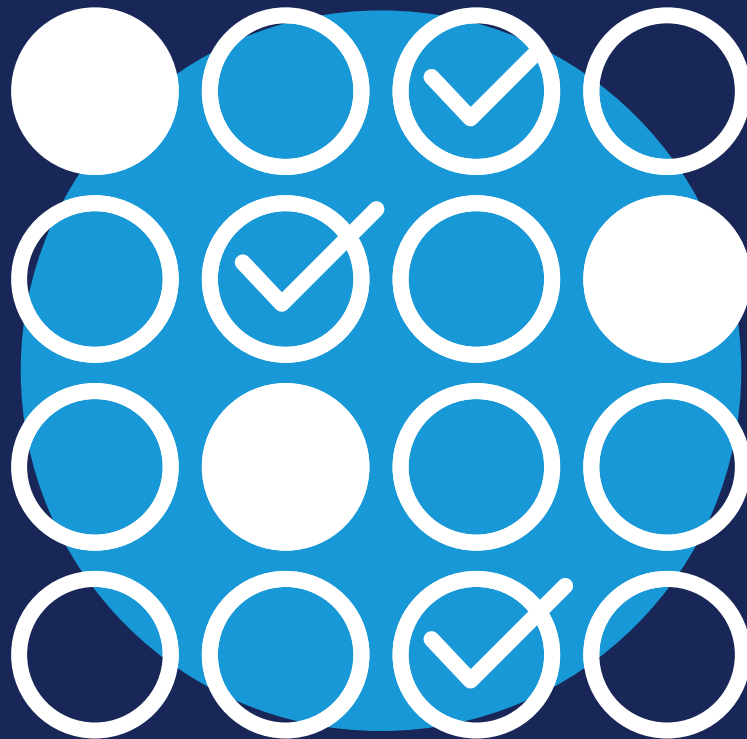


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# Malaria chemoprevention

Preferred product characteristics



World Health  
Organization



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Preferred product characteristics

Malaria chemoprevention: preferred product characteristics

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## ABBREVIATIONS

ACT	artemisinin-based combination therapy
DOT	directly observed therapy
GTS	Global technical strategy for malaria
IPTi	intermittent preventive treatment of malaria in infants
IPTp	intermittent preventive treatment of malaria in pregnancy
IPTsc	intermittent preventive treatment of malaria in school-aged children
MDA	mass drug administration
PDMC	post-discharge malaria chemoprevention
PMC	perennial malaria chemoprevention
PPC	preferred product characteristic
RDA	reactive drug administration
SMC	seasonal malaria chemoprevention
SP	sulfadoxine-pyrimethamine
SP+AQ	sulfadoxine-pyrimethamine plus amodiaquine
TDA	targeted drug administration
TPP	target product profile
WHO	World Health Organization

## OVERVIEW

The *Global technical strategy for malaria 2016–2030 (GTS) (1)* seeks to harness and expand research to accelerate progress towards the elimination of malaria and to counteract the emerging threat of drug and insecticide resistance. It encourages innovation and the development of new tools and strategies to maintain progress in malaria control and advance towards elimination. To accelerate implementation of the GTS, in 2018, the World Health Organization's (WHO) Global Malaria Programme reviewed its policy-making process to ensure that it is transparent, consistent, efficient and predictable. One of the outcomes of the review was the adoption of "preferred product characteristics" (PPCs) as a key tool to guide the development of urgently needed health products. The use of PPCs is aligned with an organization-wide effort to improve communication about public health needs and to facilitate innovation to meet those needs.

WHO PPCs aim to:

- communicate unmet public health needs;
- stimulate the development of relevant new products to meet those needs; and
- facilitate the timely assessment of new products, and the formulation of policy recommendations and prequalification listings.

The PPC published here builds on a WHO technical consultation held in December 2020, which considered the key characteristics of drugs for use in malaria chemoprevention. These characteristics include the indication, target population, safety, efficacy and duration, formulation and presentation, dose regimen, co-administration, route of administration, product stability and storage, programmatic suitability, access and affordability, and susceptibility to loss of efficacy due to resistance. These preferences and related considerations are shaped by unmet public health needs and by the realities of malaria epidemiology and delivery systems in the target geographies.

This PPC is consistent with and complementary to guidance developed by other WHO departments, such as the *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme (2)*. WHO encourages developers to consult these guidelines, alongside malaria PPCs, if they intend to seek a WHO recommendation for use or prequalification of their products.

The malaria chemoprevention PPCs were developed in accordance with the WHO Standard Procedure for Target Product Profiles, Preferred Product Characteristics, and Target Regimen Profiles (V1.02, 3 August 2020).

### Assessment and management of conflicts of interest

Declarations of any competing interests were received from all experts. WHO processes were used to assess declared interests and manage any conflicts of interest. Nine experts declared potential competing interests, including grants, donations and consultancy work for malaria-related research, previous and current participation in the Expert Scientific Advisory Committee for MMV, and travel and accommodation for participation in meetings on malaria drugs funded by Shin Poong, Guilin Pharmaceutical and Novartis. After review and due diligence by the WHO Secretariat, it was concluded that these interests were not significant for the specific topics discussed in the development of this report.



## TERMINOLOGY

**Preferred product characteristics (PPCs)** are designed to communicate unmet public health needs identified by WHO, stimulate innovation and investment in the identified areas, and communicate the desired performance and operational characteristics of health products to address those needs. The target audience consists of product developers including researchers, regulatory agencies, procurement agencies, and funders of research and development. PPCs are usually developed before a mature pipeline of products is available and should reflect the ideal characteristics of interventions required to rapidly and effectively achieve global health impact.

**Target product profiles (TPPs)** in the context of public health are planning tools used to set research and development targets for manufacturers and researchers to guide the development of specific products. TPPs provide more detailed information than PPCs and include both minimally acceptable and preferred performance characteristics. The minimum performance characteristics should be considered a “go/no-go” decision point in the product development process.



# 1. INTRODUCTION

The *World malaria report 2022* estimated that there were 247 million cases of malaria worldwide and 619 000 malaria deaths (3). The WHO African Region carried 96% of these deaths, with children aged under 5 years being the most vulnerable, accounting for 80% of malaria deaths in the Region. After many years of progress, the trajectory of malaria control has plateaued, and the world did not achieve the 2020 GTS targets for morbidity and mortality reductions. There is an urgent need to improve existing strategies and develop new approaches to control malaria.

Chemoprevention refers to the use of drugs to prevent malaria in special risk groups. WHO recommends several chemoprevention strategies for malaria control. Seasonal malaria chemoprevention (SMC) was recommended in 2012 (updated in 2022) to prevent malaria in children in age groups at high risk of severe malaria in areas of seasonal malaria transmission by providing repeated treatment with antimalarial drugs during peak transmission seasons. Intermittent preventive treatment of malaria in infants (IPTi) was recommended in 2010 and updated to perennial malaria chemoprevention (PMC) in 2022. PMC aims at preventing malaria in children in age groups at high risk of severe malaria in areas of moderate to high perennial transmission by giving them antimalarial drugs at predefined intervals to reduce disease burden. Although there has been research experience with several drug regimens, programmatically, PMC has largely relied on sulfadoxine-pyrimethamine (SP) and SMC has extensively used SP with amodiaquine (SP+AQ).

