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MMV Medicines for Malaria Venture

ARP29

Introduction of a new chemoprevention treatment for malaria in pregnancy in Sub-Saharan Africa:

An overview of barriers and key drivers to optimal adoption and implementation.

Final Report

by

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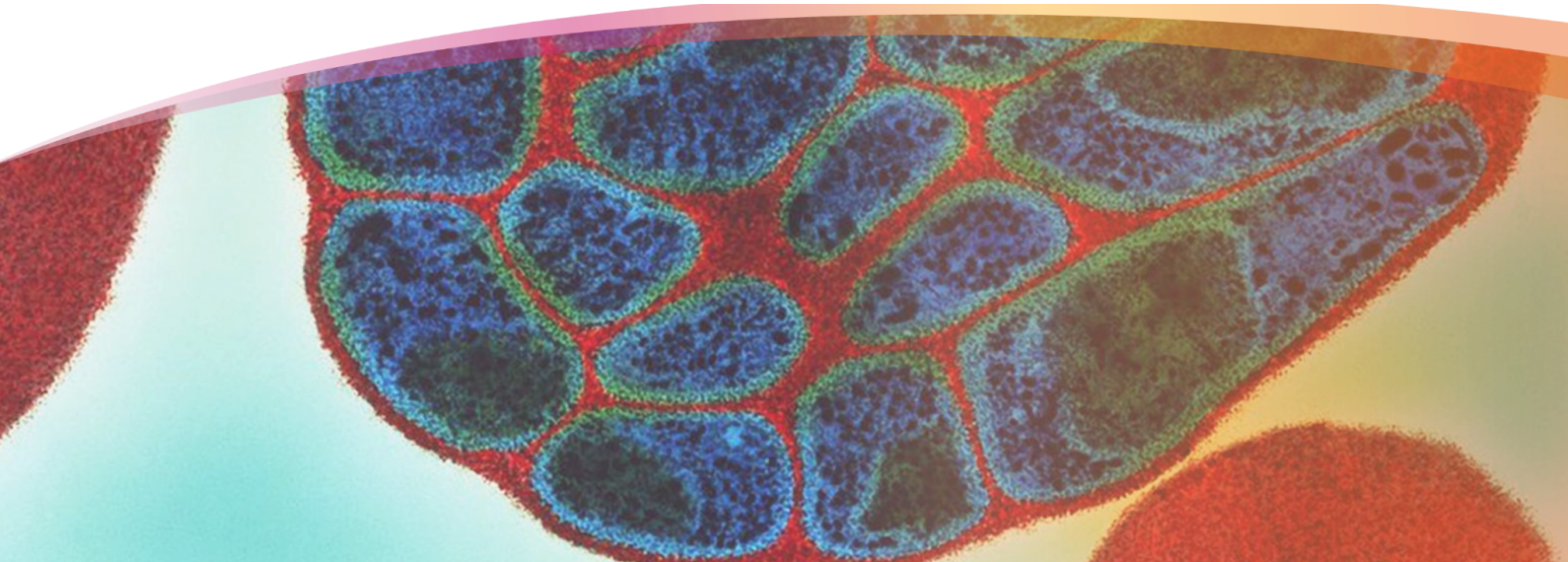

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Abbreviations List

ANC	Antenatal Care
ARP	Applied Research Project
CHWs	Community Health Workers
c-IPTp	Community Intermittent Preventive Treatment
DHA/PPQ	Dihydroartemisinin/Piperaquine
DOT	Directly-Observed Therapy
HIV	Human Immunodeficiency Virus
IPTp	Intermittent Preventive Treatment
IPTp-SP	Intermittent Preventive Treatment with the Active Ingredient SP
ITNs	Insecticide-Treated Nets
MMV	Medicines for Malaria Venture
NGO	Non-Governmental Organizations
PPQ	Piperaquine
PYR	Pyronaridine
PYR-AS	Pyronaridine-Artesunate
SMC	Seasonal Malaria Chemoprevention
SP	Sulfadoxine Pyrimethamine
SSA	Sub-Saharan Africa
WHO	World Health Organization

Introduction

Sub-Saharan Africa accounted for nearly 95% of the predicted 247 million cases of malaria that occurred globally in 2021. Furthermore, it was estimated that 40 million pregnancies occurred in the moderate- to high-transmission countries of sub-Saharan Africa, of which 13.3 million (32%) were exposed to malaria infection. Pregnancy-related malaria is a serious public health challenge. Worldwide, an estimated 125 million pregnancies are at risk of contracting malaria each year. Malaria poses a potentially fatal risk to both mother and child. Strong evidence supports chemoprevention's effectiveness in reducing malaria prevalence in selected high-risk populations like pregnant women. Sulfadoxine pyrimethamine (SP) is the recommended intermittent preventative medication for uncomplicated malaria in pregnancy, however not all pregnant women – such as those with HIV or in their first trimester of pregnancy – are eligible for it. To meet SDG 3 of universal health coverage and equitable access to healthcare services, as well as support endemic countries with their elimination agenda, there is an urgent need to fill this medicine gap.

MMV has been working on new drug recombinations to address this market failure. This is part of its commitment to advancing the gender equity agenda. MMV aims to provide informed therapeutic choices for malaria protection across all pregnant women populations living in Sub-Saharan Africa. Currently, MMV is looking at a new molecular combination of pyronaridine and piperaquine as a chemo-prophylactic treatment for malaria during pregnancy. The suggested course of action includes taking three tablets once a day for two days in a row every month till delivery. It is safe to start this treatment during the first month of pregnancy, and pregnant women living with HIV can use it in conjunction with cotrimoxazole. Fasting is not necessary. Comparable side effects and similar efficiency in preventing malaria are associated with SP while alleviating the rising worries about the increase of SP resistance. Newborn weight is not impacted by the treatment.

As such, this report aims to assist MMV in collecting additional non-clinical data evidence to inform the product development as well as its introduction plan. Its goal is to understand countries and other stakeholders' interest in adopting this new intervention and to identify early any potential implementation challenges related to the product attributes by answering the following questions: (1) what are the anticipated implementation barriers and facilitators of this new malaria prevention treatment targeting malaria in pregnancy? And, (2) what needs to be put in place to create an enabling environment to facilitate the adoption and uptake of the new product?

To address these questions, the report is organized as follows. In a preliminary part, we present the literature review on the topic and the research methodology used for this project. In the first part, we present the results of the interviews carried out, demonstrating the first spontaneous reactions of the interviewees to the introduction of the new drug and evaluating the potential demand for it. The second part is devoted to the analysis of the research, where a number of different points are addressed such as how to create an environment that facilitates the acceptance and uptake of the new product. The third and final part is a section dedicated to recommendations for the new drug to fit into current malaria elimination strategies.

Literature review

According to the WHO, in 2022, globally, an estimated 249 million malaria episodes occurred, causing the loss of 608,000 lives in 85 different nations. The African region has borne a significantly high burden of this disease, hosting 94 percent of global malaria cases, quantified at 233 million, and 95 percent of deaths, amounting to 580,000. Importantly, children under the age of 5 made up about 80 percent of fatal malaria deaths within this region (WHO, 2023).

Malaria infection during pregnancy

Detailed examination showed that malaria poses an extreme risk for pregnant women, who are more susceptible to malaria infections, with higher frequency and severity of the disease due to depressed cellular immunity during pregnancy (Dhiman, 2012). Malaria infection can cause serious risks to the mother, the fetus, and the newborn. It is critical that pregnant women living in malaria-endemic areas receive preventive care and timely treatment to reduce the risk of complications (Bauserman et al., 2019).

