Freek de Haan

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in an era of drug resistant malaria

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Understanding the formation of markets
for (triple) artemisinin-based combination therapies

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Market Formation in an Era of Drug Resistant Malaria

Understanding the formation of markets for (triple) artemisinin-based combination therapies

Markt Formatie in een Era van Medicijn Resistente Malaria

Inzicht in de formatie van markten voor (triple) artemisinin-based combination therapies

(met een samenvatting in het Nederlands)

Proefschrift

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Table of contents

List of abbreviations

ACTs – Artemisinin-based Combination Therapies
AL – Artemether + Lumefantrine
AQ – Artesunate + Amodiaquine
AMFm – Affordable Medicines Facility malaria
AMTR – Artemisinin Mono Therapy Replacement
ASMQ – Artesunate + Mefloquine
AS-PYR – Artesunate + Pyronaridine
CPM – Co-Payment Mechanism
CRO – Contract Research Organization
DDF – Department of Drugs and Food
DeTACT – Development of Triple Artemisinin-based Combination Therapies
DHA-PPQ – Dihydroartemisinin - Piperaquine
DNDi – Drugs for Neglected Diseases initiative
EMA – European Medicines Agency
FCDO – Foreign Commonwealth Development Office
FDA – Food and Drug Administration
FGD – Focus Group Discussion
GFATM – Global Fund to fight Aids, Tuberculosis and Malaria
GIS – Global Innovation Systems
GMS – Greater Mekong Subregion
LMICs – Low and Middle Income Countries
MEAF – Malaria Elimination Action Framework
MMV – Medicines for Malaria Venture
MoH – Ministries of Health
MORU – Mahidol Oxford Research Unit
MSF - Médecins Sans Frontières
NMCP – National Malaria Control Program
NMEP – National Malaria Elimination Program
NHIS – National Health insurance Scheme
NGOs – Non-Governmental Organizations
PDPs – Product Development Partnerships
PNPL – Programme National de Lutte contre le Paludisme
PPM – Public Private Mix
SC – Structural Coupling
SDGs – Sustainable Development Goals
TACTs – Triple Artemisinin-based Combination Therapies
TIS – Technological Innovation Systems
TRAC – Tracking Artemisinin Resistance Collaboration
UN – United Nations
USAID – United States Agency for International Development
VMW – Village Malaria Worker
WHO – World Health Organization
WWARN – Worldwide Antimalarial Resistance Network

Chapter 1

Introduction

1.1 Background and rationale

1.1.1 Antimalarial drug resistance

Malaria is a tropical infectious disease caused by plasmodium parasites which are transmitted through the bites of female anopheles mosquitos. There are five types of plasmodium parasites of which *Plasmodium falciparum* is the most common and by far the most deadly type. In the last decades, impressive progress has been made in reducing the global malaria burden. The estimated number of malaria deaths has declined from 897.000 in 2000 to 568.000 in 2015 (WHO 2022). Despite these achievements, progress has stalled and an estimated 619.000 people died because of malaria in 2021. This is unacceptably high when considering that malaria is easily treatable when effective therapies are administered in time. Malaria endemic countries rely on artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated *Plasmodium falciparum* malaria – referred to as 'malaria' in this thesis (WHO, 2021a). ACTs combine a highly potent, rapidly cleared artemisinin derivative and a less potent, slowly cleared partner drug.

Unfortunately, malaria parasites in the Greater Mekong Subregion (GMS) of Southeast Asia have developed multidrug resistance to these artemisinin and partner drug combinations. Artemisinin resistance was first detected in Cambodia in 2008 and from there spread to its neighbouring countries in subsequent years (Ashley et al., 2014; Dondorp et al., 2009; Imwong et al., 2021). Along the way, the artemisinin-resistant parasite lineages acquired resistance to ACT partner drugs including piperaquine and mefloquine. As a result, the therapeutic efficacy of ACTs is declining and malaria has become difficult to treat in the GMS. An even more important threat is the risk of artemisinin and partner drug resistance spreading westwards to Africa where the majority of the malaria burden is situated (Balikagala et al., 2021; Plowe, 2009). History has shown the disastrous consequences of antimalarial drug resistance originating in Asia reaching the African continent (Mulligan et al., 2006; Trape, 2001) with millions of excess malaria attributable deaths as a result of drug resistance in the 1970s and the 1980s. Although it was feared that a similar situation could repeat with the spread of artemisinin resistance, another scenario has unfolded: artemisinin resistance has emerged independently in African countries. Alarming reports of artemisinin resistant parasite lineages in Rwanda, Uganda and Tanzania have been published (Asua et al., 2021; Balikagala et al., 2021; Bergmann et al., 2021; Bwire et al., 2020; Kayiba et al., 2021; Uwimana et al., 2021, 2020) while inadequate efficacy of artemether-lumefantrine, the most commonly used antimalarial in Africa, was recently reported in Angola and Burkina Faso (Dimbu et al., 2021; Gansané et al., 2021; Rasmussen and Ringwald, 2021).

A transition to new treatment regimens is urgently required to ensure that malaria remains treatable in Southeast Asia and to mitigate the risks of resistance evolving at the African continent. New classes of drugs are not expected in the coming years (Ashley, 2018) and so solutions are needed that make use of existing drug compounds. One promising solution

is to complement current ACTs with a third compound, creating triple artemisinin-based combination therapies (TACTs) (van der Pluijm et al., 2021). The rationale is that combining the artemisinin derivative with two partner drugs with different modes of action will extend the therapeutic lifetime of each compound because they will provide mutual protection against resistance. Early efficacy studies have shown promising results (Peto et al., 2022; van der Pluijm et al., 2020) and a multi-partner collaboration named the Development of Triple Artemisinin-based Combination Therapies (DeTACT) project is underway to develop two TACT combinations (artemether-lumefantrine + amodiaquine, and artesunate-mefloquine + piperaquine) and is testing them in multiple African and Asian settings. Once these TACTs are confirmed to be safe, tolerable, efficacious and non-inferior to ACTs, they could provide direct clinical relief in Southeast Asia in case all current ACTs would fail. Moreover, a rapid and sustainable transition to TACTs in Africa could delay the emergence and further spread of artemisinin and partner drug resistance on the African continent.

1.1.2 Antimalarial drug transitions

Although initial results from clinical trials have been encouraging (Peto et al., 2022), the trajectory for TACTs towards market introduction is uncertain (Bassat et al., 2022; Krishna, 2019; White, 2019). Previous antimalarial drug transitions, i.e. the change from one dominant treatment regime to another, have been characterized as slow and challenging, even when new therapies were clinically superior to failing alternatives (Bosman and Mendis, 2007; Mulligan et al., 2006; Williams et al., 2004). Pharmaceutical companies, the traditional engines behind drug development, have ignored malaria and other diseases of the poor for a long time, which has resulted in limited output of new drug compounds (Anthony et al., 2012; Wells et al., 2015). Simultaneously, malaria endemic countries have been associated with underperforming healthcare systems, resource constraints and deficient supply chains that have obstructed the delivery of new therapies to patients in need (Mills, 2014; O'Connell, 2011; Yadav, 2009).

The most important antimalarial drug transition in recent history has been the global shift from conventional monotherapies to ACTs. At the end of the previous century, malaria parasites had developed resistance to all then-conventional monotherapies, including to widely-used chloroquine and sulfadoxine-pyrimethamine. It was clear that the future had to rely on artemisinin derivatives, the final class of drugs without compromised efficacy (Arrow et al., 2004). Because of their pharmacokinetic properties, these artemisinin derivatives (artesunate, artemether, dihydroartemisinin) were sought to be deployed exclusively in combination with a slower working partner drug (lumefantrine, amodiaquine, mefloquine, piperaquine) (Li et al., 1984; White, 1999; WHO, 2001). However, despite rapid increases in global malaria mortality, the replacement of conventional monotherapies with ACTs was a slow process. For years, falciparum malaria remained being treated with ineffective therapies that had previously fallen to drug resistance, while the circulation of substandard and counterfeit medicines also posed important problems (Bosman and Mendis, 2007; Dondorp et al., 2004; O'Connell, 2011).

Moreover, the prescription of artemisinin as a monotherapy remained a common practice, despite the high risk of infection recrudescence and accelerated artemisinin resistance.

Now it is time to learn lessons from the problematic introduction of ACTs as a global first-line therapy for the treatment of malaria. The current situation of artemisinin and partner drug resistance in Southeast Asia and the emergence of artemisinin resistance markers in Africa do not permit another slow drug transition. This would inevitably put further pressure on ACT efficacy and increase the risk of resistance spreading to other regions and continents. The latter scenario could reverse all gains that have been made against malaria (Menard and Dondorp, 2017). Therefore, it is essential to understand the dynamics of antimalarial drug transitions in order to facilitate the introduction of next-generation therapies. This thesis focuses on this important topic. Conceptual insights and methodological approaches from innovation sciences and transition studies are applied to investigate how antimalarial drug transitions unfold. The thesis particularly focuses on the formation of markets for innovative antimalarial therapies under the pressure of drug resistance.

1.2 Conceptual approach

1.2.1 The systemic nature of pharmaceutical innovation

Pharmaceutical innovation is inherently a time - and resource - intensive process with many uncertainties along the road. Traditionally, the development and introduction of new therapies has been described as a linear model and driven by technology-push and demand-pull processes (Fig. 1.1). However, the shortcomings of this narrow perspective have increasingly been recognized and attention has shifted to more open and interactive models (Moors et al., 2014; Schuhmacher et al., 2013). These days, a *systemic* perspective is considered the most appropriate to understand pharmaceutical innovation dynamics (Fig. 1.2) (Consoli and Mina, 2009; Moors et al., 2018). The main assumption is that pharmaceutical innovation does not take place in isolation but instead is regarded as a co-evolutionary process in interaction with a surrounding socio-technical system. Similar systemic perspectives have been applied in global health research and they have been valued for their integrated view and their explanatory power (Adam and De Savigny, 2012; Peters, 2014; Ramani-Chander et al., 2022).

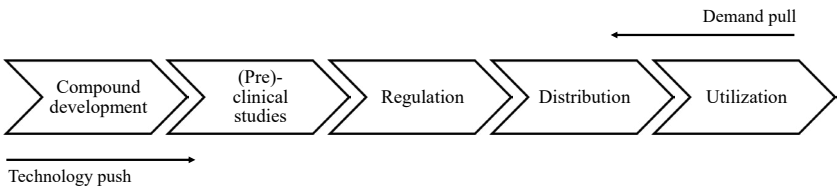

FIGURE 1.1 | Visualization of a linear model of pharmaceutical innovation.

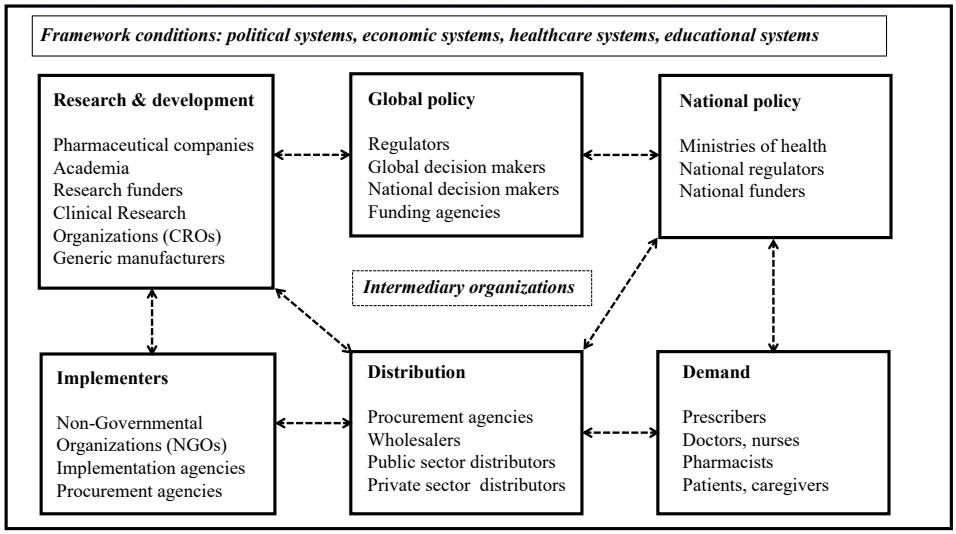

FIGURE 1.2 | Visualization of a systemic model of pharmaceutical innovation (based on Kuhlman and Arnold 2001)

A systemic perspective of pharmaceutical innovation is particularly useful for analyzing antimalarial drug transitions for three reasons. First, changing first-line malaria treatment practices involves many actor networks and institutional frameworks (Arrow et al., 2004; Williams et al., 2004). Introducing new therapies in this complex environment requires collective and coordinated actions to meet the essential activities of drug development, regulation, distribution and utilization. Systemic models of innovation are well-suited for analyzing these multifaceted innovation practices by providing an integrated, holistic perspective from compound development to societal embedding.

Second, although low-and middle-income countries (LMICs) bear the majority of the malaria burden, they generally lack resources and capabilities to develop new therapies. Instead, these countries rely on external actor groups for discovering new therapies and bringing them to the market. Linear models have insufficient explanatory power for this type of open innovation processes across various geographical areas (Schuhmacher et al., 2013). The systemic model provides a useful heuristic that enables assessing open innovation by including the full range of activities by external stakeholders.

Third, sustainability challenges are considered as wicked problems that require a systemic approach (Freeman, 1996). Unsustainable consuming patterns cannot be adjusted without the development, distribution and utilization of more sustainable alternatives. Sustainability refers to the responsible use of scarce resources to ensure that future generations can continue to benefit from them. Artemisinin is such a scarce resource. There is no antimalarial drug compound available with comparable efficacy, and losing artemisinin to resistance would jeopardize global malaria control and elimination efforts (Dhorda et al., 2021). However, at the time of writing this thesis, ACTs are still effective in most endemic settings and it is not evident

that new therapies (such as TACTs) will find their way to the market. Engaging in new therapies requires direct investments by individuals and national governments, while the potential benefits often are long-term and exceed national borders. This raises important ethical and practical questions which are further explored in Chapters 2 and 4 of this thesis.

1.2.2 Technological transitions and innovation systems

In order to better understand antimalarial drug transitions, it is important to have a framework that enables investigating the systemic nature of pharmaceutical innovation. Such a framework is provided by the academic discipline of transition studies. It is acknowledged that grand societal challenges such as global warming and antimicrobial resistance call for socio-technical transitions (Coburn et al., 2021; OECD, 2023). Understanding how these transitions unfold is complex because of the many actor networks and institutions that are involved (Edquist, 1997; Wieczorek and Hekkert, 2012). Transition studies investigates the pace and direction of technological change processes for addressing societal challenges (Loorbach et al., 2017).

One of the dominant theoretical perspectives within transition studies is the innovation systems approach which departs from the premise that innovation is a collective, non-linear process. The innovation systems approach claims that the mere development of a new technology is not sufficient to become embedded in society. Instead, modifications are also required in the societal domain. The entire societal domain is represented as a complex socio-technical system: the innovation system. The structure of the innovation system is comprised of all the actors, networks and institutions that contribute to the generation, diffusion and utilization of the innovation (Carlsson and Stankiewicz, 1991). A supportive innovation system is required for emerging technology to become embedded in society. Simultaneously, when the technology is poorly aligned with the surrounding innovation system, its development and diffusion are hampered. The innovation systems approach has increasingly become a well-established analytical tool for analyzing innovation challenges and to propose policy implications accordingly (e.g. Kukk et al., 2016; Tziva et al., 2020; van Welie et al., 2019).

Innovation system boundaries are typically set by a geographical, sectoral or technological scope. This thesis focuses on innovative antimalarial therapies and therefore we delineate the system as a *technological innovation system* (TIS). The TIS demarcation enables the assessment of system dynamics by evaluating various key processes: the technological innovation system functions (Bergek et al., 2008; Hekkert et al., 2007). Hekkert and colleagues (2007) proposed the following seven key technological innovation system functions: entrepreneurial activities, knowledge development, knowledge diffusion, search guidance, market formation, resource mobilization, and legitimacy creation (Table 1.1). In joint interaction, these seven system functions contribute to a favourable innovation ecosystem and they allow to create insight into problems that hinder the generation and the diffusion of a new technology (Hekkert et al., 2007).

TABLE 1.1 | Description of the technological innovation system functions for antimalarial therapies.

Entrepreneurial activities:	Activities to discover antimalarial therapies and to translate them into actual end-products (either through commercial or non-profit programs)
Knowledge development:	Activities to obtain data and information on the antimalarial therapy. This includes studies on the efficacy, safety and tolerability as well as studies to optimize production, dosing and prescription behavior
Knowledge diffusion:	Activities to disseminate the obtained data about the antimalarial therapy through e.g. conferences, seminars, publications and reports
Guidance of the search:	Activities that contribute to the visibility of the antimalarial therapy and activities that provide guidance for the further innovation processes
Market formation:	Activities that directly contribute to the availability and accessibility of the antimalarial therapy to its potential end-users
Resource mobilization:	Activities to obtain the required financial and human resources to facilitate the development, production and uptake of the antimalarial therapy
Creation of legitimacy:	Activities that contribute to the perceived legitimacy of the antimalarial therapy by other actors in the innovation system

In the medical domain the demand-side of the innovation system consists of a wide range of interdependent activities that are important for the emergence of novel technologies. These activities include regulatory acceptance, renumeration schemes, and creating medical guidelines (Moors et al., 2018; van Welie et al., 2019). Therefore, demand-side system functions, or valuation-focused activities, such as market formation are considered important (Yap et al., 2022). The market formation function conceptualizes all activities that directly contribute to the availability, accessibility and acceptability of the technology to its potential end-users. However, it is inherent to the technological innovation system approach to consider market formation in interplay with the entire innovation system rather than as an isolated process.

1.2.3 Market formation in technological innovation systems

Markets are essential constructs in innovation systems and they have obtained increasing interest by transition scholars (Boon et al., 2020; Dewald and Truffer, 2011; Ottosson et al., 2020; van der Loos et al., 2020). Originally, the perception of the development and evolution of markets was subject to shifting perspectives. In neoclassical economics, markets were considered as the physical or virtual places where suppliers and buyers exchange products. Later, scholars perceived markets as socially constructed arenas that exist by the virtue of human action and interaction (Fligstein and Dauter, 2007). The *systemic* interpretation of market formation processes (Hekkert et al., 2007; Vargo et al., 2017) is rooted in innovation systems literature and considers markets as the product of interactions between technological, institutional, political and user-related elements (Boon et al., 2022; Dewald and Truffer, 2011; Moors et al., 2018; Ottosson et al., 2020).

Beyond transition studies, markets and their formation have gained prominence in global health research. It is increasingly acknowledged that demand-side interventions targeting prescribers and patients, such as procurement subsidies and enhanced market regulation, are

needed to facilitate the uptake of new interventions in resource-restricted settings (Berman et al., 2022; Bloom et al., 2011) with some scholars explicitly focusing on the creation of markets for new therapies (Malhame et al., 2019; Orsi et al., 2018). The importance of markets (WHO, 2015a) and how they are shaped (GlobalFund, 2015; USAID, 2014) has become an important topic in strategic malaria policy debates, but is still considered a black box (Bloom et al., 2011; Boon et al., 2022; Mills, 2014).

This thesis investigates how markets for innovative antimalarial therapies come into existence in an era of drug resistance. We regard markets as composed of the structural elements – actors, networks, institutions – that are directly involved in making the innovative therapy available and accessible to end-users (Boon et al., 2022; Dewald and Truffer, 2011; Hekkert et al., 2007). Taking a systemic perspective enables studying market formation as interacting with and embracing *all* system components rather than only the very end of the supply chain. This thesis, therefore, perceives pharmaceutical innovation activities of drug development, regulation, distribution and utilization as interdependent and mutually contributing to the creation of markets for new therapies.

One key implication of our conceptual approach is that market formation activities for antimalarial therapies are geographically dispersed at multiple scales and locations. At the global-level, therapies need to be manufactured and subjected to review by regulators, funders and technical agencies. At the country-level, market authorization and guideline inclusion is required before the new therapy can be deployed locally. To grasp this multi-scalar nature, this thesis makes use of the global innovation systems framework (Binz and Truffer, 2017; Heiberg and Truffer, 2022), which enables perceiving multi-located systems as being made effective through the attainment of structural couplings. The global innovation systems framework also allows for studying market formation in interaction with other valuation-focused processes, such as the creation of legitimacy. Chapter 3 of this thesis demonstrates that these structural couplings emerge in various forms and that these couplings are essential to the formation of markets for antimalarial therapies under pressure of drug resistance.

A second key implication of the systemic conceptualization is that multiple stakeholder groups contribute to the creation of markets for new antimalarial therapies. Engaging these stakeholders in early stages of the innovation trajectory and capturing their expertise is essential for maximizing societal impact. In particular the role of users in pharmaceutical innovation processes has previously been advocated by innovation scholars (Hoos et al., 2015; Smits and Boon, 2008; von Hippel et al., 2017). Beyond users, there are several other actor groups involved in the generation and diffusion of antimalarial therapies. These stakeholders have often been ignored in the innovation process, even though their unique position in the system does equip them with essential expertise (Meijer et al., 2013). Policy makers and regulators are, for example, best positioned to reflect on policy procedures and the regulatory trajectory. Suppliers and prescribers are most knowledgeable about distribution, retail and prescription issues while patients have the most relevant insights into local user preferences. Chapters 5, 6

and 7 capture the expertise, visions and perceptions of these various key stakeholder groups in the innovation trajectory of new antimalarial therapies such as TACTs.

1.3 Malaria: a poverty-related infectious disease

1.3.1 Malaria trends, policies and strategies

Malaria is an acute febrile illness that is caused by *Plasmodium* parasites which are transmitted by female anopheles mosquitoes. Of the five types of plasmodium parasites that cause disease in humans, *Plasmodium falciparum* is responsible for over 95% of malaria attributable deaths. Malaria is an important global health challenge with over 3 billion people in 85 countries at risk (WHO, 2022). In 2021, more than 200 million people were infected with malaria and the disease was responsible for over half a million deaths. The malaria burden is not equally distributed over the world. As a poverty-related infectious disease, malaria mainly affects people in low-, and middle-income countries. Over 90% of infections occur in Sub-Saharan Africa, where young children account for the vast majority of malaria attributable deaths because they have not yet acquired any form of immunity (WHO, 2022). In lower transmission settings, including most of Southeast Asia, malaria mainly affects forest workers and migrant populations in border areas (Cui et al., 2012).

When bitten by an infectious mosquito, symptoms usually appear after a 2 week (range 7-40 days) incubation period. Symptoms of *uncomplicated* malaria include fever, headache, vomiting and chills. Left untreated, malaria can progress to *severe* illness in non-immune patients, which includes organ failure and coma, which has a high case fatality. Since 2006, the World Health Organization (WHO) recommends a 3-day oral course of artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated falciparum malaria. Severe malaria requires parenteral administration of artesunate.

The battle against malaria is mentioned explicitly in the 2015 Sustainable Development Goals (SDGs). The mutual relation between sustainability and healthcare is the central focus of SDG3, which aims to ensure healthy lives and promote well-being for all, at all ages (UN, 2015). SDG target 3.3 aims to end the epidemics of AIDS, tuberculosis, malaria, and neglected tropical diseases by 2030. In order to reach this ambitious goal, the WHO has formulated a global technical malaria strategy for the period from 2016-2030 with sub-targets and indicators set at regular intervals (Table 1).

The global technical malaria strategy relies on three strategic pillars: the first pillar is to facilitate universal access to malaria prevention, diagnosis and treatment in order to respond to each infection worldwide. The second pillar is to accelerate efforts towards malaria elimination and the attainment of a country's malaria-free status, and the third pillar is to transform surveillance into a core intervention in order to better target other interventions (therapies, diagnostics, preventive measures) (WHO, 2015a). An important sidenote when considering the global

technical malaria strategy is that its targets are highly ambitious and that the tropical world is not on track to achieving them (WHO, 2022). Chapter 2 further explores the interaction between malaria and the SDGs by developing an integrated framework towards a sustainable system of antimalarial drug development and diffusion.

TABLE 1.2 | Global technical malaria strategy 2016-2030 (WHO, 2015a).

Goals	Milestones		Targets
	2020	2025	2030
Reduce malaria mortality rates globally compared with 2015	≥ 40%	≥ 75%	≥ 90%
Reduce malaria case incidence globally compared with 2015	≥ 40%	≥ 75%	≥ 90%
Eliminate malaria from countries in which malaria was transmitted in 2015	≥ 10 countries	≥ 20 countries	≥ 35 countries
Prevent re-establishment of malaria in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

1.3.2 The dynamics of drug resistance

The capacity of malaria parasites to acquire drug resistance is a consequence of genetic mutations followed by natural selection (Klein, 2013). When medication is administered in an inadequate dose, some malaria parasites may develop gene mutations which allows them to survive the treatment regime. Such mutations occur frequently and those conferring drug resistance will provide the parasite with evolutionary advantage over drug susceptible parasites (as long as it is not outbalanced by a loss of fitness of this same parasite). Historically, antimalarial drug resistance usually starts in low malaria transmission settings. In particular Southeast Asia has been a cradle for the emergence and subsequent spread of *Plasmodium falciparum* parasites resistant to chloroquine, pyrimethamine and other antimalarials (Cui et al., 2012). These drug resistant parasite lineages have shown a pattern of spreading to India and Africa where the vast majority of the malaria burden is situated. This makes the current situation of resistance to artemisinin and partner drugs in Southeast Asia all the more alarming (Dondorp et al., 2017; Packard, 2014).

In low transmission settings, containment of resistance in the context of continued use of artemisinin-based combination therapies requires elimination of all falciparum malaria in areas of resistance. Five countries in the Greater Mekong Subregion (GMS) of Southeast Asia (Cambodia, Lao PDR, Myanmar, Thailand and Vietnam) have now jointly committed to eliminate falciparum malaria by 2025 and other malaria types by 2030 (WHO, 2015b). In their ambitions to achieve a malaria-free region, these countries are encouraged by the currently low malaria burden and increasing awareness of the threat of drug resistance. Reaching malaria elimination will, however, require a combination of intervention and strong policy coordination (Kaehler et al., 2019; Pell et al., 2017; Peto et al., 2018). In the short term, the discovery, development and diffusion of new and effective treatment regimens is required to ensure that malaria remains

treatable in the region and to prevent resistance from spreading further.

1.3.3 The development of triple artemisinin-based combination therapies (DeTACT) project

Following the clinical detection of artemisinin resistance in Cambodia in 2008, and the subsequent discovery of the molecular marker of artemisinin resistance, efforts to monitor the spread of resistance were prompted. For this purpose, the Tracking Artemisinin Resistance Collaboration (TRAC I & II) studies, were initiated by the Mahidol Oxford tropical medicine Research Unit (MORU) in Bangkok and funded by the UK Foreign Commonwealth Development Office (FCDO) and the Wellcome Trust of Great Britain. The TRAC I study confirmed artemisinin resistance throughout the Greater Mekong Subregion (GMS) in Southeast Asia (Ashley et al., 2014), and the follow-up TRAC II study gathered further information on the spread and genetic profiles of artemisinin and partner drug resistant parasite lineages. The TRAC II study was also the first clinical trial to test the safety, tolerability and efficacy of triple artemisinin-based combination therapies (TACTs) (van der Pluijm et al., 2020).

The TRAC II study obtained encouraging results with deploying TACTs and a follow-up project started in 2019: the Development of Triple Artemisinin-based Combination Therapies (DeTACT) project. The main goal of the DeTACT project was to translate the concept of triple therapies into practice by developing two TACTs (artemether-lumefantrine + amodiaquine, and artesunate-mefloquine + piperaquine) that are ready for market introduction and by collecting robust evidence to evaluate their potential future benefit. The development of two fixed-dose TACTs were initiated in collaboration with industrial partners. Placebo-controlled randomized trials were organized in several African and Asian countries to test the efficacy, safety and tolerability of these TACTs compared to corresponding ACTs (ClinicalTrials.gov identifiers: NCT03923725 and NCT03939104). Mathematical modelling studies were initiated to determine their longer term effect on antimalarial drug resistance and their potential health-economic impact compared to the status-quo of ACTs. Finally, bioethical and market formation studies were initiated to investigate the broader societal implications of introducing TACTs in different epidemiological settings. The DeTACT project ultimately aims to have two TACTs therapies available that are ready for deployment in order to reduce the global burden of drug-resistant malaria (Fig. 1.3).

Once TACTs are proven to be safe, tolerable and efficacious, functioning end-user markets are required to effectively deliver them to patients in need. However, as described earlier, the trajectory towards market formation for TACTs is uncertain. Sections 1.1.1 and 1.1.2 explained that antimalarial drug transitions are characterized by innovation system failures, such as the lack of collaboration between public and private organizations to engage in diseases of the poor. To address these systemic failures, adequate innovation policies are required to ensure that innovation systems emerge and that markets are created for new therapies. Sections 1.2.1 – 1.2.3 of this thesis developed a systemic conceptual framework for investigating market formation for new antimalarial therapies. In Chapters 2 – 7, the conceptual framework will be

put into practice to investigate the formation of markets for new antimalarial therapies and to identify and evaluate market formation policies accordingly. This thesis is written in the context of - and supported by - the DeTACT project and investigates how markets for innovative antimalarial therapies are formed under the pressure of drug resistance.

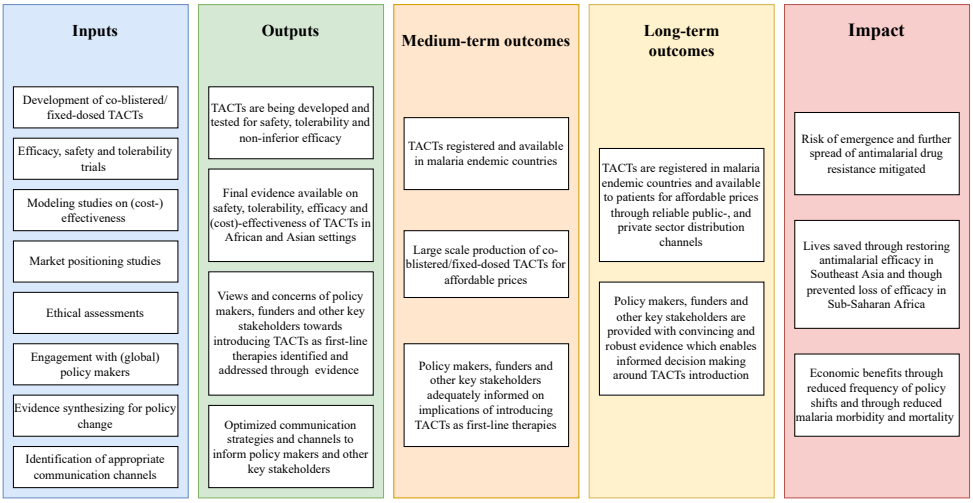

FIGURE 1.3 | Theory-of-change of the Development of Triple Artemisinin-based Combination Therapies (DeTACT) project.

1.4 Research questions and thesis outline

This introduction chapter presented the imminent global health threat of artemisinin and partner drug resistance for the treatment of malaria. It elaborated on challenges related to antimalarial drug transitions and emphasized the importance of creating markets for new therapies. A conceptual approach for investigating market formation was developed and embedded in innovation systems theory and transition studies. Given the challenging nature of previous antimalarial drug transitions and the need for forming markets for future therapies, this thesis addresses the following central research question: How are markets for antimalarial therapies being formed under the pressure of drug resistance?

1.4.1 Societal contributions

Answering the research question contributes to the ongoing battle against drug-resistant malaria. It is essential to understand how markets for innovative antimalarial therapies are being formed to address systemic failures and to design adequate innovation policies. Previous antimalarial drug transitions have been described as slow and challenging (Attaran et al., 2004; Bosman and Mendis, 2007). These transitions provide historical lessons to inform strategic decision making and resource allocation towards the introduction of future therapies

(Arrow et al., 2004; Williams et al., 2004). This is especially important in the current situation of artemisinin and partner drug resistance. The growing numbers of treatment failures with ACTs in Southeast Asia and the recent independent emergence of artemisinin resistance in African countries urgently call for new therapies and associated end-user markets (van der Pluijm et al., 2021; White, 2019). To address the worrying developments of artemisinin and partner drug resistance, this thesis draws on lessons from the previous transition from conventional monotherapies to ACTs (Part 1, Chapters 2 and 3), and examines the prospects of market formation for TACTs in African settings where current ACT therapies are still effective (Part 2, Chapters 4 and 5) and Southeast Asian settings where current ACT therapies are increasingly failing (Part 3, Chapters 6 and 7). Each Chapter describes policy recommendations derived from the research conducted. Beyond malaria, the findings of this thesis could be useful for other poverty-related infectious diseases, such as tuberculosis and HIV. These diseases confront populations and governments with similar challenges as malaria (Sheikh and Uplekar, 2016; Sunyoto et al., 2019). Drug resistance remains a major challenge for these diseases and has repeatedly demanded the introduction of new therapies. Enhanced understanding of global health transitions and market formation dynamics can benefit the continued introduction of effective therapies.

1.4.2 Scientific contributions

Scientifically, answering the research question contributes to the literature on innovative antimalarials in an era of drug resistance (Arrow et al., 2004; Hooft van Huijsduijnen and Wells, 2018; Novotny et al., 2016). By taking an innovation systems perspective, the trajectory of new antimalarial therapies is being followed from research and development to utilization by the patient. The innovation systems approach embraces both supply-, and demand-side dynamics and interactions between all relevant actors, networks and institutions (Orsi et al., 2018; Wells and Brooks, 2011). First of all, this thesis specifically contributes to the evidence-base in the field of malaria studies on strategies to address artemisinin and partner drug resistance (Peto et al., 2022; van der Pluijm et al., 2020; White, 2019) by examining the prospects of market formation for TACTs.

Second, the thesis contributes to transition studies by focusing on the underexplored field of global health transitions. Although previous transition scholars have focused on healthcare (Consoli and Mina, 2009; Kukk et al., 2015) and sanitation and hygiene in developing world settings (van Welie et al., 2019), global health transitions have received limited scientific attention. At the same time, societal challenges such as antimicrobial resistance and the COVID-19 pandemic demand enhanced understanding of science, technology and innovation dynamics in times of global health emergencies (Coburn et al., 2021). Especially the demand-side processes in global health innovation systems, such as those related to market formation, are different from those related to other sectors that have been investigated in transition studies. These demand-side processes, or what has been called valuation-focused processes (Yap et al., 2022), require further studying and nuanced operationalization. By exploring market

formation for innovative antimalarial therapies in an era of drug resistance, this thesis provides a starting point for research on the intersection of technological transitions and global health.

Third and related, the thesis contributes to the literature on markets and their formation in technological transitions. We advance the conceptualization of the emergence and evolution of markets (Boon et al., 2022; Dewald and Truffer, 2012; Moors et al., 2018) by investigating how markets for new antimalarial therapies come into existence under the pressure of drug resistance (Orsi et al., 2018). This thesis goes beyond markets as pre-existing spaces in which demand and supply for products and services meet. Instead markets are being perceived as dynamic entities and subject to interactions of stakeholders, networks and institutions, thereby aligning with the current literature on markets in transitions (Boon et al., 2022). This thesis adds a multi-scalar component to established innovation system delineations by demonstrating how markets for antimalarial therapies are formed at different geographical scales and locations (Binz and Truffer, 2017; Coenen et al., 2012; Heiberg and Truffer, 2022), thereby contributing to the relative new global innovation systems literature. This multi-scalar component is especially relevant for antimalarial drug transitions where upstream activities of research, development, policy making and regulation are geographically dispersed from downstream activities of distribution, prescription and deployment.

1.4.3 Thesis outline

The thesis is structured in three parts. **Part 1** maps the innovation system of antimalarial therapies and identifies systemic failures that jeopardize the formation of markets for new therapies. This is done by investigating in retrospect the antimalarial drug transition from conventional monotherapies to ACTs, which is done in Chapters 2 and 3. **Part 2** investigates the prospects of market formation for TACTs in African countries, where current ACTs are still effective at the time of writing this thesis. Introducing TACTs would therefore not directly benefit individual patients but instead they would mitigate the risks of future antimalarial drug resistance. Considering the introduction of TACTs in this context raises important ethical and practical questions which are discussed in Chapters 4 and 5. **Part 3** investigates the market formation prospects of TACTs in Southeast Asia, where current ACTs are increasingly failing and where TACTs can provide direct clinical relief and can protect drug compounds. However, despite the promising results in early clinical studies, the desirability and the practical feasibility of introducing TACTs compared to alternative strategies for addressing drug resistance is subject to debate. This warrants further exploration of the market formation prospects for TACTs in Southeast Asia, which is presented in Chapters 6 and 7.

Part 1: The transition from conventional monotherapies to ACTs

Chapter 2 takes a systemic perspective and examines which system reforms are required for antimalarial drug development and diffusion to become sustainable, in line with the Sustainable Development Goals (SDGs). The chapter is written based on desk research and

complemented with nine expert consultations. The flaws in the current system of antimalarial drug development and diffusion are identified and a framework towards a more sustainable system is proposed. The proposed framework comprises four interrelated components: availability, affordability, accessibility and acceptability. The framework is applied to reflect on the transition from conventional monotherapies to Artemisinin-based Combination Therapies (ACTs) and to propose system reforms towards a more sustainable system of antimalarial drug development and diffusion, which can help achieving sustainable healthcare (SDG3).

Chapter 3 investigates market formation in the antimalarial drug transition from conventional monotherapies to ACTs. An event history analysis is created based on a comprehensive literature review and complemented with in-depth interviews. The chapter investigates how ACT markets were created at multiple geographical scales and locations when all conventional monotherapies were failing. The chapter reveals the role of public institutes, academia and partnerships in early innovation system development. It demonstrates how transnational organizations created a supportive global landscape for ACT deployment and how these advancements led to the formation of public-sector and private-sector end-user markets for ACTs. Finally, chapter 3 reveals how structural couplings emerged in several forms, including funding mechanisms, product-development partnerships, and regulatory arrangements, and how these structural couplings enabled the formation of ACTs markets at multiple geographical scales and locations.

Part 2: The introduction of TACTs in Africa

Chapter 4 discusses the major ethical and practical issues that ought to be considered for introducing Triple Artemisinin-based Combination Therapies (TACTs) in Africa. The vast majority of the malaria burden is situated in African countries and the looming threat of artemisinin resistance is particularly worrisome there. Nevertheless, at the time of writing this thesis, ACTs were still effective in most African countries and introducing TACTs would benefit future patients and the broader community rather than present individual malaria patients. The chapter discusses the most important ethical tensions, implementation practicalities and provides preliminary insights on addressing them. It draws upon data from clinical trials with TACTs combined with ethical principles and published literature regarding the introduction of antimalarial therapies in African markets.

Chapter 5 investigates the extent to which the markets in African countries are ready for a transition to TACTs. The chapter takes an innovation systems perspective and collects data in two African countries: Nigeria and Burkina Faso. Qualitative research methods are employed involving in-depth interviews and focus group discussions (FGDs) with key stakeholders in the antimalarial innovation system in Nigeria and Burkina Faso. The chapter demonstrates that the market formation prospects of TACTs in both countries will depend on scientific evidence of the added value of TACTs over ACTs. Slow regulatory and implementation procedures are identified as potential barriers towards rapid TACTs deployment. Furthermore, Chapter 5 shows

that alignment with established distribution and deployment practices will be essential for the market formation of TACTs in African countries.

Part 3: The introduction of TACTs in Southeast Asia

Chapter 6 examines the prospects of introducing TACTs in Southeast Asian countries compared to alternative strategies to address ACT failure. Although the first clinical trials with TACTs are promising, there is little consensus on their timing, desirability and practical feasibility. Therefore, we conduct a two-round expert Delphi study to identify the major advantages, disadvantages and implementation challenges of introducing TACTs compared to current practices of rotating ACTs when treatment failures are observed. In the first round, prominent malaria experts identify the major advantages, disadvantages and implementation challenges for introducing TACTs in Southeast Asia. In the second round, the expert panel rate the relevance of each statement on a 5-point Likert scale. They reach consensus on 13 advantages (8 perceived as relevant, 5 as not-relevant), 12 disadvantages (10 relevant, 2 not-relevant), and 13 implementation barriers (all relevant). The chapter provides a structured oversight of malaria experts' perceptions on the major advantages, disadvantages and implementation challenges for introducing TACTs in Southeast Asia.

Chapter 7 presents a qualitative follow-up on the Delphi study (Chapter 6). It explores strategies for deploying TACTs in the Greater Mekong Subregion (GMS) of Southeast Asia. In-depth interviews are conducted in three countries in the GMS that have been confronted repeatedly with artemisinin and partner drug-resistance: Cambodia, Vietnam, and Lao PDR. Furthermore, a participatory workshop is conducted in Cambodia in which potential epidemiological and market scenarios are co-created. The study reveals that countries in the GMS currently rely on ACTs for reaching their malaria elimination ambitions. However, interview respondents consider TACTs as a useful backup strategy in case treatment failures would occur with currently used ACTs. Engaging key stakeholders in TACTs is considered a major challenge by respondents given the low malaria incidence in the GMS. Several regulatory and programmatic strategies for the deployment of TACTs in Cambodia, Vietnam and Lao PDR are being identified and discussed in this chapter.

In **Chapter 8** the main findings of the thesis are presented and summarized. We take stock of the findings by proposing an encompassing framework towards market formation in global health. Moreover, a conceptual reflection is given and general limitations of the thesis are discussed along with suggested avenues for further research. Finally, five policy recommendations are derived from the conducted research.

1.4.4 Authors contribution

This thesis is based on six peer-reviewed articles which are all authored by Freek de Haan. Chapter 2 corresponds with an Oxford University press book chapter with Freek de Haan as the first author. Chapters 3, 5, 6 correspond with peer-reviewed journal articles (in Environmental Innovation and Societal Transitions, PLOS ONE, BMC Public Health) which are all first-authored by Freek de Haan. Chapter 4 corresponds with a peer-reviewed journal article (Malaria Journal) in which Freek de Haan is the second-author, but to which he and the first author contributed equally. Chapter 7 is currently being prepared for submission to a peer-reviewed journal. Freek de Haan has been the primary researcher of all the work in this thesis. He has been responsible for study design, theory development, methodology, setup of fieldwork, data collection, analysis and reporting the findings of each chapter. The status of published work in this thesis is listed in Table 1.2.

