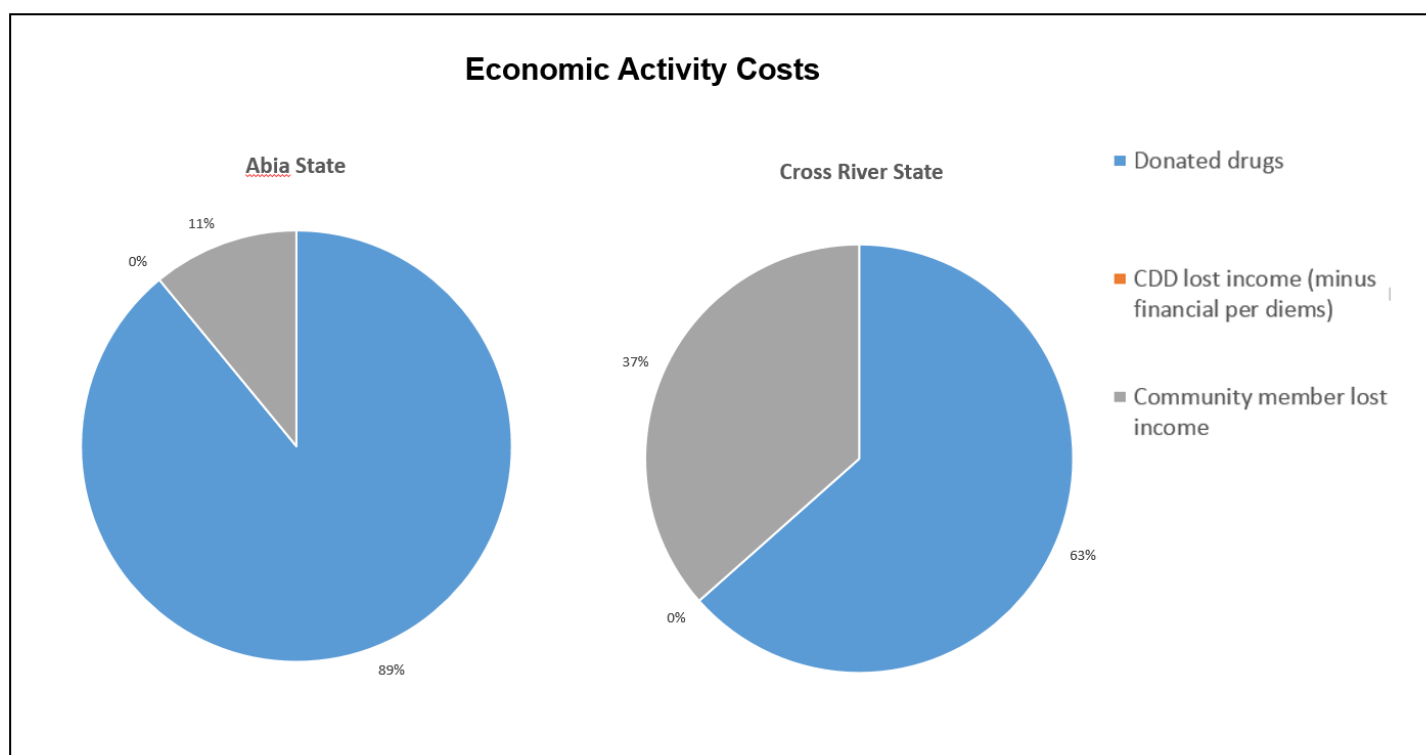


Table 6: Average unit costs (\$2015 USD), by State

	Abia State	Cross River State
Provider perspective		
MOH expenditure per treatment delivered	\$0.42	\$0.34
Societal perspective		
Financial cost per treatment delivered	\$0.46	\$0.64
Economic cost (program and community) per treatment delivered	\$4.73	\$4.04
Total cost per treatment delivered	\$5.19	\$4.68
Total cost per case averted	\$14.10	\$10.85