The literature states that the susceptibility of pregnant women to malaria stems from alterations in their immune systems during pregnancy, coupled with the introduction of a new bodily organ, the placenta, which offers novel attachment sites for parasites. Unlike adults who have developed partial immunity through recurrent malaria infections, pregnant women experience a decrease in their immunity to malaria. Consequently, malaria infection during pregnancy can result in detrimental consequences for both the mother and the developing fetus. These adverse effects include maternal anemia, fetal loss, premature birth, restricted fetal growth within the womb, and the delivery of infants with low birth weight—weighing less than 2500 grams or 5.5 pounds—posing an increased risk of mortality. This issue is particularly challenging for women in their initial and subsequent pregnancies, as well as those who are HIV-positive (CDC, 2018). The malaria infection also poses a significant risk for perinatal, neonatal, and infant mortality. In 2022, in 33 countries of the WHO African Region, an estimated 35.4 million pregnancies occurred, of which about 36 percent were exposed to malaria infection. The prevalence of malaria exposure during pregnancy was highest in parts of West and Central Africa. Despite this, between 2021 and 2022, exposure to malaria in pregnancy remained constant in the WHO African Region. It is believed that effective prevention of cases caused by malaria infection can significantly reduce neonatal and infant mortality.

The co-infection of malaria and HIV

Another considerable risk, specifically for pregnant women, is the concomitant infection of malaria and HIV which can pose significant risks to both mother and child. Involved women are particularly susceptible to complications during pregnancy because of their immunosuppressive status due to HIV. When a woman is affected by both, the risk of these complications may increase even further. In fact, malaria can accelerate the progression of HIV infection and increase the viral load in the blood, worsening the woman's immunological condition. On the other hand, HIV can affect the body's immune response to malaria, making the woman more susceptible to the complications associated with this disease. Consequently, malaria-HIV co-infection during pregnancy requires appropriate management and treatment for both conditions to minimize health risks to mother and baby. Affected women show a generally doubled

HIV viral load when affected by malaria during pregnancy.

Geographically, malaria and HIV are predominantly concentrated in tropical and subtropical areas of the world, including sub-Saharan Africa (SSA). About 70 percent of HIV-infected people globally live in this region, where 350 million individuals are at risk for malaria. Because of this overlap, a significant combined impact is expected. Malaria was identified as the third leading cause of HIV-related morbidity in a systematic review of Africa (Kwenti, 2018).

Factors Influencing its Escalation in Sub-Saharan Africa

The incidence of malaria places a heavy burden on people in endemic regions and is likely to increase due to several factors. First, favorable climate and environmental conditions for mosquitoes, inadequate mosquito control strategies, and drug-resistant malaria parasites exacerbate disease transmission. Mosquito resistance to insecticides and partial artemisinin resistance are growing threats, with the World Health Organization noting resistance in Africa, including Eritrea, Rwanda, Uganda, and Tanzania. Regular monitoring of antimalarial drug efficacy is critical to address this issue (WHO, 2023; Protopopoff et al., 2009). Second, human migration and displacement can introduce malaria to new regions, increasing outbreak risks. Natural disasters and conflicts disrupt health systems, worsen overcrowding, and deteriorate infrastructure, all of which facilitate malaria spread. Poverty, lack of healthcare access, and inadequate infrastructure further increase vulnerability, leading to delayed diagnosis and treatment, particularly in remote areas. Lastly, factors such as lack of education, low income, poor housing, and agricultural occupations increase infection risk in Sub-Saharan Africa (SSA). Public policies to reduce healthcare inequalities and improve economic and educational opportunities can mitigate malaria's impact in SSA (Degarege et al., 2019).

Protection against Malaria in Pregnancy

The WHO recommends the following options to protect pregnant women from malaria: (1) Mosquito avoidance, including the use of insecticide-treated nets (ITNs) and indoor residual spraying, (2) Intermittent Preventive Treatment with the active ingredient SP (IPTp-SP) and regular screening, detection and treatment of acute malaria cases (ISTp) (WHO, 2023). This is largely confirmed in the literature, which further emphasizes the efficacy of combining ITNs with IPTp-SP (Mlugu et al., 2020; Travassos & Laufer, 2022; Wylie & Rogerson, 2023; Schantz-Dunn & Nour, 2009; Rogerson et al., 2007).

Intermittent Preventive Treatment for Malaria in Pregnancy

Intermittent Preventive Treatment of Malaria in Pregnancy (IPTp) was developed specifically for pregnant women to reduce the burden of malaria on them and its effects on the fetus. It has been shown to prevent mother-to-child transmission of malaria and reduce other complications (Ndu et al., 2020). It was estimated that there would be about 914,000 low-birth-weight infants in 2022, compared with an estimated 393,000 low-birth-weight infants with current coverage of IPTp prophylaxis in these regions. A series of recent studies have also indicated that the current use of IPTp has averted numerous episodes of low birth weight (Slutsker & Leke, 2023).

IPTp is generally recognized as an effective method of protection for pregnant women (Sicuri et al., 2010). According to the WHO (2023), "IPTp is generally highly cost-effective, widely accepted, feasible for delivery and justified by a large body of evidence generated over several decades".

The WHO guides new malaria chemoprevention development, emphasizing drug characteristics like safety, efficacy, and resistance prevention (WHO, 2023). Sulfadoxine-Pyrimethamine (SP) is the recommended IPTp option for HIV-uninfected women, with good safety and efficacy profiles when administered during antenatal check-ups starting in the second trimester. Three or more doses are recommended, spaced a month apart (Figueroa-Romero et al., 2022; WHO, 2023). Three doses are crucial for effectiveness (Dosoo et al., 2021). IPTp-SP aligns with WHO's preferred characteristics, allowing safe administration up to delivery and suitable for direct observation therapy. It can be taken with or without food and is available in a fixed-dose formulation, enhancing compliance (WHO, 2023).

Despite the favorable product characteristics of IPTp-SP, however, uptake in Sub-Saharan Africa is still low (Darteh et al., 2021). This raises the question of what product characteristics or additional measures would be required to facilitate the implementation of a new chemoprevention. However, the further upscaling of IPTp in its current form is not without controversy (Mlugu et al., 2020). Major concerns exist about the future efficacy of SP as resistance is increasing in Africa. Currently, SP is still endorsed in areas where there is moderate-to-mid-level resistance to SP, as studies have shown that IPTp-SP continues to have a positive impact on birth outcomes. In high-resistance areas, it is advised against the use of SP (WHO, 2013).

The limitations of the current Chemoprevention for Malaria in Pregnancy

Although IPTp-SP is widely supported, its limitations in achieving total malaria elimination are increasingly recognized. A major issue is that not all pregnant women are eligible for SP. Women in the first trimester are advised against using SP due to limited evidence on fetal development effects. HIV-positive women are also ineligible due to adverse interactions between SP and cotrimoxazole, leaving some of the most vulnerable without protection (Figueroa-Romero et al., 2022).

Resistance to SP is becoming widespread in Sub-Saharan Africa, particularly in the eastern and southeastern regions, necessitating an alternative drug for IPTp (Flegg et al., 2022). Additionally, IPTp relies on current healthcare structures for administration during antenatal care visits, which poses challenges in uptake. These limitations must be addressed to improve public health policy effectiveness. To improve the effectiveness of public health policy, these limitations would need to be addressed in parallel (Ogba et al., 2022).

The WHO recently issued a new field guide recommending community-based delivery approaches of IPTp (c-IPTp) as a possible solution in addressing weaknesses in the healthcare delivery system to improve the uptake and coverage of IPTp (WHO 2024).

Given the limitations of widespread resistance to IPTp-SP, a new preventive treatment is proposed to ensure no one is left behind in high-resistance areas (Mathenge et al., 2020). The proposed alternative is a combination of approved antimalarials, specifically pyronaridine (PYR) and piperaquine (PPQ), recommended for potential use in first-trimester pregnancy by the WHO (Malaria Policy Advisory Group, 2023).