TABLE 1.2 | Publications in this thesis.

Chapter	Status	Journal	Publication
Chapter 2	Published	Oxford University Press	de Haan, F., Moors, E.H.M. Anti-Malarial Drug Development and Diffusion in an Era of Multidrug Resistance. Book title: Science, Technology, and Innovation for Sustainable Development Goals: Insights from Agriculture, Health, Environment, and Energy. Chapter 13. Oxford University Press (2020) DOI:10.1093/oso/9780190949501.003.0013
Chapter 3	Published	Environmental Innovation & Societal Transitions	de Haan, F., Moors, E.H.M., Dondorp A.M., Boon, W.P.C. Market Formation in a Global Health Transition. Environmental Innovation and Societal Transitions. 40, 40-59 (2021). https://doi.org/10.1016/j.eist.2021.05.003
Chapter 4	Published	Malaria Journal	Tindana, P., de Haan, F., Amaratunga, C. et al. Deploying triple artemisinin-based combination therapy (TACT) for malaria treatment in Africa: ethical and practical considerations. Malaria Journal 20, 119 (2021). https://doi.org/10.1186/s12936-021-03649-7
Chapter 5	Published	PLOS ONE	de Haan, F., Bolarinwa, O.A., Guissou, R., et al. To what extent are the markets in African countries ready for a transition to Triple Artemisinin-based Combination Therapies? PLOS ONE 16(8) (2021) https://doi.org/10.1371/journal.pone.0256567
Chapter 6	Published	BMC Public Health	de Haan, F., Boon, W.P.C., Amaratunga, C., Dondorp A.M. Expert perspectives on the introduction of Triple Artemisinin-based Combination Therapies (TACTs) in Southeast Asia: a Delphi study. BMC Public Health 22, 864 (2022). https://doi.org/10.1186/s12889-022-13212-x
Chapter 7	Prepared for submission		de Haan, F., Amaratunga, C., Cao, V., et al. Strategies for deploying Triple Artemisinin-based Combination Therapies (TACTs) in the Greater Mekong Subregion (GMS)

PART 1

The transition from conventional monotherapies to ACTs

Chapter 2

Towards a sustainable system of antimalarial drug development and diffusion

de Haan, F., Moors, E.H.M. Anti-Malarial Drug Development and Diffusion in an Era of Multidrug Resistance. Book title: Science, Technology, and Innovation for Sustainable Development Goals: Insights from Agriculture, Health, Environment, and Energy. Chapter 13. Oxford University Press (2020) DOI:10.1093/oso/9780190949501.003.0013.

2.1 Introduction

Sustainability has grown into a paradigm of grand societal and environmental challenges and has instigated the United Nations to set targets for 2030 by introducing the Sustainable Development Goals (SDGs). The close and mutual relation between sustainability and healthcare is the central focus of SDG3, which aims to ensure healthy lives and promote well-being for all at all ages (UN, 2015). Achieving SDG3 is however challenged by flaws in the current pharmaceutical system. There is pressure from society to develop and distribute therapies for unmet medical needs. At the same time, the development of these therapies is expensive while health budgets are inherently limited. As a result, the introduction of new therapies at affordable prices is stagnating (Moors et al., 2014).

Although these challenges have a global impact, they are particularly relevant for Low and Middle Income Countries (LMICs)[1]. This is reflected by two SDG3 targets that are explicitly devoted to improve healthcare in LMICs: First, SDG target 3.3 aims to end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases by 2030. While the burden of these diseases are low in most high-income countries, they remain endemic in most LMICs and consequently, achieving SDG target 3.3 will have most impact there (Bhutta et al., 2014). SDG target 3.8 emphasizes universal health coverage and access to safe, effective, quality and affordable medicines for all (UN, 2015). Again progress towards this goal would mostly benefit patient populations in LMICs because they generally lag behind when it comes to health coverage.

Unfortunately, there are substantial barriers towards achieving these SDG targets. The development of new medicines is resource intensive but commercially unattractive when aiming for poor populations (Arrow et al. 2004; Ubben and Poll 2013). Furthermore, actors involved in developing and introducing new therapies often have poorly aligned or even conflicting interests (Yadav, 2009). Finally, the healthcare systems in LMICs are heterogeneous in nature but overall characterized by shortages of resources and by deficient supply chains (Mills, 2014). As a result, essential medicines in LMIC often fail to flow to the ones in need.

Significant system reforms will be necessary to make the development and diffusion of therapies more sustainable. These reforms should include alternative business models such as public-private collaborations, redesigning the patent system, and encompassing policy solutions (Moors et al., 2014). Furthermore, a larger open-access role for science and public research institutes is essential to achieve societal impact (Miedema, 2022). Together these reforms can contribute towards a more sustainable pharmaceutical system and towards achieving the SDG3 targets.

1 Low-income economies are defined as those with a Gross National Income (GNI) per capita, calculated using the World Bank Atlas method, of $3,895 or less; middle-income economies are those with a GNI per capita between $3,896 and $12,055; high-income economies are those with a GNI per capita of $12,056 or more (https://iamcr.org/income) .

The proposed system reforms are particularly important in the battle against malaria. Malaria is a tropical infectious disease caused by single-celled plasmodium parasites which are transmitted through the bites of female anopheles mosquitos. In the last decades, impressive progress was made in malaria control and the global burden has been reduced significantly (WHO, 2021b). However still over half a million people in LMICs die each year because of malaria and the emergence and the rapid spread of resistance to first-line therapies in Southeast Asia threatens all progress that has been made against the disease (Menard and Dondorp, 2017). Hence, new antimalarial therapies and diffusion strategies are urgently required to restore antimalarial efficacy in areas of resistance and to prevent resistance spreading to other regions and continents. These goals are critical for achieving the SDG3 targets of ending the epidemics of malaria (SDG target 3.3) and of achieving universal health coverage (SDG target 3.8). Therefore, this chapter develops a framework for sustainable drug development and diffusion in LMICs and applies this framework to antimalarial therapies in an era of drug resistance.

2.2 Sustainable drug development and diffusion for low and middle income countries

Although new treatment commodities are commonly discovered by academic institutions, drug development has almost exclusively become the activity of pharmaceutical companies. The output of new therapies, however, has been decreasing dramatically for the last decades while the prices of new therapies have risen steadily (Moors et al., 2014). The development and deployment of medicines is strongly institutionalized through regulations, guidelines and standards. Expensive randomized controlled trials are mandatory to assess the safety and efficacy of medicines and to obtain market approval (Berg and Timmermans, 2003; Rafols et al., 2014). Moreover, active ingredients and production procedures can be costly while pharmaceutical companies require profit margins to remain commercially viable and to invest in future research and development.

The high development and production costs for innovative therapies provokes high end-user prices, which is problematic for poor populations and has become a prominent topic in societal debates (de Haan et al., 2022; Frost and Reich, 2009). In resource restricted settings, the prices of innovative medicines are often too high for governments and patients which renders them dependent on donor subsidies. Cultural habits, perceived side-effects, stigma, and inadequate information provision also negatively influence the willingness of patients to adopt new therapies (de Haan et al., 2021a; O'Connell et al., 2012). This all leads to *availability*, *affordability, accessibility* and *acceptability* problems for patients in LMICs (Table 2.1).

TABLE 2.1 | Availability, affordability, accessibility and acceptability as central concepts for sustainable drug development and diffusion

Concept	Description
Availability	Availability refers to safe and effective interventions that are approved by regulatory authorities and produced in sufficient quantities. This demands targeted research and development to address unmet medical needs and regulatory pathways that facilitate market access and timely introduction. Sustainable availability of essential medicines can be achieved through decoupling profit incentives from R&D efforts, through open access of new interventions and through facilitating public-private consortia. Efficient regulation is required to ensure rapid introduction of new therapies and decision makers should be adequately informed about new treatment modalities in a timely manner.
Affordability	Affordability refers to interventions that can be acquired within the financial possibilities of governments and patients. Pricing strategies should be adjusted to the financial position of patient populations in order to become sustainable. External funding (subsidies and reimbursements) can improve affordability of drugs but will require close monitoring to avoid misuse. Sustainable affordability furthermore requires ongoing funding rather than incidental subsidy arrangements. New therapies that are proven safe and effective require prompt eligibility to such subsidies. Intellectual property management, product competition, and economies of scale can enhance affordability of essential medicines. Affordability is heavily intertwined with availability: pricing strategies and potential profit margins are strong determinants of availability of a new intervention.
Accessibility	Accessibility refers to interventions that can be physically obtained by the ones in need. Sustainable accessibility requires adequate and timely delivery of interventions through well-functioning supply chains, both public sectors and in private sectors. Policy coordination and stakeholder engagement at all levels of the healthcare system, from procurement agencies to wholesalers, distributors and prescribers, is required for sustainable accessibility of essential medicines. This is challenging because healthcare systems in LMIC generally lack information systems for stock management and surveillance. However, health systems are heterogeneous and no single solutions towards sustainable accessibility exists. Interventions and implementation strategies should instead be adjusted to the local contexts. Accessibility is strongly related to the other framework components: sustainable availability and affordability of essential medicines is required before accessibility can be considered.
Acceptability	Acceptability refers to the appropriate uptake of interventions by prescribers and patients. Sustainable acceptability of essential medicines requires engagement at all points of prescription (doctors, nurses, pharmacists, drug vendors, general stores) and prescribers need to be stimulated to provide the right medicine to the patient in need. Inadequate utilization leads to suboptimal clinical outcomes and may accelerate drug resistance. To increase sustainable acceptance, patients need to be involved from early stages of product development. Offering interventions with limited side-effects and safety risks can enhance acceptability of essential medicines. Furthermore, branding and packaging and information campaigns to inform prescribers and patient populations are vital for sustainable acceptability. Acceptability can only be considered if the other framework components availability, affordability and accessibility are guaranteed.

Accordingly, system reforms are necessary to enhance the availability, affordability, accessibility and acceptability of essential medicines and to achieve SDGs targets 3.3 and 3.8. While there is still a strong focus on fixing the flaws in the current system, in practice a combination of reforms is necessary to make drug development and distribution sustainable. Sustainable drug development is described as a process in which medicines are accepted, safe, affordable and accessible by the ones in need (Nwaka and Ridley, 2003). The patent system, short-term

incentives and reward systems, and the marginal role of public institutions are associated with an unsustainable system (Moors et al., 2014; Muñoz et al., 2015). At the patient levels unsustainability is provoked by availability of low-quality drugs and inadequate utilization of therapies. Achieving sustainable development and diffusion of essential medicines requires a multi-sectoral approach involving governments, the pharmaceutical industry, non-governmental organisations (NGOs), and multilateral organisations (Meijer et al. 2013) while engagement of system actors including wholesalers, distributors, prescribers and patients are equally essential.

2.3 Methodology

This chapter takes a systemic perspective and applies the framework of sustainable drug development and diffusion to the situation of antimalarial drug resistance. Data was collected through desk research and comprised both literature review and expert consultations. Peer-reviewed literature was accessed via the Web of Science search engine, using a broad search terminology related to antimalarial drug development and diffusion. An example of such a search query is ("Development" OR "Implementation" OR "Diffusion" Or "Transition") AND ("Artemisinin" OR "Artemether" OR "Artesunate" OR "Dihydroartemisinin") OR ("ACT" AND "malaria").

For each publication, the titles and abstracts were examined and publications that were subjected to antimalarial drug development and diffusion were further scrutinized. Articles that did not meet these criteria (e.g. in-vitro/vivo clinical studies, gene detection studies) were excluded from the study. The references of all publications were checked for additional citations of interest. Grey literature were collected using similar search terminology and were accessed via the Google search engine. Examples of selected grey literature were the WHO malaria reports and institutional websites of the Worldwide Antimalarial Resistance Network (WWARN) and Medicines for Malaria Venture (MMV). The selected literature was screened for relevant topics which were then categorized according to the components of the sustainable drug development and diffusion framework. Moreover, when a topic was relevant to more than one framework category, this connection was further explored.

After the desk review was finished, expert consultations were initiated for triangulation purposes and to obtain additional insights. Experts that had been involved in antimalarial drug development or diffusion were identified and approached. In total nine experts consultations were conducted and each consultation took between 1 and 2 hours. Participating experts included representatives from academia, industry and NGOs. These experts were asked to share their experiences and opinions regarding the availability, affordability, accessibility and acceptability of therapies and to propose activities towards a more sustainable system of antimalarial drug development and diffusion. The nine expert consultations took place in the period between August and November 2018. Data analysis of the expert consultations was done

in a similar way as the literature study. Relevant topics were derived and categorized according to the components of the sustainable drug development and diffusion framework. The next section presents the results of the desk research by providing an overview of availability, affordability, accessibility and acceptance issues in relation to antimalarial drug resistance.

2.4 Availability, affordability, accessibility and acceptability of antimalarial therapies

The present section applies the framework for sustainable drug development and diffusion to evaluate *availability, affordability, accessibility* and *acceptability* of antimalarial therapies. Flaws in the current system are identified and reforms towards a more sustainable system are proposed. For each framework component, a general overview of the established system for ACT is included and the implications of emerging drug resistance are evaluated. Then, lessons from the integrated framework are translated into policy implications towards a sustainable system of antimalarial drug development and diffusion.

2.4.1 Availability of innovative antimalarial therapies

Pharmaceutical companies have for long failed to accommodate the availability of therapies for poverty-related diseases. This is well reflected by the history of antimalarial therapies (Ubben and Poll 2013). Nearly all medicines that have become first-line have been introduced by governmental research projects or public-private partnerships. Remarkably often they have been developed by military institutions during wartime (Kitchen et al., 2006). Examples are chloroquine and sulfadoxine-pyrimethamine that were developed during the second world war and mefloquine that was discovered during the Vietnam war. All these conventional therapies were relatively cheap to produce, off-patent, and were therefore soon adopted in the portfolios of generic manufacturers.

The antimalarial drug development system appeared unsustainable when resistance to all these traditional drugs had emerged in the late 1990s and a rapid transition to artemisinin-based combination therapies was required. However, artemisinin was only cultivated on a small scale and ACTs were not yet produced commercially. This led to initial production prices of ACT that were 20-50 fold more than the overage USD 0.10 of chloroquine (Arrow et al., 2004) and therefore unaffordable for many in LMICs.

Moreover, despite the urgent need for fixed-dosed ACTs (which combine the individual compounds in one pill), most research based pharmaceutical companies were initially reluctant to invest in ACT (Ubben and Poll 2013; Wells et al. 2013). The exemption at the time was Novartis, a Swiss pharmaceutical company, that was working on a fixed-dose combination of Artemether and Lumefantrine (AL). This first fixed-dose ACT was introduced in 2001 under the brand name Coartem® (Spar and Delacey, 2008). In the following years Coartem® was added to the WHO list

of essential medicines and received the WHO regulatory pre-qualification status which enabled its entry on the global marketplace.

A few years earlier, two organizations were established to provide the antimalarial pipeline with additional fixed-dose ACTs. The Medicines for Malaria Venture (MMV) was initiated as a collaboration between multiple European governments and philanthropic organizations. The mission of MMV was to reduce the burden of malaria by discovering, developing and delivering new therapies to patients (MMV 2016; Ubben and Poll 2013). A few years later, the Drugs for Neglected Diseases initiative (DNDi) was founded by the MSF Access Campaign. Similar to MMV, DNDi was established as a collaborative, needs-driven, not-for-profit research and development facilitator. Its aim was to develop therapies for poverty-related diseases such as aids, tuberculosis, malaria and schistosomiasis (DNDi, 2015). In 2015, DNDi transferred all their malaria related activities to MMV.

MMV and DNDi turned out to be successful in introducing new medicines by combining essential expertise and resources from industry, academia and NGO's. Funding was received from governmental and philanthropic organizations and these partnerships led to the introduction of several fixed-dosed ACTs between 2008 and 2012 (Bompart et al., 2011; Spar and Delacey, 2008; Wells et al., 2013). Different regulatory pathways were pursued, and most of these newly introduced ACTs received the WHO pre-qualification status (Pelfrene et al., 2015). Moreover, patent rights were waived for all ACTs that were launched through these partnerships. This enabled generic pharmaceutical companies to enter the market, eventually leading to price reductions (Orsi et al. 2018). For example, a fixed-dosed combination of artesunate and mefloquine (ASMQ) was produced by Indian Cipla after a technology transfer by the Brazilian company Farmanguinhos (Wells et al., 2013).

Now that ACT efficacy has started to decline because of multidrug resistance, new medicines are once more urgently required. Product development partnerships such as those managed by DNDi and MMV have proven useful in organizing and facilitating the development of new therapies. They have successfully introduced several fixed-dosed ACTs and should be considered an important instruments in addressing unmet medical needs. By combining expertise and resources from public and private organizations and institutes, this type of development partnerships have potential to reduce development costs, contributing to increased *affordability.* Moreover, lessons should be learned from past experiences in obtaining regulatory approval and in strategically positioning new therapies on the market. Standard regulatory procedures can, for example, be too lengthy to respond to drug resistance and so accelerated regulatory pathways may be required. Considering market related issues in an early stage allows for strategically anticipating on challenges and may therefore improve *accessibility* and *acceptability* of new therapies.

2.4.2 Affordability of innovative antimalarial therapies

The development of new therapies is inherently a lengthy and resource intensive process and instigates high end-user prices. Traditional pricing strategies for innovative therapies often leads to prices that are too high for populations in malaria endemic countries. Reduced R&D costs (see availability) can therefore be an important step towards more affordable antimalarial therapies. Moreover, sustainable funding programs and procurement subsidies are associated with increased affordability of antimalarial therapies (Arrow et al., 2004).

In the early days of ACTs, a first solution towards affordability was initiated in the form of a memorandum between the WHO and Novartis. Directly after the introduction of Coartem®, an agreement was signed which stated that Novartis would waive profits and deliver Coartem® at production price to the WHO. The WHO would then distribute it to the governments of malaria endemic countries. In return, the WHO would provide Novartis with a quarterly forecast of expected orders (Bosman and Mendis, 2007; Spar and Delacey, 2008) which guaranteed Novartis that they would not risk an unsold overproduction. Economies of scale further reduced the production costs when global demand increased and enabled Novartis to exponentially scale up the production of Coartem® (Spar and Delacey, 2008).

This funding structure between Novartis and WHO was resembled for many other ACTs that were later introduced, including those launched by DNDi and MMV. As a result, affordable ACTs became increasingly available within governmental controlled public sectors. Public sector affordability of ACTs was further enhanced after the Global Fund to fight Aids, Tuberculosis and Malaria (GFATM) guaranteed ongoing funding for subsidized procurement of ACTs.

In contrast to the public sector, affordability of ACTs remained a challenge in private sectors which were initially ignored by these arrangements (Arrow et al., 2004). In these private sectors, many patients continued to receive outdated, low quality or even fake therapies for their malaria infections (Littrell et al., 2011). Private sector supply chains comprise networks of procurement agents, national and regional wholesalers, traders, and dispensing outlets (Yadav 2009). Price markups throughout the ACT supply chains led to high end-user prices and initially compromised affordability at patient levels. Despite these challenges, ACTs have gradually become more affordable in private sectors because of increased production and the mirroring of public-sector institutional arrangements (Tougher et al., 2017).

Affordability of essential medicines in LMICs thus requires increased control over supply chains and touches upon *accessibility* and *acceptability* issues. Innovative antimalarial medicines need to be produced for affordable prices, which strongly depends on *availability* considerations of these medicines. Functioning supply chains are important determinants of end-user prices and touch upon several *accessibility* issues. Finally, eligibility to subsidies can stimulate affordability and should therefore be considered in an early developmental stage.

2.4.3 Accessibility of innovative antimalarial therapies

A common distinction in drug distribution for LMICs is commonly made between public versus private distribution channels. Within the governmental regulated public sectors, drugs tend to flow horizontally from national governments to the level of health districts and eventually to the retailing facilities. Public sector retailers usually are more compliant to guidelines than their private counterparts and are often associated with more reliable supply chains (O'Connell et al., 2011). The public sector includes governmental hospitals and health clinics, but also community or village health worker programs (Ajayi et al., 2008a).

Private sector supply chains, on the contrary, often consist of unregulated networks of intermediary traders before medicines reach private sector retailing outlets, clinics and hospitals (Yadav 2009). As explained earlier, these intermediaries usually require a mark-up and so the prices are incremented throughout the private sector supply chain. Private sector retailers include formal facilities such as pharmacies and private clinics, but also informal facilities such as general stores and drug traders that sell antimalarial therapies. Important to note here is that healthcare systems are heterogeneous in nature and strongly context and country dependent. Therefore, our analysis will mainly touch upon some general themes instead of going in-depth into a specific local situation.

Once fixed-dose ACTs were produced and registered, they had to be delivered to both public and private sector retailers and prescribers in malaria endemic settings. The important first step was that malaria endemic countries had to include ACTs in their national treatment guidelines. The first countries did so after WHO recommended them global first-line treatment for uncomplicated malaria in 2001. Between 2001 and 2007, nearly all malaria endemic countries did so in response to the WHO (Bosman and Mendis 2007). However, time delays from months to years were common between inclusion in treatment guidelines and the actual implementation of ACTs.

From the onset, countries experienced many challenges with the distribution of quality assured ACT to end-users (Williams et al., 2004). Weak coordination of private sector supply chains and dispensing outlets often prevented ACTs from reaching patients while outdated, low-quality or even counterfeit medicines remained present on the market (O'Connell et al., 2011; Palafox et al., 2014). Unfortunately, these problems are still ongoing in many endemic settings and this challenges the achievement of universal health coverage (SDG target 3.8) by preventing patients from receiving adequate treatment. Moreover, deployment of inadequate medicines, in particular artemisinin monotherapies, increased the jeopardy of drug resistance which puts the ability to end the endemics of malaria (SDG target 3.3) at risk.

The accessibility problems are especially worrying in the light of emerging artemisinin and partner drug resistance. Lack of accessibility of *affordable* drugs are likely to stimulate the use of inferior alternatives. This, in turn, increases the risk of resistance. Hence, investments in overall structures of drug distribution in LMIC, with a strong emphasis on private sectors, is required for

a more sustainable system of antimalarial drug development and diffusion. To tackle anti-malarial drug resistance, an important first step is the inclusion of effective and safe drugs in both global and national guidelines. This is directly related to the *availability* of such medicines and requires a viable drug pipeline in times of drug resistance. Beyond that, *affordable* therapies and effective supply chain management can improve sustainable access to essential medicines. This demands market regulation and surveillance to prevent inadequate medicines from being available.

2.4.4 Acceptability of innovative antimalarial therapies

Several factors complicate acceptability of innovative therapies in LMICs and again these factors are heterogeneous according to the setting. Issues such as perceived safety and side effects are known to affect the acceptability of medicines (Moors et al., 2014). However, in LMICs the financial possibilities are known to be other factors that affect acceptability of essential medicines (Mills, 2014).

Multiple determinants have been associated with acceptance of ACT at the population level, including nausea (with amodiaquine as partner drug) an unpleasant bitter taste (with lumefantrine as partner drug). Moreover, community perceptions, and socio-economic factors have compromised affordability of ACTs in early stages (Littrell et al., 2011). Unfortunately, there is little consensus on effective strategies to increase uptake of ACTs and other antimalarial medicines (Smith et al., 2009). No one-fits-all strategy exists to solve acceptability issues, mainly because of the diversity in settings which all deal with their own socio-economic, cultural and epidemiological situation.

A complicating factor towards a sustainable pharmaceutical system is that the interest of individual patients does not necessarily match the interest of the larger population (Arrow et al., 2004). A sick patient may want a cheap and rapid working drug (e.g. artemisinin monotherapies), while it is in the interest of the larger population and future patients that drugs with the lowest risk of emerging resistance are consumed.

Despite a lack of agreement in the acceptability literature, there is some consensus that community engagement programs can be effective in increasing the acceptance of ACT (Ajayi et al., 2008a; Yeung et al., 2008a). The same applies for promotion campaigns and appropriate branding and packaging (Novotny et al., 2016). For new therapies, these issues should be considered in an early stage to allow for strategic consideration and to anticipate on patient acceptance. Finally, information provision and educating both prescribers and populations will be useful.

Acceptability can only be considered once availability, affordability and accessibility are ensured. New therapies that become *available* should both be *affordable* and *accessible* compared to alternative regimens in order to become accepted. The acceptance and appropriate use of sustainable medicines is essential in the battle against resistant malaria and therefore deserves strategic consideration.

2.5 Discussion and concluding remarks

This chapter developed a framework for sustainable drug development and diffusion in LMICs and then applied the framework to evaluate the emergence of antimalarial drug resistance. What becomes clear is that availability, affordability, accessibility and acceptability of antimalarial therapies is interrelated and that system reforms are required towards a sustainable system of antimalarial drug development and diffusion. These system reforms involve collective actions of stakeholder groups along the value chain and should be aligned with the prevalent institutional landscapes (Yadav 2009; Moors et al. 2014).

The study identified and discussed important topics for achieving sustainable healthcare (SDG3) and other interlinked sustainable development goals. Particular focus areas were SDG target 3.3, which aims to end the epidemics of poverty-related diseases including malaria, by 2030, and SDG target 3.8 which aims to achieve universal health coverage. However, the pathway towards a system of sustainable antimalarial drug development and diffusion also affects several other SDGs. A reduced malaria burden can be associated with higher productivity and reduced poverty (SDG1) and at the same time reduces inequality between countries (SDG10). Moreover, in many settings malaria is a pediatric disease which mostly affects children. Illness caused by malaria will prevent them from going to school, and therefore reducing the malaria burden will improve education rates (SDG4).

To become sustainable and to tackle the threat of drug resistance, adjustments in the pharmaceutical system are required. First, innovative antimalarials should be developed and rapidly made available to patients through efficient regulatory pathways (Waning, 2011). To realize this, the role of the pharmaceutical industry needs to be reconsidered. Poverty-related diseases are considered commercially unattractive by pharmaceutical companies. At the same time, these companies are extremely powerful in developing drugs because they are the ones with expertise and resources to do so. To become sustainable and safeguard future R&D efforts for resource restricted populations, alternative business models such as product development partnerships are required. By combining expertise and resources of both industry and academia, such partnerships can be established and they have the potential to introduce innovative therapies at affordable prices. Promising results have been achieved through innovative approaches such as MMV and DNDi which can encourage future efforts (Bompart et al., 2011; Wells et al., 2013).

To achieve a sustainable system of antimalarial drug development and diffusion, affordability of next-generation therapies needs to be ensured. New therapies should be designed and positioned to fit established market structures and subsidy schemes. The establishment of funding programs such as the GFATM have been an important step forward to public sector affordability. Particular attention should now be given to affordability in private sector outlets, which generally lag behind its public sector equivalents. Private sector affordability requires enhancing the functioning of private sector supply chains and legal action against disproportional markups and retail prices (Novotny et al., 2016).

Sustainable accessibility at patient levels starts with inclusion of appropriate antimalarials in global and national guidelines but is also related to well-functioning supply chains (O'Connell et al., 2011). Defining a market positioning strategy to integrate essential medicines into established market structures and stimulate their procurement should be a central focus towards a sustainable system. This is even more important in an era of multidrug resistance where utilization of inadequate drugs can increase drug pressure and lead to accelerated resistance.

Finally, acceptability of appropriate drugs is essential in achieving a sustainable pharmaceutical system. This can be achieved by developing drugs without too many side effects and safety risks and by adapting drugs to end-user preferences. Promotional activities to inform populations about appropriate and rational drug use can also be effective tools (Novotny et al., 2016). We emphasize that bottom-up studies to investigate end-user perceptions should be an integrated element throughout the development and implementation of new therapies.

Our analysis shows that the four framework components are interrelated. Affordability and accessibility of innovative medicines are affected by similar distribution and market dynamics. At the same time, ensuring availability in line with institutional requirements is required for affordability and accessibility. Finally, acceptability of medicines will only become an issue if availability, affordability and accessibility are ensured. Given the interrelations and multifaceted nature, we argue that systemic approaches should be at the root of tackling antimalarial drug resistance.

Chapter 3

Market formation in a global health transition

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3.1 Introduction

Malaria is a poverty-related infectious disease caused by plasmodium parasites. Although the global malaria burden has been significantly reduced in the last decades, the disease still takes over half a million lives a year (WHO, 2021b). One important contributor to the reduced malaria burden has been the global transition from conventional monotherapies to Artemisinin-based Combination Therapies (ACTs). The transition to this radical new treatment regime took off at the end of the previous millennium when parasites in the Greater Mekong Subregion (GMS) in Southeast Asia had become resistant to all then-conventional monotherapies. As a result, malaria had become difficult to treat in the region and new therapies were urgently required. The situation even worsened when multidrug resistance spread further to India and Africa, resulting in dramatic increases in global malaria morbidity and mortality (Packard, 2014; Trape, 2001). However, despite this emerging health crisis the global uptake of ACT was slow and for years, patients were treated with outdated, substandard or even counterfeit medicines (Bosman and Mendis, 2007; Dondorp et al., 2004; Newton et al., 2006; O'Connell et al., 2011). Collective efforts at all levels of the antimalarial value chain were needed for the transition to ACTs to unfold, e.g. at the level of drug development, diffusion and actual deployment (Yadav, 2009). Moreover, the formation of markets for this life-saving class of therapies required the establishment of new institutional, regulatory and financial arrangements.

This chapter analyzes what factors delayed the transition from conventional monotherapies to ACTs and which activities at the global, national and local scales eventually enabled the shift. We particularly focus on the formation of ACT markets in the GMS, the global epicenter of drug-resistant malaria. The *innovation systems* framework is applied to understand the unfolding of this socio-technological transition. This framework claims that transitions do not occur in isolation but rather as a result of interactions between actor networks and institutions that are involved in the generation, diffusion and utilization of technologies (Edquist, 1997).

Investigating the transition from conventional monotherapies to ACTs in the GMS emphasizes two important characteristics of the innovation systems framework. First, research, development, and deployment of antimalarial therapies takes place at different geographical scales and in various countries. As this chapter will demonstrate, knowledge and production centered mostly in China and at the Thai-Myanmar border, while the market-creating activities occurred within the individual GMS countries. Transnational coordination was performed by globally operating institutes, including the World Health Organization (WHO), the Global Fund to fight Aids, Tuberculosis and Malaria (GFATM), Drugs for Neglected Diseases initiative (DNDi), and the Medicines for Malaria Venture (MMV). This incites crucial questions about how these different geographical scales and corresponding actor groups align and interact. With these questions this chapter builds on the recent interest in global innovation systems (Binz and Truffer, 2017), which calls for research into spatially open, multi-scalar systems that are linked through structural couplings.

Second, the uptake of innovative therapies for malaria and other poverty-related infectious diseases has been characterized as slow and challenging, even when drugs are clinically superior to failing alternatives (Bosman and Mendis, 2007; O'Connell et al., 2011; Sheikh and Uplekar, 2016; Waning et al., 2010). Challenges have, amongst others, been associated with uncoordinated stakeholders, misalignment with institutional frameworks, and deficient health systems (Arrow et al., 2004; Sunyoto et al., 2019; Williams et al., 2004; Yadav, 2009). A more conceptual and empirical understanding of market formation in transitions can provide guidance in addressing these types of innovation challenges (Boon et al., 2020). A relatively new line of research focuses on the processes through which markets emerge and evolve in innovation systems (Dewald and Truffer, 2012, 2011; Ottosson et al., 2020). This conceptualization of market formation has proven to be useful for analyzing transitions in the medical domain by providing insights into health-related institutional complexities (Kukk et al., 2016a; Moors et al., 2018). In the present study, market formation is multifaceted because countries and localities in the GMS display different epidemiological contexts and health system structures (Cui et al., 2012; WHO, 2017a). At the same time, the formation of markets for innovative antimalarial therapies cannot be separated from global coordination and developments.

Building on these two points, this study aims to understand how ACT markets in the GMS have been formed at multiple geographic scales and locations. Doing so, the research theoretically adds to innovation system literature, emphasizing the dynamics of system development and industry emergence across different geographical scales and locations (Binz and Truffer, 2017; Coenen et al., 2012) with a focus on market formation in a global health transition. This also contributes to the much-needed understanding of science, technology and innovation dynamics in times of global health emergencies.

An important practical contribution relates to the current epidemiological situation in the GMS. It is time to learn lessons from the market formation of ACTs because the region is on the verge of yet another antimalarial drug transition. The era of ACTs is coming to an end now that malaria parasites in the GMS have started to develop resistance to artemisinin and partner drug combinations (Amaratunga et al., 2016; Dondorp et al., 2009). As a result, efficacy of ACTs is declining and a transition to new and more sustainable therapies is once more required (van der Pluijm et al., 2021). The current situation in the GMS, with over 50% treatment failure in some areas, does not permit another slow drug transition because this would inevitably put further pressure on ACT efficacy and increase the risk of resistance spreading to Africa. The latter scenario could have major public health implications, both in terms of clinical outcomes and economic burden (Lubell et al., 2014) and could reverse all gains that have been made against the disease (Menard and Dondorp, 2017). Hence, the chapter aims to learn lessons from the transition to ACTs to facilitate the formation of markets for next-generation antimalarial therapies. These lessons also apply to other endemic regions and to other poverty-related infectious diseases such as tuberculosis and HIV, which confront populations and governments with similar challenges.

3.2 The battle against drug-resistant malaria in the Greater Mekong Subregion

Malaria continues to be a global health challenge of significant proportions. Each year, over 200 million people are infected and nearly half a million die because of malaria (WHO, 2018). The majority of the malaria burden is situated in Sub-Saharan Africa, where mainly children under five years of age are at risk. This is because those young children have not yet acquired any form of immunity against the disease, in contrast to most adults in high endemic settings. In lower transmission settings, including in the Greater Mekong Subregion (GMS), malaria is less of a pediatric disease and rather affects adults, often forest workers and migrant populations in remote border areas (McMichael and Healy, 2017).

FIGURE 3.1 | Map of the Greater Mekong Subregion.

The GMS is a region in Southeast Asia and is connected through the Mekong river and comprises five countries: Thailand, Cambodia, Myanmar, Vietnam and Lao PDR (Figure 3.1). All these five countries are represented by their own health system contexts, political structures and malaria dynamics (Cui et al., 2012). With the exemption of Thailand (an upper-middle income economy), all GMS countries are classified as lower-middle income economies (Worldbank, 2020). Significant improvements have been made in the battle against malaria in the GMS with a 74% incidence reduction between 2012 and 2017 (WHO, 2017b). A number of strategies have been associated with these achievements, including improved surveillance, mosquito control and the increased availability of diagnostic tools and effective therapies (Cibulskis et al., 2016). Despite the historic low burden, the GMS remains a focus area for malaria researchers and policy makers. This is because resistance to antimalarial therapies has repeatedly emerged in the GMS (Packard, 2014).

The ability of malaria parasites to acquire drug resistance is a consequence of genetics and natural selection, reinforced by their short lifecycle and rapid reproduction (Klein, 2013). When medication is administered to a patient in inadequate dose or form, some parasites may survive the treatment regime. Those parasites then have an evolutionary advantage over drug susceptible parasites and may become dominant in the parasite population. The reason that this has repeatedly occurred in the GMS is because there is limited genetic diversity amongst parasites in this low transmission area. Moreover, inadequate deployment practices are likely to have contributed to the repeated emergence and spread of drug resistance in the GMS (Klein, 2013; White, 1999). To mitigate the risk of future occasions of antimalarial drug resistance, it is therefore important that drug regimens eliminate *all* the parasites in the bloodstream. Deployment of subtherapeutic doses, low-quality medicines, or premature finalization of treatment courses should be avoided at all times (WHO, 2006).

3.3 Theoretical approach

In order to understand how ACT markets were created under the pressure of drug resistance, we first elaborate on pharmaceutical innovation for poverty-related infectious diseases, requiring activities that are dispersed yet coordinated (Section 3.3.1). We then introduce the Global Innovation Systems (GIS) approach as a perspective to deal with the geographic dispersion of innovation system components and the interlinking structural couplings (Section 3.1.2). Finally, we zoom in on the formation of markets for innovative therapies in the context of multi-scalar innovation systems (Section 3.3.3).

3.3.1 Pharmaceutical innovation for poverty-related infectious diseases: the need for a multi-scalar innovation system concept

To address the threat of drug resistance for poverty-related infectious diseases, transitions to more sustainable drug regimens are required. This implies that such regimens need to be discovered, developed, integrated in distribution chains and adopted by prescribers and patients (Moors et al., 2014; Tindana et al., 2021a; Yadav, 2015). These innovation processes involve multiple actors, networks and institutions on different geographic scales and locations, as is depicted in Figure 3.2. When perceiving transition activities as being distributed yet coordinated, the innovation systems framework is helpful for analysis.

Pharmaceutical research and development has traditionally been dominated by multinational organizations that collaborate with research institutes across the globe. However, pharmaceutical companies have for long ignored diseases of the poor because of lacking commercial incentives (Muñoz et al., 2015). In response, attention has shifted to alternative drug development models, including governmental research projects and product-development partnerships (Bompart et al., 2011; Hoogstraaten et al., 2020; Kitchen et al., 2006). Globally-operating institutes such as the World Health Organization (WHO) and the Global Fund to fight Aids, Tuberculosis and

Malaria (GFATM) regulate the global market place for poverty-related infectious diseases ('t Hoen et al., 2014; Arrow et al., 2004). Their authorization and support are considered a pre-requisite for safe deployment and for eligibility to institutional arrangements such as inclusion in normative guidelines and global subsidy programs. These arrangements then influence country-level market formation activities in endemic countries, including product registration and adoption in national treatment guidelines (Sheikh and Uplekar, 2016; Williams et al., 2004).

Once a new therapy is approved and registered at the country-level, implementation programs can be organized by Ministries of Health (MoH) to integrate the innovative therapy into distribution channels. Public sector distribution channels are top-down coordinated by national governments, while private sector distribution channels are generally more diverse, unsupervised and commercial in nature (Yadav, 2015). At the end of the distribution channels, the innovative therapy is delivered at local prescribers and retailers, who are responsible for administering the therapy to patients and their caregivers. Patients need to consume drugs in a rational way to achieve optimal clinical results and to mitigate the risk of drug resistance (Klein, 2013).

What becomes clear is that development, regulation, distribution and utilization of innovative therapies for poverty-related infectious diseases takes place at different geographic scales (global, national and local) and locations (Figure 3.2). If we want to investigate drug transitions for poverty-related diseases, then we need a conceptualization of innovation systems that transcends geographical scales and borders.

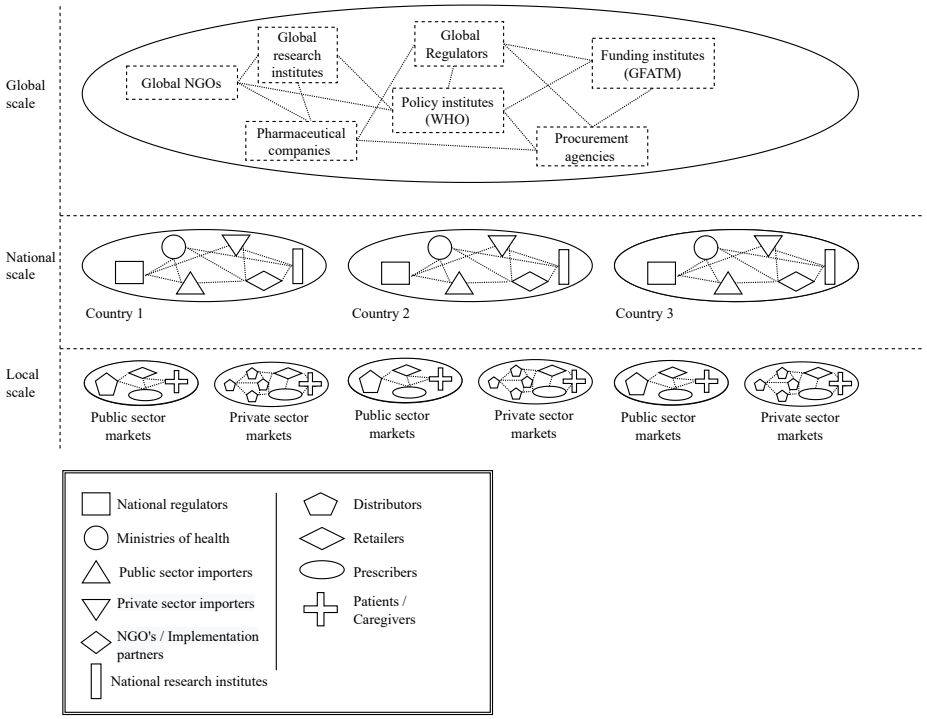

FIGURE 3.2 | Key actors in pharmaceutical innovation for poverty-related infectious diseases at the global, national and local scales.

3.3.2 Innovation systems at multiple geographic scales and locations

The innovation systems framework departs from the premise that innovation is a collective effort that involves many actor groups and institutional frameworks which are organized in a complex social system (Edquist, 1997). Innovation systems have originally been delineated by a regional, sectoral or national scope. More recently, the technological innovation system framework was introduced to analyze the emergence and societal embedding of specific technologies. The performance of technological innovation systems can be evaluated by assessing a set of seven system functions. In joint interaction, these system functions contribute to a favorable environment for emerging technology (Bergek et al., 2008; Hekkert et al., 2007). The seven system functions as identified and described in-depth by Hekkert et al (2007) plus their interpretation in terms of innovative therapies are summarized in Table 3.1.

Traditional innovation system approaches do not explain the effects of geographic dispersion of system components and the transnational nature of innovation dynamics (Coenen and Truffer, 2012). To address these lacunae, Binz and Truffer (2017) introduced the notion of Global Innovation Systems (GIS). The GIS perspective offers a framework for analyzing innovation processes in transnational contexts by focusing on the generation of resources in multi-scalar subsystems and the formation of couplings between the geographically-dispersed subsystems.