Additional use cases in children include the extension of chemoprevention as intermittent preventive treatment of malaria in school-aged children (IPTsc). As malaria control improves, the proportion of malaria disease experienced by school-aged children increases, associated with anaemia and impaired school attendance and educational outcomes. Studies have also shown that the prevalence of malaria and gametocyte carriage in school-aged children contributes substantially to ongoing malaria transmission. In settings with moderate to high malaria transmission, post-discharge malaria chemoprevention (PDMC) involves the provision of antimalarials at predefined intervals to children who were admitted to hospital with severe anaemia, following their discharge, in order to reduce re-admission and death. Such children have a marked increase in mortality in the six months following discharge, which can be reduced with PDMC. Future guidelines may want to consider the use of chemoprevention in other high-risk paediatric populations, such as those with sickle cell disease, malnutrition or HIV infection.

Intermittent preventive treatment of malaria in pregnancy (IPTp) was first recommended in 1998 (with updates in 2004, 2012 and 2022). IPTp consists of a monthly treatment course of SP given to pregnant women of all gravities from the start of the second trimester. This can reduce malaria and anaemia in the mother and increase the birthweight of the child.

Mass drug administration (MDA) involves giving a full therapeutic course of an antimalarial drug to all age groups of a population in a defined geographical area at approximately the same time, often at repeated intervals. MDA has also been used to reduce disease burden in emergency situations and to reduce malaria transmission in elimination settings. People of all ages may be at risk of malaria in emergency situations, such as a malaria outbreak or resurgence after a sustained period of high-level control. Chemoprevention in the form of reactive drug administration (RDA) can be used around a confirmed malaria case in areas approaching elimination or in post-elimination settings to prevent re-establishment. Targeted drug administration (TDA) can also be used in occupational or behavioural risk groups (e.g. to prevent

infection due to *Plasmodium vivax* malaria or other *Plasmodium* species such as *P. knowlesi* among forest goers in South–East Asia). WHO recommends that MDA be used to provide short-term reductions in disease in moderate to high transmission settings or for transmission reduction in very low to low transmission settings. However, if implemented, MDA should be one of several components of a robust malaria control programme (e.g. including good coverage of effective case management and appropriate prevention tools and strategies) to reduce the risk of resurgence when the MDA programme ends. Malaria programmes should judge the suitability of using MDA in the context of the desired impact, level of endemicity and resources required.

Malaria chemoprevention currently uses drugs administered in oral formulations, typically as multiple treatment courses at repeated intervals to protect individuals during the period of highest malaria risk. For other infectious diseases, such as HIV, long-acting injectable drugs are being explored as an alternative to oral prophylaxis, which could lead to better adherence through less frequent administration (4). Similar parenteral delivery of malaria drugs could be beneficial if a single injection is able to provide a high level of protection for the duration of a malaria transmission season. For example, injectable monoclonal antibodies for malaria prevention are currently in development and aim to provide protection for 3–6 months or longer (5–7). Parenteral malaria prophylaxis could be particularly applicable in health care settings, such as for PDMC, as described above.

The primary targets of current WHO recommendations on chemoprevention are populations living in endemic areas, but there are no formal recommendations on preventive chemotherapy for non-immune people travelling to malaria-endemic regions. However, as malaria control improves and some areas become malaria-free, people living in endemic countries may increasingly become non-immune or grow up without acquiring natural immunity to malaria. Individuals growing up in localized areas without malaria (e.g. urban settings) may be at risk when travelling to malaria-endemic areas within their own country (e.g. more rural settings). Future guidelines may need to consider how to protect non-immune travellers within and between endemic countries.

The latest version of all WHO recommendations on malaria chemoprevention, including summaries of the evidence upon which they are based, is available online at <https://app.magicapp.org/#/guideline/6832> (8).

**Table 1. Use cases for protection against malaria infection**

Target population	Use case	Current standard of care
<b>Children</b>	<p><b>Strongly seasonal transmission settings:</b> SMC in children aged 3 months to 5 years (with potential extension up to 10 years) for prevention of clinical episodes of malaria, including severe disease and death</p> <p>An SMC course (period required to administer a full course of SMC drugs) is typically given as multiple cycles (monthly interval between each course) during an SMC campaign (period when all SMC activities are implemented in a given year and location).</p>	<p>Three days of amodiaquine, one day of sulfadoxine-pyrimethamine at monthly intervals, as used in SMC</p>
	<p><b>Perennial transmission settings:</b> Preventive treatment in infants in their first year of life and children in the second (and potentially subsequent) year of life (PMC)</p>	<p>Sulfadoxine-pyrimethamine</p>
	<p><b>Populations at increased risk of severe malaria:</b> PDMC in children admitted to hospital for anaemia or children with underlying conditions (e.g. sickle cell disease)</p>	<p>None approved specifically for this indication; dihydroartemisinin-piperaquine, sulfadoxine-pyrimethamine, and artemether-lumefantrine have been evaluated.</p>
	<p><b>IPTsc up to 15 years of age in seasonal and perennial transmission settings</b></p>	<p>Sulfadoxine-pyrimethamine with amodiaquine or primaquine, sulfadoxine-pyrimethamine plus artesunate, artesunate-amodiaquine, and dihydroartemisinin-piperaquine have been evaluated for IPTsc.</p>
<b>Adults</b>	<p><b>Women in the second and third trimesters of pregnancy (IPTp)</b></p>	<p>One day of sulfadoxine-pyrimethamine at antenatal care visits</p>
	<p><b>Women of childbearing age and/or in the first trimester of pregnancy, thereby allowing MDA in the whole population</b></p>	<p>None approved</p>
<b>Travellers</b>	<p><b>Non-immune individuals living in endemic countries or moving between low- and high-transmission zones</b></p>	<p>Daily atovaquone-proguanil; weekly tafenoquine, mefloquine, doxycycline</p>
	<p><b>Occupational risk groups (e.g. forest workers and miners)</b></p>	

Given the wide variety of use cases, it is clear that drugs for malaria chemoprevention need to be safe and efficacious in the target population. Depending on the use case, the target population can include very young children, pregnant women and/or women of childbearing age.

The impact of chemoprevention may be compromised by suboptimal adherence to the full treatment course. While the treatment of malaria cases is readily achieved with timely administration of quick-acting artemisinin-based combination therapies (ACTs) with short half-lives, for chemoprevention, single-dose drugs with long half-lives are preferred to provide a long duration of protection and to clear asymptomatic infections present at the time of drug administration.