PPQ and PYR are key antimalarial drugs known for their effectiveness against *Plasmodium falciparum* and their extended half-life, which ensures prolonged action in the body. This combination would not only enhance treatment efficacy through a synergistic effect but also help prevent drug resistance, addressing a major challenge in malaria control (Mathenge et al., 2020).

Piperaquine

The fixed-dose combination of Dihydroartemisinin/Piperaquine (DHA/PPQ), known on the market as Eurartesim (WHO, 2022), has garnered significant attention and commendation from expert committees owing to its commendable risk-benefit profile. Expert recommendations highlight its safety and efficacy, even during pregnancy, presenting a valuable alternative to treatments incorporating mefloquine or amodiaquine. This combination proves efficacious in addressing uncomplicated malaria cases, showcasing promising outcomes. Its relatively low incidence of side effects, particularly among children, is noteworthy, although cautious administration is advised concerning its use in what is referred to as 'early pregnancy,' a term requiring further clarification regarding the specific gestational period.

Despite its overall positive attributes, there exist potential risks associated with PPQ, notably the small concern of cardiotoxicity marked by QT interval prolongation, necessitating vigilance in its utilization. Moreover, documented instances of increased resistance to PPQ, notably observed in Southeast Asia over the past decade, underscore the crucial need for ongoing surveillance and meticulous administration to preserve its efficacy in combating malaria (Rosenthal & Ng, 2020).

Pyronaridine

Pyronaridine-Artesunate (PYR-AS), commercially known as Pyramax, also stands as a fixed-dose combination medication (WHO, 2019) recognized for its efficacy in combating specific types of malaria caused by *Plasmodium falciparum* and *Plasmodium Vivax*. However, caution is advised regarding its administration in early pregnancy, although, in critical situations where the mother's life is endangered by malaria, healthcare providers might consider its use.

The prescribed dosage regimen typically involves a fixed-dose combination tablet administered once daily for a consecutive three-day period, constituting a complete course of treatment.

A combined solution?

The PYR-PPQ combination is sought for its potential synergistic effects, enhancing efficacy against malaria parasites while reducing resistance risk (Mathenge et al., 2020). This combination offers extended

action and broader coverage against multiple stages of the malaria parasite's life cycle. However, effectiveness may vary based on geographical location and resistance patterns. Furthermore, despite the favorable findings of the PYR-PPQ combination in clinical studies, different countries and regions may have different guidelines for treating malaria which could oppose the implementation of the new drug locally.

As such, more non-clinical data evidence must be gathered to support both the PYR-PPQ product development and its introduction strategy, as the product development is currently underway intending to receive approval from a strict regulatory body within three to four years as was detailed in the MMV ARP project brief. Additionally, according to the WHO's Global Malaria Program, there is a desire to implement the usage of the PYR-PPQ combination during the first trimester of pregnancy (WHO, 2023). Thus, it will be crucial to comprehend the motivation of nations in implementing this new intervention and to spot any possible implementation issues with the product qualities as soon as possible.

However, the drug's efficacy, side effects (or lack thereof), cost, and availability of various combinations would all play a role in how soon the drug was implemented. Case studies show the importance of qualitative research and its role in understanding the barriers and facilitators of new chemoprevention methods, and their applicability to pregnancy – as the limited knowledge on the PYR-PPQ combination, among other antimalarial treatments, is even less researched on pregnant individuals. Bridging the knowledge gap between clinical trials and “on-the-field” expertise is what our research team will attempt to undertake.

Methodology

Setting

In the interest of having a holistic view of the information we collected, we intended to interview experts from different regions in SSA for their unique characteristics – Western Africa for it is a malaria-endemic zone, Eastern Africa for its documented increase in resistance, and Southern Africa for its research. After extended discussion with MMV for coordination with a separate research team, the final selected countries were Burkina Faso, Malawi, Mali, and Tanzania. Furthermore, some of the insights gleaned from these countries were found to be applied to their region in general, due to cultural and socio-political similarities.

Research Design & Respondent Selection

Our qualitative research aimed at gaining insight into the complex context surrounding the implementation of this new malaria prevention treatment, specifically designed for use during pregnancy.

The primary focus was on understanding and delineating the barriers and facilitators anticipated in the adoption and execution of this innovative approach. Framed within this overarching objective, our study aims to address specific research questions, notably: (1) the identification and exploration of anticipated implementation barriers and facilitators of this new malaria prevention treatment in pregnancy, and (2) the formulation of a possible strategy to cultivate an environment conducive to fostering the adoption and uptake of this new drug.

Protocol:

The research methodology hinged significantly on semi-structured interviews, designed to extract comprehensive insights from key stakeholders operating within the local and global malaria community and explore their potential interests for this new intervention. The participant selection process was done through stratified sampling methods facilitated by our partner, the MMV. Stakeholders of interest spanned a diverse spectrum, encompassing representatives from National Malaria Control Programs, implementing agencies, and policymakers.

The interview protocol was carefully designed, drawing from established qualitative research guidelines, acquired through a recognized workbook (Hennink et al., 2020), and insights gleaned during the Applied Research Foundations (ARP) course session conducted on November 28th, 2023 – dedicated entirely on the conduct of qualitative methods and interviews. Our commitment to ethical conduct remained steadfast throughout the research process.

Data Collection

The interviews were conducted through online phone and video calls that lasted between 40 to 70 minutes. A questionnaire guideline was written by the ARP29 team; as well as followed through by MMV

colleagues to ensure it met their needs and standards. Between the months of April and May 2024, a total of 16 respondents were questioned – with 15 being the perceived saturation – from the abovementioned chosen countries as well as experts from international organizations and other cross-border authorities on malaria that had worked in the regions.

The respondents who provided the information in this report were from the following institutions and organizations:

- Centers for Disease Control and Prevention (1)
- JHPiego (2)
- Malaria Research and Training Centers (1)
- Ministries of Health, which includes;
    - National Institutes for Medical Research (2)
    - National Malaria Control Programs (4)
    - Reproductive and Child Health Section (1)
- Research Groups (2)
- Roll Back Malaria (1)
- Universities (1)
- World Health Organization (1)

As the majority of our respondents have had experience as implementers within the malaria community, our research predominantly reflects their perspective. Therefore, to ensure a balanced analysis, it was important to also give particular consideration to the opinions of other groups who might have different experiences or viewpoints.

Data Analysis

Inductive approach:

We adopt an inductive approach to our data (Caulfield, 2019). This signifies that the themes and patterns identified during our analysis organically emerge solely from the rich pool of information gleaned from the interviews. Importantly, these themes will not be preconceived or predetermined, allowing for an unfiltered, unbiased exploration of the interview data. The data obtained from our interviews was not transformed into quantitative data, it was digitized through a transcript writing software, and we conducted the thematic analysis manually.

Thematic analysis:

For data analysis derived from the interviews, we utilized thematic analysis – through the identification of recurring themes and patterns within the transcribed data, this allows us to collect key ideas, concerns, and expectations of the global malaria community and identify those concepts that emerge more frequently.

Since we aim to explore the potential interest of representatives of the global malaria community for this new malaria prevention and identify potential barriers and facilitators to its implementation, it is useful to have both an overview of the perceptions mentioned by our interview partners and to identify those that are frequently repeated in order to assess their priority and relevance.

Ethics:

We paid particular attention to ethical considerations, encompassing informed consent, confidentiality protocols, GGI ethical clearance, robust data protection measures, and alignment with the directives set forth by relevant ethics committees or review boards.