The GIS framework integrates the key system functions of technological innovation systems. Binz and Truffer (2017) conceptualize the functions as system resources and they particularly focus on knowledge creation, resource mobilization, market formation and legitimation processes. They add a geographical dimension by emphasizing that systems can be organized on multiple geographical locations (Bergek et al., 2015; Coenen and Truffer, 2012). These multi-located systems are made effective through the organization of so-called *structural couplings*. Structural couplings are actors, networks or institutions spanning across or overlapping between various innovation subsystems. Structural couplings can, for example, be transnationally-operating institutions, international associations and NGOs. Figure 3.2 illustrates that pharmaceutical innovation in global health transitions is a multi-scalar endeavor. In this chapter, we are interested in how structural couplings [SC] are attained between geographic scales and locations and how these SCs contribute to the performance of the innovation system in the context of a global health transition.

3.3.3 Market formation in multi-scalar innovation systems

Market formation is one of the technological innovation system functions (Bergek et al., 2008; Hekkert et al., 2007) and refers to the activities that directly contribute to the availability and accessibility of the innovative therapy by potential end-users (Table 3.1). In line with technological innovation systems literature, we emphasize the interplay of market formation with the other system functions. For example, legitimacy creation for an emerging therapy can affect how market boundaries are defined, while knowledge development on safety and efficacy of medical technologies dictates its target patient group.

TABLE 3.1 | Description of system functions and market formation subprocesses for innovative therapies.

F1. Entrepreneurial activities:	Activities to discover active drug compounds and to translate these active drug compounds into actual end-products (either through commercial or non-profit programs)
F2. Knowledge development:	Activities to obtain data and information on the innovative therapy. This includes studies on the efficacy, safety and tolerability and studies to optimize production, dosing and prescription behavior
F3. Knowledge diffusion:	The dissemination of data and information about the innovative therapy through e.g. conferences, seminars, publications and reports
F4. Guidance of the search:	Activities that contribute to the visibility of the innovative therapy compared to alternative treatment options, and activities that provide guidance for the further innovation processes
F5. Market formation:	
MF1. Market segmentation:	The establishment of market substructures and distribution channels for specific product-, or end-user categories of the innovative therapy
MF2. Market transactions:	The formation of exchange relationships between suppliers and users of the innovative therapy
MF3. End-user profiles:	The active role of end-users, i.e. patients and prescribers, in developing preference structures and deployment practices for the innovative therapy
F6. Resource mobilization:	Activities to obtain the required financial and human resources to facilitate the development, production and uptake of the innovative therapy
F7. Creation of legitimacy:	Efforts that contribute to the perceived legitimacy of the innovative therapy by other system actors

In this chapter, we build on the work of Dewald & Truffer (2011, 2012) who have studied market formation as a system function in more depth. According to them, markets are pivotal to the long-term success of innovative technologies and a more encompassing view of market formation is required. In order to arrive at such improved understanding, they introduce three market formation subprocesses [MF1-3] (Table 3.1). Given the potentially high divergence in market developments, Dewald and Truffer (2011) propose the formation of *market segmentations* [MF1] and their interactions as the first subprocess of market formation. The term market segments refers to the innovation system substructures that are oriented at specific product categories or end-user groups and include all related actors, networks and institutions.

In subsequent work, Dewald and Truffer (2012) claim that there is an important lack of attention to economic geography in market formation analysis. To address this spatial dimension, they provide a more elaborate conceptual framework by adding two subprocesses. The formation of *market transactions* [MF2] refers to the establishment of an exchange relationships between suppliers and customers. *End-user profiles* [MF3] relates to the active role of users and consumers by developing preference structures and utilization practices.

In line with Dewald and Truffer (2012), we define market formation as: the demarcation of markets and target groups [MF1], the creation of transactions [MF2], and the way in which users participate in the innovation process [MF3]. Following the related conceptualization of three critical processes by Ottosson and colleagues (2020), we conceptualize market formation as

being in continuous interaction with the other system functions. As depicted in Figure 3.2, end-user markets for innovative therapies reside at the local scale but they are determined by (and sometimes are determining) activities and structures at the national and global scales. We add a multi-scalar dimension to our conceptualization by investigating how structural couplings between geographic dispersed innovation subsystems contribute to market formation in a global health transition.

3.4 Methodology

3.4.1 Case selection and delineation

In order to analyze how markets are formed at multiple geographic scales and locations, we explored the transition from conventional monotherapies to Artemisinin-based Combination Therapies (ACTs). ACTs comprise all antimalarial therapies that combine an artemisinin compound with a partner drug (White, 1999). The GMS was selected as spatial delineation of the study because this region is considered to be the global epicenter of drug-resistant malaria (Cui et al., 2012). We followed this drug transition from the discovery of artemisinin in the early 1970s, until the completion of forming ACT markets in the GMS in the mid-2010s.

In line with the innovation system framework, we take a holistic perspective to understand the market formation of ACT in this global health transition. We consider ACTs as a new generation of technologies around which a technological innovation system has emerged and evolved on different geographical scales and locations. Our analysis follows the transition to ACT from the early stages of drug development, regulation and industry creation, until the establishment of distribution networks and prescription practices.

3.4.2 Data collection

An event history analysis was selected as research design to investigate how ACT markets were created in the GMS. This research design is considered a suitable approach for studying technological transitions that involve a wide array of actor networks and institutions (Wieczorek and Hekkert, 2012). As a first step, the actors, networks and institutions of the ACT innovation system were identified and mapped. Then, a timeline was constructed which included events that represented the transition from conventional monotherapies to ACTs, with an emphasis on market formation in the GMS. Data were collected through literature review and expert interviews.

The literature review comprised both peer-reviewed and grey literature. Peer-reviewed literature was accessed through the search engines Web of Science and Google Scholar, using broad defined search queries that aimed to retrieve all literature subjected to the transition to ACTs. Grey literature was accessed through using similar search terminologies in the search

engine Google, and by performing targeted searches at institutional websites such as the WHO[2], GFATM[3], MSF[4], USAID[5], MMV[6] and DNDi[7]. Selected grey literature included policy reports, institutional press releases, and research articles at websites of global health organizations.

The main goal of the literature review was to identify the key events that affected the transition from conventional monotherapies to ACTs with an emphasis on market formation in the GMS. To do so, the titles, summaries and abstracts of the obtained literature were examined. If the document was considered relevant for the purpose of the study, the full content was assessed. Events that - either positively or negatively - affected the transition to ACT in the GMS were listed in a database. The same literature was also used to gain contextual insights beyond the mere identification of events. For all selected articles, forward and backward citation checks were done to identify additional data sources. Eventually, the dataset was used to construct a preliminary timeline, which included a total of 85 events. To validate the timeline and complement it with additional insights, six expert interviews were conducted. For these interviews, global health professionals active in organizations that have been involved in the transition to ACTs were approached. Table 3.2 provides the list of interview respondents.

TABLE 3.2 | List of interview respondents.

ID	Affiliation of respondent	Date	Mode
Interview 1	Representative of pharmaceutical industry	25-1-2019	In person
Interview 2	Country-level malaria policy representative Cambodia	25-1-2019	In person
Interview 3	Country-level malaria policy representative Vietnam	28-5-2020	Digital
Interview 4	Country-level malaria policy representative Thailand	4-6-2020	Digital
Interview 5	Regional malaria specialist Greater Mekong Subregion	11-6-2020	Digital
Interview 6	Principal malaria researcher	23-4-2020	In person

Interviews followed a semi-structured protocol in which topics were selected based on the affiliation and expertise of the respondent. We asked general questions about the stakeholders, networks and institutions that had been involved in the global transition from conventional monotherapies to ACTs. Furthermore, the respondents were asked to identify and confirm events that led to the formation of ACT markets in the GMS and to provide contextual background to these events. Each interview took between 35 and 81 minutes and was audio recorded with consent from the interviewee. Anonymity was granted to all respondents.

2 WHO = World Health Organization
3 GFATM = Global Fund to fight Aids, Tuberculosis and Malaria
4 MSF = Médecins Sans Frontières
5 USAID = United States Agency for International Development
6 MMV = Medicines for Malaria Venture
7 DNDi = Drugs for Neglected Diseases initiative

3.4.3 Data analysis

Based on the literature review and expert interviews, a final event timeline was constructed. Then, the events were subjected to a process of coding. Each event was allocated to one of the theoretical constructs as described in Table 3.1 by using the operationalized indicators in Table 3.3. Codes were attributed to each event and included in the database.

TABLE 3.3 | Operationalized indicators.

Concept	Indicators	Example of event
F1. Entrepreneurial activities:	Exploratory research projects	Project 523 to identify new antimalarial drug compounds
	Innovative drug development projects	Novartis/ Kunming collaboration to develop Coartem®
	Generic drug development projects	Engagement in ACTs by generic producers
F2. Knowledge development:	(Pre-)clinical studies	Clinical studies with ACTs at the Thai-Myanmar border
	Process optimization studies	Improving methods of extracting the artemisinin derivatives
F3. Knowledge diffusion:	Conferences / seminars	WHO expert consultation meetings in 1998 - 2001
	(Scientific) publications	QACRG publication
	Reports	Published reports on ACT deployment
F4. Guidance of the search:	Policy guidance	Inclusion of ACT in WHO malaria treatment guidelines
	Standard setting	Deployment of fixed-dose ACTs
	Promotional activities	Promotion of ACT on billboards, tv-campaigns
F5. Market formation:		
MF1. Market segmentation	Market substructures, distribution channels	Integration of ACTs in public sector supply chains
MF2. Market transactions	Exchange relationships	Deployment of ACTs through community health programs
MF3. End-user profiles	Preference structures, deployment practices	Experimentation during early stages of deployment
F6. Resource mobilization:	Financial investments	Allocation of national funds to implement ACTs
	Subsidy arrangements	Allocation of GFATM procurement subsidies
	Human/technical resources	Knowledge transfer by pharmaceutical companies
F7. Creation of legitimacy:	Market regulation	Withdrawal of artemisinin monotherapies from the market
	Regulatory approval	Registration and market approval of ACTs
	External legitimacy creation	ACT deployment by Médecins Sans Frontières

The coded events were discussed amongst the researchers for verification purposes. Differences in interpretations were followed-up by discussion until consensus was reached. Based on the coded timeline of events, the corresponding dates, and the contextual comments, a narrative was constructed and a content analysis of the formation of ACT markets in the GMS was performed. The narrative followed the three major episodes of market formation that emerged from the collected data. We then plotted diagrams to distinguish actors and functional

dynamics at local, national and global scales, as well as the relations between them. These plots enabled us to identify structural couplings [SC] between the geographically dispersed subsystems. Finally, a case interpretation was written for each episode, in which we analyze the multi-scalar transition dynamics.

3.5 Results

Three major episodes of the formation of ACT markets in the GMS were identified. Section 3.5.1 begins with a narrative outline of the discovery of ACTs and the early evolution of the ACT innovation system from the early 1970s onwards (Episode 1). Section 3.5.2 reveals how a supportive global landscape for ACT production and distribution was created through collective efforts by transnational institutes and organizations (Episode 2). Section 3.5.3 demonstrates how these advancements led to the formation of public-sector and private-sector markets for ACTs in the GMS (Episode 3). Each episode ends with an analysis of the multi-scalar transition dynamics and the market formation processes.

3.5.1 Episode 1: The early evolution of the ACT innovation system (early 1970s to late 1990s)

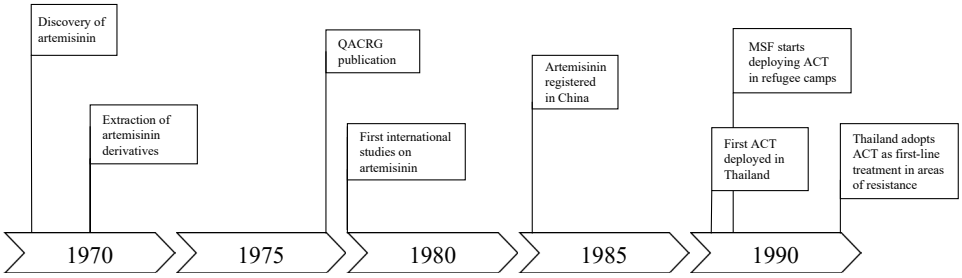

FIGURE 3.3 | Timeline of the early evolution of the ACT innovation system (Episode 1).

Historical overview

The discovery of the antimalarial potential of artemisinin can be traced back to the late 1960s. By then, Vietnamese troops were suffering heavily from malaria during the war with the United States, and drug resistance further amplified the disease burden. Because of the limited in-country capability for drug development, the Vietnamese government decided to approach neighboring China with a call for support in 1967 (Faurant, 2011). China met the request with the establishment of 'Project 523', a governmental research program in which more than 500 researchers engaged in the search for new antimalarial drug compounds (Cui and Su, 2009; Faurant, 2011). Within Project 523, a large number of drug candidates were identified and

screened, including over 200 plants that had been used in traditional Chinese medicine (Cui and Su, 2009; Liao, 2009; Tu, 2011). One of those plants, *Artemisia annua*, demonstrated promising antimalarial potential in early assessments. Follow-up studies soon confirmed the efficacy of *Artemisia annua,* and in 1972, researchers from the Academic of Military Medical Sciences, led by professor Youyou Tu, managed to extract the active ingredient of the plant (Tu, 2011). In the following years, the extraction process was further optimized, which resulted in three highly effective artemisinin derivatives that would later become the backbone of ACT therapies: artesunate, artemether, and dihydroartemisinin. Years later, in 2015, professor Youyou Tu would be awarded a Nobel prize for her role in the discovery of artemisinin and its derivatives.

Due to the cultural and political situation in China, publishing medical research in international journals was not a common practice. The few written articles that were subjected to the discovery of artemisinin and its derivatives were exclusively reported in Chinese and were hardly picked up by the rest of the world (Chang, 2016; Su and Miller, 2015). It would take until 1979 before the first article was published in English, by the Qinghaosu Antimalaria Coordinating Research Group (QACRG). In this paper, the chemical structure and pharmacological properties of the artemisinin derivatives were discussed based on a number of in-vitro studies, animal models, and clinical studies with over 2000 Chinese malaria patients (QACRG, 1979). The QACRG publication drew attention from international clinicians and researchers because by then, drug-resistant malaria had become widely acknowledged as a serious global health threat (Chang, 2016). In 1985, artemisinin was registered as a new drug compound in China, but in line with prevailing Chinese practices, no patents were requested or filed for artemisinin and its derivatives (Guo, 2016).

In successive clinical studies in China and the GMS countries, the artemisinin derivatives further proved to be safe and extremely potent in eliminating malaria parasites (Hien and White, 1993; Tu, 2011). Over twenty studies confirmed the safety and efficacy of the artemisinin derivatives between 1979 and 1992 (e.g. Hien and White, 1993; Jiang et al., 1982; Li et al., 1984). Moreover, in 1991, the Ministries of Health (MoH) of both China and Vietnam started to distribute artemisinin monotherapies to malaria patients within their borders (WHO, 1998). Initially, only a few thousand doses were disseminated in both countries, but this number substantially grew in the following years.

Although the diffusion of artemisinin in Asia was generating momentum, one significant problem remained: the short plasma half-life of the artemisinin derivatives was associated with high risk of returning infections (recrudescence) and an accelerated risk of artemisinin resistance when used as a monotherapy (White, 1999). Therefore, researchers started to advocate the exclusive deployment of artemisinin derivatives in combination with a longer-acting partner drug, creating Artemisinin-based Combination Therapies (ACTs). Thereby, recrudescence would be averted and the risk of artemisinin resistance would be reduced (Nosten and Brasseur, 2002). Artesunate, co-administered with mefloquine was first deployed in a hospital setting in Thailand in 1991 and the results of this clinical study were closely monitored. The resulting

insights demonstrated that the combination was a highly effective one, and indeed reduced the risk of recrudescence (Looareesuwan et al., 1992). In the second half of 1991, a similar combination was deployed on a larger scale in a refugee camp at the Thai-Myanmar border under coordination of Médecins Sans Frontières (MSF), a globally operating humanitarian organization that was involved in the provision of medical aid in this politically unstable region (Luxemburger et al., 1994). Again, the clinical results were monitored and a consistent over 95% cure rate was found, which prompted MSF to adopt this combination as the standard antimalarial treatment in refugee camps along the Thai-Myanmar border (Price et al., 1995).

In the following years, more and more studies confirmed the efficacy and safety of this co-administered therapy within different Asian settings (Luxemburger et al., 1994). Without exception, the superiority of ACTs compared to conventional monotherapies was demonstrated, both in terms of clinical outcome and recrudescence rates. Different dose regimens were explored and the cumulative insights of these studies suggested a 3-day oral intake as optimal (White et al., 2015). In 1995, the Thai government accepted ACTs and adopted co-administered artesunate plus mefloquine as first-line therapy in all areas where resistance to conventional antimalarial monotherapies had been observed (ACTwatch, 2016a).

Analysis of Episode 1

The first episode revealed how the pressure of multidrug resistant malaria led to the emergence and early evolution of the ACT innovation system. The narrative demonstrated that the boundaries of the ACT innovation system expanded from China, where artemisinin was discovered, to the GMS countries, where ACT deployment was further advanced. We observe how three structural couplings [SC1-SC3] between geographically dispersed subsystems appeared in this episode, which enabled the functioning of the ACT innovation system and its expansion along geographic scales and locations (Figure 3.4).

A first structural coupling [SC1] was attained between China and the GMS countries through the QACRG publication that exposed the antimalarial potential of artemisinin to the international community. Prior to this, the establishment of Project 523 [F1] had resulted in the discovery of artemisinin and its derivatives [F4], and had provided the first clinical evidence of its efficacy and safety [F2]. However, despite the promising potential of artemisinin, the acquired knowledge was only diffused beyond the Chinese border after the QACRG publication [F3]. This publication opened-up the antimalarial capacity of artemisinin to the rest of the world and coupled the Chinese discovery of artemisinin with the clinicians in the GMS countries that were in urgent need of solutions to treat drug-resistant malaria.

What we observe upon the attainment of this first structural coupling is that a reinforcing pattern, or virtuous cycle, emerges between clinical studies with artemisinin in the GMS [F2, F3], and the cumulative knowledge of these studies which collectively guided towards the optimal dose-, and prescription form of artemisinin and later ACTs [F4]. This ensuing virtuous cycle also marks the first market formation activities for ACTs in the GMS [F5]. Clinical researchers,

who were struggling to treat drug-resistant malaria infections, engaged in the prescription of ACT. Doing so, they both offered ACTs as a medical solution to their patients [F5 MF2] and simultaneously they contributed to the evidence-base [F2, F3] and optimal prescription form of ACTs [F4, F5 MF3].

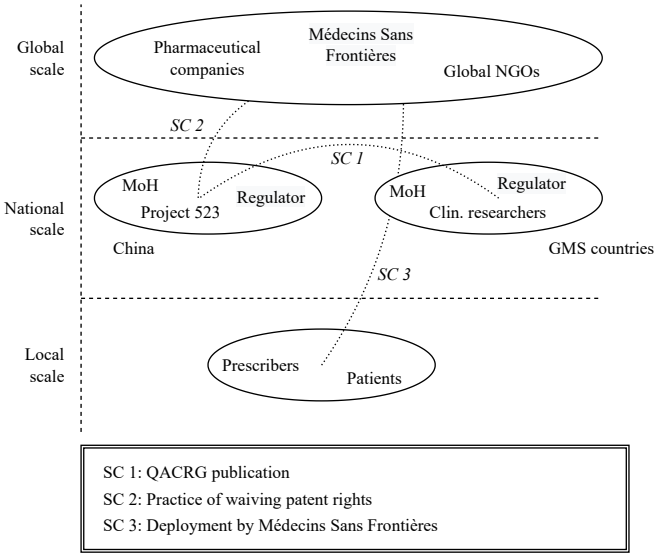

FIGURE 3.4 | Emerging structural couplings in Episode 1.

A second structural coupling [SC2], involving the global scale, appeared through the practice of waiving intellectual property rights by the research group that was responsible for the discovery of artemisinin. In contrast to common pharmaceutical innovation practices, no patents were requested for the artemisinin derivatives or the ACTs that would later be introduced. This practice of waiving intellectual property rights would eventually enable both research-based and generic manufacturers to start ACT production [F1], leading to a viable industry, product competition and eventually to price reductions [F6] (see Episode 2).

A third structural coupling [SC3] was attained between the global and the local scales when Médecins Sans Frontières (MSF) started to engage in ACT deployment in local refugee camps at the Thai-Myanmar border. Until then, ACTs were only deployed by local-scale clinicians and researchers, later endorsed by the Thai government [F7]. The involvement of MSF, a reputable global NGO, further contributed to legitimacy creation [F7], and to the uptake of ACTs [F5 MF2] as first-line therapy in areas of drug resistance.

All three structural couplings that emerged in this episode contributed to the expansion of the ACT innovation system along geographic scales and locations. The next episode further elaborates on these developments and explains how a supportive global landscape for ACT development and deployment was created through collective efforts by transnationally operating organizations.

3.5.2 Episode 2: A supportive global landscape for ACT production and distribution (late 1990s to early 2010s)

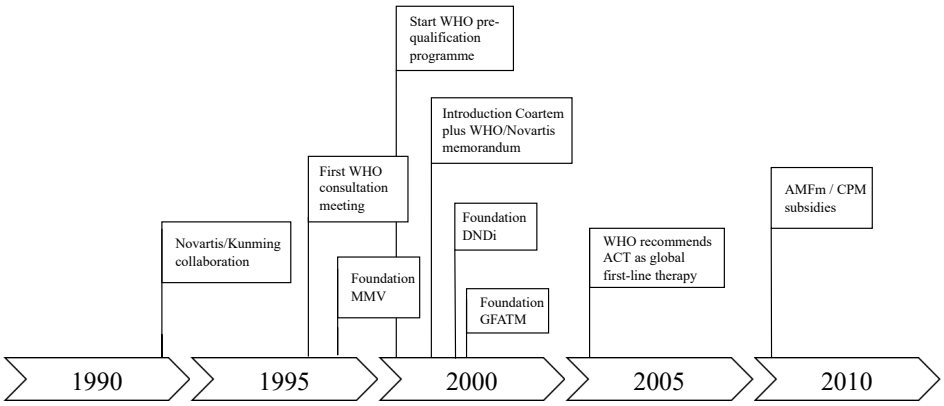

FIGURE 3.5 | Timeline of a supportive global landscape for ACT production and distribution (Episode 2).

Historical overview

By the end of the 1990s, conventional monotherapies were failing throughout the world, leading to sharp increases in global malaria mortality and morbidity (WHO, 1998). In response to this emerging health crisis, the WHO organized a series of expert consultation meetings between 1998 and 2001. The goal of these meetings was to discuss the global impact of multidrug resistance and to develop policy accordingly (WHO, 2001, 1998). The WHO consultation meetings led to three guiding principles on how drug-resistant malaria ought to be approached. First, it was decided that artemisinin-based therapies would have to be deployed as first-line therapy in all areas where conventional monotherapies were failing. Second, the artemisinin derivatives were to be used exclusively in combination with a partner drug. The prescription of artemisinin monotherapies had to be dissuaded in order to mitigate the risk of emerging artemisinin resistance. Third, it was stipulated that ACTs should be deployed as *fixed-dosed* therapies. Contrary to co-administered medication, fixed-dosed therapies combine the individual drug compounds into one pill. This prescription form would encourage patients to comply to full drug regimens and to reduce the risk of cherry picking the highly effective artemisinin compound while rejecting the unpopular partner drug, which is often associated with nausea and other side effects (Interview 2). In 2006, the WHO came with a more universal statement regarding ACT deployment by recommending ACTs as first-line therapy in *all* malaria endemic regions without any further restrictions (WHO, 2006). In that same year, the WHO also requested the pharmaceutical industry to withdraw the production and sale of oral artemisinin monotherapies. The goal of this request was to discourage the trade and the consumption of dangerous monotherapies and, in doing so, to mitigate the risk of artemisinin resistance (WHO, 2006). Most, but not all pharmaceutical companies adhered.

Meanwhile, significant supply-side challenges had to be overcome. Fixed-dose ACTs were not yet commercially produced and thus were not available for large-scale deployment. Moreover, the lengthy cultivation and extraction process of artemisinin contributed to a production price for ACTs that was estimated to be 20-50 times higher than the average 0.10 USD for chloroquine (Arrow et al., 2004). This would confront governments and populations in malaria endemic settings with an insurmountable cost barrier (Interview 2).

Efforts by globally operating organizations and the initiation of a range of institutional frameworks eventually enabled overcoming these supply and cost challenges. A first major driver was the establishment of a partnership between the Swiss pharmaceutical company Novartis (by then still named Ciba-Geigy) and Kunming, a Chinese manufacturer of artemether (Spar and Delacey, 2008). Even ahead of the WHO recommendations, these organizations had already in 1994 joined forces in order to develop a fixed-dose combination of artemether-lumefantrine. In 2000 they successfully launched this drug for international use under the brand name Coartem®. Although Coartem® did not become the dominant therapy in most GMS countries, it has contributed to the global transition to ACTs in several ways. Coartem® would become the first antimalarial drug added to the WHO list of essential medicines and to receive the WHO pre-qualification status, boosting its worldwide attention and eligibility to procurement subsidies. Initially established in 2001 during the HIV/AIDS pandemic, the WHO pre-qualification program supports resource-restricted countries with regulatory assessments to ensure that products meet global quality standards in a wide range of therapeutic areas, including malaria ('t Hoen et al., 2014). Perhaps the most important contribution of the introduction of Coartem® has been the signing of an unprecedented memorandum. In 2001, the WHO and Novartis signed a ten-year contract, in which they agreed that Novartis would waive profits and instead sell Coartem® directly to the WHO at cost price. The WHO would then distribute the drugs to endemic countries which, in return, had to report three-month demand forecasts back to Novartis. This procurement system would enable Novartis to exponentially scale-up production of Coartem® without risking an unsold overproduction (Spar and Delacey, 2008).

It would take years after the introduction of Coartem® and CV8® (a fixed-dose combination of dihydroartemisinin-piperaquine offered on the internal market in Vietnam) for other fixed-dose ACTs to be introduced. New product launches followed the initiation of two umbrella institutes that were founded to address the R&D gap for poverty-related diseases. The Medicines for Malaria Venture (MMV) was initiated by European governments and philanthropic organizations in 1999. A few years later, the Drugs for Neglected Disease initiative (DNDi) was founded for similar reasons by MSF and the WHO. Although DNDi had a broader product portfolio than just malaria, both organizations aimed to encourage partnerships between public and private organization in order to stimulate the development of medicines for poverty-related diseases, such as malaria. Since then, both MMV and DNDi have set-up and coordinated a number of product development partnerships which have led to the introduction of several fixed-dose ACTs from 2007 onwards (Bompart et al., 2011; Wells et al., 2013). In 2015, DNDi transferred all their malaria-related activities to MMV.

Patent rights were again waived for all the fixed-dose ACTs that were introduced by the MMV and DNDi partnerships. As a result, generic producers were able to enter the market which eventually led to product competition and price reductions at the global market (Orsi et al. 2018). Moreover, similar contracts as the WHO/Novartis memorandum were signed for most of the newly introduced ACT combinations, which further enhanced their affordability and availability.

Despite all these efforts, the high production costs of artemisinin made ACTs relatively expensive (Arrow et al., 2004). Malaria endemic countries would therefore still have to rely on external donor funds to be able to procure ACTs (Interview 1 & 4). Initially, a number of small-scale subsidy programs supported endemic countries with the procurement of ACTs. However, a true significant driver towards global affordability of ACTs would be the foundation of the Global Fund to Fight Aids, Tuberculosis and Malaria (GFATM), a globally operating funding institute (Interview 4 & 6). Founded in January 2002, the GFATM now supports resource-restricted countries with procurement of expensive therapies through providing an ongoing and sustainable subsidy program. Since then, the GFATM has grown into a multi-billion operation that significantly contributes to affordability of ACTs and many other therapies. In order to become eligible for GFATM donor subsidies, medicines need to be approved by a stringent regulatory authority such as EMA, FDA, or the WHO pre-qualification scheme (Orsi et al., 2018; Pelfrene et al., 2015). One critique to the initial GFATM subsidy was that it exclusively targeted public sectors while ignoring the private sector equivalents. In response to this critique, a private-sector subsidy was implemented by the GFATM in 2010, under the name Affordable Medicines Facility malaria (AMFm), and later scaled-up as Co-Payment Mechanism (CPM).

Analysis of Episode 2

The second episode revealed how the ACT innovation system further expanded from the GMS countries to the global and the local scales. We observed how a supportive global landscape for ACT development and deployment was created through collective efforts by transnational organizations including the WHO, GFATM, MMV, DNDi, and Novartis. Four structural couplings [SC4-SC7] were attained in the episode that have been critical to the functioning of the ACT innovation system along different geographic scales and locations (Figure 3.6).

The first structural coupling [SC4] emerged between the global and national scale and comprised the WHO arrangements that supported national governments with the adoption of ACTs. The WHO first synthesized and reviewed all clinical evidence in order to formulate the guiding principles on ACT deployment [F4] and then created legitimacy by recommending ACTs as global first-line therapy [F7]. Additionally, the WHO established the regulatory pre-qualification scheme [F7] and the WHO essential medicines list [F4], which enabled countries to prioritize medical needs and to define the preconditions for safe deployment of innovative therapies. These WHO arrangements cleared the road for GMS governments to start engaging in ACT and they now contribute to a coordinated global marketplace for antimalarial therapies.

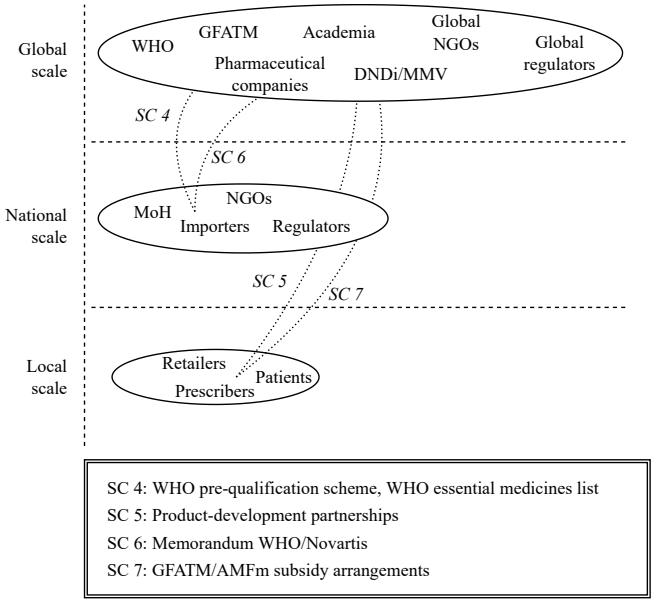

FIGURE 3.6 | Emerging structural couplings in Episode 2.

Nevertheless, two major barriers persisted towards the formation of end-user markets for ACTs. The first barrier was that fixed-dosed ACTs were not yet commercially produced [F1], and so entrepreneurial activity was required to translate the medical-technical potential into actual end-products. The second barrier was that a transition to ACTs would imply an insurmountable cost barrier for patients and governments in malaria endemic settings [F6]. Hence, financial resources were required to enhance ACT affordability. The narrative demonstrated how these barriers were addressed through attainment of three structural couplings.

The dearth of entrepreneurial activity was addressed in the form of product-development partnerships [SC5] that directly linked the global with the local scale. These partnerships were initiated as instruments to stimulate innovation for malaria as a poverty-related disease and aimed to introduce ACT end-products that were ready for deployment. The first partnership was the collaboration between Novartis and Kunming which led to the introduction of Coartem® [F1]. Subsequently, several successful product-development partnerships were initiated by DNDi and MMV, which have further fueled the antimalarial pipeline with actual end-products [F1]. The fact that patent rights were waived for these ACTs enabled generic manufacturers to become active, stimulating further entrepreneurial activities [F1] and leading to a viable industry (see Episode 1, SC2).

Two other structural couplings contributed to overcoming financial resource barriers. One structural coupling [SC6], linking the global and national scales, emerged through the signing of the WHO/Novartis memorandum. In this memorandum, Novartis agreed with the WHO to waive profit margins and instead sell ACTs at cost price [F6]. Not only did this reduce the price

of this particular ACT [F6], it also set the standard for the ACT end-products that would later be introduced through the DNDi and MMV partnerships [F6]. The practice of waiving patent rights enabled generic manufacturers to enter the market, leading to further price reductions [F6].

A fourth structural coupling [SC7] emerged between the global and local scales through the GFATM and AMFm/CPM subsidy arrangements. Both these arrangements directly aimed to reduce the prices of ACTs for malaria patients in endemic settings. The global-level pubic-sector GFATM [F5 MF1] and private-sector AMFm/CPM [F5 MF1] subsidies have been pivotal in mobilizing and channeling the necessary funds to improve affordability of ACTs at the local levels [F6, F5 MF2]. The next episode explains how these advancements and country-level activities eventually resulted in the formation of actual end-user markets for ACTs in the GMS.

3.5.3 Episode 3: The formation of actual end-user markets for ACT in the GMS (early 2000s to mid-2010s)

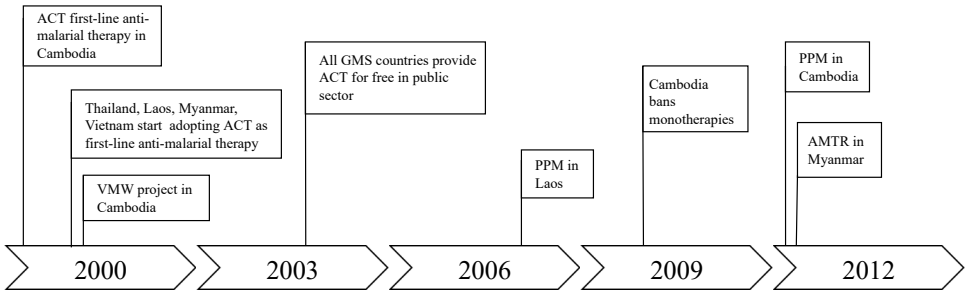

FIGURE 3.7 | Timeline of the formation of end-user markets for ACTs in the GMS (Episode 3).

Historical overview

At the beginning of this millennium, multidrug resistance to conventional monotherapies had become widespread in the GMS and it was clear that the region would have to rely on the deployment of ACTs. In 2000, Cambodia was the first country to adopt an ACT of co-administered artesunate plus mefloquine as national first-line therapy (Novotny et al., 2016). Later that year, Thailand did the same by stipulating the use of artesunate plus mefloquine for *all* malaria patients within the country (ACTwatch, 2016a). Between 2001 and 2003, Vietnam, Laos and Myanmar followed by including ACT in their national treatment guidelines. Each country mobilized resources to subsidize ACTs in public sector facilities and from 2003 onwards, this was supplemented with global-level GFATM subsidies (WHO, 2017a). Furthermore, the health ministries of each GMS country engaged in promotional activities to inform the population about the intended transition to ACTs (ACTwatch, 2016a, 2015a, 2015b; Novotny et al., 2016; Yeung et al., 2011). However, despite the clinical superiority of ACTs compared to failing alternatives, the GMS was slow in the uptake of ACTs (ACTwatch, 2016b). For years, many patients remained being treated with outdated, substandard or counterfeit medicines (Dondorp et al., 2004). Moreover,

artemisinin monotherapies remained being widely deployed in the region, despite the increased risk of infection recrudescence and accelerated artemisinin resistance.

A number of underlying dynamics have been associated with the problematic uptake of ACTs in the GMS. One major obstacle was that malaria in the GMS is mostly prevalent amongst hard to reach populations in remote border areas, such as forest workers and labor migrants (Cui et al., 2012; McMichael and Healy, 2017). These populations are often beyond the scope of public health systems. Although conventional monotherapies were so cheap and widely available that they even reached most of these remote populations, this was not the case for ACTs in the early days (Arrow et al., 2004). One intervention that turned out to be effective in improving ACT uptake amongst remote population were community-based health initiatives such as Village Malaria Worker (VMW) programs (Yeung et al., 2008a). The goal of these programs was to integrate access to ACTs in the broader goal of improving health coverage amongst hard-to-reach communities with limited access to health services. This was achieved by assigning community members with the VMW status and providing them with training and commodities, including diagnostic tools and ACTs. Thailand was the first country to start a VMW project in 1995 and Cambodia initiated a similar project in 2001. In the following years, Laos, Vietnam and Myanmar started their own VMW programs. Community-based health programs are nowadays institutionalized in public health services in the GMS and they are considered to be a key intervention in the battle against malaria.

Another problem regarding ACT uptake was that institutional arrangements such as the GFATM subsidies, exclusively facilitated the uptake of ACTs in *public sector* channels. At the same time, *private sector* channels dominated the supply of antimalarial commodities in many GMS settings, in particular in Cambodia, Myanmar and Laos (WHO, 2017a). These private sector channels remained being neglected by most arrangements. As a result, only few people in the GMS who went to private sector facilities actually received ACTs (Phok et al., 2017). The private sector challenges were even further amplified by the high amount of out-of-pocket expenditures in the GMS, which enhanced the demand for low-cost alternative therapies. Global- and national-level arrangements would eventually and gradually improve availability and affordability of ACTs in the private sector, including the AMFm/CPM subsidies which have been associated with varying degrees of success (Interview 2, Davis et al., 2013; Tougher et al., 2017).

The health ministries of the GMS countries engaged in regulatory activities to improve private sector compliance. Thailand and Vietnam, two countries in which private sector supply of medicines had traditionally been limited, exclusively mandated malaria treatment to the public sector, prohibiting the deployment of antimalarial therapies in the private sector (Interview 3 & 5). This way, it would be more feasible to ensure guideline compliance and adequate ACT prescription. However, the architecture of the healthcare systems in Cambodia, Laos and Myanmar called for alternative solutions. In those countries, significant proportions of the population relied on healthcare through private-sector channels (WHO, 2017a). Prohibiting the sale of antimalarial therapies in private-sector facilities would inevitably mean that those patients would miss out on

appropriate treatment (Phok et al., 2017). Hence, rather than following the path of Thailand and Vietnam, complementary activities were initiated to improve compliance to ACTs in the private sectors of Cambodia, Laos and Myanmar. One such initiative was the establishment of a Public-Private Mix (PPM) program in Laos, later followed by a similar project in Cambodia. The goal of these PPM programs was to enhance malaria treatment in the private sectors by providing quality commodities such as ACT therapies and diagnostic tests from the public sector, and by improving compliance to national treatment guidelines through supervision and educational activities (Novotny et al., 2016; Simmalavong et al., 2017; Yeung et al., 2011). A similar initiative was later established in Myanmar as the Artemisinin Monotherapy Replacement (AMTR) project. This project specifically aimed to discourage the deployment of artemisinin monotherapies in private sector facilities, a practice that persisted especially in Myanmar.

Despite these measures, private-sector adherence to ACT deployment remained limited in many settings in the GMS, and more drastic regulatory measures were required. In 2009, after general efforts in strengthening the public healthcare system, the Cambodian government decided to officially ban the prescription of artemisinin monotherapies and to legally act upon the deployment of any non-ACTs for the treatment of malaria. This included sending law enforcers disguised as normal clients to retailing outlets to order antimalarial therapies. Retailers and prescribers that administered inadequate therapies would receive penalties and even risked to be shut down (Novotny et al., 2016; Yeung et al., 2011). Now, the public sector is the only channel that is mandated to test and treat malaria in Cambodia, similar to Thailand and Vietnam (Interview 5). Laos and Myanmar have also engaged in regulatory measures that aim to improve private sector adherence to ACTs for the treatment of malaria (Phok et al., 2017; Simmalavong et al., 2017). However, challenges do still persist towards improving the private sector uptake of ACTs in those countries (ACTwatch, 2016b).

Analysis of Episode 3

The third episode revealed how the earlier advancements in the innovation system enabled the formation of actual end-user markets for ACTs in the GMS. The episode departed when Cambodia adopted ACTs as national first-line antimalarial therapy, soon followed by the other GMS countries [F4, F7]. At this point, only small niche ACT markets had been created (Episode 1) and the supportive global landscape was still under development (Episode 2). However, confronted with the high burden of drug-resistant malaria and encouraged by the explicit WHO support, the GMS countries started to pursue the formation of actual ACT markets [F5]. We observe how three structural couplings [SC8-SC10] emerged between the national scale and local market formation activities (Figure 3.8).

A first structural coupling [SC8] was attained through the country-level subsidy programs that enhanced access to affordable ACTs in the public sectors [F5 MF1]. The allocation of these national funds (later supplemented with GFATM subsidies) [F6], were initiated in parallel with the inclusion of ACTs in national guidelines [F7, F4] and the promotional activities by national

governments [F4]. The narrative then revealed that market transactions [F5 MF2] in the public sector market segments organically followed from the supportive institutional conditions and the distribution infrastructures.

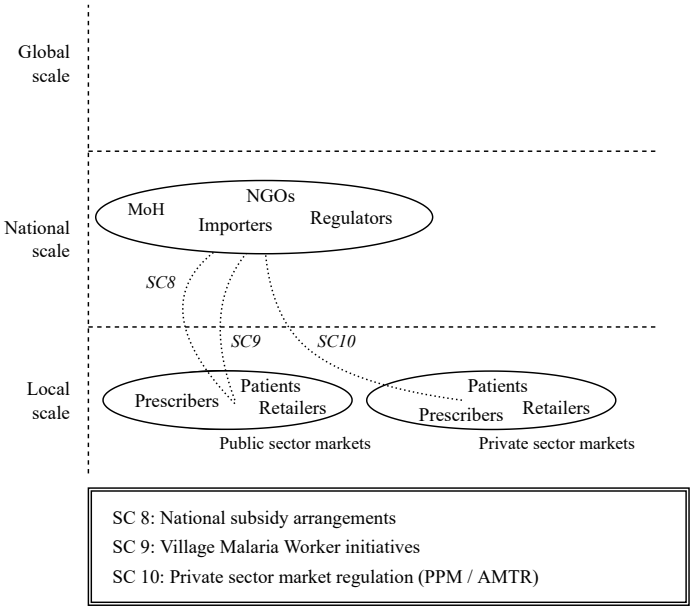

FIGURE 3.8 | Emerging structural couplings in Episode 3.

The second structural coupling [SC9] was attained in the form of the Village Malaria Worker (VMW) programs which aimed to enhance ACT availability by hard-to-reach populations. These populations were initially beyond the scope of health services, but became incorporated in public sector distribution channels through the VMW initiatives [F5 MF1] which provided them with ACTs and other health commodities [F5 MF2].