Figure 4: One-way sensitivity analyses for financial and total costs from the societal perspective, by State

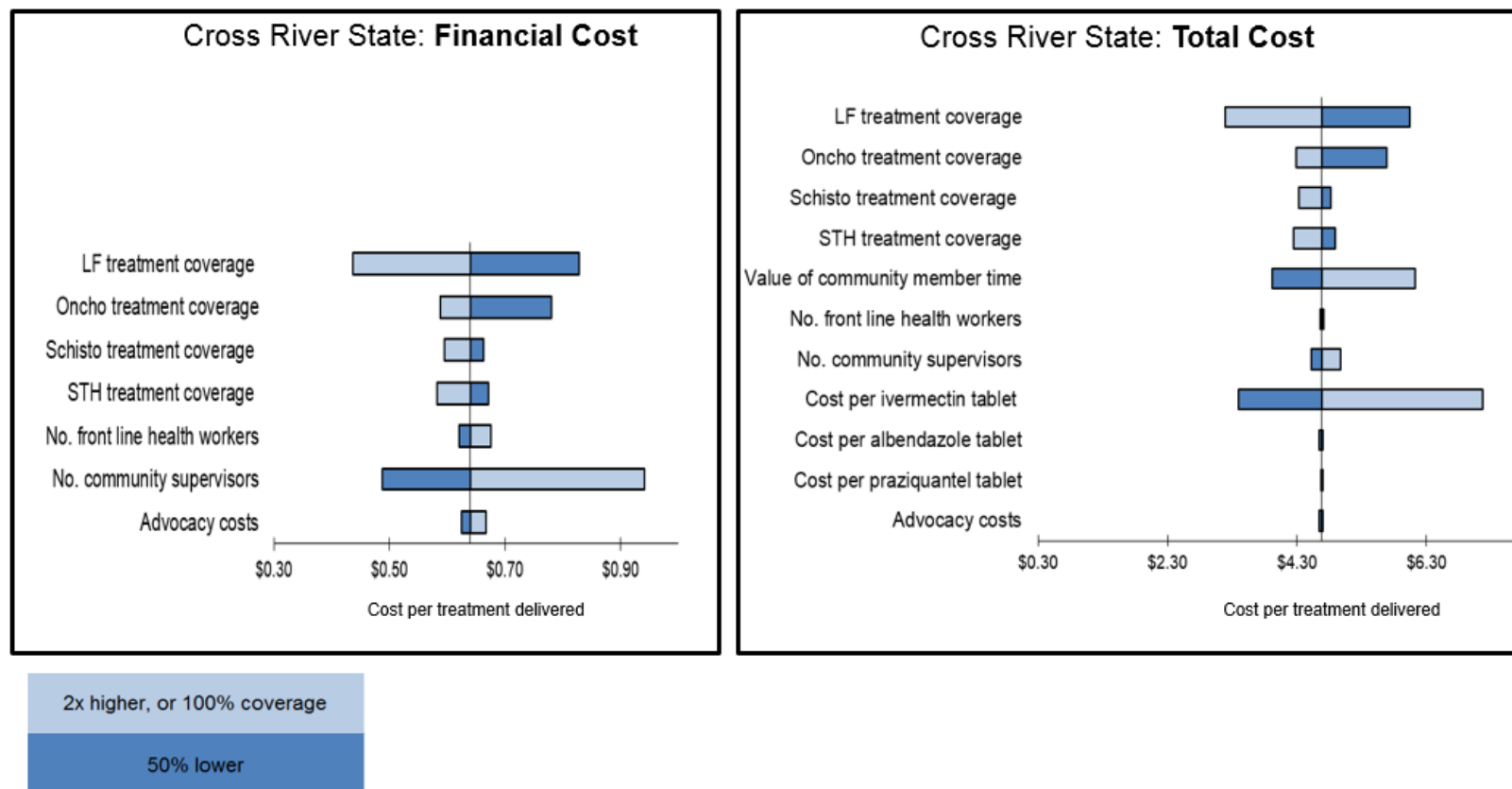


Figure 5: One-way sensitivity analysis for influence of integration on financial activity costs from the societal perspective, by State