The interviews were recorded through audio only upon receiving explicit consent from the participants, used for transcription purposes, and immediately deleted after analysis. Subsequently, management, anonymization, and secure storage of data on servers provided by the Geneva Graduate Institute fortified confidentiality and privacy safeguards.

Limitations:

In acknowledging the inherent limitations and potential biases within our chosen methodology, we recognize their potential impact on the outcomes of our study: the susceptibility to response or non-response biases, along with biases stemming from our questionnaire design, attributed to our varying levels of expertise—a dual aspect that could serve as both an asset and a hindrance to our research – as well as biases stemming from the sampling. These are reflected upon as we analyze the data collected.

Furthermore, it should be acknowledged that the country selection represents only a small sample of the countries in the SSA region and therefore does not fully encompass the range of perspectives that exist on the topic in question. It is also important to note that the selection of countries was influenced by the intention to complement the countries covered in an ongoing study at MMV, which influenced our initial country selection.

Additionally, we had assumed that time constraints may hinder our aspiration to interview all intended participants comprehensively; and indeed, we were not able to have equal amounts of respondents per chosen country. Furthermore, the remote nature of interviews posed a challenge, limiting our ability to capture non-verbal cues, thereby potentially affecting the depth of understanding during data collection.

We also acknowledge that language can significantly influence the nature of responses obtained in our research. Although our team is proficient in multiple languages – English, French, German, and Italian – the diverse linguistic landscape across the African continent surpasses our capacities. Therefore, to facilitate communication during interviews, participants needed to be proficient in at least one of the aforementioned languages, potentially resulting in some concepts being lost in translation during the interview process.

Findings

Respondents' Spontaneous Reactions to the New Drug

When the idea of the new drug was presented to the respondents, the reactions were mostly positive and the idea was well received. Having more treatment options is the most common desire, despite any complications that may accompany the new drug's implementation, respondents felt it was more important to have more alternatives available to the population. However, according to the description presented, the most common sentiment was concern about the number of pills to be taken and about the 2-day dosing regimen. This is especially because of difficulties in terms of ensuring compliance and actual uptake of the drug. The more pills to be taken, the more skeptical the respondents were. The compatibility with cotrimazoxole to include pregnant women with HIV was very surprising to a few of the interviewees. The possibility for pregnant women living with HIV to receive treatment was perceived as a brilliant and exciting idea. However, the initial reaction of many respondents was directed towards the number of pills to be taken and the way of taking them. Another positive aspect – that was highlighted by several respondents – was the possibility of taking the new medication in all trimesters, particularly the fact that it could be taken from the first trimester. Some considered this feature as less crucial, however, given that women often delayed their first ANC visit beyond the first trimester.

A common reaction was a concern over the cost: many respondents welcomed the idea of a new drug positively but were immediately concerned about the potential cost of this new intervention. A new combination could be greatly accepted – if it is at an equal or similar cost to current SP usage.

Demand

Many participants expressed interest in the new medication, recognizing a potential demand, particularly as an alternative in the face of emerging resistance against SP.

It seems that the level of demand also largely depends on elements such as price competitiveness in comparison to SP, the WHO's endorsement, and concrete evidence of the new drug's efficacy. The two-day dosing regimen was again seen as a complication that might lower demand.

Certain participants, particularly from West Africa, emphasized that demand for the new drug is likely to be area-specific, potentially higher in Eastern African countries due to higher resistance levels. Western African countries might be slower to adopt the new drug due to currently lower resistance levels and the advantages of SP over the new drug, such as its one-day dosing regimen and positive effect on birth weight. The other two positive features of the new drug, namely first-trimester safety and compatibility with cotrimoxazole, were less frequently mentioned as specific demand-generating factors.

As will be discussed in more detail below, one participant was less enthusiastic about the new agent, emphasizing the need to clarify the health community's goals with chemoprevention: whether the priority is to increase birth weight or to achieve complete malaria elimination. The demand for the new agent would likely depend on which priority is set. If the focus is on improving birth weight, SP remains the gold standard due to its positive effect on birth weight, attributed to its antibacterial properties rather than solely its malaria prevention effects. Thus, preventing malaria alone, without enhancing birth weight, would not justify recommending an alternative agent. The participant in this scenario questioned the high demand for the new agent, given its other limitations derived from its product characteristics. They suggested that the demand for the new medication would then ultimately depend on its cost, viewing it as just another additional option in the existing toolkit against malaria. It would need to be demonstrated that eradicating malaria in pregnant women significantly reduces transmission to justify higher expenditure on this new agent.

Conversely, the WHO representative, while acknowledging the above discussion around birth weight believed that despite a lack of evidence showcasing PPQ-PYN's positive effect on birth weight, there remains a demand for the new medication, particularly in regions with high resistance. While SP remains superior in areas without resistance, potentially leading to lower demand for the new medication, the new drug would have a distinct advantage and higher demand in regions with high resistance.

While there is significant interest and potential demand for the new PPQ-PYN combination, its success will likely depend on addressing key limitations deriving from its product characteristics. The potential demand seems to predominantly exist in areas with high SP resistance, where it is viewed as a suitable alternative and important addition to the malaria treatment toolkit, despite some of its less favorable characteristics.

To create a favorable environment for the introduction of the product, the interest groups must be convinced of the usefulness of the new agent and the ability to address key issues resulting from its product characteristics, with accompanying policy measures.

Anticipated implementation barriers and facilitators of new malaria prevention treatment

Barriers:

Since the new molecule combination is likely to be introduced via the existing delivery structures such as ANC, the already existing limits of the health care system, especially linked to the administration of SP, are likely to be barriers to the implementation of the new molecule combination. In fact, pregnant women in Sub-Saharan Africa are currently encountering several obstacles while accessing healthcare. These barriers which will be discussed below are logistical, financial, infrastructural, geographical, and also cultural.

First of all, a major challenge identified by experts is the necessity for supervised administration of the current malaria chemoprevention drug for pregnant women. As it has been highlighted by our respondents, there is the need to **administer the drug** which is currently in use **under supervision.** In fact, although in most cases chemoprevention drugs for malaria are available in health facilities, pregnant women must take them in front of health workers in such a way that they can properly supervise the drug administration. This is a traditional intake model, the goal of which is to make sure that pregnant women actually ingest the drug, because in some cases, due to pregnancy nausea or other reasons, there is the risk that the drug will not be taken properly unless under supervision. In fact, in Burkina Faso for example, this supervised intake, "la prise supervisée", also referred to as Directly-Observed Therapy (DOT), is considered a limitation from a logistical point of view because it requires pregnant women to compulsorily travel to health centers to receive treatment doses.

Travel and reaching centers and health facilities represent another significant obstacle: **geographical factors and consequent financial limitations arising from transport costs** reduce the accessibility to health care for pregnant women.

Having access to adequate prenatal services is not a given. As a matter of fact, in some regions and villages located in remote areas, adequate health infrastructure may be lacking, scarce, or inaccessible, forcing pregnant women to travel longer distances to access the essential health services they need. As a result, there is no easy and early access to adequate prenatal health assistance. This is also a major limitation with regard to treatment follow-up: continuous monitoring and regular frequency of the drug regimen and prenatal visits for pregnant women, either at facilities or through home visits, ensures that treatment protocols are working and, most importantly, facilitates prompt intervention in case any complications or problems that require immediate attention arise. In the case of IPTp, it is necessary to be able to ensure continuous and consecutive dosing, especially in less controlled settings, to ensure proper efficacy. Efforts are currently underway to address this problem, such as through the establishment of community maternity units staffed by trained nurses. However, funding and organizational obstacles are challenges that persist and threaten these efforts.