The final structural coupling [SC10] in this episode emerged through the regulatory and programmatic initiatives that aimed to facilitate ACT uptake in the private sectors [F5 MF1]. In these private-sector channels, the institutional environment was initially not supportive for ACT deployment and further efforts were required for market transactions to-be-formed. The narrative showed that regulatory programs were employed and adapted to local contexts to enhance the private sector uptake of ACTs. Examples of these initiatives were the Public-Private Mix (PPM) programs in Cambodia and Laos and the Artemisinin Monotherapy Replacement (AMTR) project in Myanmar [F4, F5 MF2]. Thailand and Vietnam, and later also Cambodia, took more drastic regulatory measures by exclusively mandating public-sector facilities to test and treat malaria [F4, F7]. What becomes clear is that, although market formation subprocesses predominantly took place at the local scale, they resided on activities and developments at the national and global scales.

3.6 Discussion

We explored the antimalarial drug transition to ACTs in the GMS in order to understand how markets are being formed at multiple geographic scales and locations. The study makes four contributions that we will discuss in-depth here. First, the study adds to the technological innovation system literature by investigating market formation as being interlinked to the other system functions. Three episodes of ACT market formation were distinguished. The first episode revealed the role of public institutes, academia and partnerships in early innovation system development. We observed how reinforcing patterns involving knowledge development, knowledge diffusion, and guidance of the search activities led to the optimal prescription form of ACTs. Similar reinforcing motors of change were earlier found in other areas, such as in the sustainable mobility transition (Suurs, 2009) and the plant-based protein transition (Tziva et al., 2020). The second episode demonstrated how financial and entrepreneurial barriers undermined the formation of ACT markets and how collective efforts by globally operating organizations enabled overcoming these barriers. The third episode illustrated how these advancements led to the formation of actual ACT end-user markets in the GMS.

The study applied the three market formation subprocesses as proposed by Dewald & Truffer (2012). The first two subprocesses, market segmentation and market transaction formation, were represented by the development of public-, and private-sector distribution channels for ACTs and the related exchange relationships. The third subprocess concerns the active role of end-users in developing deployment practices and mostly took place during the early stages of innovation system development. In these early stages, clinical researchers actively participated in market formation in their search for solutions to treat drug-resistant malaria infections. The acquired insights eventually led to the optimal prescription form of ACTs as well as the development of fixed-dose end-products to encourage adequate deployment. In later stages of market formation, the involvement of prescribers and patients became less prominent and market formation was rather dictated by regulatory and financial arrangements. Although there is evidence for active early user involvement in the pharmaceutical sector (DeMonaco et al., 2006) and in medical innovations in low-income countries (Hartley et al., 2019), patients and prescribers in this global health transition were mostly bound by guidelines and regulations in the later stages of market formation (Sheikh and Uplekar, 2016; Sullivan and Ben Amor, 2016).

Our conceptual approach aligns with the current literature on markets in transitions studies. We go beyond markets as pre-existing spaces in which supply and demand of products and services meet (Bleda and Chicot, 2020; Vargo et al., 2017). Instead, we perceive markets as dynamic entities and subject to the activities of several stakeholders, ranging from firms to public organizations (Fligstein and Dauter, 2007; Nenonen et al., 2019). The markets to-be-formed consist of several components that cover exchange and transactions practices

(Ottosson et al., 2020), institutions (Moors et al., 2018) and narratives that legitimize its existence and its boundaries (Navis and Glynn, 2010; Santos and Eisenhardt, 2009), as was revealed by the guidance of the search and legitimacy creation activities we found throughout the three episodes. Our findings contribute to deepening the understanding of market formation processes in the context of innovation systems and transitions, which is all the more relevant as many sustainable innovations enter a phase in which they are ready to scale-up (Boon et al., 2020; Hyysalo et al., 2018). As such, we broaden the notion of diffusion in the context of transitions.

A second extension to the current literature lies in investigating which actors and institutions play a role in the under-explored field of global health transitions (Kukk et al., 2016a; van Welie et al., 2019). We focused on a global trend that requires attention to sustainable transitions in global health: the recurrent emergence of drug resistance to therapies for poverty-related infectious diseases. Understanding how markets for new therapies are created is required for facilitating transitions towards more sustainable treatment regimens. Previous scholars have emphasized the critical role of country-level dynamics in the formation of markets for innovative therapies (Kukk et al., 2016a; Moors et al., 2018). Those studies emphasize that endeavors such as regulatory procedures, market approval and reimbursements decisions are typically organized at the national levels. In the present study, we show that the formation of antimalarial drug markets also relies on dynamics at the local and transnational levels. Taking an innovation systems perspective, we perceive these activities of drug development, regulation, distribution and utilization as being interdependent and mutually contributing to the formation of end-user markets. We additionally demonstrate that these global health transition activities play out at different geographical scales and locations.

The multi-scalar nature of global health transitions leads to a third contribution. Previous scholars have emphasized the importance of local actor networks and institutions in market formation processes (Dewald and Truffer, 2011; Martiskainen and Kivimaa, 2019; Matschoss and Heiskanen, 2018). Our study extends this with a transnational orientation that includes multiple geographic scales and locations. In doing so, this research builds on the work of Binz & Truffer (2017), who introduced the notion of Global Innovation Systems (GIS) and argued that there is a need for improved understanding of structural couplings between geographic dispersed subsystems. The three episodes showed that ACT as an emerging technology first spread from country to country (Episode 1), after which a supportive global landscape for ACT development and deployment was created through collective efforts by transnationally operating organizations and institutes (Episode 2), which was then followed by national and local market creation activities (Episode 3). We observed how the formation of public-sector markets in the GMS turned out to be relatively straightforward after the inclusion of ACTs in global and national treatment guidelines. This was, however, not yet the case with private-sector markets, which required complementary institutional, regulatory and financial arrangements.

Structural couplings were crucial in enabling interactions between the geographical scales and locations. Our study demonstrated that structural couplings in a global health transition span across different geographic scales (global, national, local) and can take several forms, including product-development partnerships (DNDi, MMV), regulatory arrangements (WHO pre-qualification scheme), subsidy programs (GFATM/AMFm subsidies), and programmatic initiatives (VMW, PPM). These structural couplings are essential for the functioning of the global innovation system and they enabled the formation of dispersed end-user markets for ACTs in the GMS. The obtained insights in structural couplings can provide lessons for future sustainability transitions at multiple scales and locations.

Fourth, the insights of this study are relevant in the context of much needed understanding of science, technology and innovation dynamics in times of global health emergencies such as COVID-19 and anti-microbial resistance. A worrying development in the field of malaria is that parasites in the GMS have started to develop resistance to artemisinin and partner drug combinations. Hence, new therapies and associated markets are again urgently required (van der Pluijm et al., 2021; White, 2019). The present study provides lessons learned that can be used to inform the formation of markets for next-generation therapies. These include the power of bottom-up initiatives by clinical researchers in optimizing deployment practices, the value of product-development partnerships in translating medical-technological potential into actual end-products, and the potential of institutional learning and sharing best practices amongst countries to optimize market transactions.

In this study, we focused on the market formation of ACTs in the GMS because this region is considered to be the epicenter of drug-resistant malaria. Future transition studies in global health should extend this work by focusing on drug transitions in other geographic regions and for other poverty-related diseases. This would add to the empirical evidence base of transition studies in global health and could inform policy makers in strategic decision making towards more sustainable treatment regimens.

3.7 Conclusion

This chapter demonstrated how markets for Artemisinin Combination Therapies (ACT) were formed at multiple geographic scales and locations. We showed how the pressure of drug resistance led to the discovery of artemisinin, a new class of antimalarial therapies, and how public institutes, academia and partnerships contributed to the early development of the innovation system. Market formation activities became heavily interlinked with other systemic activities such as knowledge development and legitimacy creation. We revealed how globally operating organizations and institutes created a supportive global landscape for ACT development and deployment and how these advancements led to the formation of ACT markets in the GMS. We demonstrated how structural couplings were attained between innovation system components at the global, national and local scales. These structural

couplings emerged in several forms, including funding mechanisms, product-development partnerships, and regulatory arrangements and they enabled the formation of end-user markets for ACTs in the GMS. We conclude that market formation activities in a global health transition are distributed along global, national and local scales and that they are facilitated through the attainment of structural couplings. The obtained insights are particularly relevant in times of global health emergencies which require new technological solutions and associated end-user markets.

PART 2

The introduction of TACTs in Africa

Chapter 4

Deploying Triple Artemisinin-based Combination Therapies (TACTs) for malaria treatment in Africa: ethical and practical considerations

Tindana, P., de Haan, F., Amaratunga, C., Dhorda, M., van der Pluijm, R.W., Dondorp, A.M., Cheah, P.Y. Deploying triple artemisinin-based combination therapy (TACT) for malaria treatment in Africa: ethical and practical considerations. Malar J 20, 119 (2021). https://doi.org/10.1186/s12936-021-03649-7

4.1 Introduction

The burden of plasmodium falciparum malaria has significantly been reduced since the beginning of the century. Still the disease claims over half a million lives a year, mainly children in Sub Saharan Africa (WHO, 2021b). While malaria incidence and mortality has declined over the years, recent reports show that this progress has stalled. Moreover, malaria control in Southeast Asia is jeopardized by the emergence of resistance to artemisinin and its partner drugs which results in decreased therapeutic efficacy of artemisinin-based combination therapies (ACTs) (Ashley et al., 2014; van der Pluijm et al., 2019). The looming threat of artemisinin and partner drug resistance spreading to (or emerging independently in) Africa is worrisome given that most of the malaria burden is situated on the African continent.

Although the global pipeline for new malaria drugs in development is healthier than it has been for decades, the most promising candidates (schizonticidals that kill the asexual blood stage of the parasite that causes the clinical manifestations of malaria) are at least five years away from being available on the market (Ashley, 2018; Burrows et al., 2017; Tse et al., 2019). In the absence of new compounds, short-, to middle-term solutions to address multidrug resistance should involve drug compounds that are currently in use. One promising solution is to add another carefully selected drug to currently deployed ACTs, creating triple artemisinin-based combination therapies (TACTs). TACTs have the potential to prevent the development or the spread of resistance at the population level. TACTs can be deployed rapidly once they are proven to be safe, well-tolerated and effective because they are based on drug compounds that are currently in use (van der Pluijm et al., 2021).

The safety and efficacy of two triple artemisinin-based combinations (dihydroartemisinin-piperaquine + mefloquine; and artemether-lumefantrine + amodiaquine) have been studied in 17 sites in Asia and 1 site in Africa (van der Pluijm et al., 2020). The rationale for deploying TACTs is that the combination of a short-acting artemisinin with two long acting-partner drugs would make parasites less likely to encounter only one long-acting partner drug at any one time, minimizing the chance of the development of resistance. In addition, TACTs are effective even in artemisinin- and multidrug-resistant infections and these triple therapies could exploit potential inverse relationships between the parasite molecular resistance mechanisms to the paired long-acting partner drugs (van der Pluijm et al., 2020; White, 2019). Deploying TACTs might soon be one of the last remaining options using currently available drugs for effective treatment of malaria in the Greater Mekong Subregion in Asia, where treatment failures with ACTs have become common (Mairet-Khedim et al., 2020; van der Pluijm et al., 2019).

In Africa, where current ACTs are still effective, the deployment of TACTs could very likely mitigate the risk of future ACT failure. However, several ethical and practical issues must be addressed prior to wide scale deployment of TACTs on the African continent. Some of the most important ethical and practical considerations and preliminary thoughts about ways

to address them are presented in the following sections. Data from recently completed randomized clinical studies using TACTs, established ethical principles, published literature and lessons learned from the introduction of ACTs in African markets are drawn upon.

4.2 Ethical and practical issues of deploying TACT

The main ethical issues related to deploying TACTs in Africa can be considered in terms of the risk–benefit balance, pediatric clinical ethics, public health ethics and individual autonomy. These are recurring themes in many public health initiatives. Furthermore, practical considerations such as resource allocation, sustainable use of artemisinin, affordability and the market positioning of TACT is discussed.

4.2.1 Increased risks to current patients versus benefits to future generations

TACTs are expected to be most effective at sustaining reductions in malaria-related morbidity and mortality in areas where resistance has not yet developed to any of the components, i.e. in most of sub-Saharan Africa. The long-acting partner drugs are envisioned to protect each other from the development of resistance to either of the partner drugs and protect the short acting artemisinin component (van der Pluijm et al., 2021, 2020), reducing the chances of the emergence of multi-drug resistance and the consequent increase in illness and death. Hence the areas where they will be most effective at preventing or at least delaying the emergence of multidrug resistance will be the ones where currently ACT remains highly effective at the individual level.

The use of TACTs in Africa differs from other examples of using combination therapy in that the objective is to prevent antimalarial drug resistance at the population level rather than at the level of the individual patient. Unlike in chronic infections, such as TB and HIV, development of de novo resistance to within an individual patient during treatment is rare for malaria infections (White, 1999). Hence individuals could be exposed to the potential additional side effects of three rather than two drugs for little or no additional benefit to themselves. However, the two triple artemisinin-based combinations that have been tested were overall very safe and well-tolerated (van der Pluijm et al., 2020). Incidence of vomiting during the first hour of treatment with both TACTs were low, but as expected, adding mefloquine or amodiaquine to the existing artemisinin-based combinations was associated with a slight increase in the incidence of vomiting. Addition of amodiaquine slightly prolonged the QTc interval (the duration of the depolarization and subsequent repolarization of the ventricles corrected for the heart rate), but not to the extent associated with cardiac arrhythmias.

This raises the moral question of whether it is ethically justifiable for current patients in Africa to take on additional risks of experiencing additional side effects commonly experienced with antimalarials, however minor they might be, for the sake of the public good. Avoiding drug

resistance implies significant benefits both for the current population as well as for future generations: prevention of malaria related mortality and morbidity, and the related social and economic costs (Lubell et al., 2014). Many public health interventions and programs, such as antimalarial mass drug administrations are rooted in utilitarian ethics which focuses on maximizing benefits for the greatest number of people, in this case future populations. Therefore, asking individuals to take on additional risks for the benefit of populations and future generations is not new. Competent adults can make decisions for themselves. They can decide whether or not to take triple artemisinin-based combinations that comes with additional risks. The challenge ahead is that in the situation of TACTs, the ones to take these additional risks are pediatric patients who cannot make decisions in their own right. Their parents or guardians must make these decisions on their behalf.

4.2.2 Challenging the best interest principle in pediatric medicine

The United Nations Conventions for the Rights of the Child emphasizes that the child's best interest is the primary consideration in all actions concerning children. Many international guidelines require that clinicians and parents adhere to the best interest principle as a guide when considering the appropriateness of the specific therapy (Rhodes and Holzman, 2014). Kopelman suggests that this should involve "selecting the option that maximizes the person's overall good and minimizes the person's overall risks of harm" (Kopelman, 2018). However, when considering the deployment of TACTs, malaria patients are potentially exposed to the additional side effects of three rather than two anti-malarial drugs for no additional immediate benefit to themselves. Conventional wisdom would argue that this would be against the best interest of the individual child to take three rather than two drugs as this would involve taking on additional risks of experiencing side effects while there is no direct clinical benefit.

Opponents of the best interest standard argue that this standard fails to take adequately into account the interests of others and hence is inadequate for public health decision-making (Dan, 2018). In the case of malaria, which is both an individual and public health issue, there is a need to balance the interest of current individuals and the interests of future malaria patients. This dilemma is not unique to TACTs. Other interventions, such as mass anti-malarial drug administration face the same challenges (Cheah and White, 2016). Another counter arguments to the best interest standard is that it is subjective, biased and that it is uncommon that there is only one single best option for a child (Rhodes and Holzman, 2014), i.e., that there can be several reasonable options. Rhodes and Holzman suggest that as long as any chosen option does not result in significant harm to the child, it is an acceptable option, and the decision of the surrogate should be respected. If TACTs only pose minimal additional side effects to patients— then a clinician recommending and a parent choosing TACTs over ACTs — is reasonable. In the absence of resistance, choosing ACTs would also be considered reasonable if Rhodes and Holzman are followed, respecting the decision of the patient/surrogate. Not taking TACTs can only be considered unreasonable or 'unjust' in the presence of resistance with unavailability of other effective treatment and assuming most people are taking the triple combinations. One

challenge that remains is that the potential population benefits of TACT could be lost if most people in the community are not taking them.

4.2.3 Additional side effects of TACT

Are additional risks of TACT minimal? For this discussion, the minimal risk standard employed in the context of research with children is borrowed. To protect children in research, procedures and interventions that are not administered in the medical interest of a child must be restricted. This is relevant for TACTs, because the majority of patients who will be asked to take the triple artemisinin-based combinations in Africa will be pediatric patients.

The majority of research with children falls into two broad categories: research with the *prospect of direct benefit* to participants (e.g. access to life saving drugs) and research with *no prospect of direct benefit* to participants. Since TACTs do not provide any direct *additional* benefit to the individual patient over ACTs (in scenarios where ACTs are still effective), the latter type of research is referred to for the purpose of discussion. It is widely agreed that research with *no prospect of direct benefit* to participants are only permissible (with some exceptions) if the research poses minimal risks to participants. What is minimal risk? The minimal risk threshold is widely debated but usually taken to mean risk where "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests".

4.2.4 Autonomy and understanding

If TACT is found to be safe, tolerable, and efficacious in clinical studies, and thereafter approved by national regulatory authorities, should patients have a choice between ACT and TACT? To respect the autonomy and freedom of choice, many would argue that patients or parents in the case of children should have a choice because ACT and TACT are equally efficacious in settings where there is no artemisinin and ACT partner drug resistance. This decision would be made by the patient or surrogate decision-maker based on available information on the risk and benefits of ACT and TACT, their own values and life experience.

However, asking each patient to make a choice between two treatments, outside the context of a clinical study is challenging and rare in clinical practice especially in low-resource settings. Having the choice in itself could create confusion, worry and mistrust in the public health system. In addition, exercising patient autonomy to choose their preferred treatment could defeat the ongoing efforts to address the potential risks of ACT failure in Africa. The potential benefits of TACT is unlikely to be realized unless all or most patients are willing to choose TACT over ACT. One approach to addressing this dilemma might be a change in national policy to make TACT the first-line treatment or for prescribers to only recommend TACT as the first option for malaria treatment, but have ACT available for those who opt out of TACT. A more drastic approach might be to phase out ACT so that they are no longer in the market, and only have

the triple artemisinin-based combinations available. Such drastic measures for public health are not new; they have been taken in the interest of public health, such as quarantining patients to contain dangerous contagions in the COVID-19 pandemic. Does the threat of artemisinin resistance in Africa warrant these measures?

The scientific rationale for the deployment TACTs in Africa could appear to be complicated for a non-scientific audience. Patients, parents and healthcare staff may not understand that TACTs offer the potential to delay or prevent resistance. Rather, they may assume that TACTs are more efficacious than ACT for their current malaria episode. Whether or not ACT is still available as an option, this potential misunderstanding is ethically problematic, and could lead to rumors and mistrust of the public healthcare system in the long run. Extensive and tailored community and public communication and engagement is, therefore, crucial prior and during deployment of TACT. In-depth consultations with communities, such as with community advisory board (Maung Lwin et al., 2014), and creative strategies such as using art and theatre may be necessary to explain these difficult-to-understand concepts to healthcare staff and affected communities (Lim et al., 2017; Maung Lwin et al., 2014).

4.2.5 Resource allocation and investments

The development and implementation of new antimalarial therapies, such as TACTs, is inherently a time and resource intensive process. To develop triple artemisinin-based combinations, there will be costs of assessing their safety and efficacy, developing appropriate formulations and obtaining regulatory approval. Some believe that the required investment and effort should instead be put into studying existing artemisinin-based combinations, such as extending treatment regimens beyond three days, instead of developing triple combinations (Krishna, 2019).

TACTs, when available, will likely be more expensive per treatment course than conventional ACTs. What should then be the pricing strategy of TACTs? Will patients or governments in African countries have to bear the cost, or should it be a global responsibility through mechanisms like the Global Fund to fight Aids, Tuberculosis and Malaria? Who will manufacture co-blistered or co-formulated triple artemisinin-based combinations at scale, and where will the product development funding come from? How can a viable industry be created and how can pharmaceutical companies be engaged into developing and manufacturing triple artemisinin-based combinations? What would a transition to TACTs imply in terms of intellectual property rights? These and other such questions need to be addressed collaboratively with relevant stakeholders, including pharmaceutical companies, regulatory authorities, funding agencies, health ministries, and other development partners. Any public health intervention should be ethical, well planned and adequately resourced. As discussed in the previous section, significant time and efforts must be invested to explain to patients and all levels of healthcare staff why deployment of TACTs is encouraged instead of ACTs, which will add to the costs.

4.2.6 Trade-offs towards sustainable use of artemisinin

Sustainability refers to the responsible use of scarce resources to ensure that future generations can continue to benefit from them. Artemisinin is a scarce resource. There are no anti-malarial compounds presently available with comparable efficacy and losing artemisinin to resistance would imply a substantial risk to global malaria control and elimination efforts (Menard and Dondorp, 2017). At the same time, changing first-line treatment practices is a lengthy and resource intensive process (Amin et al., 2007; Williams et al., 2004). In the case of a prospective transition from ACTs to TACTs, short-term investments at the country level are required whilst benefits are for the long-term and will transcend national borders. This means that complex trade-offs need to be made by decision-makers at both global and national levels. In addition, these trade-offs are time-dependent. The recent emergence of artemisinin resistance in Rwanda could change importantly the risk–benefit and cost analyses for the implementation of TACT, and might make their deployment more urgent (Uwimana et al., 2020).

In the scenario of ACT resistance spreading to or emerging locally in Africa, costs have conservatively been estimated to be over 116,000 deaths per year and the overall monetary price could add up to over USD 400 million annually (Lubell et al., 2014). Although it is hard to put a number on the exact investments that are required for changing first-line treatment to TACT in Africa, it is unlikely that such costs will come anywhere close (Mulligan et al., 2006). Hence, from a health-economic perspective, preventive investments to avoid resistance appears to be good value for money, even apart from the averted increase in mortality.

Changing malaria treatment practices requires the allocation of scarce resources and strong policy coordination. Encouraging is that successes have been achieved in the past. Artemisinin has for long been available as a monotherapy in Africa (O'Connell, 2011), despite significant risk of recurrent infections and the susceptibility to artemisinin resistance. After years of availability of these artemisinin monotherapies, they have now successfully been removed from the markets in most African countries. Simultaneously, availability of quality-assured ACT has significantly improved (M. Littrell et al., 2011). Lessons learned and best practices from previous drug transitions can be used to inform strategies to facilitate the transition to next-generation antimalarials, such as the triple artemisinin-based combinations.

4.2.7 The market positioning of TACT

Once TACT has been proven safe and (cost) effective, its rapid and sustainable deployment can mitigate the risk of artemisinin and partner drug resistance in Africa. To achieve this, triple artemisinin-based combinations will need to become available for affordable prices to governments and patients in endemic countries. However, the trajectory towards deployment in endemic African countries is a complex one. Previous episodes of resistance have shown that the implementation and uptake of a new generation of anti-malarial drugs can be slow and challenging (Amin et al., 2007; Bosman and Mendis, 2007).

A multitude of actors and institutions are involved in the process of changing first-line treatment practices. At the global level, the triple artemisinin-based combinations will need to be manufactured according to standards and be subjected to review by regulatory agencies, funders and global technical agencies. What is encouraging is that the global health landscape has become increasingly supportive for the development and uptake of new anti-malarial therapies. Institutional arrangements, such as subsidy programmes (GFATM), regulatory frameworks (WHO prequalification) and product-development partnerships (MMV) have been established at the beginning of this millennium and now contribute to this enabling environment. At the country levels, market authorization and inclusion in national guidelines are required before TACTs can be deployed on the ground. Endemic countries usually follow WHO recommendations, although delays have been reported in regulatory and implementation procedures (Amin et al., 2007; Bosman and Mendis, 2007; Williams et al., 2004). This is worrisome because time can be scarce under the pressure of drug resistance. Global and national decision-makers should, therefore, anticipate pro-actively on epidemiological trends to avoid similar delays once artemisinin and partner drug combinations start to fail in Africa.

Beyond regulatory-, and policy procedures, TACTs need to be effectively implemented and delivered to patients in need. This again has proven to be challenging in previous anti-malarial drug transitions in Africa. Challenges have, amongst others, been associated with uncoordinated stakeholders along the value chain, misalignment with institutions, and with underperforming health systems (Arrow et al., 2004; Yadav, 2015). As a result, availability of outdated, substandard or even counterfeit therapies persist in African countries, especially in (informal) private sector markets (Nayyar et al., 2012; O'Connell, 2011; Sullivan and Ben Amor, 2016). Introducing new therapies under these circumstances is complex and strategies should be aligned within the broader context of improving health coverage. Encouraging are the successes that have been achieved through programmatic and regulatory initiatives in Southeast Asia (Novotny et al., 2016; Phok and Lek, 2017). Similar regulatory initiatives are also proposed for enhancing treatment practices for multidrug resistant tuberculosis (Sheikh and Uplekar, 2016; Sullivan and Ben Amor, 2016). Integrating triple artemisinin-based combinations in retail and prescription practices may require job instructions and training, complemented with supervision and market surveillance (Zurovac et al., 2007). Addressing these multi-faceted issues is complex and requires bottom-up studies that focus on the societal embedding of TACTs. Such studies are required to inform policy makers about issues in the market positioning trajectory and to develop market positioning and implementation strategies accordingly. Given the heterogeneous nature of African countries and their healthcare systems, such strategies will need to be adapted to local contexts.

4.3 Discussion and concluding remarks

The threat of artemisinin and partner drug resistance emerging in or spreading to Africa is imminent and efforts need to be made to develop effective anti-malarial treatments. The development and deployment of TACT can be a promising strategy to delay or prevent artemisinin and partner drug resistance and also to eliminate malaria from entire circumscribed populations rapidly. A large clinical trial is underway to further characterize the safety, tolerability and efficacy of TACT over ACT in Africa and Asia (ClinicalTrials.gov Identifiers: NCT03923725 and NCT03939104). Moreover, empirical studies have been conducted to assess the extent to which anti-malarial drug markets in African countries are ready for a transition to TACT. Additionally, modelling studies to predict the impact of deploying TACT in different scenarios will model the potential of TACT to delay artemisinin resistance in Africa and also model potential economic benefits. In the present paper, pertinent ethical and practical issues regarding deploying TACT in Africa, relevant to all stakeholders involved were discussed. Considering these ethical and practical issues will be essential to determine the full potential of TACT in Africa under the threat of drug resistance.

Chapter 5

To what extent are the markets in African countries ready for a transition to Triple Artemisinin-based Combination Therapies (TACTs)?

de Haan, F., Bolarinwa, O.A., Guissou, R., Tou, F., Tindana, P., Boon, W.P.C., Moors, E.H.M., Cheah, P.Y., Dhorda, M., Dondorp, A.M., Ouedraogo, J.B., Mokuolo, O.A., Amaratunga, C.. To what extent are the markets in African countries ready for a transition to Triple Artemisinin-based Combination Therapies? PLOS ONE 16(8) (2021) https://doi.org/10.1371/journal.pone.0256567

5.1 Introduction

Artemisinin-based combination therapies (ACTs) are the global first-line therapies for the treatment of uncomplicated falciparum malaria (WHO, 2006). A worrying development is the emergence and spread of *Plasmodium falciparum* parasites resistant to both artemisinin and partner drugs, compromising ACT efficacy in large areas of Southeast Asia (Amaratunga et al., 2016; Mairet-Khedim et al., 2020; Phyo et al., 2016; van der Pluijm et al., 2019). An even more significant threat is the risk of multidrug resistance spreading further throughout Asia and to the African continent, where most of the malaria burden is clustered (WHO, 2019). In addition, artemisinin resistance can emerge independently in African countries, as has been increasingly reported in recent years (WHO, 2020). According to conservative estimates, these scenarios could lead to more than 116.000 *excess* deaths on an annual base while the economic costs could exceed USD 400 million per year (Lubell et al., 2014).

Innovative solutions are urgently required to restore antimalarial efficacy in areas where ACTs are failing and to protect the rest of the malaria-endemic world from the looming threat of resistance. However, new antimalarial drug compounds are not expected on the market before 2026 (Ashley, 2018; Burrows et al., 2017; Wells et al., 2015). A pragmatic short-term solution that could provide long-term benefits is the introduction of triple artemisinin-based combination therapies (TACTs) (Boni et al., 2016; Dondorp et al., 2017; Phyo and Von Seidlein, 2017; van der Pluijm et al., 2021; White, 2019). TACTs combine an artemisinin derivative with two partner drugs, ideally with counteracting resistance mechanisms. This will extend the therapeutic lifetime of the drug combinations, because the parasite will need to develop resistance to three drug compounds instead of two. Previous studies have shown promising results (van der Pluijm et al., 2020) and two TACT combinations are now being developed and tested to translate this potential into end-products (van der Pluijm et al., 2021). Once they are confirmed to be safe, tolerable, efficacious and non-inferior to ACTs, these TACTs could provide direct clinical relief in Southeast Asia. Moreover, a rapid and sustainable transition to TACTs in Africa could mitigate the risk of spread and *de novo* emergence of artemisinin and partner drug resistance on the continent.

Despite these promising developments, history has shown that changing first-line malaria therapies is a time and resource intensive process. Previous drug transitions have been slow and challenging, even when new therapies were clinically superior to failing alternatives (Amin et al., 2007; Bosman and Mendis, 2007; Mulligan et al., 2006; Yadav, 2009). Challenges have, amongst others, been associated with supply-side and demand-side factors and with underperforming healthcare systems in endemic countries (de Haan et al., 2021b).

A complicating factor for a transition to TACTs in Sub-Saharan Africa is that current ACTs are still effective for the treatment of falciparum malaria. TACTs would not provide direct additional clinical benefit to individual patients, but rather benefit the larger community and future patients by mitigating the risk of the emergence and spread of drug resistance. Engaging in TACTs thus

requires direct investments at the country level, whilst the benefits of TACT deployment would be long-term and transcend national borders. This, in combination with lessons learned from the problematic introduction of previous therapies, warrants an assessment of the readiness of the antimalarial drug markets in African countries for a transition to TACTs (Tindana et al., 2021a; van der Pluijm et al., 2021). Similar anticipatory studies have not been conducted for innovative antimalarial therapies and findings could support strategic decision making in the battle against drug resistant malaria. This study aims to explore the extent to which stakeholders perceive the antimalarial drug markets in African countries ready for a transition to TACTs.

5.2 Materials and methods

5.2.1 Research design

The study was conducted under the auspices of the UK Government's Foreign, Commonwealth & Development Office funded Development of Triple Artemisinin Combination Therapies (DeTACT) project and explores the readiness of antimalarial drug markets in African countries for a transition to TACTs (van der Pluijm et al., 2021). An initial pilot study was conducted in Nigeria and Burkina Faso, two countries that suffer from high malaria endemicity (WHO, 2019), yet have different healthcare systems. Table 1 provides demographic and malaria-related data for Nigeria and Burkina Faso. We used a multiple case design, that allows investigating the country-specific contexts, while enabling the extraction of overarching themes (Yin, 2003). The study employs a qualitative approach of data collection, involving in-depth interviews and focus group discussions (FGDs) with key stakeholders.

TABLE 5.1 | Demographic and malaria data on the settings in Nigeria and Burkina Faso.

		Nigeria	Burkina Faso
Demographic	Population (2019) [a]	200.9 M	20.2 M
	First language	English	French
	Capital	Abuja	Ouagadougou
	Human Development Index (2019) [a]	#158	#182
	GNI (PPP) (2019) [a]	USD 5.170	USD 2.220
	Population > USD 1.90 PPP (2019) [a]	53.5%	43.7%
Health -demographic	Life expectancy (2018) [a]	54 YRS	61 YRS
	<5 mortality per 1000 births (2019) [a]	117.2	87.5
	Health spending per capita (2018) [a]	USD 83.75	USD 40.25
	Health spending % GDP (2018) [a]	3.89%	5.63%

		Nigeria	Burkina Faso
Malaria	Drug regulation authority	National Agency for Food and Drug Administration and Control (NAFDAC)	Agence Nationale de Régulation Pharmaceutique (ANRP)
	Malaria control program	National Malaria Elimination Program (NMEP)	Programme National de Lutte contre le Paludisme (PNLP)
	Population at risk of malaria (2018) [b]	100%	100%
	Estimated malaria cases (2018) [b]	57.2 M	7.9 M
	Estimated malaria deaths (2018) [b]	95.844	12.725
	First line anti-malarial therapy	Artemether-lumefantrine Artesunate-amodiaquine	Artemether-lumefantrine Artesunate-amodiaquine Dihydroartemisinin-piperaquine
	ACT in guidelines since	2004	2005
	ACT for free in public sector?	Yes	Only for children <5 years and pregnant women
	Antimalarials prescribed over-the-counter?	Yes	Yes

[a] https://data.worldbank.org/

[b] WHO malaria report 2019

5.2.2 Theoretical and thematic approach

The study uses an 'innovation systems' approach to explore the readiness of African countries for a transition to TACTs (Edquist, 1997). The innovation systems approach assumes that integrating new technology in society is a collective effort that takes place in a complex social system. To explain or predict the success of an innovative therapy such as TACTs, one should not only consider medical-technological characteristics, but also the dynamics of the surrounding innovation system (de Haan et al., 2021b; Moors et al., 2018). An innovation system consists of all actors, networks and institutions involved in the development, distribution and utilization of the therapy.

We identified the key actor groups in the innovation system of antimalarial therapies (Figure 1). Our study focuses on country-level dynamics, and therefore the national borders are demarcated by a dashed line. To prepare for data collection, we conducted a thematic analysis in which we identified the major barriers and enablers of previous antimalarial drug transitions from literature review (Fereday and Muir-Cochrane, 2006). These barriers and enablers were grouped and assigned to the key actors in the innovation system. Finally, we constructed semi-structured interview guides per key actor group to facilitate data collection (Tindana et al., 2021b).

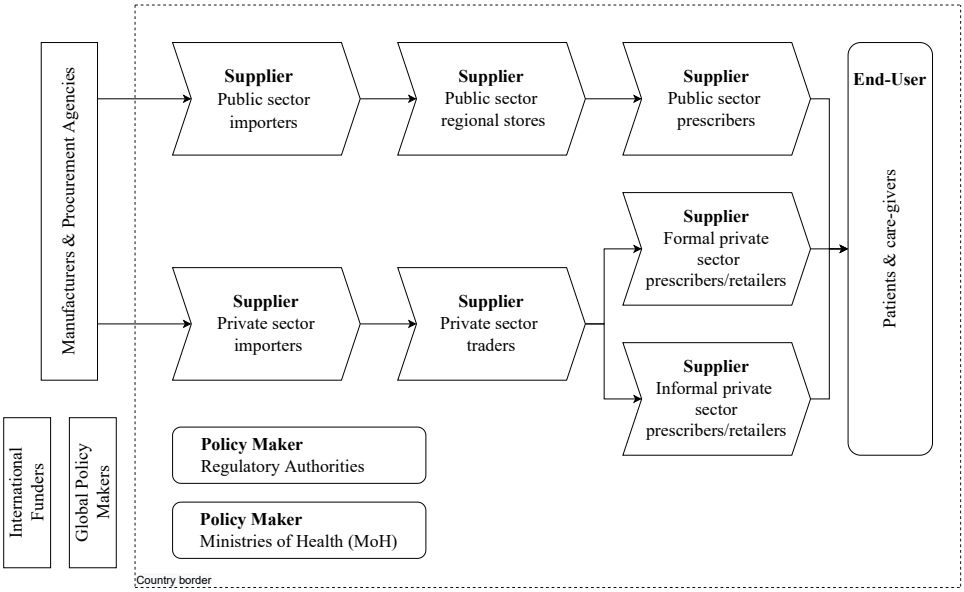

FIGURE 5.1 | Key actor groups in the innovation system of antimalarial therapies.

5.2.3 Respondent selection

Respondents at different levels of the innovation system of antimalarial therapies (Figure 1) in Nigeria and Burkina Faso were identified and invited to participate in interviews and FGDs. We divided the key actor groups into three overarching categories to facilitate data analysis: Policy makers, Suppliers, and End-users. The rationale for this categorization was that they combine an overview of the innovation system with knowledge on specific parts of the system. Policy makers are best positioned to reflect on policy procedures and the regulatory trajectory. Suppliers are most knowledgeable about distribution, retail and prescription issues, while End-users have the most relevant insights on the actual utilization of new therapies. Sampling of respondents in each country continued until data saturation was reached. The full list of respondents is provided in Table 2.

5.2.4 Data collection

Preparatory meetings were held among members of the research team prior to data collection to discuss the study aims and to prepare material for data collection. Pilot interviews were conducted to further improve mutual understanding and to reduce ambiguity. Using the semi-structured interview guides enabled flexibility to new topics while still covering the same topics between the settings and respondent groups.

Each interview and FGD was conducted by at least two interviewers; one asking questions and the other taking notes. Interviews and FGDs were conducted in prearranged venues where

there were no distractions and respondents were able to express themselves freely. On average 8 people participated per FGD. Each interview and FGD lasted between 30 and 120 minutes and were recorded with the consent of the respondent(s).

TABLE 5.2 | Respondents in Nigeria and Burkina Faso.

Country	Category	Number	Background / affiliation	Interview/FGD
Nigeria	**Policy Makers**	1	Principal malaria researcher	Interview
		3	Regulatory officials	Interview
		6	National malaria policy officials	Interview
		1	Regional malaria policy official	Interview
	Suppliers	4	Public sector prescriber	Interview
		4	Private sector prescriber	Interview
		3	Village Health Workers	FGD
		2	Public sector wholesaler /retailers	Interview
		5	Private sector wholesaler/ retailers	Interview
	End-users	7	Community members	Interview
		4	Community members	FGD
Burkina Faso	**Policy Makers**	2	Principle malaria researcher	Interview
		2	Regulatory officials	Interview
		3	National malaria policy officials	Interview
		3	Regional malaria policy officials	Interview
	Suppliers	5	Public sector prescriber	Interview
		9	Private sector prescriber	Interview
		3	Public sector wholesaler /retailer	Interview
		8	Private sector wholesaler/ retailer	Interview
	End-users	4	Community members	FGD

5.2.5 Data analysis

The tape recordings were transcribed and all non-English transcripts were translated to English. The transcripts were uploaded to NVivo12 Pro software and subjected to a process of coding. The coding process comprised both deductive and inductive techniques. A codebook was constructed based on the prior thematic analysis (deductive). New themes were developed for data that did not match the existing codes but were considered relevant for the study (inductive). The interview transcripts were coded independently by two researchers who analyzed all transcripts and discussed emerging themes. In a second round of coding, all themes were merged into overarching categories, the reflections were extracted per respondent group, and storylines were written.

5.2.6 Ethical approval

In Nigeria, ethical approval from the Institutional Review Board was obtained from the University of Ilorin Teaching Hospital (approval number ERC/PAN/2019/07/1916). In Burkina Faso, ethical approval was obtained from the Institutional Ethics Committee for Health Research (CEIRES). The Oxford Tropical Research Ethics Committee (OxTREC) approved the overall research project

(approval number 552-19). Written participant consent was obtained prior to each interview and FGD. Respondents were informed about the objectives of the study and they were asked to sign a consent form. Permission to mention the affiliation of the respondent and to audio record the conversation was asked verbally.

5.3 Results

This study explored market readiness for a transition to TACTs by probing stakeholders' perceptions in two African countries – Nigeria (NG) and Burkina Faso (BF). The findings from interviews and FGDs are categorized by the eight themes that emerged during data analysis.

5.3.1 Market approval, regulation and domestic production

Policy makers in Nigeria and Burkina Faso did not foresee major challenges in the regulatory trajectory for TACTs. Obtaining market approval for TACTs would be relatively straightforward under the assumption of supportive safety and efficacy data from clinical trials. It was, however, acknowledged that the trajectory towards market approval can be a lengthy one, while in the context of rapidly increasing drug resistance short timelines may be needed. [*"I think generally we are trying to streamline the process of registering medicines in Nigeria, we are not where we want to be but it is a lot shorter than it used to be "*- Policy maker 7, regulatory official, NG]. Internal capacity issues at the regulatory authorities and submission of incomplete dossiers were cited as common causes of delays in the regulatory trajectory. Early submission of dossiers was suggested to be the most feasible way for obtaining rapid market approval for TACTs.

Respondents mentioned several challenges they encounter in the performance of the antimalarial drug market in their countries. It was acknowledged that antimalarials are often still being prescribed over-the-counter and beyond the official channels. As a result, substandard and outdated medicines such as chloroquine are still commonly deployed in both countries. Several policy makers and suppliers mentioned that market surveillance systems remain weak and that this could be a barrier to the uptake of TACTs. *["A threat can be that there are too many medicines on the market and lack of supervision. Then there may be no incentive to choose for TACT instead of another option"* – Supplier 4, public sector clinician, NG]. The limited market surveillance and the low levels of regulatory compliance imply that patients can purchase the medicines they favor rather than those that are recommended in treatment guidelines. Challenges were particularly associated with the (informal) private sectors and respondents admitted that introducing TACTs under these circumstances is difficult. General health system reforms and increased investments in market regulation were cited as potential solutions.

Policy makers and suppliers in Nigeria emphasized that the domestic pharmaceutical industry is an important source of antimalarial drugs. Engaging domestic manufacturers in producing TACTs was therefore considered crucial to stimulate its uptake in Nigeria. A repeatedly cited challenge in this regard is that Nigerian manufacturers have not yet been able to produce

according to global quality standards, including Good Manufacturing Practice standards *["The local manufacturers produce all the ACTs, but the barrier is that none of them is WHO pre-qualified"* – Policy maker 2, national malaria policy official, NG]. This implies that domestic manufacturers cannot become eligible to international donor subsidies. Respondents in Burkina Faso indicated that there is no domestic industry for the production of antimalarial therapies. Adopting TACTs as first-line therapy would therefore require adaptations in import and procurement procedures. Some suppliers perceived a potential transition to TACTs as an opportunity to start domestic production of antimalarials in Burkina Faso. ["*If we have local production, I'm not saying that there won't be a shortage, but there is a certain guarantee. We will always be able to put pressure for more drugs.*" – Supplier 13, private sector clinician, BF].