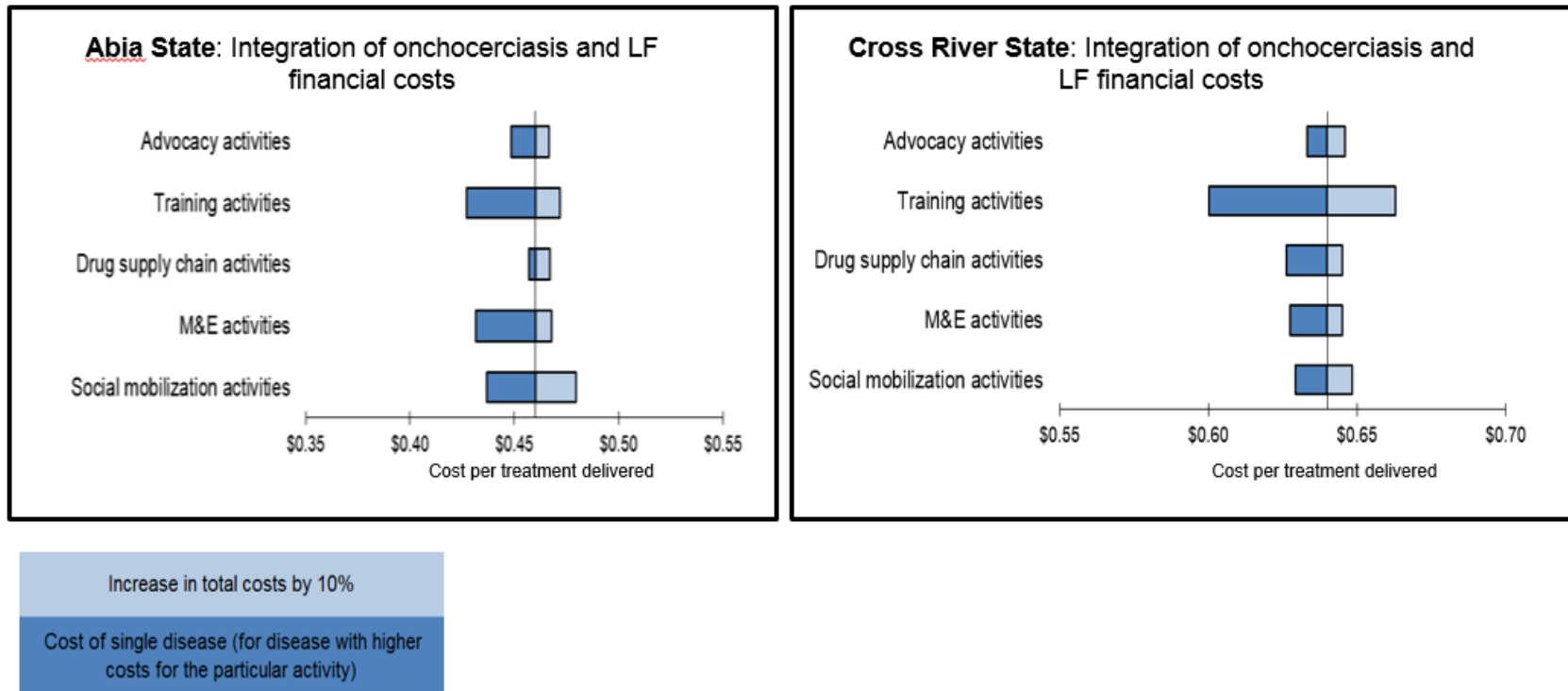


Figure 6: Average financial unit costs per treatment delivered from MOH perspective, as costs transition from NGO to MOH: Cross River State