Financial constraints constitute an additional challenge. Although current policies offer free or subsidized care for pregnant women, not all countries offer subsidized or free services for health care during maternity. In addition to this, there are difficulties regarding resource deficiencies within the healthcare system. This includes for example occasional shortages in the supply of essential drugs, shortages in the staff members, and depletion of SP supplies, which hampers access to preventive measures, especially in rural areas that are consequently underserved. Problems concerning the supply chain pose a significant obstacle. Shortages can occur at various points in the supply chain, from central procurement to local distribution, ultimately affecting pregnant women's ability to obtain the necessary drugs. Stock-outs can be due to delays in orders, deliveries, and source availability at a national level, thus disrupting continuity in care, a problem that is exacerbated by decentralized supply systems and logistical challenges that can take a long time to resolve.

Moreover, consultation fees, although they may seem to be within the norm, or relatively low, still pose non-negligible obstacles for pregnant women from impoverished backgrounds, further exacerbating challenges and inequalities while accessing health care. The cost of antenatal care is not only that of

consultation, but might also include additional expenses such as the cost of transportation to get to the facility, and the cost of essential supplies, which impose significant additional financial burdens. This financial pressure not only deters women from regular checkups but also limits their ability to access preventive measures such as chemoprevention and insecticidal mosquito nets.

Cultural aspects and pressures from society cannot be overlooked. In some communities, for example, cultural beliefs regarding early pregnancy disclosure, and consequently reluctance to reapply for early prenatal care, clearly affect timely access to care. Social taboos have had as important an impact as financial constraints. In fact, some cultural norms and traditional practices favor secrecy about the condition of pregnancy before the first movements of the fetus, which then leads to a delay in seeking medical care until just the later stages of pregnancy.

Another cultural aspect to mention is that in some regions, societal expectations often require women to seek permission from their family members, particularly their husbands, before starting any treatment. Often the spouse must compulsorily accompany the woman to visits, a practice that, while intended to encourage family involvement, inadvertently creates difficulties for single or unsupported pregnant women, highlighting the need for equitable access that is independent of the woman's marital status.

In addition to inadequate support from family and husbands, difficulties are to be seen in conjunction with other competing responsibilities, such as caring for one's children, farming, and domestic duties. Dependence on family approval may cause delays, or even dissuade, pregnant women from seeking preventive care in a timely manner, especially in the early stages of pregnancy that are crucial as far as prenatal care is concerned.

All the mentioned factors strongly contribute to **a significant delay in access to preventive treatment in pregnancy.** This is a common issue caused by different factors. First, late detection of pregnancy leads to failure to intervene early in the preventive treatment of malaria. Indeed, some pregnant women visit antenatal care centers only after entering the third trimester, which necessarily implies a delay in the implementation of chemoprevention measures. The previously mentioned requirement of controlled drug intake, and geographical, financial, and cultural factors exacerbate this situation as they further limit access to preventive treatment.

Regarding **SP** more specifically, although studies on its effectiveness in prevention during pregnancy are scarce, it is used effectively in different regions, districts, and health facilities. One of the first challenges encountered in SP administration at health structures was the need for clean water to be able to swallow the tablet, whose size to facilitate swallowing has already been mentioned. Despite being widely accepted, the need for multiple doses and the lack of differentiation in packaging cause practical problems, especially concerning community distribution programs. The same limits could arise for a new chemopreventive drug.

In Sub-Saharan Africa, there is growing concern regarding SP resistance. Although in some regions, such as Burkina Faso, difficulties have not yet been encountered in this regard, there is an urgent need to explore new drug regimens and formulas that can provide a viable alternative where, precisely, SP produces difficulties. Ideally, the characteristics most desired by experts would be those of a single-dose, low-cost drug that has a long duration of action that is well tolerated with minimal side effects.

In addition to more systemic and structural impediments linked to the current healthcare system structure, and cultural and socio-political factors, more concrete barriers could arise from the proposed product profile of the new drug. A major challenge identified by experts is the **proposed two-day regimen** of the new chemopreventive treatment. The following characteristic was identified as potentially limiting across the board by all respondents. The current chemopreventive drug is typically administered under the direct supervision of healthcare workers (DOT) to ensure compliance. The preference for pregnant women to take malaria drugs under supervision at healthcare facilities can be attributed to negative experiences with compliance in the case of self-administration by the patients. For instance, women were observed to reserve the preventive drug for future treatment in case of illness. Additionally, the **number of tablets** was identified as a potential disadvantage should it exceed three tablets per dose. Although it was suggested that a smaller number of tablets (ideally, only one) would be preferable, it was also noted that healthcare workers and women were already accustomed to the three-tablet regimen of IPTp-SP. Consequently, the proposal of three tablets per dose may not be a significant concern, and the use of blister packaging could facilitate the administration of multiple tablets.

Another impediment to mention concerns the so-called **physical aspects of the drug**. In fact, tablet sizes may pose some problems to pregnant women who find it difficult to swallow. Experts also brought to attention the taste of the tablet, which is not pleasant for all patients[1].

Facilitators:

Government policies and facilitators target specific interventions to enhance healthcare for pregnant women, addressing recognized limitations. In response to existing challenges, governments strive to improve access to preventive care through various healthcare system reforms, ensuring better accessibility for pregnant women. The following trends and established systems could already facilitate the development and introduction of the new malaria medication.

Community participation and collaboration have become crucial trends across the continent. While Community Health Workers (CHWs) increasingly are key players, it is also necessary to involve a broader range of influential actors, such as traditional and religious leaders. Acceptance and trust within the community play an important role in facilitating access to healthcare for pregnant women, without adding barriers to the adoption of new interventions. In line with this trend, there is a growing emphasis on implementing and strengthening communication strategies. The aim is to raise awareness and spread information about available interventions and treatments, highlighting the risks of the disease and the benefits of the treatments for pregnant women. In particular, younger women, who are the most vulnerable due to a lack of understanding of the risks associated with pregnancy, need to be targeted to ensure they have the opportunity to access information and treatment early. Learning about the delicacy and difficulties of the pregnant woman during training is essential to this end. The moment the woman begins treatment, it is necessary to be able to connect her to the health service properly so that accompaniment and supervision are continuous and regular.

[1] See Annex 1

The respondents suggested that **governments must recognize their responsibilities in providing the support and resources for maternal health care**, which since they pose a major challenge, implies the need for collaboration with NGOs and international partners. The government should be sensitized to prioritize allocating funds for the health needs of the most vulnerable populations, precisely including pregnant women. Efforts to improve pregnant women's access to prenatal health care, therefore, are intertwined with broader initiatives that are aimed at strengthening the health care system as a whole. For example, collaboration between health programs at both the national and regional levels.

Efforts are also made to **improve existing health infrastructure and programs**, including ANC, by promoting the network of health workers in communities that provide, as mentioned above, an important base for distributing and administering drugs. Following WHO guidelines, work is being done to appropriately and forward-looking integrate new interventions and prevention strategies into the current healthcare landscape. This is done by leveraging communication channels with NGOs and partnerships, which, given the introduction of the PYR-PPQ, would facilitate its adoption and subsequent implementation, thereby ensuring a coordinated approach among different levels of the health system.

Communities and the health professionals within them play an essential role and are increasingly involved in order to **promote more awareness and acceptance** regarding the disease and the treatments and care available. These elements would further facilitate the adoption of a new drug. Increased awareness regarding the risks of contracting and developing malaria during pregnancy, both for the mother and the fetus, would consequently also promote greater interest in researching new drug options and facilitate its societal acceptance. To do this, communities are involved in designing, implementing, and evaluating interventions, to ideally foster sustainability of new projects.

Increasingly, efforts are being made to **promote easier access to drug regimens** so that both their uptake and adherence among pregnant women can be improved. For example, simplified dosing schemes and accessibility policy measures, such as subsidies, are considered by experts to be good facilitators for the possible implementation of the proposed new molecule formulation.