5.3.2 Inclusion in treatment guidelines and subsidy arrangements

All respondent groups agreed that including TACTs in national treatment guidelines would be critical for their future uptake in Nigeria and Burkina Faso. Several policy makers emphasized that WHO endorsement would be a major enabler for inclusion in these national treatment guidelines. ["*WHO is a benchmark in management, it is a guide, it is a reference, all documents and national guidelines take reference from the WHO* "– Supplier 22, private sector clinician, BF]. Most policy makers and suppliers were skeptical about a transition towards TACTs as long as ACTs are not failing within their borders. ["*I'm not too much in favor of changing as long as ACTs are still effective. So we should continue to use them until they become resistant. If it doesn't work, then we can change!"*- Supplier 21, private sector clinician, BF].

Changing policy now to avoid resistance in the future was considered an insufficient argument to enact. This position was, however, contested by some other respondents who preferred pro-active anticipation by the government instead of passively waiting until artemisinin and partner drug resistance has been detected. [*"We should not be waiting for the emergence of resistance to happen, before steps are taken"* – Supplier 9, village health worker, NG]. Some respondents argued that the introduction of TACTs should be guided by actual data that confirms the presence of antimalarial drug resistance. *["So, countries like Nigeria want to document local evidence. You know, they want local evidence of the resistance before they could accept it.*" – Policy maker 4, national malaria policy official, NG]. A transition to TACTs would then require a strategic plan which would contain specific policy actions at pre-defined resistance thresholds.

Policy makers, suppliers and end-users emphasized the importance of subsidy arrangements for deploying TACTs. [*"You just have to integrate it into your program and subsidize it and make it available.* – Supplier 12, public sector clinician, BF]. Since price dictates consumer preferences, they expected TACTs to be unaffordable for large proportions of the population without external financial support. This was especially considered relevant for private sector deployment because of the limited availability of subsidy arrangements. For public sector deployment, willingness of the Global Fund to Fight Aids, Tuberculosis and Malaria (GFATM) to purchase TACTs was considered critical by policy makers and suppliers. In Nigeria, inclusion of

TACTs in national insurance arrangements such as the National Health Insurance Scheme (NHIS) was suggested as another tool to promote uptake.

5.3.3 Implementation programs

Implementation refers to the process of translating policy decisions into practice. Respondents in Nigeria and Burkina Faso agreed that deliberate implementation programs would be required for TACTs if it becomes the first-line therapy for the treatment of malaria. The National Malaria Elimination Program (NMEP) in Nigeria and the Programme National de Lutte contre le Paludisme (PNPL) in Burkina Faso would be responsible for coordinating a prospective implementation program. Respondents acknowledged that the implementation of ACTs had been slow and that outdated medicines persistently remain available on the market. According to them, lessons learned should be used to inform prospective implementation strategies for TACTs.

Implementation programs should first of all inform retailers (e.g. pharmacists, shop owners, drug sellers) and prescribers (e.g. clinicians, nurses) about the implications of switching to TACTs. *["The professionals must be involved: the nurses, doctors, pharmacists."* – Policy maker 6, regulatory official, BF]. Not only do these retailers and prescribers deliver the drugs to patients, they are also responsible for information dissemination to patients. [*"Who deploy the ACTs? The healthcare providers. So, you don't neglect them"* –Policy maker 2, national malaria policy official, NG]. Implementation programs should be transparent about the added benefits of TACTs in terms of delaying drug resistance and they should cover an extended period of time. *["The strategies to be used is what I've just said: advocacy, communication, mobilization, sensitization and you don't limit it to just saying you've done it […]. It has to be continuous for a certain period of time"* – Policy maker 5, national malaria policy official, NG].

Another component of an implementation strategy would be information campaigns to inform the general population. Several tools to convey the message were proposed, including radio, television, billboards, and social media channels. Posters in pharmacies were suggested as another, more targeted, way to notify malaria patients. ["*The population must not be left behind, they are the target, they must be informed. They must be informed through the different channels: radio, TV, billboards"* – Supplier 20, private sector wholesaler, BF]. Involving religious organizations and community leaders was suggested to convey the message to hard-to-reach populations. Moreover, it was deemed important to adapt information campaigns in order to reach illiterate populations. Implementation strategies should aim for early stage sensitizing and informing the population about the appropriate use of TACTs.

5.3.4 Public sector distribution

Policy makers and suppliers in Nigeria and Burkina Faso did not predict significant challenges for integrating TACTs in public sector distribution chains. Adoption of TACTs by global and national policy-, and donor organizations was considered a decisive factor to the public sector

uptake of TACTs. ["*The commodities in the public sector is mainly determined by the support from donors. And the donors procure this drug and supply it to the country. So the focus will need to be paid towards the donor"* – Policy maker 2, national malaria policy official, NG]. Respondents acknowledged that a transition to TACTs would require adaptations in importing, procurement and distribution practices, which would be relatively straightforward because public sector forecasting and stock-taking procedures for antimalarial therapies have been well-established.

Respondents expressed that there are no financial incentives for public-sector actors to deviate from guidelines, in contrast to the private sector. Some respondents mentioned that introducing TACTs in the public sector may even be an effective strategy to promote TACTs uptake in the private sectors. [*"The acceptance in the public setting is what dictates the acceptance in the private"*– Supplier 14, public sector wholesaler, NG]. In Burkina Faso, several suppliers emphasized the role of the Centre d'Achat des M**é**dicaments Essentiels G**én**eriques (CAMEG) for public sector introduction of TACTs. The CAMEG is a public organization that dictates the public sector procurement and distribution of medicines in Burkina Faso. The CAMEG exclusively focuses on the deployment of generic therapies and therefore it was suggested that TACTs should be introduced under the conditions of generic drugs rather than as a branded proprietary drug. ["*The antimalarial drugs in the public sector are essentially generics, unlike the private sector where we have the specialized drugs"*– Supplier 12, public sector clinician, BF].

5.3.5 Private sector distribution

In comparison to the public sector equivalent, more challenges were anticipated for integrating TACTs in private sector distribution channels in Nigeria and Burkina Faso. Private sector stocking decisions are usually based on patient demand and profit motives rather than inclusion in treatment guidelines. ["*Firms go for customer satisfaction. They probe to see how the patient can be satisfied*" – Policy maker 6, regulatory official, BF]. Policy makers and suppliers stressed that, once introduced, TACTs will have to compete with alternative therapies in the private sector markets. They were skeptical whether mitigating the risk of resistance would be a sufficient reason for the private sector to engage in TACTs as long as further market regulation remains absent. ["*Why would a profit maker go and procure what is unlikely to sell?"* – Policy maker 2, national malaria policy official, NG]. Enhancing market regulation practices, financial rewards for prescribers, and artificial stimulation of demand were proposed as strategies to engage private sector actors into a transition to TACTs. An example of artificial demand stimulation would be subsidies in the early stages of deploying TACTs.

Policy makers and suppliers considered an instant transition to TACTs in the private sector unrealistic in terms of adapting importation, procurement and supply procedures. [*"We just need some time to sell off the old stock"* – Supplier 1, private sector wholesaler, BF]. Many wholesalers and retailers in Nigeria and Burkina Faso have invested in contracts with providers higher up in the supply chain. They advocated for a transition period in which TACTs are gradually implemented while ACTs are simultaneously phased out. This was considered a more viable

strategy because it would allow them to clear their existing stocks and pending orders. Since most antimalarial drugs have a shelf-life of three years, a three-year period was proposed as an appropriate transition period by one supplier. Other suppliers disagreed with the necessity of a transition period stating that people will not be interested in TACTs as long as ACTs are still available on the market and therefore they preferred a direct removal of ACTs. [*"If the other one stays, there is a chance that there will be resistance. In order to protect the TACTs, the ACTs must first be removed."* – Supplier 13, private sector clinician, BF].

5.3.6 Retail and prescription

Several respondents anticipated challenges in engaging retailers and prescribers as long as TACTs are not clinically superior to ACTs and as long as alternative antimalarials remain available on the market. Some suppliers expressed that retailers and prescribers had been overlooked in the transition from monotherapies to ACTs and this had contributed to limited compliance at the time. The continuing availability of chloroquine in both countries was given as an example of the ongoing challenges.

Several policy makers and suppliers mentioned that retailers and prescribers are not always aware of the risks and implications of drug resistance, which could affect negatively their preparedness to switch to TACTs. Hence, training programs were considered essential in the early stages of deploying TACTs. These training programs should be clear and transparent about the risks of resistance and the potential benefits of TACTs. ["*Prescribers must be trained and informed about the added value and the reasons for the change*" – Supplier 6, public sector wholesaler, BF]. Conferences and educational programs were also considered suitable platforms to inform and engage prescribers and retailers. Positive experiences from other settings such as Southeast Asia could be a boost to the perceived credibility of TACTs. It was also suggested that prescribers and retailers should be given elaborate information about dosing and side-effects of TACTs, because they are responsible for further dissemination of such information to patients and caregivers. Some suppliers and end-users were concerned that private sector retailers will adjust their prices once demand for TACTs would increase.

5.3.7 Affordability

Cost-issues were considered important for a successful transition to TACTs by all respondent groups in Nigeria and Burkina Faso. *["If you come with prices like 15000 f a box, people will leave you and your drug"* - Policy maker 1, principal malaria researcher, BF]. Several policy makers and suppliers argued that TACTs should be introduced for subsidized prices because production prices would probably be too high for many patients. Subsidies were also considered a requirement to effectively compete with ACTs and chloroquine. One policy maker stated that, once affordability for TACTs is ensured, all other acceptance issues will follow. Others argued that price is not the most important determinant for effective medication of a life-threatening disease. ["*If the drug is really effective according to them, if it is really effective, whatever the price, they pay to be liberated. Health is priceless*" – Policy maker 8, regional malaria policy official, BF].

Respondents agreed that prices of TACTs should not exceed those of present ACTs, indicating patients will tend to go for the cheapest option. ["*If the price is slightly ahead of the current ACT, sir, it is dead on arrival* – Policy maker 10, regional malaria policy official, NG"]. One supplier contrasted this view, claiming that low prices of TACTs may be perceived as an indicator of limited quality and may therefore foster distrust. End-users did not consider costs as the main determinant for their willingness to adopt TACTs, and are prepared to pay more if the drug has a reputation of high efficacy and limited side-effects. [*"Money is not the most important thing because what we are really interested in is the well-being of our children and ourselves"* – End-user FGD 2, community member, NG].

5.3.8 Acceptance

In addition to clinical efficacy and affordability, all respondent groups highlighted that side-effects can be a potential barrier to TACTs uptake. In particular nausea and vomiting were mentioned as undesirable side-effects that could negatively affect acceptability. These side-effects are especially associated with amodiaquine and therefore some suppliers voiced their preferences for TACTs without this drug compound. ["*I take an example: artesunate-amodiaquine, these are combination therapies that were used at one time but very quickly it was realized that people were not tolerating the side effects and then we switched to artemether-lumefantrine*" – Supplier 7, public sector wholesaler BF]. Other suppliers and most end-users claimed that side effects are an integral aspect of antimalarial therapies. Mild nausea would not prevent end-users from engaging in TACTs and they argued that medication exists for mitigating most side-effects. Respondents emphasized that side-effects are acceptable as long as TACTs are effective and affordable. ["*If I am going to be taking that, it is my own best interest. When it works fast then there is no problem about that at all"* – End-user FGD 1, community member, NG].

Other acceptance issues raised were: tablet size and shape, taste, and the number of pills. For all these acceptance issues, the current ACT treatment regime was given as a benchmark: new drugs should not be more expensive, should not cause more side-effects, should not contain more pills and should not have a more bitter taste than ACTs. ["*As far as taste is concerned, it shouldn't be too bitter and the size should be the same as what it is present.*" – End-user FGD 2, community member BF]. Finally, respondents suggested that branding and attractive packaging could positively affect community attitudes towards TACTs.

5.4 Discussion and conclusion

The goal of the study was to explore market readiness for a transition to TACTs in African countries by exploring stakeholders' perceptions. A qualitative study was conducted in Nigeria and Burkina Faso and comprised in-depth interviews and FGDs with key actor groups at different levels of the antimalarial innovation system. A number of barriers and enablers towards deploying TACTs emerged from the data. The study revealed that the market prospects

of TACTs in Nigeria and Burkina Faso will depend on the demonstration of the added value of TACT over ACTs. National decision makers are unlikely to initiate a transition to TACTs in order to mitigate the risk of drug resistance. Instead, they will await endorsement by global institutes, in particular the World Health Organization (WHO), and funding decisions by international donors such as the Global Fund to fight Aids, Tuberculosis and Malaria (GFATM). This implies that these global-level institutes have a major responsibility in navigating the global fight against drug-resistant malaria. They should consider proactive changes to treatment policies to prevent similar delays in global coordination as those encountered during the transition to ACTs in the early 2000s (Attaran et al., 2004). This is all the more relevant now that genetic markers of artemisinin resistance have been observed in Rwanda, Uganda and Tanzania (Asua et al., 2021; Bergmann et al., 2021; Bwire et al., 2020; Kayiba et al., 2021; Uwimana et al., 2021, 2020) while inadequate efficacy of artemether-lumefantrine, the most commonly used antimalarial in Africa and elsewhere, was recently reported in Angola and Burkina Faso (Dimbu et al., 2021; Gansané et al., 2021; Rasmussen and Ringwald, 2021). These findings imply an urgent need to identify and develop alternative treatment options.

At the national levels, several barriers were raised that would affect the market prospects for TACTs in Nigeria and Burkina Faso. Respondents referred to lengthy regulatory and implementation procedures (Amin et al., 2007; Bosman and Mendis, 2007; Williams et al., 2004) and the ongoing challenges with regards to the private sector markets for antimalarial therapies (Newton et al., 2017; Palafox et al., 2016; Tougher et al., 2017). In particular the persistent demand for chloroquine and over the counter prescription of antimalarial therapies were repeatedly mentioned. The limited (private sector) compliance to first-line therapies and the widespread availability of substandard, outdated or even counterfeit drugs has been reported in several African settings by the ACTwatch group (Newton et al., 2017; O'Connell et al., 2011; Palafox et al., 2014a; Shewchuk et al., 2011). In this context of suboptimal treatment practices, it is warranted to question whether scarce resources should be dedicated to a transition to TACTs (van der Pluijm et al., 2021; White, 2019) or rather be invested in improving current malaria management practices (Krishna, 2019; Wang et al., 2020). From a health-economic perspective, investing in mitigating the risk of resistance seems justified, as the costs of a drug transition is unlikely to exceed the costs that would be provoked by artemisinin and partner drug resistance (Arrow et al., 2004; Lubell et al., 2014; Mulligan et al., 2006). Further mathematical modeling and feasibility studies are required to determine if TACTs in Africa are indeed the optimal way forward to address the threat of artemisinin and partner drug resistance.

Relatively few challenges towards implementing TACTs in public sector distribution channels were identified, under the assumption of support by policy makers and donor funders. This aligns with other studies that have demonstrated that public distribution channels are relatively adaptive for new generations of antimalarial therapies (Novotny et al., 2016; O'Connell et al., 2011). More challenges were expected for engaging private sector stakeholders in a transition to TACTs. In these private sector channels, TACTs will have to compete with alternative treatments on the market and switching to TACTs can be perceived as misaligned with profit motives of

distributors, retailers and prescribers. Similar private sector challenges have previously been reported for innovative therapies for malaria (Littrell et al., 2011) and other poverty-related diseases (Sheikh and Uplekar, 2016; Sullivan and Ben Amor, 2016; Sunyoto et al., 2019) under the pressure of drug resistance. Proposed solutions from the literature include intensified market regulation (Novotny et al., 2016; Sheikh and Uplekar, 2016) and increased investments in private sector subsidy arrangements (Arrow et al., 2004; Palafox et al., 2016; Tougher et al., 2017).

Several affordability and acceptance issues for TACTs were raised, for which current ACTs were suggested as a benchmark. Respondents advised that TACTs should not be more expensive, cause more side-effects, contain more pills and have a more bitter taste than ACTs. Furthermore, information campaigns should be transparent on the motives and the rationale of a prospective switch to TACTs. In previous studies, adoption decisions by malaria patients have been associated mostly with the availability of a particular therapy (Ajayi et al., 2008b; Alba et al., 2010). Our study adds to the limited knowledge on factors that affect the actual acceptance of innovative antimalarial therapies (Smith et al., 2009).

The innovation systems approach was applied to study the feasibility of a transition to TACTs in Nigeria and Burkina Faso. This approach has become a well-established analytical tool in transition studies for generating insight into innovation barriers and defining policy implications accordingly (Hekkert et al., 2007). Similar systemic perspectives have increasingly been applied in addressing (global) health challenges and have been valued for their integral perspective and their explanatory power (Adam and De Savigny, 2012; Atun, 2012; Moors et al., 2018; Peters, 2014). The innovation systems approach has particularly been applied for understanding sustainability transitions where complex trade-offs need to be made between short-term investment and long-term benefits. This is exactly the case for TACTs in Africa, where investments (national governments, individual patients) and benefits (entire malaria world, future patients) are not well-aligned (Tindana et al., 2021a). The systemic approach demonstrated a complex set of links, relations and interdependencies between actors, networks and institutions. For example, engagement by global and national decision makers is required for a transition to TACTs but it is not sufficient if prescribers and patients reject the use of TACTs. Similarly, positive attitudes from end-users will not be relevant unless well-functioning distribution channels are established.

The innovation systems approach indicates that a transition to TACTs would demand collective actions at all levels of the antimalarial innovation system (e.g. at the level of development, diffusion and actual deployment) (de Haan et al., 2021b). Moreover, the introduction of TACTs would require alignment with the financial, regulatory and other institutional frameworks that are prevalent for innovative antimalarial therapies. Addressing these multi-faceted issues is complex and requires strong policy coordination and systemic tools and roadmaps (Boon et al., 2020; Hekkert et al., 2011; Loorbach et al., 2017; Moors et al., 2014).

5.5 Way forward

We presented a pilot study to assess the feasibility of a transition to TACTs in two African countries. Several barriers and enablers towards deploying TACTs were found in Nigeria and Burkina Faso, which can be used to inform strategic decision-making in the battle against drug resistant malaria. Although some of these insights may be applicable to other settings, the generalizability of this study is limited. African countries are heterogeneous in nature and they are characterized by different healthcare systems. Therefore, similar bottom-up studies on the feasibility of deploying TACTs are required in other African settings. Such studies should be prioritized in countries reporting artemisinin resistance or ACT failure and countries with increased risk of resistance due to their geographic location or epidemiological situation. Moreover, the situation of drug resistance is evolving and ACT failure was not yet confirmed in Africa by the time of data collection. The recent increased reporting of artemisinin resistance and ACT failure in Africa might change important determinants of the market readiness for TACTs.

Although this study focused on country-level dynamics, the actual prospects of deploying TACTs are to a large extent determined by global decision makers such as the WHO, international funders like GFATM and support from the Medicines for Malaria Venture (MMV) in coordinating drug development. In addition, the pharmaceutical industry plays a central role, and will be required to translate the concept of TACTs into end-products and to ensure its production in sufficient quantities. Encouraging are the successes that have been achieved in the past: a supportive global landscape for the development and deployment of new antimalarial therapies is now well-established (de Haan et al., 2021b). We can draw from these experiences in terms of product-development partnerships, funding mechanisms, regulatory arrangements and intellectual property management. This will, however, require early sensitizing and engagement with global-level policy makers, pharmaceutical industry, and other stakeholders.

Finally, although the study provides insight into factors that are likely to affect the introduction of TACTs in two African countries, it does not provide final answers on whether TACTs should be introduced in Africa. A further rapid increase in artemisinin resistance in African countries would change many of the scenarios described in this study, and would render TACTs one of the last remaining treatment options for multidrug resistant falciparum malaria. Also, further clinical, health-economic and feasibility studies are required to build an evidence base to inform decision makers on the implications of deploying TACTs to delay or prevent artemisinin resistance and/or ACT failure. Such studies are now underway within the Development of Triple Artemisinin Combination Therapies (DeTACT) project (van der Pluijm et al., 2021) which combines clinical, mathematical modeling, ethical and market positioning research.

PART 3

The introduction of TACTs in Southeast Asia

Chapter 6

Expert perspectives on the introduction of Triple Artemisinin-based Combination Therapies (TACTs) in Southeast Asia: a Delphi study

de Haan, F., Boon, W.P.C., Amaratunga, C. Dondorp, A.M.,. Expert perspectives on the introduction of Triple Artemisinin-based Combination Therapies (TACTs) in Southeast Asia: a Delphi study. BMC Public Health 22, 864 (2022). https://doi.org/10.1186/s12889-022-13212-x

6.1 Introduction

The emergence and rapid spread of antimalarial drug resistance has repeatedly forced malaria endemic countries to adapt their first-line treatment practices for falciparum malaria. These drug transitions have been characterized as slow and challenging, even when new therapies were clinically superior to failing alternatives (Arrow et al., 2004; Bosman and Mendis, 2007; O'Connell et al., 2011; Williams et al., 2004). Challenges have been associated with the complex nature of the global health arena and the collective efforts that are required at the global, national, and local-levels (de Haan et al., 2021b).

At present, the malaria endemic world relies on artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated falciparum malaria (WHO, 2021a). ACT combines a highly potent, rapidly cleared artemisinin derivative and a less potent, slowly cleared partner drug such as lumefantrine, amodiaquine, piperaquine, pyronaridine or mefloquine. A worrying recent development is multidrug resistance that has emerged to these artemisinin and partner drug combinations and is now spreading through large regions of Southeast Asia (Imwong et al., 2021; Phyo et al., 2016; van der Pluijm et al., 2019). In response, policy makers in Cambodia, the country with the highest burden of multidrug-resistant malaria, opt to switch between ACTs when treatment failure is observed (Menard and Dondorp, 2017; Novotny et al., 2016). Unfortunately, this strategy of rotating ACTs has proven to be operationally difficult and will likely offer only a temporary remedy before the efficacy of new ACTs also starts to decline (Dondorp et al., 2017).

Solutions are required to ensure the continued deployment of effective antimalarial drugs in Southeast Asia and to delay the spread of antimalarial drug resistance to other regions and continents. One promising approach is to complement current ACTs with a third widely used antimalarial drug, creating triple artemisinin-based combination therapies (TACTs) (van der Pluijm et al., 2021). The rationale is that combining the artemisinin derivative with two partner drugs with counteracting resistance mechanisms will extend the therapeutic lifetime of the drug combinations, because the two partner drugs will provide mutual protection against the development of resistance. Although previous efficacy studies have shown promising results (van der Pluijm et al., 2020), there has been no consensus established yet on the desirability, timing and the practical feasibility of introducing TACTs (Krishna, 2019; van der Pluijm et al., 2021; Wang et al., 2020; White, 2019). Little structured data is available on the advantages, disadvantages and implementation challenges for introducing TACTs compared to alternative strategies to address drug-resistant malaria. This study aims to obtain prevailing insights on this important topic. A Delphi study is conducted to map systematically expert perspectives towards the introduction of TACTs compared to applying current strategies of rotating ACTs when treatment failure is observed in Southeast Asia.

6.2 Methods

6.2.1 Research design

The Delphi technique is a forecasting method that enables exploring implications of multifaceted technological and practical problems (Georghiou et al., 2008; Hasson et al., 2000). It was developed in the 1950s as a tool for decision-making in situations of insufficient or contradictory information. Delphi studies are iterative in nature and generally comprise two or more rounds of questionnaires with controlled group feedback between each round. In the first round, an expert panel is created and asked to answer open-ended questions regarding an uncertain future. The expert responses are then collected, structured and categorized by the researchers before they are provided back to the same panel. In the second round, the expert panel is asked to rank or rate the inputs of the first round in order to quantify the strength of each statement. More rounds can optionally be included to further validate the findings and to seek expert consensus (Hsu and Sandford, 2007). The Delphi technique can be modified to meet research goals as long as it includes iterative rounds of data collection with controlled feedback between each round (Nowack et al., 2011; Shawahna, 2021). Delphi studies are generally conducted through online surveys which enables the recruitment of geographically dispersed experts (Shawahna, 2017).

The Delphi technique facilitates structured communication between experts and allows the inclusion of deviant and minority insights into the collaborative thinking process (Georghiou et al., 2008). Anonymity is an essential feature to avoid conformity and social pressure (Jünger et al., 2017). The Delphi technique has become a well-established tool in (global) health research (Graham-Clarke et al., 2021; Harinarain and Haupt, 2014; Hasson et al., 2000; Li et al., 2014; Tomashek et al., 2018). Mulligan et al. (2016) demonstrated that it is a useful tool for gathering views on research priorities and impact valuations in global health research. The Delphi technique has also proven valuable for assessing decision and economic models in global health (Lubell et al., 2011) and for understanding the dynamics behind the R&D deficit for neglected diseases (Fehr et al., 2011). This paper uses the Delphi technique to systematically assess perspectives of malaria experts towards the introduction of TACTs in Southeast Asia.

6.2.2 Expert panelists

Antimalarial drug transitions are complex and multifaceted, involving a wide range of global, national and local-level stakeholders (de Haan et al., 2021b). This multifaceted nature was reflected by purposively selecting experts with different affiliations (e.g. academia, industry, non-governmental organizations, regulators, policy institutes), areas of expertise (e.g. health economics, regulation, market access, malaria drug resistance research), and geographical coverage. An initial list of experts with a track record of relevant expertise was made based on job profiles and published work. This list was then extended by contacting malaria researchers and policy makers in Southeast Asia and asking them to propose additional candidates. The

expert list was reviewed by an independent panel and adjustments were made based on their comments. The final list of panelists comprised 146 experts with a balanced representation of affiliations and expertise areas and included experts at multiple geographic locations.

6.2.3 Software, data security and ethical approval

The *Mesydel* software (https://mesydel.com/en) was used to setup the questionnaires (Jaenisch et al., 2018; Tomashek et al., 2018), which ensured the essential elements of anonymity, iteration and controlled feedback (Nowack et al., 2011). The expert panel was approached and invited via automated email to participate in the Delphi exercise. The email included an invitation letter that briefly explained the study objectives and statements on data security and consent. Furthermore, each expert received a unique link to a secured personal survey environment. This was done to grant anonymity and enabled follow-up of non-respondents. Ethical approval for the study was obtained from the Oxford Tropical Research Ethics Committee (OxTREC), reference number: 540-21.

6.2.4 Delphi procedure, data collection and data analysis

A summary of the Delphi procedure is provided in Figure 1. The first- and second-round questionnaires were developed by the research team and piloted with independent test panels before sending out to the expert panel. The experts were approached via email and reminder emails were sent out at regular intervals to maximize response rates. The questionnaires included sections with demographic questions to gather data on the participants' background.

First round*:* The first-round questionnaire comprised three sections with open-ended questions. In the first and second section, the expert panel was asked to share what they considered the most important *advantages* and the most important *disadvantages* of introducing TACTs as first-line treatment for uncomplicated falciparum malaria, over current practices of rotating ACTs when treatment failure is observed. In the third section, the expert panel was asked what they considered the most important *implementation barriers* for the introduction of TACTs in Southeast Asia.

The open-ended responses were reviewed using inductive qualitative methods. All statements were de-identified and coded, grouped and categorized by two researchers (FH and CA), first independently and after comparison differences in interpretation were discussed in multiple rounds. After removing duplicates and multiple rounds of analysis and discussion, this resulted in collated lists of 15 advantages, 15 disadvantages and 13 implementation barriers that would serve as input statements for the second round.

Second round*:* The second-round questionnaire was sent to all experts who had responded in the first round. These experts received the collated lists with items and they were asked to rate the *relevance* of each statement on a 5-point Likert scale ranging from 'highly relevant' to 'not relevant'. The following definition for relevance was provided to the experts: 'Relevance is defined

as the expert's agreement (or disagreement) with the importance of the statement and the extent to which the statement is applicable to TACTs being used in the near future as a replacement to the strategy of rotating ACTs when treatment failure is observed in Southeast Asia'.

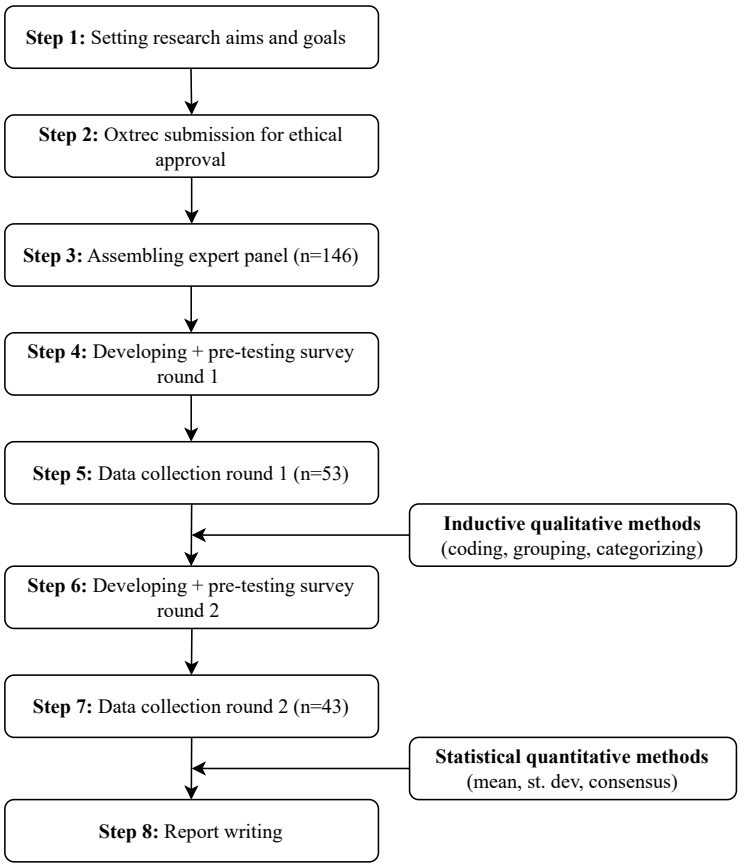

FIGURE 6.1 | The eight research steps of the two-round Delphi study.

Data analysis of the second round involved statistical methods and data visualization techniques performed in Microsoft Excel. We assigned corresponding numbers to each Likert-scale (Highly relevant = 5; Relevant = 4; Somewhat relevant = 3; Slightly relevant = 2; Not relevant = 1) in order to calculate the mean scores and the standard deviation of the expert judgements on each statement. Consensus thresholds were pre-determined at 70%: consensus was reached if 70% of participating experts rated a statement as either 'highly relevant", relevant', or 'somewhat relevant'. Similarly, if 70% of the experts rated the statement as 'somewhat relevant', 'slightly relevant' or 'not relevant' consensus was reached that the statement was not-relevant. The 70% cut-off point has proven to be a useful threshold for determining consensus in several Delphi studies using Likert scales (Graham-Clarke et al., 2021; Li et al., 2014; Veugelers et al., 2020).

6.3 Results

First-round data were collected in August and September 2021 and second-round data were collected in October and November 2021. The two rounds directly followed each other in order to keep experts engaged and to maximize response rates. Of the invited 146 experts, 53 completed the first round (36% response rate) and 43 completed the second round (81% response rate). The demographic data of the participating experts is provided in Table 1.

TABLE 6.1 | Demographic data of expert panelists in the first and second round.

		Round 1		Round 2	
		n	%	n	%
Gender	Male	36	68%	31	72%
	Female	17	32%	12	28%
Years of relevant work experience	5-10 years	4	8%	4	9%
	>10 - 20 years	16	30%	12	28%
	> 20 years	33	62%	27	63%
Affiliation*	Academic institution	22	42%	18	42%
	Research institution	10	19%	9	21%
	Government agency	6	11%	6	14%
	Non-governmental organization	12	23%	11	26%
	Donor agency	5	9%	3	7%
	UN Agency	4	8%	4	9%
	Private sector	3	6%	2	5%
	Other	4	8%	4	9%
Area of work*	Health economics	3	6%	3	7%
	Regulation	3	6%	2	5%
	Market access	4	8%	3	7%
	Malaria treatment	33	62%	30	70%
	Drug development	10	19%	8	19%
	Supply chains	4	8%	3	7%
	Drug resistance research	24	45%	20	47%
	Policy making	12	23%	9	21%
	Other	7	13%	4	9%
Affiliated to the DeTACT project**	No	42	79%	32	74%
	Yes	11	21%	11	26%
Country of residence***	Australia	3	6%	2	5%
	Bangladesh	1	2%	1	2%
	Belgium	1	2%	1	2%
	Brazil	1	2%	-	-
	Cambodia	4	8%	4	9%
	China	2	4%	2	5%
	France	1	2%	1	2%
	Germany	1	2%	1	2%
	Indonesia	3	6%	2	5%
	Kenya	1	2%	1	2%
	Lao PDR	2	4%	2	5%
	Myanmar	5	9%	4	9%
	Nigeria	1	2%	1	2%

		Round 1		Round 2	
		n	%	n	%
	Philippines	1	2%	-	-
	Portugal	1	2%	1	2%
	Switzerland	5	9%	5	12%
	Thailand	10	19%	8	19%
	UK	1	2%	1	2%
	USA	8	15%	5	12%
	Vietnam	1	2%	1	2%

* Experts could select more than one option for 'Affiliations' and 'Area of work'

** Development of Triple Artemisinin-based Combination Therapies (DeTACT) project

*** Some experts do not reside in Southeast Asia yet are involved in malaria treatment practices in the region through international organizations

6.3.1 First-round results

In the first round of data collection, the participating malaria experts identified a total of 166 advantages, 160 disadvantages and 177 implementation challenges. After grouping, coding and removing duplicates, collated lists of 15 advantages, 15 disadvantages and 13 implementation barriers emerged. The collated lists are provided in Tables 2, 3 and 4, and include brief explanations for each statement and the number of times that each statement was mentioned by individual experts in the first round. These advantages, disadvantages and implementation barriers and the associated brief explanations would serve as input statements for the second-round data collection.

TABLE 6.2 | Expert perspectives on the *advantages* of introducing TACTs over current practices of rotating ACTs when treatment failure is observed in Southeast Asia.

Advantages	Explanation	n
Protecting antimalarial drug compounds	TACTs could protect antimalarial drug compounds by preventing parasites from becoming resistant or attaining higher levels of resistance.	35
Improving efficacy	TACTs could provide improved antimalarial efficacy and avoid treatment failure.	34
Delaying spread of drug resistance	TACTs could prevent or delay the spread of multidrug resistance both locally and to other regions and continents.	22
Less frequent policy shifts	TACTs could require less frequent policy shifts and regulatory procedures, which are both time and resource intensive.	17
Consistent communication messages	TACTs could allow consistent communication to health workers and patients in terms of work instructions, training and information dissemination.	16
Less logistic disruption	TACTs could result in less frequent logistical and operational disruptions in terms of planning, procurement, import, storage and distribution.	15
Accelerating malaria elimination	TACTs could accelerate malaria elimination strategies in Southeast Asia.	11
Patient/prescriber preference	TACTs' three-drug compound regimen could be preferred by health workers and patients over the two-drug compound ACT regimen.	3
Reducing pressure on surveillance systems	TACTs could mitigate the pressure of monitoring resistance and drug efficacy levels in areas of resistance.	3

Advantages	Explanation	n
Reducing malaria transmission	TACTs could contribute to overall reductions in malaria transmission and infections.	3
Scaling up production/cost reduction	TACTs could be profitable for pharmaceutical companies by enabling the scale-up of antimalarial drug production and associated cost reductions.	2
Regional solution	TACTs could provide a regional solution instead of a solution that needs to be tailored to individual countries.	2
Effectivity on vivax malaria	TACTs could contribute in the battle against vivax and other types of malaria and could provide more time to focus on these other types of malaria.	1
Prophylactic effect	TACTs could have a malaria prophylactic effect.	1
Reduced pill intake	TACTs could reduce the number of pills and/or the days of treatment compared to current ACTs.	1

TABLE 6.3 | Expert perspectives on the *disadvantages* of introducing TACTs over current practices of rotating ACTs when treatment failure is observed in Southeast Asia.

Disadvantages	Explanation	n
More expensive	TACTs could be more expensive than current ACTs.	36
Additional side effects	TACTs could cause additional side-effects such as vomiting, fatigue and headache.	25
Unavailability of FDC TACTs	TACTs are not yet available in fixed-dose combinations (FDCs) and FDC product-development timelines could be long.	17
Losing drug compounds	TACTs could jeopardize the efficacy of current drug compounds and increase the speed of resistance spreading.	14
Toxicity/safety risks	TACTs could increase safety risks, (cardio)toxic effects and negative drug-drug interactions.	14
Increasing pill burden	TACTs could have an increased pill burden which may increase the risk of non-compliance.	13
Implementation time and costs	TACTs rollout and implementation could be time and resource intensive.	11
Limited evidence available	TACTs' safety and efficacy are not yet scientifically proven.	11
Small market size	TACTs could be considered unattractive for pharmaceutical companies because of the limited market size for antimalarials in Southeast Asia.	6
Limited timeframe for use	TACTs timeframe for use could be too narrow to warrant the investments in the context of increasing drug resistance and receding falciparum malaria.	5
Pharmacovigilance requirements	TACTs implementation could require increased investments in pharmacovigilance systems.	3
Reducing sense of urgency	TACTs deployment could reduce the sense of urgency in discovering new drug compounds.	2
Limited efficacy	TACTs could have limited clinical response when the individual drug compounds are already failing.	1
Limiting credibility of ACTs	TACTs deployment in Southeast Asia could reduce the perceived credibility of ACTs elsewhere.	1
Multiple TACTs required	TACTs could not be a 'one size fits all' solution, instead multiple TACTs are required because of a variety in drug resistance profiles.	1

TABLE 6.4 | Expert perspectives on the *implementation barriers* for introducing of TACTs in Southeast Asia.

Implementation barriers	Explanation	n
Intensified prescriber training	Intensifying training requirements for correct TACTs prescription.	27

Donor funder support	Obtaining support by donor funders to cover TACTs implementation costs and potential price increases.	24
National policy support	Obtaining support from national malaria control programs and other national decision makers.	24
WHO and global policy support	Obtaining support from the WHO and other global decision makers.	19
Availability of fixed-dose combination (FDC) TACTs	Ensuring timely development and production of fixed-dose combination (FDC) for TACTs.	17
Community acceptance	Ensuring community acceptance by providing clear communication and tackling potential misconceptions about TACTs.	12
Collecting safety and efficacy data	Collecting sufficient efficacy and safety data to support the introduction of TACTs.	11
Supply chain logistics	Adapting import, procurement and supply routes for the introduction of TACTs.	11
Regulatory approval	Obtaining timely regulatory approval for introducing TACTs in Southeast Asia.	11
Set up surveillance systems	Setting up surveillance systems to monitor drug resistance and adherence to TACTs.	9
Private sector engagement	Engaging the (informal) private sector in TACTs deployment and creating demand beyond official programs.	5
Set up pharmacovigilance systems	Setting up a pharmacovigilance system for TACTs.	4
Stockpile management	Managing stockpiles for countries that still have ACT stocks or contract deals with ACT producers.	3

6.3.2 Second-round results

Of the 53 experts that had completed the first round of data collection, 43 participated in the second round. Experts reached consensus on 13 advantages, 12 disadvantages and all 13 implementation barriers according to the consensus criteria. On average, the highest scores of experts' ratings on the 5-point Likert scales were attributed to the implementation barriers (mean score: 4.06) while the average scores of the advantages (mean score: 3.31) and the disadvantages (mean score: 3.30) were nearly identical. Figures 2, 3 and 4 provide the results of the second round of data collection.

Advantages of introducing TACTs

The expert panel reached consensus on thirteen advantages for introducing TACTs in Southeast Asia: eight statement were considered to be relevant and five were considered to be not-relevant (Figure 6.2). The panel did not reach consensus on two statements. Of the *relevant* statements, the expert panel attributed the highest scores to TACTs' potential to protect antimalarial drug compounds (mean score: 4.51), its ability to improve efficacy and avoid future treatment failures (mean score: 4.30), and the capacity of TACTs to mitigate the spread of resistance (mean score: 4.28). The same advantages were also mentioned most frequently in the first round, suggesting that the expert panel was consistent in acknowledging TACTs' potential to overcome the major clinical and epidemiological risks of artemisinin and partner drug resistance.

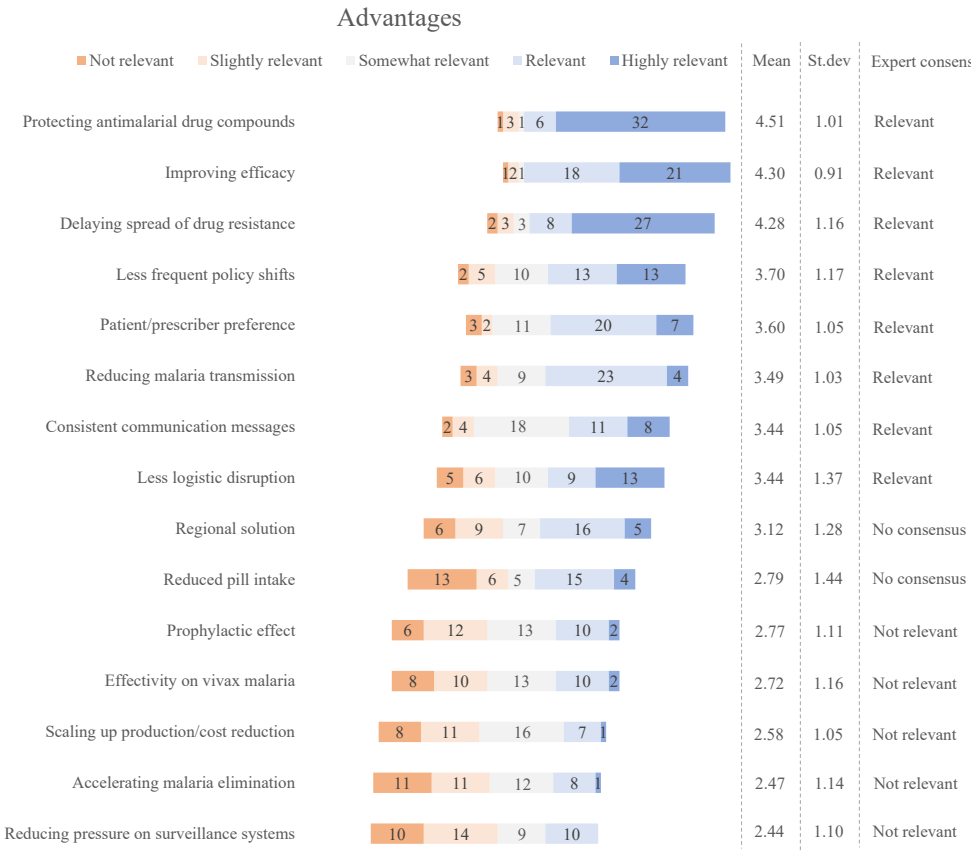

FIGURE 6.2 | Expert valuations of the advantages for introducing TACTs compared to rotating ACTs. For each item, the mean score, the standard deviation, and the degree of expert consensus are included in the figure. The lists are ranked according to the mean scores of each statement.