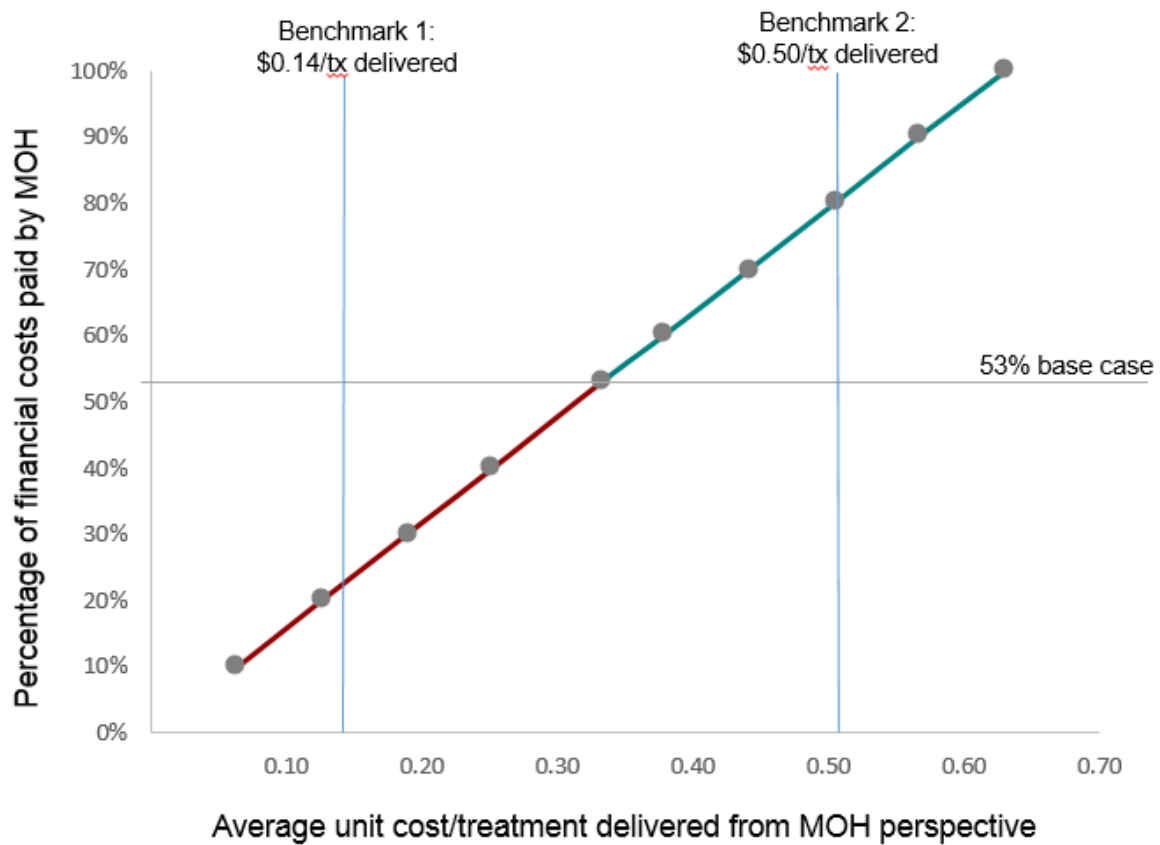
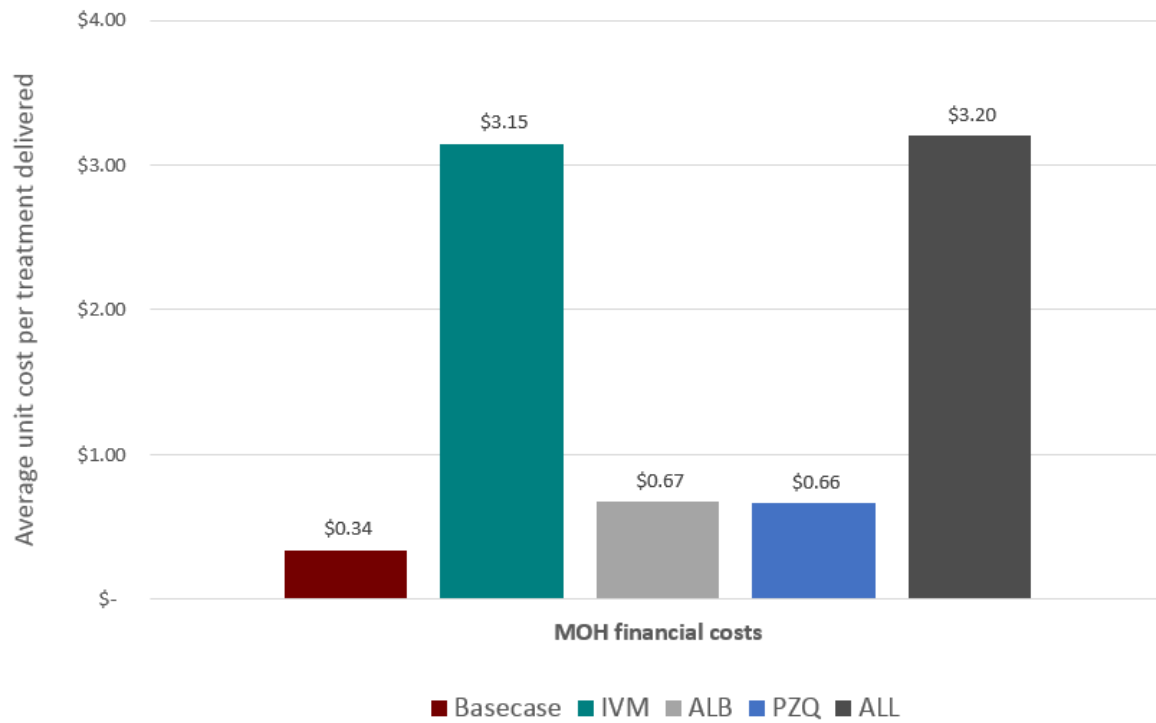


