PLANNING FOR NEW HEALTH INTERVENTIONS FOR DEVELOPING COUNTRIES

An integrated strategy to prepare for malaria vaccines and lessons for future interventions

Inauguraldissertation
zur
Erlangung der Würde eines Doktors der Philosophie
vorgelegt der
Philosophisch-Naturwissenschaftlichen Fakultät
der Universität Basel

von
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Basel, 2011

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät
auf Antrag von Professor Doktor Thomas Smith, Professor Doktor Marcel Tanner
und Professor Doktor David Schellenberg.

Basel, den 18 October, 2011

Professor Doktor Martin Spiess
Dekan

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ACKNOWLEDGEMENTS

Christine Mensch is the person with all answers to all questions about Swiss TPH operations. I undoubtedly would have overlooked some part of completing this process without her guidance.

Three friends, John Marshall, Robin Biellik, and Erin Burchfield, gave freely of their time and brains to review, comment on, edit and generally make the papers far better than I ever could have alone. I thank them deeply for their investment in me.

I thank the Citizen's Cyberscience Center, and two of its supporting organizations, the European Center for Nuclear Research (CERN) and UNOSAT, for creating an opportunity to work at and seek collaboration with the many folks at and passing through CERN. And specifically I thank Francois Grey who shares my affinity for seeking collaboration where others may see divergence, and Dan, Jacki and Adrian for welcoming me each week.

I thank Claudia and Nora Roth for ensuring that I always had a warm, welcoming place to stay in Basel.

The work in this thesis was funded by a range of donors, as acknowledged in individual papers. The largest one was the Bill and Melinda Gates Foundation, in addition to the United States Agency for International Development.

And finally, I would like to thank my family, both near and far. They never once told me that at 40 years of age and with two young children at home, I was crazy to leave my job to try and do this. Instead they encouraged me throughout. Thanks My, Niko, and Clara, and all of you out West.

SUMMARY

PLANNING FOR NEW HEALTH INTERVENTIONS FOR DEVELOPING COUNTRIES

An integrated strategy to prepare for malaria vaccines and lessons for future interventions

PhD Thesis

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September, 2011

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INTRODUCTION

Historically, new health interventions have been developed primarily to address the needs of the wealthy in the developed world. Where drugs, vaccines, diagnostic tests and other interventions happened to address diseases prevalent in the developing world, they would eventually trickle down, and in some cases be adopted and implemented through national health systems. Such new interventions were relatively rare, often separated by years or decades for a single disease area (e.g. malaria) or delivery strategy (e.g. routine immunization programs).

Since 2000, the Global Fund to Fight Aids, TB and Malaria and GAVI Alliance have committed over US$20 billion to implementing existing interventions in developing countries. Partially as a result, countries have considered and will consider implementation of many new interventions. Multiple new malaria medicines and rapid diagnostic tests are now available and bednets have been improved over approximately the past decade. Challenges may be even greater for immunizations programs as countries consider four or more new vaccines for implementation, all becoming available to the poorest countries over approximately a five year period.

It is likely that there will be even more interventions to address public health problems of the developing world in the future. An estimated $3.2 billion was spent on research and development for new interventions for the developing world in 2009 alone, up 8.2% from 2008.

Given this environment, this thesis considers two questions:

1) Have there been, and do there continue to be, delays accessing (i.e. implementing) new health interventions through national health systems in developing countries? When will they begin to prevent disease and save lives?

2) If so, are the causes of delays predictable and what additional can be done to address the causes and accelerate access?

METHODS

Chapter two addresses the first question and proposes a new strategy to address the major aspects of the second question. It uses literature review, statistical analysis and descriptive analyses of temporal patterns.

Frost and Reich (2008) propose an "access framework" which appears to capture the major themes identified in the literature and analysis. The framework suggests that access is the product of activities to address the availability, affordability, and adoption of new interventions, as well as the architecture (i.e. coordination) facilitating these activities. The chapter also uses descriptive and statistical methods to analyze the time from regulatory approval to the beginning of implementation of four vaccines and three malaria interventions. It further analyzes implementation by considering the impact of specific milestones reflecting coordination, availability, affordability, and adoption. It concludes by applying the results of the literature, descriptive analysis, and statistical analysis to propose modifications to Frost and Reich's framework.

Six chapters of the thesis go on to consider aspects of the transition of health interventions from research and development to implementation, in light of the modified framework. Many of the chapters draw upon the experience of, or research related to, RTS,S/AS01 (RTS,S). It is the most advance malaria vaccine, anticipated to complete its phase III trial by 2015. The vaccine is being developed by GlaxoSmithKline and the PATH Malaria Vaccine Initiative, in partnership with the Swiss Tropical and Public Health Institute and many other organizations. The final chapter synthesizes the findings of the previous chapters, suggests considerations for those who wish to operationalize the framework, and proposes future research questions.

RESULTS

The analyses suggest that there have been delays implementing new health interventions. Generally, a decade after each studied vaccine or malaria intervention was approved by regulators, less than 30% of developing countries, and in most cases less than 15%, had begun to implement it. The pace of implementing new health interventions in developing countries has not changed significantly since the 1980's.

In order to accelerate implementation, activities must begin earlier, during research and development, which build the foundation for later access activities. The modified access framework (Figure 1) proposes architecture (i.e. coordination), availability, affordability, and adoption activities which should be considered for each intervention prior to regulatory approval. Individual chapters report on research into or analyses of concrete strategies and examples of activities to be undertaken during research and development:

- Chapter 3. Aligning new interventions with developing country health systems: Target product profiles, presentation, and clinical trial design;
- Chapter 4. Roles of international organizations and implementation of the new health interventions in developing counties: The RTS,S/AS01 malaria vaccine;
- Chapter 5. Adoption of new health products in low and middle income settings: How product development partnerships can support country decision making;
- Chapter 6. Country planning for health interventions under development: Lesson from the malaria vaccine decision-making framework and implications for other new interventions;
- Chapter 7. Modeling the public health impact of malaria vaccines for developers and policy-makers; and
- Chapter 8. Simulated impact of RTS,S/AS01 vaccination programs in the context of changing malaria transmission.

LIMITATIONS & DISCUSSION THEMES FROM ACROSS THE CHAPTERS

LIMITATION THEMES

A number of limitations arose in multiple chapters. The perspective of the analysis was primarily that of not-for profit organizations and governments. There is no ideal means of measuring access, so the analysis used the beginning of implementation through national health systems as the proxy. However, the analysis does not consider how long it took from beginning implementation to reach nation-wide use, nor the equity of coverage within countries. Given this, it is likely that the analysis of timelines tend to understate the delays. There are reasons to assume that the experience for malaria and immunization interventions has been faster than that seen for other interventions, again suggesting that delays may have been longer than found. Finally, while many of the chapters describe evaluation approaches, it is too early to determine if the access strategies have accelerated the transition of malaria vaccines, or the other health interventions considered.

FIGURE 1. PROPOSED ACCESS FRAMEWORK INCORPORATING R&D AND IMPLEMENTATION PERIODS.
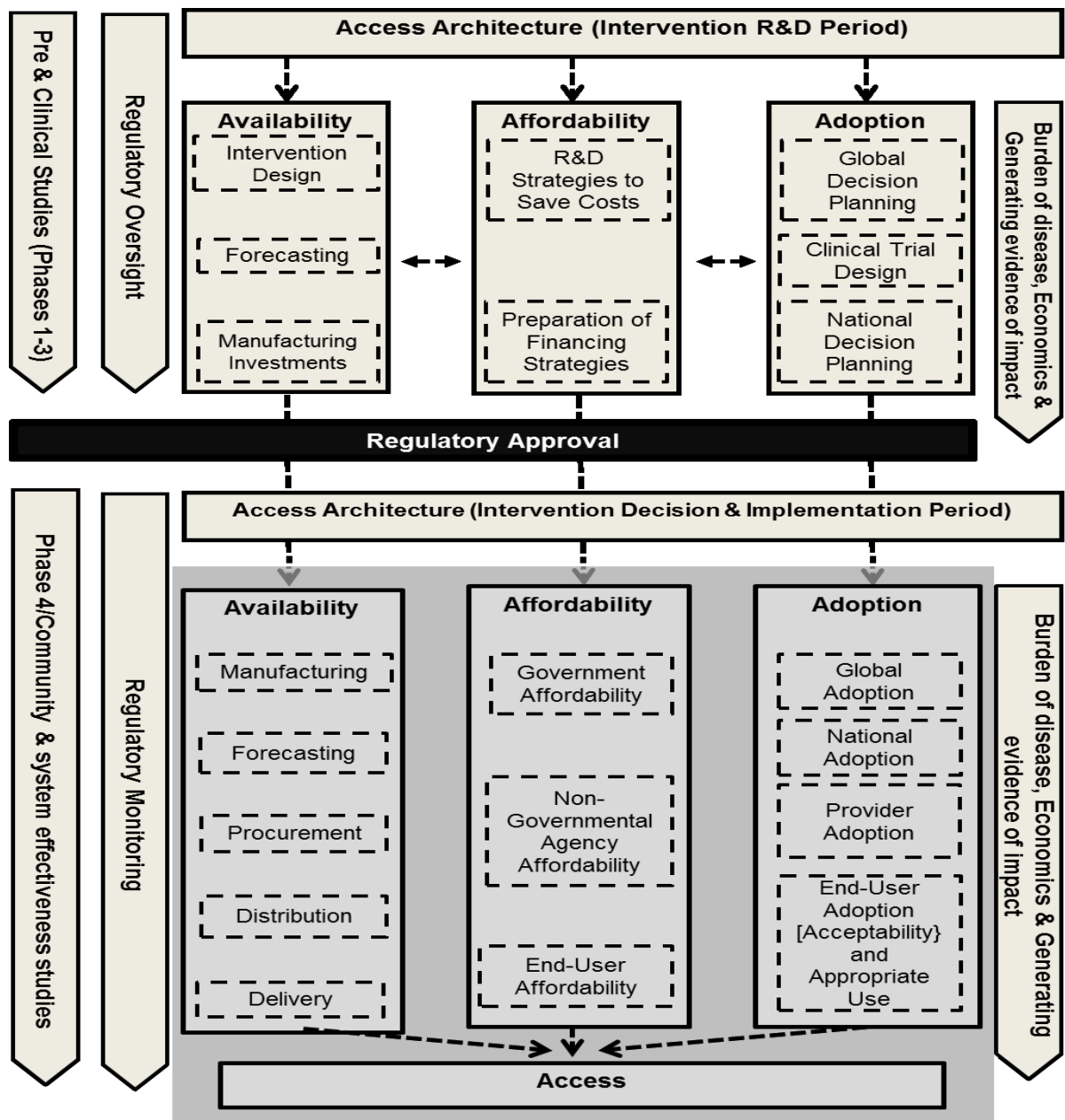
Legend: The area in grey reflects Frost and Reich's (2008) original access framework. Other areas are new to the framework. Actions that take place during the R&D period are described in the space above the black strip, "Regulatory Approval, while actions carried out in the decision and implementation period are described in the space below. Area in grey is reproduced under a Creative Commons Attribution-Noncommercial-Share Alike 3.0 License.

DISCUSSION THEMES

Accelerating access requires bridging between many complex activities, commitments of many years and deep collaboration between access and research and development specialists. Access activities must be carefully paced with scientific progress. An intervention can fail at any time, for example if a safety concern arises or efficacy is not shown in a pivotal clinical trial. Collaborators need to be careful not to overpromise.

Since interventions may always fail, the proposed strategy requires investments of time and resources be made at risk. This is particularly important to consider when weighing requests to staff in developing countries that have responsibilities for implementing proven, existing health interventions.

It may be clear which organization is best placed to fill the coordination role. However there is no reason to assume it should be a specific type of not-for profit organization. Universities, institutes, product-development partnerships, the World Health Organization (WHO) and others from the Northern and Southern hemispheres could be best positioned. Regardless of who fills the role, particular consideration should be given to WHO and its important role in the strategies in many of the chapters.

OPERATIONALIZING THE FRAMEWORK

Those seeking to operationalize the framework may want to give particular consideration to the follow issues:

- Agree who fills the coordinating role;
- Recruit the appropriate skill sets to complement research and development specialists;
- Tailor the strategy to the intervention and wider disease context;
- Consider developing activities by working backwards from the vision of desired impact and anticipated access strategies;
- Set expectations for a long-term view and process, breaking major challenges into more manageable, concrete steps;
- Agree explicitly on a mandate to undertake such activities with funders; and
- Determine the appropriate level and type of collaboration with WHO.

FUTURE RESEARCH

The thesis proposes a number of potential future research activities. Similar analyses could be undertaken from other perspectives, such as regulators, pharmaceutical companies, private health providers, or others. Further historical analyses could be undertaken of a wider sample of existing interventions.

The proposed strategy and activities in this thesis could be evaluated in the future. One could compare against other approaches taken for interventions currently in research and development. Activities reported in this thesis undertaken for malaria vaccines could be more fully evaluated after approximately 2016. In addition to asking if the correct activities were undertaken, important questions may be which activities occurred too early and which occurred too late relative to research and development progress.

CHAPTER 1. INTRODUCTION

BACKGROUND

The past decade has seen a striking increase in new interventions promising to decrease public health problems in developing countries. Just taking the fields of vaccination and malaria, the list includes: pneumococcal conjugate (PCV), rotavirus (RV), Japanese encephalitis (JE), meningococcal A conjugate (MenA), and human papillomavirus (HPV) vaccines; long-lasting insecticide-treated bednets (LLINs); rapid diagnostics tests (RDTs) for malaria; and artemisinin-based combination therapies (ACTs) for treating malaria. This growth in new interventions is partially a result of increased funding for research and development (R&D) into interventions needed in the developing world. An estimated $3.2 billion was spent on R&D in 2009, up 8.2% from the previous year, suggesting the number of new interventions will only increase in the future [1].

Prior to the upswing described above, the world saw relatively few new interventions available to the developing world. Measles vaccine was added to the expanded programme on immunization (EPI) in the 1980s, hepatitis B in the 1990s and *Haemophilus influenza* type B (Hib) around 2000. Today, seven vaccines are receiving additional focus from policy and funding bodies; the five newer vaccines noted above (PCV, RV, JE, MenA, and HPV) and two older vaccines (rubella and typhoid). But it remains unclear if the availability of more vaccines and the additional focus will lead to these vaccines being adopted and impacting public health any more rapidly than hepatitis B or Hib.

The situation is similar for malaria. While bednets have been around for decades, the inclusion of insecticide, impregnating with long-lasting insecticide, and distribution for large-scale public health uses are more recent innovations. There are now multiple rapid diagnostics tests available for malaria. In terms of drugs, chloroquine was the treatment of choice for decades, followed by sulfadoxine and pyrimethamine (Fansidar) in the 1980s and 1990's. Over the past 10 years ACTs have become the treatment of choice in many parts of the world. Multiple types of ACTs are now on the market and more are anticipated.

A *product* is a manufactured, public health tool overseen by some form of regulatory-like body. An *intervention* is a means of addressing a public health problem. Generally it may or may not involve a product (e.g. behavior change interventions do not necessarily), however for this thesis, an *intervention* means a product plus the strategies for its use.

The growing investments in R&D noted above reflect initiatives by international health and funding bodies to address the divergence in health between developed and

developing countries. Commercial realities have dictated that traditionally, new health interventions were developed to address the needs of developed countries where private investments were most likely to be recouped. In some cases, such as with hepatitis B vaccine, recognition grew that some interventions could have comparable or greater public health impact if they could be implemented in developing countries. This led to interventions "trickling down" to developing countries over decades.

The past 10-15 years has seen as a shift away from interventions only trickling down to developing countries. The Millennium Development Goals, as well as new initiatives like the Bill and Melinda Gates Foundation (Gates Foundation), Global Fund to Fight Aids, Tuberculosis, and Malaria (GFATM), and the GAVI Alliance (GAVI), partially grew out of recognition of the divergence in health, and access to health interventions. Universities, national institutes of health, research institutions, product development partnerships (PDPs) between for-profit and not-for-profit partners, the World Health Organization (WHO), and others, are creating interventions intended for use in the developed world from early R&D. The Gates Foundation and others provide critical "push" funding, investing to stimulate and accelerate R&D of new health interventions. While the GFATM and GAVI are examples of "pull" funding, providing a more predictable and lucrative market for successful producers on behalf of developing countries.

Much of the investments to date have gone to infectious diseases. In terms of disability-adjusted life years (DALYs), Africa bears two to three times the disease burden of other parts of the world, particularly because of the relatively large number of infants and children dying from pneumonia, diarrhea and malaria, and the influence of those deaths on DALY calculations (Figure 2). However, there is an as yet unanswered question of funds needed for similar investments targeting non-communicable, or chronic, diseases. Non-communicable diseases account for approximately 60% of world-wide deaths annually (Table 1).

Health care systems in the developing world which deliver interventions are characterized by a number of attributes. For example, populations are afflicted with large and diverse disease burdens. Yet diagnostic capabilities are limited, leading to challenges deciding on priorities and perceptions of a zero-sum game between diseases or interventions. There is limited infrastructure, often for power as well as delivery of supplies. Health facilities are often staffed by minimally trained workers with infrequent or irregular oversight. And budgets are very limited relative to the mandates given to the health systems.

FIGURE 2. DALYS LOST BY WHO REGION (2004).
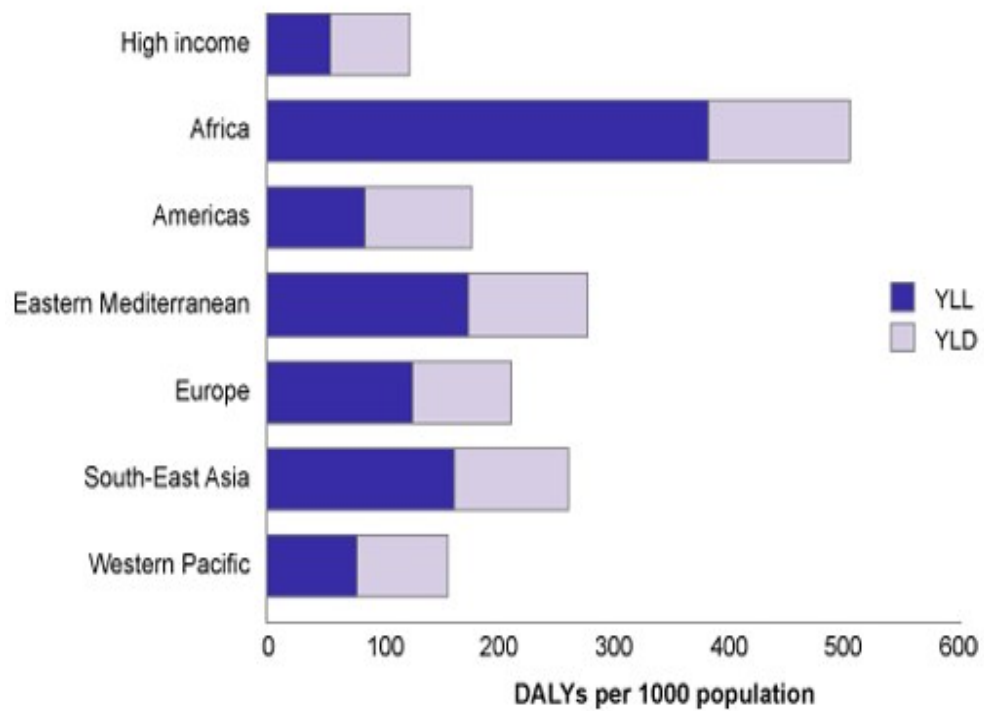
Legend

Reproduced from WHO; Available at:
http://www.who.int/gho/mortality_burden_disease/regions/dalys/en/index.html; Accessed: 1 Aug,
2011. DALY calculations assume 3% discounting and age weighting. YLL means "Years of life lost." YLD
means "Years lost due to disability".

Table 1. Estimated causes of death worldwide (1000s), 2004.

World Population (000)	6 436 826	
TOTAL Deaths	**58 772**	**100.0%**
I. Communicable diseases, maternal and perinatal conditions and nutritional deficiencies	**17 971**	**30.6**
Infectious and parasitic diseases	**9 519**	**16.2**
Tuberculosis	1 464	2.5
HIV/AIDS	2 040	3.5
Diarrheal diseases	2 163	3.7
Hepatitis B	105	0.2
Malaria	889	1.5
Other infectious & parasitic diseases	2 858	4.9
Respiratory infections	**4 259**	**7.2**
Maternal conditions	**527**	**0.9**
Perinatal conditions	**3 180**	**5.4**
Nutritional deficiencies	**487**	**0.8**
II. Non-communicable conditions	**35 017**	**59.6**
Malignant neoplasms	**7 424**	**12.6**
Other neoplasms	**163**	**0.3**
Diabetes mellitus	**1 141**	**1.9**
Nutritional/endocrine disorders	**303**	**0.5**
Neuropsychiatric disorders	**1 263**	**2.1**
Sense organ disorders	**4**	**0.0**
Cardiovascular diseases	**17 073**	**29.0**
Ischaemic heart disease	7 198	12.2
Cerebrovascular disease	5 712	9.7
Other cardiovascular diseases	4 162	7.1
Respiratory diseases	**4 036**	**6.9**
Digestive diseases	**2 045**	**3.5**
Diseases of the genitourinary system	**928**	**1.6**
Skin diseases	**68**	**0.1**
Musculoskeletal diseases	**127**	**0.2**
Congenital abnormalities	**440**	**0.7**
Oral diseases	**3**	**0.0**
III. Injuries	**5 784**	**9.8**
Unintentional injuries	**3 906**	**6.6**
Intentional injuries	**1 642**	**2.8**

Source: Modified from WHO; http://apps.who.int/ghodata/?vid=100001; Accessed 1 August, 2011.

TRANSITIONING INTERVENTIONS FROM R&D TO IMPLEMENTATION

This thesis is based upon a hypothesis that there have been re-occurring delays in implementing interventions, but that causes of delays can be foreseen and addressed by working in advance. The progression of an intervention can be broken down broadly into processes of: Development – Decision – Implementation (Figure 3). These may be more complex and time-consuming (e.g. the level of regulatory scrutiny) for a novel, or "first in class" intervention like a malaria vaccine, as compared to a generic or follow-on intervention such as a new type of antimalarial treatment.

FIGURE 3. NEW INTERVENTIONS: FROM R&D TO IMPLEMENTATION (ILLUSTRATIVE).
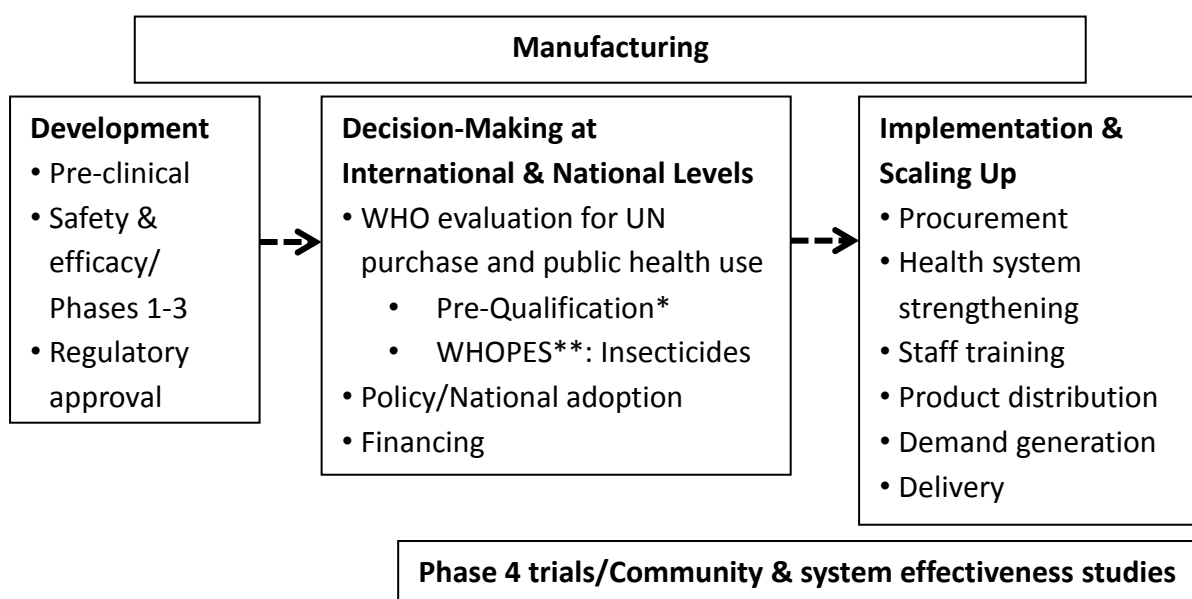
Legend
*Drugs, Vaccines Diagnostics, Reproductive health supplies. **WHOPES: WHO Pesticide Evaluation Scheme.

An unfortunate shared lesson from the immunization and malaria fields, and public health more generally over the past decade plus, is that moving health interventions from development to implementation and ultimately making them accessible to those most in need, is a slow, challenging process. It is a process which is unlikely to get quicker or easier as the number of new interventions increases, without research into appropriate, concerted changes.

This thesis focuses on what can be done to make a change from past experience. It focuses on what can be done during the development to decision process, in order to accelerate the decision to implementation process which ultimately leads to those needing a preventive, therapeutic or diagnostic interventions having access to it.

Most of the papers in this thesis use a lens of malaria and vaccines, or malaria vaccines specifically (For the status of malaria vaccines under development see: WHO; Table of Malaria Vaccine Projects Globally; Available at: http://www.who.int/vaccine_research/links/Rainbow/en/index.html; Accessed September 12, 2011). Malaria has been a focus of new intervention investment given its significant contribution to mortality in African children, and that preventive, therapeutic and diagnostic interventions are all thought to be part of a long-term solution. There has also been extensive focus on developing new vaccines as a critical preventive strategy globally, particularly for diarrhea and pneumonia for children, as well as malaria.

This thesis considers implications of its findings for other vaccines and malaria interventions, as well as health interventions more broadly, and proposes a series of concrete strategies that organizations involved in developing and supporting use of new interventions can take to accelerate their transition from development to use. It considers issues from the perspective of a not-for-profit organization (e.g. government, multi-lateral, and/or non-governmental organization) interested in new health interventions.

ACCESS FRAMEWORK

In 2008 Frost and Reich [2] released a book entitled "Access: How do good health technologies get to poor people in poor countries?" This book was a valuable landmark for those working on new interventions. It consists of six case studies of past interventions from various public health fields, and a synthesis of the implications. It proposes an "Access Framework" (see chapter 2) focusing on architecture (i.e. coordination), availability, affordability and adoption as the essential elements of planning for access to new interventions.

Frost and Reich's work, built upon a diverse evidence base of interventions, provides the foundation for the conceptual framework used in this thesis. However, this thesis extends and seeks to share new insights beyond what the book entails. Among the major distinctions:

- The access framework in the book, similar to the existing literature, focuses primarily on what happens after an intervention is available. The intervention development period is included systematically in the six case studies, however largely as a descriptive chronology. In contrast, this thesis focuses primarily on actions during the development and decision processes which can accelerate decisions on use and implementation.
- The book presents the concepts of availability, affordability, and adoption as parallel, vertical streams without emphasis on the lateral interplay between

these elements. This thesis highlights important ways each of these three concepts are intertwined with the other two.

- This thesis argues that activities need coordination during the intervention development process and during the decision into implementation process.
- The book covers a relatively wide set of points during the intervention life-cycle, leading it to be, by necessity, more general, while the thesis centering on the development and decision processes can be more concrete and specific in proposed strategies.

OBJECTIVES

- Propose key elements of strategies during the intervention development period to shorten the time to accessibility for health interventions anticipated for use in the developing world
- Detail a practical strategy to shorten the time from availability of a malaria vaccine to use in public health programs in Africa

SPECIFIC OBJECTIVES

- Analyze the time from development to accessibility for recent public health interventions intended for the developing world, and identify major reasons for delays.
- Identify strategies for ensuring that public health interventions, and particularly malaria vaccines, are tailored to meet the needs of developing world health systems.
- Improve the means for international organizations to establish and provide guidance to developing countries on use of new health interventions.
- Review the support PDPs are providing to national decision-making processes.
- Analyze the data and processes required by countries to take a decision on use of a malaria vaccine, and determine when the data is needed and the processes should take place relative to vaccine availability.
- Estimate the impact of a pre-erythrocytic malaria vaccine in the context of changing transmission, and ways that such data can be tailored to meet the needs of key policy-makers.
- Detail a model interface allowing estimates of malaria vaccine impact to be tailored for vaccine developers and policy makers.
- Synthesize the key strategies needed to shorten the time from development to accessibility for new interventions.

CHAPTER 2. DEVELOPMENT OF AND ACCESS TO HEALTH INTERVENTIONS BY DEVELOPING COUNTRIES: EVIDENCE OF DELAYS AND STRATEGY FOR ACCELERATION

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ABSTRACT

BACKGROUND

Billions of dollars are invested each year in research and development (R&D) of new health interventions intended for the developing world. However, it is unclear how quickly resulting interventions will be accessible. Activities that could be undertaken during the R&D process to accelerate access to interventions by developing countries following regulatory approval have not been extensively researched. Existing frameworks suggest that access depends chiefly on coordinated action, availability, affordability, and adoption-supporting activities. We undertook the first comprehensive analysis of these activities in the R&D period in order to identify strategies that may accelerate access.

METHODS AND FINDINGS

WHO databases, supplemented by data from John's Hopkins University, were used to determine the number of years from first regulatory approval to implementation for a number of tracer interventions: hepatitis B (HepB), *Haemophilus influenza*e type b (Hib), rotavirus (RV), and pneumococcal conjugate (PC) vaccines, as well as three malaria interventions: insecticide treated nets (ITNs); rapid diagnostic tests (RDTs); and artemisinin-based combination therapies (ACTs). The data were stratified by year of regulatory approval and country income. One to two milestones representing access activities consistent with coordinated action, availability, affordability, and adoption-supporting activities were identified for each intervention. Descriptive analyses of temporal associations, available literature, and statistical analyses supported the importance of these activities for access. Five years after regulatory approval, no low-income countries (LICs) had implemented any of the vaccines, increasing to an average of each vaccine being used by only 4% of LICs after 10 years. Each malaria intervention was used by an average of 7% of LICs after five years and 37% after 10 years. Hib, RV, PC, and ITNs, all had similar adoption rates to HepB, while this rate was slower than for ACTs and faster than for RDTs. Activities addressing coordinated action, affordability, and supporting adoption seemed to be most associated with implementation, although only adoption-supporting activities had a significant effect in all statistical analyses. A new access framework is proposed, building upon existing concepts and the present analysis of delays.

CONCLUSIONS

Our analysis suggests that unless intervention development is done differently, the billions spent on R&D of new health interventions will culminate in a delay of more than 10 years before most developing countries begin large scale access. Carefully paced activities integrated within the R&D process, and tailored to the intervention and its public health context, should contribute to new interventions realizing their goal of saving lives as rapidly as possible.

INTRODUCTION

The GAVI Alliance (GAVI) and the Global Fund to Fight AIDS, TB and Malaria (GFATM) were established in 2000 and 2002, respectively. Since then, they have committed more than USD 20 billion to address the divergence in health status and access to health interventions between developed and developing countries (DCs). In parallel, the past decade has seen unprecedented investments in research and development (R&D) for new health interventions for use in developing countries. Approximately USD 3.2 billion was invested in 2009 alone, an increase of 8.2% from 2008 [1]. Product R&D partnerships (PDPs) have grown in number, developing drugs, rapid diagnostic tests, vaccines and other interventions for developing countries [3]. Interventions arising from these R&D investments could then be implemented with support from GAVI, GFATM and other financing mechanisms.

Although many potential interventions will fail during R&D or regulatory review, it is reasonable to assume that many will be approved by regulators and become available for use. It is unclear, however, how quickly these new health interventions will be made accessible to those in need in developing countries, and hence deliver on promises to save lives and improve health. Here, access is the result of a set of coordinated activities needed to ensure that interventions will ultimately have an equitable public health impact [4]. Unfortunately, there is no optimal, widely available indicator of access when using this definition. Implementation of interventions, after policies adopting them into national health systems, is a reasonable proxy and widely discussed in the literature.

Determining if there have been access delays begins by understanding the factors that facilitate policy decisions on use, and subsequent implementation of interventions in DCs. It also requires a process to ensure that interventions are suitable for low resource health systems and users. This paper evaluates access to new health interventions in DCs. The analysis compares, for a number of tracer interventions, activities during the R&D period, prior to approval by a stringent regulatory authority, with the decision and implementation period that followed. The specific issues of access to new interventions for specific segments of populations in developed countries, for example the poorest or most remote populations, are beyond the scope of this paper.

Literature focusing on the R&D period tends to emphasize clinical trials and regulatory processes [5–9]. There is a relatively small body of literature that identifies factors facilitating policy decisions and implementation that should be considered during the R&D period of health interventions (Table 2). However, none of these papers offer comprehensive strategies intended to facilitate overall access. PDPs also identify activities undertaken during the R&D period to support implementation and access,

broadly consistent with the considerations noted in the literature, but without prioritizing them or suggesting which are most critical for which interventions [4].

TABLE 2. CONSIDERATIONS AFFECTING ACCESS TO NEW INTERVENTIONS — A LITERATURE REVIEW.

	Relevance to access	Considerations
Prior to regulatory approval	Availability & Affordability	Design of interventions specifically for the needs of DCs [10–16]
	Adoption	Clinical studies to address questions unique to DCs [6,17–21]
		Requirements for international policy recommendations [22,23]
		Preparing for country decision-making processes [24]
After regulatory approval	Coordinated action	Coordination between stakeholders [25]
	Availability	Alignment of intervention with the unique needs of developing country health systems [25–29]
		Forecasting and manufacturing plans incorporating DCs, [25,30]
		Adapted procurement mechanisms [25,30]
	Affordability	Affordability, financing, & cost-effectiveness [25–33]
	Adoption	Research aligned with policy-maker needs, including burden of disease addressed by an intervention [26,28–31,33]
		Importance of international technical consensus and recommendations, including influence of neighboring countries [28,30,34]
		Strengthened national processes, acceptability, and/or governance [27,30,35–37]

Legend: Pubmed and Web of Science® databases were searched for full names or abbreviations of hepatitis B, Haemophilus influenzae type B, pneumococcal conjugate, rotavirus, insecticide-treated net, rapid diagnostic test, or artemisinin-based combination therapies AND (malaria or vaccin*) AND (develop* OR decision* OR policy* OR adopt* OR implement*)

Understandably, papers tend to consider access factors and challenges arising after regulatory approval of new vaccines and malaria interventions rather than before (Table 2). Qualitative [25–30,33,35,37–39] and quantitative approaches [31,32,36] are used to look at single or closely-related interventions (e.g. vaccines against enteric pathogens). For ITNs and intermittent preventive treatment for malaria in infants

(IPTi), comprehensive strategies for operational and implementation research were considered [40,41].

The current literature largely takes for granted that interventions have a fixed set of characteristics, such as the target population, size of dose, packaging, and storage requirements, and attempts to determine how to take advantage of those characteristics in developing countries. It does not typically consider how and why those characteristics originated, nor if there are lessons to inform the R&D process and design of future interventions.

Obrist *et al.* (2007) propose a comprehensive access framework focusing on consumer decisions, livelihood, and the assets of poor populations with regard to health interventions [42]. They review five concepts that determine access to health interventions: availability, accessibility, affordability, adequacy, and acceptability.

Mahoney *et al.* (2007) [38] and Frost & Reich (2008) [2] propose access frameworks that acknowledge the role of decisions made during the R&D period on eventual implementation. Mahoney *et al.* (2007) identifies four criteria for access to new vaccines: availability; affordability; acceptability; and adoptability, but provides little insight into how actions in the R&D period are translated into policy decisions and implementation later. PDPs generally agree on a similar set of access criteria, and see them as relevant to any intervention during the R&D phase [2,4].

Frost & Reich (2008) analyze the history of access to six health interventions in the developing world: praziquantel; hepatitis B vaccine; malaria rapid diagnostic tests; Norplant; vaccine vial monitors; female condoms [2]. They propose that access depends on activities related to four key factors: architecture, availability, affordability, and adoption. Architecture encompasses the organizational structures and relationships that coordinate activities addressing availability, affordability and adoption (Figure 4). They also provide a historical overview of the R&D phase of each intervention. However, while they note that intervention developer choices are important for later policy decisions on use and implementation, their analyses and framework focus on access through the lens of implementation, without systematically considering the impact of decisions made during the R&D period.

Each concept Mahoney *et al.* (2007) and Obrist *et al.* (2007) use in their access frameworks is consistent with the ones identified by Frost & Reich. For example, Obrist's *et al.* concept of acceptability is consistent with Frost and Reich's "end-user adoption and appropriate use." The one exception, which is not relevant to national implementation of an intervention and therefore this analysis, is Obrist *et al.*'s adequacy concept, matching health service organization with individual client expectations.

FIGURE 4. FROST AND REICH'S (2008) ACCESS FRAMEWORK.
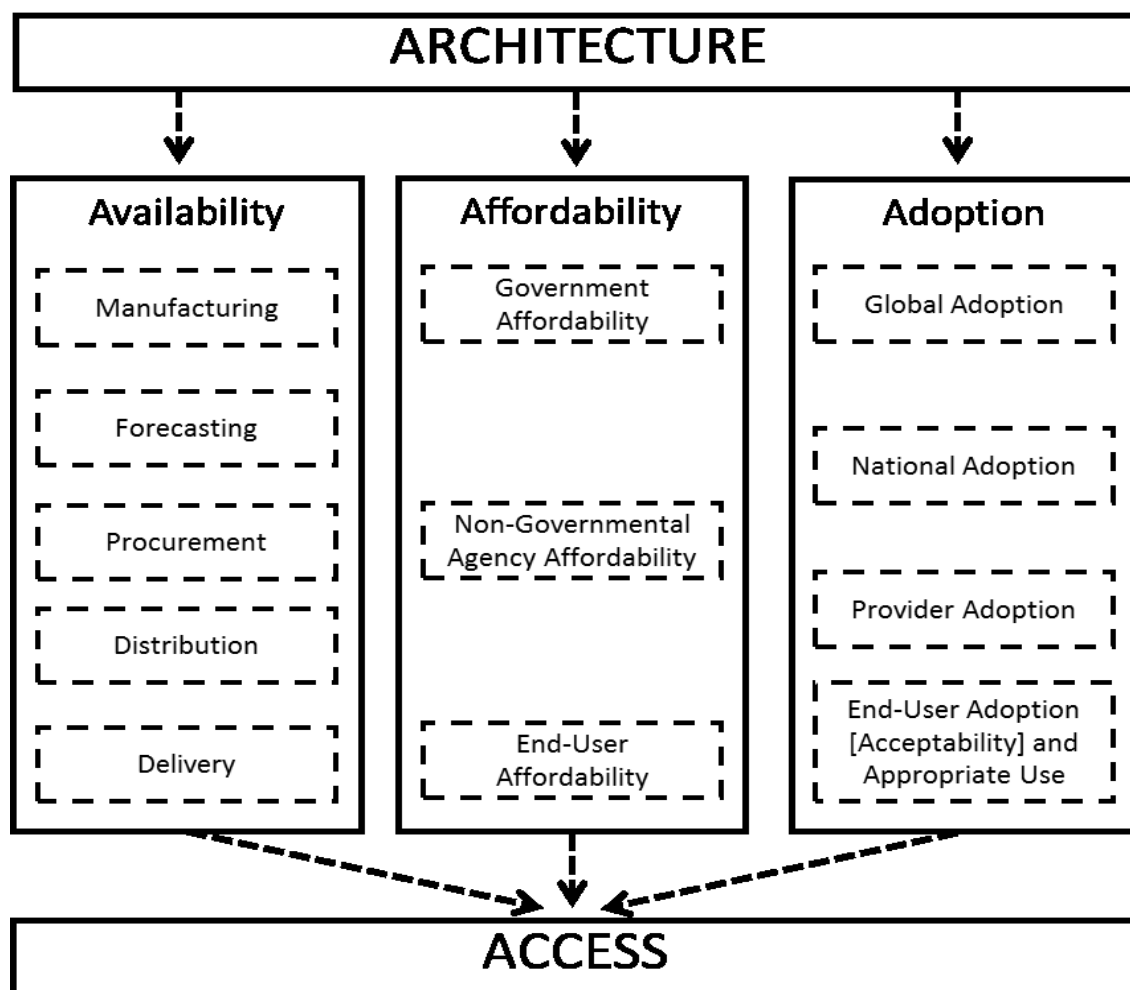
Legend

The figure presents access as depending on a coordinating architecture that ensures that availability, affordability and adoption considerations are addressed for an intervention.

Architecture: Organizational structures and relationship established with the purpose of coordinating and steering the availability, affordability, and adoption activities.
Availability: Logistics of making, ordering, shipping, storing, distributing, and delivering a new health technology to ensure it reaches the hands (or mouths) of the end-user.
Affordability: Ensuring that health technologies and related services are not too costly for the people who need them.
Adoption: Gaining acceptance and creating demand for a new health technology from global organizations, government actors, providers and dispensers, and individual patients.

The concept of "acceptability" is inherent in "End-User Adoption and Appropriate Use" but was made explicit in the graphic above to illustrate this framework's consistency with the work of other authors. Reproduced under a Creative Commons Attribution-Noncommercial-Share Alike 3.0 License [2].

The literature cited above suggests that once regulators approve an intervention, access is contingent on efforts to address availability, affordability, adoption, and the

relevant coordinating architecture. However, each of these elements is strongly influenced by, or directly follows from, decisions made during the R&D period. Therefore, by anticipating access activities during the R&D stages, delays between regulatory approval and implementation should be decreased.

This paper systematically explores access activities during the R&D period and it aims to investigate analytically the delays between the R&D phase and the implementation of new interventions in DCs. To do so we extended the Frost and Reich (2008) framework in order to propose a new approach to developing health interventions. The analysis focuses on the role of not-for profit, multilateral organizations (e.g. World Health Organization (WHO)) and governments, while discussing the role of for-profit and other collaborators.

METHODS

EVIDENCE OF DELAYS

MILESTONES
Selected interventions were assessed to determine the number of years between initial approval by a stringent regulatory body and the beginning of each country's implementation through its national health system. Similar but more limited analyses have been applied to interventions previously [25,43,44].

The year of approval by a stringent regulatory authority was intended to reflect the earliest indication of when it would be possible and ethical to consider implementation on a large scale outside of a controlled trial. This is especially critical for vaccines and drugs because of the issues of safety and quality. Some interventions, such as ITNs, while generally not overseen by regulatory authorities have mechanisms in place for reviewing safety and more recently quality. In these cases, efficacy is often evaluated through the establishment of a scientific consensus between experts on the basis of existing trial experience.

Milestones consistent with architecture, availability, affordability and adoption were drawn from the literature above. The year of establishment of an organization or a process focused on supporting development or use of the intervention was considered an indicator of coordinating architecture. Availability was reflected by the year a new version of the intervention, intentionally designed to meet the needs of DCs, was approved. A major global financing commitment by an international organization was considered an indicator of affordability. Recommendations to use the intervention reflected support for adoption from international organizations. The timing of initial and global recommendations by the World Health Organization (WHO) was documented for each intervention. The year of implementation was determined according to available country reports, as described below.

Countries were categorized as low- (LIC), lower-middle- (LMIC), upper-middle- (UMIC), and high-income (HIC) according to the World Bank stratification, corresponding respectively to 2009 gross national income per capita of $995 or less, $996 - $3,945, $3,946 - $12,195, and $12,196 or more (http://data.worldbank.org/about/country-classifications/country-and-lending-groups, Accessed March 31, 2011).

VACCINES

Four vaccines were selected for inclusion in the study based on their public health importance, diversity in year of availability, similar ages of target populations and comparable delivery strategies. The diseases they target — hepatitis, pneumonia, meningitis, and diarrhea— are among the world's leading causes of mortality and morbidity, especially in developing countries. Hepatitis B (HepB) and *Haemophilus influenza* type b (Hib) vaccines have been available for decades while pneumococcal conjugate (PC) and rotavirus (RV) vaccines are among the newest.

The regulatory approval of the first RV vaccine was a unique case. Licensed in 1998, it was removed from the market in 1999 due to concerns about intussusception (a potentially life threatening telescoping of the intestine within itself). A new RV vaccine was licensed in 2004. This analysis considered 2004 to be the year of the RV vaccine's first regulatory approval. To account for the period in 1998-99 when a RV vaccine was licensed and sold, one year was added to the time to policy recommendation.

WHO collects reports from 193 countries each year in order to assess vaccine implementation (http://www.who.int/immunization_monitoring/data/data_subject/en/index.html, Accessed March 14, 2011) (Table 3). These data were used to generate tables showing the first year of vaccine use and the number of years until coverage matched that of the third dose of diphtheria-tetanus-whole cell pertussis vaccines (DTP3), which is given to the same infant population at the same times as the other vaccines in this analysis. WHO's data cover the years 1989-2009 for HepB, 1991-2009 for Hib, and 2008-09 for PC and RV. Data for other years and for missing dates in the WHO data were taken from the Vaccine Information Management System (VIMS), a database maintained at the International Vaccine Access Center, Johns Hopkins University (http://www.jhsph.edu/ivac/vims.html, Accessed March 23, 2011). VIMS provided information on the year of application to GAVI for financial support by eligible countries. It also provided product presentation and formulation of Hib in most countries, used in this study to consider if the speed of implementation changed when the presentation of the vaccine was better aligned with the needs of DCs.

Each vaccine was improved to better align with the needs of DCs which is reflected in the availability milestone. HepB and Hib antigens were combined with the widely implemented DTP vaccines to create new "four-in-one" or "five-in-one" vaccines. New versions of PC vaccines included additional serotypes prevalent in the developing

world and smaller packaging. New RV vaccines required two doses instead of the traditional three and decreased the size of packaging. GAVI's commitment to each vaccine was used to determine the year of financing commitment, reflected in the affordability milestone.

TABLE 3. CHARACTERISTICS OF COUNTRIES INCLUDED IN THE ANALYSIS AND SUMMARY OF RESPONSES.

	Included in sample	High income	Upper middle income	Lower middle income	Low income	No income category	Intervention implemented	Not imple- mented	Did not respond
Hepatitis B vaccine	193	50	46	54	40	3	180	13	0
Haemophilus influenzae type B vaccine	193	50	46	54	40	3	163	30	0
Rotavirus vaccine	193	50	46	54	40	3	30	163	0
Pneumococc al vaccine	190	50	46	54	40	0	61	132	0
Insecticide- treated mosquito net	104	4	21	39	40	0	89	0	15
Rapid diagnostic test	104	4	21	39	40	0	40	6	58
Artemisinin- based combination therapy	104	4	21	39	40	0	63	12	29

MALARIA INTERVENTIONS

Malaria is one of the major causes of mortality and morbidity in children, and preventive, therapeutic and diagnostic interventions are available. Insecticide-Treated Nets (ITNs) and more recently developed Long-Lasting Insecticidal Nets (LLINs) prevent malaria. In this paper, "ITN" is used for both ITNs and LLINs. Immuno-chromatographic rapid diagnostic tests (RDTs) allow diagnosis of malaria with minimal training and hence are crucial to optimize treatment strategies. Artemisinin-based combination therapies (ACTs) are the current standard for malaria treatment.

In the absence of a formal regulatory structure, regulatory approval of ITNs was based on a WHO expert committee concluding they were safe for individuals, and therefore could be used outside clinical trials [45]. For RDTs, regulatory approval was considered to be the point at which the first RDT became available in the developed world where there are strong quality assurance systems.

WHO provided data on country implementation in 104 malaria-endemic countries, taken from the 2010 survey of countries by the Global Malaria Program as part of the annual World Malaria Report [46] (Table 3). The survey asked about year of

implementation of WHO-recommended malaria policies. Responses to "ITNs distributed to all age groups" or "ITNs distributed free of charge" were deemed reflective of implementation. Responses to "RDTs used in communities," and "ACT is free of charge for under 5 years olds in the public sector" or "ACT is free to all," were considered to be reflective of RDT and ACT implementation, respectively. Non-response to the specific questions about use of the interventions, while other questions in the survey were answered, was classified as not implementing the intervention. Fourteen percent of countries did not respond for the ITN questions, 56% for RDTs, and 28% for ACTs. The earliest date was used in cases where different dates were given for each policy or if parts of countries (e.g. mainland Tanzania versus Zanzibar) reported different dates.

Approvals of new versions of the interventions aligned with the needs of developing countries were considered indicators of the availability milestone. ITNs were replaced by LLINs, and an ACT specifically formulated and packaged for use in infants was developed after the initial tablet formulation. No major improvements in RDTs were identified over the course of their deployment. For malaria control, the GFATM is by far the most important donor, and its implementation date used to determine the year of financing supporting affordability.

STATISTICAL ANALYSIS

The year of country implementation of each intervention was extracted from the relevant databases into Microsoft Excel, and back-validated against the original databases for accuracy. Cox proportional hazard models were used to compare the rates of adoption of interventions between countries, as functions of the intervention and income group of the country. The analysis for each country started with the year when the intervention became available. The data were treated as right-censored where the country had not introduced the intervention by 2011. In this analysis the adoption rate corresponds to the hazard in a conventional survival analysis. Plots of the cumulative baseline hazard over time were used to assess time trends in the underlying rate of adoption, allowing for the covariates of income level and milestones described previously (i.e. a coordinating organization, an improved intervention, funding commitments by GAVI or GFATM, and WHO initial and/or global recommendations).

These analyses were carried out using the PHREG procedure in SAS (SAS Institute Inc., Cary, NC, USA, version 9.2 for Windows).

ANALYTIC FRAMEWORK

The literature findings described previously were used to extend Frost and Reich's access framework [2] retrospectively, to start from the R&D period, prior to regulatory approval. By complementing the original framework with activities that occur in

parallel to, are critical to, and are informed-by access-related activities, a more complete framework was developed.

RESULTS

EVIDENCE OF DELAYS

The implementation of all interventions is presented in Table 4 for LICs and LMICs after 5, 10 and 15 years. Generally, a decade after each studied vaccine or malaria intervention was approved by regulators, less than 30% of countries, and in most cases less than 15%, had begun to implement it.

On average, an intervention was beginning to be implemented in 3% of low-income countries after five years and 20% after 10 years. However, the speed of implementation was greater for malaria interventions, each of which was implemented by an average of 37% of countries at 10 years compared with only 4% for vaccines. No LIC implemented any of the new vaccines in the first five years.

On average, an intervention was beginning to be implemented in 6% of lower middle income countries after five years and 24% after 10 years. On average, malaria interventions were beginning to be implemented by 35% of countries after 10 years compared with 12% for vaccines. Figure 5 shows the cumulative implementation of interventions, by year and for all income groups.

TABLE 4. PERCENTAGE OF LICS AND LMICS IMPLEMENTING INTERVENTIONS AFTER 5, 10, AND 15 YEARS.