The expert panel also reached consensus on the relevance of TACTs' ability to reduce the frequency of policy shifts (mean score: 3.70) and its alignment with patient and prescriber preferences (mean score: 3.60). Of notice, the latter was only mentioned three times as open-text suggestion in the first round and thus represents a minority perspective that gained relevance in the second round. The panel furthermore agreed on TACTs' potential to reduce malaria transmission and infections (mean score: 3.49), its ability to enable consistent communication messages to prescribers and patients (mean score: 3.44), and the reduced frequency of logistical and operational disruptions that could be instigated by introducing TACTs (mean score: 3.44). The consensus that was achieved on the relevance of these statements indicates that the malaria experts recognize the advantages of introducing TACTs in terms of operational benefits and cost reductions.

Consensus was, however, not reached on the suggested advantages that TACTs could provide a regional solution for the whole of Southeast Asia (mean score: 3.12) and that introducing TACTs may result in a reduced pill intake (mean score: 2.79). The expert disagreement on the relevance of these statements suggest that they consider them as being controversial.

Five statements reached consensus as being *not-relevant*. Unsurprisingly, all five had only been mentioned few times as free-text suggestions in the first round: one expert had cited a prophylactic effect as an expected advantage of introducing TACTs (mean score: 2.77), and one panelist had suggested that TACTs might have advantageous efficacy in vivax malaria (mean score 2.72). The relevance of these statements was rated low, which indicates that the panel either disagrees with their accuracy, or that the panel considered them as only minor advantages. The expert panel rated lowest the advantage of TACTs enabling manufacturers to become profitable by scaling-up production (mean score: 2.58), TACTs' ability to contribute to accelerated malaria elimination (mean score: 2.47) and the potential of TACTs to mitigate the pressure on surveillance systems in areas of resistance (mean score: 2.44).

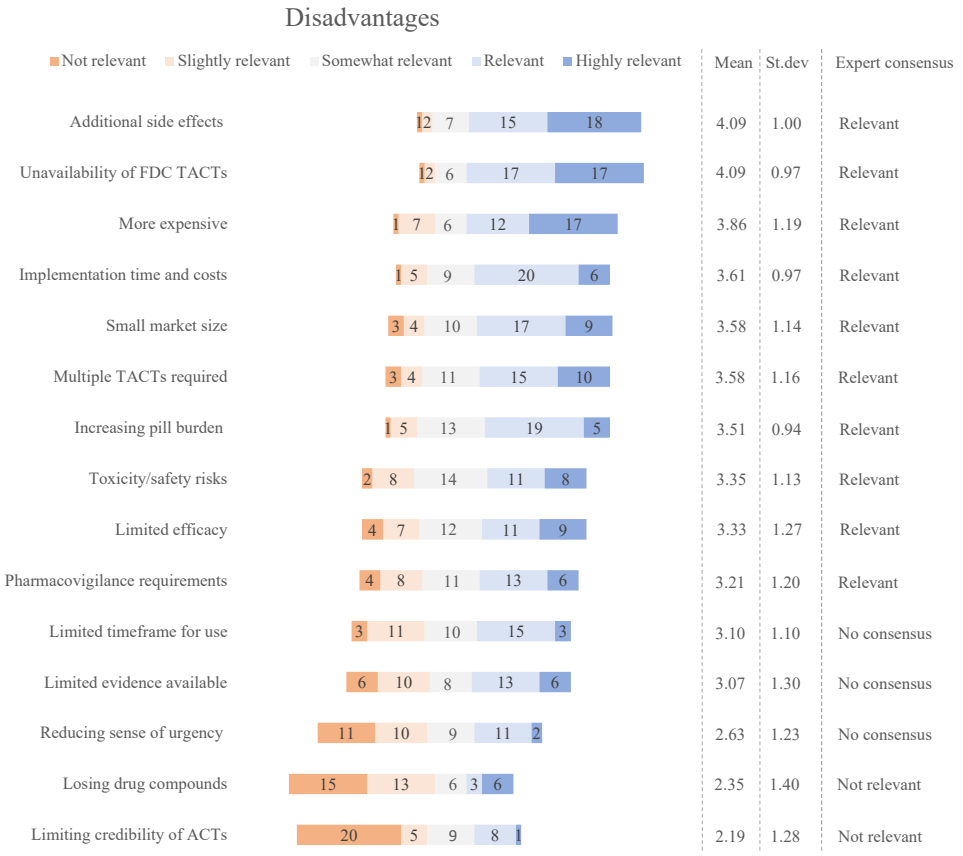

FIGURE 6.3: Expert valuations of the disadvantages of introducing TACTs compared to rotating ACTs. For each item, the mean score, the standard deviation, and the degree of expert consensus are included in the figure. The lists are ranked according to the mean scores of each statement.

Disadvantages of introducing TACTs

The expert panel reached consensus on twelve disadvantages for introducing TACTs in Southeast Asia: ten disadvantages were considered to be relevant and two were considered to be not-relevant (Figure 6.3). Panelists did not reach consensus on three disadvantages. Of the relevant disadvantages, the expert panel rated additional side-effects for TACTs compared to current ACTs (mean score: 4.09) as highest, emphasizing the importance of such potential adverse effects. High relevance was also attributed to the current unavailability of fixed-dose combinations of TACTs (mean score: 4.09) and concerns of TACTs becoming more expensive than current ACTs (mean score: 3.86). Those items were also among the top three most mentioned disadvantages in the first round, indicating that experts were consistent with their judgement on the relevance of these statements.

Consensus was furthermore reached on disadvantages related to implementation costs and timelines for TACTs (mean score: 3.61), the small market size that could deter drug manufacturers (mean score: 3.58) and concerns that multiple TACTs would be required to address different drug resistance profiles (mean score: 3.58). The latter was only mentioned once as open-text suggestion in the first-round, and thus significantly gained relevance in the second round. The expert panel furthermore agreed on disadvantages related to an increased pill burden for TACTs (mean score: 3.51), and concerns about toxicity and safety risks (mean score: 3.35). Finally, the limited efficacy of TACTs in situations where ACTs are already failing (mean score: 3.33) and the increased pharmacovigilance requirements for TACTs (mean score: 3.21) reached expert consensus as being relevant, despite only being mentioned few times in the first round of data collection.

The expert panel did not reach consensus on four disadvantages that were identified in the first round. They were inconclusive about TACTs' limited timeframe for use in the context of increasing drug resistance (mean score: 3.10), the limited availability of efficacy and safety evidence (mean score: 3.07), and the reduced sense of urgency that might be instigated by introducing TACTs (mean score: 2.63). The panel reached consensus on two disadvantages as being not relevant. The statement that deploying TACTs could jeopardize the efficacy of current drug compounds (mean score: 3.65) was mentioned by 14 individual experts in the first round but its relevance was rejected in the second round. The expert panel also agreed that introducing TACTs could reduce the perceived credibility of ACTs (mean score: 2.19) was not-relevant; this statement was rated with the lowest mean score of all items.

Implementation barriers for TACTs

The expert panel reached consensus on all thirteen implementation barriers, suggesting less ambiguity as compared to the advantages and disadvantages (Figure 6.4). There were, however, some notable differences between expert judgements in the first and second round. The panel considered as most relevant implementation barriers: obtaining timely regulatory approval (mean score: 4.60) and ensuring timely availability of fixed-dose combination TACTs (mean score: 4.57). Remarkably, neither of those barriers were among the four most mentioned in the first round of data collection.

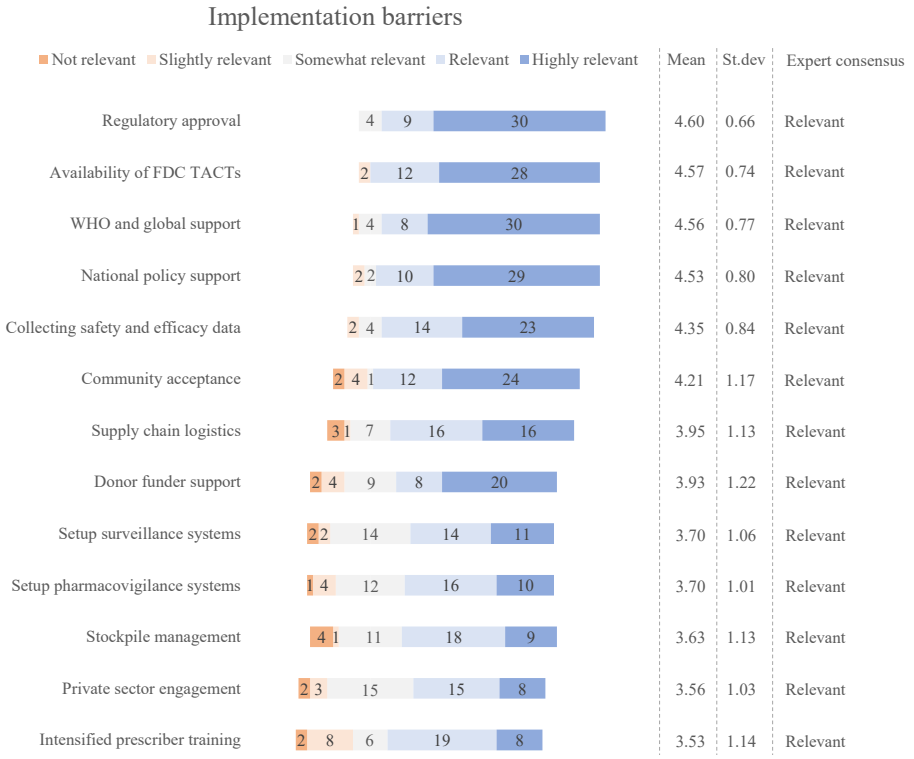

FIGURE 6.4: Expert valuations of the implementation barriers for TACTs. For each item, the mean score, the standard deviation, and the degree of expert consensus are included in the figure. The lists are ranked according to the mean scores of each statement.

Whereas global-level and national-level policy support were proposed equally often as implementation barriers in the first round, subtle differences emerged in their second-round ratings. The expert panel judged the challenges in generating support by the World Health Organization (WHO) and global decision makers (mean score: 4.56) as slightly more relevant than obtaining support at the national policy levels (mean score: 4.53). Similar high valuations were assigned to the challenges of collecting sufficient safety and efficacy data to support the introduction of TACTs (mean score: 4.35) and the prospective challenges in engaging the community by communicating in a clear way and tackling potential misconceptions about TACTs (mean score: 4.21).

Implementation challenges related to supply chain logistics (mean score: 3.95) and obtaining donor funder support (mean score: 3.93) were rated somewhat lower although the majority of the experts still considered them as relevant barriers. The relatively lower ranking of the latter is noteworthy as it was cited by 24 individual experts in the first round. The setup of surveillance systems to monitor drug resistance and adherence to TACTs (mean score: 3.70) and pharmacovigilance systems (mean score: 3.70) received equal mean scores and were rated slightly higher than challenges related to stockpile management (mean score: 3.63)

and engaging private sector actors in a transition to TACTs (mean score: 3.56). Surprisingly, the implementation barrier that was mentioned most often in the first round (27 times) was assigned the lowest relevance in the second round. Still, the relevance of intensified prescriber training (mean score: 3.53) reached expert consensus as being relevant.

6.4 Discussion

6.4.1 Advantages of introducing TACTs

The expert panel identified 15 advantages that can be grouped into three categories. The first category comprises advantages that are related to the clinical and epidemiological rationale of introducing TACTs in Southeast Asia. Our results indicate that malaria experts do acknowledge that the introduction of TACT is a valid approach to mitigate drug-resistant falciparum malaria, to protect current antimalarial drugs, and to reduce the risk of resistance spreading to other continents and regions. In support of these perspectives are recent studies showing the efficacy of TACTs to treat multidrug-resistant falciparum malaria (van der Pluijm et al., 2020) while further mathematical modelling studies are required to determine its potential in protecting drug compounds and mitigating the spread of resistance (Kunkel et al., 2021; Slater et al., 2017; van der Pluijm et al., 2021). Modeling studies could also inform about implications of introducing TACTs on transmission intensity and on achieving the malaria elimination ambitions in Southeast Asia (Kaehler et al., 2019), although the latter was considered to be a not-relevant item by malaria experts in the present study.

The second category of advantages comprises operational advantages and potential cost-reductions as a result of introducing TACTs. Most of the identified benefits in this category can be linked to the scientific rationale of introducing TACTs. For example, the reduced frequency of policy shifts would be a direct consequence of the prolonged therapeutic life time of the antimalarials (White, 2019), and the same applies to the benefit of less logistical disruption and consistency of marketing-, and communication messages (Novotny et al., 2016; Yeung et al., 2011). In the Delphi exercise, malaria experts acknowledged the relevance of these operational advantages in the context of introducing TACTs. Their perspectives align with literature on previous drug transitions, which have shown that policy shifts (Bosman and Mendis, 2007; Mulligan et al., 2006), logistical disruptions (Palafox et al., 2014) and community awareness (Amin et al., 2007; Simmalavong et al., 2017) require significant investments. Reducing the frequency of drug transitions can therefore mitigate the pressure on scarce financial resources in malaria endemic countries. The expert panel in the present study associated the prospective introduction of TACTs in Southeast Asia with these types of benefits.

The third category of advantages comprises indirect benefits of introducing TACTs. Most advantages in this category were considered to be controversial or their relevance was rejected by the malaria experts. No consensus was, for example, reached on the proposed advantage

of reducing the pill burden by introducing TACTs. Neither did the statement that a single TACT can be a regional-wide solution for resistance reach consensus. Indeed, these statements can be considered controversial and to our knowledge, there is no scientific evidence supporting them. The expert panel also assigned low relevance to the post-treatment prophylactic effect of TACTs (Kunkel et al., 2021) and to the potential of TACTs to reduce vivax malaria incidence, indicating that experts either disagree with the statements or that they are only considered minor advantages.

6.4.2 Disadvantages of introducing TACTs

The expert panel identified 15 disadvantages that can be grouped into three categories. The first category comprises statements that relate to acceptance issues. Malaria experts expressed concerns about the potential of adverse effects and other safety risks for TACTs. Indeed, an increase in adverse events such as vomiting, headache and fatigue was also mentioned as a major risk for TACTs' acceptance in Africa (Chapter 5). It is encouraging that clinical studies thus far suggest good tolerability of TACTs, except for a small increased risk of vomiting (van der Pluijm et al., 2020).

Malaria experts also shared concerns that TACTs might become more expensive than current ACTs. Malaria is a poverty-related disease and high consumer prices would likely compromise acceptance (Arrow et al., 2004), especially in private sectors (Patouillard et al., 2015; Phok and Lek, 2017). This emphasizes the importance of donor funder support (Tougher et al., 2017; Ye et al., 2015) and alignment with institutional frameworks to improve market prospects (Chapter 3). The majority of the expert panel expressed concern that an increased pill burden would negatively affect TACTs' acceptance. This concern is justified given that in its early days, ACTs were mostly deployed as co-blistered therapies which led to several compliance issues (Megan Littrell et al., 2011; Yeung et al., 2008a), highlighting the importance for TACTs to become available in fixed-dose combinations.

The second category comprises disadvantages that are related to drug development and production deficits. The expert panel voiced concerns about the current unavailability of fixed-dose combinations for TACTs, again emphasizing the importance of combining the triple combinations in one pill (White, 1999). Furthermore, the panelists were concerned that the antimalarial drug market in Southeast Asia may be too small to motivate pharmaceutical companies to pursue TACTs development and production. Similar deficits have been reported repeatedly in the context of pharmaceutical development for malaria (Wells et al., 2015) and other poverty-related diseases (Fehr et al., 2011; Muñoz et al., 2015). Encouraging is the growing track-record of successful projects in antimalarial drug development. Public-private partnerships (Bompart et al., 2011; Spar and Delacey, 2008), regulatory practices (Pelfrene et al., 2015) and intellectual property management initiatives (Orsi et al., 2018) have contributed to a better incentivized global landscape for pharmaceutical companies to invest in antimalarial drug development and production.

The third category of disadvantages relates to the policy domain. Malaria experts reached consensus that implementation timelines and costs would be a significant disadvantage of TACTs compared to rotating current ACTs (Krishna, 2019). Indeed, introducing a new therapy is time- and resource-intensive (Bosman and Mendis, 2007; Martins et al., 2012). However, these expenses should be considered against the potential costs of more widespread antimalarial drug resistance (Lubell et al., 2014). No consensus was reached about concerns on the limited timeframe for TACTs deployment in the context of receding malaria in Southeast Asia, revealing this important policy dilemma.

6.4.3 Implementation barriers for TACTs

The 13 implementation barriers that were identified by experts can be grouped into three categories. The first category relates to challenges in the trajectory toward market introduction of TACTs. The expert panel assigned highest relevance to challenges in obtaining timely regulatory approval for introducing TACTs. This aligns with delays that have been reported in the regulatory trajectory of previous ACTs (Ubben and Poll, 2013). The expert panel also attributed high relevance to in-country systems for regulation, including pharmacovigilance-, and surveillance systems (Novotny et al., 2016; Phok et al., 2017) and the importance of obtaining sufficient efficacy and safety data to support implementation efforts. Large-scale clinical trials are now underway to obtain such data in order to guide TACTs introduction and deployment (van der Pluijm et al., 2021).

The second category of implementation barriers relates to policy support for TACTs introduction in terms of inclusion in treatment guidelines and implementation programs. The expert panel envisioned challenges in obtaining support at the global policy levels, including WHO and donor funders support. The role of the WHO has been widely acknowledged in other global health transitions (Attaran et al., 2004; de Haan et al., 2021b; Orsi et al., 2018) and is likely to be essential to the market prospects of TACTs. Experts also considered relevant obtaining national-level policy support to facilitate smooth implementation. Country-level implementation delays were reported in the context of the introduction of ACTs (Bosman and Mendis, 2007) and should be avoided in case TACTs will be introduced. Encouraging are reports from Cambodia, where policy dedication at the national levels and subsequent regulatory and programmatic initiatives have contributed to a successful transition to ACTs in the early 2000s (Novotny et al., 2016; Phok et al., 2017; Yeung et al., 2011).

Community acceptance and logistical challenges, including supply chain management and stockpile management comprise the third category of prospective challenges for introducing of TACTs. Amin et al. (2007) reported that after the shift from monotherapies to ACTs in Kenya, outlets were left with remaining stock of outdated medicines without destination. Other studies have highlighted the importance of adequate and timely supply chain adaptations upon the implementation of new therapies (Simmalavong et al., 2017). These studies provide valuable lessons for the potential future implementation of TACTs or other new antimalarial therapies.

Experts furthermore agreed that community acceptance could become a challenge towards TACTs deployment, emphasizing the importance of clear communication and marketing messages. Finally, prescriber training (Zurovac et al., 2007) and private-sector engagement (O'Connell et al., 2011; Phok et al., 2017) were cited to be relevant for rapid deployment of TACTs and highlight the need for well-defined implementation strategies.

6.4.4 Limitations

The Delphi study was designed in adherence to the Conducting and REporting DElphi Studies (CREDES) guidelines (Jünger et al., 2017). Compared to other Delphi studies, a relative large expert panel was recruited for this Delphi exercise (Avella, 2016; Hasson et al., 2000) in order to reflect the heterogenous nature of antimalarial drug transitions (de Haan et al., 2021b). Given the spread in the affiliations, areas of expertise and geographical coverage of participating experts (Table 1) and the robustness of second-round findings (Figures 6.2, 6.3, 6.4), we consider it unlikely that bias has occurred in the sampling. Still it is possible that non-participating experts would have been able to provide us with complementary insights. At the same time, it is possible that some experts were not able to adequately respond to all the items in the second round. Although experts did have the possibility to leave items unrated, we could have more actively promoted the option to leave items unrated.

Attrition is a known limitation of Delphi studies (Hsu and Sandford, 2007) and attempts were made to minimize attrition rates. We followed-up with non-respondents and conducted both rounds of data collection shortly after each other. This resulted in a relative low attrition rate of 19% between the two rounds (Fehr et al., 2011; Graham-Clarke et al., 2021). Anonymity was granted throughout the data collection process to encourage creativity and to promote inclusive views. Some language bias may have occurred since the survey was only conducted in English and for many experts English may not have been their first language.

We are aware that consensus criteria in Delphi studies are subject to interpretation and that using different criteria would likely provide other results in terms of consensus. To avoid bias, we pre-determined cut-off criteria for consensus (Hasson et al., 2000). Furthermore, we used consensus rates mainly to interpret and to organize results. The goal of this study was to obtain expert perceptions about introducing TACTs. To reflect this objective, we attempted to ask questions in a neutral manner and to provide sufficient explanation with each statement. We explicitly did not aim to create a polling instrument to vote for TACTs nor did we aim to confirm or reject statements. Follow-up research is required to understand the root causes behind the advantages, disadvantages and implementation barriers and to define ways to overcome them.

6.5 Conclusion

The desirability and practical feasibility of introducing TACTs as a response to artemisinin and partner-drug resistance in Southeast Asia is subject of debate. This study systematically assessed perspectives of malaria experts towards the introduction of TACTs as first-line treatment for uncomplicated falciparum malaria in Southeast Asia, over current practices of rotating ACTs when treatment failure is observed. A two-round Delphi study was conducted. In the first round, malaria experts identified 15 advantages, 15 disadvantages and 13 implementation barriers for introducing TACTs in Southeast Asia. In the second round, consensus was reached on 13 advantages (8 perceived as relevant, 5 as not-relevant), 12 disadvantages (10 relevant, 2 not-relevant), and 13 implementation barriers (all relevant). The results of this study add to the limited information available in the public domain to aid in the ongoing debates about strategies to address drug-resistant malaria in Southeast Asia. Policy makers, academic researchers and Non-Governmental Organizations can use the results of this study for prioritizing resources and strategies towards the potential introduction of TACTs.

Chapter 7

Strategies for deploying Triple Artemisinin-based Combination Therapies (TACTs) in the Greater Mekong Subregion (GMS)

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7.1 Introduction

The prevalence of *Plasmodium falciparum* malaria in Southeast Asia is at historically low levels and the region is collectively engaging in malaria elimination strategies (WHO, 2022). At the same time, the Greater Mekong Subregion (GMS) is meeting the challenge of resistance to artemisinin and partner drugs used in Artemisinin-based Combination Therapies (ACTs). ACTs are the global first-line therapies for the treatment of uncomplicated malaria and losing them to resistance would jeopardize malaria control and elimination activities worldwide (Menard and Dondorp, 2017).

Artemisinin and partner drug resistance and subsequent ACT failures force countries in the GMS to anticipate on new treatment strategies to protect their malaria control and elimination ambitions (Dhorda et al., 2021). Countries have begun to rotate ACTs when treatment failures are observed, but rotation has repeatedly proven a temporary solution before the replacement ACT also fails (Novotny et al., 2016). Other proposed strategies include the simultaneous deployment of multiple first-line therapies, or extending ACT use from three to seven days (Boni et al., 2016; Phyo and Von Seidlein, 2017). However, each of these solutions has been associated with significant operational challenges and limited feasibility.

Another option that is now being explored in the GMS and elsewhere is the introduction of *triple* artemisinin-based combination therapies (TACTs) (Bassat et al., 2022; van der Pluijm et al., 2020). The rationale is that combining the artemisinin derivative with two carefully selected partner drugs will extend the therapeutic lifetime of each compound because the parasite will need to develop resistance to three drugs instead of two. The potential benefits of introducing TACTs would be twofold (de Haan et al., 2022): 1) they can provide direct clinical relief in case all current ACTs (including newly introduced artesunate-pyronaridine) would fail, and 2) they can protect artemisinin and its partner drugs from resistance, increasing future treatment options.

Although results from current clinical trials (Peto et al., 2022; van der Pluijm et al., 2020) and mathematical modeling studies (Nguyen et al 2023) are encouraging, the introduction of TACTs in the GMS is debated (Krishna, 2019; White, 2019). Some scholars and representatives of policy institutions perceive TACTs as a useful intervention towards malaria elimination in the GMS, while others prefer relying on current strategies of rotating ACTs until malaria elimination is established. In Chapter 6, we conducted a Delphi study in which we systematically assessed expert perspectives towards the introduction of TACTs in Southeast Asia (Chapter 6). Prominent malaria experts identified major advantages, disadvantages and implementation barriers for introducing TACTs and they rated the relevance of each item on a 5-point Likert scale. The insights of the Delphi study led to a first, tentative overview of major barriers and drivers towards TACTs deployment in the GMS. However, these insights lack contextualization to the situation in individual countries. More in-depth attention can – and should – be paid to implementation practicalities in specific countries in the GMS and to identify how markets for TACTs can be formed. The present study aims to fill this gap in literature (de Haan et al., 2021b; van der Pluijm

et al., 2021). A qualitative study is designed to identify implementation strategies towards potential TACTs deployment in three countries in the GMS: Cambodia, Vietnam and Lao PDR.

7.2 Methods

7.2.1 Research design

The study was conducted under the auspices of the UK Government's Foreign, Commonwealth & Development Office funded Development of Triple Artemisinin Combination Therapies

(DeTACT) project. A qualitative research approach was employed to investigate strategies for introducing TACTs in the Greater Mekong Subregion (GMS) of Southeast Asia. Three countries were selected for data collection: Cambodia, Vietnam, and Lao PDR. All three countries have repeatedly been confronted with artemisinin and partner drug resistance but they are characterized by their own health system characteristics. We conducted in-depth interviews in all three countries to provide insight into specific implementation challenges for TACTs and to explore strategies to overcome these implementation issues. The multi-country research approach enabled investigating country-specific dynamics in relation to the deployment of TACTs while enabling the extraction of general topics that were applicable to more than one country. Data was collected through in-depth interviews with key actors in the healthcare systems in Cambodia, Vietnam and Lao PDR. Furthermore, we conducted a participatory workshop in Cambodia. The goal of the workshop was to interactively discuss preliminary insights obtained during the interviews with key stakeholders in the antimalarial innovation system and to discuss strategic solutions towards the pre-identified problems towards TACTs deployment. Data collection took the implementation challenges for introducing TACTs in Southeast Asia identified in Chapter 6 as a starting point (Table 7.1) (de Haan et al., 2022).

TABLE 7.1 | Expert perspectives on the *implementation barriers* for introducing TACTs in Southeast Asia (derived from de Haan et al 2022; see Chapter 6).

Implementation barrier	Explanation
Intensified prescriber training	Intensifying training requirements for correct TACTs prescription.
Donor funder support	Obtaining support by donor funders to cover TACTs implementation costs and potential price increases.
National policy support	Obtaining support from national malaria control programs and other national decision makers to engage in the deployment of TACTs.
WHO and global policy support	Obtaining support from the WHO and other global decision makers to engage in the deployment of TACTs.
Availability of fixed-dose combination (FDC) TACTs	Ensuring timely development and production of fixed-dose combination (FDC) for TACTs.
Community acceptance	Ensuring community acceptance by providing clear communication and tackling potential misconceptions about TACTs.
Collecting safety and efficacy data	Collecting sufficient efficacy and safety data to support the introduction of TACTs.

Implementation barrier	Explanation
Supply chain logistics	Adapting import, procurement and supply routes for the introduction of TACTs.
Regulatory approval	Obtaining timely regulatory approval for introducing TACTs in Southeast Asia.
Set up surveillance systems	Setting up surveillance systems to monitor drug resistance rates and adherence to TACTs.
Private sector engagement	Engaging the (informal) private sector in TACTs deployment and creating demand beyond official programs.
Set up pharmacovigilance systems	Setting up a pharmacovigilance system for TACTs.
Stockpile management	Managing stockpiles for countries that still have ACT stocks or contract deals with ACT producers.

7.2.2 Respondent selection

The study was conducted in Cambodia, Vietnam and Lao PDR. In each of the countries, we collaborated with co-authoring research institutes and social scientists. Interview respondents were mapped by the local social scientists and invited to participate in the in-depth interviews. The aim was to include interviewees who represent a wide variety of stakeholder types. Selected respondents included representatives from national malaria control programs, regulatory authorities, academia, healthcare professionals and NGOs. Sampling of respondents in each country continued until data saturation on the pre-identified implementation barriers for the introduction of TACTs occurred.

7.2.3 Data collection

Preparatory meetings were held between the principal investigators (FH and CA) and the social scientists in Cambodia, Vietnam and Lao PDR. The purpose of these meetings was to discuss the research aims, identify relevant stakeholders and prepare data collection tools. Semi-structured interview guidelines were designed using the pre-identified implementation barriers Chapter 6) as starting questions. In line with progress of the DeTACT project, we took the introduction of a prospective TACT that combines artemether-lumefantrine plus amodiaquine (AL+AQ) as the starting point of the interview. For each interview, themes that were considered most relevant to the specific background of the respondent were selected and included in a personalized interview guideline. Pilot interviews were conducted to improve mutual understanding between principal investigators and the social scientists in Cambodia (LO), Vietnam (VC) and Lao PDR (MV). Using the semi-structured interview guides enabled exploring the same topics between the countries and respondents, while remaining flexible for newly emerging themes. Data collection was iterative: insights from previous interviews were incorporated in guidelines of later interviews.

7.2.4 Data analysis

Interviews were recorded with consent of each respondent. All interviews in Cambodia, Vietnam and Lao PDR and the participatory workshop in Cambodia were transcribed verbatim and translated into English by the social scientists or by professional translators. Each transcript was then uploaded to NVivo 12 software and subjected to coding. The transcripts were coded line-by-line by FH, and codes were assigned to both the pre-defined implementation barriers (Table 7.1) and to newly emerging themes. After the coding, a process of thematic analysis was employed using deductive and inductive techniques: emerging themes were merged into overarching categories and storylines were written to present narratives of implementation challenges and strategies to overcome these implementation challenges.

7.2.5 Ethical approval

The Oxford Tropical Research Ethics Committee (OxTREC) approved the overall research project, approval number 508-22. In Cambodia, approval was obtained from the National Ethics Committee for Health Research (NECHR), reference number 120-04733775. In Vietnam, approval was obtained from the Institutional review board of the National Institute of Malariology, Parasitology and Entomology (NIMPE), approval number 40-2022/HDDD. In Lao PDR approval was obtained from the National Ethics Committee for Health Research (NECHR), approval number 2022.32. Written or verbal participant consent was obtained prior to each interview and the participatory workshop. Respondents were informed about the objectives of the study and asked to sign a consent form. Permission to mention the affiliation of the respondent and to audio record the conversation was sought either verbally or written.

7.2.6 Study setting: introducing the three country contexts

Cambodia, Vietnam and Lao PDR have low falciparum malaria incidence and all three countries are engaging in malaria elimination strategies. In 2021, Cambodia (16.6 million inhabitants) reported 19.064 malaria cases (both *falciparum* and *vivax*), Lao PDR (7.4 million inhabitants) reported 6.403 malaria cases and Vietnam (97.5 million inhabitants) reported 453 malaria cases (WHO, 2022). These numbers include both Plasmodium falciparum and other types of malaria. All three countries share goals to eliminate falciparum malaria by 2025 and all other types of malaria by 2030 (WHO, 2015b).

Cambodia: Cambodia has repeatedly changed its first-line ACT as a response to failures for the treatment of uncomplicated falciparum malaria. In 2017, artesunate-mefloquine (ASMQ) was re-introduced as first-line therapy in response to treatment failures with dihydroartemisinin-piperaquine (DHA-PPQ). At the time of writing, ASMQ maintained adequate treatment efficacy in Cambodia, but the national malaria control program is preparing for the implementation of artesunate-pyronaridine (AS-PYR) as first-line therapy for the treatment of malaria. The National Center for Parasitology, Entomology and Malaria Control (CNM) coordinates malaria-

related activities and the Department of Drugs and Food (DDF) is responsible for drug regulation in Cambodia.

Vietnam: The official first-line therapy for the treatment of uncomplicated falciparum malaria in Vietnam is DHA-PPQ. However, DHA-PPQ is failing in some areas in the central-highlands and AS-PYR is being used for the treatment of falciparum malaria in these areas. From November 2022 onwards, AS-PYR was used throughout the entire country. Malaria control activities in Vietnam are coordinated by the National Malaria Control Program (NMCP) and the Drug Administration Department (DAD) is responsible for drug regulation in Vietnam.

Lao PDR: The first-line therapy for the treatment of uncomplicated falciparum malaria in Lao PDR is artemether-lumefantrine (AL). Moreover, AS-PYR was added to national treatment guidelines as second-line therapy in 2021. In Lao PDR, malaria control efforts are coordinated by the Center of Malariology, Parasitology and Entomology (CMPE) and the Food and Drugs Department (FDD) is responsible for drug regulation.

7.3 Results

A total of 29 interviews were conducted (12 in Cambodia, 12 in Vietnam and 5 in Lao PDR) between May and December 2022. Selected respondents included representatives from national malaria control programs, regulatory authorities, academia, healthcare professionals and NGOs. The goal of the interviews was to explore implementation challenges for TACTs in Cambodia, Vietnam and Lao PDR. Furthermore, a participatory workshop with 11 participants from Cambodia was held in Phnom Penh in October 2022. The goal of the workshop was to interactively discuss preliminary insights obtained during the interviews, to validate emerging insights, and to discuss strategic solutions towards the pre-identified implementation challenges for TACTs (Table 7.1). This results section is organized around four strategic themes that emerged from data obtained in the interviews and the participatory workshop: 1) policy support, 2) data and evidence, 3) logistics and operation, and 4) downstream engagement.

7.3.1 Policy support

A positive attitude towards potential deployment of TACTs was expressed by almost all respondents in Cambodia, Vietnam and Lao PDR. TACTs were considered a promising backup strategy in case current first-line ACTs would start to fail. At the same time, some respondents expressed concerns related to exposing the parasite to three drugs, which may jeopardize future efficacy of these compounds. *"Introducing TACT is a way to address drug resistant malaria. […]. If we use TACTs, the chance of genetic change and resistance to the three compounds will be reduced and we will have higher efficacy of treatment. However, we do not have many alternatives for malaria treatment, therefore we need to be careful in using the existing malaria drugs." (Lao PDR, #3)*

It was emphasized that current first-line ACTs, in particular AS-PYR, are still effective in all three countries. Most respondents expected to rely on their current ACTs for reaching the regional ambitions to eliminate falciparum malaria by 2025. Hence, the introduction of TACTs was considered not a direct, urgent need but rather a useful strategy in case alternative treatments would fail. In contrast to the other two countries, Cambodia is also actively anticipating the potential introduction of TACTs. During the workshop it was mentioned that decision makers in Cambodia are currently considering AS-PYR as first-line therapy, after which TACTs could be included as second-line therapy once TACTs are WHO pre-qualified and available for deployment. This would enable Cambodia to accelerate their large-scale introduction if treatment failures would occur with AS-PYR. *"So in the future it is necessary to have a drug so that when Plasmodium falciparum becomes resistant to Pyramax [brandname artesunate-pyronaridine], we still have an effective and safe drug to treat people who have malaria." (Vietnam, #1)*

"In Cambodia, the CNM [national malarial control program Cambodia] has decided to include TACTs in the malaria elimination policy already. The WHO also agreed that Cambodia can include TACT as second line therapy. The CNM has to use all resources to reach our elimination goals." (Cambodia, #1)

Some respondents in Cambodia, Vietnam and Lao PDR indicated that implementing new therapies can be a lengthy process. Expected timelines of several months to more than a year were proposed from inclusion in national treatment guidelines to full implementation on the ground. This was considered potentially too long when dealing with problems of drug resistance. References were made to the slow implementation of other malaria interventions, in particular to the introduction of tafenoquine for *P. vivax* malaria in Vietnam, and the switch from DHA-PPQ to ASMQ in Cambodia. It was suggested that lessons should be learned from these past experiences: the introduction of TACTs should be initiated well in advance and in accordance with key stakeholders such as regulators, national decision makers and providers. "*There is need for many documents to support the decision makers. I think it will take more than a year." (Lao PDR, #2)*

"If we want to change from ACT to TACT, it will take a lot of time, it can be 2 years, from revising guidelines to full implementation." (Cambodia, workshop)

Some respondents were skeptical if engaging in TACTs would be worth the investment in this pre-elimination era. Malaria incidence is receding and nearly all respondents expected that falciparum malaria in the GMS will be eliminated in the next few years. At the same time, it was mentioned that even if falciparum malaria is eliminated in 2025 (according to the Malaria Elimination Action Framework), effective therapies still need to be maintained in stock in case a resurge of malaria incidence occurs. Respondents did foresee a role for TACTs as such a back-up therapy. "*Therefore, the market is very small, and getting smaller as the number of infected cases declines. So, introducing a new drug, or even conducting the trial, is difficult." (Vietnam, #10)*

"[…] Like in China: they may encounter malaria drug resistance imported from Southeast Asia. So China needs to have drugs in stock and needs to be alert." (Cambodia, #5)

Respondents in Cambodia, Vietnam and Lao PDR agreed that support from international institutions, in particular the World Health Organization (WHO), would add to the credibility of introducing TACTs. National decision makers said they are unlikely to recommend a new therapy that is not recommended by the WHO. The WHO is considered as a guiding institute and their recommendations usually define country-level strategies against resistance. At the same time, it was indicated that national governments could deviate from general recommendations in case of an emergency situation. It was furthermore emphasized that procurement subsidies from the Global Fund to fight Aids, Tuberculosis and Malaria (GFATM) would add to TACTs credibility and would be important for their affordability nationwide in case they would become deployed as first-line therapy. "*I think as a general rule health authorities are always more keen to do something if it's backed up by WHO recommendations." (Cambodia, #11)*

"In terms of malaria, then the role of the sponsor is vital, I mean the Global Fund. As you know, about 80% of the funding for malaria prevention, control and elimination comes from the Global Fund." (Vietnam, #2)

7.3.2 Data and evidence

Safety and efficacy data are needed to support the licensing and subsequent market introduction of TACTs in Southeast Asia. Respondents in Cambodia and Vietnam expressed a preference of such data collected in their own countries, because this would add to the credibility of the therapy within local contexts. At the same time, difficulties in collecting clinical evidence in the context of the receding malaria incidence were acknowledged. Some interviewees in Cambodia and Vietnam referred to the previous TACT-CV study (2017-2020) in which good efficacy and safety of the TACT artemether-lumefantrine plus amodiaquine was demonstrated in Cambodia and Vietnam. They suggested this evidence as a starting point for obtaining market authorization for TACTs. *"I assume they would ask for safety data, obtained from participants from Southeast Asia, and perhaps even from Cambodia." (Cambodia, #11)*

"With such a small number of cases, it will be hard to evaluate treatment effects. Previously in the study from 2015 to 2018, there were 4000 to 5000 cases in Vietnam and the majority was plasmodium falciparum. […]. But now, it will be more difficult to have a sample size of a few hundred to evaluate the effectiveness and safety [of TACTs]." (Vietnam, #10)

Cambodia, Vietnam and Lao PDR all operate under the ASEAN regulatory system. Stringent regulatory approval such as WHO pre-qualification was considered an important driver for registration in the countries. Respondents in Vietnam indicated that AS-PYR is currently being deployed as an unauthorized drug: a special import license was obtained to enable its use prior to registration, which was deemed necessary when treatment failures with DHA-PPQ were observed. By then, there was no time to go through extended regulatory procedures and AS-PYR was urgently needed to treat patients with drug-resistant infections. It was suggested that a similar procedure could be followed for the introduction of TACTs in case they are urgently needed in Vietnam. In Cambodia and Lao PDR no references to this type of regulatory shortcuts

were made. *"At the moment, Pyramax [brand name artesunate-pyronaridine] is used in Vietnam as an unregistered drug. It is not registered to be distributed in Vietnam, but it is being imported according to a special license. It does not have the market authorization, so it is called off-label medicine." (Vietnam, #10)*

Timelines for obtaining regulatory approval and market licenses varied between countries. Respondents in Vietnam and Lao PDR expected that they would need several months for regulatory procedures from dossier submission to obtaining prescription licenses. Shorter timelines of approximately 1 month were expected for the regulatory trajectory in Cambodia, as long as complete dossiers would be submitted. One respondent from Vietnam indicated that as long as TACTs are deployed as single tablets, their registration is rather straightforward and less time consuming. This is because all the individual compounds of the TACTs are already registered. Registration of a potential fixed-dose combination (FDC-) TACT would require more extensive regulatory procedures and timelines. *"The process of approving and regulations for TACTs will take about 6-12 months, dependent on the availability of the documents." (Lao PDR, #1)*

Respondents in Cambodia and Lao PDR expressed concerns about the administrative burden of a prospective transition to TACTs. National treatment guidelines need to be adjusted, pharmacovigilance systems would need to be setup and malaria surveillance procedures would need to be adjusted. Furthermore, data obtained by pharmacovigilance and surveillance systems needs to be collected and adequately processed. Respondents indicated budget restraints and a lack of human resources which would complicate these procedures. Also challenges related to broader information management practices and IT systems were mentioned as possible challenges to adequately follow-up on a change in treatment practices. One respondent in Cambodia opposed this view, and was rather confident that routines could easily be adjusted, referring to the surveillance system of Cambodia as the most elaborate and most experienced in the world. "*We will provide the training to staff to work on the pharmacovigilance systems and work with DDF about side effect of drug. I know it is difficult to train and report on those cases, it takes time." (Cambodia #1)*

"So I forgot to tell you something about the surveillance formation system which we have in Cambodia I think that is one of the best in the region, I will not be lying to you if I say it is the best one in the world." (Cambodia #2)

7.3.3 Logistics and operations

Interview respondents in Cambodia, Vietnam and Lao PDR were generally optimistic about the operational aspects of introducing of TACTs. Some logistical and operational challenges were nevertheless mentioned. Several respondents again referred to the low malaria incidence in this pre-elimination era in which key stakeholders stated that malaria is not considered a major health issue anymore. They pointed out challenges in engaging suppliers and local health staff and also challenges in mobilizing resources for procuring and distributing TACTs. Other respondents expressed concerns about high implementation costs for introducing a new

therapy and questioned if resources should not be invested in elimination activities instead. "*There are cost that we have to think about. When you are introducing a new drug into a country, then you have to change your treatment guidelines, train human resource, fill the supply chain […], so we need more resources, and not only for procurement and distribution of the drug." (Cambodia, #2)*

General challenges in malaria management in Southeast Asia were mentioned as potential challenges for delivering TACTs to patients. Malaria in Southeast Asia is mostly common among hard to reach populations such as migrant populations and illegal labor forces. These people often operate beyond the scope of the official channels and reaching them with appropriate interventions is considered complicated. This was brought forward in each country as an existing challenge for malaria case management that would also apply to TACTs. Furthermore, respondents emphasized that stockpile issues should be considered before implementing TACTs. These include storage conditions, temperature requirements, climate control and expiry dates. These challenges especially need to be considered in light of relative small quantities needed for TACTs in the GMS. "*A challenge is the limitation of quantity and quality of the human resources. Ownership and knowledge of the staff in all levels is required but this is also a challenge. In particularly for supply, distribution and reporting." (Lao PDR, #1)*

"Now there are a few things that may be difficult in monitoring, detection, prevention, and treatment. The first thing is that, as I mentioned from the beginning, the at-risk people are in remote areas and mobile. They are migrant population from the North to across the border without declaration to the local authorities, which is difficult for early detection and timely treatment and is a risk of an outbreak. The second thing is that now the malaria is no longer endemic in large areas." (Vietnam, #7)

"Another challenge is the coordination of many stakeholders: donors, purchasers and factories. Document processing is time consuming, and so sometimes the drugs nearly reach their expired dates when arrive in our country, and sometimes it is already beyond the expired date after distributed to provinces or districts." (Lao PDR, #2).