Figure 7: Average unit costs if MOH purchases drugs in Cross River State, by drug and overall



CHAPTER 5: Conclusions on the effectiveness and efficiency of integrated neglected tropical disease programming

This research indicates that integration of public health programs occurs on a spectrum, wherein certain activities may be more compatible for integration than others and integrated packages must necessarily be tailored to the specific needs of the beneficiary population. Given that these findings are not fully aligned with standard practice, we suggest a re-focusing of the current approach; integration should be pursued as a means to delivering better public health services rather than as an end in of itself. The NTD community must begin to systematically name and measure the type and degree of integration between programs in order to ensure robust evaluations of their effectiveness and efficiency. In this regard, this body of work provides new terminology and differentiation of integration approaches. This is not only relevant to the sustainability and scalability of NTD programs in terms of fostering stronger, tangible linkages within the health system, but also provides useful insight for building a continuum of preventative health services in the context of universal health coverage (UHC).

As a whole, this compendium of research indicates that a “diagonal approach” to NTD integration may be superior to the status quo because it lends itself to a more nuanced understanding of program compatibilities. The diagonal approach, predominantly discussed within the context of HIV programs, stresses the importance of coordination between vertical interventions, community-based initiatives, and health facilities. The approach aims to bridge the differences between horizontal and vertical approaches as well as intersectorial and sectorial policies by offering an alternative through which effective interventions become the drivers for health-system improvements (118).

Research on diagonal approaches to healthcare delivery requires “methodological pluralism”, or utilization of a variety of appropriate cross-discipline methods, to ensure that multi-sectorial programs are appropriately implemented, evaluated, and scaled (119). Accordingly, this

dissertation uses a multidisciplinary approach to describe the process of integration in NTD programs, effectiveness of multisectoral integrated services, and the efficiency of integrated NTD programs operating at scale. Our findings suggest that the diagonal approach may be the most appropriate strategy for balancing the political, administrative, epidemiological, cultural, and financial complexities of integrating large, decentralized public health platforms.