	5 years		10 years		15 years	
	LIC	**LMIC**	**LIC**	**LMIC**	**LIC**	**LMIC**
Hepatitis B	0%	6%	3%	24%	10%	41%
Haemophilus influenzae **type B**	0%	0%	3%	0%	15%	26%
Rotavirus	0%	15%	--	--	--	--
Pneumococcal	0%	0%	5%	13%	--	--
Insecticide-treated mosquito nets	3%	5%	30%	33%	95%	72%
Rapid diagnostic test	0%	3%	10%	15%	--	--
Artemisinin-based combination therapy	18%	15%	70%	56%	--	--
Average Vaccines	0%	5%	4%	12%	--	--
Average Malaria	7%	8%	37%	35%	--	--
Average All	3%	6%	20%	24%	--	--

Legend

LIC = Low income countries; LMIC = Lower middle income countries

FIGURE 5. PROPORTION OF IMPLEMENTING COUNTRIES OVER TIME IN EACH INCOME CATEGORY, STRATIFIED BY INTERVENTION.
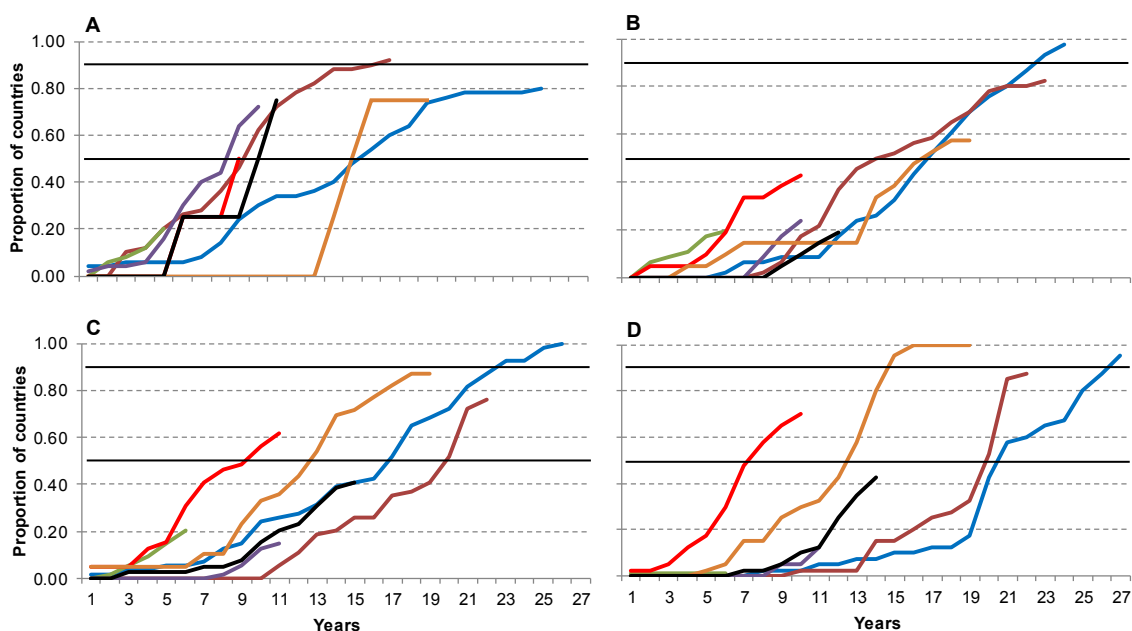
Legend

Figure 5 presents the proportion of countries implementing each intervention by year since regulatory approval.

Panel A = High income countries; B = Upper middle income countries; C = Lower middle income countries; D = Low income countries.

Color code: Hepatitis B vaccine = Blue; Haemophilus influenzae type b vaccine = Dark red; Rotavirus vaccine = Green; Pneumococcal vaccine = Purple; Artemisinin-based combination therapy = Light red; Insecticide-treated mosquito net = Orange; Rapid diagnostic test = Black.

Solid lines indicate the arbitrary thresholds of 50% or 90% of countries implementing each intervention.

Table 5 shows the average time elapsed between regulatory approvals and beginning implementation for HepB, Hib, and ITNs, three interventions which nearly all countries have begun to implement. The average was 12.2 years across all malaria-endemic countries to begin implementing ITNs, and 14.6 years for Hib and 16.7 years for HepB across all countries. Beginning implementation in LICs took an average of 12.2 years for ITNs, 18.8 years for Hib vaccine and 21.2 years for HepB vaccine as compared to 15.0, 9.0 and 13.2 years in HICs.

TABLE 5. AVERAGE NUMBER OF YEARS (RANGE) TO IMPLEMENTATION FOR INTERVENTIONS APPROACHING UNIVERSAL ADOPTION, 2011.

	High income	Upper middle income	Lower middle income	Low income	All countries
Hepatitis B	13.3 (1-25)	16.9 (6-24)	16.0 (1-26)	21.2 (8-27)	16.7 (1-27)
Haemophilus influenzae **type B**	9.0 (3-17)	14.3 (8-23)	17.5 (11-22)	18.8 (10-22)	14.6 (3-23)
Insecticide-treated mosquito net	15.0 (14-16)	12.9 (4-18)	11.7 (1-18)	12.2 (5-16)	12.2 (1-18)

For HepB and Hib vaccines it was possible to estimate the average time it took for coverage to match DTP3 levels. After combination vaccines became available in 1997, which allowed the antigens to be administered in a single injection with DTP, countries tended to require approximately one year less to reach full implementation than they did prior to a combined vaccine.

There were significant statistical differences in adoption rates between interventions relative to hepatitis B vaccine in high income countries (likelihood ratio statistic (LRS): 30.6; 6 degrees of freedom (d.f.); P<0.001, adjusted for effects of income level and of the different milestones) (Table 6). The fastest intervention to be adopted was ACTs, with a rate 1.85 times that of HepB (95% CI 1.07-3.19) (Table 7). The slowest adoption was of RDTs with a rate of 0.80 (95% CI 0.55-1.14; P=0.2164). Hib, RV, and PC all had similar adoption rates to HepB, intermediate between ACTs and RDTs.

There was also a highly significant difference between level of income of countries in the rate of adoption (LRS 27.2; 3 d.f.; P<0.0001), this difference being almost entirely accounted for by the difference between high income countries and the others. There was very little difference in adoption rates between the different categories of middle income countries, or between middle and low income countries (Table 6); each of these categories was associated with adoption rates only just over half that of high income countries.

TABLE 6. RELATIVE ADOPTION RATES BY INTERVENTION AND COUNTRY INCOME (FROM COX PROPORTIONAL HAZARD MODEL).

	Adoption rate	95% confidence interval
Haemophilus influenzae type B vaccine	0.83	(0.62-1.11)
Rotavirus vaccine	0.76	(0.38-1.54)
Pneumococcal vaccine	0.95	(0.57-1.57)
Insecticide-treated mosquito nets	0.97	(0.69-1.36)
Rapid diagnostic test	0.56	(0.34-0.92)
Artemisinin-based combination therapy	1.85	(1.07-3.19)
Low income	0.51	(0.40-0.64)
Lower middle income	0.56	(0.44-0.70)
Upper middle income	0.52	(0.41-0.67)

Legend

Adoption rates are calculated relative to the rate of adoption of HepB vaccine in high income countries in the absence of any of the facilitating milestones. All likelihood ratio statistics (interventions having 6 degrees of freedom and income groups having 3) testing these effects were highly significant, with P<0.001.

ACCESS MILESTONES

Table 7 summarizes milestones for each intervention. Figure 6 presents the cumulative implementation of each intervention by countries, stratified by income group. The figure also indicates when each milestone from Table 7 was reached relative to initial regulatory approval.

Twenty-seven years after the HepB vaccine was first approved, nearly all countries had implemented it for routine infant use. A few HICs in Europe recommend it instead for adolescents or high-risk individuals. It has taken more than 20 years for 90% of LICs to use Hib. The lowest coverage of Hib (76% of countries) was in the LMICs, many of which are too wealthy to receive financing from GAVI. The average time from GAVI application to implementation was approximately 1.5 years for HepB and 1.2 years for Hib

For rotavirus vaccines, 15-20% of HICs, UMICs, and LMICs countries had implemented it after five years, an equality across these income levels of countries that did not occur for other vaccines. This speed of implementation was only seen in HICs for the PC vaccine. 15% of LMICs were using RV vaccines after five years, while it took 11 years for PC to reach that level. However, no LICs had implemented RV vaccines as of early 2011, a situation that was similar to that seen with HepB, Hib, and PC vaccines where LIC early adopters did not begin implementation until almost 10 years after the vaccines were available. For PC, there was a three to five year delay between use in UMICs relative to HICs, and a six-year delay so far for LMIC and LICs.

TABLE 7. ACCESS MILESTONES FOR EACH INTERVENTION.

	1) Regulatory approval	2) Coordinating group (Architecture)	3) Improved intervention (Availability)	4) Financing commitment (Affordability)	5) Initial WHO recommendation (Adoption)	6) Global WHO recommendation (Adoption)
HepB	1982	1986	1996	2000	n/a	1992
Hib	1988	1998	1997	2000	1998	2006
RV	2004	2003	2008	2007	2007	2009
PC	2000	2003	2009	2007	n/a	2007
ITN	1991	1998	2001	2002	1995	2007
RDT	1995	2003	n/a	2002	2006	2010
ACT	1999	1999	2009	2002	2002	2006

Legend

Data sources below relate to the column number for each intervention. All websites were accessed on April 14, 2011.

Hepatitis B vaccine: 1) [47]; 2) [48]; 3) Personal communication, Marie-Claude Dubois, April 11, 2011 ; 4) GAVI: http://www.gavialliance.org/vision/programme_support/new_vaccines/hepatitis/index.php;5) n/a; 6) [49].

Haemophilus influenzae type b vaccine: 1) [22]; 2) [50]; 3) Personal communication, Marie-Claude Dubois, April 11, 2011 ; 4) GAVI: http://www.gavialliance.org/vision/programme_support/new_vaccines/index.php; 5-6) [22].

Rotavirus vaccine : 1) [22]; 2) GAVI: http://www.gavialliance.org/performance/commitments/rotavirus/index.php; 3) European Medicines Agency: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000639/human_med_001043.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124; 4-6) [22].

Pneumococcal vaccine: 1) [22]; 2) GAVI: http://www.gavialliance.org/vision/programme_support/new_vaccines/adips/index.php; 3) GlaxoSmithKline: http://www.gsk.com/media/pressreleases/2009/2009_pressrelease_10039.htm; 4) GAVI: http://www.gavialliance.org/vision/programme_support/new_vaccines/adips/index.php; 5) n/a; 6) [22].

Insecticide-treated net: 1) [45]; 2) Roll Back Malaria Partnership: http://www.rollbackmalaria.org/rbmmandate.html; 3) [51]; 4) GFATM: http://www.theglobalfund.org/en/whoweare/?lang=en; 5) [52]; 6)[53].

Rapid diagnostic test: 1) National Institute for Allergy & Infectious Diseases: www.niaid.nih.gov/labsandresources/techdev/Pages/paraSight.aspx; 2) [2,54], Page 103; 3) n/a; 4) GFATM: http://www.theglobalfund.org/en/whoweare/?lang=en; 5) [55]; 6) [54].

Artemisinin-based combination therapy: 1) [56]; 2) Medicines for Malaria Venture (MMV): http://www.mmv.org/about-us/faqs; 3) MMV: http://www.mmv.org/achievements-challenges/achievements/coartem-d?page=0; 4) GFATM: http://www.theglobalfund.org/en/whoweare/?lang=en; 5) [56]; 6) [57].

FIGURE 6. IMPLEMENTATION OF EACH INTERVENTION BY COUNTRIES, STRATIFIED BY INCOME GROUP, INCLUDING MILESTONES.
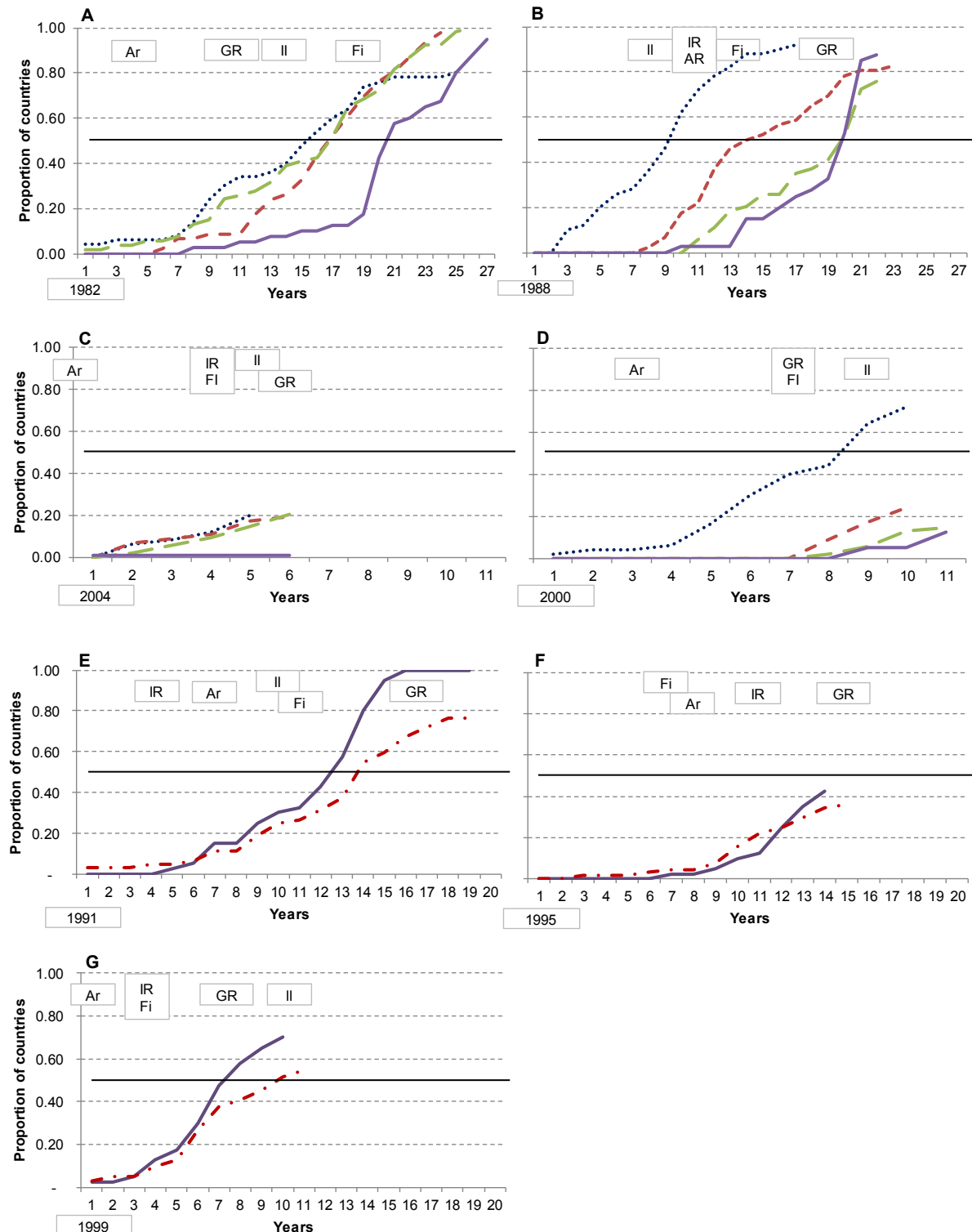
Legend

Panels A-G present the proportion of countries implementing each intervention by year since the year of regulatory approval. Panel A= Hepatitis B vaccine; B= Haemophilus influenzae type b vaccine; C=

Rotavirus vaccine; D= Pneumococcal vaccine; E= Insecticide-treated mosquito net; F= Rapid diagnostic test; and G= Artemisinin-based combination therapy.

For vaccines, countries are stratified according to World Bank income groups: High = Blue dotted line; Upper middle = Red short dashed line; Lower middle = Green long dashed line; Lower = Purple line.

Malaria-endemic countries are stratified by low income versus all other endemic countries. LICs = Purple line; Other endemic countries = Red dash and dot line.

Year of regulatory approval (year 0) is provided in the bottom left hand corner of each panel. Ar indicates establishment of a group providing coordination (i.e. architecture). II indicates availability of an improved intervention better aligned with the needs of developing countries. Fi indicates year of a global financing commitment, such as through GAVI or GFATM. IR indicates year of initial WHO recommendation. GR indicates year of global WHO recommendation.

A solid line indicates the arbitrary threshold of 50% of countries implementing each intervention.

Malaria interventions were implemented more quickly in LICs relative to wealthier endemic countries. It took approximately 16 years to reach global implementation of ITNs in LICs. Initially, RDTs were implemented faster in wealthier countries, but LICs surpassed them after 12 years. ACTs were implemented at approximately the same pace in LICs and other countries during the first seven years, after which LICs accelerated implementation. These differences are consistent with the differences in disease burden in these countries, with higher levels in the poorest countries.

Patterns of temporal associations between access milestones, and between milestones and implementation, can be drawn from Figure 6. A coordinating architecture was put in place years before global WHO recommendations were made in all situations, and prior to initial WHO recommendations in all cases except for that of ITNs. Implementation of HepB, Hib, PC, ITNs, and ACTS did not accelerate until after a WHO recommendation, except in HICs. Global WHO recommendations for use of the malaria interventions did not come until 40% or more of LICs were already implementing the interventions, while for HepB, RV and PC, global recommendations came prior to any significant implementation in LICs. There was a sharp increase in coverage of HepB and Hib vaccines after GAVI's advent and associated financing commitments. For ITNs, HepB, Hib and RV, financing commitments came after an initial recommendation, but before a global recommendation. RDT financing came before any recommendation, and for RV, PC and ACTs, a recommendation and financing came in the same year. Improved vaccines became available when only about 20% of LIC and LMICs had implemented each vaccine. Improved malaria interventions arrived after 30-70% of countries had implemented each type of intervention.

Figure 7 shows the number of years from regulatory approval to initial and/or global WHO recommendation, and financing commitment, for each intervention. Five interventions had initial recommendations, which took on average 6.4 years. The

additional time for those five interventions to receive a global recommendation was an average of 6.2 years. For all seven interventions, the average time from regulatory approval to global recommendation was 11.4 years, with a range of 7-18 years. On average it took 8.7 years, with a range of 3-18 years, from regulatory approval to a financing commitment.

FIGURE 7. TIME FROM REGULATORY APPROVAL TO WHO RECOMMENDATION AND FINANCING, BY INTERVENTION.
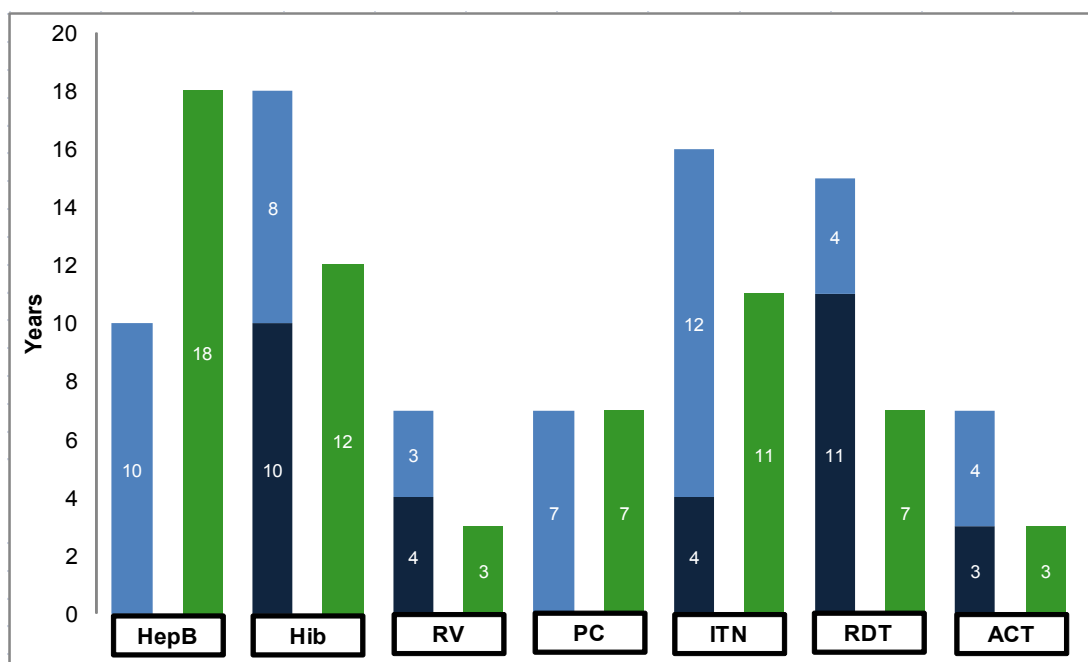
Legend

Dark blue bars indicate the number of years to an initial recommendation, when relevant, while light blue bars indicate the number of years to a global recommendation. Green bars indicate the number of years to a financing commitment.

An initial proportional hazard model analyzed the relative rates associated with each of the milestones separately, adjusted for levels of income groups of countries and interventions. Initial WHO recommendation (relative uptake rate 1.87; 95% confidence interval (CI) 1.30-2.70)), coordinating group (relative uptake rate 2.12; CI 1.41-3.19), and financing commitment (relative uptake rate 1.89; CI 1.38-2.59) were all positively associated in this analysis, while global recommendation (relative uptake rate 0.51; CI 0.38-0.69) was negatively associated. An improved intervention seemed to have little effect on the rate of implementation (relative uptake rate 0.94; CI 0.68-1.30). Since the timing of these steps was unlikely to be independent, a further analysis was conducted in which the effects were fitted simultaneously to adjust for possible confounding (Table 8). In this analysis the estimated effect sizes were similar to those in the unadjusted analysis, while the only statistically significant milestones were the positive

effect of initial WHO recommendation, and the association of global WHO recommendation with a slowing down of uptake.

TABLE 8. EFFECTS OF ACCESS MILESTONES ON ADOPTION RATES (FROM COX PROPORTIONAL HAZARD MODEL).

	Relative adoption rate	95% confidence interval	Likelihood ratio statistic	P-value
Coordinating group (Architecture)	1.37	(0.86-2.20)	1.7	0.2
Improved intervention (Availability)	0.95	(0.65-1.36)	0.1	0.8
Financing commitment (Affordability)	1.38	(0.98-1.94)	3.4	0.06
Initial WHO recommendation (Adoption)	2.00	(1.34-2.97)	11.7	<0.001
Global WHO recommendation (Adoption)	0.53	(0.37-0.76)	12.0	<0.001

Legend
Adoption rates are calculated relative to the rate of adoption of HepB vaccine in high income countries.

Plots of the rate of adoption (cumulative baseline hazard from the Cox model) for analysis including only high income countries (Figure 8A), suggested a more or less linear increase with time. This corresponds to a constant underlying rate of adoption, once the effects of the different milestones are allowed for. In contrast, the cumulative baseline hazard for low income countries (Figure 8B) increased with the time for which the intervention had been available, indicating a tendency for interventions to be more likely to be adopted the longer they were available, even allowing for the effects of the milestones.

FIGURE 8. EFFECT OF TIME SINCE REGULATORY APPROVAL ON RATE OF ADOPTION.

Years since initial availability of intervention
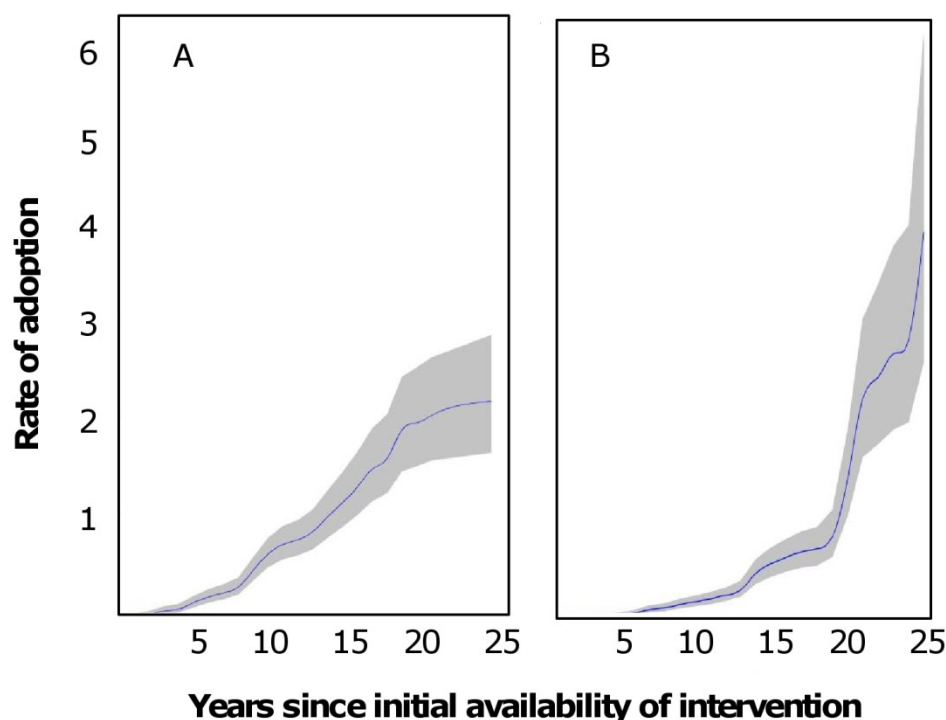
Legend

The vertical axis shows the rate of adoption of interventions according to the number of years since regulatory approval. All interventions are included, except where too few countries were relevant to the analysis, as noted below. The grey area indicates the 95% confidence region around the result. A. High income countries only. Analysis includes all interventions except those against malaria. B. Low income countries only. Analysis includes all interventions except rotavirus vaccination.

ANALYTIC FRAMEWORK

On the basis of our findings, we developed a modified access framework (Figure 9). The new framework includes a coordinating architecture in the R&D period and in the decision and implementation period. The **coordination** role during the R&D period should advance activities related to availability, affordability and adoption, so that each comes to maturity as close to the date of regulatory approval as possible.

Activities to address **availability** prior to regulatory approval seek to ensure that interventions completing R&D are suitable for the programmatic needs of DC health systems and users of health services. Another important consideration will be that sufficient supplies are available. Activities aimed at improving **affordability** include ensuring that future prices will not prohibit use in DCs and to plan for future financing to subsidize implementation. Affordability activities also seek to minimize the implementation costs to health systems (e.g. requirements for additional refrigeration.) **Adoption** activities relate to planning by international organizations to

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identify and ensure that information needed for normative guidance on use and policy recommendations are developed at pace with, or as part of, clinical development. If an intervention is going to be used in the developed world, research questions specific to DCs need to be addressed as well. Adoption also encompasses working with countries and communities to anticipate and generate the data and processes they will need to make decisions about implementation and whether or not to accept an intervention once available.

A number of other actions that directly inform, and that may be directly informed by, access activities are reflected in the framework although they are beyond the scope of this analysis. Regulatory oversight of clinical trials extends throughout R&D and evolves into regulatory monitoring and pharmacovigilance in the implementation period. Pre-clinical and clinical studies lead into phase four effectiveness studies and operational research, which may extend and refine how an intervention is used. These in turn inform country decisions and may impact access. Epidemiological studies of disease burden and economic and modeling studies may also directly inform decisions on use of a specific intervention or they may relate much more generically to a disease area. For example, a study on the direct and indirect costs of malaria to a health system may inform use of a specific intervention but also informs societal resource planning more generally. Therefore, such studies are reflected under the coordinating architecture of the framework, in both the R&D and implementation periods, but not presented here as necessarily following directly from that coordination.

FIGURE 9. PROPOSED ACCESS FRAMEWORK INCORPORATING R&D AND IMPLEMENTATION PERIODS.
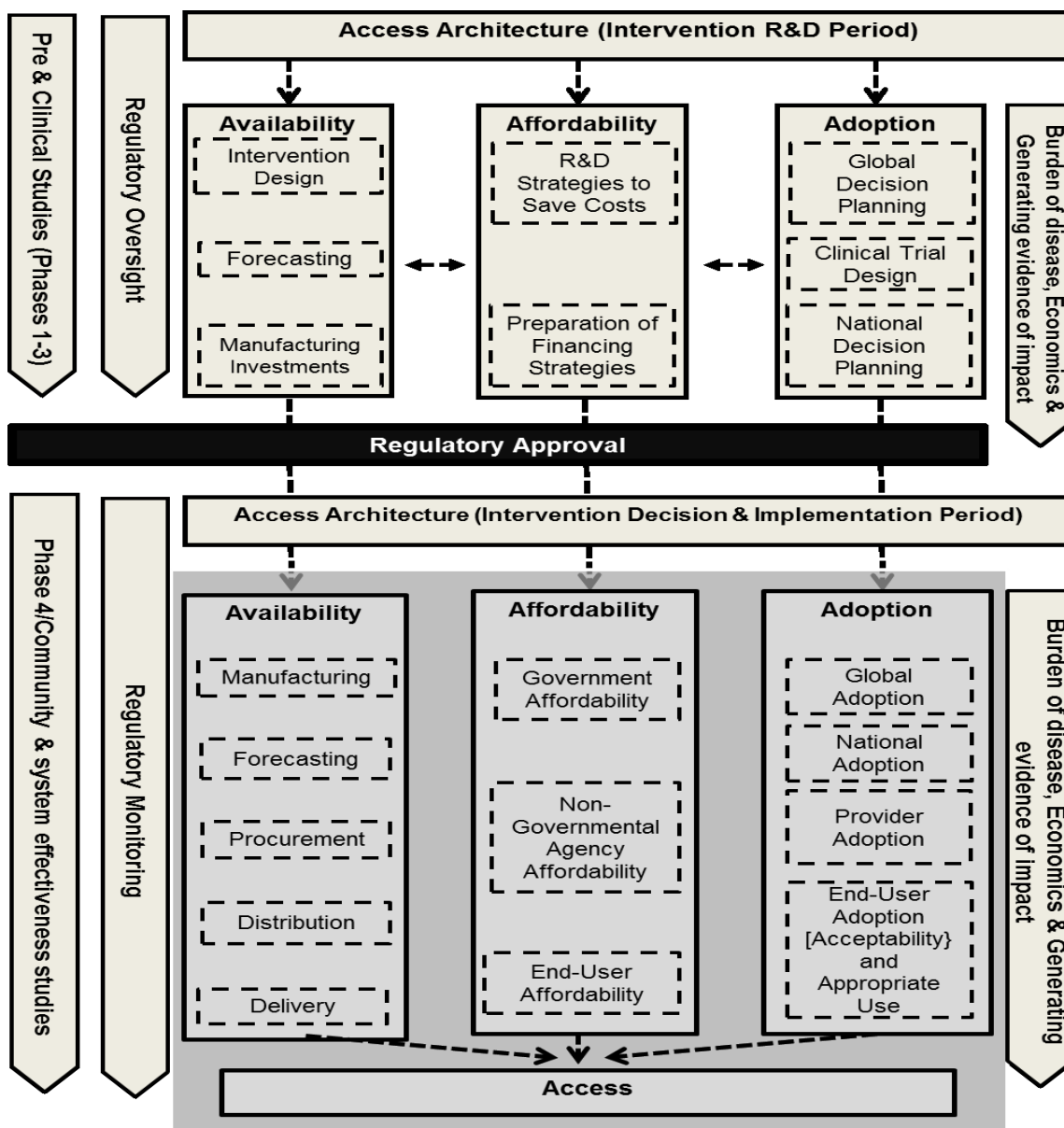
Legend

The area in grey represents the original access framework as shown in Figure 4. Other areas are new to the framework. Actions that take place during the R&D period are described in the space above the black strip, "Regulatory Approval, while actions carried out in the decision and implementation period are described in the space below. Area in grey is reproduced under a Creative Commons Attribution-Noncommercial-Share Alike 3.0 License [2].

DISCUSSION

This paper describes the systematic delays observed in the period between regulatory approval and implementation of seven interventions, four vaccines and three malaria interventions. The interventions target diseases responsible for a substantial

proportion of the overall global burden of disease, particularly for children. According to WHO, each of these interventions should be used globally in all countries, or all malaria-endemic countries for the malaria interventions.

Despite varied experiences, there have been consistent delays of 10 or more years until implementation in developing countries. The delays suggest that focusing efforts on supporting adoption and scaling-up of interventions only after regulatory approval is likely insufficient on its own. Organizations need to begin working systematically on access-related issues earlier on, during the R&D stages. Carefully paced activities during R&D would lead to action supporting decision-making processes shortly after regulatory approval. Activities during R&D may decrease the time and resources needed for ongoing efforts supporting implementation and scaling-up of interventions where appropriate.

CHALLENGES AND LIMITATIONS TO THE ANALYSIS

The analysis focuses on not-for-profit organizations, including academia, governments, multi-lateral organizations like WHO, product-development partnerships, public-private partnerships, foundations, and others. It is concerned with implementation of interventions through national health systems as a way of reaching enough people to achieve an equitable public health impact, consistent with the definition of access. Future analyses would benefit from looking at the issue of delays from other perspectives, such as private for-profit organizations (e.g. manufacturers), regulators, and private sector health providers; these perspectives are consistent with other possible causes of delays, such as supply shortages. However, delays caused by such groups can be at least partially attributed to failure in the not-for-profit sector to anticipate and address access challenges. Thus, not including their perspectives does not undermine the basic findings of this paper. For example, a supply shortage may be caused in part by insufficient planning during the R&D period between the not-for-profit sector and manufacturers on issues of availability and/or affordability for the developing world.

The analysis did not consider country characteristics apart from income group, given that each of the interventions has been recommended for use globally. The analysis is also likely to be conservative, understating the delays, given that it focused on beginning of implementation, not the point at which nation-wide coverage was achieved. Coverage is already analyzed by WHO and others elsewhere [46,58].

Data used in the analysis are imperfect. However, we found no evidence of a systematic reporting gap or bias from any group of countries. Imperfect data were partially offset by including every country in the world. The only relatively small income group was HIC malaria-endemic countries, of which there are only four (Table 3). It is important to recognize that countries can choose not to implement any intervention, or use it in a different fashion, which may not be captured in databases.

Selecting milestones required the authors to make judgment calls. For example, ITNs were deemed safe for use in 1991, which was considered the point of regulatory approval for this analysis. However, the first recommendation for use of ITN's based upon demonstrated efficacy was made by WHO in 1995 [52]. International organizations did not develop a shared commitment to initiate large scale implementation of ITNs until 1997 and later.

There is no reason to assume that the pattern of delays in the adoption of vaccines and malaria interventions is unique. It is possible that the delays for other interventions are longer than those for immunization and malaria, which enjoy a relatively high profile within public health arenas.

ACCELERATING ACCESS

High income countries generally introduce new interventions within a reasonably short period after they become available, and experience with the more recent RV and PC vaccines suggest the delays are becoming shorter. Middle and low income countries require years or decades longer to implement, with an increased pace of implementation happening only 15 to 20 years after regulatory approval. Vaccines continue to be implemented in developing countries at approximately the same pace as HepB in the 1980s and 1990s. ACTs have been implemented relatively quickly which would be expected given the crisis situation seen over the past decade as resistance grew to antimalarial treatments. Even so, one may question if implementation of ACTs was fast enough. ITNs are about on pace with HepB vaccine, while RDTs are being implemented significantly slower.

From the literature and empirically, WHO's initial recommendation had the strongest, and only statistically significant, effect on adoption. This may not be surprising as countries and financing bodies often follow WHO's guidance. This suggests that those developing new interventions should work systematically to anticipate the research questions WHO and international organizations, including financing bodies, will need addressed to make policy decisions. It is noteworthy that countries often did not choose to wait for more comprehensive, global WHO recommendations, particularly when deciding to implement malaria interventions, suggesting that activities strengthening country decision-making may also accelerate implementation. Coordinating groups and financing appear to have important effects. Statistically the impact of an improved intervention, better aligned with developing country needs had limited impact. This suggests that many countries do choose to begin implementing interventions even if they are less than optimally designed. The analysis of Hep B and Hib combination vaccines suggested that improved interventions may have led to faster scaling up. And the literature and anecdotal reports from the field about the challenges implementing interventions not well-suited to developing countries suggest poor alignment is a re-occurring cause of delays. The literature and data analyzed in

this paper argue for the need to work more comprehensively during R&D, tailoring activities to each intervention which anticipate and can accelerate access.

ANALYTIC FRAMEWORK

This paper proposes a new framework for interventions in the R&D period to accelerate the process from regulatory approval to decision and implementation. The framework builds on and extends existing research on architecture, availability, affordability, and adoption to identify enabling activities that could occur earlier in the R&D process. Multiple activities happen during the R&D phase of an intervention. The major regulatory, clinical trial and epidemiological activities included in this framework complement activities specifically addressing future access in the form of country decisions and implementation. If the coordinating architecture is well integrated with clinical trials and related activities, there is greater potential for synergy. The coordinator must ensure that access activities neither outpace nor lag behind the accumulation scientific evidence.

Activities relating to the four access factors in the framework can guide those working to develop interventions to accelerate the transition period between R&D to implementation. The activities are not in themselves prescriptive, nor do they attempt to overly simplify the R&D and implementation continuum. Activities during the R&D phase must be tailored to each intervention, and account for each partnership contributing to that intervention, the type of disease burden, and other contextual factors. The R&D process for a new intervention is lengthy and complex and requires a long-term and systematic approach to associated access activities. Coordination in the R&D, decision, and implementation periods may be by the same or different organizations, but the role of the coordinating body evolves from one period to the next.

The new framework also assumes that no single activity will lead to implementation. The HepB vaccine was the subject of a strong, global WHO recommendation more than a decade before implementation accelerated. The Hib vaccine had assured financing years before it took off. ITNs had a well-established architecture in the Roll Back Malaria Partnership from the late 1990s but implementation accelerated only years later and after the development of an improved intervention in the form of the LLIN. Moreover, the global recommendation for ITNs came only after most LICs had already adopted ITNs as part of its public health policy.

Available interventions need to be tailored to fragile developing country health systems and their users, and scientific questions resolved to facilitate eventual implementation. Target product profiles, and subsequent formulation, clinical trial design or other R&D steps, need to explicitly consider the needs of health systems. For example, additional investments during the R&D phase to increase the heat stability of a vaccine could lead to a greater likelihood of reaching remote populations, while

minimizing the amount of vaccine wasted, facilitating more equitable use and saving money over the long term. Forecasting is also a key part of availability, aligning supply and demand. This is particularly important for pharmaceuticals, as supply planning, including decisions on production capacity and building a manufacturing facility, is completed years before regulatory approval [59].

Affordability-related decisions during R&D seek to minimize future purchase and implementation costs. Decisions should seek to minimize the indirect costs and time requirements eventually borne by countries and health care workers. An example of a heat-stable vaccine is presented above. In addition, the interaction with international financing bodies needs to be initiated years before funds are required. Organizations like GAVI and the GFATM need to anticipate future financing requirements and raise funds accordingly.

Anticipating adoption decisions at the global and country levels during R&D can increase the transparency and efficiency of normative and policy-making processes. One key element is the identification, prior to phase 3 trials, of the type of data that will be needed by various policy-making and financing organizations so that suitable studies can be designed [22].

RISK OF STARTING TOO EARLY

There are risks to planning for access during the R&D phase. Interventions can always fail due to safety, efficacy or other concerns. One risk is the possibility of over-promising to countries. A second is that time is finite, and for some organizations and countries, time spent on activities anticipating future intervention is time lost for implementing existing interventions. A third is the financial loss that may occur if an intervention eventually fails. These risks need to be balanced with the evidence of delays presented in this paper. The optimal strategy is not to wait until an intervention is available before planning for access-related issues. It is important to carefully select and pace access-related activities with the R&D process and scientific progress. Access activities should not get ahead of clinical and regulatory progress, but they should also not lag years behind as has happened thus far. Effective coordination can prepare for the availability of phase 3 trial data and regulatory approval, so that promising interventions move efficiently from R&D towards impact.

CONCLUSION

The analysis in this paper confirms that 5-10 years after a proven public health intervention becomes available, only a small fraction of countries in need in the developing world will have access to it. As a result, lives are being lost unnecessarily. The enormous investments in carrying out high-quality clinical trials and regulatory processes as fast as possible are at risk of being wasted. During this extended period, manufacturers may be left with idle capacity or may decide to exclude LMICs and LICs

entirely from their supply plans, in favor of more reliable markets in HICs. This paper proposes a new approach, challenging the international community to systematically address questions of access during the R&D period of new interventions, instead of waiting until regulators have given approval. All critical factors need to be identified early for potential new interventions, and the process of supporting their later implementation started as early as possible.

Our approach has implications throughout the international public health community, including researchers, manufacturers, WHO, funders, countries, and others. It raises a challenge to each organization, asking them to identify ways they can contribute to new interventions during R&D, anticipating and beginning to address likely bottlenecks in advance. Early foresight in the development process has the potential to significantly shorten the time elapsed before developing countries access new interventions, and as a consequence, reduce the unnecessary loss of life that is experienced today.

AUTHOR CONTRIBUTIONS

AB developed the analysis strategy with input from TS, DdS, and CL. AB conducted the analysis and drafted the manuscript. TS conducted the statistical analysis. TS, DdS, and CL reviewed and critically edited the manuscript. AB, TS, DdS, and CL read and approved the final manuscript.

COMPETING INTERESTS

AB, TS, DdS, and CL have no competing interests.

CHAPTER 3. ALIGNING NEW INTERVENTIONS WITH DEVELOPING COUNTRY HEALTH SYSTEMS: TARGET PRODUCT PROFILES, PRESENTATION, AND CLINICAL TRIAL DESIGN

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ABSTRACT

A growing number of interventions are being created to address health problems of the developing world. However, most developing countries have fragile health systems and find it difficult to accommodate new interventions. Consequently, it is important that the design of these new interventions aligns with the needs of health systems and their users in developing countries. Establishing target product profiles (TPPs) is a critical, early step towards tailoring interventions to suit both of these constituencies. Specific analyses may be needed to identify and establish relevant TPP criteria such as optimal formulation, presentation and packaging. Clinical trials for a new intervention should be designed to address both TPP-specific questions and anticipated use of the intervention in target countries. Examples are provided from applied research on malaria vaccines that are applicable to other new public health interventions.

INTRODUCTION

Health systems in developing countries (DCs) are more fragile than those in the developed world. Major challenges include inconsistent energy supply, limited health infrastructure, highly constrained financing and the large and diverse disease burdens borne by populations. Unless new interventions are specifically designed to facilitate integration into, and be acceptable to users of such systems, these challenges may be exacerbated.

The world is seeing a welcome commitment to creating new means of addressing public health problems in DCs. The G-Finder report, which tracks funding for interventions that target neglected diseases, lists 31 diseases and 134 product areas for these diseases, including drugs, vaccines, microbicides, diagnostics, and vector control [60,60]. To avoid delays in use after approval by regulatory authorities, the specific needs of the developing world must be considered from the earliest stages of intervention development.

Frost and Reich (2008), and others [2,4,38,42], suggest that access to health interventions involves multiple considerations following regulatory approval; particularly availability, affordability, decisions on adoption, and effective coordination (i.e., architecture) of all these considerations. Availability covers factors relating to manufacturing, storage and distribution. Affordability represents the cost to purchasers and end-users. Adoption requires a series of positive decisions to be made by governments, providers, and individuals. The authors provide insights into the many factors that ultimately influence access to health interventions, and the realization of a positive and equitable public health impact.

All three considerations—availability, affordability, and adoption—are directly influenced by decisions taken and studies conducted by developers and collaborators well before regulatory approval. To achieve public health impact in the context of DC health systems, an available intervention must have characteristics that are acceptable to end users and facilitate implementation; for example, suitability for tropical climates and a low logistical burden. Affordability is not limited to initial purchase price; it also takes account of total delivery costs, including storage, transport, health worker time, and the quantity of unused or wasted product. Adoption partly depends upon providing data that responds to questions specific to DC health systems and populations.

If issues of availability, affordability and the adoption are not considered during development, additional studies and investment may be needed after regulatory approval; expending time and money that might have been more efficiently used

during the development phase. The associated public health impact of delayed implementation—possibly years—can be even more significant. The GAVI Alliance (GAVI) invested approximately US$100 million to address supply constraints and outstanding research questions in support of implementing *Haemophilus influenzae* type B (Hib), pneumococcal, and rotavirus vaccines [61]. The Hib vaccine prevents one of the most important causes of pneumonia and meningitis in infants. GAVI's expenditure began after Hib was offered free to countries in the year 2000. Target countries were unfamiliar with the disease and did not have data on its burden, a situation which could have been foreseen and addressed while the vaccine was still in research and development (R&D). Consequently, very few countries adopted the vaccine, and few children were protected. GAVI had to make additional investments to strengthen the evidence base to inform the use of Hib, and to prevent a similar situation with pneumococcal and rotavirus vaccines.

This paper presents an applied research strategy to foresee challenges and align interventions with DC health systems from the early stages of development. Published literature is used to complement Frost's framework. Examples from a number of public health interventions and the work of the PATH Malaria Vaccine Initiative (MVI), a product-development partnership, demonstrate the application of this approach. The paper's second section proposes a target product profile (TPP) template that should be utilized for public health interventions intended for the developing world.

Since the ideal target for every attribute in a TPP may not be readily apparent, the third section of this paper provides an example of research efforts to determine the optimal formulation, presentation, storage and packaging of a malaria vaccine candidate intended for DCs. These attributes influence availability, affordability, and decisions on adoption. A similar approach informed the establishment of the TPP for the US$1.5 billion advance market commitment for pneumococcal vaccines [62].

The paper's fourth section considers research questions specific to the data requirements for adoption in DCs. Such requirements may not be explicitly stated in a TPP, but highlight the need for careful alignment of research studies with TPP targets and desired health impact. The fifth section of the paper discusses the implications of the previous sections, prior to the conclusion.

TARGET PRODUCT PROFILES

BACKGROUND

There is no universal understanding of a TPP and its use. At its most generic, a TPP can be a list of the attributes of an intervention. A TPP can be a formal document used in discussions with regulators, as part of a summary of a drug development program leading to specific label claims [63–65]. It can also be used as a commercial tool, to

compare a product with a competitor's and set pricing strategies [66]. Alternatively, a TPP can be used as a tool that transparently identifies the major characteristics of a public health intervention, thereby unifying those working on the intervention so as to achieve the intended health impact [16,67–69]. Several documents provide guidance on potential structures or categories when developing TPPs; however, most of these relate to experience from the developed world and are tailored to for-profit companies focused on market share [16,64,65,67–72].

TPPs are living documents evolving over time as research, analyses, and consultations clarify the ideal targets, and as interventions move from pre-clinical to the late development stage [71,72]. Within an organization or consortium there should be a formal mechanism for approving a TPP template; individual TPPs for specific classes of interventions, and a formal change control system for revisions to the template and to individual TPPs over time. One way to manage product evolution is to identify an acceptable range for each characteristic, and then to indicate where an individual intervention's characteristics fall within that range as it enters late development. If its characteristics move outside the identified acceptable range, an assessment must be made to determine whether continued development is justified.

CASE STUDY: TPP DEVELOPMENT

MVI began a process in 2009-10 to formalize both the development of TPPs for the candidate malaria vaccines it was developing, and the role of TPPs in guiding the work of the organization. A multi-disciplinary team was led by experts on policy and access, accountable for envisioning the eventual implementation process for malaria vaccines. The team included members with clinical, regulatory, and commercial expertise. It adapted, with permission, a TPP format that was developed by the Bill and Melinda Gates Foundation (Gates Foundation). In parallel, the malaria eradication research agenda (malERA) initiative agreed upon a TPP template for vaccines that could contribute to malaria elimination and eradication by interrupting transmission, informed by MVI and the Gates Foundation templates [67]. Following iterative modifications to the Gates Foundation template, a final MVI TPP template was agreed upon by team members, and formally approved by MVI's Portfolio Management Committee (PMC), which oversees development of the organisation's vaccine candidates. MVI decided that the PMC would approve, and MVI's external advisory body review, all TPPs and any significant changes to them. Approved TPPs were shared with collaborators and made publicly available.

MVI's TPP template was a table that identified a range of target characteristics, from desired to minimally acceptable, for each class of malaria vaccines, as well as the attributes of a specific product as it moved into late development (Figure 10). Targets were intended to be concrete, evidence-based, and/or measurable. Key components

of the TPP would be described on the vaccine package insert. Definitions and examples are provided in Table 9 and Table 10.

FIGURE 10. TARGET PRODUCT PROFILE TEMPLATE.

Product Class:	
Product Name:	*To be completed once product approaches phase 2b*
Date of TPP Endorsement	
Dates of TPP Revisions	

	Desired		Minimally Acceptable		*"Insert Product Name"* Profile (Completed as product approaches Phase 2b)	
	Target	**Rationale**	**Target**	**Rationale**	**Target**	**Rationale**
Indication						
Expected Efficacy						
Target Population(s)						
Route of Administration						
Formulation & Presentation						
Dosage schedule						
Safety profile						
Co-administration						
Shelf-Life & Storage						
Manufacturability						
Price						
Product registration and WHO prequalification						

One distinguishing attribute of MVI's TPP was that each target was accompanied by a rationale. The rationale could be based upon published studies, modeling or, at a minimum, the logic that justifies the chosen target. The rationale provided a critical means for others to understand the driving forces behind individual targets. This was particularly important because development activities can take many years, teams often evolve, and it can be challenging to ensure consistent assumptions among targets within a TPP.

MVI's TPP included explicit consideration of affordability in the form of purchase price, or relative cost-effectiveness. It also included the preferred route of administration, formulation and presentation, dosage schedule, co-administration, shelf-life and storage, and manufacturability. These characteristics will eventually inform country adoption decisions [73].

TABLE 9. TPP TEMPLATE DEFINITIONS: STRUCTURAL ELEMENTS.

Structural elements	Definitions
Product Class:	Category of product. Example (Ex): Blood-stage malaria vaccine
Product Name:	How product will be known publicly. To be completed once product approaches phase 2b
Date of TPP Endorsement	Date TPP formally adopted by organization
Date of TPP Revisions	Means of tracking changes over time
Desired target	Optimal characteristics
Minimally acceptable target	Minimal characteristics that would allow product to continue development
Product profile target	Characteristics specific to a product in late development (e.g. phase 2b), which should fall between desired and minimal targets
Rationale	Identifies data and publications to justify each target, or at minimum the reasoning behind each target

Table 10. TPP template definitions: Characteristic categories.

Categories	Definitions
Indication	Intended use against a measurable outcome. Ex: Prevention of uncomplicated malaria.
Expected Efficacy	Anticipated efficacy level for the indication, measured in a clinical trial.
Target Population(s)	Ages, parts of the world, and/or defining characteristics of those who could receive the intervention. Ex: Children under five years of age in malaria-endemic countries.
Route of Administration	Ex: Oral ; intra-muscular injection.
Formulation & Presentation	Formulation, Ex: liquid or lyophilized (a dried powder) which needs to be reconstituted (mixed with a liquid) before injection; presence of a preservative; and volume of each injection. Presentation, ex: size and type of vial; vial labelling.
Dosage schedule	How may doses, at what intervals. Ex: three doses at one month intervals
Safety profile	Anticipated or acceptable levels of adverse events; populations or individuals that should not receive the product, or receive it with caution. Ex: safety allows for use in the target population, or comparable to similar interventions used in the target population.
Co-administration	Other interventions that can be administered at the same health visit.
Shelf-Life & Storage	Shelf-life relates to how long the product can be stored after it leaves the manufacturer, and storage indicates packaging requirements and temperature at which it needs to be maintained.
Manufacturability	Scalability of the production process to quantities anticipated for the developing world.
Price	Absolute or cost-effectiveness relative to peer interventions.
Product registration and WHO prequalification	Rigour of the regulatory bodies anticipated to register the product, and expectations for pre-qualification. Ex: Licensure by WHO-evaluated fully-functional regulatory agency. Pre-qualified by WHO.

FORMULATION, PRESENTATION, SHELF-LIFE AND STORAGE

BACKGROUND

Once an intervention becomes available, the extent to which its final characteristics comply with the TPP will directly impact affordability and the adoption decisions.

Some public-private collaborations, intervention developers and advocates seek to align product characteristics with the needs of DCs [16]. For example, a public-private partnership recently formulated and packaged an appropriately flavoured and easy to swallow dispersible artemisinin-based combination therapy (ACT) for the treatment of malaria in children [74]. Similarly, vaccines have been formulated to combine multiple antigens into single injections [75,76]. The number of doses in a vaccine vial can be optimized for DC immunization programs [77]. Novel pharmaceuticals can be evaluated under hot and humid storage conditions common in DCs [78,79]. Packaging can be minimized to reduce shipping and handling costs [80]. Research has considered the perceptions of malaria and vaccines, and the acceptability of malaria vaccines, to users of health services [81]. Each of the considerations above relates to one or more aspects of a TPP that responds to the preferences of the public health community and of DCs. If an intervention is modified in late development, or after licensure, this may cause delay and impose additional costs, i.e., additional/extended clinical trials, modifications to manufacturing systems, and requirements for health worker retraining.

Systematic alignment of interventions with the needs of DCs builds upon an analytic foundation supported by clearly stated rationales and trade-off comparisons; particularly when there is collaboration with private sector partners. Most of the authors above do not report analyzing and/or quantifying the trade-offs. Alignment is also most likely when preferred characteristics are integrated into the TPP and product development plans early in the development process, which may be years before anticipated availability.