Another consideration for the development of chemoprevention drugs is the emergence and spread of drug resistance. Although the beneficial effects of IPTp with SP have been found to be surprisingly resilient to resistance, the efficacy of SP in preventing or clearing malaria infections during pregnancy is compromised in settings with very high levels of resistance, especially in the form of quintuple and sextuple *dhfr-dhps* mutations. PMC deployment was originally challenged by the lack of a formulation suitable for very young children, while SMC depends on a three-day amodiaquine-containing regimen that carers are expected to give to symptom-free children.

Against this backdrop, considering the known benefits of chemoprevention when drugs are administered as intended and the ongoing high burden of malaria, a review of the clinical development of drugs for chemoprevention is warranted.

This document presents PPCs for drugs to be used in malaria chemoprevention in children (use case 1), in pregnancy (use case 2) and in non-immune travellers (use case 3).

Several broad approaches may be considered for new malaria chemoprevention drugs, each of which will have different timelines for clinical development ([Annex 1](#)). These approaches include: i) **repurposing** approved malaria treatments (drug combinations or single-dose cures) for use as chemoprevention, ii) **recombining** approved individual drugs into new combinations for malaria prevention and iii) **developing** new drug combinations specifically for chemoprevention.

## 2. PPCs FOR DRUGS USED IN MALARIA CHEMOPREVENTION

The tables below describe the PPCs for new drugs for malaria chemoprevention that may be the result of several development approaches:

i) **repurposing** approved malaria treatments (drug combinations or single-dose cures) for use as chemoprevention, ii) **recombining** approved individual drugs into new combinations for malaria prevention and iii) **developing** new drug combinations specifically for chemoprevention. These approaches are described in further detail in Annex 1.

### 2.1 Use case 1: paediatric chemoprevention

Characteristic	Description	Comments
<b>Indication for use</b>	Prevention of symptomatic infection with <i>P. falciparum</i> and/or <i>P. vivax</i>	<p>Prevention of infection will lead to reduced clinical malaria, including severe malaria, most frequently caused by <i>P. falciparum</i>.</p> <p>The intervention should cure asymptomatic infections present at the time of drug administration.</p> <p>Activity against non-falciparum species would be an advantage, such as the development of new drugs for chemoprevention of <i>P. vivax</i> and <i>P. ovale</i> with liver-stage activity, schizonticidal activity in the blood stage and/or anti-hypnozoite activity to prevent relapse.</p> <p>See "Section 2.1.1. Indication for use".</p>
<b>Target population</b>	<p>Children at highest risk of adverse outcomes from malaria infection. The current <i>WHO Guidelines for malaria (8)</i> include the following use cases for chemoprevention in children:</p> <ul style="list-style-type: none"> <li>• SMC in areas of seasonal transmission</li> <li>• PMC in areas of moderate to high transmission intensity</li> <li>• for children in areas where MDA is deployed, e.g. emergency situations such as malaria epidemics</li> <li>• PDMC for children admitted to hospital with severe anaemia</li> <li>• IPTsc</li> </ul>	<p>According to current recommendations, chemoprevention can be deployed in children from the age of 2 months (PMC) up to 15 years (IPTsc), although the greatest benefits are expected in children under 5 years, as they tend to be at highest risk of severe disease and death.</p> <p>See "Section 2.1.2. Target population".</p>

Characteristic	Description	Comments
<b>Safety</b>	<p>Given that chemoprevention will be provided to asymptomatic individuals, safety and tolerability of the drugs recommended for chemoprevention should provide a favourable risk–benefit profile, with, at most, only mild, transient drug-related adverse events and very rare drug-related serious adverse events that can be promptly referred to and managed by the health care system.</p> <p>Any impact on safety and efficacy due to food interactions should be manageable.</p> <p>Ideally, safety should be demonstrated in high-risk (including immunocompromised) groups, such as HIV-infected children and children with malnutrition.</p>	<p>Safety evaluation should consider the potential for cumulative toxicity of repeat doses. For example, up to five rounds of SMC have been implemented. Under PMC, children have received 3–6 doses in the first year of life and up to 12 doses in the second year of life (up to 15 months of age), all at monthly intervals.</p> <p>See “Section 2.1.3. Safety”.</p>
<b>Efficacy &amp; duration</b>	<p>The drug should reduce the incidence of new symptomatic malaria infections and cure existing asymptomatic infections. This will reduce clinical malaria episodes, severe disease and death.</p> <p>Preventive efficacy against all symptomatic malaria infections of at least 90% over a one-month period is preferred, or 80% preventive efficacy sustained for at least four months through monthly administration. A rational target level of efficacy should be justified in conjunction with targets for the duration of protection and other key product characteristics that influence the intervention’s overall public health impact in the target population.</p>	<p>It could be rational to set a benchmark based on existing drugs used for chemoprevention, requiring products to demonstrate similar levels of efficacy, but not necessarily requiring non-inferiority trials. Use of standardized follow-up times is encouraged, such as those outlined in the WHO chemoprevention efficacy study protocol (9) in order to enable better comparability between studies.</p> <p>Preventive efficacy can be defined as 1 minus the incidence rate ratio of symptomatic infections during 28 days of follow-up after each treatment course in the intervention versus control/placebo groups.</p> <p>Where it is not acceptable to recruit a placebo group, studies should compare the intervention to the locally required standard of care.</p> <p>See “Section 2.1.4. Efficacy and duration”.</p>



Characteristic	Description	Comments
<b>Dose regimen &amp; schedule</b>	Single dose given as directly observed therapy (DOT), ideally no more frequently than once per month	<p>Currently used chemoprevention regimens include three days of SP+AQ for SMC, but this is not preferred.</p> <p>A broad therapeutic range and similar dose ratio (i.e. mg/kg) across body weight bands will facilitate administration by age or weight.</p> <p>The frequency of chemoprevention administration should be informed by the length of protective efficacy of the selected drug, the duration of the risk period and the feasibility of delivering each additional treatment.</p> <p>See “Section 2.1.5. Dose regimen and schedule”.</p>
<b>Route of administration</b>	Oral	<p>Single-dose long-acting injectable drugs that provide improved duration of protection and effectiveness and/or simplified dosing may be feasible for some populations, such as in health care settings for PDMC.</p> <p>See “Section 2.1.6. Route of administration”.</p>
<b>Co-administration</b>	Any drug–drug or food–drug interactions, including with antiretroviral, anthelmintic or other antimalarial drugs, should be manageable in practice.	See “Section 2.1.7. Co-administration”.
<b>Formulation/ presentation</b>	<p>Dispersible fixed-dose combination (or equivalent, e.g. granules) with taste-masking if needed</p> <p>Dose per tablet/sachet designed for maximum versatility</p>	See “Section 2.1.8. Formulation/presentation”.
<b>Product stability and storage</b>	At least two-year shelf life of the final product at 30 °C ± 2 °C and relative humidity of 75% ± 5%	<p>See guidance regarding long-term stability testing.<sup>a</sup></p> <p>See “Section 2.1.9. Product stability and storage”.</p>