Chapter 2: Despite calls to widely implement integrated NTD programs in co-endemic areas, strategies for operationalizing integrated NTD activities have not been systematically assessed. We undertook a cross-sectional qualitative research study with NTD stakeholders to understand different approaches to and perspectives on program integration. The stakeholders highlighted different definitions of the term “integration”, the differential effectiveness of specific activities when integrated, the influence of integration on community member engagement, the influence of funders on integrated programming, facilitators and barriers to effective integration, and the effects of integration on health system strength. Our analysis suggests that there are three types of integration to consider: structural, process, and technical. We use these categories to make ten recommendations to stakeholders that might be used to improve integrated NTD programming moving forward.

In the context of the Integration Principle Results Framework (Figure 1), it is clear that the main themes from this study align with evidence from other disease sectors including HIV, family planning, and maternal and child health. Because the necessary inputs into integrated programs are similar across disease sectors (Figure 1), a diagonal approach to NTD integration could have wider benefits for both decentralized healthcare as well as facility-based services. For example, in our study stakeholders identified inefficient organization of human resources as a barrier to integrated programs. Through strategic integration of the time that facility-based supervisory nurses spend in the field overseeing MDA campaigns, they may be able to maximize their time providing antenatal services in facilities. And, by coordinating the organization and timing of the

programs, each initiative could draw participants to the other via the shared personnel involved. This is an example of a diagonal approach to healthcare delivery.

Findings from this qualitative study also highlight that NTD programs will necessarily be structured differently across different endemic countries because each setting has a unique collage of partners, epidemiological profiles, and program attributes such as longevity and scale. But, in each setting, integrated programs will be more acceptable if there is an alignment across stakeholder approaches to program delivery; alignment in strategy and measured outcomes is critical to removing barriers to cooperation, which is at the core of effective integration.

Chapter 3: More than 2 billion people are infected with soil transmitted helminths (STH) and schistosomiasis globally. In addition to deworming with albendazole and praziquantel, water, sanitation, and hygiene (WASH) interventions may be needed to reduce the risk of helminth reinfection and ultimately to break transmission. However, while integration of deworming and WASH was enthusiastically supported by stakeholders in Chapter 2, evidence on the effectiveness of such programs is mixed. Using data from a randomized controlled trial of deworming among HIV-infected adults in Kenya, we evaluated the associations between different packages of deworming and WASH interventions with helminth prevalence. We also aimed to understand if there was an additive benefit to accessing both WASH and deworming (i.e. synergy). Our findings indicate that deworming was effective in reducing the probability of infection with most helminth species. With the exception of safe flooring and latrine access, WASH interventions did not significantly reduce the probability of helminth infections among adults with access to treatment. However WASH interventions may play a more prominent protective role among individuals without access to deworming treatments. These findings also suggest minimal additive benefit of coordinated anthelmintic chemotherapy and WASH interventions in this population.

This research highlights two key points. First, integrated NTD programs should be tailored according to the needs of specific target populations. For example, the families of adults with HIV who do not have access to deworming treatments should perhaps be purposefully targeted with other preventative services such as WASH, which could be delivered in conjunction with child-targeted deworming treatments. Or, given that this study indicates that deworming is effective in preventing helminth infections in adults, and our team's prior research indicates that deworming delays HIV disease progression amongst helminth-infected adults (84), HIV-infected adults could be newly provided deworming medications in conjunction with antiretroviral medications in HIV care settings (120).