One set of interrelated characteristics that lends itself to analysis is the optimal targets for formulation, presentation, and shelf-life and storage of malaria vaccines based on direct trade-offs between vaccine wastage and health system costs. For example, a multi-dose lyophilized vaccine or a multi-dose liquid vaccine formulated without a preservative cannot be reused from one immunization session to the next when unused doses remain in a vial; this leads to more vaccine wastage than a liquid multi-dose vial with a preservative [82]. Presentation of a vaccine in a multi-dose vial is more space-efficient for transport and storage; consequently when a single-dose, lyophilized or few-dose, preservative-free vaccine is adopted in order to reduce wastage, this will inevitably generate greater logistics costs. Similarly, a vaccine with a short shelf-life

will often lead to increased wastage if health care workers have to destroy expired, unopened vials. A mandatory requirement for refrigerated storage and transport also increases costs, particularly if the packaging is not optimized for developing country distribution systems.

CASE STUDY: PUBLIC SECTOR PREFERENCES FOR RTS,S/AS01(RTSS) MALARIA VACCINE FORMULATION, PRESENTATION, SHELF-LIFE AND STORAGE

RTS,S, under development since the 1980s, has progressed over the last decade through a collaboration between the PATH Malaria Vaccine Initiative (MVI) and GlaxoSmithKline (GSK). Its phase III clinical trial began in 2009 [83]. If all goes well in phase III testing, WHO has indicated that a policy recommendation for RTS,S is possible as early as 2015, paving the way for implementation in countries through the Expanded Program on Immunization (EPI).

The process of defining the targets for a number of specific vaccine characteristics evolved into a five-step process, which started in November 2006 and was completed in September 2007.

STEP 1 – STRUCTURED DISCUSSIONS WITH A PUBLIC - PRIVATE SECTOR WORKING GROUP

A working group from WHO, MVI and GSK was established in 2006, agreeing on a terms of reference to systematically analyze and/or quantify public sector preferences in order to:

(1) Align RTS,S presentation and packaging with WHO/UNICEF procurement specifications and previous experience with other childhood vaccines used in EPI to:

- Ensure that the packaging requires as little volume as possible, particularly in the cold chain and in dry storage.
- Ensure that lyophilized product and adjuvant cannot be separated in shipping, storage, and handling at health centers.
- Evaluate implications of pre-filled syringes versus vials.
- Consider the implications of formulating RTS,S with other EPI antigens.
- Ensure consistency with standard auto-disable syringe sizes and volumes.
- Minimize medical waste implications.

(2) Determine the factors governing the choice of preferred vial size(s).

(3) Consider the use of preservatives in the vaccine.

(4) Consider thermostability issues.

(5) Consider implications of liquid vs. lyophilized formulations.

(6) Consider health worker training and workload issues.

STEP 2 – QUANTITATIVE ANALYSIS USING THE VACCINE PRESENTATION ASSESSMENT TOOL (VPAT)

An Excel-based Vaccine Presentation Assessment Tool (VPAT) was developed and refined over the course of the project to provide the working group with quantitative analyses of trade-offs among characteristics. It assessed the volumetric impact of alternative formulations and presentations of a vaccine, and associated commodities (syringes and safety boxes), with those for a typical immunization schedule in sub-Saharan Africa. The tool used as its unit the Fully Immunized Target Group (FITG), which comprised a fully immunized child plus his/her mother's tetanus toxoid immunization.

In addition to this volumetric analysis, the tool incorporated sufficient cost data to perform a 'break-even' analysis. This analysis indicated which presentations were likely to have implementation costs comparable to, or cheaper than, a baseline presentation of the same vaccine in a single-dose vial. The tool used a goal-seeking algorithm to calculate the wastage rates at which the total cost per administered dose (vaccine purchase + vaccine storage + vaccine distribution + consumables purchase + consumables distribution) for each presentation was equal to the baseline presentation. The calculated break-even wastage rates for each possible presentation and vaccine purchase price point were then compared with wastage rates for similar presentations achieved in the field. If the calculated break-even wastage rate was higher than that typically achieved in the field, the presentation/price combination was considered to be potentially viable.

STEP 3 – INCORPORATING DATA FROM AFRICAN EXPERTS AND WHO NORMATIVE MATERIALS

A questionnaire on product profile options for RTS,S was developed in consultation with the working group. This questionnaire was administered at two regional immunization programme managers' meetings held in Zimbabwe and Burkina Faso during March 2007 to determine the preferences of immunization experts in Africa. At each session a presentation on malaria vaccine development was given before the questionnaire was administered. The 71 respondents included 35 country staff and 36 international agency staff from 31 malaria endemic African nations. Responses were consolidated and analyzed in Excel.

The working group reviewed WHO materials relevant to the study analyses in parallel with the survey-related activities. Applicable recommendations and norms were synthesized according to the study's topics and carefully referenced.

STEP 4 - DISCUSSIONS BY PUBLIC SECTOR EXPERTS AND ENDORSEMENT BY WHO STAFF

A complete report was drafted synthesizing the findings from the steps above and conclusions on formulation, presentation, shelf-life, storage, and packaging. It was discussed by a public sector expert group drawn from PATH and WHO. The report was

updated in response to the comments received and to take into account improvements in the break-even modeling arising from a parallel GAVI Alliance-commissioned PATH study on pneumococcal conjugate vaccines [62]. The updated report was then reviewed and conclusions formally endorsed by senior immunization staff in WHO at a meeting in September 2007.

STEP 5 – SHARING PUBLIC SECTOR RECOMMENDATIONS WITH THE MANUFACTURER

The final project report set out the agreed-upon public sector priorities for the presentation, shelf-life, and storage of RTS,S [84]. This report was shared with GSK representatives in September 2007. The manufacturer considered its findings, along with other constraints, such as production challenges and process validation, in the determination of the final product profile for RTS,S.

A complete list of conclusions endorsed at a meeting with WHO representatives is available in the final report, which includes the detailed methodologies associated with each step summarized in this paper. The conclusions related to vial size are presented in Table 11 to illustrate the complexity of aligning an intervention with the needs of developing countries. Factors contributing to the optimal vial size for RTS,S included price per dose, anticipated usage, vial dimensions, and estimates of likely wastage. The optimal vial size for RTS,S was found to be a two-dose vial if the price was above US$2.50/dose or a three-dose vial if the price was lower than US$2.50.

TABLE 11. PUBLIC SECTOR PREFERENCES FOR RTS,S VIAL SIZE.

Vial size	Public sector preference
Mono-dose vial	A mono-dose RTS,S presentation is not recommended at any of the costs per purchased dose that were investigated. The advantage of the low opened-vial wastage rate associated with mono-dose vials is offset by the need to approximately double the volume of refrigerated storage required as compared with a basic schedule of vaccines. In addition, reconstituting mono-dose vials would have an excessive impact on health worker workload.
2-dose vial	The current 2-dose presentation appears to offer the best compromise between volume-per-dose, cost-per-dose, and wastage in routine immunization settings at a price point greater than around US2.50 per purchased dose.
3-dose vial	A 3-dose vial appears to offer the best compromise for routine use at a cost per purchased dose below the US$2.50 price point.
5-dose vial	A 5-dose vial looks unlikely to be viable at any price point unless it can be supplied in compact, purpose-made vials at a cost per administered dose that is competitive with 3-dose.
10-dose vial	A 10-dose presentation would be welcomed by countries but would only be economical at the lower price points (around US$1.00 per dose) as a supplementary presentation for use in larger urban and campaign settings, where opened-vial wastage levels can be assured to be around 10% or less.

ANTICIPATING SUPPLEMENTAL RESEARCH QUESTIONS FOR THE DEVELOPING WORLD WHEN DESIGNING CLINICAL TRIALS

BACKGROUND

The targets in a TPP help to define the research questions that need to be addressed in trials and studies in order to be confident that an intervention meets expectations. The targets also assist in identifying data which may be sought by countries to inform adoption decisions. Clinical trials are generally designed to address indication, efficacy and safety, although these may not be straightforward to define or evaluate in the DC context. Less apparent research questions may arise from characteristics in the TPP, which also require explicit consideration in trial designs.

There are many examples in the literature that highlight the important challenge of foreseeing research questions specific to DCs, which may not be as relevant in developed countries, and might, therefore, be overlooked [85]. A partially efficacious, preventive intervention may not be of interest to developed countries, but may be used in DCs where treatment is less accessible and the disease burden is higher [86]. Given the diverse disease load carried by many individuals in DCs, interventions may have indirect effects on unrelated pathogens [87]. The safety and efficacy of interventions in HIV positive individuals needs to be evaluated given its prevalence in Africa and the challenge of screening people [88–90]. Studies assessed whether the birth dose of Bacillus Calmette-Guerin (BCG) vaccination should be delayed in low birth-weight newborns [91]. Studies also evaluated the impact of breastfeeding on the efficacy of rotavirus vaccine [92].

When designing TPPs and associated clinical trials in DCs, such considerations, should be foreseen in anticipation of adoption decisions by international and national policy-makers. There is no formal requirement for policy-making bodies, particularly WHO, to inform or approve clinical development plans. However, it seems prudent to design pivotal studies that anticipate and address as many questions needed to establish policy as possible. Although it is desirable to be comprehensive during the clinical development program, it may not be practical to address all research questions arising from a TPP; developers may decide some questions are best be answered in studies after regulatory approval.

CASE STUDY: TPPS AND CLINICAL TRIAL DESIGN FOR MALARIA VACCINES

MVI, GSK and partners developed iterative plans for the phase III trial of RTS,S from 2005 through 2008. At the beginning of the process, there was no clear agreement on the trial endpoints or the best way to measure them. WHO, with support from MVI, organized an international consultation in 2006, culminating in a consensus position that a primary study endpoint for licensure of uncomplicated, clinical malaria was appropriate for submission to regulators and policy-makers, and that additional data on efficacy against severe malaria might be useful [93]. Once the primary endpoint was defined, WHO convened a consultation to establish standards for measuring efficacy of a malaria vaccine against uncomplicated, clinical malaria [94]. The measurement is less straightforward for malaria than for other diseases because individuals can have multiple episodes while developing natural immunity over time.

WHO's efforts were complemented by MVI. MVI reviewed past policy recommendations for vaccines and malaria interventions to anticipate the policy process and to consider what data might be needed for a policy recommendation [95]; findings were reported to WHO's Malaria Vaccine Advisory Committee (MALVAC). MVI, WHO and others also worked with African countries to identify what data were

needed for policy decisions [22,96]. The iterative, collaborative applied research, with WHO's leadership, to define standards in trial design were critical to ensuring that the target product profile characteristics were aligned with what could be measured and would be used by regulators and policy-makers.

RTS,S trials were designed to address as many questions potentially affecting adoption decisions as feasible. Among the questions investigated were efficacy in settings with different malaria epidemiology; efficacy against severe, hospitalized malaria and all-cause mortality; duration of protection to 30 months and beyond; co-administration with current and anticipated vaccines and need for a booster dose.

The target population and safety requirements identified in the TPP also led to specific research questions. RTS,S is intended for infants in Africa. It was determined that the Phase III study should be undertaken in as representative a population as ethically feasible in order for the vaccine to be used widely in this target population, and in anticipation of potential WHO requests for studies in the target subjects before issuing a policy recommendation. Therefore the study design included subjects that would often be removed from typical trials. For example, only subjects that were acutely malnourished or had late-stage AIDS were excluded, while infants and children with more mild forms or low birth-weight were included. An additional safety study was planned in HIV positive infants and children in parallel with the phase III efficacy study, rather than after regulatory approval. Including these subjects and collecting robust data during phase III studies will enable regulatory agencies to conclude on its use in these higher-risk groups in parallel with use in healthy infants. Without such data, universal immunization in countries could be overshadowed by the unknown risk to these vulnerable segments of the population.

DISCUSSION

The applied research and approaches described herein reflect lessons, which, if implemented, help ensure that new interventions incorporate characteristics suited to the unique needs of DCs. The approaches also reflect the links between intervention characteristics, affordability, and decisions on adoption in DCs. TPPs should state a clear rationale for desired characteristics to ensure continuity throughout the intervention development period, and increase the likelihood of achieving the desired public health impact. In some cases, the rationale should be the product of specific research activities to quantify the trade-offs, particularly if the trade-offs have implications for private sector collaborators. Trials need to be carefully designed to be consistent with the TPP and unique challenges of DCs. Examples from malaria vaccine development illustrate these points.

There are many challenges to consider in the development of TPPs. A TPP can be a complex document with many different targets, and it can be difficult to ensure that the targets are mutually consistent. For example, if one target is used in a large proportion of a population, such as part of a disease eradication initiative, the intervention would likely need to be relatively inexpensive, easy to store and transport at ambient temperatures, require one or few doses, and be the product of a manufacturing process that is very scalable. It follows from this example that targets in a TPP interact with and influence each other. This is why an interdisciplinary team is best positioned to develop TPPs, perhaps led by someone familiar with implementation of interventions, as MVI has done. Modeling can help identify critical targets, and their significance in achieving the desired public health impact.

Questions may arise as to who bears which costs for achieving TPP targets and whether or not these targets can be addressed through studies after regulatory approval; this forces developers to clearly define their responsibilities. For example, developers of a DC intervention could spend additional resources and time striving to improve its thermostability because this would save money for countries and donors later. Alternatively, they may decide to seek regulatory approval as quickly as possible; leaving the costs associated with cold chain expansion and associated implementation to others. If developers assume that their TPP role ends at regulatory approval, this may lead to inconsistently defined targets and lack of accountability because important outstanding questions have to be addressed by others during later studies. Clearly, some final characteristics of an intervention may not be discerned until late in development. For characteristics that can be foreseen, such as product presentation and packaging, the public sector must make its preferences and requirements clear; for interventions such as pharmaceuticals, perhaps five years, or more, ahead of regulatory approval. The public sector cannot wait to discuss alignment of interventions with DC needs until after regulatory approval has been granted.

WHO can play an important role in standard-setting during the research and development process. Regulatory agencies, international financing organizations and donors, and developing country governments look to WHO for guidance. It takes years to put such standards into place. Partners involved in the development of interventions can support WHO in its role, without influencing its neutrality. Central to WHO's role is long-term predictability, looking ahead to clarify what type of data it will need to set policies, prior to finalizing the design of late clinical trials and years before regulatory approval of interventions, as was largely done for malaria vaccine candidates.

CONCLUSION

Misalignment of novel interventions with DC needs can delay access to essential innovations, and may add years to the delivery of their potential public health impacts. However, developers can anticipate the needs of DCs in a systematic manner before making an intervention available. We have shown how concrete strategies can be developed to achieve well-structured and carefully reasoned target product profiles. The rationale behind a well-structured TPP may be as, or more, important than the TPP target itself. One way to strengthen collaboration with private sector partners, and to increase the likelihood that TPP characteristics sought by DCs will be realized, is to work with partners years in advance of regulatory approval, and to support public sector requirements and preferences with solid data. Identifying the research questions needed to address TPP characteristics also helps developers time their studies and efficiently tackle those questions. This approach can help minimize the duration between the development and successful implementation of new interventions.

ACKNOWLEDGEMENTS

ROLES OF AUTHORS

AB drafted the manuscript, oversaw the TPP activities, conceptualized and managed the product presentation activities, and contributed to trial design decisions. JN managed the TPP activities and contributed to the manuscript. AG was the primary author on the product presentation report, with contributions from RB and AB. AG and RB contributed to the manuscript. DL contributed to the TPP and trial activities, and contributed to the manuscript. AJB contributed to the TPP activities and to the manuscript. CL contributed to the TPP, product presentation and trial activities, and contributed to the manuscript. AB, JN, AG, RB, DL, AJB, and CL read and approved the final manuscript.

COMPETING INTERESTS

AB: None
JN: None
AG: None
RB: None
DL: None
AJB: None
CL: None

CHAPTER 4. ROLES OF INTERNATIONAL ORGANIZATIONS AND IMPLEMENTATION OF NEW HEALTH INTERVENTIONS IN DEVELOPING COUNTRIES: THE RTS,S/AS01 MALARIA VACCINE

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Working Paper

ABSTRACT

BACKGROUND

International organizations are essential for transitioning health interventions from research and development (R&D) into use within developing country health systems. Their decisions (e.g. policies, recommendations, and guidelines), and the associated actions, directly inform country decisions, including those related to the use and subsequent implementation of an intervention. However it is unclear for a new intervention like a malaria vaccine, which international organization takes what decisions, when, to facilitate the transition from R&D to implementation.

METHODS

Literature review, semi-structured interviews, and temporal relationship mapping with Gantt charts were used to analyze the roles, decisions, timing, and interactions of international organizations which may impact the implementation of the RTS,S/AS01 (RTS,S) malaria vaccine in developing countries. The work was undertaken by the PATH Malaria Vaccine Initiative. International organizations were identified based upon the experience of existing vaccines and malaria interventions. Websites and publications outlining each organization's roles were reviewed. Semi-structured interviews were conducted with representatives from, or key informants knowledgeable about, each organization. Actions and decisions were classified into categories of policy, regulation, financing, manufacturing, and procurement. The sequence of actions and decisions from each group or organization were placed into a decision pathway (i.e. Gantt chart) relative to the timing of critical R&D and regulatory milestones.

RESULTS & DISCUSSION

Fourteen decision-making groups were identified within the following seven international organizations: the World Health Organization; European Medicines Agency; GAVI Alliance; Global Fund to Fight AIDS, Tuberculosis, and Malaria; Roll Back Malaria Partnership; GlaxoSmithKline; and UNICEF. Most organizational representatives had relatively little insight into the overall path for an intervention from R&D to implementation in developing countries beyond their discrete roles, particularly for a novel intervention. The findings illuminated who might provide technical recommendations, pay for, and procure RTS,S as well as who might coordinate these processes with regulators and the manufacturer. The implications of various RTS,S phase III trial results were considered for their potential impact on decisions by these organizations. Safety concerns in the trial appeared to have the largest potential impact on decision processes. Interim efficacy findings could speed or slow planning for eventual decisions and implementation, pending final study data and regulatory review.

CONCLUSIONS

The research described in this paper helped provide clarity into the potential roles of different organizations relative to an intervention that is in R&D. Such clarity should contribute to efficient processes, and more rapid evidence-based decisions than has been seen for past interventions. Similar research into international decisions should be considered for other interventions under development.

INTRODUCTION

The way international organizations fulfill their roles have global repercussions. Their decisions and associated actions leading up to and following from those decisions impact developing countries. They impact country decisions to use new health interventions, and the subsequent implementation processes through national health systems. For example an organization could establish a policy recommending countries use an intervention or agreeing to finance it. Supportive decisions mean hundreds of millions of individuals may be protected from or treated for a disease, while decisions that are cautioning, unclear, or absent may slow or stop national decisions to implement an intervention. This paper considers the need for and reports on research into the roles of international organizations in relation to the RTS,S/AS01 (RTS,S) malaria vaccine.

New health interventions can pose systemic challenges to international organizations. New coordination or advisory structures may be needed. Weighing decisions for a "first in class" intervention, like a malaria vaccine, may be more complex than decisions for a second generation intervention like a new anti-malarial drug.

Published literature reflects the important and diverse roles played by multiple international organizations prior to national decisions and implementation of new health interventions. Critical decisions of such organizations at the international level broadly relate to the following categories:

Providing recommendations on safety, quality and use:
- Regulatory agencies provide a critical determination of safety, quality, and efficacy. The World Health Organization (WHO) complements regulators through its pre-qualification function which considers the appropriateness of interventions for procurement by international agencies and use in developing countries [9,97–99].
- Input from WHO is critical for many developing countries' policies [100–102]. WHO routinely issues regional or global policy positions and guidelines, often in consultation with external experts, which inform decisions by financing organizations, countries and others [53,103–105]. WHO also provides technical guidelines on treatment or use of interventions, "how to" manuals which may have recommendations embedded [106–108].

Subsidizing costs: International financing organizations (e.g. Global Fund to Fight AIDS, TB, and malaria (GFATM); GAVI Alliance (GAVI)) take decisions on which purchase and implementation costs they will subsidize for an intervention [109,110].

Manufacturing: Manufacturers, typically private companies, determine the quantity and pricing of interventions they produce [111–113].

Procurement: Individual countries, or international agencies on behalf of countries, determine which interventions they will purchase [114–117].

Actions and decisions by international organizations have also been associated with delays in countries deciding to use and implementing new interventions. For example, a new form of anti-malarial treatment, artemisinin-based combination therapies (ACTs), was first licensed in 1999. In 2004 WHO and the GFATM were continuing to support countries purchasing chloroquine and sulfadoxine-pyrimethamine for treating malaria. These drugs were relatively cheap but malaria had high levels of resistance to them in many countries. Significant changes in malaria treatment only occurred after international pressure and charges of "medical malpractice":   WHO clarified its treatment policies and GFATM decisions moved systematically to supporting the newer, more effective treatment, ACTs. Nonetheless, WHO's formal, new treatment guidelines took an additional two years to be published, seven years after the drugs were first licensed [57,118]. More generally, Senior WHO staff identify timeliness of their recommendations as a re-occurring, systemic problem [105]. Supply shortages from manufacturers have caused delays in implementation by countries [112] (UNICEF Supply Division; http://www.unicef.org/supply/index_55207.html; Accessed August 24, 2011). Decisions of international organizations impacting procurement approaches by countries have also been identified as a cause of delayed implementation of interventions [119].

In addition to the ACT example above, examining policy and financing decisions associated with recent vaccines reveals that critical international decisions can take most of, or more than, a decade after an intervention is approved by regulators. Lives are lost during such delays. The first pneumococcal conjugate vaccine was licensed in 2000 but did not receive a WHO recommendation until seven years later [95]. GAVI signaled its commitment to funding in the same year (Available at: http://www.gavialliance.org/vision/programme_support/new_vaccines/adips/index.php; Accessed: April 14, 2011). *Haemophilus influenzae* type B (Hib) vaccine required 18 years from licensure to global recommendation and financing. Although it was licensed in 1988, it did not receive its initial WHO recommendation for 10 years [95]. The financing commitment was made two years later by GAVI (Available at: http://www.gavialliance.org/vision/programme_support/new_vaccines/index.php; Accessed: April 14, 2011) and WHO issued a global recommendation for use after an additional six years, in 2006 [95]. The lengthy timeframes for decisions seen with ACTs and pneumococcal and Hib vaccines do not appear to be unique.

There are reports of efforts to strengthen or accelerate the decision processes of international organizations for new interventions, although the ultimate impact of most is unclear. Some authors consider steps to inform regulatory and policy decisions [8,86,120–123]. Others provide economic and costing data to inform prioritization and

financing decisions by international organizations [110,124–126]. Forecasting to match manufacturer supply with demand from countries is an important function of the Roll Back Malaria Partnership (RBM), GAVI, UNICEF and other organizations [127]. Authors have also sought to foresee and address procurement strategies [128]. A number of authors describe efforts across multiple roles and international organizations for individual interventions [23,129–131].

Research reported here centers upon GlaxoSmithKline Biological's (GSK's) RTS,S, the most advanced malaria vaccine candidate. RTS,S, is in phase III trials in Africa, the region of the world with the most deaths from malaria. It is being developed in collaboration with the PATH Malaria Vaccine Initiative (MVI) and researchers across Africa [83]. The vaccine is being evaluated in two age groups: infants from six weeks administered at the same visits as routine EPI vaccines; and older than traditional EPI ages and up to 17 months at first dose. Phase III data is anticipated to be available in three batches in late 2011, late 2012, and 2014 (Available at: http://malariavaccine.org/from-the-field.php; Accessed: September 1, 2011). During 2007-08, MVI researched the roles, decisions, timing, and interactions of international organizations which may impact the transition of RTS,S from R&D to implementation in developing countries. The work was carried out in order to help accelerate, strengthen and increase the efficiency of those processes.

METHODS

The research was conducted primarily using literature review and semi-structured interviews. The data was analyzed using Gantt charts to visualize the relationships and sequences of actions and decisions for each organization.

An initial list of international organizations, or groups within those organizations, whose decisions might impact the transition of RTS,S from R&D to country implementation was developed and categorized. The list and categorization were based upon the literature and informal interviews with experts with experience from Hib, rotavirus, pneumococcal, and other vaccines, as well as ACTs and intermittent presumptive treatment of infants (IPTi) for malaria. Websites and publications describing the mandates of each organization were reviewed for formal descriptions of their roles which would have implications for RTS,S, and compiled into a draft working document.

Eighteen semi-structured interviews were conducted with representatives of, or key informants about, the organizations and groups identified. The interviewees were informed about the latest progress in the development of malaria vaccines, and were asked about:

- Their organization's/group's potential role(s) in regards to international decisions for malaria vaccines.
- When their role(s) takes place.
- What organizations/groups they rely on prior to being able to fulfill their role(s) (i.e. who should take a decision before they can begin).
- What organizations/groups rely on them in order to fulfill its role(s) (i.e. who comes after them).
- What other organizations/groups that should be contacted as part of this research.

Based on the interview data, a decision pathway (i.e. Gantt chart) was created in Microsoft Project of the international decisions related to RTS,S. It mapped the major activities leading up to and culminating in decisions by each organization, and the dependencies between the organizations and individual decisions. Activities and decisions on the pathway were categorized as related to policy, regulation, financing, manufacturing, and procurement. The decision pathway was constructed relative to the two most fundamental milestones that determine if a vaccine will be safe, of assured quality and efficacious: the estimated timings of phase III trial data and regulatory approval.

The interviews and decision pathway were used to expand the draft working document noted above so that it would describe what role each organization was thought to play in regards to RTS,S and to summarize the relevant processes within the organizations. Interviewees were given an opportunity to review the decision pathway and draft working document for accuracy.

A meeting was hosted by WHO to get collective feedback from the organizations to the decision pathway. Six of the organizations playing critical roles attended. One organization, WHO, had participants from five discrete departments or areas of expertise. The European Medicine's Agency (EMA) was the only organization which did not attend, although other regulatory experts participated as key informants. The group spent a half day discussing potential roles and responsibilities, and the implications of and revisions to the pathway. Revisions were subsequently made and electronically shared with participants for feedback.

RESULTS

ORGANIZATIONS, OR GROUPS WITHIN ORGANIZATIONS, WITH ROLES IN CRITICAL DECISIONS FOR RTS,S

All seven organizations identified at the outset of the research were found to be responsible for critical decisions related to RTS,S (Table 12 and Table 13). Within one of these organizations, WHO, there were eight offices, departments or groups contributing to decisions, as well as a number of additional sub-groups.

POLICY

Formal policy positions of WHO were found to be issued by the Director General, drawing upon advice from WHO departments and regional offices, and recommendations from their respective external advisory committees. RBM was found to assist partner organizations to align malaria-related policies.

WHO HEADQUARTERS - MALARIA

The malaria department, the Global Malaria Programme (GMP), sought external advice and malaria-related recommendations from the Strategic and Technical Advisory Group (STAG), as well as more narrowly mandated Technical Expert Groups (TEGs).

WHO HEADQUARTERS - IMMUNIZATION

The Immunization Vaccines and Biologicals (IVB) department, sought external advice and immunization-related recommendations from the Strategic Advisory Group of Experts (SAGE). A number of more narrowly mandated groups reported to the SAGE, including one for early malaria vaccine R&D (MALVAC) and one for quantitative research (QUIVER). IVB also convened the Expert Committee on Biological Standardization (ECBS) which established production standards for vaccines referenced by companies and which may be used by regulators when licensing vaccines. The department was home to an advisory body which evaluated the safety of vaccines, the Global Advisory Committee on Vaccine Safety (GACVS). The Quality Safety and Standards unit within IVB pre-qualified vaccines, determining their appropriateness for purchase by other United Nations (UN) agencies.

WHO REGIONAL OFFICE FOR AFRICA (AFRO)

AFRO informed global policies, and played a key role supporting implementation of policies by countries. The African Advisory Committee on Malaria and the Task Force on Immunization were external groups which informed and made recommendations for AFRO's work.

JOINT TECHNICAL EXPERT GROUP (JTEG)

WHO's GMP, IVB, and AFRO came to recognize, partially supported by this research, that there was no clear pathway to establish WHO recommendations for implementation of a malaria vaccine. The challenge was that each group had discrete

advisory processes and no clear means to bring them together. Therefore in 2009 WHO established a JTEG to advise all parts of the organization, with terms of reference approved by the SAGE. (Available at: http://www.who.int/vaccine_research/jteg/en/index.html; Accessed: June 7, 2011)

REGULATORY

The European Medicines Agency was anticipated to evaluate the safety, quality and efficacy of RTS,S as the primary regulatory reviewer, given that it was manufactured in Belgium. RTS,S was planned to be submitted to the EMA under Article 58, a regulatory pathway allowing EMA, at WHO's request, to provide an approval similar to licensure but for an intervention to be used outside of Europe [9].

FINANCING

Both the GFATM and GAVI were identified as possible financing organizations for RTS,S, although with different internal procedures and requirements of countries. There was no established process to resolve if one organization was better placed to support the vaccine, or if both should provide support. A number of differences would need to be resolved if both were to eventually provide support. For example, it was noted that the GFATM supported a larger number of countries, including wealthier, middle-income countries, than GAVI. They had different means of determining which interventions countries may request. GFATM could begin to support interventions requested by countries and recommended by WHO, while GAVI required that a WHO recommendation and a formal investment case be approved by its board prior to allowing countries to request support for a vaccine. GAVI also required countries to achieve certain levels of coverage with existing vaccines prior to supporting introduction of new vaccines. Finally, GFATM and GAVI had different approaches and requirements for the amount of co-financing countries must provide from national budgets.

MANUFACTURING & PROCUREMENT

GSK's decisions were found to relate primarily to supply, regulatory, pricing, and procurement strategies. UNICEF's decisions related primarily to forecasting, pricing, procurement, and shipping. RBM, GAVI, GFATM and others also contributed to forecasting, and similar activities helping to match supply and demand.

TABLE 12. WHO AND RBM CONTRIBUTIONS TO DECISIONS IMPACTING RTS,S' TRANSITION FROM R&D TO IMPLEMENTATION.

Organization	Department/group (if relevant)	Decisions
WHO	Global Malaria Programme	Guidelines on implementation and integration with other malaria prevention and treatment activities, in the context of malaria epidemiology
	Strategic and Technical Advisory Group for malaria, supported by Joint Technical Expert Group	Recommendations to WHO from independent malaria experts, contributing to an organization-wide policy
	Immunization Vaccines and Biologicals (IVB) Department	Guidelines on implementation and integration with other vaccines
	Strategic Advisory Group of Experts for immunization, supported by Joint Technical Expert Group	Recommendations to WHO from independent immunization experts, contributing to an organization-wide policy
	Quality Safety and Standards Unit in IVB	Determination of vaccine suitability for UN purchase (pre-qualification)
	Expert Committee on Biological Standardization, coordinated by IVB	Guidelines on vaccine production
	Global Advisory Committee on Vaccine Safety, coordinated by IVB	Determination of safety
	African Regional Office, Brazzaville (AFRO), supported by the Joint Technical Expert Group	Guidelines on implementation for African countries, in coordination with GMP and IVB; contributing to an organization-wide policy
RBM		Support harmonized policies across international organizations

TABLE 13. ADDITIONAL INTERNATIONAL ORGANIZATIONS CONTRIBUTING TO DECISIONS IMPACTING RTS,S' TRANSITION FROM R&D TO IMPLEMENTATION.

Function	Organization	Decisions
Regulatory	European Medicines Agency (EMA)	Determination of vaccine quality, efficacy and if there are safety concerns
Financing	GFATM	Policy to financially subsidize vaccine procurement and implementation costs
	GAVI	Policy to financially subsidize vaccine procurement and implementation costs
Manufacturing	GlaxoSmithKline Biologicals (GSK)	Determination of supply matched with demand; Determination of public sector price with procurement and financing organizations; Recommendation of post approval activities to EMA (Risk Management Plan)
Procurement	UNICEF Supply Division	Policy to procure vaccine and ensure shipment; Determination of price with funders and GSK

TIMING AND SEQUENCE OF SPECIFIC ROLES OF ORGANIZATIONS FOR RTS,S

The pathway synthesized how and when the role of each organization contributed to international decisions, and how they related to those of other organizations. The timing of activities and decisions were established relative to the anticipated timings of phase III data and EMA regulatory approval, summarized in Figure 11. The findings facilitated the identification of and planning for critical actions and decisions, and supported the efforts of international organization to strengthen and accelerate decision-processes.

The pathway assisted organizations to anticipate and schedule work that needed to be done in preparation for, or prior to, the availability of phase III data (Table 14 and Table 15). Although this R&D period will not be complete until approximately 2014/15, there are preliminary indications of results supported by or arising from the decision pathway and associated research. For WHO it assisted in highlighting the need to establish a means to coordinate across the malaria and immunization decision processes, a need which WHO ultimately decided to address by the establishment of the JTEG noted above. It also highlighted WHO's contributions to the design of the clinical trial program, such as the importance of WHO identifying in advance the data its advisory bodies would need for eventual policy decisions. It led MVI to conduct, with input from WHO staff, an analysis of past WHO policy decisions and supporting data, in order to project what data might be needed for a policy decision on a malaria

vaccine [95]. MVI was invited to present the outcomes of the analysis to a WHO meeting. The pathway highlighted the timing of ECBS work on production standards so that they would be completed prior to the anticipated date of regulatory submission. It allowed GACVS to anticipate and schedule reviews of safety data from the trial.

A particularly striking result of WHO's preparatory work, such as described above, and supported by the decision pathway, has been reflected in public statements from WHO. It has indicated that if all goes well in the phase III trial, a policy recommendation for RTS,S is possible as early as 2015, only one year after trial completion, paving the way for implementation in countries through their expanded programs on immunization (EPI) (Available at: http://www.who.int/vaccine_research/diseases/malaria/vaccine_candidate_policy/en/index.html; Accessed September 1, 2011).

The pathway helped highlight the potential value of releasing the phase III data in three batches to regulators and WHO pre-qualification staff. Doing so would allow the organizations months or years to review elements of the dossier which draw upon data that is unlikely to change, such as that from phase II studies or about the vaccine's chemistry. The review could take place while the phase III trial continues, potentially allowing the final review by regulators and WHO to be done in months instead of years since it would only need to consider the new data.

The decision pathway also led to a series of analyses and preliminary discussions between technical staff of GAVI and the GFATM related to possible means of future collaboration between the organizations in relation to funding a malaria vaccine. The pathway identified the need for early demand forecasting to inform manufacturing, financing and procurement plans. It highlighted that the public sector needed to provide input to GSK on vaccine characteristics, such as the formulation, presentation and packaging of RTS,S in order for the vaccine to be acceptable and integrate smoothly within developing country health systems. A report of public sector preferences for vaccine characteristics was developed jointly with WHO and the conclusions were endorsed by senior WHO immunization staff [84]. The report was provided to GSK to inform its planning.

The pathway also demonstrated the potential implications for decisions in future stages of the transition from R&D to implementation by looking forward to the period between phase III data becoming available and EMA regulatory approval. The pathway highlighted that international organizations would begin to consider the data and prepare for possible decisions. WHO advisory bodies would intensify their consideration of RTS,S including beginning to weigh implementation options and guidance to countries but without issuing implementation recommendations. It was found that ECBS guidelines needed to be issued, and GACVS would review safety data. Discussions between GSK and financing and procuring agencies would intensify. GSK

would submit regulatory dossiers to African authorities for review in parallel with EMA review.

After approximately 2015 when the final EMA regulatory approval is anticipated, RTS,S would be the first malaria vaccine to be of assured quality, safety, and efficacy. WHO could pre-qualify RTS,S in parallel with, or immediately following, EMA approval. After EMA approval it would be ethical for countries to move concretely towards decisions on use, and subsequent implementation. The pathway highlighted that WHO's advisory committees could then finalize their recommendations. When integrated with input from its departments and AFRO, WHO would issue a policy position. The recommendations and WHO's policy positions would assist RBM to coordinate partner policies regarding support for implementation by countries. WHO's decision would also inform final decisions by funding and procuring bodies, leading them to conclude supply and pricing negotiations with GSK. GAVI and the GFATM could begin to accept proposals from countries for support. GSK would continue to seek approval from individual African regulatory authorities and need to implement its post-approval commitments as outlined in an agreed Risk Management Plan with the EMA.

FIGURE 11. FLOW-CHART SUMMARIZING MAJOR DECISIONS AND ACTIONS BY INTERNATIONAL ORGANIZATIONS FOR RTS,S'S TRANSITION FROM R&D TO IMPLEMENTATION.
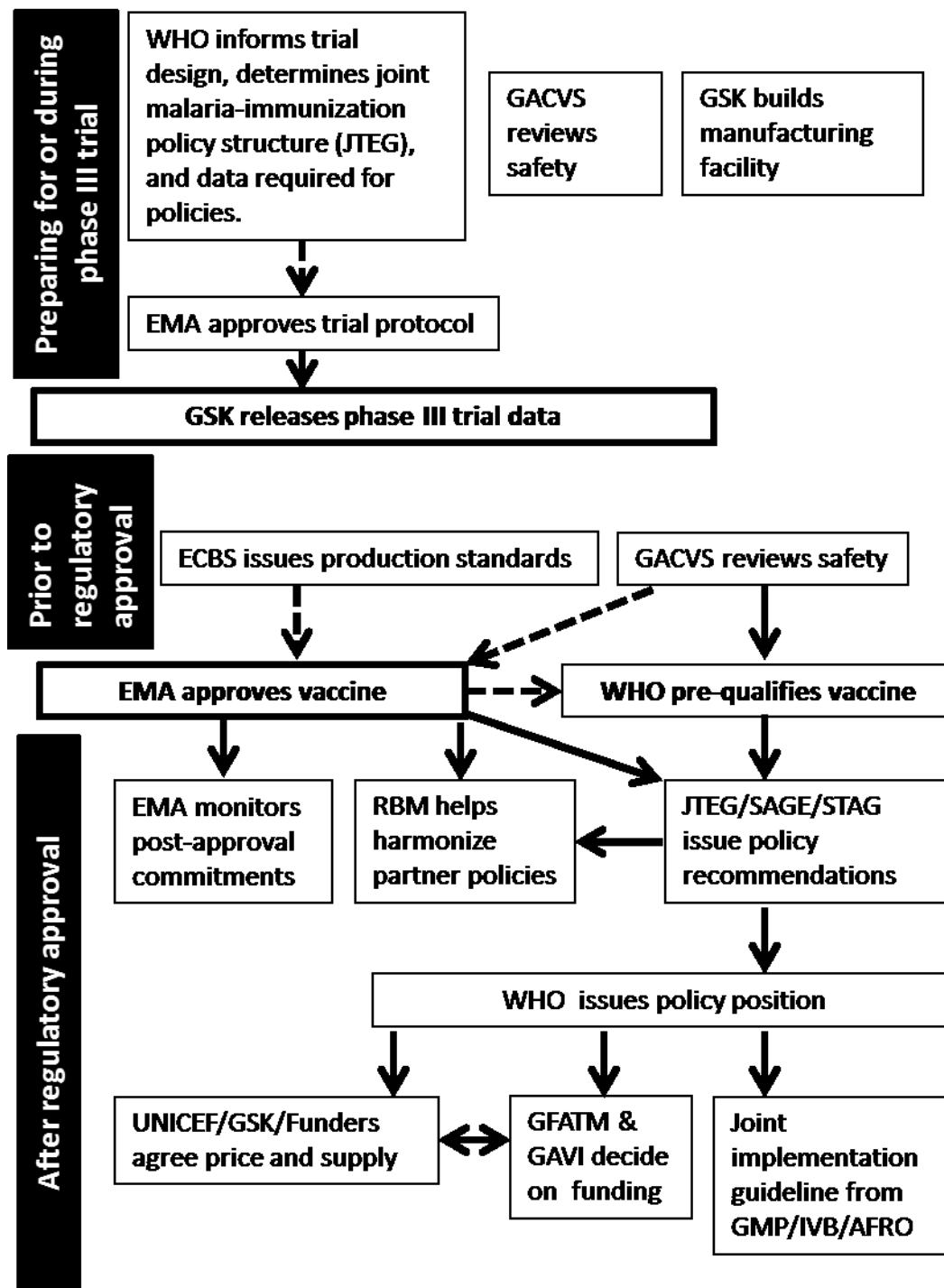
Legend

The vertical text in black boxes indicates major time periods from late R&D through regulatory approval. Bold outlined boxes determine if RTS,S can progress to the next period. Solid arrows reflect an essential sequence in decisions, while dotted arrows reflect informal or optional sequences.

TABLE 14. SUMMARY OF WHO AND RBM ROLES RELATIVE TO R&D TIMEPOINTS.

Organization	Department/group	Prior to phase 3 data	Prior to regulatory approval	After regulatory approval	Approximate time required
WHO	Global Malaria Programme	Inform trial design; Anticipate ancillary data	Prepare for policy process and guidelines	Propose policy position; Issue guidelines	Ongoing
	STAG (Malaria advisory body; supported by the JTEG)	Monitor progress	Monitor progress	Recommend policy position	Every 1-3 years
	Immunization Vaccines & Biologicals Department	Inform trial design; Anticipate ancillary data	Prepare for policy process and guidelines	Propose policy position; Issue guidelines	Ongoing
	SAGE (Immunization advisory body; supported by the JTEG)	Monitor progress	Monitor progress	Recommend policy position	Every 1-3 years
	Quality Safety & Standards Unit	Inform regulatory considerations	Review for pre-qualification	Pre-qualify the vaccine	1-2 years
	Expert Committee on Biological Standarization	Develop standards	Issue standards	N/A	2 years
	Global Advisory Committee on Vaccine Safety	Review safety data	Review safety data	Review safety data	Every 1-3 years
	AFRO (Supported by the JTEG)	Inform trial design; Anticipate ancillary data	Prepare for policy process and guidelines	Propose policy position; Issue guidelines	Ongoing
RBM		Monitor progress	Prepare for policy process	Harmonize decisions of partners	Ongoing

TABLE 15. SUMMARY OF ROLES OF ADDITIONAL INTERNATIONAL ORGANIZATIONS RELATIVE TO R&D TIMEPOINTS.

Function	Organization	Prior to phase 3 data	Prior to regulatory approval	After regulatory approval	Approximate time required
Regulatory	European Medicines Agency	Approve protocol and monitor trial	Review data for safety, quality and efficacy	Monitor post-approval commitments	Ongoing
Financing	GFATM	Monitor progress (Secretariat)	Monitor progress; Potentially indicate future support	Accept country proposals, after WHO recommendation	Every 1-2 years
	GAVI	Monitor progress (Secretariat)	Monitor progress; Potentially indicate future support	Accept country proposals, after WHO recommendation	Every 1-2 years
Manufacturing	Glaxo-SmithKline	Inform other processes; Align intervention with DC needs; Generate demand forecasts; Plan manufacturing; Build facility	Inform other processes; Generate demand forecasts; Negotiate price; Propose post-approval commitments	Inform other processes; Generate demand forecasts; Agree price; Implement post-approval commitments	Ongoing
Procurement	UNICEF Supply Division	Monitor progress; Inform demand forecasts	Generate demand forecasts; Negotiate price	Generate demand forecasts; Agree price; Procure	Every 1-2 years

DISCUSSION

The interactions and decision-making processes of international organizations are complex. There is no "how-to manual" with instructions for developers of new health interventions. In the case of RTS,S, which spanned two distinct domains of expertise— vaccines and malaria—it was not clear who would coordinate the process to achieve technical consensus leading to recommendations for countries, who would pay for the vaccine, who would procure it, and who would ensure that these steps were coordinated with the roles of regulators and the manufacturer.

A collaborative research approach led to unique insights into how a malaria vaccine might progress from R&D, through activities and decisions by international organizations, towards being ready for decisions on use by countries and potentially implementation through national health systems. Without forward planning, and associated predictable and transparent processes, interventions will be delayed in getting to those in need in developing countries by most of, or more than, a decade. It also means that if millions, or tens of millions of dollars, are invested in innovative, accelerated clinical trial designs, the value of these funds could be lost because of delays by international organizations.

OPPORTUNITIES ARISING FROM A DECISION PATHWAY

The future will only get more complex for international organizations. There are a growing number of new health interventions on the horizon due to the significant funds now flowing into research and development (R&D) that targets diseases prevalent in developing countries [60]. Those developing new interventions can collaborate with international organizations to anticipate decisions and their associated actions. Without such collaboration and planning, international organizations could have a negative impact on national decision processes and implementation, decreasing the public health impact of new interventions. They may take decisions based upon incomplete information, become bottlenecks due to unclear decisions or be unable to make a timely decision due to a lack of essential evidence.

Completing phase II and III trials can easily span 5-10 years for a new intervention, or more as will be the case with RTS,S. During such a length of time, there will be many staff transitions in organizations. Such timelines support the importance of strategies which strengthen the continuity and predictability of processes over time. This research reportedly helped improve the understanding for other organizations, and WHO staff, of the multiple WHO entities. The pathway helped stimulate questions about the relative roles of WHO's immunization and malaria departments and AFRO. WHO created a new advisory body, the JTEG, designed from its inception with collaboration from all three, relevant parts of WHO. The pathway identified questions regarding the status of the malaria program's advisory body, the STAG, given that it

had not operated regularly in recent years, and how it would relate to the highly active SAGE for immunization. It challenged GAVI and the GFATM to begin discussing similarities and differences in their systems and requirements of countries. For example GAVI primarily supports group procurement through UNICEF, while GFATM has traditionally encouraged countries to procure interventions independently.

Part of planning is identifying the relationships between activities of different organizations, and when each needs to begin in order for other activities and decisions to progress efficiently. This can lead to strategies as simple as determining if the release of scientific data can be coordinated with calendars of advisory bodies which may only meet once or twice per year. It can also assist in ensuring that those advisory bodies receive sufficient background data well in advance to allow decisions to be taken when convened. This is not to suggest that corners be cut, but instead that coordination and planning leading to predictability and transparency will make processes more efficient and faster.

Decisions which are foreseen in advance also can be stronger or more conclusive. They can draw upon appropriate evidence created for those decisions. This suggests that, when possible, data requirements should be stipulated by agencies in sufficient time for the design of phase II and III trials. It also suggests that researchers seek input from international organizations, particularly WHO, on trial designs, as was done extensively for RTS,S.

FURTHER ANALYSES BUILDING UPON THE PATHWAY

MVI built upon the decision pathway to independently analyze and anticipate ways in which results from the phase III trial might impact the pathway. It identified potential scenarios related to endpoints being studied in the phase III clinical trial which could impact decisions of one or more international organizations. Possible results for the following trial endpoints were identified:

- Safety;
- Efficacy against a) first or only episode of uncomplicated, clinical disease, b) multiple episodes of uncomplicated, clinical disease, c) severe disease, and d) mortality;
- Duration of efficacy;
- Additional efficacy from a booster dose administered 18 months after the primary vaccination;
- Efficacy in different transmission settings; and
- Results in each of the two age groups in phase III.

A series of scenarios were generated by creating tables with the results of one endpoint on each axis (e.g. safety versus efficacy against severe disease). Over 500 scenarios of trial results were generated and evaluated against pre-determined criteria

(Table 16). A key interpretation was that any scenario with a concerning safety imbalance in RTS,S vaccinees over the control group, regardless of the efficacy, may lead to meetings with key stakeholders to discuss overall implications for study continuation.

TABLE 16. FIVE POSSIBLE RESULTS FOR EACH SCENARIO ANALYZED, WITH POSSIBLE IMPLICATIONS.

Score	Category of result	Possible implications
1	Exceptional	Potential change of course; evaluate options for acceleration. Meet with key stakeholders to discuss overall implications
2	Equivalent to phase II	Proceed with current plans
3	Worse than phase II on a key variable	Cautious planning for implementation; ensure strong contingency plans in place
4	Slightly worse than phase II on multiple variables	Decision based upon final study data and/or booster dose before moving to implementation planning; look for site- or transmission setting-specific trends
5	Significantly worse than expected	Meet with key stakeholders to discuss overall implications

LIMITATIONS AND CHALLENGES

The research had a number of limitations. The decision pathway was premised upon organizations making largely supportive decisions; i.e. planning for success. Initial decisions can be qualified or limited; potentially leading to more comprehensive decisions after additional data is available. This was the case with WHO's initial decisions regarding ACTs and Hib vaccine, which were followed by more comprehensive decisions recommending implementation of the interventions some years later. The analysis of scenarios by MVI, described above, was one strategy to anticipate the implications of different trial data on organizations' decisions. The phase III trial design also seeks to increase the likelihood of comprehensive recommendations. The trial includes eleven sites in settings with different malaria epidemiology in order to be able to provide data leading to policy recommendations across sub-Saharan Africa. If RTS,S is safe and efficacious, decisions on trials in other parts of the world would need to follow.

The research was limited to roles and decisions (e.g. policies, recommendations, and guidelines) of international organizations, while use of an intervention by an individual person in a developing country requires many additional steps. It excluded the decisions of international organizations about the technical assistance they might provide to support regulatory review and/or implementation by countries. MVI and WHO worked separately with African countries on regulatory strengthening through the African Vaccine Regulatory Forum (AVAREF). It intentionally excluded decision-making of individual countries, and communities and individuals as it was felt those groups were best addressed with different methodologies. MVI, WHO, and partners worked with countries to anticipate the processes and data needed for national decisions on malaria vaccines, and MVI worked with African collaborators on community and individual acceptability of malaria vaccines [81,96]. These activities have been mutually reinforcing. For example countries identified that they wanted to give input into decisions on characteristics of a malaria vaccine to ensure they would be programmatically suitable for developing country health systems and acceptable to end-users. Including country input into intervention characteristics was identified in parallel as an activity on the decision pathway as contributing to policy decisions, and addressed as noted above.

It is unclear what organization is best placed to implement, or serve as the coordinator for such research. In this situation, MVI foresaw the need and supported it financially and managerially. This role was consistent with its mandate as a product-development partnership (PDP) building collaborations between non-profit and for-profit organizations. Universities and research institutes in the developed or developing countries, WHO, and others could all implement such research. It is most likely important for WHO to be deeply involved, regardless of who leads it. MVI did not explicitly show up on the pathway. MVI's main responsibilities related to the clinical development plan and supportive coordination, while international decisions were seen as the role for WHO and others. MVI did help address specific research questions arising from the pathway, such as analyzing historical data required for WHO decisions, as described previously.

The use and maintenance of a decision pathway is not without challenges. After completing the first decision pathway, maintenance may be complex and time consuming as R&D and organizational timelines shift. It can also be difficult to manage confidential and non-confidential information if the pathway is widely shared. In addition, some may see it as a workplan, particularly if developed with target dates for activities and decisions. However it is probably better seen as a strategic plan or roadmap while an intervention is some years before regulatory approval. It can trigger someone to enquire if an activity should still be done in a given timeframe and show up on an organization's internal workplan, as opposed to being a list of deliverables at

the end of a year. It can also get more concrete and precise in each iteration as an intervention progresses through clinical development.

A new health intervention, particularly one that is on track to be the first of its kind, requires an at-risk commitment of time and resources from international organizations; an intervention can fail at any point. This risk needs to be balanced against the delays documented previously from not acting. Activities need to be carefully paced to match scientific milestones. Planning should not get ahead of scientific progress, but also not fall behind as appears to have happened for other interventions.

OPPORTUNITIES FOR INNOVATION AND FURTHER ACCELERATION

The RTS,S decision pathway helped inform, and was informed by, an innovative phase III design. Data will be available in a series of three batches, over approximately four years. This design was intended to support faster, more conclusive and more efficient decision processes by making as much data available as soon as possible. It allows regulators and other international organizations more time to consider data and prepare for their decisions, strengthening predictability and planning. It should further accelerate decisions once the final data is released, as WHO has suggested is possible relative to the years needed for past interventions.

The release of trial data in three batches raises an intriguing strategy for acceleration. It raises the possibility that some organizations might consider making preliminary decisions after the first or second batch of data. For example, GAVI and/or GFATM could decide in late 2012 or 2013 that if the final data were to be consistent with or better than the initial batches and RTS,S were to be approved by regulators and recommended by WHO, then they would anticipate subsidizing its use in countries from 2015. Such a financing indication might impact organizations across the decision pathway. Perhaps most importantly, it could strengthen GAVI and/or GFATM given that they may require multiple years of advance planning to generate funds for future commitments.