Several respondents doubted whether pharmaceutical companies would be prepared to engage in TACTs if they are targeted exclusively to the GMS. They questioned whether TACTs would be considered profitable given the low malaria incidence in the GMS. Parallels were drawn with recent challenges encountered in Cambodia with orders of pediatric doses of ASMQ. When Cambodia switched to ASMQ in 2017, they had to order stocks at a private sector company who intended to deliver ASMQ at a minimum amount of half a million doses. However, only a fraction of this number was needed given the low malaria prevalence in the country, which resulted in wastage of unused drugs. During the participatory workshop in Cambodia, a regional procurement system for antimalarials in the GMS was suggested as a potential solution to such stockpile issues in case multiple countries would collectively engage in TACTs. "*It is difficult because of the quantity of drugs. For example, for the current ACT we must use the foreign content, because they do not produce them domestically anymore due to the reduction of malaria. The requested quantity of drugs is not enough to balance the cost of production. So they stop producing the drug." (Vietnam, #5)*

"I just want to share experience during last time, Cambodia change the treatment guideline after the piperaquine started to fail and we shifted to ASMQ. So at that time, we needed to buy from a factory by at least half million doses. If less than half million dose, the factory would not produce. […]. Now, maybe Cambodia is a first country to use this TACTs. Whereas malaria case in Cambodia sharply drops and low cases. How to convince the manufacturer to produce TACTs?" (Cambodia, workshop)

Respondents in all three countries indicated that public sector supply chains for antimalarials are well-established due to many years of experience. Of the three countries, Lao PDR is the only country in which the private sector plays a major role in malaria management. In Vietnam and Cambodia, private sector clinics, hospitals and pharmacies are only involved in case detection but they are no longer permitted to prescribe antimalarial therapies (see Chapter 3). Some respondents in Lao PDR emphasized that the private sector should be actively involved in the potential introduction of TACTs to ensure their proper usage and to avoid misuse. References were made by interview respondents to the Public-Private Mix (PPM) program as a promising instrument to engage private sector actors in Lao PDR (Chapter 3). Through the PPM program, private sector prescribers receive training and instructions by their public-sector counterparts, which enables them to act in accordance with treatment guidelines. "*Currently, malaria drug treatment is free, and is supported by international organizations. I think it should not be sold in general [including private sector prescribers], because it will be difficult to follow up and it may lead to drug resistance. But we can discuss about the service fee of the private sector that participated in the PPM project." (Lao PDR, #5)*

7.3.4 Downstream engagement

Several respondents in Cambodia, Lao PDR and Vietnam indicated that prescriber training will always be required once a new therapy is introduced, and in the case of the introduction of TACTs that would be no exception. Such training programs should include information about potential adverse effects, such as the increased risk of vomiting. It was also emphasized that the rationale for introducing TACTs in terms of addressing drug resistance should be made explicit in training modules. Respondents in all three countries highlighted that training programs would especially need to target village malaria workers (VMWs), because they are at the frontline for malaria management in Cambodia, Lao PDR and Vietnam. "*With the reduced number of cases we need to ensure that they get picked up early and they are given adequate treatment in a timely manner. And that is harder and harder where health professionals are not seeing malaria that much. And that is why malaria is not always on the top of their differential diagnosis." (Cambodia, #3)*

"The training needs to be detailed the reason why we change to TACT. The training would have to focus on the 5 provinces in the southern part of Lao." (Lao PDR, #1)

Pricing issues were considered of limited importance for engaging community members in TACTs. All antimalarial therapies in Cambodia and Vietnam, and most antimalarial therapies in Lao PDR, are available for free through public sector channels. Hence, financial considerations generally play a minor role in the adoption decisions of community members. Respondents

furthermore indicated that malaria patients generally comply to prescribed therapies when diagnosed with malaria. Side-effects and the number of pills to be taken per day were mentioned as factors that could negatively affect acceptance of TACTs. Some respondents expected higher rates of adverse effects such as vomiting and nausea for a TACT of AL+AQ because of the inclusion of the amodiaquine compound. Thorough explanation of side-effects through information leaflets or prescriber explanations would be required according to them. *"I thinks there is no problem about community acceptance, because the community does not know what this drug is, whether it is new or old, as long as it is prescribed . right? The doctor prescribes and the patient will take it. But the most important thing is that it's only for short term (a few days) and must be fixed-dose in the one tablet."(Vietnam, #2)*

"The important thing is we explain to community; explain to community members or patients the side effects of the drug and the benefits of using the new drug. As for the side effects of the drug, how does it affect the patients and what are the benefits to the patients." (Cambodia #10)

Respondents in all three countries emphasized that fixed-dose combinations (FDC) would be preferred over single tablets. Prescribing FDCs would enhance patient compliance and would be more convenient for prescribers. Moreover, some respondents referred to other ACT regimens with single tablets to explain risks of non-compliance to partner drugs that are associated with adverse effects. More importantly, most respondents stressed that the number of pills would be an important reason for preferring FDC TACTs: more pills will increase risks of non-compliance. Some references to non-compliance of earlier single tablet ACT regimens were made by respondents from Cambodia and Lao PDR. *"As a past experience has shown, control programs are much happier when the drug is in a single pill rather than having to separated or co-blistered or whatever. It's easier in terms of implementation in the field. And that would also be the case for TACTs." (Cambodia, #11)*

"I think, in fact, the fixed-dose combination will have more advantages because taking one dose including three ingredients in a pill will enhance drug adherence, avoid forgetting medication, and it will be more convenient for patients." (Vietnam, #11)

7.4 Discussion and concluding remarks

Countries in Southeast Asia are experiencing a historically low malaria burden and they are increasingly dedicating resources and efforts towards the elimination of falciparum malaria (WHO, 2015b). Respondents in Cambodia, Vietnam and Lao PDR indicated a general reliance on their current ACTs in reaching their malaria ambitions. In particular newly introduced artesunate-pyronaridine (AS-PYR) was mentioned as an important approach towards malaria elimination and, indeed, treatment failures with AS-PYR have not yet been reported in the GMS or elsewhere. Although malaria elimination is without doubt the most effective way to contain drug resistance, there is a risk on over-relying on current elimination strategies while alternative scenarios are being overlooked. Resistance pathways are unpredictable and epidemiological

developments can unfold rapidly (Dhorda et al., 2021). For example, the instable political situation in Myanmar and subsequent weakening of health services there could result in a resurgence of falciparum malaria not only in Myanmar, but also neighboring countries in the GMS (WHO, 2022). Moreover, future treatment failures with AS-PYR can potentially emerge and can threaten malaria elimination ambitions when countries remain unprepared. Therefore, decision makers in the GMS health care system would benefit from increasing number of treatment options. Triple artemisinin-based combination therapies (TACTs) are currently being developed and they have potential to ensure treatment efficacy in case ACTs would fail (Peto et al., 2018; van der Pluijm et al., 2020) while they can also protect drug compounds from resistance, increasing future treatment options.

This chapter explored strategies towards TACTs deployment in three GMS countries that have repeatedly been confronted with ACT resistance: Cambodia, Vietnam and Lao PDR. A qualitative research approach was employed to identify implementation challenges for TACTs deployment in the GMS and to discuss strategies to overcome these challenges. The results were organized around four strategic themes. The first strategic theme that emerged from the data was policy support for the deployment of TACTs. Respondents indicated that key stakeholders in the antimalarial innovation system such as national decision makers, regulators and suppliers need to be engaged in early stages to prevent implementation delays for TACTs from occurring. In contrast to Vietnam and Lao PDR, Cambodia is already anticipating the potential introduction of TACTs. The National Malaria Control Program is considering adopting TACT as a second-line therapy in their national treatment guidelines. This will make it easier for them to rapidly switch to TACTs in case artesunate-mefloquine (ASMQ) would fail again followed by AS-PYR failures. Other countries in the GMS should also consider such a pro-active strategy instead of relying on reactive approaches towards drug resistance (Bosman and Mendis, 2007; Novotny et al., 2016). Clinical trials are not able to predict the potential impact of introducing TACTs on potential future antimalarial resistance rates and so there is an important role for mathematical modeling studies in obtaining supportive evidence. Mathematical modeling studies can also predict the (cost-) effectiveness of TACTs compared to alternative strategies to address antimalarial drug resistance. These type of mathematical modeling studies are now underway within the Development of Triple Artemisinin-based Combination Therapies (DeTACT) project. Furthermore, ensuring sufficient stockpiles of effective therapies even beyond malaria elimination was mentioned as a necessary strategy to prevent resurgence of the disease. Indeed, interruptions in stockpiles have been associated with challenges in changing treatment practices (Arrow et al., 2004; Zurovac et al., 2007), especially when low demand is expected (Patouillard et al., 2015).

The second strategic theme that emerged from the data related to the collection of safety and efficacy data. Before TACTs can be deployed, evidence from clinical trials will be required to obtain market authorization in Cambodia, Vietnam and Lao PDR. Regulatory procedures have repeatedly been suggested as delaying factors in changing malaria treatment routines (Ubben and Poll, 2013). They are often considered inflexible, while dealing with drug resistance

requires pragmatic approaches (Pelfrene et al., 2015). Established regulatory procedures entail large-scale clinical studies and approval by a stringent regulatory authority (such as WHO pre-qualification) before country-level authorization can be considered. A pragmatic strategy was suggested by respondents in Vietnam. They referred to the current off-label prescription of AS-PYR. AS-PYR has been deployed even prior to its country-level registration because a new therapy was urgently needed after DHA-PPQ failures were observed. It was suggested that similar strategies could be established for the introduction of TACTs.

The third strategic theme that emerged from the data were logistical and operational considerations. Although malaria incidence in the GMS has significantly been reduced in the last decades, references were made to several persisting general malaria management and control challenges. Malaria in the GMS is mostly prevalent amongst hard to reach populations in remote border areas, such as forest workers and labor migrants (Cui et al., 2012; McMichael and Healy, 2017). Interventions will need to reach these remote populations and they will need to be adequately adopted. Community-based health initiatives such as Village Malaria Worker (VMW) programs have become key intervention in malaria control strategies in the GMS (Yeung et al., 2008b). They have become institutionalized in public health services and are now considered to be a key intervention in the battle against malaria. New interventions such as TACTs need to strategize targeting VMWs and similar initiatives to reach their full potential.

The fourth and final strategic theme was downstream engagement for TACTs deployment. A recurrent question that emerged from the results is how to engage stakeholders in TACTs while falciparum malaria incidence is receding in the GMS. Changing first-line treatment practices indeed requires substantial investments and collective actions by multiple stakeholder groups such as decision makers, regulators and prescribers (de Haan et al., 2021a). Antimalarial drug transitions can be lengthy and this justifies considerations around the timing of introducing new therapies. Previous studies have emphasized that downstream engagement strategies are essential to the successful introduction of new therapies (Arrow et al., 2004; Williams et al., 2004). This should include health education messages to address misconceptions, health professionals training and integrated disease management approaches. For the introduction of TACTs, communication strategies should highlight advantages in terms of clinical benefits and their potential to protect antimalarial drugs as well as indirect benefits such as reduced frequency of policy changes (Chapter 6).

Four limitations should be considered when interpreting the study results. An important disclaimer is that this chapter does not seek to determine whether TACTs should be introduced in the GMS. In this chapter, we present strategic considerations for the market introduction of TACTs. Second, the generalizability of the findings is limited. Although some of the findings of this study are also relevant to other countries in the GMS, countries are heterogeneous and characterized by their own healthcare systems and epidemiological factors. We propose that similar studies should also be conducted in other countries that are confronted by drug-resistant malaria. Third, we conducted in-depth interviews with key stakeholders in the antimalarial drug

innovation system in Cambodia, Vietnam and Lao PDR. Selection of respondents has occurred in close collaboration with local research institutes, but nevertheless it is possible that important stakeholders and perspectives were not included. Fourth, interviews were conducted in local languages and translated into English, hence translation bias could have occurred.

Chapter 8

General discussion and conclusions

The subject of this thesis was prompted by the imminent global health threat of artemisinin and partner drug resistance for the treatment of uncomplicated falciparum malaria. Chapter 1 presented challenges related to antimalarial drug transitions and emphasized on the importance of forming markets for new therapies. A conceptual approach was developed and embedded in transition studies and innovation systems theory. Given the challenging nature of previous antimalarial drug transitions and the need for forming markets for future therapies, the following central research question was posed: How are markets for antimalarial therapies being formed under the pressure of drug resistance?

In the subsequent Chapters 2 - 7, a thorough examination of antimalarial drug transitions was presented with an emphasis on market formation processes. To understand how markets for new antimalarial therapies come into existence, the thesis was divided into three parts. **Part 1** (Chapters 2 and 3**)** mapped the innovation system of antimalarial therapies and identified systemic failures that jeopardize the formation of markets for new therapies. This was done by investigating in retrospect the antimalarial drug transition from conventional monotherapies to Artemisinin-based Combination Therapies (ACTs) in the early 2000s. Parts 2 and 3 of this thesis were devoted to the potential introduction of Triple Artemisinin-based Combination Therapies (TACTs), as a response to artemisinin and partner drug resistance in Africa and Southeast Asia. **Part 2** (Chapters 4 and 5) investigated the prospects of forming markets for TACTs in African countries, in which current ACTs are still effective at the time of writing this thesis. **Part 3** (Chapters 6 and 7) investigated the prospects of market formation for TACTs in Southeast Asian countries, in which current ACTs have repeatedly fallen to resistance.

This concluding chapter first presents the main findings of the individual parts and chapters (Section 8.1). It then synthesizes the main finding by proposing a multifaceted framework towards market formation in global health transitions (Section 8.2). After that, a reflection of the conceptual framework is given (Section 8.3) and general limitations of the thesis are being discussed (Section 8.4). Finally, five policy recommendations are presented that can benefit future efforts to form markets for new antimalarial therapies (Section 8.5).

8.1 Main findings

Part 1: The transition from conventional monotherapies to ACTs

The first part of this thesis examined in retrospect the major antimalarial drug transition from conventional monotherapies to Artemisinin-based Combination Therapies (ACTs). **Chapter 2** developed an integrated framework towards a sustainable system of antimalarial drug development and diffusion in the context of drug resistance. Data were collected through literature review and complemented with nine expert consultations. The chapter evaluated the major flaws in the antimalarial innovation system and identified reforms that are required towards a more sustainable system: one that can ensure the ongoing delivery of effective

antimalarial therapies to both present and future patients. The integrated framework was proposed along four components: availability, affordability, accessibility and acceptability. *Availability* was described as safe and effective interventions that are produced in sufficient quantities and that are approved by regulatory authorities. *Affordability* was described as interventions that can be acquired within the financial possibilities of governments and patients. *Accessibility* was described as interventions that can be physically obtained by those in need. *Acceptability* was described as the appropriate uptake of interventions by prescribers and patients.

The integrated framework presented in Chapter 2 evaluated the challenging antimalarial drug transition from conventional monotherapies to ACTs. The analysis demonstrated that sustainable availability for future therapies will involve reconsidering the incentive structure for global health innovation, expanding public-private partnerships and improving efficiency of regulatory trajectories. Sustainable affordability will require inclusive pricing strategies and encompassing subsidy arrangements which pay specific attention to affordability in private sector facilities. Sustainable accessibility will require functioning supply chains, policy coordination and encompassing stakeholder engagement strategies. Sustainable acceptability will demand information campaigns and user-involvement from early stages of product development onwards. Chapter 2 concluded that sustainable availability, affordability, accessibility and acceptability are interrelated: improvements in one of the framework components will sort effect in the other components. All four framework components are equally important for achieving a sustainable system of antimalarial drug development and diffusion and thereby for achieving sustainable healthcare (Sustainable Development Goal, SDG 3). Subsequently, a reduced malaria burden can be associated with reduced poverty (SDG 1), improved education (SDG 4) and reduced inequality between countries (SDG 10).

After developing an integrated framework towards a sustainable system of antimalarial drug development and diffusion, the thesis continued with analyzing market formation in a major global health transition. **Chapter 3** demonstrated how markets for Artemisinin-based Combination Therapies (ACTs) were formed at multiple geographical scales and locations when all conventional monotherapies had fallen to resistance. Data were collected through conducting a literature review and complemented with six in-depth interviews. Three episodes of market formation were identified and described. The first episode showed how the public health importance of drug resistance led to the discovery of artemisinin, a completely new class of antimalarial therapies. It then showed how public institutes, academia and partnerships contributed to early innovation system expansion. The second episode demonstrated how transnational organizations created a supportive global landscape for ACT development and deployment through the establishment of financial, regulatory and institutional arrangements. The third episode revealed how these advancements led to the formation of public-, and private-sector end-user markets for ACTs in the Greater Mekong Subregion (GMS), a region in Southeast Asia that is considered as the global epicenter of drug resistant malaria.

Several theoretical contributions regarding market formation in multi-scalar innovation systems came to the fore in Chapter 3. It combined the technological innovation systems approach with the global innovation systems approach to investigate market formation in a global health transition. We revealed how the ACT innovation system emerged across multiple geographical scales and locations. The evolution of the innovation system was mapped in three distinctive episodes: first from country to country at the time of ACT discovery (Episode 1), after which a supportive global-level landscape for ACT development and deployment was created (Episode 2), which was then followed by national-level and local-level market formation activities (Episode 3). The chapter, furthermore, demonstrated how structural couplings - defined as actors, networks or institutions spanning across innovation subsystems - were attained between subsystems in the antimalarial innovation system. These structural couplings emerged in multiple forms, including funding mechanisms, product-development partnerships, regulatory arrangements and programmatic initiatives. Chapter 3 concluded that market formation activities in a global health transition are distributed along multiple geographical scales and locations. Market formation activities are interlinked with other systemic activities, such as resource mobilization and legitimacy creation. The chapter provided insights into a geographical complex socio-technical transition and proposed conceptual and theoretical starting points for future research into multi-scalar transitions and global health innovation systems.

Part 2: The introduction of TACTs in Africa

The second part of this thesis examined the prospects of market formation for Triple Artemisinin-based Combination Therapies (TACTs) in African countries. In Africa, current ACTs were still effective during data collection in 2019 and 2020. Therefore, introducing TACTs would imply direct investments at the patient-, and country-levels (higher prices and increased risks of side-effects), while the benefits (mitigated risks of evolving drug resistance and increased protection of drug compounds) would be long-term and rather affect the broader community. This justified the assessment of ethical considerations and practical implementation challenges for introducing TACTs in African settings as presented in Chapters 4 and 5.

Chapter 4 explored the major ethical and practical considerations for forming TACTs markets in African countries. The chapter drew upon insights from the randomized TACT-CV clinical trials (Section 1.3.3), combined with ethical principles and published literature on the previous introduction of antimalarials in Africa. Chapter 4 presented major ethical considerations for introducing TACTs in terms of public health ethics, individual autonomy and pediatric clinical ethics. The chapter explained that deploying TACTs in Africa may expose patients, mainly children under five years of age, to the risk of additional side-effects of three drug compounds instead of two. In the case of introducing a triple combination of artemether-lumefantrine + amodiaquine, this would imply an increased risk of vomiting and a slightly prolonged QTc interval(albeit not clinically relevant). The chapter used the lens of utilitarian ethics which aims

for maximizing benefits for the greatest number of people to discuss if requesting individuals to take on these additional burdens for the sake of the public good is ethically justified. Related to these discussions, we explored whether the potential adverse effects of deploying TACTs can be considered minimal and to what extent autonomous decision making by juvenile patients is required to make an ethically justified decision in choosing between ACTs and TACTs.

Upon discussing these ethical tensions, Chapter 4 continued with examining practical implementation challenges for the market formation of TACTs in African countries. The chapter elaborated on complexities in resource allocation and the investment requirements for deploying TACTs. In most African countries, engaging in TACTs would require short-term investments (costs + additional side-effects), while the benefits (mitigated risks of drug resistance) would be for the long-term and would transcend national borders. This confronts decision makers and funders with complex trade-offs that need to be made. Chapter 4 explained that transitioning from ACTs to TACTs in Africa may be warranted from a health-economic perspective. The economic impact of widespread ACT failures in Africa would likely exceed the costs of a drug transition although further research is required to assign cost estimations to these benefits. Finally, the chapter discussed challenges around market authorization, guideline inclusion and implementation programs that may impact the market formation prospects for TACTs in African countries. These market formation considerations were briefly analyzed in Chapter 4 and investigated more in-depth in Chapter 5.

After the exploration of ethical tensions and implementation practicalities, **Chapter 5** continued with a qualitative study at the African continent. The Chapter investigated the extent to which antimalarial drug markets in African countries are ready for a transition to TACTs. The study was conducted in Nigeria and Burkina Faso and comprised 68 in-depth interviews and 11 focus group discussions with key actor groups in the antimalarial innovation system. The study revealed that the market formation prospects of TACTs in Nigeria and Burkina Faso will likely depend on reported ACT failures in Africa and on active recommendations by the WHO. Respondents indicated high readiness for forming TACTs markets in public sectors,which are government controlled, but they suggested more challenges for market formation in private sectors, which are driven by commercial motives. Slow regulatory and implementation procedures were identified as potential barriers towards rapid market formation for TACTs in Nigeria and Burkina Faso. The chapter emphasized that TACTs need to be benchmarked against current ACTs to avoid jeopardizing their acceptance at the population levels: TACTs regimens should not be more expensive, should not contain more pills and should not cause more side-effects than current ACTs for end-user markets to be formed. Chapter 5 concluded that the market formation prospects of TACTs in Nigeria and Burkina Faso will depend on evidence of their clinical superiority over current ACTs, their endorsement by global institutes (WHO, GFATM), and their alignment with local distribution and deployment practices. The recent increasing reporting of artemisinin resistance and ACT failures in Africa might change important determinants of the market readiness of TACTs.

Unfortunately, the antimalarial drug resistance situation at the African continent has evolved in the years after data collection for Chapters 4 and 5. Artemisinin resistant parasite lineages have recently been detected in Rwanda, Uganda and Tanzania (Asua et al., 2021; Balikagala et al., 2021; Bergmann et al., 2021; Bwire et al., 2020; Kayiba et al., 2021; Uwimana et al., 2021, 2020) while inadequate efficacy of artemether-lumefantrine was reported in Angola and Burkina Faso (Dimbu et al., 2021; Gansané et al., 2021; Rasmussen and Ringwald, 2021). These new developments may change important determinants of market formation for TACTs. At the same time, they highlight the urgency of forming markets for new antimalarial therapies in Africa, making the studies described in Chapters 4 and 5 even more relevant.

Part 3: The introduction of TACTs in Southeast Asia

The third part of this thesis examined the prospects of forming markets for TACTs in Southeast Asian countries. In contrast to the situation in Africa, artemisinin and partner drug resistance and subsequent ACT failures have repeatedly been reported in Southeast Asia (Amaratunga et al., 2016; Ashley et al., 2014; Phyo et al., 2012). Countries in the Greater Mekong Subregion (GMS) of Southeast Asia now rotate with ACTs when treatment failures are observed, but this has proven to be only a temporarily solution before efficacy of the replacement ACT also declines. Other proposed strategies include the simultaneous deployment of multiple first-line therapies or extending ACT intake from 3-7 days (Dhorda et al., 2021; Phyo and Von Seidlein, 2017), but both solutions have been associated with operational challenges and limited feasibility. Transitioning to TACTs is therefore considered a promising strategy to address artemisinin and partner drug resistance (van der Pluijm et al., 2021; White, 2019). At the same time, the introduction of TACTs in Southeast Asia remains subject to debate: some scholars and representatives of policy institutes believe that efforts and resources should instead be invested in malaria elimination activities or in alternative strategies to address drug resistance (Chen and Hsiang, 2022; Krishna, 2019). Part 3 of this thesis contributed to these debates by exploring the major advantages, disadvantages and implementation challenges for introducing TACTs in Southeast Asia (Chapter 6), and by investigating strategies for TACTs deployment in the GMS (Chapter 7).

Chapter 6 investigated the major advantages, disadvantages and implementation challenges of introducing TACTs in Southeast Asian countries. A two-round Delphi study was conducted to systematically assess malaria experts' perspectives towards the introduction of TACTs compared to current practices of rotating ACTs when treatment failures are observed. In the first round of data collection, 53 prominent malaria experts answered open-ended questions on what they consider the most important advantages, disadvantages, and implementation barriers for introducing TACTs. In the second round, the same expert panel rated the relevance of each statement.

Malaria experts identified 15 advantages, 15 disadvantages and 13 implementation barriers for introducing TACTs in the first round of data collection. In the second round of data collection, consensus was reached on 13 advantages (8 perceived as relevant, 5 as not-relevant), 12 disadvantages (10 relevant, 2 not-relevant), and 13 implementation barriers (all relevant). Advantages that were attributed the highest relevance related to the clinical and epidemiological rationale of introducing TACTs, in particular the potential of TACTs to protect drug compounds from future drug resistance. Disadvantages that were attributed the highest relevance related to concerns about adverse effects, unavailability of fixed-dose combinations (FDC) of TACTs, and potential cost increases as a result of transitioning to TACTs. Implementation barriers that were attributed the highest relevance related to obtaining timely regulatory approval, the timely availability of FDC TACTs, and generating global-level and national-level policy support for introducing TACTs. The obtained insights from this Delphi exercise provided a systematic and contextualized insight into important elements that may – either positively or negatively - affect the market formation of TACTs in Southeast Asia.

Chapter 7 was designed as a follow-up to the Delphi study. It presented a qualitative study in which strategies for the market formation of TACTs in the Greater Mekong Subregion (GMS) of Southeast Asia were investigated. In-depth interviews were conducted in three countries that have repeatedly been confronted with ACT failures: Cambodia, Vietnam, and Lao PDR. A total of 29 key stakeholders in the innovation system of antimalarial therapies were interviewed. Furthermore, one participatory workshop was conducted in Cambodia, in which stakeholders discussed potential scenarios around epidemiological developments and market formation developments. The study revealed that countries in the GMS currently rely on ACTs for reaching their ambitions to eliminate falciparum malaria by 2025. TACTs were, however, considered as a useful backup in case future treatment failures would occur and as a strategy to prevent the re-establishment of malaria. Chapter 7 showed that a major challenge ahead is to engage decision makers into TACTs given the low case incidence of falciparum malaria in the GMS. Interview respondents were skeptical if providers would be willing to engage in new therapies for a disease they hardly encounter anymore. Hence, elaborate information dissemination strategies were considered appropriate and should especially target Village Malaria Workers (VMW), which are the current frontline of malaria management in the GMS. Finally, respondents proposed several regulatory and programmatic strategies to anticipate on the formation of TACTs markets in the GMS. These strategies should include early trial dossier submission to accelerate regulatory procedures, early stakeholder engagement to shorten implementation timelines, and inclusion of TACTs as second-line therapy to accelerate their introduction in case they are urgently needed.

8.2 Towards a framework for market formation in global health transitions

This thesis focused on market formation in an era of drug resistant malaria. In recent years, there has been increasing interest in markets and their formation in the context of global health research (Berman et al., 2022; Bloom et al., 2011; Orsi et al., 2018) and policy debates. Several prominent global health organizations including USAID[8], GFATM[9], GAVI[10] and the Stop TB partnership[11] have proposed market formation policies, such as advanced market commitments. Although these policies generally agree that market pull interventions are needed, market formation in the global health context is mainly regarded as safeguarding access and sales volume (Boon et al., 2022; Malhame et al., 2019). To open the black box, we emphasize that work is to be done to understand how prescribers, patients and other stakeholders contribute to the formation of end-user markets.

In answering the question of how markets for antimalarial therapies are formed under the pressure of drug resistance, this thesis takes a broader perspective on market formation. Our systemic conceptualization (Section 1.2) implies that market formation in global health is multifaceted. Markets for antimalarial therapies are created through interactions between multiple actor groups and institutions across the globe. Market formation in global health transitions is a multi-scalar undertaking: global-level market formation activities determine national-level and local-level activities and vice versa. Structural couplings enable the functioning of the innovation system: these couplings are important in connecting dispersed innovation subsystems and in channeling efforts, resources and commodities along geographical scales and locations. Below, we take stock of the findings of this thesis and we propose a multifaceted framework for market formation in global health transitions (Figure 8.1). Figure 8.1 synthesizes the insights obtained throughout the thesis, and refers to the chapters in which additional information for each framework component can be found.

The framework in Figure 8.1 can be used by global health researchers and policy makers with an interest in market formation. It provides starting points that will enable them to broaden their scope and to define more encompassing innovation for future global health market formation efforts. It is important to acknowledge that the framework in Figure 8.1 was developed by thoroughly investigating the antimalarial innovation system: it should be contextualized to alternative disease areas before applying there.

8 USAID: https://www.usaid.gov/cii/market-shaping-primer

9 GFATM: https://www.theglobalfund.org/en/sourcing-management/market-shaping-strategy/

10 GAVI: https://www.gavi.org/our-alliance/market-shaping

11 Stop TB partnership: https://www.stoptb.org/global-drug-facility-gdf/market-partner-coordination

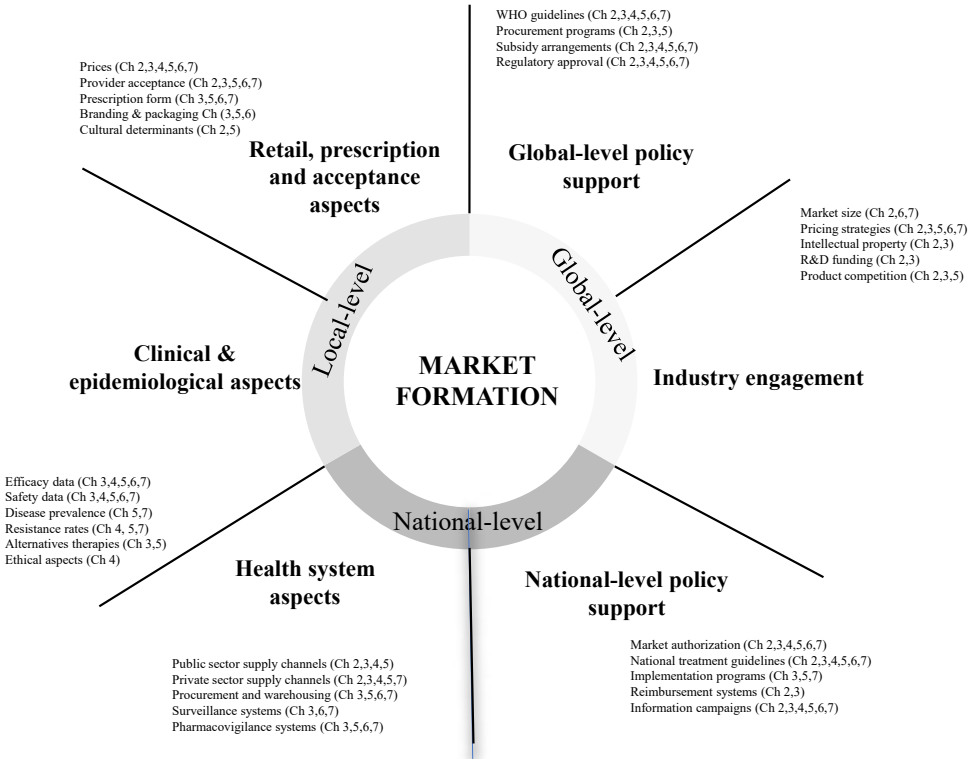

FIGURE 8.1 | A multifaceted framework for market formation in global health transitions.

8.3 Conceptual reflection

We applied the innovation systems approach to investigate how markets for new antimalarial therapies are formed under the pressure of drug resistance. In contrast to traditional innovation models, the innovation systems approach assumes interdependence between drug development, diffusion and utilization, in which innovation is seen as a collective activity. It is a powerful approach for assessing the full societal embedding of (medical) technologies by taking into account interactions between actors, networks and institutions (Hekkert et al., 2007; Moors et al., 2018). The innovation systems approach has been much applied to analyze technological transitions in the context of grand societal challenges, such as global warming and environmental pollution. This thesis presented a first effort to apply the innovation systems approach to a global health transition, which leads to advancements in the field of medical innovation for global health and in the field of transition studies.

The thesis contributed to the field of medical innovation for *global health*, especially to the way in which new medicinal products are developed, introduced and implemented in markets. We demonstrated that market formation in global health is not merely a matter of mainstreaming,

mass deployment and one-size-fits all diffusion. Rather, we showed that nations, regions and local contexts are important in the way new medicinal products are adopted and incorporated in health related practices. Contextualized diffusion is important and characteristics like ethical considerations (Chapter 4), industry engagement (Chapters 2, 3, 5, 6), and alignment with local distribution and deployment practices (Chapters 3, 5 ,7) determine how markets for new antimalarial therapies are formed.

Moreover, introducing and diffusing new medical products does not merely concern the positioning of a new therapy on the market, because markets themselves need to be formed. As was demonstrated in Chapter 3, various institutional frameworks, such as subsidy arrangements, regulatory schemes and programmatic initiatives needed to be actively created in order to form ACT markets. We also demonstrated that multiple actor groups, including industry, policy makers, regulators, suppliers, prescribers and patients contribute to the market formation of new therapies in global health settings. Our conceptual approach aligns with earlier evidence promoting active stakeholder engagement in pharmaceutical innovation (DeMonaco et al., 2006; Hartley et al., 2019; Meijer et al., 2013; Miedema, 2022; Smits and Boon, 2008). All these actor groups have a unique position in the innovation system and this position equips them with important contextual knowledge that can benefit the formation of end-user markets for new therapies. In this thesis, we first mapped the multiple actor groups in the antimalarial innovation system (Chapters 2 and 3) and we probed for their visions, perceptions and expectations towards the market formation for TACTs in African countries (Chapter 5) and Southeast Asian countries (Chapters 6 and 7). This resulted in a variety of elements that likely influence market formation for TACTs and other future medical innovations for global health (Figure 8.1).

In the context of *transition studies*, we advanced the innovation systems approach by proposing a systemic conceptualization of market formation in global health transitions. We regarded markets as subsystems of technological innovation systems that are composed of all actors, networks and institutions that are directly involved in making global health interventions available to patients (Boon et al., 2022; Dewald and Truffer, 2012). Market formation is one of the Technological Innovation Systems (TIS) functions (Table 1.1). However, previous TIS studies focused on investigating emerging sustainable energy or transport technologies rather than on medical technologies. This implies that some functions, such as knowledge creation and diffusion have been over-emphasized or have been unpacked in ways that do not align well with (global) healthcare. Market formation is a function that would look differently in global health, as healthcare has specific demand-side regulations and policies that dictate user preferences, user practices and adoption (Kukk et al., 2016b; Moors et al., 2018). Examples of such demand-side aspects from the thesis include the emphasis on developing fixed-dose TACTs combinations (Chapters 3, 5, 6), needs for information campaigns to inform prescribers and patients (Chapters 5, 6, 7) and preferences for therapies with limited pills and side effects (Chapters 5 and 7).

In Chapters 4, 5, 6 and 7 we applied a systemic conceptualization of market formation to investigate the prospects of market formation for Triple Artemisinin-based Combination Therapies (TACTs). We learned that the antimalarial innovation system reached a mature stage, although challenges towards market formation persist, also in relation and interaction with other system processes. Based on the empirical results in Chapters 4, 5, 6 and 7, we expect most challenges ahead in resource mobilization, legitimacy creation and overcoming health system challenges that directly jeopardize market formation for new therapies. Overcoming these challenges will be location-, and epidemiological situation dependent. For example, legitimacy creation for TACTs in Africa will rely on clear communication and decision making around ethical considerations (Chapter 4), while legitimacy creation in Southeast Asia will require emphasizing the added value for TACTs in the context of malaria elimination strategies (Chapter 7). At the same time, supportive institutions (e.g. product development partnerships, global subsidy arrangements, and the WHO pre-qualification scheme) have become globally institutionalized in the antimalarial innovation system, improving the prospects for resource mobilization and market formation for future therapies such as TACTs worldwide. So, next to a different articulation of market formation as a function in the antimalarial innovation system, we found that market formation is interrelated with TIS functions such as resource mobilization and legitimacy creation. Analysing market formation through a systemic lens enabled identifying systemic failures in the antimalarial innovation system (Chapters 1, 2 and 3) and evaluating innovation policies to support market formation for future therapies (Chapters 4, 5, 6 and 7).

Moreover, we found that it is important to perceive market formation as taking place on several interrelated geographical levels. In Chapter 3, we added a multi-scalar component to the systemic conceptualization of market formation. The chapter revealed how markets for ACTs were created as a response to multidrug resistance to conventional monotherapies. To deal with the geographical complexity, we combined the TIS approach with the Global Innovation Systems (GIS) approach. The GIS approach was proposed by Binz & Truffer (2017) as a framework for the analysis of technological innovation processes in transnational contexts. In their work, Binz & Truffer claim that multi-scalar innovation systems are made effective through the attainment of structural couplings - defined as actors, networks or institutions spanning across dispersed innovation subsystems. Although they emphasize the importance of interconnecting dispersed innovation subsystems, Binz & Truffer acknowledge a lack of empirical understanding into *what* structural couplings actually are, and *how* they affect the functioning of a GIS (Binz and Truffer, 2017; Tsouri et al., 2021). This thesis empirically contributed to these gaps in the context of the antimalarial innovation system.

In Chapter 3, we illustrated how structural couplings were attained between dispersed antimalarial innovation subsystems and how these structural couplings eventually led to the formation of ACT markets (Binz and Truffer, 2017; Heiberg and Truffer, 2022). Structural couplings emerged in several forms, including product-development partnerships (MMV/DNDi) to establish entrepreneurial activities, regulatory arrangements (the WHO prequalification scheme) to create legitimacy, and procurement subsidies (GFATM and AMFm subsidy arrangements) to

mobilize resources. These structural couplings enabled overcoming a broad range of systemic challenges and eventually resulted in the formation of ACT markets (Chapter 3).

Integrating the TIS approach with the GIS approach allowed us to assess the evolution of the geographically complex antimalarial drug innovation system. It enabled to focus on the formation of innovation subsystems (both in terms of resource mobilization and legitimacy creation) and the attainment of structural couplings that connected them. This thesis adds to the GIS approach by demonstrating that market formation for malaria therapies relies on resource mobilization and legitimacy processes at the global-level but is also determined by (and sometimes is determining) market formation activities at the country-, and local-levels. We provide empirical understanding of structural coupling and we demonstrated how these structural couplings enabled the functioning of the antimalarial innovation system (Binz and Truffer, 2017; Heiberg and Truffer, 2022).

Overall, the thesis demonstrated that the systemic conceptualization of market formation is useful in the global health domain. Not by providing yet another theoretical lens, but by providing an integrated view and an actual set of conceptual and methodological tools (Boon et al., 2022; Hekkert et al., 2011). The conceptual approach enabled us to analyze barriers and drivers towards market formation for new therapies and to derive policy implications accordingly. Whereas the transition to new antimalarial therapies has previously been analyzed from policy viewpoints (Amin et al., 2007; Bosman and Mendis, 2007; Williams et al., 2004), health-economic viewpoints (Arrow et al., 2004), and market intelligence viewpoints (Novotny et al., 2016; Tougher et al., 2017), we presented the first lessons from an innovation systems perspective. This resulted in a multifaceted framework (Section 8.2) that can benefit future scholars and policy makers with an interest in market formation in global health. This thesis focused on the formation of markets for antimalarial therapies, but the obtained insights are also applicable to other poverty-related infectious diseases areas worldwide, such as leishmaniasis, schistosomiasis, tuberculosis and HIV. These diseases confront patients and governments with challenges similar to those experienced with malaria: effective drug compounds are scarce and drug resistance threatens the few options that are available (Byarugaba, 2004; Keshavjee and Farmer, 2012; Sullivan and Ben Amor, 2016). Enhanced understanding of transition dynamics and market formation processes is important to ensure that these diseases remain treatable for present-day and future patients.