Secondly, this study highlights the importance of identifying appropriate metrics of success for integrated programs. There is no consistent indication of synergy between WASH and deworming in the literature or within our own research. Yet we know that WASH not only plays a role in preventing NTDs and other diarrheal infections, but is also a basic human right. Thus, rather than measure synergy, metrics such as intervention coverage, cost per output, beneficiary satisfaction, and retained involvement in NTD program activities could be considered as other indications of effective deworming and WASH integration. These metrics also align with longer term goals of health systems strengthening. Given the recent launch of a joint global NTD-WASH strategy to intensify integrated activities (without established metrics or indicators) (121), we suggest that researchers and Ministry personnel ensure *a priori* that selected strategies and monitoring and evaluation indicators are aligned and framed appropriately.

Chapter 4: In Chapter 2 of this dissertation, stakeholders at all levels identified increased program efficiency as one of the primary rationale for pursuing integrated NTD programs. However there is very little information available regarding the relative efficiency of integrated NTD programs operating at scale, as opposed to within research studies, and at a sub-national level, as opposed to within a study site or aggregated at a national level. We analyzed the costs and affordability of

integrated NTD programs in two Nigerian States in order to compare the distribution of costs by State, unit costs, and drivers of costs and affordability. We found that the average financial unit costs of integrated NTD programs were aligned with the benchmark of \$0.50 per treatment delivered, which is commonly cited in the NTD literature and by NTD stakeholders in our research as the appropriate cost per integrated treatment delivered. However when financial costs were stratified by payer, and the provider (i.e. government) perspective was assumed, the programs were not affordable without the external support of non-governmental organizations. Similarly, if governments assume drug purchasing costs the programs were not affordable according to any of the pre-identified benchmarks.

Primary drivers of financial and economic costs included treatment coverage and the cost of drugs used in MDA campaigns, respectively. Importantly, the average total costs per treatment delivered were higher in this study as compared to most examples in the published literature. This is because we accounted for opportunity costs related to the time spent by volunteer drug distributors and community members participating in campaigns, as well as donated drugs. In our sensitivity analyses, we found that further integration of NTD program activities in Nigeria would be associated with small cost-savings (around 7% of total costs) however much larger efficiencies would be observed for integrated activities that result in time savings for participating community members (around 12% of total costs).