CONCLUSIONS

Research leading to the creation of the decision pathway reported in this paper should contribute to faster, more conclusive and more efficient decisions by international organizations regarding the potential implementation of what is anticipated to be the first malaria vaccine. It should lead to decisions in months or a few years, as opposed to years or decades. The indications to date suggest that such promises can be realized. Five years in advance of the end of the RTS,S phase III trial, WHO has already indicated it may be able to make a policy recommendation within a year of trial data being available. Such an indication is unprecedented from WHO, to the author's knowledge. This also reinforces the vision arising from the collaboration with countries

described above, that each country will be in a position to take a decision to use, or not, RTS,S within one to three years of its availability.

A full measurement of the impact of the decision pathway work will only become feasible from 2015 and beyond as final decisions by international organizations and countries are made on RTS,S. But the evidence and experience to date gives confidence that such an approach will have a positive impact, leading to more timely decisions, early implementation of interventions, and additional lives saved. And as such, it should be considered for other new interventions that are being developed.

CHAPTER 5. ADOPTION OF NEW HEALTH PRODUCTS IN LOW AND MIDDLE INCOME SETTINGS: HOW PRODUCT DEVELOPMENT PARTNERSHIPS CAN SUPPORT COUNTRY DECISION MAKING

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ABSTRACT

When a new health product becomes available, countries have a choice to adopt the product into their national health systems or to pursue an alternate strategy to address the public health problem. Here, we describe the role for product development partnerships (PDPs) in supporting this decision-making process. PDPs are focused on developing new products to respond to health problems prevalent in low and middle income settings. The impact of these products within public sector health systems can only be realized after a country policy process. PDPs may be the organizations most familiar with the evidence which assists decision making, and this generally translates into involvement in international policy development, but PDPs have limited reach into endemic countries. In a few individual countries, there may be more extensive involvement in tracking adoption activities and generating local evidence. This local PDP involvement begins with geographical prioritization based on disease burden, relationships established during clinical trials, PDP in-country resources, and other factors. Strategies adopted by PDPs to establish a presence in endemic countries vary from the opening of country offices to engagement of part-time consultants or with long-term or ad hoc committees. Once a PDP commits to support country decision making, the approaches vary, but include country consultations, regional meetings, formation of regional, product-specific committees, support of in-country advocates, development of decision-making frameworks, provision of technical assistance to aid therapeutic or diagnostic guideline revision, and conduct of stakeholder and Phase 4 studies. To reach large numbers of countries, the formation of partnerships, particularly with WHO, are essential. At this early stage, impact data are limited. But available evidence suggests PDPs can and do play an important catalytic role in their support of country decision making in a number of target countries.

INTRODUCTION

For health innovations to have their full impact, they must reach those in need. This job of achieving access is a multifaceted endeavor[132–134] requiring consideration of issues such as financing [135], manufacturing [136], pricing [137], international policies [138], regulatory approval [139], translational research [140], end-user acceptance [141] and a strategic communication approach to decision makers [142]. Here we consider country decision making – the process by which a country weighs evidence and decides whether or not to adopt a new product into its national guidelines and practice [143,144]. Such policy decisions are necessary, but not sufficient, for subsequent implementation and public health impact [145], as has been shown by the delays from decision to implementation of artemisinin-based combination therapies for malaria treatment [146].

Although the policy change process is ultimately controlled by the country, in low and middle income settings in particular there are many other actors who provide input and can strengthen local decision making [147]. One such set of actors is the product development partnerships (PDPs). These not-for-profit organizations were formed because commercial incentives had proven insufficient to draw for-profit companies into certain important areas, such as drug development for tuberculosis (TB), malaria, sleeping sickness and visceral leishmaniasis, vaccine development for HIV, TB, malaria, dengue fever, meningococcal meningitis and pneumonia, microbicide development for HIV, and insecticide development for vector-borne diseases [148].

Over the last several years, these not-for-profit organizations have catalyzed the production of an increasing number of health products designed specifically for use in low and middle income settings, such as drugs for malaria and trypanosomiasis and diagnostics for TB. Although PDPs have been focused primarily on product development, they share a vision of realizing the public health impact promised by new products. PDPs have generally translated this vision into catalytic support both for global policy change and, in a limited number of countries, for activities which could lead to decisions on use, and therefore support uptake and introduction of the resulting products. Such activities are implemented in partnership with endemic countries and other organizations.

Here, we explore how the PDPs can assist in the country decision making aspect of product introduction. Although we recognize the leadership of other actors including, most notably, country stakeholders themselves, our primary focus for this article is on the role of PDPs. Certain other organizations, such as the Hib Initiative, have focused on product introduction specifically, rather than on product development; these are considered more briefly for relevant lessons. After defining country decision making, we investigate the various roles for PDPs, how those roles are prioritized geographically, the partnerships required, and the specific approaches used by a

number of PDPs. This paper provides a set of baseline insights into support by PDPs for country decision-making. It will not define exactly what should be done in each situation, but provides extensive, concrete examples of what has been done and analyses why these approaches were chosen. It also summarizes the initial, as yet limited, data evaluating the impact of such work by PDPs. Although the role of PDPs in supporting country decision making is still evolving, we find some themes that we believe will be generally applicable for future efforts.

HOW PDPs FIT INTO COUNTRY DECISION MAKING

CORE AND VARIABLE CONTRIBUTIONS BY PDPs

A definition of country decision making will be a useful starting point, before discussing a possible PDP role. Previously, country decision-making on new health interventions has been investigated from a variety of perspectives. This has resulted in decision-making frameworks [145,149–152], guidance on introduction [134,153], and descriptions of the types of evidence considered [143,154,155] or the methods [156] or processes [157] used for considering them. Multi-variate analyses have suggested which interventions are related to faster uptake [158]. Although some authors have described supportive roles played by outside actors [147,151,152], in general the possible mechanisms for PDPs to support country decision making remain largely undocumented.

Decision-making processes occur within the unique socio-political and economic context of an individual country, whereas a multi-country analysis such as this one must rely instead on broad process categories (see below). The relative importance of other elements influencing decision-making, such as media pressure, corruption and politics, may vary greatly from country to country [159], and therefore are not addressed in detail here. Furthermore, we acknowledge that in any political system the use of evidence-based decision making is a goal, and not always a reality.

For the purposes of this paper, we have adopted a simplified framework, assuming country decision making requires background information (to elicit problem identification [160]), evidence to feed into decision making, and a process to consider that evidence. Within the information and evidence categories are many sub-categories to be considered by country stakeholders, including public health priority, disease burden, efficacy, quality, safety, comparison with other available interventions, presentation, supply (procurement and distribution), financial impact, and programmatic strength [153]. The process category includes, critically, the identification and convening of a sufficiently broad group of stakeholders who have the mandate and resources to identify and review evidence; this group can be under the aegis of the government (a specific disease control program, the broader Ministry of Health, the Ministry of Finance, a specific agency for technical assessment, or some

combination of these agencies) or independent of but mandated by the government [144,147]. The final result should be a policy conclusion and, if the decision is supportive, implementation. At the center of this process is the country itself, supported by a range of local stakeholders and partner organizations.

As noted by Frost and Reich, "the production of acceptance [is] an active process of social construction, not a passive process of waiting for various experts to agree on key elements related to the use of a health technology" [132]. If this active process is missing or under-resourced, effective country decision making is jeopardized. Indeed, many challenges have arisen during country decision making. For example, malaria regimen change in Kenya was delayed due to a lack of national and international standards (e.g., varied criteria for chloroquine sensitivity and efficacy markers), insufficient evidence (of side-effect incidence and the true costs of new drug implementation), no national compendium of relevant data, uncoordinated local research studies that could not be compared to each other, and ineffective mechanisms for communicating research evidence to sub-national stakeholders. This resulted in national guideline change happening 6 years after a call for evidence review and 14 years after the first local data on resistance [161], with the consequence that millions of patients were treated with ineffective regimens. In the area of TB regimens, the current data available (e.g., on drug resistance patterns) are useful for programmatic monitoring of current TB treatment but leave gaps for decision-making around future regimen changes [162]. On the process side, there were delays in another malaria regimen change due to insufficiently broad participation in decision making (e.g., exclusion of local manufacturers, the Ministry of Finance, and sub-national implementers) [163]. Similarly, the change from 8- to 6-month TB regimens was delayed in high burden countries not only by insufficient evidence but also, in some countries, by unclear or non-existent procedures or bodies to consider regimen change [143].

Table 17 presents examples of how PDPs can contribute to the core activities of country decision making. These contributions build on the familiarity of PDPs with the research programs and evidence base surrounding a particular intervention.

There are a variety of additional PDP activities that can support country decision making but are only important under certain circumstances (Table 17). Such PDP access strategies and activities are project specific and focus on identified gaps: an awareness gap requires burden of disease studies or advocacy; whereas an evidence gap may require a cost-effectiveness study or operations research. Some of these activities require substantially more investment by a PDP. Furthermore, it cannot be assumed that global activities will reach policy makers in each country.

TABLE 17. EXAMPLES OF COUNTRY DECISION MAKING ACTIVITIES.

Country activity	PDP support role
Background information	
• Define national health priorities. • Obtain information on the future products that are likely to become available.	• Conduct research to understand priority of disease area, generally, and likely desire for proposed product, specifically. • Disseminate product and pipeline information.
Process and people	
• Ensure a decision-making body (or person) is identified, active, and has members empowered to make decisions based upon available evidence. • Define a clear, step-wise and timely process for country decision-making in general (in a particular disease or intervention area) and then for adoption of new products specifically.	• Facilitate awareness raising and transparent information sharing among appropriate stakeholders.
Evidence base	
• Define the specific evidence base required for decision making, including local data requirements. • Make plans to generate this required local evidence base.	• Determine what information is expected to be needed for national decision-making (e.g., what efficacy endpoints). • Integrate consideration of these information needs into R&D activities. This affects, for example, clinical trial planning, development of regulatory strategies, and post-introduction strategies to monitor safety and impact. • Assist countries to define data needs and gaps, including clarifying if the information (e.g., on program and budget impact) should be generated in a country or internationally. • Gather and disseminate a standard evidence package informing decision making, or see that others do so. The data should come from a source or partnership that is credible to countries. • Train key personnel to respond to questions about the data or lack thereof. • Address concerns that are common across countries (e.g., price, cost-effectiveness, ease of use, source and geography of manufacturing, and impact on supply chain and existing program delivery).

A number of these PDP activities are focused on capacity building for decision making in general, including the capacity for a country to decide not to adopt a PDP-related intervention. For example, a PDP can help to catalyze the establishment of decision-making structures or processes by identifying current gaps and highlighting future decision-making needs [164]. These capacity building efforts are likely to be insufficient for health systems in general, however, given the limited geographic and product foci of PDPs, and the lack of mandate from the PDPs' donors for open-ended capacity building. For example, the categories in Table 17 and Table 18, and the case studies provided below, are based on the PDPs' analyses of the bottlenecks within a specific modality and disease area. Thus, the activity of other organizations to implement broader capacity building efforts, such as the establishment of National Immunization Technical Advisory Groups (NITAGs) [165], will remain critical and can be complemented by the work of PDPs.

Experience from the Hib Initiative suggests that generating data, and bringing the data to the attention of country stakeholders, may be an important part of catalyzing decision-making [142]. PDPs are one contributor to this activity, as part of the complex decision-making environment described previously. Each of the many stakeholders will bring some perspective, history, and perceived conflict. For PDPs, they may be seen as contributing a product or technology-biased emphasis. In contrast, a local researcher may emphasize the need for additional studies for which he or she would be funded, or a government official may be under pressure from a politician. It is critical to note that PDPs, to the authors' knowledge, do not have direct profit motives, unlike manufacturers, when supporting decision-making. The underlying rationale for PDPs is to help address a public health problem, for which the intervention arising with PDP support can be evaluated by a country for its role, or not, as one locally appropriate solution.

TABLE 18. EXAMPLES OF ADDITIONAL SUPPORT ACTIVITIES BY PDPs.

Additional support activity by PDP	Situation when needed or not needed
Background information	
Investigate disease burden, and share information with policy-makers.	Less need if disease is well characterized and recognized, and if there is already sufficient baseline surveillance to monitor impact.
Prioritize product introduction activities geographically based on disease burden, resistance patterns, or risk in specific populations.	Less relevant if disease is widespread and resistance patterns and risk factors vary little.
Process and people	
Catalyze the establishment of decision-making structures.	More need if bridging two fields in public health (e.g., immunization and malaria); less need if strong, defined structures already exist.
Support local advocacy or communications activities to inform policy makers about a disease and/or options for addressing a disease.	Depends on involvement of others who may undertake this, e.g., WHO and/or global disease partnerships. Global communications cannot be assumed to reach country level.
Evidence base	
Influence key aspects of the product development process that impact decision-making, such as pricing, supply, financing and regulatory issues, and demand estimation. Support the development and sharing of international policies, and of a post-introduction surveillance plan.	Depends on specific role of PDP in a country and in developing the product.
Generate or compile local evidence required for decision making, potentially including the funding and/or running of Phase 4 studies or operations research.	Depends on clearly defined needs from a country, whether the country can act as a regional or global source of data, and the willingness, local staffing, and available resources from PDP.
Support countries to make decisions about a complementary mix of interventions.	Only relevant if other interventions for the disease are widely used or being considered.

BASIS IN RESEARCH

Country decision-making, if it is evidence based, should be a mechanism to link research to policy. For PDPs, such a link forms most readily in countries where PDP-sponsored clinical trials are underway. In turn, a PDP's access strategy, and in particular its approach to country decision making, often emerges from engagement at country level during the clinical trial stage.

During the clinical trial approval process, PDPs naturally form links with countries via national regulatory authorities and ethics committees. But it is local researchers who generally lead the local implementation of PDP-supported clinical trials. To date, PDPs have found that it is important to proactively support a link between these local researchers and other endemic country stakeholders. This link can be through formal committees from the conception of the project and during the clinical trial phase, or via regular, informal briefings. If initiated early enough, this allows the PDP to share relevant background information with the country, increase the trust in and interpretability of resulting trial data, and ensure the product developed meets the country's needs. Local stakeholders can become partners in the project and can help to build country ownership of, and familiarity with, a product.

Once it is time for a decision, local researchers (rather than the PDPs) are best suited to present evidence to local decision makers and communicate directly with a government agency. Furthermore, it is more credible for the PDP to engage local stakeholders on technical grounds, and to provide them with the technical arguments they need so that they (rather than the PDP) can take part in the later, more political parts of the decision making process. In countries where no clinical trials are underway, the scientific and academic community is a key partner and translator of research findings in policy discussions.

MORE EXTENSIVE PDP INVOLVEMENT: THE ACCESS ARCHITECT AND LOCAL EVIDENCE

Ultimately, it is country stakeholders who drive the two critical processes: defining what evidence base is necessary for product adoption and launch; and making the decision itself. The extent to which international actors assist this process depends on the country: it occurs more in the lowest income countries and less in more technically experienced, research-intensive countries [143]. At the country level, as at the global level, the PDP can provide information on programmatic implications and a standardized public health case weighing the evidence for and against adoption. This may represent a time-limited, targeted commitment from a PDP.

Typically, however, passive provision of this information is not enough to lead to clear country decisions [132]. Financing solutions are a key additional requirement, and there is often a need for an organization specifically responsible for tracking and coordinating all of the activities needed for access, including those activities needed

before decision makers will reach an adoption decision. Others have referred to such an organization as providing the "architecture" for access [132]. PDPs may either be prominent in this role or it may be taken by others such as a local research institute, an implementing NGO, or an international partner such as the World Health Organization (WHO) (see section below on partnership).

Whichever organization is primarily responsible for supporting decision-making, they must interact extensively and directly with country stakeholders, particularly in countries identified as potential early adopters. This is not a role to be undertaken lightly.

The other, often overlapping area in which PDPs may become more heavily involved is the generation of local evidence. PDPs have an awareness of the evidence currently available, so they can help countries to determine which data need to be generated at a local level, versus provided from global studies. To support local processes, PDPs can also introduce models that can be adapted to generate local data for multiple countries (e.g., the International Vector Control Consortium (IVCC)'s monitoring tool (see below) and the PATH Malaria Vaccine Initiative's (MVI) impact and cost models). Finally, PDPs can minimize the need to generate local data by uncovering existing local data at universities (programs and WHO may be unaware of these data) and by explaining why certain data were not needed if they would not affect the final decision.

Some PDPs devote considerable resources to the generation of local data; others devote almost none. This variability is determined in part by the earlier gap analysis – local data may or may not exist or be needed. The effort to generate local data is also determined by how novel an intervention is, either within its disease arena (e.g., a malaria vaccine coming into malaria control raises a number of local data questions) or by the existence of a program with clear accountability in the country which is already collecting such data (e.g., TB programs already hold extensive data on existing treatment regimens).

When PDPs do engage in these local processes, it is important that they do so with a health system rather than single product perspective. The PDP should define how the new intervention will fit with, affect, and strengthen other aspects of the existing public health environment, including all current and potential strategies to address a disease. This is how decision-makers in disease control programs think and they will be more likely to engage with the PDP if such an approach is demonstrated [166]. A disease approach can also bring in allies from other areas that might otherwise be competitors. An example of this is the Introducing New Approaches and Tools (INAT) sub-working group of the Stop TB Partnership, which looks at ways to encourage the adoption both of new technologies and of new guidelines and practices [167]. Finally, if necessary, PDPs and other partners should facilitate the formation of a normative

decision making process that covers all interventions in an area, not just those sponsored by the PDP [147].

THE GEOGRAPHY OF PDP SUPPORT OF COUNTRY DECISION MAKING

ROLE OF INTERNATIONAL PROCESSES

International institutions reach decisions and issue guidelines that are often precursors to country-level decision making. For example, WHO recommendation will be essential for adoption of PDP-related products in many if not all of the relevant endemic countries. PDPs generally interact extensively with WHO to discuss what evidence is available or needs to be generated for the international guidelines process.

For some new health interventions, there is no specific, historical pathway for establishing international policies. This was the case for a candidate malaria vaccine, so MVI analyzed past WHO policy processes for vaccines and malaria interventions, identified data that could be required for a policy on malaria vaccines, and considered additional options for adjusting policy processes to accommodate a malaria vaccine [138]. PDPs can support the formation of international advisory and advocacy boards such as the Pneumococcal Awareness Council of Experts (PACE) and the All-Party Parliamentary Group on Pneumococcal Disease Prevention in the UK. These initiatives were instrumental in supporting the GAVI Alliance investment case and advance market commitment (AMC). It is reasonable to assume that working with or modifying existing policy processes, where feasible, will be less costly and more efficient for international partners than developing new processes.

HOW MANY COUNTRIES CAN A PDP REACH?

The number of individual countries with which a PDP can expect to interact directly is not clear. It seems likely that most PDPs would interact significantly with perhaps 5-8 countries – notably those that have high disease burdens, are potential early adopters and are countries where the PDP is supporting clinical trials – but many PDPs would then rely on existing multilateral, NGO, and pharmaceutical partners to reach other countries for detailed work on adoption and implementation.

At one extreme is the PDP-like Hib Initiative, which worked together with WHO to support directly or indirectly 72 countries [142]. GAVI supported this group with a four-year, $37 million grant, after noting the existing 15-20 year uptake delay in most low income countries. The Hib Initiative had no real role in product development but was funded to support evidence-driven decisions on *Haemophilus influenzae* type b (Hib) vaccine use at global, regional and country levels. Their approach, which involved engaging directly or indirectly with a larger number of countries, was seen to be necessary to implement a global recommendation for use of a long-available product. Substantial savings may be realized and less engagement needed if appropriate steps –

on financing, global policy and market preparation, for example – are taken during product development.

<u>PRIORITIZING COUNTRIES FOR ACCESS ENGAGEMENT</u>

If a PDP is going to invest significantly in supporting a country, it first needs to determine which countries are the highest priority. Prioritization generally considers two goals, which may or may not overlap: maximizing final public health impact; and identifying early adopters. Prioritization may also reflect an effort to include settings reflecting the full range of epidemiologic patterns of the disease (e.g., for malaria).

Prioritizing countries for engagement on access-related issues is not a science – there is no perfect answer. Different PDPs are likely to use shorter or longer lists of criteria in making such decisions. However, most PDPs will consider a number of the following criteria, with the more important listed first: prior engagement via PDP-sponsored trials; high burden of disease (absolute or reflecting specific patterns of resistance or vulnerability); potential health benefit (e.g., based on drug resistance patterns); political stability; capacity of national program to deliver treatment (e.g., focusing new vaccine interventions on those countries with strong EPI programs); existence of local champions and openness to change; research capability for a pilot, which would generate evidence for other countries; regional importance of country; regulatory capacity and influence; and availability of other information for decision making.

WHO regional advisers can also provide prioritization guidance. In support of the introduction of Hib vaccine, WHO regional EPI officers helped the Hib Initiative to identify issues and barriers for each country and define whether country stakeholders were already including Hib in their multi-year plans. A country's application to the Global Fund to Fight AIDS, TB and Malaria can provide similar insights. History can provide some hints about likely future actions [143], although the history of Hep B adoption provided the Pneumococcal Vaccines Accelerated Development and Introduction Plan (Pneumo-ADIP [140]) with few clues for the introduction of the pneumococcal vaccines, probably because of turnover of decision makers and different local champions for the two vaccines.

Once countries are prioritized, they may express an interest in conducting demonstration projects. As product developers, PDPs are focused on generating evidence from randomized, controlled clinical trials. Often, however, such evidence is not sufficient for adoption. After Phase 3 trials are complete, a deep investment may be needed in a few countries to help generate examples or evidence that an intervention works under real-world conditions (e.g., community effectiveness). Although countries vary, such test cases can boost the profile of a new intervention and result in funding for roll out in further countries. PDPs may help to build these early success cases and formulate roll-out plans.

STRATEGIES FOR ESTABLISHING A LOCAL PRESENCE

Once a country has been prioritized, a PDP must decide whether and how to establish a local presence. A PDP with staff in an endemic country will have clear opportunities for improved information flow and closer engagement with local stakeholders. However, PDPs were primarily founded as research organizations, so budgets for an endemic country presence are usually driven by organizational needs such as those related to clinical trials. Aside from the Medicines for Malaria Venture (MMV)'s office in Uganda, offices associated with PDPs are not generally set up primarily for an access-related purpose.

The options for establishing a local presence, listed from most to least committed, include: country or regional offices, including with a partner organization; consultants on partial retainer; sustained engagement with existing committees or structures; engagement with ad hoc committees or structures formed at the prompting of a PDP; or ad hoc engagement with existing structures (e.g., regional or sub-regional disease-specific committees or meetings organized by WHO).

Local expertise, in the form of either PDP staff or consultants, is critical to ensure a high quality interaction with government officials and partner organizations. For example, disease-specific and health systems knowledge, and sufficient standing to collaborate with government officials, physicians and researchers are important. Such individuals can help to design and facilitate local research and to provide local researchers and policy makers with PDP support for decision-making activities. Even beyond their own staff and consultants, PDPs may also help to strengthen the pool of scientists, who at the same time become stronger advocates within their regions and countries; examples include MVI's annual Malaria Vaccine Advocacy Fellowship Program, the Drugs for Neglected Diseases Initiative (DNDi)'s research platforms, or Pneumo-ADIP and Hib Initiative's local advocates.

PDPs vary in their in-country presences (Table 19), with the extent usually increasing as products move further through the pipeline. PDPs within larger institutions such as PATH are also able to leverage competencies in multiple offices.

TABLE 19. PDP OFFICES IN ENDEMIC COUNTRIES.

PDP	Offices in endemic countries
Drugs for Neglected Disease Initiative (DNDi)	Kenya, Brazil, Democratic Republic of the Congo, India, Malaysia, where it may be as small as a 1-person office
PATH Malaria Vaccine Initiative (MVI)	PATH office in Kenya with dedicated MVI program staff, plus PATH offices that can be called upon such as in Senegal, Ghana, Ethiopia, Uganda, Tanzania, Zambia, and South Africa
Medicines for Malaria Venture (MMV)	Uganda, initially for pilot of AMFm (Affordable Medicines Facility – malaria), now for regional interactions on guideline revisions
Institute for One World Health (iOWH)	India
Global Alliance for TB Drug Development (TB Alliance)	South Africa – focused on clinical trial conduct rather than access
Foundation for Innovative New Diagnostics (FIND)	India, Uganda
International AIDS Vaccine Initiative (IAVI)	India, Kenya, South Africa
Aeras Global TB Vaccine Foundation (Aeras)	South Africa
International Partnership for Microbicides (IPM)	South Africa

In sum, the rationale for the country presence of PDPs has been driven by research and development (R&D) or organizational needs (including limited funding), with access activities building upon that presence. This suggests that access teams should seek to be part of decisions on where R&D activities are undertaken. PDPs have also tended to take advantage of less costly means for engaging with greater numbers of countries by working through existing committees and structures (including WHO), developing new structures for sustained engagement where feasible, or otherwise working through ad hoc collaborations.

THE ESSENTIAL ROLE OF PARTNERSHIP

For PDPs to achieve their goals, partnership is essential. PDP access staff can initiate these partnerships by bringing together different parties, such as scientists, manufacturers, regulators, and implementers. This combination of perspectives from the scientific, commercial and public health worlds can support more informed decision making [165].

In order to reach multiple countries, the involvement of WHO headquarters, country and, in particular, regional offices has been and will remain critical, particularly for diseases such as HIV/AIDS, TB and malaria that have a significant number of WHO staff. Regional WHO offices can track the progress of multiple countries as they move through the multi-part decision process. Table 20 describes possible partners, including WHO, and some of their advantages and disadvantages.

Manufacturers have traditionally supported some aspects of country decision-making and all the aspects of product launch. However, many originator companies may have limited experience of introduction into low and middle income country markets (some Indian and Chinese generics may be more established in these markets). Companies may also be concerned that they could be perceived to be self-serving if supporting decision-making around the introduction of a new product directly in countries. Thus, the initial information sharing and country decision making step will generally require the involvement of other actors, including PDPs.

An interesting example of division of labor comes from Uganda, where PATH, a not-for-profit that has worked extensively as a PDP, is supporting a demonstration project for human papilloma virus (HPV) vaccines (E. Mugisha, pers. comm.). Before any activities started, PATH signed a Memorandum of Understanding (MOU) with the Government of Uganda (GoU) to specify who would do what. The GoU committed to provide health services delivery infrastructure, human resources in the districts, and EPI staff for delivery of the vaccine. The two PATH technical staff members, located in the WHO Uganda office, provided technical and logistical support. PATH also provided transport allowances (but no per diems) to health workers in the field and funded local university researchers to conduct the formative research and operations research. WHO and UNICEF participated in a technical advisory committee set up by the Ministry of Health (MoH) to oversee the demonstration project, and also helped with monitoring of vaccination. The relevant pharmaceutical company (GlaxoSmithKline Biologicals (GSK)) donated and shipped vaccines to Uganda, but had no other role in the project. UNFPA and other stakeholders provided input on reproductive health issues, and NGOs (e.g., CARE and Save the Children) helped with mobilization in the districts. Thus, PATH served as the glue across the various organizations in support of the MoH.

TABLE 20. PARTNERS WHO CAN SUPPORT COUNTRY DECISION MAKING, IN COLLABORATION WITH PDPS.

Partner	Advantages	Disadvantages
Multilaterals such as WHO	Extensive reach and impartiality	Limited staff and restricted funding; May be overwhelmed by other initiatives and thus lack time and resources to devote to new interventions
Organizations dedicated to new product access, such as those funded by GAVI (e.g., Hib Initiative, Accelerated Vaccine Introduction Initiative (AVI))	Dedicated funding for access activities	Typically have a multi-country remit which limits depth of engagement in individual countries
Local academia, researchers and/or professional organizations	Close to in-country processes, needs and data; Credible with local policy-makers	May not have a broad view of a problem; May be influenced by personal research interests
NGOs	Some have specific expertise in new product introduction	May require funding specific to the new product to support their activities, and may not be involved in official decision-making bodies
Pharmaceutical and/or manufacturing partners	Product-specific expertise, regulatory expertise, and in some cases extensive sales networks in some markets	May be seen as a biased source of decision making information; may lack experience in the disease and/or in low and middle income settings

CHALLENGES TO PDP IMPLEMENTATION

There are many challenges for PDPs in supporting country decision making. Creating a success story in one location is certainly important, but just getting the process right in one country won't necessarily allow replication, as each country is different. The PDP, however, is unlikely to have the resources to replicate the same breadth of activities with all endemic countries.

There is also an issue of managing expectations. Country decision making is driven by the country, not the PDP. Conveying this idea of public sector policy change to R&D staff, PDP boards and funders can be challenging. Furthermore, PDP boards often think that local implementation partners can do it all, so local engagement by the PDP is not necessary. But partners are focused on many other issues, and often do not have the full depth of information on a given intervention.

Finally, optimal engagement timelines are unclear. Advance planning is risky as product timelines are uncertain, but without early engagement (e.g. 5 years pre-licensure), country decision making may be delayed and products will sit unused on shelves. In terms of PDP access budgets, a critical step will be to address the number and cost of Phase 4 studies, determine who will bear the burden of financing them (e.g., donors and PDPs, manufacturers, countries or some combination), and define models to bring those costs down.

SPECIFIC PDP APPROACHES FOR SUPPORTING COUNTRY DECISION MAKING ACTIVITIES

Despite these challenges, successful PDP support of country decision making is possible. The case studies below illustrate that PDPs have taken many distinct approaches to facilitating country decision making. These are examples of what has been done, rather than normative descriptions of what would be ideal. They were selected to represent a range of modalities (e.g., vaccine, drug, and insecticide) and disease areas, and the kinds of activities conducted at different stages of the decision process (presented below in roughly chronological order). Different PDPs have undertaken a range of activities, such as shown in Table 17 and Table 18, with this selection depending on needs identified by each PDP, typically in consultation with partners like WHO and countries. Not surprisingly, the more extensive experience generally lies with the PDPs who have approved products.

ENGAGEMENT PRIOR TO PRODUCT AVAILABILITY

For DNDi, country engagement begins with the identification of needs by and with endemic country stakeholders. Certain key research organizations in endemic countries contributed to DNDi's founding, are represented on its Board of Directors, and greatly inform the definition of needs and of the related Target Product Profiles

(TPPs). These organizations also facilitate clinical and intervention trials and, ultimately, national decisions on adoption.

Three additional PDPs, whose activities are outlined below, do not yet have products approved by regulatory agencies but nonetheless conduct activities related to country decision making. For malaria vaccines, MVI initiated a 3 year process with countries, WHO and, in the later stages, the Roll Back Malaria Partnership (RBM) to develop decision-making frameworks, initially for 9 individual countries and then for the African region [164]. The final framework builds upon existing WHO guidelines [153], and lays out what data are needed from different sources (global vs national), in different thematic areas (disease burden, other malaria interventions, impact, financial, efficacy, safety, programmatic, sociocultural), and at different times (pre-licensure, licensure, and post-licensure); it also notes whether each is essential or desirable. It provides a similar framework for policy processes.

The framework process has and will structure dialogues around malaria vaccines with countries around technical issues. In some countries, it has led to the formation of ongoing structures that have begun to collect data to inform an eventual decision (e.g., technical working groups – MVI now sponsors three of these).

In contrast to MVI, the Global Alliance for TB Drug Development (TB Alliance) is entering an area that has existing products. There was, however, relatively little analysis of the market, of decision making, or of how new products would be considered. TB Alliance therefore focused on conducting sequential stakeholder studies in the following areas: the size and structure of the existing TB drug market; what local stakeholders want from a new TB regimen; how the experience with past TB regimen changes can inform future approaches; and what producers and products are dominant in the private sector. These studies helped to identify issues and categories of data relevant for future country decision making [143,162], initiate engagement with local stakeholders, provide opportunities for the promotion of regimen change issues in international fora, and frame conversations with local stakeholders during TB Alliance participation in WHO review missions. Finally, the findings of each study influenced the design and content of the next, and provided essential feedback for the research and development team [133]. TB Alliance selected this approach due to the opportunities and challenges presented by the availability of existing TB treatment regimens and partnerships.

The long-term aim of IVCC is to facilitate the development and introduction of new insecticides. Already, however, IVCC is engaging country decision makers to address an identified gap in field implementation – the monitoring and evaluation of vector control programs. This gap is addressed via IVCC's Malaria Decision Support System (MDSS), which is used to track clinical and survey data and insecticide resistance (T. McLean, pers. comm.). This tool is applicable to a wide range of diseases and, in

addition to monitoring and evaluation, it supports the management of advanced insecticides, and decision making on adopting new vector control products. Based on existing partnerships with the ministries of health, IVCC has validated the methodology in 3 countries – Mozambique, Malawi, and Zambia – with varied infrastructure and ecological environments; it is now planning wide-ranging implementation. As a central objective, the MDSS should be adopted and owned by the national malaria control program and serve their information needs.

COUNTRY CONSULTATIONS AND REGIONAL MEETINGS

Early and frequent consultations with countries are essential for the development of products that are suited to end users [133]. For DNDi, input is channeled via disease platforms, which were formed to assist and strengthen clinical research around specific diseases in a geographic area, e.g., VL in East Africa, sleeping sickness in West Africa, and Chagas Disease in Latin America. These platforms include country program staff, researchers, regulatory officials, NGOs and WHO and meet twice a year. Platform members became natural partners for country decision making as they gather relevant information on in-country issues, programs, and processes and convey key information to in-country decision makers.

The Pneumo-ADIP (now part of the International Vaccine Access Center (IVAC)) built on experience with Hib and Hepatitis B vaccine introductions to support pneumococcal vaccine introduction [140]. Under the Pneumo-ADIP, the establishment of surveillance networks had two positive outcomes: it provided the requested data on projected coverage and impact and, via annual investigators' meetings, led to the identification of local advocates. In addition, regional meetings organized in collaboration with WHO provided an opportunity to check back in and to move countries to put their decisions and proposed actions on paper by presenting their conclusions in front of others (L. Privor-Dumm, pers. comm.). These meetings included EPI managers, directors of health services, researchers, pediatricians, economists, and sometimes donors and financing people from MoH or other ministries, and were a particularly useful mechanism to support decision-making in countries not directly targeted through other interactions.

MMV and its drug development partners have also made extensive use of country-level dialogues such as subregional meetings (of WHO AFRO and Roll Back Malaria) and, in select cases, day-long workshops (G. Jagoe, pers. comm.). These provide opportunities to give product-specific briefings and to reinforce recommendations of normative entities (primarily WHO) in terms of best practice for the development and revision of treatment guidelines and for the correct use of new, quality medications in combination with proper diagnosis (case management). Longer-term programmatic collaborations in specific-countries are very limited; the focus is on any initiative (e.g., piloting of an affordable medicines private sector subsidy in Uganda) that address

specific access challenges and could serve as guiding lights for policy makers and funders across the larger stage of all malaria endemic countries. In terms of impact, as of September 2010, almost 42 million treatments of Coartem® Dispersible (co-developed with MMV) had been delivered to 32 countries [168].

Regional meetings have been convened by the TB Alliance and partners to gain consensus around regulatory issues [169]. Existing TB drugs were developed more than 40 years ago, in a very different regulatory environment. Agreement was needed on the regulatory approach to development of not just individual new drugs, but new regimens. With the participation of national TB program managers in these meetings, these individuals became part of the conversation about what types of evidence would be available for decision making.

IMPLEMENTATION STUDIES AS A BRIDGE TO ADOPTION

When existing evidence is insufficient, implementation studies may be necessary. In India, the Institute for One World Health (iOWH) has supported studies to generate data for advocacy and decision making on Visceral Leishmaniasis (VL) treatment and elimination. In collaboration with a research institute of the Government of India, they documented the incidence of VL, the financial burden of disease, households' willingness and ability to pay, and treatment-seeking behaviors in both public and private sectors (R. Sarnoff, pers. comm.). In addition, building on the necessary Phase 3 study, iOWH sponsored a Phase 4 study with an effectiveness module that provided training, clinical support, and guidance on pharmacovigilance reporting, and demonstrated effective delivery in public and private facilities. The clinical trial investigators formed a core constituency for local advocacy for improved products.

At the national level, iOWH leadership engaged with key stakeholders in the Indian government, World Bank and WHO to inform them of the progress of the studies, identify their key questions and concerns, and address future funding issues. Training modules and community communication models were developed for smooth transfer to the national authorities.

DNDi has also used intervention or field trials as an essential step to demonstrate feasibility and generate necessary data for adoption into national programs (F. Camus-Bablon, pers. comm.). For example, Brazil conducted a 25,000-subject malaria intervention trial prior to adopting artesunate and mefloquine (ASMQ) for treatment of falciparum malaria in the Amazon basin. The trial monitored the effects of ASMQ introduction; during the study, a significant impact on malaria cases and related hospitalization also resulted from a more rational use of complementary resources such as insecticides, detection and reporting system, and from training of local human resources. In this study, one year after the introduction of the ASMQ fixed-dose combination (FDC) and the treatment of 17,000 patients, *P. falciparum* malaria cases were reduced by nearly 70% and malaria-related hospitalizations dropped by over

60%. Following the study, the Brazilian National Program updated the national malaria treatment guidelines and introduced ASMQ FDC as the first line treatment in the region. Advocacy is also a key component of DNDi implementation work, to inform both international audiences and endemic countries.

In some areas, DNDi relies on pharmaceutical and other international partners. For example, WHO Neglected Tropical Diseases (NTD) department and Médecins Sans Frontières (MSF) are key drivers for the adoption of nifurtimox-eflornithine combination therapy (NECT) for the treatment of sleeping sickness, which, within a year, has been adopted in the national treatment policy of nine endemic countries and ordered by six. Sanofi-Aventis (SA), within two years of WHO pre-qualification, was planning to distribute 50 million artesunate-amodiaquine (ASAQ) treatments in 2010. Today, ASAQ is registered in 27 African countries and in India. SA is conducting a 15,000 patient pharmacovigilance program in partnership with DNDi and MMV in Ivory Coast, and developed a specific package for social interventions and home based management programs.

EVALUATION OF IMPACT

There are significant challenges in estimating the impact of PDPs on country decision making. First, most PDPs are relatively young, being established in the last 10 years. Given the time required to develop a product, many have not yet had products launched, and the product launches that have occurred are recent. Second, there is not yet agreement on how to measure impact – in particular, whether to focus on usage (e.g., number of individuals treated; see the data on new product usage noted in this paper) or on process (the number of countries conducting a policy process and reaching the decision that is best for their particular situation; see [170] for an example). Third, if a product is suboptimal – too expensive, insufficiently efficacious, or too difficult to use, for example – it is unlikely to be rescued by PDP support of country decision making, even if those support activities are well executed. In other words, success under the first ("usage") definition is only likely when the new product continues to meet identified country needs. This is why access input is essential throughout the product development process [133].

There have, however, been efforts by PDPs to define metrics of success and to evaluate PDP work in support of country decision-making. For impact using the "process" definition of success, one example is the malaria vaccine decision-making framework [170]. The development of this framework has been independently evaluated [171]. Out of 84 respondents from 10 countries, 90% felt that the framework developed will be extremely or very useful in preparation for a decision (i.e., in deciding what activities to undertake prior to having a licensed product), and 88% indicated the same for taking a decision after a vaccine is licensed. Facilitators were reported to be neutral instead of supporting one product.

A 2007 study by the GAVI Alliance tried to quantify the impact of the Pneumo- and Rotavirus ADIPs and Hib Initiative as compared to what may have happened if they had not been in place [172]. The authors found that the Pneumo-ADIP is likely to shave at least five years off the time from development to availability of vaccines in the poorest countries, and that the work of the Rotavirus ADIP may result in the poorest countries accessing vaccines only one year after availability in the developed world, which is years and decades shorter than historically. Based upon this, the authors reported "value in terms of lives saved and hospitalizations averted."

Given the constraints noted above, the current paper does not aim to provide a rigorous evaluation of PDP impact and strategies, but instead provides a situation analysis, reflecting the range of strategies undertaken by PDPs and detailing the rationale behind their choice. It is clear that having no engagement specifically around new products leads to lengthy delays in availability [132]. At the same time, it is too early to determine the optimal strategies for each situation and type of intervention. However, the current analysis provides an important baseline or reference point for a later impact analysis of PDP work on access.

CONCLUSION

A country's decision to adopt a new health technology requires more than the existence of a good product. In low and middle income settings, a wide range of organizations can support country decision making. The role of PDPs in this process is based on the PDPs' vision to see public health impact from the products they develop, and on their intimate familiarity with the products under discussion.

A PDP as a whole can cover a wide spectrum of activities ranging from basic research to implementation of interventions. At the implementation end of this spectrum, there is no single definition of where the PDP role ends, as the technical needs and available partners in endemic countries vary for each intervention. However, as more PDP-related products progress, additional experience will assist in defining the areas in which PDPs are effective and should be held accountable. Funder, partner and country participation in the development of improved means to evaluate the relative roles and impact of PDPs will also be important. Building on the insights described here, PDPs, partners and country stakeholders can continue to provide critical support for decisions on interventions that will ultimately decrease the global burden of disease.

COMPETING INTERESTS

The authors are or have been employed by product development partnerships. The authors declare that they have no other competing interests.

AUTHOR CONTRIBUTIONS

WAW initiated the review concept, analyzed suggested inputs from various organizations, wrote the first draft of the manuscript, and revised subsequent drafts; AB helped analyze the suggested inputs, contributed key concepts, and revised manuscript drafts. Both authors read and approved the final manuscript.

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ACKNOWLEDGEMENTS AND FUNDING

CHAPTER 6. COUNTRY PLANNING FOR HEALTH INTERVENTIONS UNDER DEVELOPMENT: LESSONS FROM THE MALARIA VACCINE DECISION-MAKING FRAMEWORK AND IMPLICATIONS FOR OTHER NEW INTERVENTIONS

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ABSTRACT

A growing number of new public health interventions targeting diseases found in developing countries are under development. Traditionally it has taken years or decades for these interventions to be accessible to those most in need. One reason for the delay has been insufficient anticipation of the eventual processes and evidence required for decision-making by countries. Development partners, international organizations, researchers, and product developers have not systematically identified the elements needed for national decision-making during intervention development, a factor that exacerbates the delays. This paper describes research into the anticipated processes and data needed to inform decision-making on malaria vaccines, the most advanced of which is still in phase 3 trials. From 2006-2008, a series of iterative country consultations in Africa led to the development of a guide to assist countries in creating a malaria vaccine decision-making framework. The guide identifies the processes and data countries believe would be critical or helpful, when the data would be needed relative to the development timelines of the intervention, and who should be responsible, broadly speaking, for generating the data. This generic guide can now be applied to any future malaria vaccine. The paper discusses the opportunities and challenges to early planning for country decision-making—from the potential for timely, evidence-informed decisions to the risks of over-promising around an intervention still under development. Careful and well-structured planning by countries is a critical way to ensure that new interventions do not remain unused for years or decades after they become available.

INTRODUCTION

An increasing amount of money, $3.2 billion dollars in 2009 alone, is being spent on research and development for new products intended to address diseases prevalent in the developing world [1]. Assuming that even a fraction of these funds realizes the goal of creating new health interventions, low- and middle-income countries (LMICs) will face a growing number of decisions on which new interventions to use in the coming decade.

This paper focuses on decisions related to the use of new interventions that are provided as part of national health systems in LMICs through public or donor funds. In this regard, it focuses on national decisions on whether or not to adopt a new intervention, once it becomes available (i.e. approved by the appropriate regulatory authorities and produced in sufficient quantities by a manufacturer.) Such decisions would be distinct from largely regulatory determinations to allow sales of a product through private-sector channels.

National decision-making processes for public policies, and health policies more specifically, have been under study for decades. They can be seen as complex, non-linear processes, balancing evidence, policy alternatives and domestic and international politics [173–175]. Substantial efforts have been made to understand and therefore improve decision-making processes [176–181] and to generate the data needed by countries to facilitate decision-making, including data on burden of disease and on cost-effectiveness of interventions [182–185]. Countries also need to consider many factors specific to the targeted disease and the characteristics of the intervention, some of which are informed by international organizations and global experts (e.g. World Health Organization (WHO) policy positions; donor funding commitments) [176,186–189]. Within countries, there may be questions about coordination among different entities, particularly for an intervention that cuts across areas of specialization in public health. One example would be the human papillomavirus (HPV) vaccine that has required collaboration across reproductive health, immunization, and school health experts [190].

The track record for adoption decisions and implementation of new health interventions in LMICs suggests that it takes years or decades for many countries to realize the benefits of new public health interventions [184,191–194]. Decisions are likely more complex for a novel, "first in class" intervention like a malaria vaccine, but less complex for a second-generation or follow-on intervention, such as a new anti-malarial drug that is meant to replace a less effective drug. While detailing the multiple reasons for these delays is beyond the scope of this paper, a recurrent theme has been the need for more thought during the development of a health intervention on what processes and data LMICs would need in order to make timely decisions on whether or not to introduce the intervention.

Evidence that insufficient planning for country decision-making is a major cause of delays in the use of health interventions is apparent in a number of areas. The GAVI Alliance (GAVI) has pinpointed challenges in decision-making as a key factor in the delay to implement the *Haemophilus influenzae* type b (Hib) conjugate vaccine [195], a vaccine available in the developed world since 1987. The delay led GAVI in 2005 to invest USD$37 million in establishing the four-year Hib Initiative to provide support to countries wishing to decide if Hib vaccine is a priority for introduction and provide programmatic support to countries who have already decided to use it [196]. Reports on the process that is required to change malaria treatment policy suggest that the policy decision process itself takes one to five years, with an equal length of time for implementation [191,197–199]. One estimate suggests that changing treatment is likely to cost roughly $1 million in today's currency for a reasonably large country like Tanzania [198]. Both GAVI and the Global Fund to Fight AIDS, TB, and Malaria (GFATM), the world's largest organizations supporting adoption of new health interventions, recognize the challenges country-level decision-makers face. Proposals to either organization for support must demonstrate the functioning presence of a local partner and government coordination mechanism to support decision-making and implementation [200,201]. These requirements would not be called for if those organizations did not recognize the challenges inherent in national decision-making processes.

The Hib Initiative and similar efforts are generally meant to "catch up" years or decades after an intervention is already available. Variability naturally exists between situations and across countries, at the same time, accelerating clinical trials to save one or two years on timelines to licensure of a new intervention only to have the policy and implementation process add years or decades suggests that more forethought is needed around national planning processes during intervention development.

A different approach is for product developers, countries, and their development partners to plan in advance for new health interventions. Using the example of a malaria vaccine, this paper lays out a multi-year collaboration that was designed to anticipate the processes and data that countries would need to make decisions on whether or not to introduce a new health intervention. Such work was called for by the Malaria Vaccine Technology Roadmap, a plan laid out by 230 experts representing 100 organizations from 35 countries [202].

The most advanced malaria vaccine candidate is part-way through phase 3 clinical trials in Africa, the region where an estimated 91% of the nearly 800,000 annual malaria-related deaths occur, almost entirely among children under five years of age [46,83]. If all goes well, WHO has indicated that a policy recommendation for RTS,S is possible as early as 2015, and implementation through routine infant immunization programs in Africa could follow. Anticipating national decision processes during the vaccine

development period is a critical part of making such a novel intervention accessible to those most in need.

This paper will report on research to address the following specific questions during the clinical development period:

1) What processes need to take place to allow countries to decide whether or not to use a malaria vaccine and when do they need to take place relative to the projected availability of a vaccine?

2) What data would countries need for a decision on whether or not to introduce a malaria vaccine and when would they need the data relative to projected availability of the vaccine?

The paper will go on to discuss the lessons gained from answering these questions for other new health interventions.

METHODS

The decision-making framework guide was developed through an iterative process from 2005-2008 (Figure 12). The process was designed to create a framework applicable to any malaria vaccine developed. It was intended to understand what will be needed in order to achieve the following vision: *National governments of malaria-endemic countries will have information to make timely and well-informed decisions about the appropriate use of a malaria vaccine within their national health systems within one to three years of licensure.*

A set of briefing papers was developed to provide background information on issues related to adoption of malaria control policies and new vaccines, and to serve as a foundation for consultations with countries. A series of country consultations was convened with a few dozen to more than 50 participants at each. The consultations included plenary presentations allowing African scientists and immunization, malaria, and other government and partner staff to discuss their shared experiences with researching and taking decisions on new interventions. Facilitated break-out groups used a semi-structured guide to identify what processes and data would be needed to take a decision to adopt, or not, a malaria vaccine, and when these processes and data would be needed. Plenary discussions were used to reach consensus on which processes and data points were critical, and which merely helpful. Draft meeting reports were circulated back to all participants for input prior to finalization. Meeting materials and reports were systematically posted to a public website [203].

FIGURE 12. TIMELINE FOR DMF GUIDE DEVELOPMENT PROCESS.

2005
Steering Committee established by MVI and WHO
- Designed DMF development process.
- Wrote background papers.

2006
Development of a draft guide for establishing a malaria vaccine DMF
- Consultation hosted by the Minister of Health of Benin, WHO, and MVI.
- Participants from 13 African countries, representing malaria, immunization, planning, finance, and academic sectors.
- Identified the processes and data that would be needed for a decision on malaria vaccines, and when they would be needed relative to vaccine availability.
- Processes and data requirements synthesized into a draft DMF guide.

Individual country consultations
- Two-day consultations organized by MVI and WHO in Gabon, Ghana, Kenya, Mali, Mozambique, and Tanzania. Countries selected because they were ongoing sites for research on a malaria vaccine and because they offered geographic and language diversity.
- Participants analyzed and adapted the draft guide for local context.
- Meeting reports integrated into second draft of the DMF regional guide.

2007
Pilot of second draft of the regional guide
- Similar consultation process completed for Burkina Faso, Ethiopia, and Malawi.

2008
Validation of regional DMF guide
- MVI, WHO, and Roll Back Malaria Partnership convened full-day consultations following three WHO-RBM regional malaria meetings.
- 30 countries participated, including malaria and immunization staff.
- Considered if the guide correctly reflected timings and common processes and data that would be needed in the region for a decision on malaria vaccines.

Independent, external evaluation of DMF development process
- Emailed survey to 184 individuals from 2006-7 consultations, of which 81 responded from 10 countries.

Countries begin applying DMF guide to individual vaccine candidates 3-5 years before licensure

Meeting outcomes were analyzed to identify consistent findings across two or more countries. Outliers were considered according to their merit relative to published and grey literature. Resulting processes and data points were put into a regional decision-making framework guide which was validated through consultations with countries. The process was independently evaluated through an online survey using qualitative and quantitative methods [204].

RESULTS

AFRICA REGIONAL GUIDE TO A MALARIA VACCINE DECISION-MAKING FRAMEWORK

The validated regional guide contains 25 processes identified as critical, and six identified as helpful to have. The guide identifies 43 data points as critical and a further 10 as helpful to have. The processes and data are also categorized by accountability for action—whether countries see them as largely being done by an international (e.g. global or regional-level) entity with data extrapolated to an individual country, or in an individual country with local data.

Both processes and data points are presented according to a timeline related to product development, from as many as 5 years pre-licensure and availability of critical phase 3 data on safety and efficacy, to licensure and decision on use, to as many as 5 years post-licensure if introduced. The processes are presented in two rows, reflecting either international or national responsibility (Figure 13). The data are presented in seven rows based upon WHO guidelines on new vaccine introduction (Figure 14) [189]. Only "critical" processes and data are presented in the figures. Full guides can be found online. (www.malvacdecision.net)

An initial step identified by countries for national-level processes was to establish technical working groups (i.e. local expert groups) on malaria vaccines prior to availability of the phase 3 data. They then suggested that, when the vaccine is licensed and a decision taken, such groups would issue advice to inform the government's policy decision. The guide leaves it up to each country to determine the specific remit and membership of such groups where they are established. Examples of the activities of such groups to date are discussed later.

Initial global processes called for by countries included the importance of integrating country requirements into product development plans to ensure the programmatic suitability of a vaccine. Countries also called for global advocacy to fundraise for malaria vaccines starting prior to licensure, and identified WHO policy recommendations and guidelines on use as critical.