8.4 Limitations

The research limitations of the individual chapters were already reported there and will not be repeated in this section. Instead in this section we provide general limitations and related suggestions for future research avenues. First, an important disclaimer should be made for Chapters 4, 5, 6 and 7. This thesis does not seek to determine whether introducing TACTs is the best way forward to address antimalarial drug resistance. Instead clinical studies are needed to

demonstrate the safety and efficacy of TACTs, while mathematical modeling studies need to evaluate the potential of deploying TACTs in delaying drug resistance. These studies are now underway within the development of triple artemisinin-based combination therapies (DeTACT) project (van der Pluijm et al., 2021). Successful innovation of TACTs will be dependent on the full amount of evidence from the clinical, mathematical, market formation and bio-ethical studies (Figure 1.3) and the findings of this thesis should be considered as part of this broader scientific evidence base.

Second, epidemiological developments unfold at a rapid pace. When considering Chapters 4 and 5, it is important to note that data for both chapters was collected in 2019 and 2020. That is before reports of artemisinin resistance on the African continent were published. Since then, the epidemiological situation of artemisinin and partner drug resistance in Africa has evolved. Artemisinin resistance is further increasing in Southeast Asia and is also beginning in Africa (Bwire et al., 2020; Kayiba et al., 2021; Uwimana et al., 2021, 2020). The results of this thesis should be considered in the context of these rapid evolving epidemiological developments. We presented market formation studies at one specific moment in time, and follow-up research is required to update the study insights to the most recent developments.

Third, Chapter 5 and 7 assessed the feasibility of introducing TACTs in two African and three Asian countries. The multiple case design allowed investigating local market formation determinants while enabling the identification of themes that apply to more than one country or setting. However, the generalizability of these studies to other settings is limited. Malaria endemic countries are heterogeneous in nature and they are characterized by different healthcare systems and epidemiological characteristics. Therefore, similar market formation studies for TACTs should be conducted in other countries. Market formation studies should be prioritized in countries reporting artemisinin resistance and/or ACT failure and countries with an increased risk of resistance due to their geographical location or epidemiological situation. The studies described in Chapters 5 and 7 can serve as pilot studies for designing such future market formation studies.

Fourth, data collection for Chapters 5 and 7 comprised in-depth interviews in Nigeria, Burkina Faso, Cambodia, Vietnam and Lao PDR. In each country, we collaborated with local social scientists to facilitate data collection and analysis. This enabled us to understand the health system context of each country and to practically arrange data collection. However, having data collected in multiple countries by dispersed researchers implies that data collection procedures might not be uniform amongst settings. To enhance reliability of the studies, participating social scientists have been trained extensively before collecting data. In these trainings, the study backgrounds and aims were extensively discussed and pilot interviews were conducted to reduce ambiguity. Nevertheless, it is possible that certain themes were extensively explored in one locality but only received limited attention in others.

Fifth, this thesis investigated how markets for antimalarial therapies are formed under the pressure of evolving drug resistance. We took a systemic conceptualization towards market

formation and embedded this conceptualization in innovation systems theory and transition studies. Although the systemic conceptualization proved useful for analyzing the transition to ACTs (Chapters 2 and 3) and the potential market formation of TACTs (Chapters 4, 5, 6 and 7), it also comes with an important limitation in terms of system demarcation. We focused on the technological innovation system of TACTs which implies that alternative technologies to address antimalarial drug resistance have not been included in the analysis. Recent advances in the antimalarial drug innovation system (such as the promising development of ganaplacide-lumefantrine as a new therapy) were not extensively incorporated in this thesis while they will likely affect the prospects of market formation for TACTs and, broader, the future of the antimalarial drug market. Follow-up research should therefore emphasize on the relation between TACTs and alternative technological solutions to address antimalarial drug resistance.

8.5 Policy recommendations

Each chapter in this thesis presented policy recommendations based on the conducted research. While acknowledging that establishing change in global health is challenging, we derive five overarching policy implications that could benefit future efforts to form markets for antimalarial therapies.

Facilitate information exchange between countries

First, Chapters 2 and 3 demonstrate that malaria endemic countries built a track-record in forming markets for new therapies. These chapters reveal how governments created ACT markets through implementation programs, market regulation and programmatic initiatives. We emphasize that these lessons learned are valuable assets in the battle against drug resistant malaria. Decision makers within endemic countries should share their lessons-learned and related best-practices from previous market formation achievements. Instead of reinventing the wheel, past experiences should be documented and disseminated in order to benefit market formation efforts elsewhere: experiences from one country can effectively inform decision making in other countries. Chapter 3, for example, demonstrated how Cambodia implemented a range of regulatory-, and programmatic activities that catalyzed the formation of functioning ACT markets. These activities included village malaria worker (VMW) programs and the public-private mix (PPM) to exchange knowledge between public/private sectors. Chapter 3 then demonstrated how similar initiatives in neighboring countries (Vietnam, Lao PDR, Myanmar) boosted the formation of ACT markets there. Such lessons learned can serve as educational material for decision makers in other countries that are confronted with similar market formation challenges. We acknowledge that global health transitions are multifaceted, contextualized, and difficult to document in detail. Information exchange beyond country-borders can be especially complex due to language barriers and a lack of geographical proximity. A solution to these challenges would be the establishment of a transnational taskforce to create a central information base and actively disseminate market formation insights between countries.

Strategically prepare for the market formation of TACTs in Africa

Second, Chapters 4 and 5 explored the market positioning of TACTs in African countries. These chapters focused on the major ethical tensions and implementation practicalities for introducing TACTs in settings where ACTs are still largely effective. Data obtained from Nigeria and Burkina Faso (Chapter 5) suggested that external incentives would be necessary to stimulate TACTs uptake as long as their clinical superiority over ACTs is not proven in Africa. These incentives could, for example, be in the form of subsidy arrangements or through further regulating the distribution and prescription of antimalarials through private sector markets. Additionally, Chapter 5 showed that market formation for TACTs should be considered in the context of ongoing health system challenges. The majority of the malaria burden is carried by resource restricted populations in areas with deficient healthcare systems. During the interviews in Nigeria and Burkina Faso we learned that antimalarial therapies in both countries are often still prescribed over-the-counter and that chloroquine often still remains, whereas the malaria parasite is highly resistant to this drug. In this context of suboptimal treatment practices, introducing TACTs should not be an isolated goal, but instead be integrated in broader ambitions to improve treatment practices. Chapter 5 furthermore emphasized that TACTs should be benchmarked against current ACTs to avoid jeopardizing their acceptance in Nigeria and Burkina Faso: TACTs prices should not exceed ACTs prices, TACTs should not cause more side-effects than ACTs, and TACTs should not contain more pills than ACT regimens. Having these determinants explicit at early stages will enable strategically preparation for the potential market introduction of TACTs.

Strategically prepare for the market formation of TACTs in Southeast Asia

Third, Chapters 6 and 7 focused on the potential introduction of TACTs in Southeast Asia. Countries in Southeast Asia are experiencing a historical low malaria burden and they are increasingly dedicating resources and efforts towards malaria elimination. Although eliminating malaria is indeed the most effective way to contain drug resistance, there is a risk on over-relying on elimination strategies and overlooking alternative epidemiological scenarios. Chapter 7 revealed that a major challenge ahead is to engage stakeholders in forming markets for TACTs, while malaria numbers are low and patients, prescribers and decision makers are only infrequently confronted with the disease. Nevertheless, the long implementation timelines of previous therapies in the GMS (Chapter 3), in combination with only few treatment options available, highlights the risks of over-relying on these approaches. Countries in Southeast Asia should not neglect possibilities of a resurgence in malaria incidence and they should not ignore the risks of remaining ACTs failing before malaria elimination is established. For example, the current political instability in Myanmar could be a starting point for a resurgence of malaria in neighboring countries, including Bangladesh, India and Thailand. Several countries in the Greater Mekong Subregion (GMS) now rely on artesunate-pyronaridine for reaching the last mile towards malaria elimination, but Chapter 7 revealed that they generally lack back-up strategies to deal with a potential scenario of artesunate-pyronaridine failures. Epidemiological developments can be rapid and pathways of resistance are difficult to predict. We, therefore,

recommend that ministries of health should pro-actively engage in strategic scenario planning regarding malaria control. One encouraging example is Cambodia: the national malaria control program is taking efforts to include TACTs as second-line therapy which enables them to rapidly react in case future artesunate-pyronaridine failure would occur.

Highlight TACTs potential to preserve antimalarial drug compounds

Fourth, effective antimalarial drug compounds are scarce and drug resistance threatens the few treatment options that are available. We emphasize that awareness among global-level and national-level decision makers should be created on the importance of protecting the drugs available now so that their useful lifetime can be extended for future treatment combinations. In the Delphi study in Chapter 6, prominent malaria experts acknowledged that TACTs' potential to protect drug compounds could be a major rationale for introducing them: this was rated the most important advantage of introducing TACTs in Southeast Asia. However, the rationale of preserving drug compounds from emerging resistance is new in the malaria domain, which means that decision makers are ill-prepared for this type of decision making. Lessons can be learned from other disease areas, such as tuberculosis and HIV, where triple therapies have already been introduced to mitigate risks of drug resistance and to protect drug compounds (Sheikh and Uplekar, 2016).

Include market formation studies in global health innovation initiatives

Fifth, the formation of markets for new therapies is a time- and resource-intensive process with many uncertainties along the road. New therapies need to be developed, tested and submitted to regulatory agencies before they can be implemented, distributed and deployed (OECD, 2023). Simultaneously, time is scarce when dealing with global health emergencies such as drug resistance. We therefore emphasize that market formation studies, similar to the ones presented in this thesis, should be integrated in future global health innovation programs. Conducting market formation studies in early stages of product development enables defining implementation strategies that can benefit the introduction of new therapies (Bloom et al., 2011; Malhame et al., 2019). This thesis provides conceptual and methodological starting points for future market formation studies Chapters 4, 5, 6 and 7 present anticipatory studies to identify market formation determinants for TACTs and proposed several strategic recommendations. Examples include the option of submitting clinical evidence on a rolling base to accelerate regulatory procedures of TACTs (Chapter 5), the timely investments into fixed-dose combinations that align well with patient preferences (Chapters 6), and early inclusion of TACTs as second-line therapy to facilitate their rapid introduction in case urgently needed (Chapter 7).

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Summary

Malaria is a poverty-related infectious disease that is prevalent in large areas of Africa and Asia. Each year, over half a million people die because of malaria, mainly children under five years of age in Sub Saharan Africa. This is particularly tragic because malaria is easily treatable when effective therapies are administered in time. These days, the world relies on artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated falciparum malaria ('malaria' in the remainder). ACTs combine a highly potent, rapidly cleared artemisinin derivative (artesunate, artemether, dihydroartemisinin) and a less potent, slowly cleared partner drug (mefloquine, amodiaquine, lumefantrine, piperaquine of pyronaridine).

A recurrent problem in the battle against malaria is the phenomenon of drug resistance. Throughout history, we repeatedly lost important first-line antimalarial therapies as a result of drug resistance. A worrying recent development is that the process of drug resistance is repeating. Malaria parasites in the Greater Mekong Subregion (GMS) of Southeast Asia have managed to become resistant to artemisinin and partner drug combinations. A major global health threat is the risk of artemisinin and partner drug resistance spreading westwards to Africa, where the majority of the malaria burden is situated. New drug compounds are years away in the pharmaceutical pipeline and therefore pragmatic solutions are required that make use of existing drug compounds. These solutions need to be developed and markets need to be formed to ensure their timely access by patients.

In this thesis, we investigate how markets for new antimalarial therapies are developed under the pressure of drug resistance. Conceptual insights and methodological approaches from innovation sciences and transition studies are applied to investigate how antimalarial drug transitions unfold with a focus on market formation processes. Chapter 1 develops a systemic conceptualization of market formation and embeds this conceptualization in innovation systems theory. We regard markets as subsystems of technological innovation systems. Markets are composed of all the actors, networks and institutions that are directly involved in making the interventions available and accessible to end-users. In the empirical Chapters 2 -7, we apply the systemic conceptualization of market formation to empirically investigate market formation for malaria therapies.

The empirical work in this thesis is divided in three parts. The **first part** of the thesis (Chapters 2 and 3) maps the antimalarial innovation system and identifies *systemic failures* that jeopardize market formation for new therapies. This being done by investigating the transition from conventional monotherapies to ACTs at the start of this millennium. In Chapter 2, we develop an integrated framework towards a sustainable system of antimalarial drug development and diffusion. We evaluate major innovation system flaws and we identify four framework components that are essential for a sustainable system: availability, affordability, accessibility and acceptability. *Availability* is described as safe and effective interventions that are produced in sufficient quantities and that are approved by regulatory authorities. *Affordability* is described

as interventions that can be acquired within the financial possibilities of governments and patients. *Accessibility* is described as interventions that can be physically obtained by those in need. *Acceptability* is described as the appropriate uptake of interventions by patients and prescribers.

The integrated framework is then used to evaluate the transition from conventional monotherapies to ACTs. The analysis demonstrates that sustainable availability for future therapies will involve reconsidering the incentive structures for pharmaceutical innovation, expanding public-private partnerships and improving the efficiency of regulatory trajectories. Sustainable affordability will require inclusive pricing strategies and encompassing subsidy arrangements which pay specific attention to private-sector affordability. Sustainable accessibility will require functioning supply chains, policy coordination and encompassing stakeholder engagement strategies. Sustainable acceptability will demand information campaigns and user-involvement from early stages of product development onwards. Chapter 2 concludes that sustainable availability, affordability, accessibility and acceptability are interrelated: improvements in one of the framework components will sort affects in the other components. All four framework components are equally important for achieving a sustainable system of antimalarial drug development and diffusion and subsequently to achieving sustainable healthcare (Sustainable Development Goal, SDG 3).

Chapter 3 then demonstrates how markets for ACTs were formed at multiple geographical scales and locations when all conventional monotherapies had fallen to resistance in the early 2000s. Data are collected through extensive literature review and complemented with six in-depth interviews. Three episodes of market formation are identified in Chapter 3. The first episode shows how the pressure of drug resistance led to the discovery of artemisinin, a new class of antimalarial therapies. The episode then reveals how public institutes, academia and partnerships contributed to early innovation system expansion. The second episode demonstrates how transnational organizations created a supportive global landscape for ACT development and deployment through the establishment of financial, regulatory and institutional arrangements. The third episode reveals how these advancements led to the formation of public-, and private-sector end-user markets for ACTs in the Greater Mekong Subregion (GMS) of Southeast Asia, the global epicenter of drug resistant malaria.

Chapter 3 provides several theoretical contributions regarding market formation in multi-scalar innovation systems. It combines the technological innovation systems approach with the global innovation systems approach to investigate market formation in a global health transition. We reveal how the ACT innovation system emerged across multiple geographical scales and locations. The Chapter demonstrates how structural couplings - defined as actors, networks or institutions spanning across innovation subsystems - were attained between innovation subsystems. These structural couplings emerged in several forms including funding mechanisms, product-development partnerships, regulatory arrangements and programmatic initiatives. Chapter 3 concludes that market formation activities in global health transitions

are distributed along multiple geographical scales and locations. Market formation activities are interlinked with other systemic activities including resource mobilization and legitimacy creation. Structural couplings emerge in multiple forms and they are essential to the formation of end-user markets for new antimalarial therapies. The thesis provides a unique insight into a geographical complex transition and provides conceptual and theoretical starting points for future research into multi-scalar transitions and global health innovation systems.

The second and third part of this thesis are devoted to the potential introduction of Triple Artemisinin-based Combination Therapies (TACTs) as a potential response to artemisinin and partner drug resistance in two epidemiological settings. Artemisinin and partner drug resistance is considered a major threat in the battle against malaria worldwide. New therapies are not expected in the coming years and therefore pragmatic solutions are required that make use of existing drug compounds. The development and introduction of TACTs is considered a promising approach to address ACT resistance. The rationale is that combining an artemisinin derivative with two partner drugs with different modes of action will extend the therapeutic lifetime of each compound because they will provide mutual protection against resistance. Early efficacy studies have shown promising result and a multi-partner collaboration is underway to develop two TACT combinations (artemether-lumefantrine + amodiaquine, and artesunate-mefloquine + piperaquine) and is testing them in multiple African and Asian settings. Once these TACTs are confirmed to be safe, tolerable, efficacious and non-inferior to ACTs, they can provide direct clinical relief in Southeast Asia in case current ACTs would fail. Moreover, a rapid and sustainable transition to TACTs in Africa could delay the emergence and spread of artemisinin and partner drug resistance on the African continent. Although initial results from clinical trials have been encouraging, the trajectory for TACTs towards market introduction is uncertain. Previous antimalarial drug transitions have been characterized as slow and challenging, even when new therapies were clinically superior to failing alternatives. Therefore it is essential to investigate the prospects for market formation for TACTs in Africa and in Southeast Asia.

The **second part** of this thesis examines the prospects of market formation for Triple Artemisinin-based Combination Therapies (TACTs) in African countries where current ACTs are still fully effective at the time of data collection. Therefore, introducing TACTs would not directly benefit individual patients but rather mitigate the risks of future drug resistance. This justifies the assessment of ethical considerations and practical implementation challenges for introducing TACTs in African settings, as is presented in Chapters 4 and 5.

Chapter 4 explores the major ethical considerations and implementation practicalities for forming TACTs markets in African countries. Ethical considerations around public health ethics, individual autonomy and pediatric clinical ethics are presented and embedded in medical ethics literature. Chapter 4 then advances from discussing ethical tensions to examining implementation practicalities for the market formation of TACTs in African countries. The Chapter elaborates on complexities in resource allocation and investment requirements for

introducing TACTs in Africa. In most African countries, engaging in TACTs would require short-term investments (costs + additional side-effects) while the benefits (mitigated risks of drug resistance) would be for the long-term and would transcend national borders. This confronts decision makers and funders with complex trade-offs that need to be made. Chapter 4 explains that transitioning from ACTs to TACTs in Africa may be warranted from a health-economic perspective. The economic impact of widespread ACT failures in Africa would likely exceed the costs of a drug transition. Finally, the Chapter discusses considerations around market authorization, guideline inclusion and implementation programs that may impact the market formation prospects for TACTs in African countries.

Chapter 5 then continues with a qualitative study at the African continent. This Chapter investigates the extent to which antimalarial drug markets in African countries are ready for a transition to TACTs. Data are collected in Nigeria and Burkina Faso through 68 in-depth interviews and 11 focus group discussions with key actor groups in the antimalarial innovation system. The study reveals that the market formation prospects of TACTs in Nigeria and Burkina Faso will likely depend on reported ACT failures in Africa and on active recommendations by the WHO. Respondents expected high readiness for forming TACTs markets in public sectors (which are government controlled) but they suggested more challenges for market formation in private sectors (which are driven by commercial motives). Slow regulatory-, and implementation procedures were identified as potential barriers towards rapid market formation for TACTs in Nigeria and Burkina Faso. The Chapter emphasizes that TACTs need to be benchmarked against current ACTs to avoid jeopardizing their acceptance at the population levels: TACTs regimens should not be more expensive, should not contain more pills and should not cause more side-effects than current ACTs for end-user markets to be formed.

The **third part** of this thesis focuses on the prospects of market formation for TACTs in Southeast Asia. In contrast to the situation in Africa, artemisinin and partner drug resistance and subsequent ACT failures have repeatedly been reported in Southeast Asia. Therefore, introducing TACTs can potentially provide direct clinical benefit in case all current ACTs are being lost to resistance. Moreover, introducing TACTs can help to protect antimalarial drug compounds. However, the introduction of TACTs in Southeast Asia remains subject to debate: some scholars and representatives of policy institutes believe that efforts and resources should instead be invested in malaria elimination activities or in alternative strategies to address drug resistance. This warrants further exploration of the market formation prospects for TACTs in Southeast Asia, which is presented in Chapters 6 and 7.

Chapter 6 investigates the major advantages, disadvantages and implementation challenges of introducing TACTs in Southeast Asian countries. A two-round Delphi study is conducted to systematically assess malaria experts' perspectives towards the introduction of TACTs compared to current practices of rotating ACTs when treatment failures are observed. In the first round of data collection, 53 prominent malaria experts answer open-ended questions on what they consider the most important advantages, disadvantages, and implementation barriers

for introducing TACTs. In the second round, the same expert panel rate the relevance of each statement.

Malaria experts identify a total of 15 advantages, 15 disadvantages and 13 implementation barriers for introducing TACTs in the first round of data collection. In the second round of data collection, consensus is reached on 13 advantages (8 perceived as relevant, 5 as not-relevant), 12 disadvantages (10 relevant, 2 not-relevant), and 13 implementation barriers (all relevant). Advantages that are attributed the highest relevance relate to the clinical and epidemiological rationale of introducing TACTs, in particular the potential of TACTs to protect drug compounds from future drug resistance. Disadvantages that are attributed the highest relevance related to concerns about adverse effects, unavailability of fixed-dose combinations (FDC) of TACTs, and potential cost increases as a result of transitioning to TACTs. Implementation barriers that are attributed highest relevance relate to obtaining timely regulatory approval, the timely availability of FDC TACTs, and generating global-level and national-level policy support for introducing TACTs. The obtained insights from this Delphi exercise provide a systematic and contextualized oversight of determinants for the market formation of TACTs in Southeast Asia.

Chapter 7 is designed as a follow-up to the Delphi study. It presents a qualitative study in which strategies for the market formation of TACTs in the Greater Mekong Subregion (GMS) of Southeast Asia are investigated. In-depth interviews are conducted in three countries that have repeatedly been confronted with ACT failures: Cambodia, Vietnam, and Lao PDR. A total of 29 key stakeholders in the innovation system of antimalarial therapies are being interviewed. Furthermore one participatory workshop is conducted in Cambodia in which potential scenarios around epidemiological developments and market formation developments are discussed. The study reveals that countries in the GMS currently rely on ACTs for reaching their ambitions to eliminate falciparum malaria by 2025. TACTs are, however, considered to be a useful backup in case future treatment failures would occur and as a strategy to prevent the re-establishment of malaria. Chapter 7 shows that a major challenge ahead is to engage decision makers into TACTs given the low case incidence of falciparum malaria in the GMS. Interview respondents are also skeptical if providers would be willing to engage in new therapies for a disease they hardly encounter anymore. Hence, elaborate information dissemination strategies are considered appropriate and should especially target Village Malaria Workers (VMW), which are the current frontline of malaria management in the GMS. Finally, respondents propose several regulatory and programmatic strategies to anticipate on the formation of TACTs markets in the GMS. These strategies include early trial dossier submission to streamline regulatory procedures, early stakeholder engagement to shorten implementation timelines, and inclusion of TACTs as second-line therapy to accelerate their introduction in case they are urgently needed.

Chapter 8 presents a general discussion and the conclusions of the thesis in which we answer the central research question of how markets for antimalarial therapies are being formed under the pressure of drug resistance. We conclude that market formation for antimalarial therapies is multifaceted. Markets are created through interactions between multiple actor groups and

institutions across the globe. Market formation is a multi-scalar undertaking: global-level market formation activities determine national-level and local-level activities and vice versa. Structural couplings enable the functioning of the antimalarial innovation system by connecting dispersed innovation subsystems and in channeling efforts, resources and commodities along geographical scales and locations. Based on the empirical chapters of the thesis, Chapter 8 proposes a multifaceted framework that can be used by global health researchers and policy makers with an interest in market formation. Furthermore, the Chapter presents a conceptual reflection general limitations of the thesis. Finally, a set of policy recommendations is derived. These policy recommendations include the facilitating of information exchange around market formation considerations between countries. Moreover, several strategic measures are recommended to prepare for the market formation of TACTs in African and Southeast Asian countries. Finally, we recommend that market formation studies, similar to the ones presented in this thesis, should be included in future global health innovation initiatives.

Samenvatting

Malaria is een armoede-gerelateerde infectieziekte en komt voor in grote delen van Afrika en Azië. Jaarlijks overlijden er wereldwijd meer dan een half miljoen mensen aan malaria, voornamelijk kinderen in Sub-Sahara Afrika. Dit is tragisch aangezien malaria eenvoudig te behandelen is wanneer effectieve medicijnen op tijd aan de patiënt wordt verstrekt. Op dit moment is de wereld afhankelijk van artemisinin-based combination therapies (ACTs) voor de behandeling van ongecompliceerde falciparum malaria ('malaria' in de rest van deze samenvatting). ACTs bestaan uit een zeer potent en snel werkend artemisinin component (artesunate, artemether, dihydroartemisinin) in combinatie met een langzamer werkend partner component (mefloquine, amodiaquine, lumefantrine, piperaquine of pyronaridine).

Een terugkerend probleem in de strijd tegen malaria is het fenomeen van medicijn resistentie. Door de geschiedenis heen zijn eerstelijns malaria medicijnen herhaaldelijk onbruikbaar geraakt doordat parasieten resistentie hebben ontwikkeld tegen deze medicijnen. Een zorgelijke ontwikkeling is dat het proces van resistentie zich lijkt te herhalen. Malaria parasieten in de Greater Mekong Subregion (GMS) in Zuidoost Azië zijn de afgelopen jaren resistent geworden tegen artemisinin en partner drug combinaties. Een groot gevaar is dat ACT resistentie zich verder verspreid naar Afrika, waar het leeuwendeel van de malaria infecties plaatsvindt. Aangezien nieuwe medicijnen nog jaren verwijderd zijn in de farmaceutische pijplijn, is het van belang dat er snel pragmatische oplossingen komen welk gebruik maken van bestaande medicijnen. Om dit te realiseren moeten er nieuwe medicijn combinaties ontwikkeld worden en moeten markten worden gevormd om deze tijdig bij de patiënt te krijgen.

In deze thesis onderzoeken we hoe markten voor nieuwe malaria therapieën worden gevormd onder druk van medicijn resistentie. Concepten en methoden vanuit innovatie wetenschappen en transitie studies worden gebruikt om malaria medicijn transities te onderzoeken, met een nadruk op markt formatie processen. In de introductie in Hoofdstuk 1 ontwikkelen we een systemische conceptualisatie van markt formatie, ingebed in innovatie systeem theorie. We beschouwen markten als subsystemen van technologische innovatie systemen: markten bestaan uit alle actoren, netwerken en instituties die direct betrokken zijn bij het toegankelijk maken van malaria medicijnen voor eindgebruikers. In de empirische Hoofdstukken 2 – 7 wordt de systemische conceptualisatie toegepast om marktformatie voor malaria medicijnen empirisch te onderzoeken.

De empirische hoofdstukken uit deze thesis zijn opgedeeld in drie delen. Het **eerste deel** van de thesis (Hoofdstuk 2 en 3) brengt het antimalaria innovatiesysteem in kaart en identificeert *system failures* die de formatie van markten voor nieuwe malaria medicijnen blokkeren. Dit doen we aan de hand van de transitie van conventionele monotherapieën naar ACTs aan het begin van dit millennium. In Hoofdstuk 2 ontwikkelen we een framework voor een duurzaam systeem voor antimalaria medicijn ontwikkeling en diffusie. We stellen vast waar het huidige systeem niet duurzaam is, en identificeren vier framework componenten die cruciaal zijn voor een duurzaam

systeem: availability, affordability, accessibility en acceptability. Availability wordt beschreven als veilige en effectieve interventies welke in voldoende hoeveelheden worden geproduceerd en zijn goedgekeurd door regulatoren. Affordability wordt beschreven als interventies welk kunnen worden aangeschaft binnen de financiële mogelijkheden van overheden en patiënten in endemische gebieden. Accessibility wordt beschreven als interventies die fysiek bereikbaar zijn voor degene die ze nodig hebben. Acceptability wordt beschreven als de correcte adoptie en consumptie van de interventie door patiënten en verzorgenden.

Ons framework wordt vervolgens toegepast op de transitie van conventionele monotherapieën naar ACTs. De analyse toont aan dat availability van toekomstige therapieën kan worden gestimuleerd door de drijfveren voor farmaceuten om in armoede gerelateerde ziekten te investeren te herzien. Daarnaast moet de rol van publiek-private samenwerkingen worden uitgebreid en moeten regulatoire trajecten worden gestroomlijnd om te voorzien in duurzame availability van malaria medicijnen. Duurzame affordability zal afhankelijk zijn van inclusieve prijsstrategieën en subsidieregelingen welke met name aandacht besteden aan betaalbaarheid binnen de private sector. Duurzame accessibility is afhankelijk van functionerende distributiekanalen, beleidscoördinatie en van stakeholder engagement strategieën. Duurzame acceptability is afhankelijk van informatiecampagnes en kan worden gestimuleerd door eindgebruikers direct bij het innovatieproces te betrekken. Hoofdstuk twee concludeert dat duurzame availability, affordability, accessibility en acceptability onderling verbonden zijn: verbeteringen in één framework component zal direct effect hebben op de andere framework componenten. Alle vier de componenten zijn essentieel voor een duurzaam systeem van malaria medicijn ontwikkeling en diffusie.

Hoofdstuk 3 toont vervolgens aan hoe markten voor ACTs zijn gevormd op verschillende geografische niveaus en locaties nadat alle conventionele malaria therapieën waren weggevallen door resistentie aan het begin van dit millennium. Data is verzameld aan de hand van een uitgebreide literatuurstudie en aangevuld met zes diepte-interviews. Drie episodes van markt formatie worden geïdentificeerd in Hoofdstuk 3. De eerste episode toont aan hoe de druk van resistentie heeft geleid tot de ontdekking van artemisinin, een nieuw soort malaria medicijn. De episode toont vervolgens aan hoe publieke instellingen, academica en partnerships hebben bijgedragen aan vroege evolutie van het innovatiesysteem. De tweede episode toont aan hoe transnationale organisaties een bevorderend globaal innovatielandschap voor ACT ontwikkeling en gebruik hebben gerealiseerd. De derde episode toont aan hoe deze ontwikkelingen uiteindelijk hebben geleid tot de formatie van zowel publieke-sector als private-sector markten voor ACTs in de Greater Mekong Subregion (GMS), een regio in Zuidoost-Azië welk bekend staat als globaal epicentrum van medicijn resistente malaria.

Hoofdstuk 3 biedt verschillende theoretische contributies met betrekking tot markt formatie in geografisch complexe innovatie systemen. De technologische innovatiesysteem benadering wordt gecombineerd met de globale innovatiesysteem benadering om markt formatie in de transitie naar ACTs te onderzoeken. Het hoofdstuk toont aan hoe structurele koppelingen

– gedefinieerd als actoren, netwerken of instituties die tussen innovatie subsystemen spannen – zijn ontstaan en hoe deze hebben bijgedragen aan ACT markt formatie. Een grote verscheidenheid aan structurele koppelingen wordt geïdentificeerd en beschreven in het hoofdstuk. Hoofdstuk 3 concludeert dat marktformatie in global health transities plaatsvindt op verschillende geografische niveaus en locaties. Marktformatie activiteiten zijn direct gelinkt aan andere systemische activiteiten zoals de mobilisatie van resources en het creëren van legitimatie. Structurele koppelingen ontstaan in verschillende vormen en zijn essentieel voor marktvorming voor nieuwe malariatherapieën. Het hoofdstuk biedt een unieke inkijk in een geografisch complexe transitie en biedt conceptuele en theoretische beginpunten voor toekomstig onderzoek naar global health innovatiesystemen.

Het tweede en derde deel van de thesis richten zich op de vooruitzichten van markt formatie voor Triple Artemisinin-based Combination Therapies (TACTs) in verschillende epidemiologische settings. Artemisinin en partner drug resistentie wordt gezien als een grote bedreiging voor malaria management wereldwijd. Nieuwe medicijnen zijn nog in premature staat van ontwikkeling en hierdoor zijn pragmatische oplossingen nodig om ACT resistentie tegen te gaan. De ontwikkeling en introductie van TACTs wordt beschouwd als een veelbelovende aanpak in de strijd tegen ACT resistentie. De rationale is dat het combineren van een artemisinin component met twee partner medicijnen met verschillende actiemodi de therapeutische levensduur van elk van de componenten kan verlengen doordat ze wederzijdse bescherming tegen resistentie bieden. Eerdere klinische studies hebben positieve resultaten opgeleverd en een multi-partner samenwerking genaamd het Development of Triple Artemisinin-based Combination Therapies (DeTACT) project is van start gegaan om twee TACT combinaties (artemether-lumefantrine + amodiaquine, en artesunate-mefloquine + piperaquine) te ontwikkelen en te testen in verschillende Afrikaanse en Aziatische gebieden. Zodra deze TACTs veilig, effectief en niet-inferieur aan ACTs worden bevonden, kunnen ze worden geïmplementeerd om medicijnen te beschermen tegen resistentie. Daarnaast kan de introductie van TACTs in Zuidoost Azië directe klinische verlichting bieden in het geval alle huidige medicijnen daar verloren gaan. Ten slotte kan een duurzame transitie naar TACTs in Afrika het ontstaan-, en verspreiden van artemisinin en partner drug resistentie op het Afrikaanse continent vertragen. Echter, hoewel initiële resultaten van klinische studies veelbelovend zijn, is het vooruitzicht van marktformatie voor TACTs in Afrikaanse en Aziatische landen onzeker. Eerdere malaria medicijn transities zijn traag en moeizaam verlopen, zelfs als medicijnen klinisch superieur waren aan falende alternatieven. Daarom is het cruciaal om onderzoek te doen naar de vooruitzichten van marktformatie voor TACTs in Afrikaanse en in Zuidoost Aziatische landen.

Het **tweede deel** van de thesis richt zich op het perspectief van marktformatie voor TACTs in Afrikaanse landen, waar huidige ACTs nog volledig effectief zijn ten tijde van data collectie. De introductie van TACTs zou hierdoor niet direct klinisch voordeel bieden aan individuele patiënten maar in plaats daarvan de risico's op toekomstige resistentie verkleinen. Dit impliceert belangrijke ethische en praktische vragen rondom de mogelijke markt formatie van TACTs welke in Hoofdstukken 4 en 5 worden behandeld.

Hoofdstuk 4 onderzoekt de belangrijkste ethische en praktische afwegingen voor de formatie van TACTs markten in Afrikaanse landen. Ethische afwegingen rondom public health ethiek, individuele autonomie en pediatrische klinische ethiek worden gepresenteerd en ingebed in medische ethiek literatuur. Na de ethische discussie vervolgt Hoofdstuk 4 met enkele praktische zaken voor de implementatie van TACTs in Afrika. Het hoofdstuk onderzoekt uitdagingen in resource allocatie en de investeringen die benodigd zijn voor het vormen van TACTs markten in Afrika. In de meeste Afrikaanse landen zou de keuze voor TACTs impliceren dat korte termijn investeringen nodig zijn (kosten + toename in bijwerkingen) terwijl de voordelen voor de lange termijn zouden zijn (verminderd risico op artemisinin en partner medicijn resistentie). Dit confronteert beleidsmakers met complexe afwegingen tussen hedendaagse investeringen en toekomstige opbrengsten. Ten slotte analyseert Hoofdstuk 4 afwegingen omtrent markt autorisatie, opname in behandelrichtlijnen en implementatie programma's en de impact hiervan op de vooruitzichten van markt formatie voor TACTs in Afrikaanse landen.

In Hoofdstuk 5 voeren we een kwalitatieve studie uit op het Afrikaanse continent. Dit hoofdstuk onderzoekt de mate waarin de malaria medicijn markten in Afrikaanse landen klaar zijn voor een transitie naar TACTs. Data is verzameld in Nigeria en in Burkina Faso aan de hand van 68 interviews en 11 focus groep discussies met belangrijke actoren in het malaria innovatiesysteem. De studie toont aan dat de markt formatie vooruitzichten voor TACTs in Nigeria en Burkina Faso zullen afhangen van bevestiging van ACT resistentie op het Afrikaanse continent en van actieve aanbevelingen door de WHO. Respondenten verwachtten dat markt formatie voor TACTs in publieke sector relatief eenvoudig zal zijn maar ze verwachtten meer uitdagingen voor markt formatie voor TACTs in de private sector. Trage regulatie-, en implementatie procedures werden genoemd als mogelijke barrières voor de marktformatie van TACTs in Nigeria en Burkina Faso. Hoofdstuk 5 benadrukt dat TACTs moeten worden gebenchmarkt tegen huidige ACTs om acceptatie op populatieniveau te bewerkstelligen: TACTs zouden niet duurder moeten zijn dan ACTs, niet meer pillen moeten omvatten dan ACTs, en niet meer bijwerkingen moeten hebben dan de huidige ACTs.

Het **derde deel** van de thesis richt zich op de vooruitzichten van market formatie voor TACTs in Zuidoost-Azië. In tegenstelling tot Afrika zijn malariaparasieten in Zuidoost-Azië in toenemende mate resistent geworden tegen huidige ACTs. Hierdoor kan introductie van TACTs directe klinische verlichting bieden in het geval alle huidige ACTs verder verloren gaan door resistentie. Daarnaast kan de introductie van TACTs helpen medicijn componenten te beschermen tegen resistentie. Echter, door sommige onderzoekers en beleidsbepalers worden vraagtekens geplaatst bij de wenselijkheid en de praktische haalbaarheid van de introductie van TACTs in Zuidoost-Azië. Volgens hen kunnen resources en inspanningen beter in malaria eliminatie activiteiten en andere strategieën tegen resistentie worden geïnvesteerd. Dit rechtvaardigt een verdere verkenning van markt formatie vooruitzichten voor TACTs in Zuidoost-Azië, zoals beschreven in Hoofdstukken 6 en 7.

Hoofdstuk 6 onderzoekt de belangrijkste voor- en nadelen van-, en de belangrijkste implementatie-uitdagingen voor de introductie van TACTs in Zuidoost-Aziatische landen. We voeren een Delphi-onderzoek uit om de percepties van prominente malaria-experts op deze onderwerpen te identificeren en te analyseren. In de eerste ronde van dataverzameling beantwoorden 53 prominente malaria-experts open vragen over wat volgens hen de belangrijkste voor-, en nadelen zijn en wat de belangrijkste implementatie barrières zijn voor de introductie van TACTs in Zuidoost Azië. In de tweede ronde beoordeeld dezelfde expertpanel de relevantie van elke uitspraak op een 5-punts Likertschaal.

In de eerste ronde identificeren malaria experts 15 voordelen, 15 nadelen en 13 implementatie barrières voor de introductie van TACTs. In de tweede ronde wordt overeenstemming bereikt over 13 voordelen (8 relevant, 5 niet relevant), 12 nadelen (10 relevant, 2 niet relevant) en 13 implementatie barrières (allemaal relevant). Voordelen die het hoogst scoren op relevantie hebben betrekking op de klinische en epidemiologische rationale voor de introductie van TACTs, met name TACTs potentie om geneesmiddelen te beschermen tegen toekomstige resistentie. Nadelen die het meest relevant worden geacht hebben betrekking op zorgen omtrent bijwerkingen, het huidige gebrek aan beschikbaarheid van fixed-dose combinaties (FDC) van TACTs en mogelijke kostenstijging als gevolg van een transitie naar TACTs. Implementatie barrières die het meest relevant worden geacht, hebben betrekking op het verkrijgen van tijdige regulatoire goedkeuring, de tijdige beschikbaarheid van FDC-TACTs en het genereren van beleidsondersteuning op mondiaal en nationaal niveau voor de invoering van TACTs. De verkregen inzichten uit deze Delphi-oefening geven een systematisch overzicht van belangrijke elementen voor de marktformatie van TACTs in Zuidoost-Azië.

Hoofdstuk 7 is ontworpen als vervolgonderzoek op de Delphi studie en presenteert een kwalitatief onderzoek waarin strategieën voor de marktvorming van TACTs in de Greater Mekong Subregion (GMS) van Zuidoost-Azië worden onderzocht. 29 belangrijke actoren in het innovatiesysteem van malariatherapieën worden geïnterviewd in Cambodja, Vietnam en Laos. Verder wordt een participatieve workshop georganiseerd in Cambodja waarin mogelijke scenario's rond epidemiologische ontwikkelingen en marktvormingsontwikkelingen worden besproken. Uit de studie blijkt dat landen in de GMS momenteel inzetten op ACTs om hun malaria eliminatie ambities te realiseren. TACTs worden echter beschouwd als een nuttige back-up strategie voor het geval alle ACTs, inclusief artesunate-pyronaridine zouden wegvallen door resistentie en als een strategie om een heropleving van malaria te voorkomen. Hoofdstuk 7 toont aan dat het een grote uitdaging is om besluitvormers te betrekken bij TACTs, gezien de lage prevalentie van falciparum-malaria in de GMS. Respondenten zijn daarnaast sceptisch of zorgaanbieders bereid zouden zijn om nieuwe therapieën te adopteren voor een ziekte die ze nauwelijks meer tegenkomen. Uitgebreide informatie-strategieën worden noodzakelijk geacht en moeten zich idealiter richten op Village Malaria Worker (VMW) programma's, de huidige frontlinie voor malaria management in de GMS. Ten slotte stellen de respondenten verschillende beleids-, en programmatische strategieën voor om te anticiperen op de markt formatie voor TACTs in de GMS.

Hoofdstuk 8 presenteert een algemene discussie en de conclusies van de thesis. Hierin beantwoorden we de centrale onderzoeksvraag over hoe markten voor malaria therapieën worden gevormd onder de druk van resistentie. We concluderen dat markt formatie veelzijdig is. Markten worden gecreëerd door interacties tussen meerdere actoren en instituties wereldwijd. Marktformatie is een multi-scalaire onderneming: markt formatie activiteiten op mondiaal niveau bepalen activiteiten op nationaal-, en lokaal-niveau en vice versa. Structurele koppelingen faciliteren de werking van het innovatiesysteem voor malaria medicijnen door innovatie subsystemen met elkaar te verbinden en door het kanaliseren van activiteiten, resources en materialen langs geografische schalen en locaties. Op basis van de bevindingen van de empirische hoofdstukken stellen we een multifaceted framework voor dat kan worden gebruikt door onderzoekers en beleidsmakers met interesse in markt formatie in global halth. Daarnaast presenteren we een conceptuele reflectie en geven we algemene limitaties van het proefschrift. Tot slot wordt een reeks beleidsaanbevelingen gedefinieerd. We adviseren dat informatie-uitwisseling rond markt formatie afwegingen tussen landen moet worden gefaciliteerd. Daarnaast worden verschillende strategische maatregelen gedefinieerd ter voorbereiding van de markt formatie van TACTs in Afrika als Zuidoost-Azië. Ten slotte bevelen we aan dat onderzoeken naar markt formatie, vergelijkbaar met die in dit proefschrift, moeten worden opgenomen in toekomstige global health innovatie-initiatieven.

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