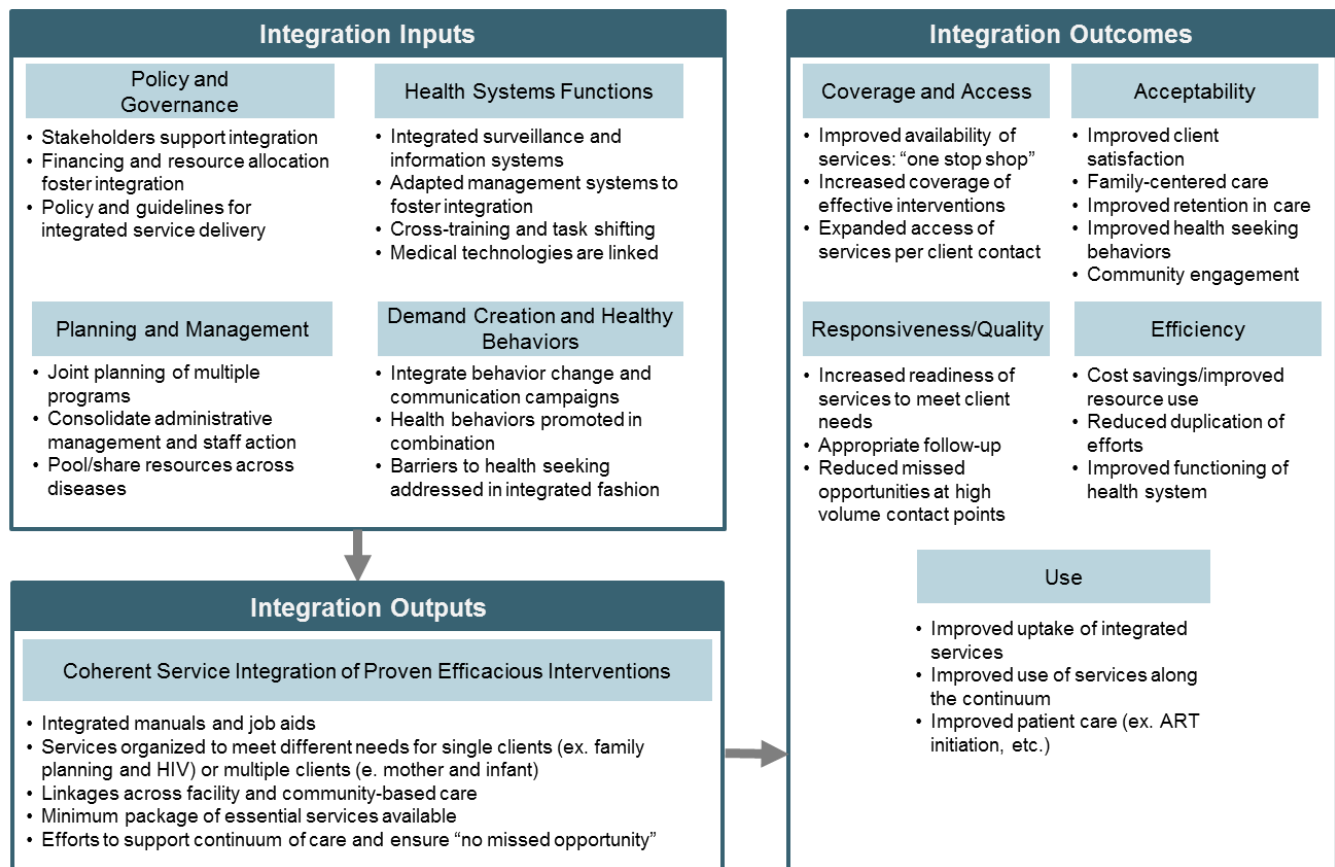
These findings highlight two important points. First, increasing treatment coverage results in economies of scale, where start-up costs and fixed costs are distributed over a larger treated population and unit costs are smaller as a result. Given London Declaration goals, endemic countries can expect decreasing average financial unit costs per treatment delivered as integrated programs are scaled up. As elimination outcomes are achieved, unit costs may rise. Additionally, this study suggests that as programs integrate and economies of scope are observed, there will be financial efficiencies and yet the largest efficiencies will be observed amongst economic costs

associated with time expenditures of program beneficiaries. To truly evaluate the efficiency of integrated programs, researchers and implementers must start to systematically measure these large, non-financial opportunity costs.

In summary, there are two primary rationale for integrating NTD programs: increased effectiveness of interventions and improved efficiency in low income countries. We used qualitative research methods to generate a number of testable hypotheses regarding activities that may be more effective (i.e. synergistic) if integrated. Upon analysis of stool samples from Kenya, we found no such synergy for one set of integrated multisectorial activities: combined access to WASH and deworming. Additionally, upon evaluating sub-national integrated NTD programs operating at scale we found that, while financial program costs are a relatively small component of overall government expenditure, the programs were only affordable for the country government so long as there were significant inputs from non-governmental partners. Notably, community members had the most to gain economically should NTD program activities be further integrated.

This research is important because, in comparison to other disease programs, there is a dearth of information evaluating the policy of integrated program delivery for NTDs. Given high community acceptability of integrated NTD programs and the potential for significant cost savings for community members in our research, it is clear that the well-being of beneficiaries should be the primary catalyst for integration. However given that barriers to integration are often funding and governance related, the drive for more intentional approaches to integration will need to be top-down. We suggest that a diagonal approach to NTD integration is adopted by policy makers and implementers. The resulting intentional integration will have greater specificity regarding the type and degree of cross-disease coordination. This adjustment to current practice is necessary for ensuring that integrated NTD programs are appropriate, effective, efficient, and adaptable within a continuum of high-quality care.

Figure 1: Integration Principle Results Framework (adapted from (122))



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