FIGURE 13. REGIONAL MALARIA VACCINE DECISION MAKING FRAMEWORK: CRITICAL PROCESSES
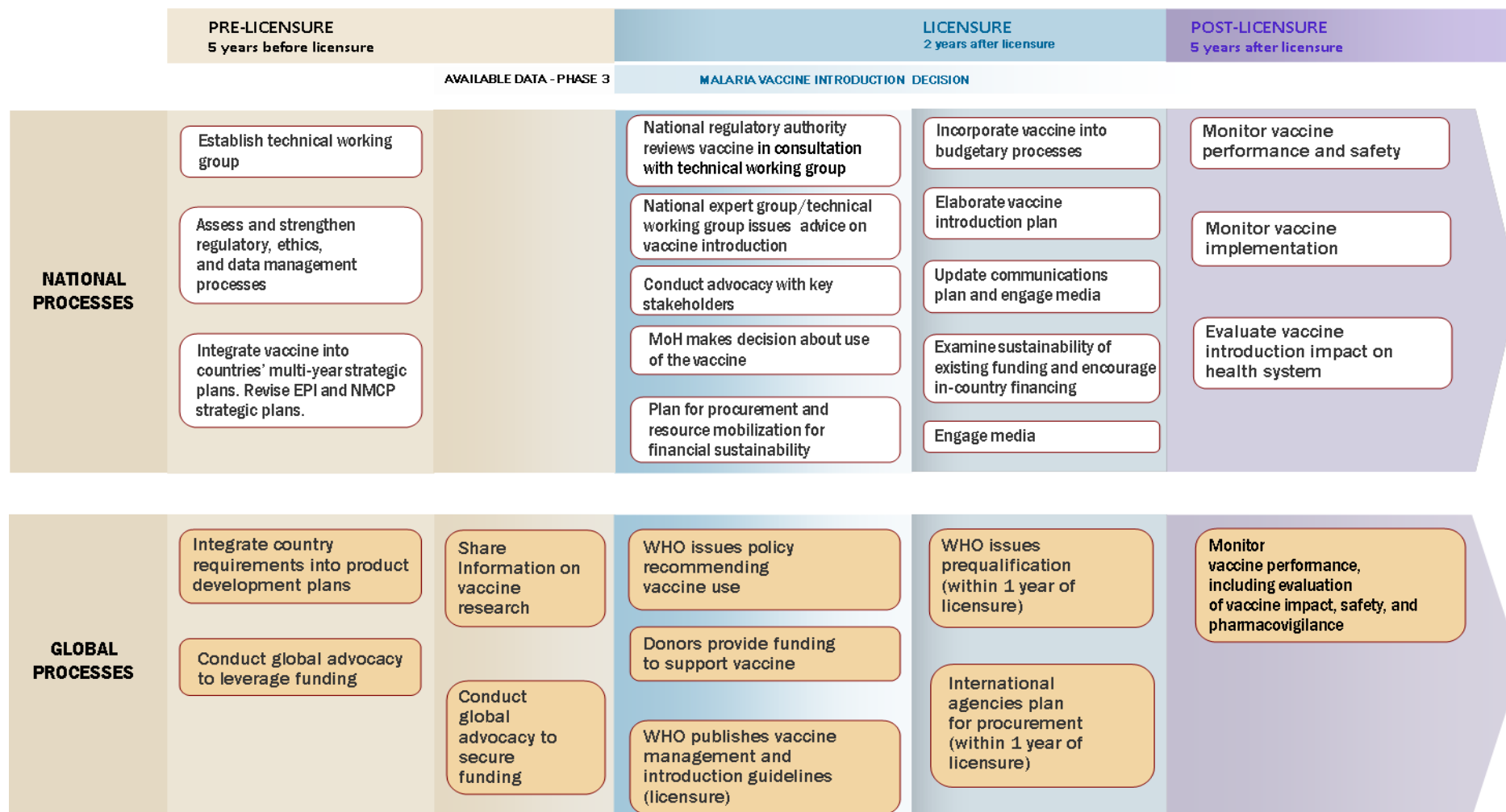
FIGURE 14. REGIONAL MALARIA VACCINE DECISION MAKING FRAMEWORK: CRITICAL DATA

	PRE-LICENSURE 5 years before licensure	AVAILABLE DATA - PHASE 3	LICENSURE 2 years after licensure MALARIA VACCINE INTRODUCTION DECISION	POST-LICENSURE 5 years after licensure
MALARIA DISEASE BURDEN	• Reported and confirmed cases by age group • Malaria cases in pregnant women and in HIV+ individuals • Malaria epidemiological profile by district		• Update on current malaria situation	• Reported and confirmed cases by age group • Reported malaria-related deaths by age group
OTHER MALARIA INTERVENTIONS	• Coverage and impact of current malaria-control interventions • Impact and cost-effectiveness estimates of current malaria control interventions			• Changes in impact and in cost-effectiveness of other malaria interventions
MALARIA VACCINE IMPACT	• Impact on mortality and morbidity by age group	• Marginal impact with other malaria interventions		• Vaccine coverage • Vaccine effectiveness studies
ECONOMIC AND FINANCIAL ISSUES	• Cost-effectiveness estimates of vaccine	• National affordability • Vaccine price for public • Donor subsidy for vaccine and sustainability of subsidy	• Sustainable national commitment	• Updated vaccine cost-effectiveness estimates • Estimates of recurrent direct and indirect costs
MALARIA VACCINE EFFICACY, QUALITY, & SAFETY	• Vaccine safety • Adverse events • Interaction with other vaccines • Vaccine efficacy	• Vaccine efficacy (clinical and severe malaria, anemia, parasitemia, in HIV+ populations) • Duration of efficacy	• Efficacy, quality, and safety data from other countries	• Vaccine safety and efficacy data
PROGRAMMATIC CONSIDERATIONS	• Anticipated vaccine characteristics and presentation	• Vaccine demand forecast • Health systems capacity for malaria vaccine • Vaccine supply availability • Product characteristics and storage information	• Defined target groups and communications plan	• Evidence of supply security
SOCIO-CULTURAL ENVIRONMENT				• Community knowledge, attitudes, and practices related to vaccines and malaria interventions

Legend: White boxes reflect country data; Shaded boxes reflect global data.

Countries indicated that they would want data on other malaria interventions from within their own countries as well as from international organizations prior to the availability of a malaria vaccine. The local data included coverage and impact of existing interventions. Countries would also want international data on the impact and cost-effectiveness of the range of available malaria-control interventions. The international data could come from WHO, the Roll Back Malaria Partnership (RBM), modeling, published literature and other sources. If a vaccine is introduced, they would then want to have local data on the changes in impact and cost-effectiveness of other interventions. Countries indicated that they would want national estimates of the affordability of a malaria vaccine at the same time as phase 3 data, with a sustainable national commitment in place after licensure but prior to an introduction decision.

Countries indicated it was critical that the global community estimate the vaccine price for public use and provide information on donor subsidies at the same time as phase 3 data, when countries would evaluate national affordability. Countries also indicated that data on the vaccine supply would be critical at the same time as phase 3, with additional evidence of supply security provided in the post-licensure period.

SUMMARY FINDINGS OF THE EXTERNAL EVALUATION

Participants gave the DMF guide development process high marks, with 96% indicating that they would recommend it to a colleague. More specifically, 90% indicated that the guide will be extremely or very useful for the preparation process prior to vaccine licensure, while 88% indicated it would be extremely or very useful for making decisions after a vaccine is licensed. In addition, 77% indicated it would be extremely or very useful when considering the decision-making process for other vaccines, 79% felt that the meeting facilitators were neutral (neither promoting nor discouraging introduction of a malaria vaccine), and an equal percentage felt that facilitators did not promote any specific vaccine under development.

Interestingly, 70% indicated that the timing of the DMF guide preparation was about right, 5% indicated it was already too late, and 25% felt it was too early. The recommendations received form participants called for similar meetings to support technical development and central coordination of the information identified in the DMF guide. Such a process was seen as valuable to build the foundation of rapport, awareness, and coordination among high-level decision-makers, given that many had divergent expertise (e.g. malaria and immunization; research and program implementation).

DISCUSSION

The research described above demonstrates that it is possible to plan for national decision-making for a new intervention and that African health officials value this

process. The research also shows that developers, partners, and countries should begin to consider what will be needed by countries at least three to five years before an intervention is anticipated to be approved by the appropriate regulatory authorities. The actual timing of a decision relative to licensure, as well as the ultimate process, will vary among countries and interventions. A guide developed jointly with countries to establish the decision framework should increase the likelihood of evidence-based and timely decisions within that variability, but would not guarantee such an outcome.

After the Africa regional guide was validated in 2008 as a common resource, MVI engaged a number of malaria and immunization program managers within African health ministries in a discussion on if, and if so, how, to start working on the requirements that will guide a decision on a possible first-generation malaria vaccine. Burkina Faso, Ghana, Tanzania and Uganda organized technical working groups to coordinate the process. The focus of the working groups is to assemble the evidence needed for a policy formulation and ensure systems are in place for a smooth decision-making process. Under the guidance of each group's chair, they develop annual or bi-annual workplans, and members may choose to carry out the planned activities (e.g. if their institution conducts studies that can provide the information needed) or they may seek services elsewhere (such as for the conduct of a desk review pertaining to particular data needs). Composition and their modes of operating vary, but common features include: 1) They are linked to an existing group within the malaria control or immunization programs; 2) Members are from Ministries of Health (MoHs), research institutes and universities, and partner organizations (e.g. WHO country offices); 3) They are officially established by the senior management at the MoH; and 4) They report to a formal advisory body to the MoH. In Ghana and Burkina Faso, the coordination is led by the National Malaria Control Program and WHO. In the two other countries, the coordination is led by local, parastatal research institutions. MVI also began discussions in 2010 with Nigeria as it has more recently becoming involved in malaria vaccine trials.

The process for the malaria vaccine decision-making framework benefited from a commitment to create a guide, building upon existing WHO guidelines, that was generic to any malaria vaccine to come and a focus on all vaccines under development instead of only one potential product [189]. Only after the guide was validated was there discussion of its application to specific products.

The iterative nature of such a process creates an important forum for those who may not normally collaborate for reasons that may include different specialties in public health and splits between researchers and implementers, academia and government [177,197]. By creating a forum with a shared technical task, each group is able to apply

its unique skills to the shared technical challenge, which also strengthens and prepares messages informing political processes.

One valuable outcome of research to plan for decision-making is the voice that countries can have. The process provides a structured means for countries to provide their input to those developing interventions. By identifying critical processes and data and by assigning responsibility to the international level, countries are signaling their expectations of developers and international organizations. The process also identifies areas, such as the product profile, in which countries would like to explicitly inform the work of developers, and it helps countries understand when such contributions are possible (i.e. years before an intervention is available.) Identifying the elements for which countries feel they should be held accountable informs and strengthens national planning capacity and management processes and provides a means for local researchers to collaborate and seek complementarities in their research.

The process of developing the malaria vaccine decision-making framework guide also illustrated some of the challenges inherent in planning for decisions on whether or not to introduce an intervention that is still under development. The most significant challenges relate to the time constraints of national staff in light of current program priorities, to risks of interventions failing in late development, and to over-promising by developers. LMIC health system managers are typically pulled in multiple directions, responding to the immense challenges faced every day. It is essential to find an appropriate balance, not asking for too much time but keeping future interventions within view when looking to the future. Because of the many time constraints, concrete planning activities will generally require a local organization or part of the government to fill a secretariat and coordination role. This was described in the previous section. Secondly, this kind of planning also means helping those involved understand that a new intervention, particularly a novel one, could fail at any time. For example, a safety concern might arise during late clinical trials or efficacy may not be seen in certain populations. Lastly, development timelines, and to a lesser extent final intervention characteristics, are notoriously difficult to predict. Countries need to understand that timelines are rarely shortened, and that they are more typically lengthened by years. These three aspects can be mitigated by transparency, education, and care in not letting activities get ahead of accumulated scientific evidence. Taken together, these three aspects necessitate a cautious, carefully planned approach when discussing future health interventions with national decision-makers.

Another challenge is to properly contextualize discussions on a new health intervention relative to existing health interventions targeting the same disease, to other interventions of the same modality (e.g. drugs, vaccines), and to priorities within the wider health system [187,189]. A novel intervention like a malaria vaccine will

enter a complex arena of existing malaria control measures, an environment of multiple new vaccines being considered by countries, and a series of established health system priorities. In some cases, interventions may replace existing ones (e.g. an improved medication), although perhaps it is more cautious to assume a new intervention will co-exist for at least some time with others. For this reason, those supporting early planning should not be seen to be pushing a single product onto countries to the exclusion of other approaches.

The basic processes and lessons described above are relevant for novel health interventions under development. Second-generation or follow-on interventions may not require the same level of research over multiple years. Precedents and advisory bodies may already exist [179]. Data may already have been collected on many essential aspects. However, a structured approach to confirm the processes and data needed, the pieces already in place, those that should be generated, and the relevant timelines, remains a valuable step during the development period of an intervention.

Such exercises do not guarantee that policy decisions will be based only on evidence and all countries will go through a predictable process. Political decisions in some situations will triumph other factors [174]. Or there can be a last-minute scramble to agree on the evidence needed to support the decision and collect it.

A structured approach provides clear insights into what data countries will need for a decision [177]. The process can help governments, researchers, community activists, and others to reach consensus on the type of evidence to base the decision on and have realistic expectations on what to expect from new interventions, the relevant timeframes, as well as funding requirements. It informs the work of those developing an intervention, allowing the clinical activities to respond to questions for public health/policy as well regulatory requirements. It is a capacity building and health systems strengthening exercise creating a pool of expertise to inform government decisions after the intervention is available, while allowing greater clarity on roles and responsibilities for different stakeholders and parts of government.

When anticipating a decision-making process, those providing support must understand that their efforts may lead a country to decide to adopt an intervention, to decide not to adopt it, or to call for further studies. Countries with timely "no" decisions help international funding bodies, procurement agencies and manufacturers as they do their own long-term planning. Countries that are undecided can be the most challenging for these bodies.

CONCLUSION

This paper argues for the importance of early planning for country decisions on new health interventions. Malaria vaccines provide one example of an approach and

multiple lessons, identified above, should be considered for other new interventions. With any new intervention, the balance will remain between working "at risk" to anticipate an intervention versus the more traditional path of waiting until after licensure. The priority for health systems is to address health challenges, which means first using available tools. In addition, a small amount of time invested early on new interventions has the promise to pay off immensely down the road in terms of addressing those same health challenges.

While there is always a risk that an intervention under development will fail as it gets into late development, the chances get slimmer and slimmer. One means of managing the development risk is for countries to do nothing until an intervention is approved. A second, preferred alternative is to determine which planning steps are appropriate and minimally invasive to take prior to intervention availability. One guaranteed outcome of the former, historical approach is that effective new interventions sit unused after development. This paper argues that the latter approach leads to better public health decisions and greater public health impact through accelerated decisions on whether or not to use a new intervention once available.

AUTHORSHIP

AB and ABN co-led the research, analysis and interpretation. AB drafted the manuscript and ABN provided critical additions and revisions.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

AB and ABN declare that they have no conflicts of interest regarding this work.

FUNDING

CHAPTER 7. MODELING THE PUBLIC HEALTH IMPACT OF MALARIA VACCINES FOR DEVELOPERS AND POLICY-MAKERS

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ABSTRACT

INTRODUCTION

Efforts to develop malaria vaccines show promise. Model-based estimates can be used to inform decisions by vaccine developers and policymakers on the use of malaria vaccines as complements to existing interventions. However, the complexity of such models often makes them inaccessible to non-specialists. This paper reports on a Malaria Vaccine Model (MVM) tailored to the needs of developers and policymakers.

METHODS

The MVM has three modules: supply and demand forecasting; public health impact; and implementation cost and financing requirements. These modules include pre-entered reference data and also allow for user-defined inputs. The model includes an integrated sensitivity analysis function. Model functionality was demonstrated by estimating the public health impact of a pre-erythrocytic malaria vaccine with 85% efficacy against uncomplicated disease and a half-life of efficacy of four years, similar to internationally-established targets for 2025. Demand was estimated by adjusting historical vaccine implementation rates for routine infant immunization in 40 sub-Saharan African countries over a 10-year period. Assumed purchase price was $5 and injection equipment and delivery costs were $0.40 per dose.

RESULTS

The model projects the number of doses needed, uncomplicated and severe cases averted, deaths and disability-adjusted life years (DALYs) averted, and cost to avert each. In the demonstration scenario, based on a projected demand of 532 million doses, the MVM estimated that 150 million uncomplicated cases of malaria and 1.1 million deaths would be averted over 10 years. This is equivalent to 943 uncomplicated cases and 7 deaths averted per 1,000 vaccinees. In discounted 2011 US dollars, this represents $11 per uncomplicated case averted and $1,482 per death averted. If vaccine efficacy were reduced to 75%, the estimated uncomplicated cases and deaths averted over 10 years would decrease by 14% and 19%, respectively.

DISCUSSION/CONCLUSIONS

The MVM can provide valuable information to assist decision-making by vaccine developers and policymakers.

INTRODUCTION

Modeling can provide key input into public health decisions to use, or not use, new health technologies in the developing world [205,206]. Models provide data on a given intervention's impact, cost-effectiveness, and/or financing requirement estimates. Models can help inform responses to critical public health questions that are not addressed in field trials. They allow analysis of situations that are difficult or impossible to replicate in real life, such as the absolute impact of a new malaria control intervention in the absence of any existing interventions. They can help determine which parameters, and their ranges, are the most important. They provide insight into complex questions by analyzing different scenarios and identifying the ones most likely to occur [207]. It is imperative that modeling estimates be made available to support evidence-based decision-making. This paper describes a new model for vaccines against malaria, a disease that caused almost 800,000 deaths in 2009, mostly of children in sub-Saharan Africa [208]. The Malaria Vaccine Model (MVM) was designed to assist vaccine developers and policymakers in developing countries and at global organizations to make informed public health decisions.

Given the expense of research and development (R&D), those developing new public health interventions for use in poor countries must invest in interventions with the appropriate attributes (e.g., level of efficacy, costs, mode of delivery) to realize desired health impacts. As new, often more expensive, interventions become available, the pressure for global, regional, and country policymakers to make evidence-based decisions is likely to increase. Such decisions will need to be supported by modeled estimates, such as potential impact and financial requirements. The GAVI Alliance (GAVI) has invested close to $100 million since 2000 into activities related to *Haemophilus influenzae* type B (Hib), pneumococcal conjugate, and rotavirus vaccines. Establishing the value of these vaccines through the generation of impact estimates was one of GAVI's three key investment activities. GAVI's investment in these activities arose from the recognition that multi-year delays occurred in the introduction of Hib vaccine by countries, partly because of the lack of data on the burden of disease and potential impact from vaccines [209]. If the needs of intervention developers and policymakers are not anticipated far in advance, developers may waste investments, and policy and financing bodies will not be able to make timely decisions--a situation that could lead to delays in getting new interventions to those in need.

A number of models have recently focused on interventions worldwide. Some have focused on individual interventions, such as human papilloma virus, HIV, and rotavirus vaccines, in an effort to inform global policies [210–212]. By contrast, the Lives Saved Tool (LiST) estimates the impact of up to dozens of child survival interventions (including malaria interventions) across 42 low- and middle-income countries worldwide. This model, which was intended to help global policymakers prioritize

interventions, is being extended for use in individual countries [181]. Another tool, which is web-based, builds on modeled data to assist African policymakers in making local decisions on the use of intermittent preventive treatment of malaria in infants, and the ProVac Initiative in the Americas includes a model to support country decision-making on the use of new vaccines [213,214].

These examples reflect the importance of being clear about a model's purpose and target audiences, and of taking into account the impact of multiple interventions against diseases. A malaria vaccine model needs to inform vaccine developers as well as policy and financing decision-makers at global, regional, and country levels. Among other requirements, it needs to reflect the changing epidemiology in each country and allow for the consideration of malaria vaccines in the context of other malaria interventions available to countries.

Two dynamic models, recently published, estimate the potential impact of malaria vaccines. One model has been under development since 2003 at the Swiss Tropical and Public Health Institute (Swiss TPH) [215]. The second, more recent model was developed at Imperial College London [216]. Both models consider the dynamics of malaria transmission and of natural immunity to *Plasmodium falciparum*. To do so, both models use simulation approaches to reflect the underlying relationship between interventions and averted disease. However, these approaches can be difficult for non-specialists and policymakers to utilize. To obtain predictions of likely malaria vaccine impact in countries where malaria is an important public health problem or to obtain regional estimates across sub-Saharan Africa, such models need to be linked to data on geographical variation in transmission. In addition, published economic analyses of malaria vaccination based on these models [217] so far have not considered supply-side considerations, such as manufacturing capacity, which influence implementation and ultimately impact.

With global efforts to develop malaria vaccines showing promise, the PATH Malaria Vaccine Initiative (MVI) worked with the Boston Consulting Group and Swiss TPH to build on the Swiss TPH model and to increase access to the model's simulations by vaccine developers and policy audiences. An initial version of the Malaria Vaccine Model (MVM version 1.0) was developed and utilized between 2005 and 2007. It extended the Swiss TPH model, allowing for supply-side considerations and country-specific estimates, and it contributed to the MVI and Swiss TPH experience in generating predictions. For example, MVI and its collaborators used this version to inform discussions regarding the establishment of an Advance Market Commitment for malaria vaccines [218].

Version 2.0 of the Malaria Vaccine Model (MVM) was completed between 2008 and 2010. MVI led the project, collaborating with Swiss TPH and a private consulting company, Applied Strategies (AS).The first intended purpose of MVM version 2.0 was

to inform understanding at the country level of the potential impact of malaria vaccines as complements to existing health interventions. The model's second purpose was to inform global and regional policymakers of the potential impact, eventual delivery strategies, and financing needs for malaria vaccines. Thirdly, it was intended to inform R&D decisions by public-sector organizations working on vaccine development.

This paper describes the major design features, critical parameters, and outputs of MVM 2.0. A demonstration scenario was created that is used to illustrate the model utility. This demonstration scenario draws on targets for the development of a malaria vaccine set by the international community in 2006 through the Malaria Vaccine Technology Roadmap [219]. The Roadmap calls for the development and licensure of a first-generation malaria vaccine by 2015, with 50% protective efficacy lasting longer than one year against severe disease and death. The Roadmap also calls for the development, by 2025, of a vaccine with protective efficacy of more than 80%, against clinical disease and lasting longer than four years. This paper concludes with lessons from developing the MVM, and implications for others developing models that target vaccine developers and policymakers.

METHODS

OVERVIEW OF MODEL STRUCTURE

The MVM is composed of three distinct modules (Figure 15). The first module, focused on vaccine supply and demand, was developed by MVI and AS. The second module, based on Swiss TPH's model simulations, describes the public health impact expected from different malaria vaccines deployed in varying populations through several modes of delivery. The third module uses data from the first two modules and adds vaccine price and cost of delivery to estimate the total investment that would be required to achieve the potential public health gains and costs per event averted. Each module includes a built-in sensitivity analysis function for some key parameters.

One demonstration scenario was selected to illustrate the model's functionality. Descriptions of each module are provided below, followed by descriptions of the input values used in the demonstration scenario.

FIGURE 15. STRUCTURE OF THE MALARIA VACCINE MODEL (MVM).
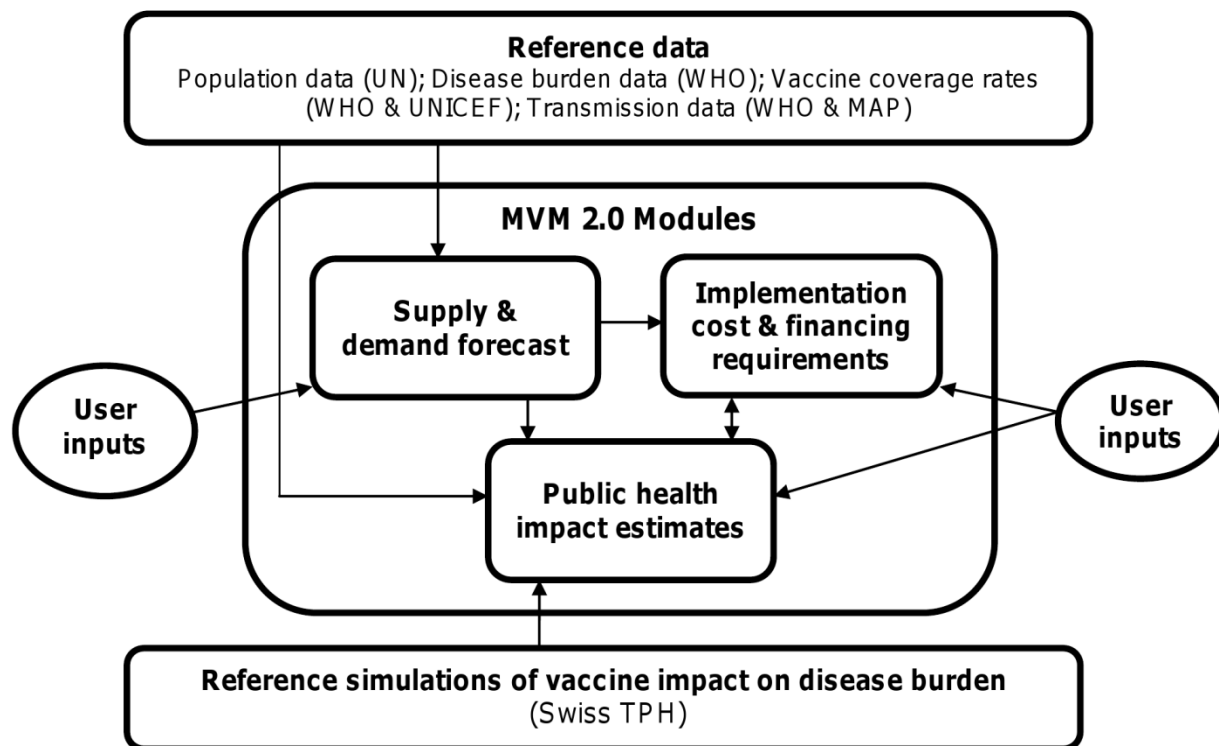
Legend: This figure depicts the MVM structure. The central box contains the three modules within the MVM: supply and demand forecast, public health impact estimates, and financial analysis. Above and below the MVM modules box are two rectangles describing the underlying reference data accessed by the modules. Arrows represent the interaction between reference data and user inputs and modules within the MVM, as well as between modules of the MVM.

SOFTWARE AND INTERFACE

MVM was built as a Microsoft® Windows desktop application using the Microsoft® .NET framework (version 3.5). The criteria considered in the software selection process, drawing on experience from the first model, were ease of use by non-experts, familiarity (similar to Microsoft Windows), ability to interface well with large datasets containing elements from the Swiss TPH model, and ease of updating new reference datasets. Microsoft Excel was considered but not selected as it would have been challenging to efficiently manage the complex data underpinning the model, and it would have been less user-friendly.

Model inputs are either selected from drop-down menus or entered as numbers. The outputs include graphics displayed on the screen, with an option to export data into Excel for customized reports.

SUPPLY AND DEMAND FORECAST

Based on user inputs and reference data, the supply and demand forecast module predicts the quantity of vaccines that will be available at a given time and the number of doses that are in demand by countries (Table 21 and Table 22).

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TABLE 21. SUPPLY AND DEMAND MODULE: USER INPUTS FOR SUPPLY PARAMETERS.

Parameter name	Definition	Input values
Manufacturing capacity	Describes current known or estimated capacity, and timelines of new facilities.	Number of doses and year available
Year of vaccine approval	The user determines the year of approval by a national regulatory authority (NRA) and World Health Organization (WHO) prequalification, which are assurances of vaccine quality as a prerequisite for availability. The user then selects whether NRA approval or WHO prequalification is required by each country.	Year

All countries with an annual average birth cohort estimate and projection from the Population Division of the Department of Economic and Social Affairs of the United Nations (UN) as of 2008 were included in the MVM. Users may create classifications and/or groupings of these countries to help facilitate and focus a particular analysis. For example, users could select only those countries that are GAVI-funding eligible, they may focus on 40 high malaria disease burden countries in sub-Saharan Africa, or they may generate estimates for a single country.

REFERENCE DATA

Population: Data on the population of each country were drawn from the UN Population Division [220]. Users may select the age range of the target population consistent with the expected vaccination strategies of potential malaria vaccines (Table 22).

Vaccine coverage: The MVM included historical and projected vaccine coverage for Bacille Calmette-Guerin (BCG); first, second, and third doses of diphtheria-tetanus-pertussis (DTP1, DTP2, DTP3); and measles-containing vaccine (MCV) for each country. Users may set the maximum vaccine coverage for each country equal to historical data for any of the above vaccines, or they may set maximum vaccine coverage at any level from 0–100%. Data on the 2005–2007 coverage rates were obtained from the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) [221]. Future coverage levels were based on projections from WHO (Lara Wolfson, WHO ICE-T v4.0, Oct 2007, unpublished data).

TABLE 22. SUPPLY AND DEMAND MODULE: USER INPUTS FOR DEMAND PARAMETERS.

Parameter name	Definition	Input values
Manufacturing capacity	Describes current known or estimated capacity, and timelines of new facilities.	Number of doses and year available
Year of vaccine approval	The user determines the year of approval by a national regulatory authority (NRA) and World Health Organization (WHO) prequalification, which are assurances of vaccine quality as a prerequisite for availability. The user then selects whether NRA approval or WHO pre-qualification is required by each country.	Year
Years between vaccine approval and country adoption	Identifies time between the first year that a vaccine is available and the year that each country implements a vaccine.	Number of years
Maximum coverage	Describes the largest percent of the target population reached in each country.	%
Years for each country to reach maximum coverage	Describes the number of years between implementation and achievement of maximum coverage.	Number of years
Number of doses per regimen	Describes the number of doses required to fully vaccinate each person at efficacy levels described under the public health impact module.	3,4
Vaccine wastage	Describes the proportion of doses that will not be administered. Vaccine wastage is a percentage set by the user, but suggestions are provided in the MVM based on the number of doses per vial, according to WHO projected vaccine wastage (available at: http://www.who.int/immunization_delivery/systems_policy/logistics_projected_wastage/en/index.html; accessed: 2011 Apr 28). The model does not take buffer stock (a one-time 25% increase of vaccine doses distributed in a logistics system in the first year of implementation) into account.	%
Target population	The age group in which the vaccine is used: infants (represented by the annual birth cohort for each country), 5-17 month olds, 1 year olds (yos), 0-4 yos, 1-4 yos, 1-39 yos, 5-39 yos, or the total population	Age range
Product preference	In the case of multiple available vaccines, the user may model scenarios in which particular countries prefer one vaccine over another.	Product name
Maximum acceptable price	The maximum price a country is willing to pay for a vaccine.	Dollars

Supply estimates are based on user inputs describing each manufacturer's anticipated capacity, timing of expected increases in capacity, and year of vaccine availability, assuming development success and regulatory approval. Demand estimates in the form of total doses required per year are based on the size of the target population in each country, the maximum level of coverage and time taken to reach this level, and the number of doses in a regimen. Along with the above inputs and reference data, the model outputs include the year the vaccine is available for use in each country (from both supply and approval perspectives), the number of doses demanded, and the number of doses available to meet demand in any given year.

For the demonstration scenario, it was assumed that supply would not be constrained by manufacturing capacity and that all countries would require vaccine prequalification by WHO. Forty countries in sub-Saharan Africa that experienced a malaria disease burden in 2006 of 100 deaths per year or greater, or that experienced a malaria mortality rate of 10 deaths per 100,000 per year or greater, were included. The criteria were intended to allow inclusion of large countries with many cases at a relatively low rate, and small countries with few absolute cases but which have a significant rate relative to the population size. The time horizon modeled in the demonstration scenario was 10 years of vaccine use.

Demand in the demonstration scenario assumed a vaccine regimen of three doses delivered to a target population of infants and a wastage rate of 10%. No product preference or maximum acceptable price was modeled. Year of country adoption of the modeled malaria vaccine, maximum coverage, and the time to reach maximum coverage were benchmarked from historical data, based on the uptake of Hib vaccine from 2001 to 2010 (either on its own, in the form of a tetravalent vaccine with DTP, or as a pentavalent vaccine with DTP and hepatitis B). WHO data on Hib coverage served as a reference point for the number of years post vaccine availability that each country began implementation, each country's maximum coverage (DTP3 coverage was selected to represent maximum), and the time it took for Hib3 to match DTP3 levels (available at: http://www.who.int/immunization_monitoring/routine/immunization_coverage/en/index4.html; accessed November 2010) (Figure 16. Estimated number of malaria vaccine doses delivered per year over a 10-year period.). Malaria is a much better recognized health threat than Hib, and countries have gained experience in vaccine implementation since Hib introduction began. Therefore, all countries that did not adopt Hib in the first two years of its availability were modeled as adopting a malaria vaccine two years earlier than they adopted Hib. Time to maximum coverage was not adjusted.

FIGURE 16. ESTIMATED NUMBER OF MALARIA VACCINE DOSES DELIVERED PER YEAR OVER A 10-YEAR PERIOD.
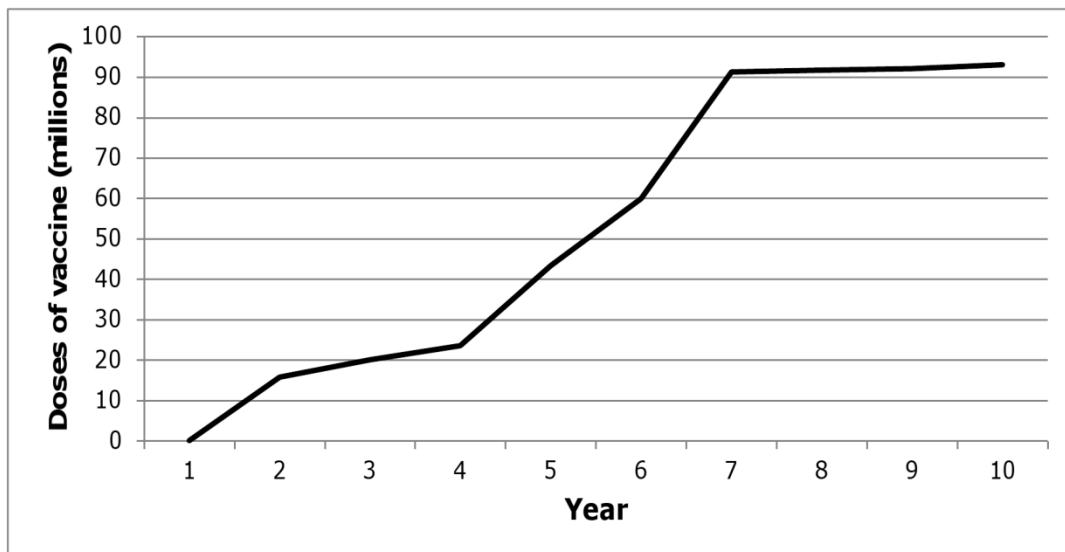
Legend

Numbers of doses delivered are based upon reports of the use of Hib vaccine to WHO between 2001 and 2010 from 40 countries in sub-Saharan African with significant malaria burden.

If countries did not introduce Hib by 2010, they were excluded from the demonstration scenario. The exception was Nigeria, which appears to be moving more quickly to adopt more recent vaccines than it did with Hib [222]. Nigeria was assumed to adopt the malaria vaccine midway through the time horizon analyzed, and reach maximum coverage in two years.

PUBLIC HEALTH IMPACT ESTIMATES

The natural history and epidemiology of *P. falciparum* were modeled using a stochastic simulation model developed at Swiss TPH and described in detail in previous publications [223–228]. The age structure of the simulated human populations was based on Ifakara, Tanzania [229]. Model parameters were estimated by fitting the model to field data from a variety of settings across sub-Saharan Africa [230]. Pre-vaccination transmission intensity was scaled to give the different required values of the initial exposures (e.g. 1, 10, or 100 ibpa as described below). Pathogenesis and case management (including hospitalization of severe cases) was also simulated as described in previous publications [225,228,231]. Thus, any changes in transmission intensity induced by a vaccination program (due to herd immunity or other indirect effects) were captured, but the vectorial capacity followed the identical periodic pattern as in the absence of vaccine. The MVM allowed the Swiss TPH outputs to be estimated for key parameters found in the first MVM to be of interest to developers and policymakers—for example, specific populations in specific transmission settings and utilization of particular modes of delivery (Table 23).

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TABLE 23. PUBLIC HEALTH MODULE USER INPUTS.

Parameter name	Definition	Input values
Type of vaccine	Describes the antigens targeted. Options include pre-erythrocytic (PE), blood-stage (BS), or a combination of these plus a vaccine component targeting sexual, sporogonic, and/or mosquito (SSM) antigens to interrupt transmission from an infected person to the next.	PE, BS, PE + BS, PE + SSM, BS + SSM, PE + BS + SSM
Vaccine efficacy	Describes the efficacy of the vaccine immediately after completing the full regimen. For a pre-erythrocytic vaccine, efficacy is defined as the proportional reduction in incidence of blood-stage infection. For a blood-stage vaccine, efficacy is defined as the proportional reduction in blood-stage parasite density. For a vaccine targeting the SSM antigens, efficacy is defined as the proportion by which the probability that a mosquito is infected during one bite is reduced [232].	35%, 50%, 60%, 75%, 85%
Half-life of efficacy	Describes the point at which the efficacy (as described above) has fallen to half of its initial value. Half-life of efficacy assumes an exponential decay of efficacy.	2, 4, 10 years
Future malaria transmission	Transmission is described as the percent of the population of the country of interest residing in each of five categories of entomological inoculation rate (EIR), which is a measure of how many infectious bites a person receives per year (ibpa) in a given setting. The starting transmission level for each country is derived from the reference data described below. The user can choose to keep transmission fixed at this level throughout the time period under consideration, or can enter scenarios of future transmission, for example, specific to an individual country.	See Supplement A
Mode of vaccine delivery	Describes the means by which the vaccine is delivered to its target population. The options include routine vaccination via a country's immunization system and campaign delivery.	See Table 24
Booster compliance rate	Percentage of population originally vaccinated who receive a single booster dose.	50%, 80%, 95%

Disease burden: Morbidity and mortality rates were obtained from the WHO for both the entire population and the population under 5 years of age [233]. In situations where no data specific to the under-5 population were available, the total population's

malaria morbidity and mortality rates were applied. Projections of future disease burden were based on each country's current morbidity rate or current mortality rate multiplied by the country's population forecast for the selected population. Options for changing the future disease burden, such as from implementation of other interventions, are described below.

Malaria transmission: In the MVM, transmission is represented by the entomological inoculation rate (EIR). EIR, a measure of the intensity of malaria parasite transmission, is the product of the human biting rate of mosquitoes and the proportion of mosquitoes infected with sporozoite-stage malaria parasites. EIR is measured in the number of infective bites per person per annum (ibpa). Two sources of data on transmission were incorporated into the MVM, allowing the user to choose between them. Data from WHO were in the form of the percentage of each country's population at high or low risk for malaria infection [233]. Alternatively, the Malaria Atlas Project (MAP) data were in the form of *P. falciparum* parasite prevalence [234]. Neither the WHO nor the MAP source data were provided in the form of EIR, requiring the data to be converted using methodology endorsed by both MAP and an external expert panel (see Supplement A for details). The MVM calculates the percentage of each country's population that falls into each of five EIR levels (0, 0.1, 1, 10, and 100 ibpa). The user is also free to input future changes in levels of transmission for countries.

VACCINE IMPACT ON DISEASE BURDEN

Pre-erythrocytic vaccination was simulated as described in previous publications [232,235], assuming that vaccination leads to both a reduction in the proportion of inoculations from the bites of infected mosquitoes and resulting blood-stage infection (an estimate of efficacy which is substantially higher than the proportion of clinical episodes prevented by such a vaccine [236]). Blood-stage vaccination was simulated by assuming that the vaccine reduced blood-stage parasite densities [232]. Vaccination scenarios were paired with non-vaccination comparator simulations to provide impact estimates of the outcomes found to be of greatest interest from the first MVM: the numbers of cases (uncomplicated and severe), deaths, and disability-adjusted life years (DALYs) averted through vaccine use over time periods of interest.

MVI, AS, and Swiss TPH agreed on possible combinations of input parameters anticipated to be of interest to vaccine developers and policymakers, resulting in over 100,000 scenarios to be simulated (Table 24). Each scenario was run multiple times, and mean frequencies of events were computed in order to reduce stochastic variability in the estimates of health effects. The results of these simulations are stored in look-up tables as reference data in the MVM, drawn upon as necessary according to the particular combinations of inputs for specific populations in the scenario chosen by the user.

Estimates of the public health impact of a vaccine are generated based on the type of vaccine, initial efficacy and half-life of efficacy, mode of vaccine delivery, and transmission setting. The model outputs from this module are the total number of uncomplicated cases, severe cases, deaths, and DALYs averted through use of the vaccine. The model also provides the number of each of these events averted per 1,000 vaccinees.

For the demonstration scenario, a pre-erythrocytic vaccine with an efficacy of 85% against uncomplicated malaria cases was assumed. The half-life of efficacy was four years, meaning that four years after receiving the third dose, vaccine efficacy would be 42.5%. These values of efficacy and half-life were selected for the demonstration scenario as they were expected to be broadly consistent with targets set by the international community [237]. Routine infant immunization (via the Expanded Program on Immunization) was selected as the mode of delivery. As described above, the user enters the projected country EIR into the MVM. Three different projections were created to reflect decreases in transmission from current levels, due to implementation of existing interventions. The projection applied to the demonstration scenario used the MAP-derived EIR distribution across countries, shifting one-quarter of the population at each EIR level (0, 0.1, 1, 10, and 100 ibpa) into the next lower category (e.g., from EIR of 10 down to 1). The other two scenarios shifted either one-half or three-quarters of the population at each level to the next lower level of EIR. It was assumed that the percentage of the population residing in each EIR level decreased in a linear fashion to the next lowest level over a period of five years, and remained constant for the remaining five years modeled.

TABLE 24. VACCINATION STRATEGIES AND NUMBER OF SIMULATIONS OF EACH SCENARIO GENERATED BY SWISS TPH.

Strategy #	Strategy name	Scenarios	Replications of each strategy
0	No vaccination	5	2,500
1	Routine infants with a boost 2 years later	6,480	55,232
2	Routine infants (no boost)	2,160	18,492
3–4	Routine infants with a boost 2 years later PLUS a catch-up of 5–17 month olds (no boost)	19,440	166,869
5–6	Routine infants (no boost) PLUS a catch-up of 5–17 month olds (no boost)	6,480	55,634
7–8	Routine infants with a boost 2 years later PLUS a catch-up of 1–5 year olds (no boost)	19,440	168,160
9–10	Routine infants (no boost) PLUS a catch-up of 1–5 year olds (no boost)	6,480	55,685
11–12	Routine infants with a boost 2 years later PLUS a catch-up of 1–39 year olds (no boost)	19,440	166,318
13–14	Routine infants (no boost) PLUS a catch-up of 1–39 year olds (no boost)	6,480	55,408
15	Routine 5–17 month olds with a boost 2 years later	6,480	55,143
16	Routine 5–17 month olds (no boost)	2,160	18,787
17–18	Periodic 1–5 year olds every 5 years (no boost) PLUS a catch-up of 6–39 year olds (no boost)	6,480	55,684

Legend: Strategies reflect different implementation approaches and target population. Scenarios are the variations of each strategy to cover potential user-selected transmission settings and vaccine characteristics such as efficacy and half-life. "Infants" mean children approximately six weeks of age at first vaccination. "Routine" vaccination means that it is happening continuously as individuals reach the target age. "Catch-up" campaign means a one-time, mass vaccination targeting the indicated age range. "Periodic" campaign means regular mass vaccinations targeting the indicated age range, at the indicated frequency.

IMPLEMENTATION COST AND FINANCING REQUIREMENTS

The implementation cost and financing requirements module estimates the total investment that would be required to purchase and deliver the vaccine simulated in

the public health impact module, and the cost of each event averted in US dollars. User inputs are presented in Table 25.

TABLE 25. FINANCIAL MODULE USER INPUTS.

Parameter name	Definition	Input values
Vaccine price	The cost of the vaccine in dollars as set by the manufacturer, including insurance and delivery to the airport of a country specified by the consignee.	$
Cost of injection equipment and disposal	The cost of the syringes and waste disposal equipment.	$
Cost of vaccine delivery	Different costs can be entered for each country, allowing customized estimates that take into account factors such as the cold-chain capacity and transport needs of each.	$
Discount rate	A distinct discount rate can be entered for the supplier and the donor, reflecting the cost of capital of each.	%
Financing scenario	Users select the financing start and end dates, and the level of country co-pay to complement support from donor organizations. Users can create various financing scenarios.	Dates; dollars

REFERENCE DATA

This module does not include pre-entered reference data.

MODULE SUMMARY AND DEMONSTRATION SCENARIO

Based on the user inputs of vaccine price and implementation costs, the module generates the total investment required to achieve the public health gains estimated in the public health impact module. Depending on the assumed financing scenario, for example, if donors support a portion of the purchase and implementation costs, the model provides a break-down by donor and country contributions for each year of vaccine use—a breakdown that was found to be of significant interest to those using the original MVM. A discount rate can be used to calculate the present values of the total investments, and can be summed to estimate the net present value.

The demonstration scenario assumed a vaccine price remaining constant at $5/dose, including insurance and delivery to the airport of a country as specified by the consignee. Inflation was not included. This price is broadly consistent with the assumed cost of other new vaccines for low-income countries, such as pneumococcal

conjugate and human papilloma virus vaccines. In addition to the vaccine price, the implementation cost modeled was $0.33/dose and injection equipment costs were $0.07/dose, totaling $1.20/fully immunized child (FIC). Costs were based upon a simulation study of the cost of introducing a malaria vaccine into the routine immunization system in Tanzania [238], and were also consistent with results from a similar study following the introduction of a pentavalent DTP-hepatitis B-Hib vaccine in Ethiopia [239].

SENSITIVITY ANALYSIS

The MVM allows the user to perform sensitivity analyses to determine the magnitude of the impact of select factors on the model outputs. Sensitivity-analysis outputs can be generated for any given year, or over the entire period modeled. Sensitivity-analysis results indicate the impact of the adjusted parameter(s) on the public health and financial estimates. The following model inputs can be increased or decreased by a percent of the value set by the user: country willingness to pay (maximum price); discount rate; price of vaccine or injection equipment; and percentage of product wastage. Country adoption and product availability inputs can be increased or decreased by a number of years relative to a baseline. Alternatively, for those parameters not included in the formal sensitivity analysis, such as vaccine efficacy, half-life of efficacy, transmission, or the use of a booster dose, model outputs from several scenarios can be saved and compared.

RESULTS

The demonstration scenario was run to illustrate the functionality of the MVM. The inputs selected for this scenario were described above in the Methods section. The outputs of the demonstration scenario are presented below.

SUPPLY AND DEMAND MODULE

Based on the historical data from Hib, adapted as described above, in its first two years of use, over 16 million (M) doses of malaria vaccine were required to meet demand, plateauing at 93 M between years 7 and 10 (Figure 16). Over the course of 10 years of vaccine use, the MVM outputs from the demonstration scenario indicated that a total of 532 M doses would be used in the 40 African countries in the analysis.

PUBLIC HEALTH IMPACT MODULE

The output from the supply and demand module on the number of doses of vaccine required directly contributed to the calculation of public health impact. While the underlying calculations were made for each country, the results were presented at an aggregate level to give a sense of impact across all of sub-Saharan Africa.

Based on the demonstration scenario inputs, an estimated 150.4 M uncomplicated cases of malaria would be averted over 10 years of vaccine use (Table 26), with 44.3 M

averted in year 10 alone (Figure 17). Over this same period, 5.1 M severe cases of malaria would be averted, along with 1.1 M deaths and 28.4 M DALYs. The number of severe cases, deaths, and DALYs averted annually increased over the whole time period, with the largest number seen in the final year: 1.3 M, 258,000, and 6.9 M, respectively (Figure 17). MVM provides these data as ratios of the number of events averted per 1,000 vaccine recipients, as well. Averaged over the 10-year time period, the inputs for the demonstration scenario led to 943 uncomplicated cases averted/1,000 vaccinees, 32 severe cases averted/1,000 vaccinees, 7 deaths averted/1,000 vaccinees, and 178 DALYs averted/1,000 vaccinees (Table 26).

TABLE 26. CUMULATIVE NUMBER AND RATIO OF MALARIA EVENTS AVERTED, AND COST PER EVENT AVERTED.

	Total events averted over 10 years	Events averted/1,000 vaccinees	$/event averted (undiscounted)	$/event averted (discounted)
Uncomplicated malaria	150,394,000	943	19	11
Severe malaria	5,114,000	32	561	309
Death	1,067,000	7	2,690	1,482
DALY	28,394,000	178	101	56

IMPLEMENTATION COST AND FINANCING MODULE

The cost per event averted was calculated in the MVM for each year of the analysis using the non-discounted total investment (vaccine price plus injection equipment plus delivery costs). It could also be informative to consider the present value (PV) of the investments, calculating the cost per event averted with a discounted number. These data are presented in Table 26 as the aggregate over the entire period. In the demonstration scenario, the undiscounted cost was $19 per uncomplicated malaria case averted, $561 for each severe case averted, $2,690 for each death averted, and $101 for each DALY averted. After discounting the total investments at 5% to a net present value, the costs were $11, $309, $1,482, and $56, respectively.

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FIGURE 17. ANNUAL MALARIA EVENTS AVERTED IN 40 HIGH-BURDEN AFRICAN COUNTRIES BY THE SIMULATED VACCINE.
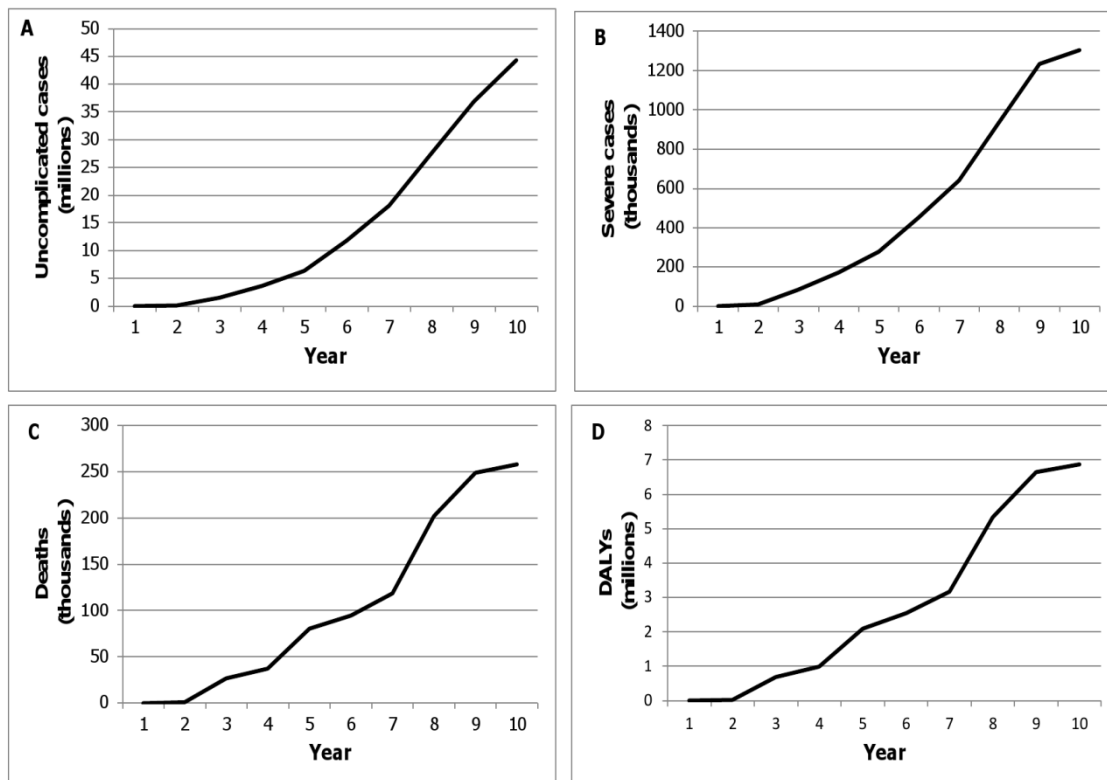
Legend

MVM projections of the number of A) uncomplicated cases; B) severe cases; C) deaths; D) DALYs averted by use of an 85% efficacious PE vaccine with an efficacy half-life of 4 years over 10 years in sub-Saharan Africa.