To facilitate the implementation of new interventions, experts suggest that the focus should also and especially be on **continuous monitoring of treatments, research, and data collection** regarding the efficacy of the new drug formulation. Ongoing research activities make a major contribution to building trust among stakeholders.

In conclusion, the ongoing efforts on enhancing access to preventive care, engaging influential community leaders, and promoting awareness among vulnerable populations facilitate the sucessfull implementation and uptake of the new drug. Governments must allocate resources, integrate new interventions, and ensure continuous monitoring to further foster sustainability and societal acceptance of initiatives.

Analysis & Recommendations

Creating an enabling environment to facilitate the adoption and uptake of the new product

As previously identified, structural barriers within the healthcare system which present challenges for SP, could also impede the introduction of a new medicine into existing healthcare structures. Some of the most pressing issues are limited access to healthcare due to geographical and financial barriers, delayed initiation of ANC mainly due to cultural and awareness factors, and the gap between participation in ANC and actual uptake of IPTP caused by supply shortages, limited staff, and quality of care. Furthermore, the product profile of the new drug – which necessitates a two-day dosing regimen – was identified as a significant challenge by all interview participants. Nevertheless, several strategies to mitigate the problems were also mentioned. To create a favorable environment for the introduction of the new molecule combination, both existing structural barriers and those arising from the profile of the new drug need to be addressed.

Innovative Distribution Channels

The two-day dosing regimen emerged as a key concern in the interviews regarding the profile of the new drug with the potential to make compliance more difficult. Since it is unfeasible to require women to return to the health facility on two consecutive days, the second dose would have to be distributed to them for self-administration the following day. As DOT is not possible, most participants pointed out that follow-up must be ensured Nevertheless, as previously mentioned, participants expressed concern that women might forget or deliberately refrain from taking the medication because they do not perceive themselves to be unwell. It was also suggested that women might store the medication for future use as a treatment when they become seriously ill.

Community Distribution, Outreach Services, and Village Clinic Administration

As previously stated, IPTP distribution at the **Community level** is seen by many participants as a turning point and a solution for better coverage, particularly in light of the WHO's endorsement in the recent 2024 guidelines. The approach was referenced by all respondents in the course of the interviews. It appears to be a favored approach among international stakeholders. Moreover, our national interview partners have indicated that the approach is currently being piloted in numerous Sub-Saharan African countries to scale it up. Furthermore, community distribution was identified as a potential means of enhancing trust in a dosing regimen, given that it is administered by a known individual.

The majority of participants agreed on the importance of introducing **community IPTp** (c-IPTp) alongside ANC. It is recommended that the initial dose of the medication be administered at a health facility – or via outreach services. Subsequently, CHWs could be employed to ensure compliance with the second dose of the preventive treatment through the provision of reminders, follow-ups, and assistance with intake.

The necessity for complementarity was emphasized due to the concern that women might be deterred from regular ANC attendance as a result of this initiative. Some participants expressed concern that administering all doses through a purely community-based approach might deter women from returning for subsequent ANC visits. This could have the effect of compromising the comprehensive ANC services that are necessary for an overall healthy pregnancy, which should continue to be the main goal of ANC and IPTp.

A complementarity approach would require good coordination between the community level and health care centers, especially in registering women who have gotten a first dose during ANC, to know when and where to follow up with a second dose. Furthermore, data collection at the community level seems to be challenging. In the case of further push for community delivery the collaboration between CHWs and ANC health centers would have to be fostered to ensure data collection and effectively track the new drug's performance.

Group ANC

Some participants mentioned group ANC as a new innovative approach, piloted in multiple countries for IPTp-SP administration. The approach consists of grouping women living in proximity and having similar estimated dates of delivery for ANC attendance and consultation/information sessions. Group antenatal care aims to increase the social, psychological, and informational support found to be lacking in traditional antenatal care[2].In the context of a two-day regimen, this would allow women also to check up on each other to hold each other accountable for effectively taking the second dose. According to our participants, the approach has been working well in piloting studies.

Community engagement:

The communities in which the women live seem to play a big role in deterring or supporting the follow-through with the dosing regimen in general. It was mentioned that in some areas women were discouraged from taking SP due to the fear of its potential harm to the fetus. The information and the engagement of communities to ensure women comply with the regimen dosing could improve follow-through. Engaging communities in program design and implementation would furthermore foster ownership and acceptance and have the potential to enhance the program's success.

Improving Access to healthcare: addressing distance, financial barriers

Access barriers are a structural issue that is currently hindering coverage and the further upscaling of SP. A new medication would most likely face similar struggles and to create a favorable environment they would need to be addressed. **Community distribution,** was once again, the most mentioned measure to improve access to prenatal care in hard-to-reach areas. It would also facilitate women accessing ANC with a limited budget to cover transportation costs and reduce their reliance on family funds and approval to attend ANC.

[2] (Sawtell et al., 2023)

Other measures that are often less measured include the improvement of health care center capacity as well as village-level staff training to perform services related to IPTp. **Improving the health center's capacity** to perform regular outreach services – monthly or even weekly – would allow health workers to offer ANC services in the villages themselves. This would facilitate access and reduce the burden of distance. **Training village-level staff to perform certain services related to IPTP** and promoting a more active role of community health workers in service distribution could also help improve access to care, especially in systems with village-level health care centers. Currently, CHWs play an important role in information dissemination and referral to health facilities[3]. Educating them to perform further tasks was seen as promising in terms of IPTp administration.

The respondents also indicated that it is crucial to ensure the provision of free ANC services and to prevent the unauthorized sale of de facto free services and supplies that occur at certain health facilities.

Communication and Social and behavioral change campaigns

The **late initiation** of ANC visits was again mentioned as one of the key issues in achieving higher coverage. One of the main potential beneficial features of the proposed PYR and PPQ molecule combination was its safety in the first trimester. This feature would only be useful if early ANC attendance was promoted.

Social pressure and cultural norms make women reluctant to attend clinics early in pregnancy and hide it, especially in the first trimester. As an example, the taboo of talking about pregnancy before fetal movement could be mentioned. Respondents highlighted the importance of **awareness campaigns as well as Social and Behavioral Change** measures among women to raise awareness of the risks of late ANC attendance and in general increase knowledge about the risks of malaria in pregnancy. Furthermore, the new medication would require, as it is for SP, ideally three doses until delivery for ideal protection. Early ANC attendance is crucial to be able to ensure complete dose administration throughout the pregnancy and ideal compliance with IPTp.

Women often also lack complete **decision autonomy**. In some countries women need the permission of their partner, the mother-in-law, or the village chief - often in the absence of marriage - for ANC attendance. **The education of men, the family, and the community** about the adverse effects of malaria in pregnancy and especially about the risks of late or no ANC attendance is crucial to raise their support for women's ANC attendance. It was mentioned multiple times that the implication of husbands in the decision-making process has the potential to enhance treatment adherence and encourage women to seek healthcare earlier. The education of men and family members is even more so important as in some countries women, especially younger women, are not financially independent and have to rely on their partners and/or families' support for covering transportation and potential health care fees.

The malaria community and especially the general population are highly accustomed to the use of SP in chemoprevention. The (partial) switch to PYR and PPQ would therefore have to be accompanied by **large-scale information campaigns**. Public communication is essential to inform about the rationale

[3] (Burke et al., 2021)

behind the introduction and/or switch to the new medication, the medication itself, and changes in the administration regime. One participant mentioned the idea of finding so-called "champions", meaning women who have already taken the new medication and whom it has helped, to promote it within their communities. This could enhance the acceptability of the new drug, as these women could share their personal experiences and raise trust as well as transmit knowledge about best practices for administration among their community.