Characteristic	Description	Comments
<b>Programmatic suitability</b>	A broad therapeutic index will enable wide weight bands or age-based dosing.	Appropriate packaging in course-of-therapy packs with easy-to-understand pictograms may facilitate ease of use.  See “Section 2.1.10. Programmatic suitability”.
<b>Access and affordability</b>	Dosage, regimen and cost of goods should enable affordable supply. Cost of delivery should be no more than current interventions. Price should not be a barrier to access in low- and middle-income countries.	Cost-effectiveness should be evaluated.  See “Section 2.1.11. Access and affordability”.
<b>Susceptibility to loss of efficacy due to resistance</b>	A combination of drugs should be developed with i) different modes of action, ii) lack of reported resistance in humans to either component and iii) limited cross-resistance between partner drugs.  Closely matched pharmacology should ensure that periods exposed to monotherapy are minimized and coincide only with low parasitaemia.  Ideally, one or more of the components should have causal prophylactic activity for any species, targeting the pre-erythrocytic stage.	Chemoprevention drug combinations should ideally differ from the antimalarials used as first-line treatment of malaria. This can be accomplished either by excluding long-acting partner drugs currently used in first-line treatment or by combining partner drugs with similar pharmacokinetic profiles to reduce the risk of drug resistance.  See “Section 2.1.12. Special consideration: potential loss of efficacy due to resistance”.

<sup>a</sup> Section 3.2.P.8.1 of the Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part (2).

### 2.1.1 Indication for use

The primary need is for drugs that prevent and cure infection with *P. falciparum*, the parasite responsible for most severe malaria disease and death.

However, *P. vivax* and *P. ovale* also cause substantial morbidity in South-East Asia, Latin America and parts of Africa (e.g. Ethiopia and Sudan); there are currently no drugs recommended for chemoprevention of these species. Therefore, improved drugs for chemoprevention with liver-stage activity against relapsing malaria species (*P. vivax* and *P. ovale*) would be particularly valuable to prevent hypnozoite formation and reactivation.

Separate recommendations exist for the use of chemoprevention in perennial and seasonal transmission settings. Drugs requiring a wash-out period may be better suited to settings with intensely seasonal transmission, where chemoprevention is given during the high transmission season and the period of lower transmission becomes a wash-out period with no drug administration in order to mitigate potential adverse outcomes related to drug accumulation.

### 2.1.2 Target population

Malaria chemoprevention has been largely used in children aged from 2 months (PMC) to 5 years (SMC). However, some countries are expanding the use of SMC to children up to 10 years, and new WHO recommendations have also extended the use of chemoprevention to school-aged children up to 15 years (IPTsc). Although the majority of severe malaria and malaria-associated mortality occurs in children under 5 years of age, older children continue to experience malaria episodes that may compromise not only their health, but also their educational performance. Chemoprevention in school-aged children (IPTsc) has been shown to decrease parasite prevalence, anaemia and clinical malaria across a range of transmission settings (10). In addition, three months of chemoprevention in children recently discharged from hospital after recovery from severe anaemia has been shown to reduce post-discharge death and hospital re-admissions (11). By targeting a substantial proportion of the reservoir of malaria infection, chemoprevention may also reduce transmission, especially when given to a broader age range (12). In the future, it would be beneficial to determine the potential benefit of chemoprevention in special populations at increased risk of severe malaria, such as children with underlying disease (e.g. sickle cell disease, malnutrition or HIV infection) (13,14).

### 2.1.3 Safety

Drugs for chemoprevention will be administered repeatedly, necessitating the evaluation of potential drug accumulation and associated toxicity. In SMC and PDMC, doses are delivered over a limited period – usually three to five months – with the intention of maintaining protective blood levels for the entire risk period. However, children may receive SMC for five or more consecutive years. As part of PMC, children in perennial transmission settings can receive 3–6 treatments in the first year of life and 1–12 treatments in the second year of life; these children are, therefore, particularly prone to the risks of drug accumulation.

Regulatory agencies have informally indicated that safety data on 3000 exposed individuals may be sufficient when evaluating a combination of two new chemical entities. Such sample sizes should detect uncommon adverse events (up to one event per 1000 treatments) with confidence. As a reference point for the expected number of exposed individuals by transmission intensity, chemoprevention is currently recommended in settings with moderate to high transmission intensity, defined as a *P. falciparum* parasite prevalence greater than 10% or an annual parasite incidence of above approximately 250 *P. falciparum* cases per 1000 people (8).

Note that these are approximate thresholds that are indicative of transmission; they should not be regarded as absolutes for determining the applicability of chemoprevention.

#### **2.1.4 Efficacy and duration**

The drug should reduce the incidence of new symptomatic malaria infections and cure existing asymptomatic infections.

A preventive efficacy of at least 90% over one month is highly desirable, or 80% efficacy sustained over at least four months through monthly administration. The level of efficacy should be considered together with preferred targets for the duration of protection and other key product characteristics (such as feasibility of dose regimen) when determining the potential public health impact in the target population.

The protective efficacy of existing strategies may be considered as a benchmark. For example, in effectiveness evaluations across seven countries in the sub-Saharan region of Africa, SMC with a treatment course consisting of a daily dose of SP+AQ for three days reduced the incidence of clinical malaria by 79–96% in the 28 days following the start of the treatment course (15). Similarly, PMC with SP in the first year of life has been shown to reduce the incidence of clinical malaria in the 35 days after treatment by 42–97% at 3 months of age and by 34–89% up to 12 months of age (16). PDMC with monthly dihydroartemisinin-piperazine has reduced both clinical malaria and hospital re-admissions by 69% and post-discharge deaths by 92% (17). WHO has developed a standard chemoprevention efficacy study protocol (9), which recommends follow-up over a period of 28 to 63 days, depending on the medication being used. Details on drugs and regimens used in existing chemoprevention strategies are included in Table 1.

#### **2.1.5 Dose regimen and schedule**

Ideally, the drug should be administered as a single dose of a single drug or fixed-dose combination under DOT at regular intervals. The current standard of care for SMC is three days of treatment with SP+AQ monthly, with the first day as DOT and the second and third days unsupervised, which is not ideal. For the development or selection of drugs for chemoprevention, monthly dosing schedules are likely to be optimal; however, sustaining effective drug levels for a month with a single-dose regimen is challenging. Weekly single-dose treatments could be an alternative to a three-day monthly regimen, depending on the balance of benefits and costs. Ultimately, the aim is to achieve a balance between drug efficacy and the simplicity of the drug regimen. While high-efficacy/single-dose regimens are ideal, moderately efficacious drugs with easy-to-follow regimens could be effective in practice if they result in increased adherence compared to more complex regimens.

The target dose per kilogram body weight should be similar across the range of body weights.

A broad therapeutic margin will facilitate dosing by weight or age.

The operational feasibility of the dose regimen will be a major consideration when chemoprevention is deployed at scale.

The frequency of administration should be informed by the length of protective efficacy of the selected drug treatment course, the duration of the risk period and the feasibility of delivering each additional course.