SENSITIVITY ANALYSIS

Lower vaccine efficacy and a larger decrease in malaria transmission were considered (Figure 18). If efficacy was set to 75% instead of the demonstration scenario level of 85%, the estimated uncomplicated cases averted over 10 years would decrease by 14%, from 150.4 M to 130 M. Similarly, the total number of severe cases, deaths, and DALYs averted were predicted to decrease by 14%, 19%, and 18%, respectively (data not shown). While the total investment would remain the same, fewer events would be prevented, increasing the undiscounted (and discounted) cost/event averted from $19 ($11) per uncomplicated case to $22 ($12). The cost per severe case averted would increase to $652 ($359), per death averted to $3,340 ($1,840), and per DALY averted to $124 ($68).

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FIGURE 18. IMPLICATIONS OF CHANGING VACCINE EFFICACY OR TRANSMISSION INTENSITY ON IMPACT.
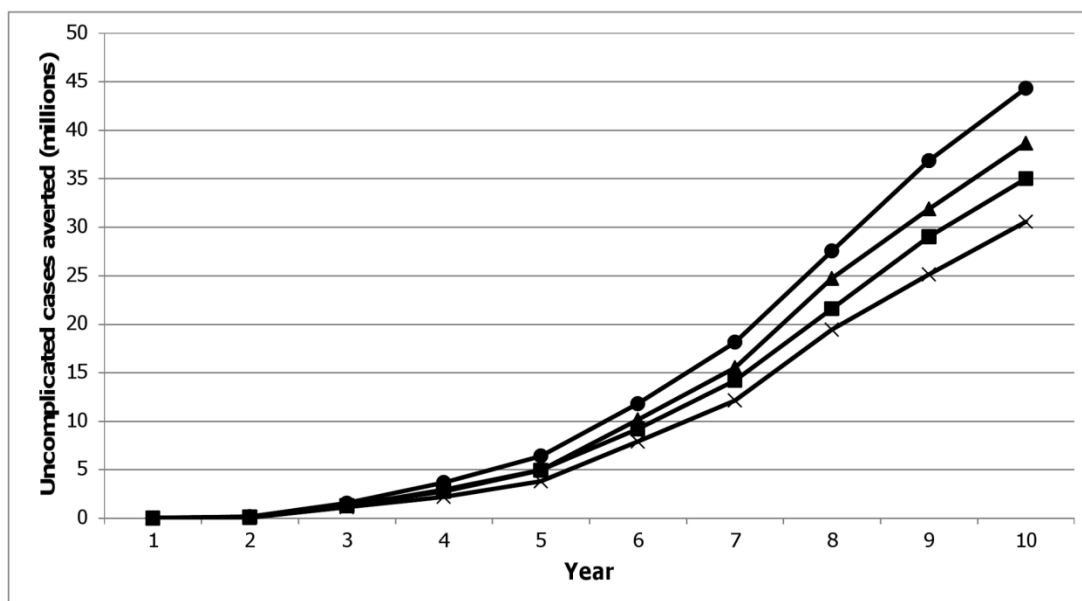
Legend

The impact of vaccine efficacy and transmission setting on the potential number of uncomplicated malaria cases averted annually over a 10-year period of vaccine use. The demonstration scenario of 85% efficacy at one-quarter step reduction in transmission averted the most cases (●), followed by 85% efficacy at one-half step reduction in transmission (▲), 75% efficacy at one-quarter step reduction in transmission (■), and 75% efficacy at one-half step reduction in transmission (×).

Great progress has been made over the past decade in scaling up the current malaria control interventions [208]. While our demonstration scenario shifted one-quarter of the population in each EIR category to the next lower level of risk, it is possible that national malaria control programs and their partners will achieve greater success in lowering transmission. To understand the potential public health gains that could be attributed to the vaccine in a setting with lower transmission, and therefore many fewer cases to avert, we also modeled the scenario described in the Methods section in which one-half of the population in each EIR category is shifted to the next lower level of risk. MVM outputs indicated that such a shift would lead to approximately 21% fewer events averted across all categories over the 10-year period, relative to the demonstration scenario.

DISCUSSION

This paper describes a collaborative effort to develop a malaria vaccine model of supply, demand, public health impact, and costs that is sufficiently robust to generate reliable outputs, yet simple enough to allow application to diverse audiences at country, regional, and global levels. The functionality of the model was demonstrated

by estimating the impact and implementation costs associated with a vaccine broadly consistent with international targets. The estimates suggest that such a malaria vaccine could have an important public health impact.

The model is intended to have the flexibility to include real-life data in order to generate outputs. For example, implementation in the demonstration scenario took place over 10 years according to historical data from Hib, which means implementation and impact did not smoothly increase year to year, but increased in rate particularly as large countries began implementing.

In the future, the model will also be applied to other types of malaria vaccines that are being considered or that are in R&D currently—for example, vaccines that have different efficacy levels, delivery strategies, and costs. Data from studies of the most advanced malaria vaccine, RTS,S, indicate that it may cut episodes of clinical malaria in young children by about half [240]. Additional modeling will need to be done to inform planning for such a vaccine. The MVM also allows for the generation of estimates if multiple vaccines were to be available.

MODEL DESIGN

The balancing of a comprehensive approach with simplicity can lead to models that attempt to include all considerations and field data, yet lose their usability and interpretability. On the other hand, a complex, vector-borne, parasitic disease, like malaria, is not well-reflected by overly simplified assumptions. Collaborators settled on a compromise to integrate the strengths of a comprehensive and computationally intensive model associating epidemiological patterns and vaccine characteristics with impact from Swiss TPH with simpler, specially designed, component modules for less computationally intensive elements such as the number of individuals that might be immunized. The MVM integrates pre-defined inputs from Swiss TPH with the other models through a tailor-made user interface, providing a seamless means of inputting data and generating outputs. The design of the second MVM reflects the understanding gained about underlying model design and software, parameters, potential uses, and associated outputs.

The first MVM was developed in Microsoft Excel. However, the large amount of data and the complexity of the model made this a less user-friendly option. The second MVM moved to the Microsoft .NET framework. It greatly improved the usability of the model. One negative consideration of the second MVM's software is that it is proprietary (although granted with an unrestricted license for use in the MVM). This may make it more challenging for others wanting to extend the MVM interface for other uses. Secondly, the program requires 2.98 gigabytes of storage space. The majority (about 90%) of the required space is needed to hold the Swiss TPH simulation reference data.

USES AND OUTPUTS

The MVM and outputs are intended to be freely available to public and not-for-profit organizations. The interface is intended to provide an accessible means for users to enter data and generate results. The outputs of the MVM are intended to address questions arising from three distinct audiences: country policymakers, regional and global policymakers, and vaccine developers. Each of these audiences could seek different but interrelated information from the MVM.

While misinterpretation of results is a consideration for any model, the MVM is designed to decrease this likelihood, in part by emphasizing relatively straightforward outputs. The authors anticipate that guidance and interpretation will be required to allow other groups to properly use and interpret the results of the MVM.

The MVM can provide country policymakers with estimates of impact and costs of malaria vaccines tailored to their local transmission setting, and based on local assumptions about implementation, such as delivery strategy, coverage, and cost. For regional and global policymakers it can provide multi-country estimates that may support the setting of standards on the use of a malaria vaccine. The types of outputs generated by the MVM are relevant to policymakers seeking information on the role of malaria vaccines as complements to other strategies to address malaria. Information can be made available to countries through pre-formatted two-page or customized reports, or countries may choose to run scenarios themselves. Similar pre-formatted or customized reports can be generated for individual countries or aggregated across multiple countries for regional and global-level policymakers.

For malaria vaccine developers and global organizations, the MVM can help inform trade-offs between various product characteristics, delivery options, impact, and costs, as well as supply and demand considerations. Reports generated by the MVM can be customized to address questions arising from vaccine candidates being considered for development.

PARAMETERS

The MVM includes pre-entered reference parameters where possible, while allowing users the flexibility to enter a wide range of scenario-specific parameters when desired. The number of parameters and associated ranges led to more than 100,000 scenarios from Swiss TPH. A number of the parameters and associated assumptions in the MVM merit specific discussion.

There is no universally agreed-upon means for converting malaria transmission data from WHO and the Malaria Atlas Project into EIR for each country. Furthermore, there is no standard for projecting how transmission may change for each country. MVI sought the participation and validation of expert collaborators and arrived at an approach, as described in Supplement A, which transparently translates existing data

into EIR-equivalents. Users are able to customize assumptions of underlying and changing transmission. Perhaps in the future there will be greater standardization on one means of measuring the prevalence and transmission of malaria.

One of the strengths brought by building upon the Swiss TPH model is that it is parameterized with extensive field data on malaria. A challenge is that the current standard for mathematical models of malaria (Swiss TPH and Imperial College London) is to assume that efficacy decays according to an exponential decay with a certain half-life. The demonstration scenario assumed a four-year half-life. However, the relationship between the half-life of efficacy and vaccine duration for malaria vaccines is not yet fully clear.

The purpose of the demonstration scenario presented in this paper was not to forecast when individual countries might adopt a malaria vaccine. Rather, the purpose was to demonstrate the functionality of the model. That said, the timing of implementation by countries, and time to maximum coverage, are important drivers of impact. Large country adoption can influence estimates due to their size, as the model is built upon estimates for individual countries.

CONCLUSION

The field of malaria is rapidly changing, with malaria transmission decreasing, partly due to other effective interventions, and the potential for an efficacious vaccine on the horizon. These changes are important to those developing malaria vaccines as well as those who make policy decisions on the use and financing of vaccines. This paper presents the iterative work undertaken towards developing a robust and user-friendly model on supply, demand, public health impact, and costs, to inform this changing field. Not-for profit partnerships invest millions of dollars each year on the development of malaria vaccines. The current MVM, future iterations, and other models like it can provide additional reassurance that those investments are well-targeted. Policymakers at national, regional, and global levels must make decisions on the optimal means to prevent the millions of malaria cases each year and, more broadly, on the means to address diseases and health problems prevalent in developing countries. The MVM can help inform these critical public health decisions.

ACKNOWLEDGEMENTS

FINANCIAL DISCLOSURE

COMPETING INTERESTS (PERSONAL, FINANCIAL, OR PROFESSIONAL)

JN – No competing interests.
VC – No competing interests.
CL – No competing interests.
NM – No competing interests.
TS – No competing interests.
CS – No competing interests.
KM – No competing interests.
AB – No competing interests.

ROLE OF AUTHORS

JN and AB drafted the manuscript. JN generated the model results. NM, TS, KM, and AB were involved in the design and/or analysis of MVM 1.0 as the foundation for MVM 2.0. KM's contributions were largely while a student at the London School of Hygiene and Tropical Medicine. VC, CL, NM, TS, CS, and AB were involved in the design and development of MVM 2.0. All authors contributed to, reviewed, and approved the manuscript.

CHAPTER 8. SIMULATED IMPACT OF RTS,S/AS01 VACCINATION PROGRAMS IN THE CONTEXT OF CHANGING MALARIA TRANSMISSION

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ABSTRACT

Background: The RTS,S/AS01 pre-erythrocytic malaria vaccine is in phase III clinical trials. It is critical to anticipate where and how this new intervention should be implemented if trials are successful. Such planning may be complicated by changing malaria levels, as existing interventions are scaled-up.

Methods and results: Computer simulations were used to examine RTS,S/AS01 impact, using a vaccine profile based on phase II trial results, and assuming that protection decays only slowly. Settings were simulated in which baseline transmission (in the absence of vaccine) was fixed or varied between 2 and 20 infectious mosquito bites per person per annum (ibpa) over ten years. Four delivery strategies were studied: routine infant immunization (EPI), EPI plus infant catch-up, EPI plus school-based campaigns, and EPI plus mass campaigns. Impacts in changing transmission settings were similar to those in fixed settings. At 2 ibpa, the vaccine averted approximately 5 – 7 deaths per 1000 doses of vaccine when delivered via mass campaigns, but decreased rapidly at higher transmission levels. EPI, catch-up and school-based strategies averted 2 – 3 deaths per 1000 doses in settings with 2 ibpa. In settings where transmission was decreasing, naturally increasing or increasing after a sudden breakdown of malaria control EPI, catch-up and school-based strategies averted approximately 3 – 4 deaths per 1000 doses.

Discussion and conclusion: For situations with changing malaria transmission levels, it appears to be sufficient to consider simulations of pre-erythrocytic malaria vaccine impact at a range of initial transmission levels. At 2 ibpa, mass campaigns could avert the most deaths and reduce transmission, but this requires further verification and study. If delivered via established EPI systems, RTS,S/AS01 could avert approximately 6 – 11 deaths per 1000 vaccinees in all examined settings. This ratio is similar to that of approximately 7 per 1000 vaccinees estimated for pneumococcal conjugate vaccine in African infants. These results support implementation of RTS,S/AS01 via EPI in contexts where vector control interventions are already in place, providing that the phase III trials provide support for our assumptions about efficacy.

INTRODUCTION

RTS,S/AS01 (RTS,S) is the most advanced malaria vaccine under development. Work started in the 1980's, and the phase III, or final trial prior to seeking regulatory approval, began in 2009 in Africa [241]. If all goes as planned, the trial could be completed around 2015. Meanwhile, malaria continues to kill close to 800,000 people each year, almost entirely among children under five years of age living in Sub Saharan Africa [242]. Nevertheless, the epidemiology of malaria is changing across Africa. This is primarily due to the growing use of control interventions, most importantly long lasting insecticide treated bednets (LLINs), indoor residual spraying (IRS), and improved medicines for treating malaria [243]. A malaria vaccine could be a valuable, additional tool to prevent malaria mortality and morbidity.

Two major mathematical models of malaria and pre-erythrocytic malaria vaccines, such as RTS,S, have been published in the past ten years [244,245]. Both models run probabilistic micro-simulations in populations of thousands of people. The models are systematically fitted to an extensive library of field data from varying transmission settings. The transmission in an area is reflected by the entomological inoculation rate (EIR), which is a direct measure of the number of infectious mosquito bites per person per annum (ibpa). In the published model studies, the EIR is modeled at fixed levels of 2, 5, 11, 20, 42, 84, and 168 infectious bites per annum (ibpa) [232,235,246] or 3, 43, 46 81, 586, and 675 ibpa [244].

The model studies estimate that RTS,S is likely to have an important and varying public health impact, primarily according to assumed transmission in an area and delivery strategy [232,235,244,246]. Impact is quantified in terms of reduced transmission and/or cases and deaths averted. The decision to use RTS,S will partially depend on if the impact sought, apart from saving lives, includes transmission reduction. For transmission reduction, the initial transmission level and the feasibility of the delivery strategy are critical considerations. At low EIRs, such as 2 ibpa and below, transmission becomes more focal and less stable.

Model studies quantifying impact in terms of malaria transmission suggest that RTS,S will reduce transmission primarily in areas where it is already low (e.g. 3 ibpa) [244], and when delivered through mass campaigns, reaching 50% [246] or more [244] of the entire population. These studies also suggest that RTS,S will save lives and avert cases in all but the highest transmission settings in Africa when implemented through the Expanded Programme on Immunization (EPI) [232,235].

EPI programs have delivered infant vaccines in developing countries for decades. Among African infants in 2009, 73% were immunized with three doses of Diphtheria-Tetanus-Pertussis (DTP3) vaccine scheduled at approximately 6, 10 and 14 weeks of age [247]. This is the same initial schedule as is being anticipated for RTS,S. The current

clinical trials of RTS,S and regulatory plans include children aged six weeks through 17 months at first RTS,S vaccination. EPI and catch-up strategies, targeting this age range, thus represent the near-term options for implementing RTS,S. When delivered through EPI, RTS,S is likely to have greatest efficacy and impact in low to medium transmission settings [232,235], and to be most cost-effective in areas with EIR from 2 – 20 ibpa [248]. This suggests that the value of RTS,S, as a complementary intervention to save lives and prevent morbidity, is likely to grow in importance with anticipated decreasing transmission trends resulting from the scaling up of malaria interventions across Africa. Impact through EPI is questionable in very high transmission settings (e.g. 168 ipba), where a large proportion of disease episodes prevented early in life may simply be experienced with a delay and are thus not fully prevented.

Vaccine delivery strategies other than EPI, such as school-based and population-wide mass campaigns, target incrementally wider age ranges and greater numbers of people. Mass campaigns are estimated to have relatively little impact on mortality and morbidity at a transmission above an EIR of 5 ibpa [232]. School-based and mass campaign strategies for delivering RTS,S may require additional multi-year clinical studies and regulatory decisions, beyond those currently anticipated. They may also require large, specialized initiatives for which there is limited precedent, suggesting feasibility studies would be needed.

The recognition that RTS,S may have varying efficacy and associated impact in different transmission settings has been considered in the design of its phase III trial: the trial includes 11 sites spread across Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania, intended to reflect the wide range of transmission levels seen in Africa [241]. While possible to select sites over a range of transmission levels, it was not possible to select sites according to changing transmission dynamics.

RTS,S is, however, likely to be implemented in environments where baseline malaria transmission levels are changing. In some countries still scaling up interventions, transmission will likely be decreasing. Other countries, after initial successes, may be struggling to maintain suppressed malaria transmission levels and may see malaria transmission increase. Predictions of the potential impact of RTS,S, to be used by policy-makers at global and country levels [249,250], will need to consider such contexts of changing transmission. It is unclear if the findings of models using fixed annual transmission levels hold where annual transmission is changing.

This paper uses simulations to examine how, depending on the delivery strategy, the expected impact of RTS,S may be affected when implemented in the context of increasing or decreasing malaria transmission trends.

METHODS

SIMULATION MODEL

The study made use of the same ensemble of 14 inter-related models as in our recent study of RTS,S in settings with vectorial capacities oscillating seasonally around fixed values [246]. The base model [215], comprising a computer representation of the acquisition of *P. falciparum* infections [251], regulation of parasite densities [223], morbidity [228], mortality [225] and case management [231], was thus complemented by other models, capturing different assumptions about decay of immunity, heterogeneities in exposure, case management, susceptibility and comorbidity.

Each model run was a stochastic simulation of a stable population of 100,000 people, run with five day time steps for an observation period of 10 years. The simulated populations had approximately stationary age-distribution typical of rural Tanzania, achieved by adjusting birth and out-migration rates to the required values [223].

The models were programmed in C++ as part of the open source software platform OpenMalaria (http://code.google.com/p/openmalaria/). SAS GPLOT was used to generate the figures (SAS Institute Inc., Cary, NC, USA, version 9.2 for Windows).

TRANSMISSION SETTINGS

In the absence of vaccination, baseline transmission was modeled to follow the seasonal patterns observed in Namawala, Tanzania, as in previous studies [235,246], but with the EIR scaled to be in the range of 2 ibpa to 20 ibpa. Although transmission becomes less stable at the lower end of this range, a consistent cycle of transmission was assumed for the purposes of the modeling, unless changed as described below. In this range, comparable to EIRs achievable with existing interventions in most of rural Africa, the previous modeling studies suggest that RTS,S will be highly effective. In each case, the initial immune status of the simulated humans was set to that of a population recurrently exposed to an EIR of 20 ibpa. Simulations of vector control programs were then implemented so that in the absence of vaccination, the profile of transmission during the period of the vaccination program followed one of the following seven patterns (Figure 19):

a) EIR = 11 ibpa, approximately, throughout the ten year observation period.
b) EIR = 2 ibpa, approximately, throughout the ten year observation period.
c) Decreasing: EIR decreasing linearly from 20 down to 2 ibpa over a ten year period.
d) Increasing after brief suppression: EIR initially reduced to 2 ibpa, then increasing linearly to 20 ibpa over the ten year observation period.
e) Increasing after ten years suppression: EIR which had been brought from 20 down to 2 ibpa and maintained there for ten years, increasing again up to 20 ibpa over the ten year observation period due to decreased use of IRS.

f) Suppressed: EIR decreased rapidly from 20 down to 2 ibpa, and subsequently maintained at 2 ibpa during the ten year observation period.

g) EIR = 20 ibpa, approximately, throughout the ten year observation period.

Figure 19. Simulated transmission settings.
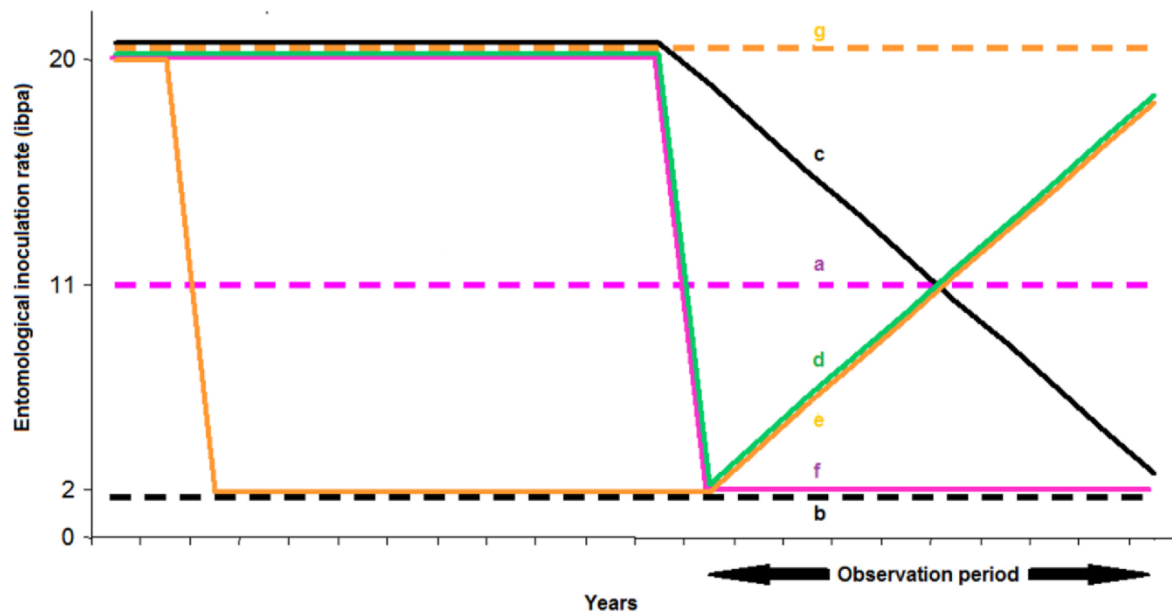
Legend: **a** (dashed purple line): EIR=11 ibpa; **b** (dashed black line): EIR=2 ibpa; **c** (solid black line): EIR decreasing from 20 down to 2 ibpa over 10 years; **d** (solid green line): EIR increasing after brief suppression from 2 to 20 ibpa over 10 years; **e** (solid orange line): EIR increasing from 2 to 20 ibpa after being suppressed for 10 years; **f** (solid purple line): EIR suppressed from 20 down to 2 ibpa, and subsequently maintained at 2 ibpa; **g** (dashed orange line): EIR=20 ibpa.

Settings a, b, and g correspond to settings with stable transmission. In these cases, the populations were simulated as having been exposed to these EIRs for a warm-up period corresponding to a full lifetime, before the start of the observation period during which vaccines were introduced.

Settings c, d, e, and f had changing baseline levels of transmission. The simulated populations were exposed to an annual EIR of 20 ibpa during the 'warm-up' period but then changes in the transmission, and hence the EIR during the observation period were induced by simulating IRS programs carried out in parallel with the simulated vaccination programs. The simulated coverage and effectiveness of the IRS programs were adjusted to achieve approximately linear trends in EIR in the absence of vaccination.

VACCINE DELIVERY STRATEGY

Four delivery strategies were considered:

(i) EPI. Coverage of 89%, based upon Tanzania's DTP3 coverage in 2002. 95% of subjects received one dose, 93% two doses, and 89% all three doses.

(ii) EPI plus catch-up. In addition to delivery through EPI (i above), children up to 18 months of age were vaccinated at monthly campaigns with three doses at program initiation only. Coverage of children through campaigns was 80% selecting randomly for each dose, thus 51% of children up to 18 months of age received all three doses.

(iii) EPI plus vaccination of school children. In addition to delivery through EPI (i above), primary school age children (aged 6 to 11 years) were vaccinated in monthly campaigns with three doses at program initiation only. Coverage of children through campaigns was 80% selecting randomly for each dose, thus 51% of children 6 – 11 years of age received all three doses. Each subsequent year, only new students were vaccinated. Children who were initially vaccinated as infants received a single (booster) dose upon entry into the school system, also at 80% coverage.

(iv) Mass vaccination. People from all ages were vaccinated in an initial campaign for three doses at one month intervals. Coverage through campaigns was 80% selecting randomly for each dose, thus 51% of people of all ages receive all three doses. Subsequent campaigns delivered a single booster to 80% of the population every five years.

VACCINE EFFICACY AND HALF LIFE

RTS,S was modeled to have an efficacy of 60% against the force of infection from the time of completing the full, three dose vaccination course. Efficacy after a single dose and two doses was modeled as 40% and 50%, respectively. The same moderate level of heterogeneity among individuals in the level of protection was assumed as in previous simulations [236,246]. Efficacy against clinical disease in these models is lower than efficacy against force of infection [236,246], as is the efficacy against severe disease found in a clinical trial. Field studies have not yet associated efficacy against clinical disease with efficacy against deaths. Vaccine efficacy against force of infection was modeled to decay exponentially with a half-life of ten years. Past modeling has suggested that vaccine impact is not particularly sensitive to the length of the half-life in the 4 – 10 year range [235], but that if half-life is shorter than this it will narrow the settings in which the vaccine may be useful. In these models, clinical efficacy wanes more rapidly than efficacy against the force of infection [246].

RESULTS

NUMBER OF DOSES REQUIRED

Figure 20 shows the cumulative number of doses per capita (in the all age population) required for each delivery strategy over a ten year period. EPI (strategy i), vaccinating infants from six weeks of age, required the fewest doses, ranging from 0.67/capita over five years to 1.50/capita over ten years. For a population of 100,000 this is equivalent to 67,000 doses over five years and 150,000 over ten years. An EPI plus catch-up strategy (ii), which involves a single campaign in the first year, targeting the cohort of children up to 18 months of age, required an additional 0.10 doses/capita. The EPI plus school-based strategy (iii), which assumed 51% of kids fully vaccinated, required 1.14 doses/capita over five years and 2.12/capita over ten years. The mass campaign (strategy iv), which assumed 51% of the population fully vaccinated, progressed in a stepped fashion. The year-one campaign required 2.37 doses/capita, or 237,000 for a population of 100,000. A total of 3.38 doses/capita was required after the booster in year five.

FIGURE 20. CUMULATIVE DOSES PER CAPITA, BY DELIVERY STRATEGY, IN A DYNAMIC POPULATION.
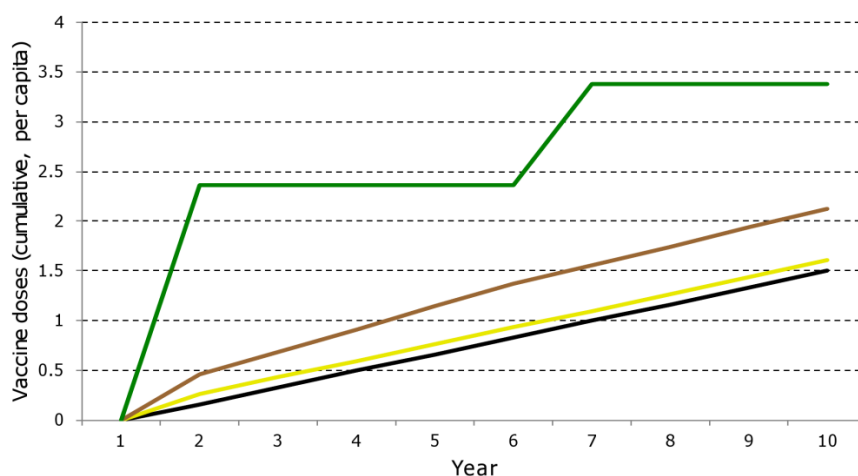
Legend: Black = EPI; Yellow = EPI plus catch-up of children up to 18 months of age; Brown = EPI plus school-based immunization of children 6-11 years of age; Green = Mass campaigns in entire population. The per capita estimates assume a dynamic population, modeled upon the age distribution in rural Tanzania.

IMPACT OF DELIVERY STRATEGY ON TRANSMISSION

Figure 21 presents the impact of RTS,S, delivered through EPI or mass vaccination, on malaria transmission over a ten year period, in each transmission setting except EPI plus catch-up and EPI plus school-based strategies. These were similar to those with EPI alone. Also, results for EIR = 20 ibpa, similar to those of EIR = 11 ibpa, are not shown.

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FIGURE 21A – F. MODIFICATION OF TRANSMISSION TRENDS, BY DELIVERY STRATEGY, OVER TEN YEARS.
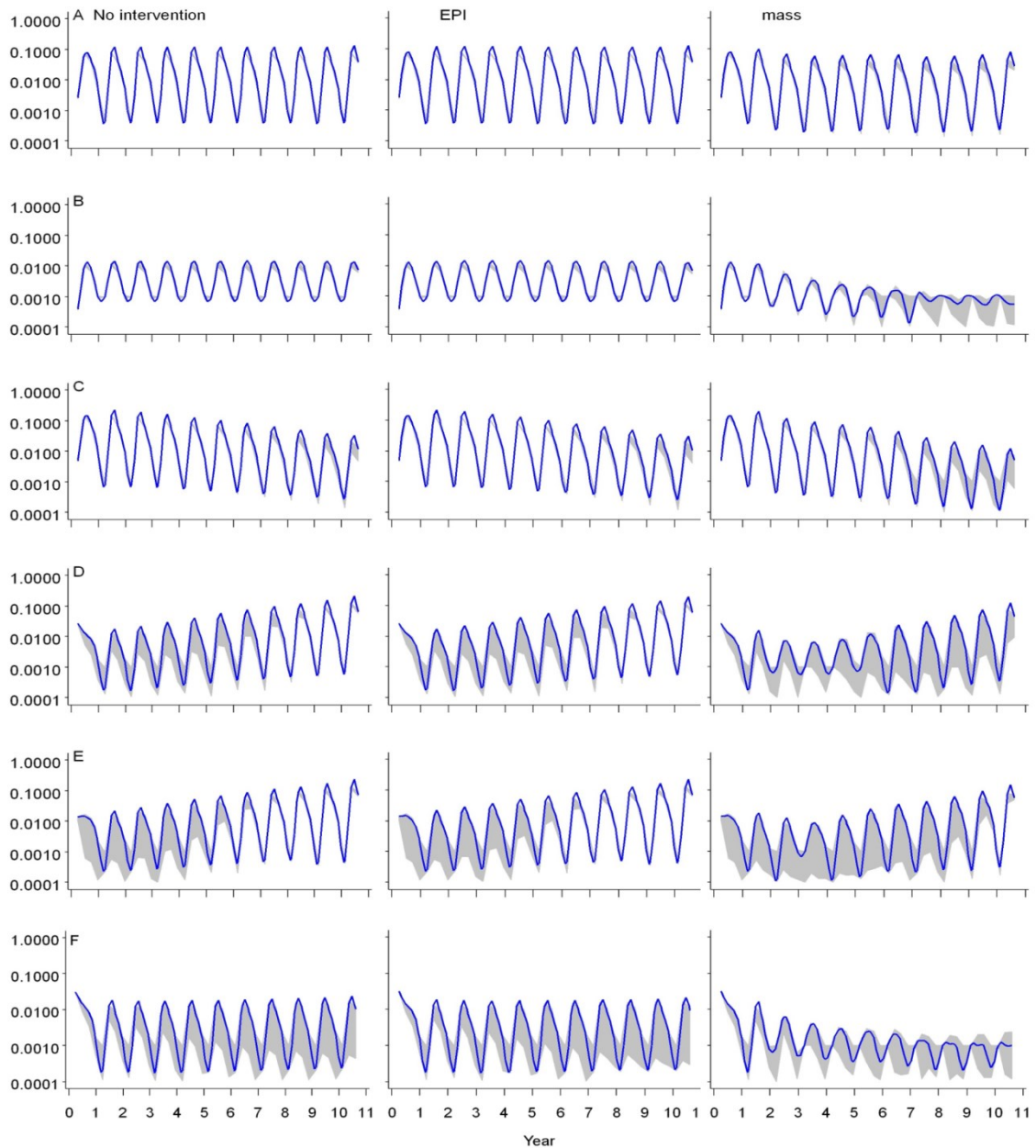
Legend: The first column corresponds to no vaccine, the second corresponds to vaccine delivered through EPI and the third corresponds to vaccination through mass campaigns to all ages of the population. The vertical axis for each panel is EIR on a log scale measured in infectious bites per person per night. The horizontal axis for each panel is time in years. The blue line corresponds to the median transmission of the 14 models, while the grey shading reflects the range of medians from each of the models.

Panel A: EIR=11 ibpa; B: EIR=2 ibpa; C: EIR decreasing from 20 down to 2 ibpa over 10 years; D: EIR increasing after brief suppression from 2 to 20 ibpa over 10 years; E: EIR increasing from 2 to 20 ibpa after being suppressed for 10 years; F: EIR suppressed from 20 down to 2 ibpa, and subsequently maintained at 2 ibpa.

The annual patterns were a result of seasonality of vector abundance and the timing of the IRS rounds, if implemented. Consistent with past analyses using a fixed level of transmission [232,244], RTS,S did generally not have much impact on transmission in the higher EIR ranges modeled. At EIR = 2 ibpa, whether naturally occurring, or suppressed to that level through use of IRS, the vaccine lowered transmission initially when delivered through mass campaigns but the effect leveled off after seven years.

IMPACT ON UNCOMPLICATED MALARIA CASES

Table 27 presents the number of uncomplicated malaria cases experienced in each setting and the percentage of those cases which could be averted by RTS,S, depending on the delivery strategy.

TABLE 27. UNCOMPLICATED CASES AVERTED WITH RTS,S BY TRANSMISSION SETTING AND DELIVERY STRATEGY.

Transmission setting	Cases/Person-year (without vaccine)	Percentage of cases averted (Range)			
		EPI	Catch-up (plus EPI)	School-based (plus EPI)	Mass campaign
a) EIR = 11	1.63	6.0 (4.8-7.0)	7.1 (5.6-8.4)	12.0 (8.6-13.1)	24.5 (20.2-30.6)
b) EIR = 2	1.38	5.2 (4.1-6.0)	6.6 (5.4-7.3)	17.6 (15.0-21.7)	73.0 (70.4-76.5)
c) Decreasing (EIR 20 to 2)	1.35	7.1 (5.5-8.0)	8.6 (6.6-9.7)	14.0 (10.0-16.4)	30.0 (25.4-37.9)
d) Increasing after brief suppression (EIR 2 to 20)	1.96	5.1 (3.7-6.8)	5.2 (3.7-7.0)	11.9 (7.8-20.5)	32.1 (26.4-59.7)
e) Increasing after 10 year suppression (EIR 2 to 20)	2.97	3.4 (2.5-4.5)	4.1 (3.0-5.8)	8.3 (5.2-12.6)	20.7 (16.7-50.2)
f) Suppressed (EIR = 2)	1.46	5.1 (3.0-6.1)	6.6 (4.6-7.8)	15.3 (9.9-17.8)	48.5 (20.2-50.1)
g) EIR = 20	1.53	6.0 (4.1-7.1)	7.0 (4.4-8.2)	10.0 (5.4-11.6)	15.5 (6.6-20.7)

Legend: The first column presents transmission settings. The second column presents the total estimated cases in the population of 100,000 people per person-year in the absence of vaccination. The remaining columns present the percentage of cases averted by each delivery strategy, as the median and (range) estimated from 14 models.

All-age rates of uncomplicated disease in simulated stable settings were rather insensitive to the average level of EIR, corresponding to the data used to fit the models [228,252], where the effect of varying transmission is to shift the age-pattern, rather than the overall incidence of uncomplicated disease. However, changes in EIR, and in particular an increase in transmission has a substantial effect on simulated incidence. In the absence of vaccination, each person was estimated to have between 1.35 cases per year (in a decreasing transmission setting) and 2.97 cases (setting where control was lost).

EPI averted 3.4 – 6.0% of malaria cases depending on the transmission, while EPI plus catch-up averted 4.1 – 8.6% of cases. EPI plus school-based strategies averted 8.3 – 17.6% of cases, depending on transmission, while mass campaigns averted 15.5 – 73.0% of cases. The range of estimates was widest for the mass campaign strategies and most narrow for EPI strategies.

Figure 22 presents the ratio of uncomplicated cases averted to 1000 doses administered. This standardized measure allows comparison of the efficiency of different delivery strategies across transmission settings.

Across all settings, the cumulative number of cases averted per1000 doses was highest with mass campaigns, followed by EPI plus school, EPI plus catch-up, and EPI alone. After ten years, EPI and EPI plus catch-up averted 500 – 700 cases per 1000 doses across all settings. An EPI plus school-based strategy averted 800 – 1100 cases per 1000 doses across all settings. Results from mass campaigns were more variable. In settings with EIR = 11 ibpa (Panel A), decreasing EIR (Panel C), and increasing EIR after a brief suppression (Panel D), RTS,S averted 1100 – 1300 cases per 1000 doses. In a setting with EIR increasing after ten years suppression (Panel E), it averted approximately 2000 cases per 1000 doses from year eight onwards but the effect appeared to be plateauing. In a setting with EIR suppressed to 2 ibpa (Panel F), it averted a similar ratio of cases over the ten year period, but the curve suggested increasing efficiency beyond year ten. The highest efficiency was seen in EIR = 2 ibpa where the models predicted that RTS,S could avert more than 2000 cases per 1000 doses after 5 – 8 years.

FIGURE 22A – F. UNCOMPLICATED CASES AVERTED PER 1000 DOSES ADMINISTERED, BY DELIVERY STRATEGY AND TRANSMISSION SETTING, OVER TEN YEARS.
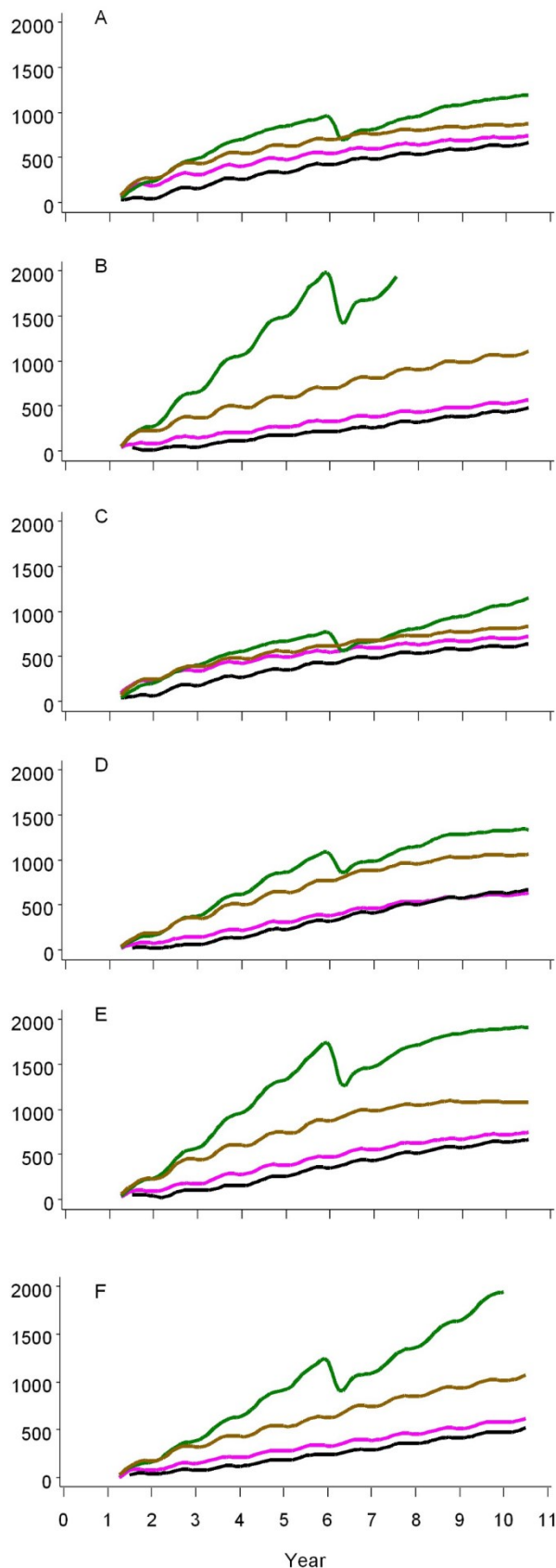
Legend: Vertical axis for each panel is number of cumulative uncomplicated cases averted per 1000 doses administered. Horizontal axis is years. Vaccination is assumed to begin at year one with the vaccination schedule completed three months later for the first subjects.

Black = EPI; Purple = EPI plus catch-up of children up to 18 months of age; Brown = EPI plus school-based immunization of children 6-11 years of age; Green = Mass campaigns in entire population.

Panel A: EIR=11 ibpa; B: EIR=2 ibpa; C: EIR decreasing from 20 down to 2 ibpa over 10 years; D: EIR increasing after brief suppression from 2 to 20 ibpa over 10 years; E: EIR increasing from 2 to 20 ibpa after being suppressed for 10 years; F: EIR suppressed from 20 down to 2 ibpa, and subsequently maintained at 2 ibpa.

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Impact on malaria deaths

Table 28 presents the number of malaria deaths, per 1000 person-years, occurring in each transmission setting, and the percentage of deaths which simulations suggested could be averted by RTS,S. Figure 23 complements this data, presenting the cumulative deaths averted per 1000 persons over 10 years for each of the 14 models.

Table 28. Deaths averted with RTS,S by transmission setting and delivery strategy.

Transmission setting	Deaths/1000 person-years (without vaccine)	Percentage of deaths averted (Range)			
		EPI	Catch-up (plus EPI)	School-based (plus EPI)	Mass campaign
a) EIR = 11	3.8	13.7 (10.3-16.2)	14.8 (11.9-16.7)	15.9 (10.3-20.9)	18.8 (7.1-25.7)
b) EIR = 2	3.7	10.2 (7.2-14.3)	11.9 (9.0-16.7)	22.4 (14.5-26.0)	68.1 (65.5-72.2)
c) Decreasing (EIR 20 to 2)	3.3	15.5 (11.3-17.7)	17.2 (14.1-20.9)	19.0 (12.4-20.7)	25.2 (13.1-32.8)
d) Increasing after brief suppression (EIR 2 to 20)	5.0	10.3 (8.0-11.5)	9.8 (7.3-11.4)	14.9 (9.0-20.1)	28.3 (13.8-58.5)
e) Increasing after 10 year suppression (EIR 2 to 20)	7.8	6.8 (3.1-8.3)	7.2 (4.9-9.0)	9.4 (3.7-12.1)	14.2 (1.8-42.5)
f) Suppressed (EIR = 2)	3.7	10.5 (5.6-12.7)	11.7 (4.4-14.7)	18.7 (10.8-21.1)	45.4 (21.0-47.5)
g) EIR = 20	3.8	13.3 (9.6-15.7)	14.0 (9.7-17.8)	13.6 (8.1-18.8)	9.9 (1.6-15.7)

Legend: The first column presents transmission settings. The second column presents the total estimated malaria deaths in the population of 100,000 people per person-year in the absence of vaccination. The remaining columns present the percentage of deaths averted by each delivery strategy, as the median and (range) estimated from 14 models.

FIGURE 23A – F. DEATHS AVERTED PER 1000 POPULATION, BY TRANSMISSION SETTING, OVER TEN YEARS.
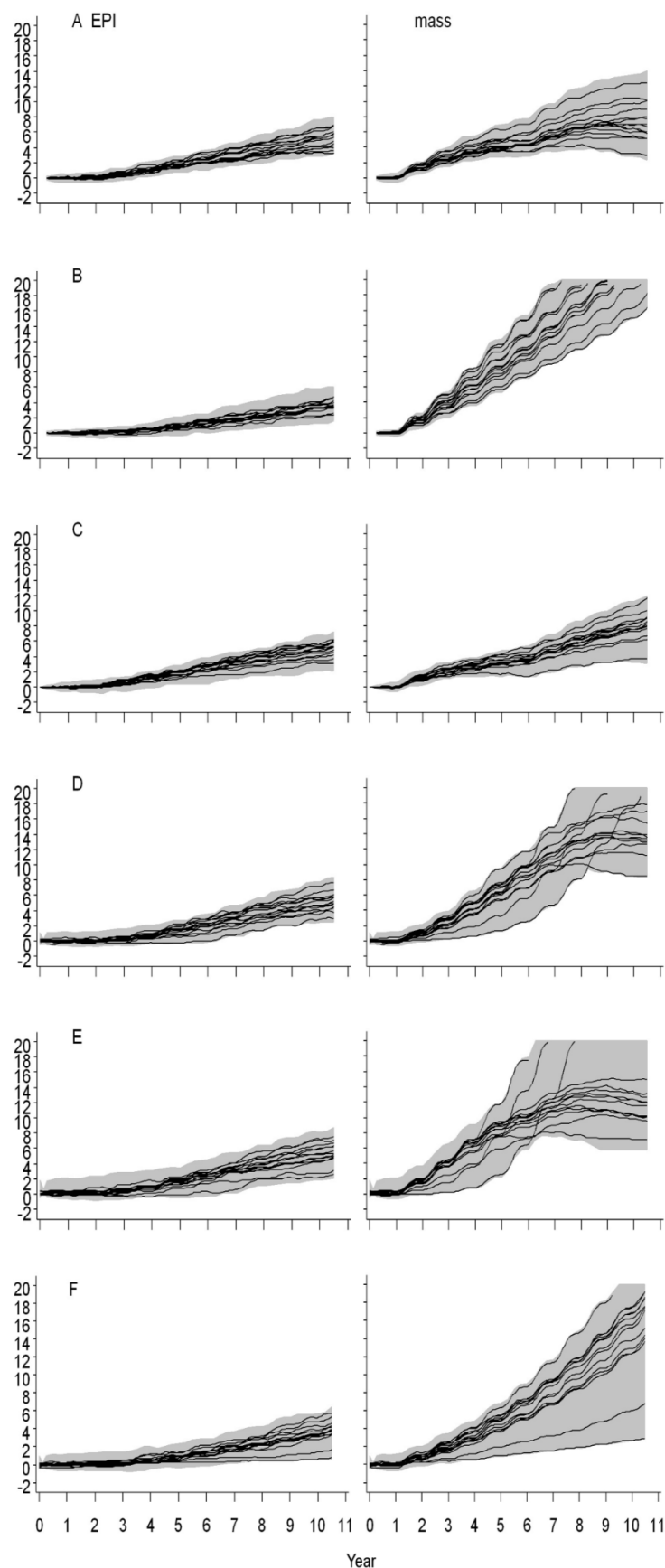
Legend: The first column corresponds to vaccine delivered through EPI and the second corresponds to vaccination through mass campaigns to all ages of the population. The vertical axis for each panel is number of cumulative deaths averted per 1000 population. The horizontal axis for each panel is years. The black lines correspond to the median effect estimated by each of the 14 models, while the grey shading reflects the range of model medians. Vaccination is assumed to begin at year one with the vaccination schedule completed three months later for the first subjects.

Panel A: EIR=11 ibpa; B: EIR=2 ibpa; C: EIR decreasing from 20 down to 2 ibpa over 10 years; D: EIR increasing after brief suppression from 2 to 20 ibpa over 10 years; E: EIR increasing from 2 to 20 ibpa after being suppressed for 10 years; F: EIR suppressed from 20 down to 2 ibpa, and subsequently maintained at 2 ibpa.

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Delivery through EPI was estimated to avert 6.8 – 15.5% of malaria deaths, depending on the transmission, while EPI plus catch-up averted 7.2 – 17.2% of deaths. EPI plus school-based strategies averted 13.6 – 22.4% of deaths, depending on transmission, while mass campaigns averted 9.9 – 68.1% of deaths. The range of estimates was widest for the mass campaign strategies and narrowest for EPI strategies. This is illustrated by the variation between model medians shown in Figure 23. The only setting where all model medians showed higher impact from mass campaigns than from EPI was in settings with EIR = 2 ibpa (Panel B). A high level of uncertainty was associated particularly with settings where the EIR was increasing after a brief suppression (Panel D), increasing after a ten year suppression (Panel E), or continuously suppressed to 2 ibpa (Panel F).

The efficiency of RTS,S averting deaths is presented as a ratio of the number of deaths averted to 1000 doses administered (Figure 24). The results for the setting of EIR = 20 ibpa is not shown as it was similar to the setting of EIR = 11 ibpa.

Across all settings, the cumulative number of deaths averted per 1000 doses of RTS,S generally leveled off at a maximum of 3 – 4. Such efficiency was realized only after approximately seven years in settings with increasing transmission, either after brief or ten year suppression (Panels D and E), while it was reached after only two to three years in the setting with decreasing transmission (Panel C) with delivery through EPI plus catch-up or EPI alone. The highest impact after ten years was approximately 5 – 7 deaths averted per 1000 doses with mass campaigns (reaching 51% of people with three doses) in settings where the EIR was naturally at or suppressed to 2 ibpa (Panels B and F). Note that in these settings, RTS,S not only protected those vaccinated, but also reduced transmission (Figure 21).

FIGURE 24A – F. DEATHS AVERTED PER 1000 DOSES ADMINISTERED, BY DELIVERY STRATEGY AND TRANSMISSION SETTING, OVER TEN YEARS.

Legend: Vertical axis for each panel is number of cumulative deaths averted per 1000 doses administered. Horizontal axis is years. Vaccination is assumed to begin at year one with the vaccination schedule completed three months later for the first subjects.

Black = EPI; Purple = EPI plus catch-up of children up to 18 months of age; Brown = EPI plus school-based immunization of children 6-11 years of age; Green = Mass campaigns in entire population.
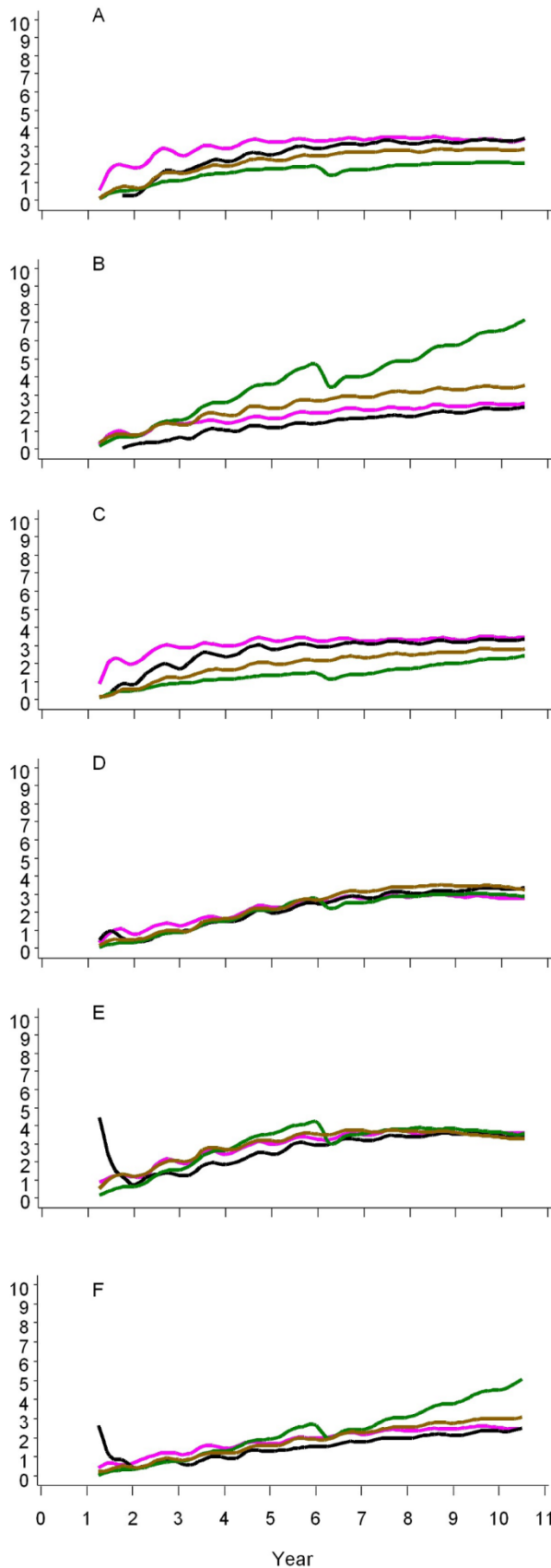
Panel A: EIR=11 ibpa; B: EIR=2 ibpa; C: EIR decreasing from 20 down to 2 ibpa over 10 years; D: EIR increasing after brief suppression from 2 to 20 ibpa over 10 years; E: EIR increasing from 2 to 20 ibpa after being suppressed for 10 years; F: EIR suppressed from 20 down to 2 ibpa, and subsequently maintained at 2 ibpa.