The **further education of healthcare workers** and the provision of better training are essential to ensure the quality of care provided since the lack of respectful treatment experienced by women can result in them being discouraged from returning for further care.

Technology

About five participants mentioned the advantages of using technology such as electronic databases for registering pregnant women coupled with potentially sending out follow-up messages to CHWs to remind them to check up on women. This could especially be useful given a two-day dosing regimen in which women are required to take the second dose at home.

Furthermore, improving malaria dashboards and pharmacovigilance systems to monitor drug safety and efficacy could facilitate evaluating the progress and performance of SP and the new medication. This combined with enhanced resistance monitoring could help the decision-making process on where and how to implement the PPQ-PYR - as a replacement or a complementary remedy.

Stakeholder engagement and international endorsement

The importance of international recognition, such as being included in WHO guidelines, was highlighted as a crucial factor for influencers - through platforms such as Technical Working Groups - to facilitate discussions on the adoption of a new product.

Particular emphasis was placed on the necessity of having the new product included in the WHO guidelines. As countries tend to adhere to the WHO's recommendations on such matters, the adoption of a new product without WHO endorsement would be challenging. This would entail the validation of the drug and the formulation of policy recommendations, which are of crucial importance for the revision of national guidelines.

The collection and presentation of evidence through piloting about the product's efficacy would assist in persuading national authorities to adopt the new product. It would be beneficial to engage national malaria control programs from the outset, as this would facilitate the gathering of inputs and opinions, which could subsequently facilitate the adoption of the medication once it is available.

Countries where the drug is piloted should disseminate best practices and lessons learned. This entails facilitating the sharing of experiences such as lessons learned, best practices for scale-up, and general results with other governments.

It was also deemed crucial to sensitize governments and convince them of the necessity of allocating greater resources to this area. In contexts where resources are scarce, medication procurement is often not a priority. Long-term solutions that facilitate the adoption of new malaria medications, in general, involve sensitizing governments to prioritize and fund healthcare needs, possibly through increased budget allocation. Collaboration with stakeholders, NGOs, civil society, and community actors is essential for implementing new protocols and processes operationally.

Impact on Birth Weight

Throughout the interviews, an important point was raised regarding the generally positive effects of SP on infant birth weight and overall pregnancy outcomes, though it was not frequently mentioned (Unger et al., 2019; Chico et al., 2017). One participant questioned the usefulness of a new agent in the absence of evidence supporting the promotion of higher birth weight. They suggested that the broader impact of SP should be considered before implementing a new drug in malaria elimination strategies.

The respondent highlighted that IPTp was originally designed to prevent low birth weight and improve infant outcomes from a maternal-child health perspective. They stressed the need to reassess the goals of IPTp, determining whether the primary focus should be on improving birth weight or preventing malaria in pregnant women. The participant then pointed out that pregnant women represent a small proportion of the population and may not be significant drivers of malaria transmission[4]. Therefore, preventing malaria alone without improving birth weight might not justify recommending an alternative agent.

There is thus an emphasized need for more evidence on the role of pregnant women as reservoirs for malaria transmission. If preventing malaria in pregnant women does not significantly reduce overall transmission, then the focus may remain on birth weight improvement. Studies have shown that the positive impact of SP on birth weight persists even in areas with high resistance, suggesting that SP's broader benefits should be considered (Waltmann et al., 2022; Unger et al., 2019).

Upon inquiry, a WHO respondent confirmed these ongoing discussions and the added value of SP, likely due to its antibiotic effect that clears pathogens, especially in the genitourinary tract, benefiting pregnancy outcomes overall. They noted, however, that another drug lacking this broader beneficial effect could still be useful in high-resistance areas but should be weighed against SP, the gold standard, in regions with lower resistance. This respondent emphasized the need to consider the implementation of a new medication in a holistic manner, introducing it area-specifically.

It follows that for an ideal, tailored introduction of the new drug, it is essential to work with the different stakeholders and to evaluate the objectives of IPTp, as this could have a significant impact on how

[4]It should be noted that, in contrast, two studies highlighted the importance of pregnant women as a reservoir for malaria transmission in the community (Boudová et al., 2014; Fried & Duffy, 2017).

the new drug fits into existing malaria elimination strategies and how best to introduce it in different areas. A comprehensive assessment of the objectives of IPTp is needed, balancing the two objectives of improving birth weight and preventing malaria. Implementation strategies should take into account both health outcomes and transmission dynamics.

Different interview participants already had varying opinions on how the new drug could fit into existing malaria control programs, which will be detailed in the following recommendation section of the report.

Fitting into current malaria elimination strategies?

Although there is a general interest in the new drug combination – particularly as an alternative to SP in light of emerging resistance – opinions diverge on how the new medication could fit into existing malaria elimination strategies.

Alternative for SP in High Resistance Areas

The majority of participants perceived the introduction of the new drug as an opportunity, particularly in light of the growing and intensifying SP resistance. Accordingly, they envisioned the new medication playing a role, particularly in areas with high SP resistance and high malaria transmission rate, helping to alleviate the burden on SP. Within the group supporting the introduction of the new drug targeting high-resistance areas, there were different perspectives. Some participants suggested that the new drug should be available in those areas as a complementary alternative to SP, and one participant from Burkina Faso explicitly advocated for a phasing out of old interventions rather than maintaining parallel systems, especially in high SP-resistant areas, with the new drug being administered through the existing healthcare structures currently used for SP.

Some participants also indicated that while the new drug should be used in areas with high resistance, SP should continue to be favored in other regions due to its overall advantages and certain inconveniences of the new drug. Some participants from West Africa emphasized that the East African regions currently most affected by high SP resistance would probably be the most suitable for the introduction of the new intervention.

Complementary Use Alongside SP

For areas with lower resistance patterns, many participants favored the use of the new drug alongside SP rather than as a replacement. Some participants suggested in this regard using the new combination in the first trimester, where SP is currently not an option, and continuing with SP from the second trimester onwards in areas with low SP resistance. In areas with high resistance, the new combination could be used throughout the entire pregnancy.

General Alternative Option to SP :

Several participants favored the use of new drugs alongside SP to provide alternative prevention options for people in all regions (regardless of the resistance level). This approach would provide flexibility, allowing individuals to choose the most beneficial option based on specific regional or individual needs.

The new product could reduce reliance on SP and help mitigate the risk of resistance associated with its widespread use. One participant suggested that rather than relying on a single drug, the new drug could be used in a complementary way, with different long-acting antimalarials rotated according to time and geography. This strategy of regularly changing the drugs used could maintain the effectiveness of the drugs over a longer period of time.

Despite some skepticism about overall demand due to administration challenges, the new drug could provide an important alternative for pregnant women, particularly those who may experience adverse reactions to SP.

Mass Administration/SMC Rather than Chemoprevention

Two participants suggested that the new drug could be used for mass treatment rather than prevention, since it could be administered in a broad manner, without a particular safety concern for pregnant women in their first trimester, as has been the norm so far. One of these participants emphasized the drug's utility primarily in SMC settings rather than prevention, since the focus there is to reduce malaria infection instead of improve birth weight.

Use for HIV-Affected Women

One participant mentioned the potential use of the new medication especially for HIV-infected women across countries, regardless of the SP resistance rate. This application could provide an additional option for a vulnerable population previously excluded from chemoprevention with SP.

Preference for SP

Overall, the majority of participants preferred to continue using SP in areas or for groups of women where it remains efficacious, particularly in regions with low SP resistance and from the second trimester onwards. SP was favored over the new drug due to its superior product characteristics and proven positive impact on birth weight. The familiarity of SP and its maintained effectiveness, even in areas with some resistance buildup, contributed to the perception that it is unlikely to be completely replaced in the near future.