### **2.1.6 Route of administration**

Oral administration is the preferred route.

Single-dose, long-acting injectable formulations that provide improved duration of protection and effectiveness and/or simplified dosing could also be beneficial, particularly in health care settings, such as for PDMC.

### **2.1.7 Co-administration**

There should be no serious drug–drug or food–drug interactions. The potential for interaction with the immunological response to vaccines should also be considered (18). This could be a beneficial interaction, for example through reduction of the immunosuppressive effect of ongoing *Plasmodium* infection (19), or a negative interaction that reduces vaccine effectiveness.

A requirement for co-administration with food is likely to be a major operational challenge and should be avoided.

Potential synergies between different malaria control strategies should also be considered. For example, seasonal deployment of vaccination has been associated with reduced incidence of clinical malaria during the transmission season. Typically, individuals will not receive SMC if they have malaria at the time SMC is due or if they have been very recently treated with ACTs. Many drugs used in SMC have a longer half-life than the ACTs used for treatment. SMC recipients therefore benefit from a longer period of post-treatment protection than those treated with ACTs. Protection through vaccination results in a lower incidence of malaria and, thus, fewer individuals receiving treatment with ACTs on the days when SMC is due. As a result, more vaccinated children may receive SMC and benefit from an increased period of protection compared to those who are unvaccinated. However, the choice of drugs for malaria treatment will vary according to national guidelines, and some ACT partner drugs, such as piperazine, may have a longer half-life (20).

### **2.1.8 Formulation/presentation**

A dispersible tablet formulation facilitates administration in the field and is highly preferred.

Palatability in children under 5 years old should be well established, ideally with flavour-masking. A neutral taste may reduce the likelihood of drug intoxication compared to sweet formulations.

The dose per tablet should be carefully selected to ensure maximum versatility.

### **2.1.9 Product stability and storage**

Malaria chemoprevention drugs need to be stable for prolonged periods at ambient temperatures in malaria-endemic countries. In practice, this means at least two years at temperatures of 30°C ± 2°C and a relative humidity of 75% ± 5%.

### **2.1.10 Programmatic suitability**

A broad therapeutic margin will allow for wide weight bands or age-based administration, enhancing the programmatic feasibility of the regimen. Well designed course-of-therapy packs with pictograms to increase adherence to treatment doses can also improve the programmatic suitability of the drug.

### 2.1.11 Access and affordability

Cost and cost-effectiveness are impacted not only by the unit cost of the drug, but also by the operational costs of delivery. A single-dose regimen of a relatively long-acting antimalarial will have a longer dosing interval and require fewer treatments than a shorter duration drug requiring multiple days of treatment. Simpler regimens that achieve better adherence and deliver greater impact are preferable to shorter acting options.

Although the costs of the drug are likely to be similar everywhere, the costs of delivery and treatment vary markedly across time and space. The mode of delivery (e.g. facility-based versus home-based) will influence the reach of the intervention and its cost-effectiveness, as will the use of other preventive interventions (e.g. long-lasting insecticide-treated nets, malaria vaccines). Local costing data are important to inform local decisions.

The minimum acceptable approach is likely to include DOT on day 1. If a multi-dose regimen is needed, subsequent doses will likely be unsupervised. If that is the case, it will be important to evaluate the effectiveness of the regimen as deployed in real life (i.e. with realistic adherence to subsequent doses) and to evaluate cost-effectiveness on this basis.

### 2.1.12 Special consideration: potential loss of efficacy due to resistance

Drugs used for chemoprevention should have, as far as can be predicted, a minimal risk of inducing resistance. Useful characteristics from this perspective, not all of which are essential for the chemopreventive effects, include:

- a combination of drugs with different mechanisms of action;
- no resistance reported in humans for either drug within the combination;
- limited cross-resistance described between the partner drugs;
- closely matched pharmacology such that no component is present in the absence of the other components for more than a minimum amount of time in order to reduce the risk of new infections encountering only a single drug;
- any period of monotherapy coinciding only with low parasite densities;
- a component that has causal prophylactic activity, targeting the pre-erythrocytic stage;
- gametocytocidal effects.

These characteristics are preferred, but are not absolute requirements. For example, the relationship between resistance and chemoprevention efficacy is currently unclear. There is evidence that the clinical benefits of IPTp with SP are present despite high levels of resistance, suggesting that some level of resistance may not necessarily preclude development of the product (8,21). It is conceivable that a third component may be needed to ensure that a product with two long half-life drugs has adequate curative efficacy; even if not all components have “closely matched pharmacology”, the potential exposure of parasites to monotherapy will be minimized. As recommended in the *WHO Guidelines for malaria* as of 2022 (8), it is encouraged that drugs used for chemoprevention differ from those used as first-line malaria treatment in a given setting, which may vary according to national treatment guidelines. The aim is to avoid undermining any first-line treatments either by excluding long-acting partner drugs currently used in treatment regimens from a new chemoprevention drug combination, or by using two long-acting partner drugs with similar pharmacokinetic profiles to protect against the development of drug resistance. Gametocytocidal effects would be particularly valuable in drugs used for MDA to prevent onward transmission.

## 2.2 Use case 2: chemoprevention in pregnancy

The development of drugs for malaria chemoprevention in pregnancy is considered a priority because of the high risk and adverse consequences of malaria in pregnancy, and the unmet needs in the first trimester of pregnancy and for women coinfecting with HIV. Many of the PPC considerations for this use case are the same as for paediatric chemoprevention. In this section, attention is drawn to important additional considerations for chemoprevention in pregnancy.

Characteristic	Description	Comments
<b>Indication for use</b>	Prevention of <i>P. falciparum</i> malaria infection in pregnant women living in malaria-endemic settings	See "Section 2.2. Use case 2: Chemoprevention in pregnancy".
<b>Target population</b>	Pregnant women and/or women of childbearing age travelling to or living in malaria-endemic areas.	Drugs that are safe and efficacious in all trimesters, including early in the first trimester, enabling drugs to be taken as soon as pregnancy status is known or, in the case of MDA, enabling women of childbearing potential with unknown pregnancy status to receive drugs without pregnancy testing.
<b>Safety</b>	<p>Safety profile that is comparable to or better than WHO-recommended preventive treatments for pregnant women in endemic countries, providing a favourable risk–benefit profile. In addition, demonstrated safety in the first trimester is particularly desirable.</p> <p>Only mild, transient drug-related adverse events and very rare, manageable drug-related serious adverse events</p> <p>Favourable risk–benefit of potential embryo–fetal toxicity should be quantified and fully assessed.</p> <p>Tolerability in pregnancy should be assessed early in development.</p>	<p>The balance of benefits and risks is particularly important during pregnancy and may differ between preventive and therapeutic uses. Safety and tolerability data from exposure of pregnant subjects will be required, in addition to data following exposure of non-pregnant subjects, in order to support WHO recommendations and regulatory submissions.</p> <p>Post-approval evaluation of the safety of new drugs during pregnancy typically requires data from pregnancy registries, case reports or spontaneous reporting; in the absence of enough evidence, more robust data may need to be generated through additional studies (e.g. retrospective studies of secondary data, prospective observational studies or interventional clinical trials for non-teratogenic combinations) (23).</p>