DISCUSSION

Modeled estimates of the effect of the RTS,S vaccine allow for comparisons of uncomplicated cases and deaths averted, and the efficiency of different delivery strategies to avert those cases and deaths, in a variety of malaria transmission settings.

In most transmission settings studied, an approximately proportional relationship between the number of deaths averted and the number of doses administered through EPI, EPI plus catch-up and EPI plus school-based campaigns, was observed over the ten year period simulated. That is, among the delivery strategies that target a portion of the population, the greater the number of doses administered, the greater the total number of lives that can be saved.

The EPI strategy immunized the fewest people over ten years, and consequently averted the fewest deaths, but with a relatively high efficiency per 1000 doses administered across transmission settings. EPI has demonstrated its feasibility and is compatible with current clinical trial and regulatory plans. The opportunity to make use of the thus far successful EPI infrastructure is a strong argument to use this strategy in (all) transmission settings where it is likely to be cost-effective to deliver RTS,S this way.

Supplementing EPI delivery with a one-time catch-up vaccination reaching children below 18 months may be particularly appealing in an environment with decreasing transmission (setting c). The catch-up delivery round would require additional investment and planning beyond that seen for EPI, although most likely less than required for repeated school-based or mass campaigns.

School-based delivery strategies did not increase efficiency in any of the transmission settings studied, so its main benefits are in reaching a greater number of people. A recent pilot of school-based strategies for delivering human papilloma-virus (HPV) vaccine could be part of the momentum to strengthen and expand school-based strategies over time [253].

The findings for mass campaigns were more complex. Mass campaigns reached many times more people than EPI alone, and simulations suggested this delivery strategy could be expected to avert more cases and deaths in some situations. Highest efficiency was seen in very low transmission settings (e.g. EIR of 2 ibpa), whether naturally occurring or achieved by other interventions (settings b and f). Efficiency decreased as transmission increased, making mass campaigns much less efficient than EPI at EIRs above 2 ibpa.

The impact of mass campaigns varied the most between different transmission settings, and there were wide ranges in the model predictions. The expected benefits

of mass vaccination were highly sensitive to model assumptions about transmission heterogeneity and immunity. There is a clear need to improve the evidence base for parameterizing these aspects of the models. Part of the uncertainty about impact of mass-vaccination (also reaching adults) arose because relatively sparse data about disease incidence in older people were available when the models were fitted [225,228]. In our models, the main effect of reducing transmission on disease is to shift morbidity to older ages. It is not clear how important this shift is in settings where transmission is currently reducing. If this shift is less important, independently of the effects of the vaccine, we might have expected to see larger effects of reducing transmission on morbidity and mortality rates. In contrast to most field datasets, the presented rates are calculated over the entire population and simulated events in adults dilute the effects on children. Thus, caution is advised when interpreting model results of mass campaigns until further data is available.

Mass vaccination also appears the most distant potential RTS,S delivery strategy. New clinical trials, in older age groups potentially with different safety questions and needing different doses, may be necessary. Regulatory, cost-effectiveness and feasibility considerations related to mass campaigns may also need to be addressed. The findings suggest that further work is needed to more clearly understand the impact and feasibility of mass campaigns, potentially when partnered with other interventions to rapidly decrease transmission. The potential for significant impact in some settings may make it worth beginning to anticipate such work.

Estimates of efficiency in this paper are expressed using the ratio of deaths averted per 1000 doses of vaccine. This can be converted to deaths averted per 1000 vaccinees, a ratio used by the GAVI Alliance (GAVI) when considering the impact of various vaccines it supports financially [254]. The ratio of deaths averted by pneumococcal conjugate vaccine in African infants is estimated from trial data to be 7 per 1000 vaccinees (59 deaths averted in 8000 vaccinees) [255]. Immunizing 1000 infants with RTS,S via EPI, given the coverage assumptions stated earlier, equates to delivering approximately 2770 doses of vaccine. Given the ratios under transmission settings above, simulations suggest RTS,S in EPI would avert 2 − 4 deaths per 1000 doses, equivalent to 6 − 11 deaths per 1000 vaccinees. These ratios compare favorably with the pneumococcal vaccine, for which implementation planning is progressing rapidly in Africa and some $3 billion in financing have been committed [184].

The findings across the different settings suggest that for understanding the potential impact of pre erythrocytic vaccines, it is probably sufficient to use fixed transmission settings in modeling efforts, even for situations where the underlying baseline transmission is believed to be decreasing or increasing. The simulations used in this paper used IRS to create trends in transmission. Effects would have been slower if the

transmission changes were induced by LLIN use, but there is no reason to assume that the relative impact of the delivery strategies would be different.

The effect for RTS,S was expected to be at maximum in the transmission range studied in these simulations (2 – 20 ibpa). It is reasonable to expect that EPI, EPI plus catch-up and EPI plus school-based strategies will have comparable effects to those seen in this paper at somewhat higher transmission settings than studied. Although cost-effectiveness estimates for EPI are available [248], the other impact estimates could be further informed by cost and cost-effectiveness analyses which were beyond the scope of this paper

CONCLUSION

The development of the RTS,S malaria vaccine is progressing. If the vaccine is shown to be safe and efficacious in the current phase III trial, as has been shown in earlier trials, and it is made available to countries in Africa, there will be a complex decision-making process to determine how and where it should be used. In order to help this process, the authors studied the potential impact and efficiency of RTS,S delivered through various strategies and under changing levels of malaria transmission patterns, although findings suggest that it is probably sufficient for future simulations to consider constant EIR levels. The type of impact sought, whether on mortality and morbidity, or on transmission as well, together with assumptions about feasibility of different delivery strategies, may lead to different conclusions about the role of RTS,S.

Findings support further investigation of RTS,S to determine its potential contribution to malaria transmission reduction through high coverage of an all age population in low transmission settings. At 2 ibpa, mass campaigns could avert the most deaths and decrease transmission; however, a lot of uncertainty was associated with these findings. Also, the feasibility of mass campaigns delivering a multi-dose immunization requires assessment. Further consideration of the regulatory implications, clinical studies required to address questions of the extent of the benefit, and other product development activities will be important to anticipate, prior to RTS,S being used in mass campaigns. Such considerations would benefit from early planning due to their lengthy nature.

The findings also support going forward with EPI delivery as an initial strategy for RTS,S. If delivered via established EPI systems, RTS,S could avert approximately 6 – 11 deaths per 1000 vaccinees in all examined settings, an efficiency consistent with or superior to other new vaccines being implemented across Africa. However, it would have little effect on transmission when delivered via EPI. The number of events averted increases somewhat with the EPI plus catch-up and the EPI plus school-based strategies. The increase is essentially proportional to the larger population covered, and because that larger population coverage is modest, it is not an enormous added

benefit. These results, combined with those of other modeling studies, should provide information to help policy-makers at international and country-levels to take evidence-based decisions on optimal strategies to avert malaria cases and deaths in Africa.

ACKNOWLEDGEMENTS

FINANCIAL DISCLOSURE

COMPETING INTERESTS (PERSONAL, FINANCIAL, OR PROFESSIONAL)

AB, OB, DH, RS, and TS declare that they have no competing interests.

ROLE OF AUTHORS

AB drafted the manuscript and interpreted the simulations. AB and TS designed the model simulations. TS and DH ran the model simulations. OB provided critical input into the interpretation of simulations and the manuscript. RS informed the strategies modeled and provided critical input into the manuscript. All authors reviewed and edited the manuscript, and approved the final draft.

CHAPTER 9. SYNTHESIS, FUTURE RESEARCH AND CONCLUSIONS

INTRODUCTION

This thesis proposes a novel approach for transitioning health interventions from research and development (R&D) to decisions on use and implementation through health systems in developing countries. It is about accelerating access to interventions for those most in need. It is built upon a hypothesis that there have been re-occurring delays in implementing interventions, and that the causes of those delays can be foreseen and minimized by beginning to address them during R&D. It details elements of a strategy to address the delays, building upon the access framework created by Frost and Reich (2008), and research and practical examples from work relating to malaria vaccines and other interventions. It intertwines the implications and lessons for new health interventions into each chapter. Only through a new approach can the decade plus of delays between development and implementation of most interventions be decreased. Such a decrease holds the promise of saving millions of lives.

Chapter one establishes the context of the thesis, highlighting that a growing number of new interventions are under development and being approved by regulatory bodies for use in developing countries. Chapter two addresses how long it has typically taken for interventions to be implemented, determining that over the past decade the pace of implementation appears to have remained largely unchanged from that in the 1980s. The chapter introduces the major themes found in the remainder of the thesis and proposes modifications to Frost and Reich's access framework, identifying key activity milestones which can be anticipated and worked towards during R&D in order to accelerate later access. Chapter three considers the importance of strategies for ensuring that as products become available they are aligned with the needs of and acceptable to health systems and health system users. Chapter four analyses the roles and decisions of international organizations, such as setting policies, making recommendations, and issuing guidelines, which impact adoption decisions by countries. Chapter five reviews the support provided by product development partnerships (PDPs) for decision-making in developing countries (DCs), while chapter six reports on research related to national decision-making on malaria vaccines more specifically. Chapters seven and eight provide examples of two complementary modeling approaches which support R&D and adoption decisions.

NEW STRATEGY TO ACCELERATE ACCESS

Frost and Reich's access framework focuses primarily on the implementation period, after interventions have been approved by regulators. Yet the activities in the framework are impacted by decisions and activities undertaken during the R&D period. This realization led to the modified access framework in this thesis (Figure 25).

The modified access framework identifies activities to be undertaken during R&D, prior to regulatory approval, as a new strategy to accelerate access. The framework, elaborated upon in chapter two, summarizes major themes which are considered in subsequent chapters. Briefly, it consists of activities related to: 1) establishment of an architecture coordinating the activities related to an intervention; 2) availability of the intervention; 3) affordability; and 4) decisions on adoption at international, national, and individual levels. Activities occur in the context of and in coordination with regulatory oversight, and pre-clinical, clinical, and effectiveness studies. Epidemiologic, economic and impact data inform adoption decisions, implementation and access but may have far wider relevance than a single intervention, represented by their position in parallel to other activities but also considered by the same overall coordinating architecture.

The framework represents a strategy which should be relevant to most new health interventions targeting the developing world, but should not be seen as fixed or one-size-fits-all. Activities in the framework will need to be tailored to the context of each intervention. As noted in chapter two, the activities impact and are impacted by each other. The interrelationships are likely to vary, such that the framework is a starting point to tailor activities specific to each interventions' needs, as seen in the individual chapters. Subsequent sections will reflect on how the individual chapters relate to the access framework.

ACCESS ARCHITECTURE (COORDINATOR)

A coordinating architecture during the R&D period ensures that plans for and activities addressing availability, affordability, and adoption are undertaken. It serves as "glue." It also anticipates what needs to occur during the decision and implementation period so that access activities smoothly transition after regulatory approval. The coordinator helps to see that access activities integrate well with complementary R&D work, for example that clinical studies address the needs of policy-makers (Chapters 3-6) and that burden of disease studies are generating timely, relevant data (Chapters 7 and 8). The coordinator should understand and foresee the needs of health systems and individuals, and play a critical role helping to balance those needs with R&D and manufacturing decisions, such as during the establishment of target product profiles (TPPs) (Chapter 3). The coordinator should be deeply familiar with the timing of R&D decisions and data in order to be sure that access planning does not fall behind R&D activities. On the other hand it should also be cautious to not get ahead of R&D findings and risk overpromising. The not-for profit partner in a product development partnership (PDP), a university, WHO, or a similar group may be well positioned to act as the coordinator.

FIGURE 25. PROPOSED ACCESS FRAMEWORK INCORPORATING R&D AND IMPLEMENTATION PERIODS.
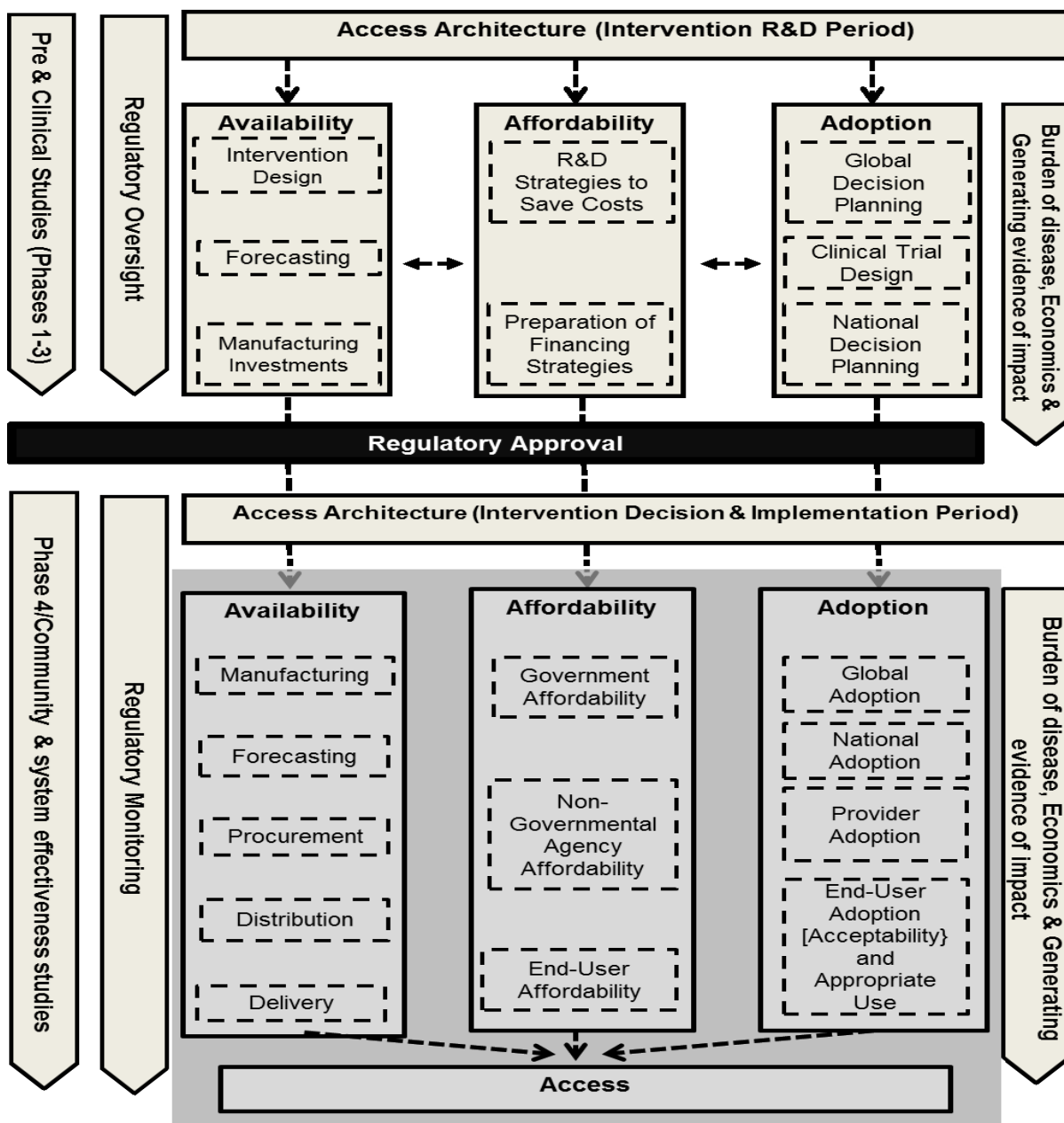
Legend: The area in grey reflects Frost and Reich's (2008) original access framework. Other areas are new to the framework. Actions that take place during the R&D period are described in the space above the black strip, "Regulatory Approval, while actions carried out in the decision and implementation period are described in the space below. Area in grey is reproduced under a Creative Commons Attribution-Noncommercial-Share Alike 3.0 License.

AVAILABILITY

Availability reflects the importance of, and strategies to ensure that, an intervention approved by regulators will be produced in sufficient quantities for developing

countries. Forecasting and manufacturing planning are important to ensuring that sufficient product will be available for demand in the developing world, and at an affordable price. Available interventions should also be designed and have characteristics aligned with the needs of relatively fragile developing world health systems and acceptable to health system users.

Chapter three considers target product profiles (TPPs) and research into the design of interventions. For example, an available intervention should have characteristics which minimize its implementation costs, impacting affordability, such as avoiding special handling requirements by distributors and health workers. The alignment of an intervention with developing country needs arises in chapter four regarding international organizations, as one factor determining if WHO will pre-qualify an intervention and provide a recommendation on use. Countries also indicate in chapter six that they want to give input into intervention characteristics. Modeling plays a key role, as reflected in chapters seven and eight, estimating the impact of various intervention characteristics and delivery strategies in order to inform R&D and policy decisions.

<u>AFFORDABILITY</u>

Affordability activities seek to ensure that purchase price and implementation costs will not prevent developing countries from using an intervention. They include planning for financial subsidies from international organizations as well as ways to minimize capital and recurrent implementation costs. Specific studies to further address or complement affordability considerations could target the willingness and ability of donors, countries, and individuals to pay (e.g. budget impact analyses), financial sustainability, and/or determining if an intervention is a wise use of funds such as through cost-effectiveness analyses.

As noted above and in chapter three, planning for the characteristics of an intervention should include their impact on affordability. Chapter four considers the importance and timing of policy decisions by international financing organizations, particularly GFATM and GAVI, to subsidize procurement and implementation of new interventions. It notes that these organizations tend to rely upon WHO recommendations regarding adoption and use when deciding to commit funds. Chapter five considers the ways PDPs are supporting countries to address affordability. Chapter six finds that affordability, financial sustainability of national and donor commitments, and cost-effectiveness are important considerations in DC decision-making. Chapter seven reports on modeling work which includes estimates of the costs and financing requirements of averting events (e.g. uncomplicated malaria cases; deaths) for different malaria vaccines in different epidemiological settings and using different delivery strategies. Chapter eight raises trade-offs between delivery

strategies, such as mass campaigns, that may provide more public health impact than infant immunization, but which may not be financially or technically feasible.

ADOPTION

Activities during the R&D period need to address the data required by international organizations to set policies, make recommendations and issue guidelines on the use of an intervention. Activities should also address research questions specific to and anticipated from developing country governments, and ensure that interventions will be acceptable to users of health systems. As much data as reasonably possible for international and country-level decision-makers should be available at the time of regulatory approval. Otherwise, years of additional work may be required to generate data informing adoption decisions, while a licensed intervention sits waiting.

Chapter three considers the importance of clinical trials addressing the questions and populations specific to use of an intervention in DCs. Chapter four highlights the role of early collaboration of developers with WHO and other international organizations to anticipate their requirements, as much as feasible, in study designs. Chapters five and six focus on activities in support of country processes to decide on the adoption, or not, of interventions into national health systems, including the importance of having an intervention that is acceptable to health system users. Chapters seven and eight present modeling approaches intended to inform adoption decisions by international and national policy-makers.

REGULATORY OVERSIGHT/REGULATORY MONITORING

The work of regulatory agencies, or in some cases WHO or others playing a regulatory-like role for interventions, is not part of Frost and Reich's original access framework. As noted in chapter two, regulation was added to the modified framework as it directly impacts access activities. During the R&D period, regulatory agencies impact decisions on intervention and trial design (Chapter 3.) The determination by a regulatory agency that an intervention is of assured safety and quality, and is efficacious, then monitoring to assure quality and safety do not change, is a critical input to WHO and other policy-making groups, as well as DCs (Chapters 4-6).

PRE-CLINICAL AND CLINICAL STUDIES; PHASE FOUR/COMMUNITY EFFECTIVENESS AND SYSTEM EFFECTIVENESS STUDIES

Clinical, phase four, and community effectiveness studies are also not part of Frost and Reich's original framework. They impact, and are impacted by, TPP decisions as described in chapter three. They are critical to decisions of international organizations (Chapter 4) as well as countries (Chapters 5-6). Modeling (Chapters 7-8) helps translate data from such studies into estimates for policy-makers to inform adoption decisions.

BURDEN OF DISEASE, ECONOMICS, AND GENERATING EVIDENCE OF IMPACT

The range of studies necessary to complement access activities depends greatly on the disease and intervention. For example, recent interventions like rotavirus and pneumococcal vaccines became available while DCs remained unfamiliar with their underlying burdens of disease from these pathogens. In contrast, a new intervention targeting *P. falciparum* malaria in Africa does not need to be accompanied by new data seeking to determine if malaria is a problem, but instead by data regarding the role the intervention may play relative to existing interventions. The coordinating architecture must ensure that the critical studies are in place to support the other access activities at the appropriate times.

Chapters seven and eight describe models intended to help understand the roles of interventions in the context of changing disease burden and use of other interventions, and to generate impact and economic estimates. Chapter three highlights that the TPP should be consistent with the intended impact, a consistency that is likely explored through models. Chapter four recognizes the importance of data arising from studies for international organizations to take decisions. Chapter five reviews how PDPs are supporting such studies. Chapter six addresses the need for such studies from a country perspective, and if such studies need to be done in each country or whether the decision-makers felt that data extrapolated from other countries or models was sufficient.

TAKING ACTION: OPERATIONALIZING THE STRATEGY

The chapters in this thesis cover a wide range of activities, many developed or researched over multiple years. Incorporating access planning into the R&D period of a new intervention is not a small or simple undertaking. However, such an undertaking should be seen in the context of investments to develop and license a new intervention which can take a decade or more, costing tens or hundreds of millions of dollars. The experience from malaria vaccines, and interventions more generally, suggest a number of lessons for those seeking to incorporate access planning into the R&D period. The lessons reflect the conclusions of the author only, and in no way reflect those of any individual organizations.

RECRUIT THE APPROPRIATE SKILL SETS

The R&D team working on an intervention should be complemented by individuals deeply familiar with developing countries and health systems, and able to bring those insights to R&D discussions when needed. While it may be sufficient to draw upon such skill sets on an ad hoc, consultancy basis if interventions are only in early development, a dedicated unit may be needed as products move towards late development. An organization should consider how accountabilities may shift as R&D

progresses, for example with the staff focused on access having regular roles in R&D decisions as an intervention moves into late development.

AGREE WHO FILLS THE COORDINATING ROLE

There may be many organizations that could provide the coordinating architecture for an intervention. Perhaps the most likely is whichever is most deeply involved in R&D. PDPs, universities, research institutes, and WHO have all filled the coordinating role. The organization could be from the developed or developing world. The role requires investment in terms of staff, collaboration with partner organizations, and support for access-related research.

TAILOR THE STRATEGY TO THE INTERVENTION AND WIDER CONTEXT

Those responsible for the access strategy during R&D need to begin with an understanding of the context of the disease in developing countries, and the most likely means of implementation. From this understanding, one can create a timeline backwards from the envisioned access to the current phase of development. The framework and chapters in this thesis provide conceptual as well as practical ideas about what may need to be addressed and when. It may be helpful to structure the timeline and activities to be addressed according to critical time points in the R&D process (e.g. transition from phase I to II, or phase II to III of clinical trials; regulatory decisions.)

SET EXPECTATIONS FOR A LONG-TERM VIEW AND LONG-TERM PROCESS

As with intervention development, addressing access-related issues is a multi-year process. Consideration of access-related issues should begin early in the R&D process, as part of establishing TPPs. The work intensifies as interventions move into late development. Expectations need to be set not only within the coordinating organization or with those leading the R&D, but also with funders and with groups like WHO which may be challenged to foresee their data needs years in advance.

AGREE ON MANDATE WITH FUNDERS

Planning for access may be seen as tangential to core R&D activities. It is important to explicitly agree with funding agencies supporting an organization on roles and discrete support for activities related to access during R&D.

WHO COLLABORATION

WHO plays a unique role in relation to health systems in developing countries. It also plays a key policy-setting role that is relied on by other organizations. It is important to work with WHO as early as possible to find the appropriate level and timing of collaboration relative to key R&D time-points, as detailed in chapter four, and discussed in chapters three, five, and six.

FUTURE RESEARCH

This thesis raises a number of future research questions. The perspective of the thesis is largely that of not-for profit organizations working on interventions intended for use through national health systems in DCs. It could be valuable to explore the access framework and findings of the individual chapters through the perspectives of for-profit partners, such as pharmaceutical companies, or private health practitioners in developing countries. Regulatory agencies may also have unique perspectives on the issues raised in this thesis.

The work focused most on interventions targeting malaria, vaccines, and malaria vaccines, while attempting to generalize findings to other interventions. Malaria and vaccines reflect a broad range of intervention types and diseases, addressing some of the most important causes of mortality and morbidity in the developing world. However the fields of malaria and vaccines are among the highest-profile, with wide support at international, country, and community levels. It could be valuable to apply this access strategy to a relatively neglected disease and/or type of intervention.

As a growing number of interventions specifically intended to address diseases of developing countries are approved by regulators, it will become feasible to conduct a comparative evaluation of access activities undertaken during and after R&D relative to the level of access achieved by an intervention. In the meantime, individual activities are strengthened by incorporating validation steps and evaluations. Examples include surveys of African immunization specialists to validate modeling findings as described in chapter three; validation of findings with international organizations described in chapter four; validation steps with African immunization experts, malaria experts and national policy-makers, as well as an independent external evaluation, described in chapter six; and parameterizing models such as described in chapters seven and eight to historical data (e.g. on uptake of a new intervention) or findings from clinical studies.

Affordability is touched on in each chapter of the thesis. However, there remains room for additional work by the international community to try and standardize reasonable country co-financing expectations for a new intervention. GFATM and GAVI have each set co-financing requirements which they expect countries to meet. Clarity of expectations could inform target product profile characteristics, and other assumptions about a new intervention.

If progress continues as anticipated for the first generation malaria vaccine, the full set of access activities described in this thesis in support of malaria vaccines could be evaluated sometime after approximately 2016. Among the opportunities in such an evaluation would be to try and associate the time and resource commitments to access planning during R&D, with any years saved in implementation relative to other

interventions. An evaluation could also look historically to consider which access activities started too early relative to R&D progress and which started too late. Such an evaluation would need to be qualified by recognition of the risk that an intervention under development could always fail, although the risk decreases as the intervention progresses through late development.

CONCLUSION

New interventions hold the promise of decreasing the divergence in health between developed and developing countries. Growing international political and financial commitments to develop interventions and support their implementation, such as through the GFATM and GAVI, create room for hope. However promise and hope are insufficient for interventions to rapidly realize their potential of impacting public health throughout the developing world. Interventions need to be created not only with an ethereal vision that they will be used in developing countries, but with the unique needs and perspectives of an intervention intended for developing countries integrated into and complementing R&D activities from the earliest days. The strategy proposed in this thesis, summarized by the modified access framework, identifies concrete activities to transition promise and hope into a reality. Only by such actions can new interventions avoid the decade plus of delay seen traditionally, but instead realize their potential of preventing disease and saving lives as rapidly as possible.

SUPPLEMENTARY MATERIAL

SUPPLEMENT A: CHAPTER 7. MODELING THE PUBLIC HEALTH IMPACT OF MALARIA VACCINES FOR DEVELOPERS AND POLICY-MAKERS

In order to provide public health impact estimates, the Swiss Tropical and Public Health Institute (Swiss TPH) model requires malaria transmission data in entomologic inoculation rate (EIR) format. As such, the PATH Malaria Vaccine Initiative (MVI) created the following five EIR buckets (or categories) for grouping data:

- A: intended to approximate an EIR of 0
- B: intended to approximate an EIR of 0.1
- C: intended to approximate an EIR of 1.0
- D: intended to approximate an EIR of 10.0
- E: intended to approximate an EIR of 100

Neither the World Health Organization (WHO) nor the Malaria Atlas Project (MAP) currently provides their transmission data in EIR format. The need then, is to create a distribution of each country's population across these five EIR buckets, such as depicted here. The goal is to find the best representation of transmission risk—in EIR format—for each country.
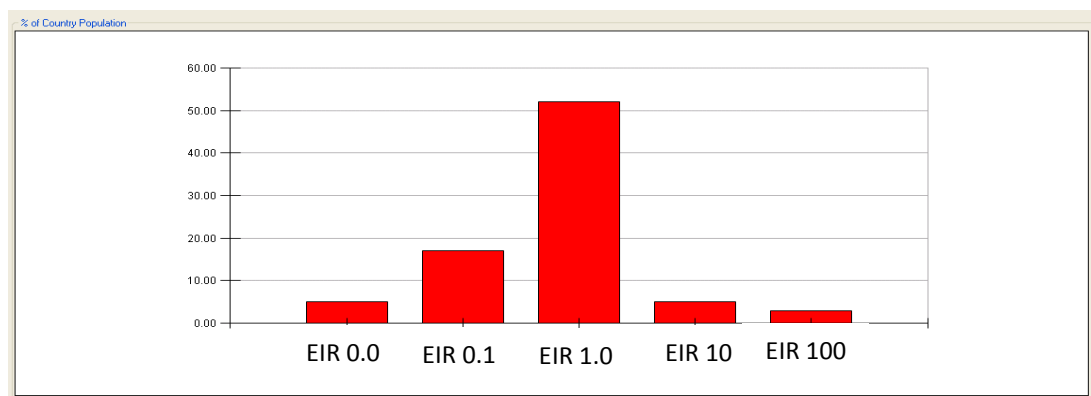
WHO-BASED TRANSMISSION SCENARIO

For the WHO-based transmission scenario, MVI elected to create distributions such that simulated (i.e. modeled) disease burden approximates WHO disease burden, as shown below.
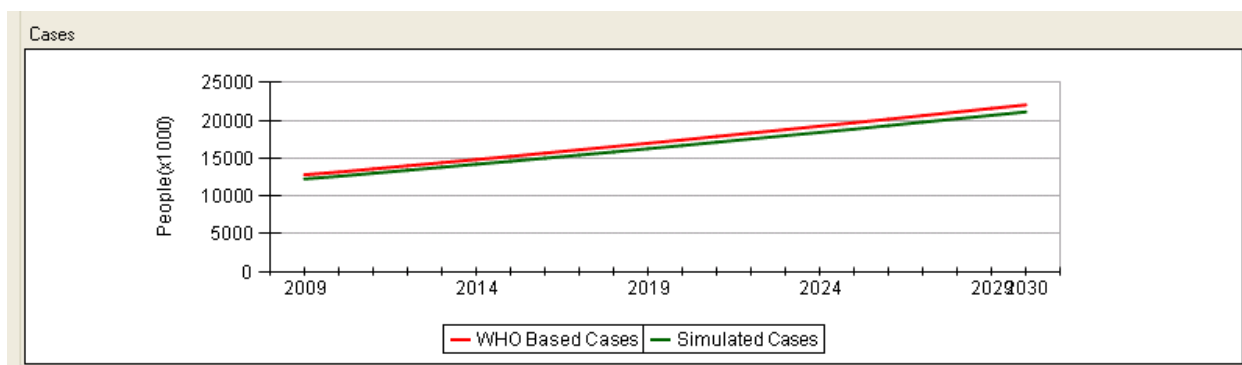
In the WHO *World Malaria Report 2008* (WMR), WHO expresses transmission risk as the percentage of population in each country at:

- high risk of transmission
- low risk of transmission

For some countries, the total percentage reported does not amount to 100%. In these cases, it is assumed that the missing percentage is not endemic for malaria. WHO data also includes the *%P. falciparum* (*Pf*) in each country (as opposed to *P. vivax (Pv)*).

E.g. Tanzania

- High transmission: 75%
- Low transmission: 25%
  (assume 0% is non-endemic for malaria)
- *%Pf*: **100%**

WHO-BASED TRANSMISSION SCENARIO METHODOLOGY

High and low transmission percentages for each country were multiplied by the *Pf* percentage to arrive at the high and low transmission that is specific for *Pf* for each country. This assumes that *Pf* and *Pv* are similarly distributed in each country—an assumption made for lack of information to the contrary.

E.g. Tanzania

High transmission: 75% x **100%** = 75%
Low transmission: 25% x **100%** = 25%

Countries were then ranked by the total cases per 100,000 people (as provided in the WMR) and divided into the following 13 categories:

- 0 – 400 cases/100,000
- 400 – 900 cases/100,000
- 900 – 1500 cases/100,000
- 1500 – 2000 cases/100,000
- 2000 – 5000 cases/100,000
- 5000 – 10000 cases/100,000
- 10000 – 16000 cases/100,000
- 16000 – 25000 cases/100,000
- 25000 – 30000 cases/100,000
- 30000 – 34000 cases/100,000
- 34000 – 38000 cases/100,000
- 38000 – 41000 cases/100,000
- 41000+ cases/100,000

Within each of the 13 categories, each country's population was distributed across each of the five EIR buckets for the two levels of transmission risk (high and low). As a reminder, the goal was to determine the distribution that best approximates WHO disease burden. Through trial and error, distributions were set for each of the 13 categories.

E.g. 25,000-30,000

All countries falling into this category were ascribed the same distribution for low and high transmission.

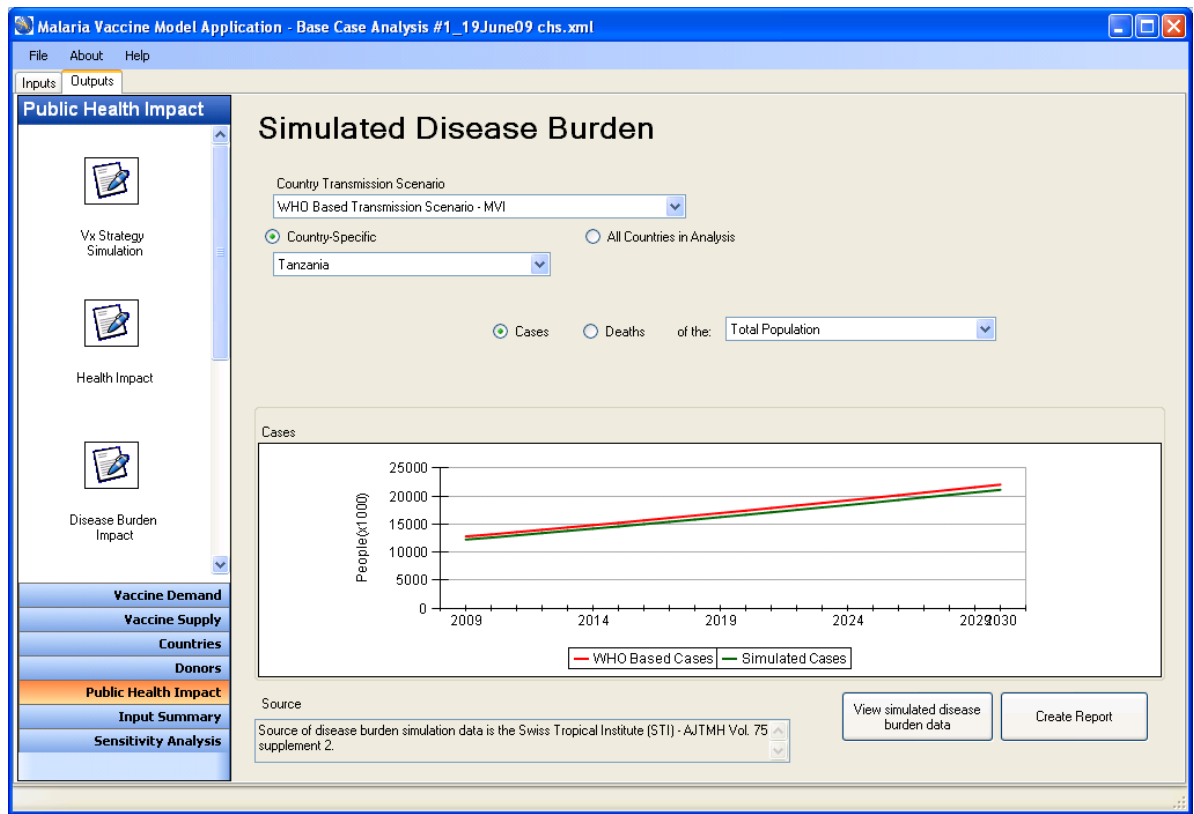|	High transmission	Low transmission
EIR 0.0	47.5%	52.0%
EIR 0.1	25.0%	25.0%
EIR 1.0	20.0%	20.0%
EIR 10	6.0%	3.0%
EIR 100	1.5%	0.0%

Note: The EIR 0.0 category is not actually assigned, rather it receives the unassigned distribution. In other words, it is presumed to be the difference between 100% and the sum of the four other buckets (i.e. EIR 0.0 = (100 − (EIR 0.1 + EIR 1.0 + EIR 10.0 + EIR 100.0)).

For example, according to WHO, Tanzania has a disease burden of 29,245 cases per 100,000 population. As a result, Tanzania falls into the 25,000 – 30,000 cases/100,000 category, as defined above.

For each EIR bucket, the distributions were weighted by the high and low transmission risk percentages for that country, and then summed across the high and low transmission settings.

E.g. Tanzania			
	High transmission	Low transmission	Sum
EIR 0.0	47.5% * 75%	52.0% * 25%	35.6 + 13.0 = 48.6%
EIR 0.1	25.0% * 75%	25.0% * 25%	18.8 + 6.3 = 25%
EIR 1.0	20.0% * 75%	20.0% * 25%	15.0 + 5.0 = 20.0%
EIR 10	6.0% * 75%	3.0% * 25%	4.5 + .8 = 5.3%
EIR 100	1.5% * 75%	0.0% * 25%	1.1 + 0.0 = 1.1%
% of Population in EIR = 0	**% of Population in EIR = 0.1**	**% of Population in EIR = 1.0**	**% of Population in EIR = 10**	**% of Population in EIR = 100**
49%	25%	20%	5.3%	1.1%

The WHO-based transmission scenario holds the transmission risk constant over time. However, users are free to create scenarios in which transmission risk varies over time or in which views about transmission risk varies across countries. Applying the country's population to the distribution in the transmission scenario provides the modeled disease burden over time. This modeled disease burden may then be compared to the expectation of the WHO disease burden, as shown here for Tanzania, in a screen shot from the Malaria Vaccine Model.

It is important to note that this WHO-based transmission scenario is but one representation of how low and high transmission risk may be translated to EIR. Users are free—and encouraged—to create their own transmission scenarios.

> **Note**: Transmission scenarios require significant computer memory. The user is advised to keep this in mind when creating multiple scenarios.

MAP-BASED TRANSMISSION SCENARIO

For the MAP-based transmission scenario, MVI relied on the opinion of MAP experts to translate their population at risk assessment to an EIR distribution.

MAP expresses transmission risk in the following *Pf* population at risk categories, according to the *P.f.* parasite rate (*Pf*PR)

- % of Total Population Living in No Malaria
- % of Total Population Living in Unstable Malaria
- % of Total Population Living in 0% < *P.f.* PR <= 5%
- % of Total Population Living in 5% < *P.f.* PR <= 40%
- % of Total Population Living in 40% < *P.f.* PR <= 100%

As an example, MAP reported the following *Pf*PR distribution to MVI for Tanzania.

E.g. Tanzania

- % of Total Population Living in No Malaria: 5%
- % of Total Population Living in Unstable Malaria: 0%
- % of Total Population Living in 0% < *P.f.* PR <= 5%: 13%
- % of Total Population Living in 5% < *P.f.* PR <= 40%: 70%
- % of Total Population living in 40% < P.f. PR <= 100%: 12%

MAP-BASED TRANSMISSION SCENARIO METHODOLOGY

In working with MAP experts, MVI arrived at the following methodology for translating MAP's *Pf* parasite rate estimates to EIR:

- EIR 0.0 = (% of Total Population living in No Malaria + % of Total Population living in Unstable Malaria + 1/4 * % of Total Population living in 0%< *Pf* PR<= 5%)
- EIR 0.1 = (3/4 * % of Total Population living in 0%< *Pf* PR<= 5% + 1/2 * (% of Total Population living in 5% < *Pf* PR <= 40%)
- EIR 1.0 = 1/2 * (% of Total Population living in 5%< *Pf* PR<=40%) + 7/10 * (% of Total Population living in 40% < *Pf* PR <= 100%)
- EIR 10.0 = 2/10 * (% of Total Population living in 40% < *Pf* PR <= 100%)
- EIR 100.0 = 1/10 * (% of Total Population living in 40% < *Pf* PR <= 100%)

This methodology results in the graphic below, as shown for Tanzania.
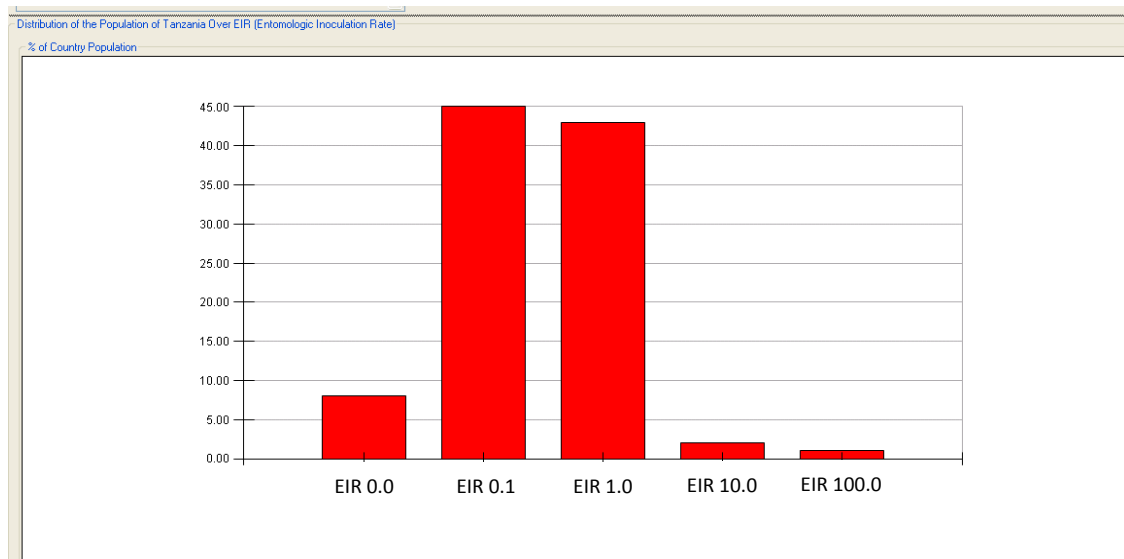
The MAP-based transmission scenario holds the transmission risk constant over time. However, users are free to create scenarios in which transmission risk varies over time, or in which views about transmission risk varies across countries.

It is important to note that this MAP-based transmission scenario is but one representation for translating *Pf*PR to EIR. Users are free—and encouraged—to create their own transmission scenarios.

- **Note**: Transmission scenarios require significant computer memory. The user is advised to keep this in mind when creating multiple scenarios.

REFERENCES

1. Policy Cures (2011) The G-FINDER Report 2010: Neglected disease research and development: Is the global financing crisis changing R&D?

2. Frost, L. J. and Reich, M. R. (2008) Access: How do good health technologies get to the poor people in poor countries? Cambridge: Harvard Center for Population and Development Studies.

3. Moran M (2005) A breakthrough in R&D for neglected diseases: new ways to get the drugs we need. PLoS Med 2: e302.

4. Brooks AD, Wells WA, McLean TD, Khanna R, Coghlan R, Mertenskoetter T, Privor-Dumm LA, Krattiger A, Mahoney RT (2010) Ensuring that Developing Countries have Access to New Healthcare Products: The Role of Product Development Partnerships. Innovation Strategy Today 3: 1-5.

5. Salako L (1998) Artemisinin and its derivatives: the regulatory and policy implications for African countries. Med Trop (Mars) 58: 82-84.

6. World Health Organization, UNAIDS (2002) Scientific considerations for the regulation and clinical evaluation of HIV/AIDS preventive vaccines: report from a WHO-UNAIDS Consultation 13-15 March 2001, Geneva, Switzerland. AIDS 16: W15-W25.

7. Brennan MJ, Fruth U, Milstien J, Tiernan R, de Andrade NS, Chocarro L (2007) Development of new tuberculosis vaccines: a global perspective on regulatory issues. PLoS Med 4: e252.

8. Mahoney R, Chocarro L, Southern J, Francis DP, Vose J, Margolis H (2011) Dengue vaccines regulatory pathways: a report on two meetings with regulators of developing countries. PLoS Med 8: e1000418.

9. Milstien J, Belgharbi L (2004) Regulatory pathways for vaccines for developing countries. Bull World Health Organ 82: 128-133.

10. Alonso PL, Ballou R, Brown G, Chitnis C, Loucq C, Moorthy V, Saul A, Wirth D (2011) A research agenda for malaria eradication: vaccines. PLoS Med 8: e1000398.

11. Andre FE (1999) Development and clinical application of new polyvalent combined paediatric vaccines. Vaccine 17: 1620-1627.

12. Braun LJ, Tyagi A, Perkins S, Carpenter J, Sylvester D, Guy M, Kristensen D, Chen D (2009) Development of a freeze-stable formulation for vaccines containing aluminum salt adjuvants. Vaccine 27: 72-79.

13. Capiau C, Poolman J, Hoet B, Bogaerts H, Andre F (2003) Development and clinical testing of multivalent vaccines based on a diphtheria-tetanus-

acellular pertussis vaccine: difficulties encountered and lessons learned. Vaccine 21: 2273-2287.

14. Milstien J, Munira SL, McKinney SL (2003) Issues in selection of DTwP-based combination vaccines. Vaccine 21: 1658-1664.

15. Yates A, N'Guessan R, Kaur H, Akogbeto M, Rowland M (2005) Evaluation of KO-Tab 1-2-3: a wash-resistant 'dip-it-yourself' insecticide formulation for long-lasting treatment of mosquito nets. Malar J 4: 52.

16. Vaccine Presentation and Packaging Advisory Group (2009) Generic preferred product profile for vaccines, Version 2.1.

17. Bresee JS, Glass RI, Ivanoff B, Gentsch JR (1999) Current status and future priorities for rotavirus vaccine development, evaluation and implementation in developing countries. Vaccine 17: 2207-2222.

18. Glass RI, Bresee JS, Turcios R, Fischer TK, Parashar UD, Steele AD (2005) Rotavirus vaccines: targeting the developing world. J Infect Dis 192 Suppl 1: S160-S166.

19. Goveia MG, Nelson CB, Ciarlet M (2010) RotaTeq: Progress toward developing world access. J Infect Dis 202 Suppl: S87-S92.

20. Moorthy V, Reed Z, Smith PG (2007) Measurement of malaria vaccine efficacy in phase III trials: report of a WHO consultation. Vaccine 25: 5115-5123.

21. Newton S, Owusu-Agyei S, Ampofo W, Zandoh C, Adjuik M, Adjei G, Tchum S, Filteau S, Kirkwood BR (2007) Vitamin A supplementation enhances infants' immune responses to hepatitis B vaccine but does not affect responses to Haemophilus influenzae type b vaccine. J Nutr 137: 1272-1277.

22. Milstien J, Cardenas V, Cheyne J, Brooks A (2010) WHO policy development processes for a new vaccine: case study of malaria vaccines. Malar J 9: 182.

23. Moorthy VS, Reed Z, Smith PG (2009) MALVAC 2008: Measures of efficacy of malaria vaccines in phase 2b and phase 3 trials--scientific, regulatory and public health perspectives. Vaccine 27: 624-628.

24. Wells WA, Brooks A (2011) Adoption of New Health Products in Low and Middle Income Settings: How Product Development Partnerships Can Support Country Decision Making. Health Res Policy Syst 9: 15.

25. Bosman A, Mendis KN (2007) A major transition in malaria treatment: the adoption and deployment of artemisinin-based combination therapies. Am J Trop Med Hyg 77: 193-197.

26. DeRoeck D, Clemens JD, Nyamete A, Mahoney RT (2005) Policymakers' views regarding the introduction of new-generation vaccines against typhoid fever, shigellosis and cholera in Asia. Vaccine 23: 2762-2774.

27. Diap G, Amuasi J, Boakye I, Sevcsik AM, Pecoul B (2010) Anti-malarial market and policy surveys in sub-Saharan Africa. Malar J 9 Suppl 1: S1.

28. Widdus R (1999) Introduction of vaccines into the Third World
2. C R Acad Sci III 322: 999-1010.

29. World Health Organization (2000) New perspective: Malaria Diagnosis. Report of a joint WHO/USAID informal consultation. WHO/MAL/2000.1091.

30. Levine OS, Hajjeh R, Wecker J, Cherian T, O'Brien KL, Knoll MD, Privor-Dumm L, Kvist H, Nanni A, Bear AP, Santosham M (2010) A policy framework for accelerating adoption of new vaccines. Hum Vaccin 6.

31. Miller MA, McCann L (2000) Policy analysis of the use of hepatitis B, Haemophilus influenzae type b-, Streptococcus pneumoniae-conjugate and rotavirus vaccines in national immunization schedules. Health Econ 9: 19-35.

32. Shearer JC, Stack ML, Richmond MR, Bear AP, Hajjeh RA, Bishai DM (2010) Accelerating policy decisions to adopt haemophilus influenzae type B vaccine: a global, multivariable analysis. PLoS Med 7: e1000249.

33. Wenger JD, DiFabio J, Landaverde JM, Levine OS, Gaafar T (1999) Introduction of Hib conjugate vaccines in the non-industrialized world: experience in four 'newly adopting' countries. Vaccine 18: 736-742.

34. Resuts for Development Institute (2011) Synthesis report: New vaccine adoption in lower-middle income countries.

35. Cliff J, Lewin S, Woelk G, Fernandes B, Mariano A, Sevene E, Daniels K, Matinhure S, Oxman A, Lavis J (2010) Policy development in malaria vector management in Mozambique, South Africa and Zimbabwe. Health Policy Plan 25: 372-383.

36. Glatman-Freedman A, Cohen ML, Nichols KA, Porges RF, Saludes IR, Steffens K, Rodwin VG, Britt DW (2010) Factors affecting the introduction of new vaccines to poor nations: a comparative study of the Haemophilus influenzae type B and hepatitis B vaccines. PLoS One 5: e13802.

37. Kramer RA, Dickinson KL, Anderson RM, Fowler VG, Miranda ML, Mutero CM, Saterson KA, Wiener JB (2009) Using decision analysis to improve malaria control policy making. Health Policy 92: 133-140.

38. Mahoney RT, Krattiger A, Clemens JD, Curtiss R, III (2007) The introduction of new vaccines into developing countries. IV: Global Access Strategies. Vaccine 25: 4003-4011.

39. Munira SL, Fritzen SA (2007) What influences government adoption of vaccines in developing countries? A policy process analysis. Soc Sci Med 65: 1751-1764.

40. (1996) Net Gain: A new method for preventing malaria deaths. Geneva: World Health Organization.

41. Institute of Medicine (2008) Assessment of the Role of Intermittent Preventive Treatment for Malaria in Infants: Letter Report.

42. Obrist B, Iteba N, Lengeler C, Makemba A, Mshana C, Nathan R, Alba S, Dillip A, Hetzel MW, Mayumana I, Schulze A, Mshinda H (2007) Access to health care in contexts of livelihood insecurity: a framework for analysis and action. PLoS Med 4: 1584-1588.