Altogether, the incorporation of the novel PPQ-PYN combination into malaria elimination strategies should be implemented on a regional basis, with due consideration given to the specific patterns of resistance observed in each region and the country's specific needs in terms of malaria elimination. How the new drug could be incorporated into existing health infrastructure would therefore differ from one country to another. Several potential applications were identified:

- PPQ-PYN in combination with SP as a general alternative,
- PPQ-PYN mainly in areas with high resistance,
- PPQ-PYN in the first trimester and then SP in the following trimesters, with complete replacement possible in areas with high resistance.

Consequently, the introduction of the drug should follow a comprehensive approach that accounts for the diverse opinions of stakeholders and the health outcomes that countries prioritize, if it wishes to be successfully implemented.

Conclusion

Through our observations, we can state that the introduction of a novel malaria prophylaxis for pregnant women in Sub-Saharan Africa is generally welcomed, although there is a divergence of opinion regarding the place it should occupy in the existing malaria elimination strategy.

The implementation may encounter several challenges. Among the principal obstacles, are the planned two-day dose and the number of tablets, the implementation of which will present a logistical challenge and will necessitate the implementation of accompanying measures to address potential difficulties arising from the fact that the drug cannot be administered under supervision on the second day. The introduction of the drug into existing healthcare structures is also expected to be hindered by many key structural factors. These include geographical barriers that limit access to healthcare facilities, financial constraints on the part of patients and healthcare providers, cultural norms that delay early disclosure of pregnancy and seeking antenatal care, and stockouts and prioritization of IPTP at government and healthcare levels.

In contrast, the current facilitators include existing government measures aimed at improving access to maternal healthcare and involving communities in distribution. The development is favored by the issuance of the latest WHO recommendations on community IPTp (c-IPTp). The increased demand for research into alternatives to sulfadoxine-pyrimethamine (SP) due to emerging resistance could further facilitate the acceptance of the drug in the global malaria community.

Several measures could create a more conducive environment to introduce the new malaria prophylaxis. Firstly, since the effective implementation of the new drug depends on existing health infrastructures, structural barriers in the health system need to be addressed, such as limited access due to geographical, financial, infrastructural, and logistical constraints. Possibly by capacity building at health centers, better training of village health workers, and the prevention of stockouts.

Secondly, innovative distribution channels, such as community-based distribution (c-IPTP) and ANC groups, are essential to manage the two-day dosing regimen effectively. Greater community involvement and awareness campaigns can remove cultural barriers, promote early access to ANC, and inform about the new chemoprophylaxis.

Thirdly, the use of technology to register patients, sending out reminders and to monitor resistance levels could be advantageous for oversight, coordination in implementation, and the successful monitoring of the uptake and efficacy of the new drug for up-to-date data collection, research & evaluation of the program.

Finally, Stakeholder involvement and international support, especially from the WHO, are of paramount importance to foster trust in the new chemoprophylaxis and ensure funding.

The successful integration of the new drug into existing malaria elimination strategies requires greater collaboration between different stakeholders and the evaluation of the objectives of IPTp considering both the health & pregnancy outcomes (i.e. birth weight), and malaria prevention objectives (inhibition of transmission dynamics). Depending on the priority, decisions can be made about the optimal

positioning of the drug within existing malaria elimination strategies and the most effective way of introducing it in different regions.

The incorporation of the novel PPQ-PYN combination should be tailored to each region and country's specific needs in terms of malaria elimination. Whether mainly in high-resistance areas, in combination with SP as a general alternative, or mainly in the first trimester with SP in subsequent trimesters, with the possibility of complete substitution in high-resistance areas, the introduction should follow a comprehensive approach that takes into account the different views of stakeholders and the health outcomes that countries prioritize.

MMV should therefore take into account these inputs of the malaria community, as well as the primary implementation challenges related to the proposed product's characteristics and the general context in Sub-Saharan Africa, to ensure optimal product development, adoption, and implementation.

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Annexes

Annex 1: Instructive & Accessible Packaging

Several participants mentioned that packaging could be a way to mitigate potential issues arising from the large number of tablets or the two-day dosing regimen and to address certain access barriers. Instructive packaging and tablet recognisability, for instance, could facilitate self-administration or administration by community health workers.

The benefits of attention to packaging are as follows:

- **Recognisability of the tablets:** Distinguishing the tablets from other medicines - through differences in size, color, shape, or distinctive packaging - could foster trust by reassuring women that they have received the medicine they had requested during their ANC visit or from the CHWs.
- **Good visual instructions** and diagrams on the packaging could ensure that women know exactly how to use the medication when self-administering at home. Instructive visual packaging could thus also reduce the access barriers that arise for women with varying levels of literacy.
- **Blister packaging** was also suggested as a solution to support the administration of a larger number of tablets. This could make distribution easier for health workers, facilitate transport, support community distribution, and make it more convenient for women to take the medication home. Consequently, proposing three tablets per dose may not be as challenging if combined with such measures, which could help facilitate the administration of multiple tablets.

Furthermore, as previously mentioned, respondents were particularly insistent on certain characteristics of the pills. Some participants emphasized that the new drug should **not have a bitter taste, strange odor, or unpleasant side effects** to ensure acceptability and adherence. Sugar-coated pills of an easy-to-swallow size and shape could help in this respect.

Tackling Supply Chain Issues:

As mentioned previously, stockouts were mentioned as a major barrier to SP coverage. One participant mentioned efforts of ensuring regional manufacturers of SP in Africa to ensure better access to the drugs to address this issue. This could potentially be envisioned also for the new molecule combination.
However, it was also mentioned that in general, it was rather the prioritization of SP by the government and/or health facilities that caused a drug shortage at the central or district level. (Lacking Funds and reliance on donors to procure the drug, prioritization of e.g. military expenditure). It is therefore a big question if regional manufacturing centers would significantly contribute to addressing the issue of stockouts. The mentioned points however further emphasize the crucial need to get governments on board by providing the data evidence of the efficacy of the new product, showing the WHO support, and through intergovernmental information exchange. Often, as mentioned, the mismanagement of orders and supply between the community and central level is an issue.

Annex 2: Collaboration with Ministries

Fostering collaboration between key departments within the Ministry of Health is critical in order to improve the management of malaria and of pregnancy initiatives. Although it has not been a primary focus of the interviews, some respondents highlighted the need to improve the coordination between the different reproductive health and malaria control programs and departments. This improved cooperation would potentially benefit and increase the effectiveness of malaria elimination programs. It would also facilitate a more coherent policy implementation and lead to the formulation of more consistent guidelines and recommendations.

The main issue, at both national and regional levels, is considered by the respondents to be the lack of coordination between the National Malaria Control Program and the National Reproductive Health Group. An effective collaboration between these two entities is fundamental, yet is often lacking, limiting progress. This lack of coordination also extends to external partners, creating challenges in sharing costs and in ordering supplies.

As a result of this, important commodities such as SP often run out. Even when these supplies are available at the national level, the lack of collaboration that could facilitate their transportation to the regional and district levels exacerbates the problem. To improve any malaria and pregnancy health outcomes, it is essential to address these coordination and logistical challenges.

Annex 3: Respondent Satisfaction Levels of the New Prouduct's Characteristics

Product characteristics	Respondent Satisfaction
2-Day Dosing Regiment	Very Unsatisfied
Alternative to SP	Satisfied
Compatibility with Cotrimoxazole	Somewhat Satisfied
First-trimester Usage	Very Satisfied
Newborn Birth Weight	Somewhat Unsatisfied
No Fasting	Neutral
Number of Tablets	Unsatisfied
Pill Format	Neutral
Proposed combination of molecules	Somewhat Satisfied