Characteristic	Description	Comments
<b>Efficacy &amp; duration</b>	<p>Preventive efficacy against malaria infections in the mother, including placental malaria, of at least 75% over a six-month period is preferred.</p> <p>A rational target level of efficacy should be justified in conjunction with targets for the duration of protection and other key drivers of public health impact in the target population, such as dose regimen and adherence when delivered through routine health care systems.</p>	<p>Efficacy should primarily be demonstrated in terms of the prevention of any malaria infection, regardless of symptoms, in the mother.</p> <p>During the WHO malaria guidelines development process for chemoprevention drugs, key additional outcomes of interest included maternal anaemia and low birthweight, both of which may be mediated by non-malarial effects. It is likely that impact on one or both of these outcomes will be needed, in addition to malaria-specific outcomes in the mother, prior to use for IPTp.</p> <p>Other outcomes of interest include maternal placental infection, severe malaria, safety (adverse events) in the mother, hospitalization, and death, and fetal/infant adverse pregnancy outcomes (spontaneous abortion, stillbirth or pre-term delivery), malaria infection, anaemia, severe malaria, hospital admissions and death.</p> <p>Documentation of fetal outcomes (fetal loss, birthweight) will facilitate evaluation of the full effects of the drug.</p>
<b>Dose regimen &amp; schedule</b>	<p>Single-dose administration, ideally in one tablet, with a duration of protection of at least one month</p>	<p>Monthly administration is likely to be more feasible and acceptable than weekly dosing. Single-dose regimens with multiple tablets are likely to have greater impact than single tablets given over multiple days.</p> <p>Pharmacokinetics should be evaluated in the second and third trimesters and necessary dose adjustments identified. No adjustments should be needed between the second and third trimesters of pregnancy.</p>
<b>Route of administration</b>	<p>Oral</p>	<p>Single-dose, long-acting injectable drugs that provide improved duration of protection and effectiveness and/or simplified dosing may be acceptable for pregnant women if administered at antenatal clinics, but there should be evidence to demonstrate feasibility and acceptability.</p>



Characteristic	Description	Comments
<b>Co-administration</b>	<p>Drug–drug and food–drug interactions should be evaluated in pregnant women and manageable in practice.</p> <p>Potential interactions should be evaluated with vaccinations (e.g. tetanus), other drugs (e.g. folate, iron) given routinely during pregnancy, relevant genetic considerations (e.g. haemoglobinopathies) and comorbidities including HIV infection.</p>	<p>A regimen that does not allow for food intake prior to arriving at the antenatal clinic is unlikely to be realistic, but some brief food restrictions after treatment may be acceptable.</p>
<b>Formulation/ presentation</b>	<p>Fixed-dose formulations are preferred, but co-packaged tablets may be more acceptable for chemoprevention in pregnancy than for chemoprevention in children.</p>	
<b>Product stability and storage</b>		
<b>Programmatic suitability</b>		
<b>Access and affordability</b>	<p>Same as for use case 1.</p>	<p>Same as for use case 1.</p>
<b>Susceptibility to loss of efficacy due to resistance</b>		

The indication in pregnancy is the prevention of any malaria infections with the expectation that this will reduce clinical malaria and moderate to severe anaemia in the mother and improve birth outcomes.

IPTp is recommended for the prevention of malaria in pregnant women living in malaria-endemic settings. This intervention consists of SP administered at monthly intervals during the second and third trimesters; therefore, women may receive as many as six doses of SP during pregnancy. Given that currently available drugs for IPTp are not recommended earlier than 13 weeks, products that are safe and efficacious in all trimesters, i.e. including early in the first trimester, would enable women of childbearing potential with unknown pregnancy status to be protected, a particularly useful attribute where MDA is being considered.

The safety of drugs to be used during pregnancy is a key consideration for the mother and fetus. For the second and third trimesters of pregnancy, products should have a safety profile that is comparable to or better than WHO-recommended preventive treatments with SP. There should be only mild, transient drug-related adverse events and rare, manageable drug-related serious adverse events. The risk-benefit of potential embryo-fetal toxicity should be quantified and fully assessed. Tolerability is particularly important for the use of chemoprevention in pregnancy and should be assessed early in development. In addition, the use of antimalarials for the prevention of malaria in the first trimester of pregnancy will differ from the treatment of uncomplicated malaria in terms of risk-benefit assessment.

Efficacy should primarily be demonstrated in terms of the prevention of any malaria infection, regardless of symptoms, in the mother. IPTp with SP has also been shown to reduce maternal anaemia and low birthweight outcomes (21). Therefore, maternal anaemia and low birthweight are key outcomes of interest to policy-makers. Other outcomes of interest include maternal placental infection, severe malaria, safety (adverse events) in the mother, hospitalization and death, and fetal/infant adverse pregnancy outcomes (spontaneous abortion, stillbirth or pre-term delivery), malaria infection, anaemia, severe malaria, hospital admissions and death. Documentation of fetal outcomes (fetal loss, birthweight) will facilitate evaluation of the full effects of the drug. When IPTp with SP has been given in settings with high levels of resistance to SP, studies have found the effects on low birthweight to be less affected by resistance than the malaria-specific outcomes, suggesting that some of the effects of SP on fetal growth may be mediated through non-malarial pathways (22). The protective efficacy of existing strategies may be considered as a benchmark and evaluated in non-inferiority studies against the local chemoprevention standard.

The ideal regimen for next-generation chemoprevention in pregnancy would be one tablet that provides protection for one month or longer. Although fixed-dose formulations are preferred, co-packaged tablets may be more acceptable for chemoprevention in pregnancy than for chemoprevention in children. As with chemoprevention in children, monthly administration is likely to be more feasible and acceptable than weekly dosing.

Pharmacokinetics should be evaluated and any necessary dose adjustments identified. No adjustments should be needed between the second and third trimesters of pregnancy. Any safety and efficacy risks due to drug-drug and food-drug interactions should be evaluated and manageable in practice. A regimen that does not allow for food intake prior to arriving at the antenatal clinic is unlikely to be realistic, but some brief food restrictions after treatment may be acceptable. Potential interactions should be evaluated with vaccinations (e.g. tetanus), other drugs (e.g. folate, iron) given routinely during pregnancy, drug allergies, relevant genetic considerations (e.g. G6PD deficiency) and comorbidities including HIV infection.

The balance of benefits and risks is particularly important during pregnancy and may differ between preventive and therapeutic uses. Safety and tolerability data from exposure of pregnant subjects will be required, in addition to data following exposure of non-pregnant subjects, in order to support WHO recommendations and regulatory submissions. Post-approval evaluation of the safety of new drugs during pregnancy typically requires data from pregnancy registries, case reports or spontaneous reporting; in the absence of enough evidence, more robust data may need to be generated through additional studies (e.g. retrospective studies of secondary data, prospective observational studies or interventional clinical trials for non-teratogenic combinations) (23). The follow-up time for maternal and/or fetal outcomes will depend on several factors, such as the drug half-life, metabolic pathways, the nature of potential adverse events weighed against expected benefits, the prevalence of relevant comorbidities and potential confounding risk factors.