43. Levine OS, Knoll MD, Jones A, Walker DG, Risko N, Gilani Z (2010) Global status of Haemophilus influenzae type b and pneumococcal conjugate vaccines: evidence, policies, and introductions. Curr Opin Infect Dis 23: 236-241.

44. Ojo LR, O'Loughlin RE, Cohen AL, Loo JD, Edmond KM, Shetty SS, Bear AP, Privor-Dumm L, Griffiths UK, Hajjeh R (2010) Global use of Haemophilus influenzae type b conjugate vaccine. Vaccine 28: 7117-7122.

45. World Health Organization (1991) Technical Report Series: Safe use of pesticides. 14th report of the WHO expert committee on vector biology and control. 813.

46. World Health Organization (2010) World Malaria Report.

47. World Health Organization (2001) Introduction of hepatitis B vaccine into childhood immunization services: Management guidelines, including information for health workers and parents. WHO/V&B/01.31.

48. Muraskin, William (1995) The War Against Hepatitis B: A History of the International Task Force on Hepatitis B Immunization. Philadelphia: University of Pennsylvania Press.

49. World Health Organization (1991) Weekly Epidemiological Record 3: 9-16.

50. PATH (2004) PATH's Children's Vaccine Program.

51. World Health Organization (2001) Report of the 5th WHOPES Working Group Meeting. WHO/CDS/WHOPES/2001.4.

52. World Health Organization (1995) 45th Session of the WHO Regional Committee for Africa: Final report.

53. World Health Organization (2007) Insecticide-treated mosquito nets: a position statement.

54. World Health Organization (2010) Guidelines for the treatment of malaria, second edition.

55. World Health Organization (2006) The role of laboratory diagnosis to support malaria disease management: Focus on the use of rapid diagnostic tests in areas of high transmission. Report of a WHO Technical Consultation, 25-26 2004. Pre-publication copy.

56. Premji ZG (2009) Coartem: the journey to the clinic
    3. Malar J 8 Suppl 1: S3.

57. World Health Organization (2006) Guidelines for the treatment of malaria.

58. UNICEF (2011) State of the World's Children.

59. Center for Global Development (2007) A Risky Business: Saving money and improving global health through better demand forecasts.

60. The George Institute for International Health (2009) The G-FINDER Report: Neglected disease research and development: New times, new trends.

61. Milstien J, Cohen J, Olsen IT (2007) An evaluation of the GAVI Alliance efforts to introduce new vaccines via the Accelerated Development and Introduction Plans (ADIPs) and the Hib Initiative (HI).

62. PATH (2007) Vaccine presentation for pneumococcal vaccines: WHO consultation for the development of a TPP for pneumococcal vaccines.

63. Raw AS, Lionberger R, Yu LX (2011) Pharmaceutical Equivalence by Design for Generic Drugs: Modified-Release Products. Pharm Res .

64. US Food and Drug Administration (2007) DRAFT Guidance for Industry and Review Staff. Target Product Profile - A Strategic Development Process Tool.

65. Yu LX (2008) Pharmaceutical quality by design: product and process development, understanding, and control. Pharm Res 25: 781-791.

66. Lee BY, McGlone SM (2010) Pricing of new vaccines. Hum Vaccin 6: 619-626.

67. Alonso PL, Ballou R, Brown G, Chitnis C, Loucq C, Moorthy V, Saul A, Wirth D (2011) A research agenda for malaria eradication: vaccines. PLoS Med 8: e1000398.

68. Lee BY, Burke DS (2010) Constructing target product profiles (TPPs) to help vaccines overcome post-approval obstacles. Vaccine 28: 2806-2809.

69. Tebbey PW, Rink C (2009) Target Product Profile: A renaissance for its definition and use. J Med Market 9: 301-307.

70. Ellis RW (2001) Product development plan for new vaccine technologies. Vaccine 19: 1559-1566.

71. Garg S, Tambwekar KR, Vermani K, Kandarapu R, Garg A, Waller DP, Zaneveld LJ (2003) Development pharmaceutics of microbicide formulations. Part II: formulation, evaluation, and challenges. AIDS Patient Care STDS 17: 377-399.

72. Lambert WJ (2010) Considerations in developing a target product profile for parenteral pharmaceutical products. AAPS PharmSciTech 11: 1476-1481.

73. World Health Organization (2005) Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. WHO/IVB/05.19.

74. Abdulla S, Sagara I (2009) Dispersible formulation of artemether/lumefantrine: specifically developed for infants and young children. Malar J 8 Suppl 1: S7.

75. Andre FE (1999) Development and clinical application of new polyvalent combined paediatric vaccines 3298. Vaccine 17: 1620-1627.

76. Di Fabio JL, de QC (2001) Considerations for combination vaccine development and use in the developing world. Clin Infect Dis 33 Suppl 4: S340-S345.

77. Drain PK, Nelson CM, Lloyd JS (2003) Single-dose versus multi-dose vaccine vials for immunization programmes in developing countries. Bull World Health Organ 81: 726-731.

78. Bott RF, Oliveira WP (2007) Storage conditions for stability testing of pharmaceuticals in hot and humid regions. Drug Dev Ind Pharm 33: 393-401.

79. Kerdpanich A, Chokephaibulkit K, Watanaveeradej V, Vanprapar N, Simasathien S, Phavichitr N, Bock HL, Damaso S, Hutagalung Y, Han HH (2011) Immunogenicity of a human rotavirus vaccine (RIX4414) after storage at 37 degrees C for seven days. Hum Vaccin 7: 74-80.

80. Schreuder B, Arentsen H, Matosse M (1997) How important are airfreight rates and vaccine packaging in cost-saving efforts for the Expanded Programme on Immunization? Bull World Health Organ 75: 315-321.

81. Ojakaa DI, Ofware P, Machira YW, Yamo E, Collymore Y, Ba-Nguz A, Vansadia P, Bingham A (2011) Community perceptions of malaria and vaccines in South Coast and Busia regions of Kenya. Malar J 10: 147.

82. World Health Organization (2000) WHO Policy Statement: The use of opened multi-dose vials of vaccine in subsequent immunization session. WHO/V&B/00.0.

83. Vekemans J, Leach A, Cohen J (2009) Development of the RTS,S/AS malaria candidate vaccine. Vaccine 27 Suppl 6: G67-G71.

84. PATH Malaria Vaccine Initiative (2008) Public-sector preferences for RTS,S/AS01 malaria vaccine formulation, presentation, and packaging.

85. Deen JL, Clemens JD (2006) Issues in the design and implementation of vaccine trials in less developed countries. Nat Rev Drug Discov 5: 932-940.

86. Moorthy V, Reed Z, Smith PG (2007) Measurement of malaria vaccine efficacy in phase III trials: report of a WHO consultation. Vaccine 25: 5115-5123.

87. Shann F, Nohynek H, Scott JA, Hesseling A, Flanagan KL (2010) Randomized trials to study the nonspecific effects of vaccines in children in low-income countries. Pediatr Infect Dis J 29: 457-461.

88. Mangtani P, Mulholland K, Madhi SA, Edmond K, O'Loughlin R, Hajjeh R (2010) Haemophilus influenzae type b disease in HIV-infected children: a review of the disease epidemiology and effectiveness of Hib conjugate vaccines. Vaccine 28: 1677-1683.

89. Sartori AM (2004) A review of the varicella vaccine in immunocompromised individuals. Int J Infect Dis 8: 259-270.

90. Steele AD, Cunliffe N, Tumbo J, Madhi SA, De VB, Bouckenooghe A (2009) A review of rotavirus infection in and vaccination of human immunodeficiency virus-infected children. J Infect Dis 200 Suppl 1: S57-S62.

91. Roth A, Jensen H, Garly ML, Djana Q, Martins CL, Sodemann M, Rodrigues A, Aaby P (2004) Low birth weight infants and Calmette-Guerin bacillus vaccination at birth: community study from Guinea-Bissau. Pediatr Infect Dis J 23: 544-550.

92. Moon SS, Wang Y, Shane AL, Nguyen T, Ray P, Dennehy P, Baek LJ, Parashar U, Glass RI, Jiang B (2010) Inhibitory effect of breast milk on infectivity of live oral rotavirus vaccines. Pediatr Infect Dis J 29: 919-923.

93. Moorthy V, Reed Z, Smith PG (2007) Measurement of malaria vaccine efficacy in phase III trials: report of a WHO consultation. Vaccine 25: 5115-5123.

94. Moorthy VS, Reed Z, Smith PG (2009) MALVAC 2008: Measures of efficacy of malaria vaccines in phase 2b and phase 3 trials--scientific, regulatory and public health perspectives. Vaccine 27: 624-628.

95. Milstien J, Cardenas V, Cheyne J, Brooks A (2010) WHO policy development processes for a new vaccine: case study of malaria vaccines. Malar J 9: 182.

96. Malaria vaccine decision-making framework (2010) .

97. Blomberg B, Kitler ME, Milstien J, Dellepiane N, Fanning A, Norval PY, Spinaci S (1999) Availability of quality fixed-dose combinations for the treatment of tuberculosis: what can we learn from studying the World Health Organization's vaccine model? Int J Tuberc Lung Dis 3: S371-S380.

98. Brennan MJ, Collins FM, Morris SL (1999) Propelling novel vaccines directed against tuberculosis through the regulatory process. Tuber Lung Dis 79: 145-151.

99. Caudron JM, Ford N, Henkens M, Mace C, Kiddle-Monroe R, Pinel J (2008) Substandard medicines in resource-poor settings: a problem that can no longer be ignored. Trop Med Int Health 13: 1062-1072.

100. Bryson M, Duclos P, Jolly A (2010) Global immunization policy making processes. Health Policy 96: 154-159.

101. Results for Development Institute (2011) Synthesis report: New vaccine adoption in lower-middle income countries.

102. Waning B, Kyle M, Diedrichsen E, Soucy L, Hochstadt J, Barnighausen T, Moon S (2010) Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets. Global Health 6: 9.

103. Duclos P, Okwo-Bele JM (2007) [Global immunization policies and recommendations: objectives and process]. Med Sci (Paris) 23: 409-416.

104. Duclos P, Okwo-Bele JM, Salisbury D (2011) Establishing global policy recommendations: the role of the Strategic Advisory Group of Experts on immunization. Expert Rev Vaccines 10: 163-173.

105. Oxman AD, Lavis JN, Fretheim A (2007) Use of evidence in WHO recommendations. Lancet 369: 1883-1889.

106. World Health Organization (2001) Introduction of hepatitis B vaccine into childhood immunization services: Management guidelines, including information for health workers and parents. WHO/V&B/01.31.

107. World Health Organization (2003) Guidelines for WHO Guidelines. EIP/GPE/EQC/2003.1.

108. World Health Organization (2010) Guidelines for the treatment of malaria, Second edition.

109. Lydon P, Levine R, Makinen M, Brenzel L, Mitchell V, Milstien JB, Kamara L, Landry S (2008) Introducing new vaccines in the poorest countries: what did we learn from the GAVI experience with financial sustainability? Vaccine 26: 6706-6716.

110. Ravishankar N, Gubbins P, Cooley RJ, Leach-Kemon K, Michaud CM, Jamison DT, Murray CJ (2009) Financing of global health: tracking development assistance for health from 1990 to 2007. Lancet 373: 2113-2124.

111. Abelin A, Colegate T, Gardner S, Hehme N, Palache A (2011) Lessons from pandemic influenza A(H1N1): the research-based vaccine industry's perspective. Vaccine 29: 1135-1138.

112. Bosman A, Mendis KN (2007) A major transition in malaria treatment: the adoption and deployment of artemisinin-based combination therapies. Am J Trop Med Hyg 77: 193-197.

113. Vandersmissen W (2001) WHO expectation and industry goals. Vaccine 19: 1611-1615.

114. DeRoeck D, Bawazir SA, Carrasco P, Kaddar M, Brooks A, Fitzsimmons J, Andrus J (2006) Regional group purchasing of vaccines: review of the Pan American Health Organization EPI revolving fund and the Gulf Cooperation Council group purchasing program. Int J Health Plann Manage 21: 23-43.

115. GFATM (2009) Guide to the Global Fund's policies on procurement and supply management.

116. UNICEF (2009) Supply Annual Report.

117. Woodle D (2000) Vaccine procurement and self-sufficiency in developing countries. Health Policy Plan 15: 121-129.

118. Attaran A, Barnes KI, Curtis C, d'Alessandro U, Fanello CI, Galinski MR, Kokwaro G, Looareesuwan S, Makanga M, Mutabingwa TK, Talisuna A, Trape JF, Watkins WM (2004) WHO, the Global Fund, and medical malpractice in malaria treatment. Lancet 363: 237-240.

119. Tren R, Hess K, Bate R (2009) Drug procurement, the Global Fund and misguided competition policies. Malar J 8: 305.

120. Edelman R, Hombach J (2008) "Guidelines for the clinical evaluation of dengue vaccines in endemic areas": summary of a World Health Organization Technical Consultation. Vaccine 26: 4113-4119.

121. WHO, UNAIDS (2002) Scientific considerations for the regulation and clinical evaluation of HIV/AIDS preventive vaccines: report from a WHO-UNAIDS Consultation 13-15 March 2001, Geneva, Switzerland. AIDS 16: W15-W25.

122. WHO, UNAIDS, IAVI (2007) Executive summary and recommendations from the WHO/UNAIDS/IAVI expert group consultation on 'Phase IIB-TOC trials as a novel strategy for evaluation of preventive HIV vaccines', 31 January-2 February 2006, IAVI, New York, USA. AIDS 21: 539-546.

123. Wood D, Shin JH, Duval B, Schmitt HJ (2006) Chapter 22: Assuring the quality, safety and efficacy of HPV vaccines: the scientific basis of regulatory expectations pre- and post-licensure. Vaccine 24 Suppl 3: S3-187-S3/192.

124. Beatty ME, Beutels P, Meltzer MI, Shepard DS, Hombach J, Hutubessy R, Dessis D, Coudeville L, Dervaux B, Wichmann O, Margolis HS, Kuritsky JN (2011) Health economics of dengue: a systematic literature review and expert panel's assessment. Am J Trop Med Hyg 84: 473-488.

125. Vassall A, Compernolle P (2006) Estimating the resource needs of scaling-up HIV/AIDS and tuberculosis interventions in sub-Saharan Africa: a systematic review for national policy makers and planners. Health Policy 79: 1-15.

126. Wolfson LJ, Gasse F, Lee-Martin SP, Lydon P, Magan A, Tibouti A, Johns B, Hutubessy R, Salama P, Okwo-Bele JM (2008) Estimating the costs of achieving the WHO-UNICEF Global Immunization Vision and Strategy, 2006-2015. Bull World Health Organ 86: 27-39.

127. Center for Global Development (2007) A risky business: Saving money and improving global health through better demand forecasts.

128. Kumaresan J, Smith I, Arnold V, Evans P (2004) The Global TB Drug Facility: innovative global procurement. Int J Tuberc Lung Dis 8: 130-138.

129. Andrus JK, Sherris J, Fitzsimmons JW, Kane MA, Aguado MT (2008) Introduction of human papillomavirus vaccines into developing countries - international strategies for funding and procurement. Vaccine 26 Suppl 10: K87-K92.

130. Crawley J, Hill J, Yartey J, Robalo M, Serufilira A, Ba-Nguz A, Roman E, Palmer A, Asamoa K, Steketee R (2007) From evidence to action? Challenges to policy change and programme delivery for malaria in pregnancy 25. Lancet Infect Dis 7: 145-155.

131. Lang T, Greenwood B (2003) The development of Lapdap, an affordable new treatment for malaria. Lancet Infect Dis 3: 162-168.

132. Frost, L. J. and Reich, M. R. (2008) Access: How do good health technologies get to the poor people in poor countries? Cambridge: Harvard Center for Population and Development Studies.

133. Brooks AD, Wells WA, McLean TD, Khanna R, Coghlan R, Mertenskoetter T, Privor-Dumm LA, Krattiger A, Mahoney RT (2009) Ensuring that

developing countries have access to new healthcare products: the role of product development partnerships. Innov Strat Today 3: 1-5.

134. Stop TB Partnership and World Health Organization (2007) New technologies for tuberculosis control: a framework for adoption, introduction and implementation.

135. Kane MA, Brooks A (2002) New immunization initiatives and progress toward the global control of hepatitis B. Curr Opin Infect Dis 15: 465-469.

136. Alliance TB (2007) Pathway to Patients: Charting the Dynamics of the Global TB Drug Market.

137. MMV UMHW (2008) Understanding the antimalarials market: Uganda 2007. An overview of the supply side.

138. Milstien J, Cardenas V, Cheyne J, Brooks A (2010) WHO policy development processes for a new vaccine: case study of malaria vaccines. Malar J 9: 182.

139. Moran M, Guzman J, McDonald A, Wu L, Omune B (2010) Registering new drugs: the African context: new tools for new times.

140. Levine OS, Cherian T, Shah R, Batson A (2004) PneumoADIP: an example of translational research to accelerate pneumococcal vaccination in developing countries. J Health Popul Nutr 22: 268-274.

141. Alliance TB (2009) New TB regimens: What countries want. The value proposition of existing and new first-line regimens for drug-susceptible tuberculosis.

142. Hajjeh RA, Privor-Dumm L, Edmond K, O'Loughlin R, Shetty S, Griffiths UK, Bear AP, Cohen AL, Chandran A, Schuchat A (2010) Supporting new vaccine introduction decisions: lessons learned from the Hib Initiative experience. Vaccine 28: 7123-7129.

143. Wells WA, Konduri N, Chen C, Lee D, Ignatius HR, Gardiner E, Schwalbe NR (2010) TB regimen change in the high burden countries. Int J Tuberc Lung Dis 14: 1538-1547.

144. Williams HA, Durrheim D, Shretta R (2004) The process of changing national malaria treatment policy: lessons from country-level studies. Health Policy Plan 19: 356-370.

145. Levine OS, Hajjeh R, Wecker J, Cherian T, O'Brien KL, Knoll MD, Privor-Dumm L, Kvist H, Nanni A, Bear AP, Santosham M (2010) A policy framework for accelerating adoption of new vaccines. Hum Vacc 6.

146. Bosman A, Mendis KN (2007) A major transition in malaria treatment: the adoption and deployment of artemisinin-based combination therapies. Am J Trop Med Hyg 77: 193-197.

147. Senouci K, Blau J, Nyambat B, Coumba Faye P, Gautier L, Da Silva A, Favorov MO, Clemens JD, Stoeckel P, Gessner BD (2010) The Supporting Independent Immunization and Vaccine Advisory Committees (SIVAC) initiative: a country-driven, multi-partner program to support evidence-based decision making. Vaccine 28: A26-A30.

148. Moran M, Ropars A, Guzman J, Diaz J, Garrison C (2005) The new landscape of neglected disease drug development.

149. Mann G, Squire SB, Bissel K, Eliseev P, Du Toit E, Hesserling A, Nicol M, Detjen A, Kritski A (2010) Beyond accuracy: creating a comprehensive evidence base for tuberculosis diagnostic tools. Int J Tuberc Lung Dis 14: 1518-1524.

150. Gericke CA, Kurowski C, Ranson MK, Mills A (2005) Intervention complexity--a conceptual framework to inform priority-setting in health. Bull World Health Organ 83: 285-293.

151. Andrus JK, Toscano CM, Lewis M, Oliveira L, Ropero AM, Davila M, Fitzsimmons JW (2007) A model for enhancing evidence-based capacity to make informed policy decisions on the introduction of new vaccines in the Americas: PAHO's ProVac initiative. Public Health Rep 122: 811-816.

152. Byskov J, Bloch P, Blystad A, Hurtig AK, Fylkesnes K, Kamuzora P, Kombe Y, Kvale G, Marchal B, Martin DK (2009) Accountable priority setting for trust in health systems--the need for research into a new approach for strengthening sustainable health action in developing countries. Health Res Policy Syst 7: 23.

153. WHO (2005) Vaccine introduction guidelines. Adding a vaccine to a national immunization programme; decision and implementation.

154. Munira SL, Fritzen SA (2007) What influences government adoption of vaccines in developing countries? A policy process analysis. Soc Sci Med 65: 1751-1764.

155. Makinen M (2010) Lower-middle income countries: study results on adoption and financing of new vaccines.

156. Brownson RC, Fielding JE, Maylahn CM (2009) Evidence-based public health: a fundamental concept for public health practice. Annu Rev Public Health 30: 175-201.

157. Bryson M, Duclos P, Jolly A, Cakmak N (2010) A global look at national Immunization Technical Advisory Groups. Vaccine 28: A13-A17.

158. Shearer JC, Stack ML, Richmond MR, Bear AP, Hajjeh RA, Bishai DM (2010) Accelerating policy decisions to adopt haemophilus influenzae type B vaccine: a global, multivariable analysis. PLoS Med 7: e1000249.

159. Kingdon, J. W. (1995) Agendas, alternatives and public policies. New York: Longman.

160. Walt, G. (1994) Health policy: an introduction to process and power. London: Zed Books Ltd.

161. Shretta R, Omumbo J, Rapuoda B, Snow RW (2000) Using evidence to change antimalarial drug policy in Kenya. Trop Med Int Health 5: 755-764.

162. Wells WA, Konduri N, Chen C, Lee D, Ignatius HR, Gardiner E, Schwalbe NR (2011) Implications of the current TB treatment landscape for future regimen change. Int J Tuberc Lung Dis .

163. Amin AA, Zurovac D, Kangwana BB, Greenfield J, Otieno DN, Akhwale WS, Snow RW (2007) The challenges of changing national malaria drug policy to artemisinin-based combinations in Kenya. Malar J 6: 72.

164. Malaria vaccine decision-making framework (2010) .

165. Duclos P (2010) National Immunization Technical Advisory Groups (NITAGs): guidance for their establishment and strengthening. Vaccine 28: A18-A25.

166. Challenges for product development partnerships in facilitating equitable access to new health products in low income countries: Report from a meeting at Divonne les Bains, France, 27-28 July 2010.

167. Introducing new approaches and tools for enhanced TB control (INAT) subgroup of the DOTS Expansion Working Group.

168. MMV at a glance: building the malaria drug pipeline for the future.

169. Open Forum 4 - Key Issues in TB Drug Development.

170. [Anonymous] (2011) Malaria vaccine decision-making framework: project vision.

171. Princeton Survey Research Associates International for USAID (2008) Survey evaluation of the malaria vaccine decision making framework process.

172. Milstien J, Cohen JC, Olsen IT (2007) An evaluation of GAVI Alliance efforts to introduce new vaccines via the Accelerated Development and Introduction Plans (ADIPs) and the Hib Initiative (HI).

173. Grindle MS and Thomas JW (1991) Public Choices and Policy Change: The political economy of reform in developing countries. Baltimore.

174. Kingdon JW (1995) Agendas, alternatives and public policies. New York: Longman.

175. Walt, G (1994) Health Policy: An introduction to process and power. London: Zed Books, Ltd.

176. Bryson M, Duclos P, Jolly A, Bryson J (2010) A systematic review of national immunization policy making processes. Vaccine 28: A6-A12.

177. DeRoeck D (2004) The importance of engaging policy-makers at the outset to guide research on and introduction of vaccines: the use of policy-maker surveys. J Health Popul Nutr 22: 322-330.

178. Gericke CA, Kurowski C, Ranson MK, Mills A (2005) Intervention complexity--a conceptual framework to inform priority-setting in health. Bull World Health Organ 83: 285-293.

179. Gessner BD, Duclos P, DeRoeck D, Nelson EA (2010) Informing decision makers: experience and process of 15 National Immunization Technical Advisory Groups. Vaccine 28 Suppl 1: A1-A5.

180. Grundy J (2010) Country-level governance of global health initiatives: an evaluation of immunization coordination mechanisms in five countries of Asia
3244. Health Policy and Planning 25: 186-196.

181. Victora CG (2010) LiST: using epidemiology to guide child survival policymaking and programming. Int J Epidemiol 39: 650-652.

182. Hutubessy R, Chisholm D, Edejer TT (2003) Generalized cost-effectiveness analysis for national-level priority-setting in the health sector. Cost Eff Resour Alloc 1: 8.

183. Kim SY, Sweet S, Slichter D, Goldie SJ (2010) Health and economic impact of rotavirus vaccination in GAVI-eligible countries. BMC Public Health 10: 253.

184. Levine OS, Knoll MD, Jones A, Walker DG, Risko N, Gilani Z (2010) Global status of Haemophilus influenzae type b and pneumococcal conjugate vaccines: evidence, policies, and introductions. Curr Opin Infect Dis 23: 236-241.

185. World Health Organization (2004) Review panel on *Haemophilis influenzae* type b (Hib) disease burden in Bangladesh, Indonesia and other Asian countries. Weekly Epidemiological Record 79: 173-175.

186. Shearer JC, Stack ML, Richmond MR, Bear AP, Hajjeh RA, Bishai DM (2010) Accelerating policy decisions to adopt haemophilus influenzae type B vaccine: a global, multivariable analysis. PLoS Med 7: e1000249.

187. Stop TB Partnership, World Health Organization (2007) New Technologies for Tuberculosis Control: A framework for their adoption, introduction and implementation. WHO/HTM/STB/2007.40.

188. World Health Organization (2002) Operational guide for national tuberculosis control programmes on the introduction and use of fixeddose combination drugs. WHO/CDS/TB/2002.308 and WHO/EDM/PAR/2002.6.

189. World Health Organization (2005) Vaccine Introduction Guidelines: Adding a vaccine to a national immunization programme: decision and implementation. WHO/IVB/05.18.

190. Katahoire RA, Jitta J, Kivumbi G, Murokora D, Arube WJ, Siu G, Arinaitwe L, Bingham A, Mugisha E, Tsu V, LaMontagne DS (2008) An assessment of the readiness for introduction of the HPV vaccine in Uganda. Afr J Reprod Health 12: 159-172.

191. Bosman A, Mendis K (2007) A Major Transition in Malaria Treatment: The Adoption and Deployment of Artemisinin-Based Combination Therapies. Am J Trop Med Hyg 77(6_Suppl): 193-197.

192. Frost LJ, Reich MR (2009) Creating access to health technologies in poor countries. Health Aff (Millwood) 28: 962-973.

193. Kane MA, Brooks A (2002) New immunization initiatives and progress toward the global control of hepatitis B. Curr Opin Infect Dis 15: 465-469.

194. World Health Organization, UNAIDS, UNICEF (2010) Towards Universal Access: Scaling up priority HIV/AIDS interventions in the health sector.

195. Mitchell V, Walker D, Zuber P, Lydon P, Ahun M (2005) Evidenced-based decision making about Hib vaccination. Lancet 365: 936-937.

196. GAVI Alliance (2004) Report of the Hib Task Force, 14th GAVI Board Meeting.

197. Amin AA, Zurovac D, Kangwana BB, Greenfield J, Otieno DN, Akhwale WS, Snow RW (2007) The challenges of changing national malaria drug policy to artemisinin-based combinations in Kenya. Malar J 6: 72.

198. Mulligan JA, Mandike R, Palmer N, Williams H, Abdulla S, Bloland P, Mills A (2006) The costs of changing national policy: lessons from malaria treatment policy guidelines in Tanzania. Tropical Medicine & International Health 11: 452-461.

199. Williams HA, Durrheim D, Shretta R (2004) The process of changing national malaria treatment policy: lessons from country-level studies. Health Policy Plan 19: 356-370.

200. GAVI Alliance (2008) GAVI Alliance Handbook: Country proposal and monitoring processes.

201. GFATM (2010) Guidelines and requirements for country coordinating mechanisms.

202. Malaria Vaccine Funders Group (2006) Malaria Vaccine Technology Roadmap.

203. Malaria vaccine decision-making framework (2011) .

204. Princeton Survey Research Associates International (2008) Survey Evaluation of the Malaria Vaccine Decision Making Framework Process.

205. GAVI Alliance (2004) Guidelines for the preparation of proposals for GAVI/VF funding. Second draft, Version 4.

206. World Health Organization (2005) Vaccine Introduction Guidelines-Adding a vaccine to a national immunization programme: decision and implementation. WHO/IVB/05.1.

207. Mitchell, S (2009) Unsimple truths: Science, complexity and policy. Chicago: University of Chicago Press.

208. World Health Organization (2010) World Malaria Report.

209. Milstien J, Cohen JC, Olsen IT (2007) An evaluation of GAVI Alliance efforts to introduce new vaccines via the Accelerated Development and Introduction Plans (ADIPS) and the Hib Initiative (HI).

210. Atherly D, Dreibelbis R, Parashar UD, Levin C, Wecker J, Rheingans RD (2009) Rotavirus vaccination: cost-effectiveness and impact on child mortality in developing countries. J Infect Dis 200 Suppl 1: S28-S38.

211. Goldie SJ, O'Shea M, Diaz M, Kim SY (2008) Benefits, cost requirements and cost-effectiveness of the HPV16,18 vaccine for cervical cancer prevention in developing countries: policy implications. Reprod Health Matters 16: 86-96.

212. Stover J, Bollinger L, Hecht R, Williams C, Roca E (2007) The impact of an AIDS vaccine in developing countries: a new model and initial results. Health Aff (Millwood) 26: 1147-1158.

213. Jauregui B, Sinha A, Clark AD, Bolanos BM, Resch S, Toscano CM, Matus CR, Andrus JK (2011) Strengthening the technical capacity at country-level to make informed policy decisions on new vaccine introduction: lessons learned by PAHO's ProVac Initiative. Vaccine 29: 1099-1106.

214. Carneiro I, Smith L, Ross A, Roca-Feltrer A, Greenwood B, Schellenberg JA, Smith T, Schellenberg D (2010) Intermittent preventive treatment for malaria in infants: a decision-support tool for sub-Saharan Africa. Bull World Health Organ 88: 807-814.

215. Smith T, Killeen GF, Maire N, Ross A, Molineaux L, Tediosi F, Hutton G, Utzinger J, Dietz K, Tanner M (2006) Mathematical modeling of the impact of malaria vaccines on the clinical epidemiology and natural history of *Plasmodium falciparum* malaria: Overview. Am J Trop Med Hyg 75: 1-10.

216. Griffin JT, Hollingsworth TD, Okell LC, Churcher TS, White M, Hinsley W, Bousema T, Drakeley CJ, Ferguson NM, Basanez MG, Ghani AC (2010) Reducing Plasmodium falciparum malaria transmission in Africa: a model-based evaluation of intervention strategies. PLoS Med 7.

217. Tediosi F, Hutton G, Maire N, Smith TA, Ross A, Tanner M (2006) Predicting the cost-effectiveness of introducing a pre-erythrocytic malaria vaccine into the expanded program on immunization in Tanzania. Am J Trop Med Hyg 75: 131-143.

218. GAVI Alliance (2006) Independent Expert Committee Recommendation for AMC Pilot.

219. Malaria Vaccine Funders Group (2006) Malaria Vaccine Technology Roadmap 3253.

220. UN Population Division (2008) World Population Prospects.

221. World Health Organization, United Nations Children's Fund (2009) Immunization Summary: A statistical reference containing data through 2007.

222. Oguntola S (2010 July 8) Experts recommend inclusion of pneumococcal vaccine in immunisation programme. Nigerian Tribune.

223. Maire N, Smith T, Ross A, Owusu-Agyei S, Dietz K, Molineaux L (2006) A model for natural immunity to asexual blood stages of *Plasmodium falciparum* malaria in endemic areas. Am J Trop Med Hyg 75: 19-31.

224. Ross A, Killeen GF, Smith T (2006) Relationships of host infectivity to mosquitoes and asexual parasite density in *Plasmodium falciparum* . Am J Trop Med Hyg 75 (Suppl 2): 32-37.

225. Ross A, Maire N, Molineaux L, Smith T (2006) An epidemiologic model of severe morbidity and mortality caused by *Plasmodium falciparum*. Am J Trop Med Hyg 75: 63-73.

226. Smith T, Killeen GF, Maire N, Ross A, Molineaux L, Tediosi F, Hutton G, Utzinger J, Dietz K, Tanner M (2006) Mathematical modeling of the impact of malaria vaccines on the clinical epidemiology and natural history of Plasmodium falciparum malaria: Overview
42. Am J Trop Med Hyg 75: 1-10.

227. Smith T, Maire N, Dietz K, Killeen GF, Vounatsou P, Molineaux L, Tanner M (2006) Relationship between the entomologic inoculation rate and the force of

infection for Plasmodium falciparum malaria
41. Am J Trop Med Hyg 75: 11-18.

228. Smith T, Ross A, Maire N, Rogier C, Trape JF, Molineaux L (2006) An epidemiologic model of the incidence of acute illness in Plasmodium falciparum malaria. Am J Trop Med Hyg 75: 56-62.

229. INDEPTH Network (2002) Population, Health and Survival at INDEPTH Sites. Ottawa: IDRC.

230. Smith T, Maire N, Ross A, Penny M, Chitnis N, Schapira A, Studer A, Genton B, Lengeler C, Tediosi F, de Savigny D., Tanner M (2008) Towards a comprehensive simulation model of malaria epidemiology and control 22. Parasitology 135: 1507-1516.

231. Tediosi F, Maire N, Smith T, Hutton G, Utzinger J, Ross A, Tanner M (2006) An approach to model the costs and effects of case management of Plasmodium falciparum malaria in sub-saharan Africa. Am J Trop Med Hyg 75: 90-103.

232. Penny MA, Maire N, Studer A, Schapira A, Smith TA (2008) What should vaccine developers ask? Simulation of the effectiveness of malaria vaccines. PLoS One 3: e3193.

233. World Health Organization (2008) World Malaria Report.

234. Hay SI, Guerra CA, Gething PW, Patil AP, Tatem AJ, Noor AM, Kabaria CW, Manh BH, Elyazar IR, Brooker S, Smith DL, Moyeed RA, Snow RW (2009) A world malaria map: Plasmodium falciparum endemicity in 2007. PLoS Med 6: e1000048.

235. Maire N, Tediosi F, Ross A, Smith T (2006) Predictions of the epidemiologic impact of introducing a pre-erythrocytic vaccine into the expanded program on immunization in sub-Saharan Africa. Am J Trop Med Hyg 75: 111-118.

236. Maire N, Aponte JJ, Ross A, Thompson R, Alonso P, Utzinger J, Tanner M, Smith T (2006) Modeling a field trial of the RTS,S/AS02A malaria vaccine. Am J Trop Med Hyg 75: 104-110.

237. Malaria Vaccine Funders Group (2006) Malaria Vaccine Technology Roadmap 3253.

238. Tediosi F, Maire N, Penny M, Studer A, Smith TA (2009) Simulation of the cost-effectiveness of malaria vaccines. Malar J 8: 127.

239. Griffiths UK, Korczak VS, Ayalew D, Yigzaw A (2009) Incremental system costs of introducing combined DTwP-hepatitis B-Hib vaccine into national immunization services in Ethiopia. Vaccine 27: 1426-1432.

240. Asante KP, Abdulla S, Agnandji S, Lyimo J, Vekemans J, Soulanoudjingar S, Owusu R, Shomari M, Leach A, Jongert E, Salim N, Fernandes JF, Dosoo D, Chikawe M, Issifou S, Osei-Kwakye K, Lievens M, Paricek M, Moller T, Apanga S, Mwangoka G, Dubois MC, Madi T, Kwara E, Minja R, Hounkpatin AB, Boahen O, Kayan K, Adjei G, Chandramohan D, Carter T, Vansadia P, Sillman M, Savarese B, Loucq C, Lapierre D, Greenwood B, Cohen J, Kremsner P, Owusu-Agyei S, Tanner M, Lell B (2011) Safety and efficacy of the RTS,S/AS01(E) candidate malaria vaccine given with expanded-programme-on-immunisation vaccines: 19 month follow-up of a randomised, open-label, phase 2 trial. Lancet Infect Dis (In press) .

241. Vekemans J, Leach A, Cohen J (2009) Development of the RTS,S/AS malaria candidate vaccine. Vaccine 27 Suppl 6: G67-G71.

242. World Health Organization (2010) World Malaria Report.

243. Steketee RW, Campbell CC (2010) Impact of national malaria control scale-up programmes in Africa: magnitude and attribution of effects. Malar J 9: 299.

244. Griffin JT, Hollingsworth TD, Okell LC, Churcher TS, White M, Hinsley W, Bousema T, Drakeley CJ, Ferguson NM, Basanez MaG, Ghani AC (2010) Reducing *Plasmodium falciparum* Malaria Transmission in Africa: A Model-Based Evaluation of Intervention Strategies. PLoS Med 7: e1000324.

245. Smith T, Maire N, Ross A, Penny M, Chitnis N, Schapira A, Studer A, Genton B, Lengeler C, Tediosi F, de Savigny D, Tanner M (2008) Towards a comprehensive simulation model of malaria epidemiology and control. Parasitology 135: 1507-1516.

246. Smith T, Ross A, Maire N, Chitnis N, Hardy D, Studer A, Brooks A, Penny M, Tanner M (2011) Ensemble modeling of the likely public health impact of the RTS,S malaria vaccine. Under review by PLoS Medicine .

247. UNICEF (2011) State of the World's Children.

248. Maire N., Shillcutt S, Walker DG, Tediosi F, Smith T (2011) Cost effectiveness of the introduction of a pre-erythrocytic malaria vaccine into the Expanded Program on Immunization in sub-Saharan Africa: analysis of uncertainties using a stochastic individual-based simulation model of Plasmodium falciparum malaria. Value Health (In Press) .

249. Malaria vaccine decision-making framework (2011) Available at: http://www.malvacdecision.net, Accessed: 19 September, 2011.

250. Milstien J, Cardenas V, Cheyne J, Brooks A (2010) WHO policy development processes for a new vaccine: case study of malaria vaccines 151. Malar J 9: 182.

251. Smith T, Maire N, Dietz K, Killeen GF, Vounatsou P, Molineaux L, Tanner M (2006) Relationship between the entomologic inoculation rate and the force of infection for *Plasmodium falciparum* malaria. Am J Trop Med Hyg 75: 11-18.

252. Trape JF, Rogier C (1996) Combating malaria morbidity and mortality by reducing transmission. Parasitol Today 12: 236-240.

253. Biellik R, Levin C, Mugisha E, LaMontagne DS, Bingham A, Kaipilyawar S, Gandhi S (2009) Health systems and immunization financing for human papillomavirus vaccine introduction in low-resource settings. Vaccine 27: 6203-6209.

254. GAVI Alliance (2011) Guidelines on Country Proposals.

255. Cutts FT, Zaman SM, Enwere G, Jaffar S, Levine OS, Okoko JB, Oluwalana C, Vaughan A, Obaro SK, Leach A, McAdam KP, Biney E, Saaka M, Onwuchekwa U, Yallop F, Pierce NF, Greenwood BM, Adegbola RA (2005) Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet 365: 1139-1146.

CURRICULUM VITAE

CAREER SUMMARY_____

I have a rich experience base and proven leadership and management expertise from approximately 15 years as a professional, working primarily on public health in the developing world. My experience spans: working on targeted public health issues and developing strategies behind global initiatives; developing and implementing new health interventions and strengthening health systems; and using existing health resources more efficiently and establishing innovative financing mechanisms. I have worked within countries and at the international level, and with not-for profit organizations and with the private sector.

My management experience includes leading small teams and leading large, multi-organization collaborations; hiring staff and removing staff; and making grants and writing successful proposals seeking grants. In each aspect of my career I have sought to improve the lives of vulnerable populations.

PROFESSIONAL EXPERIENCE_____
PATH, Ferney-Voltaire, France, 2001 to 2010
Director, Policy & Access Unit, Malaria Vaccine Initiative (MVI), 5/2007-9/2010

- Ensured malaria vaccines in research and development were aligned with the needs of developing countries and able to be integrated into existing health systems.

- Led MVI's strategic and technical collaborations at global and regional levels with WHO, UNICEF, GAVI, GFATM, and UNICEF.

- Managed MVI's collaborations with governments, public health and bilateral partners in African countries.

- Led the development of the research plan for post-approval studies in Africa for the anticipated first generation vaccine.

- Collaborated regularly with other PATH projects in such areas as health system strengthening, reproductive health, and logistics.

- Co-managed collaboration with large pharmaceutical organization as member of small decision-making team on $180 million project.

- Developed and oversaw implementation of multi-year unit strategy, including metrics, administration, staffing, financing and staff professional development.

- Managed international team of 3.5 staff

- Member of the Leadership Team of MVI's Directors, overseeing organizational strategy and development, including development and implementation of a matrixed management structure, and donor relations and reporting.

- Raised funds as one of the lead authors on successful grants to PATH of almost $300 million.

Senior Program Officer, Malaria Vaccine Initiative, 2/2005 to 4/2007

- Led the design and establishment of MVI's policy and access unit and strategy. Accountable for implementing this strategy through annual work plans, budgets and management of 3 staff based in the US, Europe, and Africa.

- Collaborated in the planning and management of MVI research and development activities, contributing policy-related considerations and planning as appropriate.

- Managed operational research to create and validate a framework of processes and data sought by African countries in order to take eventual decisions on use of malaria vaccines. In partnership with WHO, implemented 7 country consultations, each with up to 50 participants, over a 12 month period.

- Led analyses of factors important to global and regional policy-makers for the uptake of new vaccines and health interventions in the developing world.

- Managed modeling activities to predict the impact, cost-effectiveness, and financing requirements of malaria vaccines.

- Analyzed innovative financing mechanisms, including a critical role determining the feasibility of creating a multi-billion dollar advance market commitment for vaccines.

- Co-created and rotating chair of formal standing collaboration mechanism with large pharmaceutical company.

- Chaired or member of the Leadership Team which oversaw organizational strategy, development, donor relations and reporting.

- Co-created and implemented a multi-program management and administration structure for the PATH office in France.

- Raised funds as one of the lead authors on successful grants to PATH of over $100 million.

Senior Program Officer, Children's Vaccine Program (CVP), 9/2001 to 1/2005

- Led PATH activities, and managed multi-million dollar investments, to improve the financial sustainability of immunization programs and wider health systems. Served as a core member of GAVI's Financing Task Force.

- Managed developing country programs and supported PATH country staff working on health system and immunization strengthening, adoption of new vaccines, and/or financial sustainability, such as in Cambodia, India and Indonesia.

- Led PATH's collaboration and contributed to GAVI's work establishing innovative financing mechanisms, such as the International Financing Facility for immunization which is anticipated to raise $4 billion over 10 years.

- Catalyzed collaboration across PATH programs, particularly those working on vaccine-related issues, as well as reproductive health.

- Developed jointly with staff in Seattle, an innovative distance learning module,

particularly contributing to issues relating to new vaccine decision-making, financing and economics, and supply and procurement.

- Managed the analysis of group procurement mechanisms for vaccines in order to evaluate potential cost savings for countries in Eastern Europe and the Newly Independent States.

- Represented PATH to immunization partners and countries as member of the Eastern and Southern Africa sub-Regional Working Group.

PATH, Seattle, USA, 6/1999 to 8/2001
Program Officer, CVP

- Provided core analytic and strategic input to the establishment of the Global Alliance for Vaccines and Immunization and Global Fund for Children's Vaccines (now called the GAVI Alliance). Analyzed and provided projections of impact, financing, and demand implications of strategic decisions for GAVI on behalf of its Secretariat and Board. Co-developed original country application mechanism.

- Evaluated opportunities for new country projects.

- Established and managed a grant-making system, including application and review.

- Provided technical assistance to developing country health programs and supported PATH country staff working on immunization strengthening and/or adoption of new vaccines.

- Managed epidemiological studies in developing countries. Managed, with the Thai government, a burden of disease study of bacterial pneumonia, meningitis, and sepsis with over 100,000 children under surveillance.

PATH, Bangkok, Thailand, Feb-May, 1999
Consultant, Bill & Melinda Gates Children's Vaccine Program

- Posted to the Ministry of Public Health, Thailand.

- Early design and planning for a burden of disease study for invasive bacterial disease.

London School of Hygiene and Tropical Medicine, Infectious Disease Epidemiology Unit and Children's Vaccine Initiative, London, Geneva, and Seattle, 10/1998 to 2/1999
Consultant

- Studied new vaccine adoption in developing countries.

Washington State Reformatory, Department of Corrections, Monroe, WA, 10/1994 to 8/1997
Registered Nurse II

- Facilitated health promotion and disease prevention for inmates in maximum-

security prison; managed acute and chronic illnesses

- HIV-Test Counselor

- Infectious Disease Trainer - Designed and taught communicable disease and safety curricula to prison staff

Western State Psychiatric Hospital, Legal Offender Unit, Ft. Steilacoom, WA, 1994
Nursing Student

Ministry of Public Health/National School of Nursing, Quito, Ecuador, 1993
Nurse Intern

University of Washington, Department of Psychology, Seattle, WA, 1992 to 1993
Research Assistant to Kristin Rytter, PhC

EDUCATION_____

- PhD Candidate, Epidemiology and Public Health, Thesis title: Planning for new health interventions in Africa: An integrated strategy to prepare for malaria vaccines and lessons for future interventions, Swiss Tropical and Public Health Institute/University of Basel, Oral exam October 28 2011, Anticipated completion November 2011

- MSc, Public Health "Control of Infectious Diseases", London School of Hygiene and Tropical Medicine, UK, 1998

- Bachelor of Science, Nursing, *Summa Cum Laude*, University of Washington, Seattle, 1994

- Additional education:

    o Multiple courses in leadership and working with the media.

    o Advanced Methods in Cost-Effectiveness Analysis (short-course), Oxford, July 2005

COUNTRY EXPERIENCE_____

- Managed projects and/or worked in all regions outside of the Middle East

HONORS/AWARDS_____

- Best PhD Student's Presentation - Swiss Society of Tropical Medicine and Parasitology, Student's Conference, 2010

- Fulbright Grant—postgraduate study, London School of Hygiene and Tropical Medicine, 1997-1998

- Outstanding Service Award—University of Washington School of Nursing Alumni

Association, 1994

- Outstanding Humanitarian Award—University of Washington School of Nursing, 1994

- Dean's Club Special Scholar—Grant to support health care work in South America, 1993

- Fuld Fellow—National award and scholarship to attend International Council of Nurses Conference in Madrid, Spain, 1993

EXAMPLES OF VOLUNTEER ACTIVITIES_____

- President, Board of Directors, United Nations Association, Seattle Metropolitan Chapter, 1995-1997

- Member, Board of Directors, United Nations Association, Seattle Metropolitan Chapter, 1992-1995

- United Nations Elections Observer, international expatriates voting in USA; South Africa-1994, Eritrea-1993

- State Conference Organizer, State of Washington, Associated Nursing Students, 1993-1994

- Hospital Fray Guillermoe, Guatemala, part-time volunteer, 1991

SELECTED PROFESSIONAL ACTIVITIES AND PRESENTATIONS_____

- Chairman, WHO Standing Committee on Programmatic Suitability of Vaccines for Pre-Qualification, From September 2011.

- Founding Co-Chair, Product-Development Partnership (PDP) Access Steering Committee. Led a collaboration across 11 PDPs sharing strategies by different organizations to ensure that developing countries have access to newly developed health interventions. 2009 to 2010.

- PATH Representative to Eastern and Southern Africa sub-Regional Working Group (Immunization). 2001 to 2010.

- Brooks A. Planning ahead for the first malaria vaccine: The path from development to impacting health. Presented at the Multilateral Initiative on Malaria (MIM); November, 2009.

- Brooks A. Investment case for malaria vaccines. Roundtable presentation at the Global Health Council annual conference. May 2006.

- PATH Representative to GAVI Financing Task Force. 2000 to 2004.

- Chairperson. WHO Meeting on post-introduction evaluations of hepatitis B and Hib vaccine introduction in developing countries. June 2003. WHO/HQ, Geneva.

- Lydon P. Brooks A. and Simpson J. Microsoft excel e-learning course for developing country senior managers. 2002.

- Brooks A and Masambichaka K (co-authors), Mutabaruka E. Planning immunization activities at the national, provincial, and district levels. Curriculum for WHO AFRO Mid-Level EPI Managers Training. Namibia. June, 2002.

- Brooks A. Vaccine preventable diseases: The changing landscape. Workshop presentation. American Public Health Association annual conference. Atlanta. October 2001.

- Brooks A (Session Organizer.) New directions for immunization in developing countries: The Global Alliance for Vaccines and Immunizations (GAVI) and the Vaccine Fund. American Public Health Association annual conference. Atlanta. October 2001.

- Brooks A. Protecting children of all nations and of all socioeconomic levels against vaccine-preventable diseases. Plenary presentation. US National Immunization Program Annual Conference. Washington DC. July 2000.

- Brooks A. (Workshop organizer.) Global Alliance for Vaccines and Immunizations. US National Immunization Program Annual Conference. Washington DC. July 2000.

- Founding Co-Chair. GAVI Hepatitis B and Hib Vaccine Demand Forecasting Group. 1999-2000.

PUBLICATIONS AND REPORTS_____

Smith T, Ross A, Maire N, Chitnis N, Studer A, Hardy D, Brooks A, Penny M, and Tanner M. **Ensemble modeling of the likely public health impact of the RTS,S malaria vaccine.** PLoS Medicine (in press).

Leach A, *et al*. **Design of a phase III multicenter trial to evaluate the efficacy of the RTS,S/AS01 malaria vaccine in children across diverse transmission settings in Africa.** *Malaria Journal* 2011, 10:224.

Milstien J, Cardenas V, Cheyne J, and Brooks A. **Analysis of WHO Policy Development Processes for a New Vaccine: Malaria Vaccine.** *Malaria Journal* 2010, 9:182.

Brooks AD and Wells WA (co-authors), McLean TD, Khanna R, Coghlan R, Mertenskoetter T, Privor-Dumm LA, Krattiger A and Mahoney RT. **Ensuring that Developing Countries have Access to New Healthcare Products: The Role of Product Development Partnerships**. *Innovation Strategy Today.* 2010; 3:1-5. www.biodevelopments.org/innovation/index.htm

Garnett A., Brooks A, and Biellik R. **Public-sector preferences for RTS,S/AS01 malaria vaccine formulation, presentation, and packaging.** Report from the PATH Malaria Vaccine Initiative. October, 2008.

Garnett A., Biellik R., and Brooks A. **Vaccine presentation for pneumococcal vaccines: WHO consultation for the development of a target product profile for pneumococcal vaccines.** Report to the GAVI Alliance from PATH. October, 2007.

Soeung SC, Grundy J, Maynard J, Brooks A, Boreland M, Sarak D, Jenkinson K, and Biggs BA. **Financial sustainability planning for immunization services in Cambodia.** *Health Policy Plan*. 2006 Jul;21(4):302-9.

Soeung SC, Grundy BM, Ly CK, Samnang C, Boreland M, Brooks A, Maynard J, and Biggs BA. **Improving immunization coverage through budgeted microplans and sub-national performance agreements: early experience from Cambodia.** *Asia Pac J Public Health*. 2006;18(1):29-38.

DeRoeck D, Bawazir SA, Carrasco P, Kaddar M, Brooks A, Fitzsimmons J, and Andrus J. **Regional group purchasing of vaccines: review of the Pan American Health Organization EPI revolving fund and the Gulf Cooperation Council group purchasing program.** *Int J Health Plann Manage*. 2006 Jan-Mar;21(1):23-43.

Roberts P, Brooks A. **Advanced market commitment for malaria vaccines.** Feb 2006. Report to Italian Ministry of Finance, Global Alliance for Vaccines and Immunizations, and the World Bank.

Rerks-Ngarm S, Treleaven SC, Chunsuttiwat S, Muangchana C, Jolley D, Brooks A, Dejsirilert S, Warintrawat S, Guiver M, Kunasol P, Maynard JE, Biggs BA, and Steinhoff M. **Prospective population-based incidence of *Haemophilus influenzae* type b meningitis in Thailand.** *Vaccine*. 2004 Feb 25;22(8):975-83.

DeRoeck D, Brooks A, McArthur A, and Mort M. **Comprehensive e-learning curriculum on the global vaccine market and immunization financing, for senior managers in developing countries.** Web published. 2003.

Kane MA and Brooks A. **New immunization initiatives and progress toward the global control of hepatitis B.** *Curr Opin Infect Dis*. 2002 Oct;15(5):465-9.

Brooks A, Cutts F, Walt G, Justice J. **Factors affecting the introduction of new vaccines into national immunization programs of developing countries.** Children's Vaccine Initiative Study. 1998.