WHO has helped to support greater inclusion of pregnant and breastfeeding women in the evaluation of new drugs, such as facilitating the workshop “Approaches to enhance and accelerate study of new drugs for HIV and associated infections in pregnant women”, co-convened with the IMPAACT Network (24). Key topics discussed included the timing and interpretation of non-clinical reproductive toxicity studies, early inclusion of pregnant women or women who become pregnant in clinical trials, alternative and innovative study designs and methods, and strengthening of existing active surveillance systems.

Requirements for product stability and storage, access and affordability, and potential loss of efficacy due to resistance are the same as for paediatric chemoprevention.

## 2.3 Use case 3: non-immune travellers

As malaria control improves and some areas become malaria-free, people living in endemic countries may increasingly become non-immune or grow up without acquiring natural immunity to malaria. As a result, individuals growing up in localized areas without malaria (e.g. urban settings) may be at risk when travelling to malaria-endemic areas within their own country (e.g. more rural settings). Therefore, it will become increasingly important to protect travellers of all ages who are travelling within and between endemic countries. Adult travellers may also include those in high-risk occupational groups, such as miners and agricultural workers, who may be regular or irregular workers at high risk of malaria infection and not formally employed; they may also have sustained exposure, requiring a longer duration of protection. Inconsistent use of chemoprevention may result in incomplete protection, delayed treatment-seeking, and enhanced risk of severe malaria, suboptimal parasite detection and potential selection for resistance. Long-acting formulations requiring minimal engagement with health care services may, therefore, be advantageous. As in other use cases, the aim is to prevent *P. falciparum* and, by extension, all other human *Plasmodium* species. Some travellers and unofficial workers may only be identified after they return home. A post-exposure chemoprevention use case may be considered in which liver- and blood-stage activity is important. Travellers within endemic countries are less likely than tourists from non-endemic countries to support the high costs of many chemoprophylaxis regimens.

## 3. WHO PREQUALIFICATION

WHO prequalification of health interventions enables procurement through United Nations agencies and other global mechanisms and provides international assurance of product quality, safety, efficacy and suitability for low- and middle-income country programmes. WHO encourages developers and manufacturers to be aware of the WHO prequalification process, even at the early stages of development, and to discuss product and regulatory requirements with the WHO Prequalification Team early in the process. Regulatory pathways impact eligibility for prequalification. Readers are encouraged to refer to the WHO Coordinated Scientific Advice Procedure, which ensures that consolidated advice is provided on clinical development strategies from all relevant WHO departments, including the Prequalification Team (25).

The WHO Prequalification Team – Medicines will review and prequalify generic products (“full assessment” or “abridged assessment” if the generic product is one that has approval from a stringent regulatory authority) and, on occasion, originator products (“abridged assessment”) that have stringent regulatory authority approval.

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## ANNEX 1. GENERIC APPROACHES AND INDICATIVE TIMELINES FOR THE DEVELOPMENT OF DRUGS FOR MALARIA CHEMOPREVENTION

Three broad approaches may be considered for the development of new drugs for malaria chemoprevention: (i) repurpose, (ii) recombine and (iii) develop.

### Approach I: Repurpose

This approach sees the repurposing of approved malaria treatments for use as chemoprevention and could result in deployment by 2025. These treatments could include three-day drug combinations (such as dihydroartemisinin-piperaquine, pyronaridine-artesunate or atovaquone-proguanil) used for monthly, three-day drug combination chemoprevention regimens similar to those currently used for protecting children (SMC with SP+AQ), or single-dose cures similar to those used for IPTp with SP and PMC with SP.

The deployment of any drug brings with it some risk of an increase in the emergence and spread of resistance. At the outset, it is important that this risk is assessed as acceptable for each drug in a drug combination. Implementation will need to balance short-term gains (in terms of cases averted and lives saved) against longer term risks, should deployment lead to an increase in resistance and the loss of a drug class as an effective therapeutic.

### Approach II: Recombine

The recombination of approved individual drugs into new combinations for malaria prevention could be achieved in 2024–2029. For example, two 4-aminoquinolines (such as pyronaridine-piperaquine or pyronaridine-chloroquine) could be combined, or a monthly treatment dose of atovaquone-proguanil could be combined with a 4-aminoquinoline to protect against the development or spread of resistance. The development of novel combinations brings a risk of unforeseen adverse events and tolerability challenges. Each component could be used at the dose already approved by stringent regulatory authorities. If used at a new dose or combined with a drug of the same class, further studies may be required to demonstrate the efficacy of each component and of a fixed-dose combination at the proposed new dose, as well as the additive (or synergistic) effect of the combination. To avoid undermining any first-line treatments, either long-acting partner drugs currently used in treatment regimens should be excluded from new chemoprevention drug combinations, or any partner drugs used in a drug combination should have similar pharmacokinetic profiles to reduce the risk of drug resistance.

### Approach III: Develop

This approach aims at developing novel antimalarials in new drug combinations to be used specifically for chemoprevention and would likely only result in the launch of a new product after 2030. Approval through a stringent regulatory authority/WHO joint process (such as the European Medicines Agency's Article 58 procedure or Swissmedic's "Marketing Authorisation for Global Health Products") would be



valuable. For novel products, WHO prequalification requires regulatory approval by a stringent regulatory authority. At the time of this publication, the most advanced candidate molecules are in Phase 2 clinical development and include long-acting oral or injectable molecules, prodrugs and formulations (1).

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## ANNEX 2. CLINICAL DEVELOPMENT PATHWAYS FOR MALARIA CHEMOPREVENTION DRUGS

The primary aim of any chemoprevention strategy is the prevention of malaria disease and death. Drugs that effectively prevent infection will also prevent disease and have a subsequent effect on transmission. Drugs that cure blood-stage infections will reduce disease burden. The ideal drugs for chemoprevention will possess both pre-erythrocytic and blood-stage activity to prevent new infections and cure existing infections. However, an emphasis on causal prophylaxis, directed against the pre-erythrocytic stage to prevent parasites from progressing to blood-stage infection, may be appropriate given:

- the low proportion of individuals likely to be infected at the time of treatment in most situations;
- the availability of alternative treatments, should they be needed;
- the benefits in terms of reduced risk of resistance: Causal prophylactics target a stage with fewer parasites, reducing the risk of a mutation that provides the parasite with protection. In addition, prevented infections will reduce the pressure on any blood schizonticides;
- the simplification of evaluation studies if using infection end-points in a controlled human malaria infection study and/or under conditions of natural exposure, which may reduce the required sample size, trial duration and study costs.

Chemoprevention is given to people who are asymptomatic. Therefore, compared to the development of drugs for case management, chemoprevention drugs must have a very good safety profile if community acceptability and favourable risk–benefit outcomes are to be achieved. This may result in a higher attrition rate along the product development pathway for drugs for malaria chemoprevention compared to those for treatment.

The time required to prepare new chemoprevention drugs will depend on the development approach and the amount of data already available. Data from Phase 1 studies in healthy adults are needed to characterize the safety, tolerability and pharmacokinetics of the individual agents. Such data should already be available for products delivered using approaches 1 and 2 (Annex 1), but would need to be generated for new products.

In vitro evidence of efficacy against *P. falciparum* requires in vivo confirmation. Efficacy and pharmacodynamic data are needed to demonstrate the ability of the drug to prevent malaria. Controlled human malaria infection studies could be used to demonstrate protective efficacy or the ability of the drug or drug combination to clear *P. falciparum* asexual blood-stage parasites in healthy adults inoculated intravenously with *P. falciparum*-infected erythrocytes (PfPZ). Clinical trials of naturally exposed individuals with an infection end-point, rather than clinical disease, may allow for smaller sample sizes. Product developers should become familiar with the WHO malaria chemoprevention efficacy study protocol (1).

Phase 2 and Phase 3 clinical studies aim at demonstrating efficacy, safety and tolerability, and evaluating pharmacokinetics in the identified target population(s). When designing these clinical trials, careful consideration is needed with regard to the number of trial sites, their geographical region, level of malaria seasonality, intensity of transmission, drug sensitivity patterns and other preventive interventions

that are in place. The duration of the studies should reflect the duration of the intended use of the drug. The assessment of tolerability and palatability (e.g. minor adverse events, taste) is important given the potential of these characteristics to undermine adherence in target groups, who will generally be well when receiving chemoprevention.

There are ethical considerations in the evaluation of new preventive interventions in settings where existing chemoprevention strategies are used. The choice of comparator and trial designs considered appropriate will depend on the context in which the intervention is intended for use, the view of local ethical committees, the needs of regulators to support licensure and the opinion of public health stakeholders involved in decision-making for implementation. A placebo-controlled study design enables the measurement of the baseline infection rate and establishes the level of protection against new infections, calculated from the incidence rate ratio of positive parasitaemia/symptomatic malaria in the active treatment arm compared to the placebo arm. However, where placebo-controlled trials are not possible, a Phase 3 study might consider evaluating the superiority or non-inferiority of a new drug or drug combination with respect to the currently used chemoprevention drugs. Alternatively, safety could be used as a primary end-point to demonstrate an adequate safety threshold that is non-inferior to the standard of care.

Phase 2 chemoprevention studies should consider the length of the transmission season in selected study sites to enable accurate assessment of the duration of protection anticipated for the drug being evaluated.

Phase 3 chemoprevention trials are conducted in relevant target areas and populations. The Phase 3 trial(s) efficacy end-points will be informed by the primary aim of the chemoprevention intervention. Where high efficacy against infection has been demonstrated in Phase 2, a primary end-point of infection may suffice, with clinical malaria, anaemia, hospital admissions (all-cause and/or malaria-specific), severe malaria according to WHO criteria, and death (all-cause and/or malaria-specific) as secondary outcomes. For example, assessment of efficacy against new infections, using a combination of active and passive surveillance, could potentially be carried out alongside clinical disease end-points using parallel cohorts or in a randomly selected subpopulation (2,3). However, use of infection as a primary end-point in Phase 3 would require early consultation with regulatory authorities on its acceptability for licensure. Developers are strongly encouraged to discuss product-specific evaluation plans and end-points with regulators and WHO. Where lower efficacy against infection has been demonstrated, it will be necessary to conduct larger studies to evaluate the effect on clinical malaria as a primary end-point. The safety and tolerability of the drug combination should also be evaluated in the Phase 3 trial(s).

Phase 3 chemoprevention studies will normally be double-blind, randomized trials designed to demonstrate superior efficacy over placebo (if the sample size allows) or non-inferiority in terms of efficacy and/or safety compared to recommended chemoprevention interventions in the region. The primary end-point (and its attack rate), design, comparator and expected level of efficacy are key drivers of sample size. The sample size of the Phase 2 and 3 studies will also be driven by safety considerations, as the size of the dataset will have to ensure adequate characterization of the safety and tolerability profile of the combination in the target population. Safety and tolerability are particularly important for new products to be used for chemoprevention in pregnancy.

The incidence rate ratio of all symptomatic *P. falciparum* episodes is a reasonable primary end-point for pivotal studies. Studies should generate estimates of cases averted; in high transmission settings, modestly efficacious interventions may still be cost-effective.

Individual randomization is preferred for the demonstration of the direct effect of the intervention on infection and disease end-points in the recipients, while the effects on malaria transmission will require studies measuring incidence across the community, rather than only in individuals known to have received the intervention. Data on the effect on community-level transmission could be collected through cluster-randomized trials and/or operational monitoring of malaria incidence reduction and evaluation of malaria in households not receiving the drug once a strategy has been deployed at scale.

The amount of human data required to determine drug safety in pregnancy may vary depending on the agents used. If there are indications of a teratogenic effect (e.g. from preclinical animal studies), this will be particularly critical. There may also be potential cumulative toxicity associated with repeat drug administration for chemoprevention, compared to single use for treatment, and this should be considered during preclinical development. Developers are directed to existing guidance (4).

The selection of drug-resistant parasites can be monitored in clinical trials if markers of resistance are well established; measuring changes in drug efficacy can be guided by the WHO chemoprevention efficacy study protocol (1,5). However, the implications of such observations for the spread of resistant parasites across a community are not readily evaluated by such studies, and the relationship between drug resistance and chemoprevention efficacy is poorly understood (6).

Phase 4 studies provide an opportunity to consolidate the long-term safety profile and effectiveness of strategies, assessing whether adherence and/or coverage can be sustained and if the intervention is cost-effective when delivered at scale. Such studies can take place before or after a policy decision is made.

WHO prequalification should be sought for drugs intended to be used for malaria chemoprevention. The clinical data generated from Phase 1, 2 and 3 studies will be carefully reviewed by WHO to support inclusion in guidelines and subsequent prequalification. If a new drug is developed specifically for chemoprevention, acting prophylactically in the pre-erythrocytic stage, it may not be necessary to demonstrate efficacy for the treatment of disease if this is not the indication for use. Product development strategies should be discussed with regulators and WHO early in the development process and when planning pivotal trials in order to ensure that the data package meets regulatory and guideline development expectations and unnecessary delays are avoided. Acceptability, equity, costs and cost-effectiveness are key determinants of the potential public health impact and results of their assessment will be considered as part of the WHO guideline development process. Developers are encouraged to refer to the WHO Coordinated Scientific Advice Procedure (7) to ensure that their planned data packages, especially regarding the extent of the safety data, are likely to meet the needs of Global Malaria Programme and Prequalification Team reviews.

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