WHO preferred product characteristics for medicines for malaria chemoprevention

Draft for Public Consultation – July 2022

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Overview

The Global Technical Strategy for Malaria 2016 – 2030 (GTS) aims 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 (GMP) 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 key characteristics of medicines for use in malaria chemoprevention. These include the indication, target population, safety and efficacy, formulation and presentation, dose regimen, co-administration, route of administration, product stability and storage, and access and affordability. The preferences and related considerations are shaped by the unmet public health needs and the realities of malaria epidemiology and delivery systems in 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.[1] WHO encourages developers to consult this document, alongside malaria PPCs, if they intend to seek a WHO recommendation for use or prequalification of their products.

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 (R&D). 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 R&D targets for manufacturers and research 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.

Introduction

The 2021 World Malaria Report estimated 241 million cases of malaria worldwide, and 627,000 malaria deaths[2]. The WHO Africa 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 Global Technical Strategy targets for morbidity and mortality reductions. There is an urgent need to improve existing approaches and develop new approaches to control malaria to get back on track.

Chemoprevention refers to the use of medicines to prevent malaria in special risk groups. WHO recommends several chemoprevention strategies for malaria control. Seasonal malaria chemoprevention (SMC) was recommended in 2012 and updated in 2022 to prevent malaria in children in areas of seasonal malaria transmission in age groups at high risk of severe malaria with repeated treatment with antimalarial medicines during peak transmission seasons. Intermittent preventive treatment in infants (IPTi) was recommended in 2010 and updated to Perennial Malaria Chemoprevention (PMC) in 2022. PMC aims to prevent malaria in children belonging to age-groups at high risk of severe malaria in areas of moderate-to-high perennial transmission by giving antimalarial medicines at pre-defined intervals to reduce disease burden. Although there is research experience with several drug regimens, programmatically, IPTi has largely relied on sulphadoxine-pyrimethamine (SP) and SMC has extensively used SP with amodiaquine (SP-AQ). Intermittent preventive treatment in pregnancy (IPTp) was first recommended in 1998 (with updates in 2004, 2012 and 2022), and consists of a monthly treatment course of SP to pregnant women of all gravidities 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) consists of the use of a full therapeutic course of an antimalarial medicine, at approximately the same time, and often at repeated intervals, to all age groups of a population in a defined geographic area. MDA has been used both 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. MDA is recommended for disease reduction in moderate and high transmission settings, and for transmission reduction in very low and low transmission settings.

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://www.who.int/news/item/16-02-2021-who-launches-consolidated-guidelines-for-malaria.

Two further preventive strategies have been identified for malaria medicines. In settings with moderate to high malaria transmission, post-discharge malaria chemoprevention (PDMC) involves the post-discharge provision of antimalarial medicines at pre-defined intervals to reduce disease burden in children admitted to the hospital with severe anaemia. Such children have a marked increase in mortality in the 6 months following discharge, which can be reduced by PDMC. Another use case is the extension of chemoprevention as intermittent preventive treatment in school-aged children (IPTsc). As malaria control improves, the proportion of malaria disease experienced by school-aged children increases and this is associated with anaemia, 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.

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 localised 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). Thus, it will become important

to protect travelers within and between endemic countries. Occupational or behavioural risk factors can also identify other risk groups who may benefit from chemoprevention e.g. *P. vivax* malaria or other *Plasmodium* species amongst forest goers in South-East Asia.

Given the wide variety of use cases it is clear that medicines for malaria chemoprevention need to be safe and efficacious in very young children, pregnant women, and women of child-bearing age, and ideally also in the elderly.

The impact of drugs used for chemoprevention may be compromised by suboptimal adherence to full treatment courses and the emergence and spread of drug resistance. While the treatment of malaria cases is readily achieved with timely administration of quick-acting artemisinin-based combination therapies (ACTs) with short half-lives, single dose drugs with long half-lives are preferred for chemoprevention. Although the beneficial effects of IPTp-SP have been found to be surprisingly resilient to resistance, the efficacy of SP in preventing or clearing malaria infections in pregnancy is compromised in settings with very high levels of resistance, especially in the form of quintuple and sextuple *dhfr-dhps* mutations. PMC (formerly IPTi) deployment was originally challenged by the lack of a formulation suitable for very young children, while SMC depends on a 3-day amodiaquine-containing regimen which 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 medicines intended for 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 medicines for malaria chemoprevention, each of which will have different timelines for clinical development (Annex 1). These approaches include: i) **re-purposing** of approved malaria treatments (drug combinations or single-dose cures) for use as chemoprevention, ii) **re-combination** of approved individual drugs into new combinations for malaria prevention and iii) **developing** new drug combinations specifically for chemoprevention.

Preferred product characteristics for malaria chemoprevention

The tables below describe preferred product characteristics for new medicines for malaria chemoprevention that may be the result of several development approaches: i) re-purposing of approved malaria treatments (drug combinations or single-dose cures) for use as chemoprevention, ii) re-combination of approved individual drugs into new combinations for malaria prevention and iii) developing new drug combinations specially for chemoprevention. These are described in further detail in Annex 1.

Use case 1: Paediatric chemoprevention

Characteristic	***Description***	***Comments***
Indication for use	Prevention of symptomatic infection with *P. falciparum* and/or *P. vivax*	Prevention of infection will lead to reduced clinical malaria, including severe malaria, most frequently caused by *P. falciparum.* The intervention should cure asymptomatic infections present at the time of drug administration. Activity against non-*falciparum* species would be an advantage. *P. vivax* chemoprevention can include drugs with pre-erythrocytic activity to prevent hypnozoite formation, schizontocidal activity in the blood stage, and/or anti-hypnozoite activity to prevent relapse.
Target population	Children at increased risk of the adverse outcomes of malaria infection. Current WHO malaria guidelines[3] include the following use cases for chemoprevention in children: i. seasonal malaria chemoprevention (SMC) in areas with seasonal transmission and perennial malaria chemoprevention (PMC) in children in areas of moderate to high transmission intensity ii. for children in areas where Mass Drug Administration is deployed, e.g.	According to current recommendations, chemoprevention could be deployed in children from age 2 months (PMC) up to 15 years (IPTsc), although the highest benefits are expected in children <5 years as they tend to be at highest risk of severe disease and death.

	emergency situations such as malaria epidemics iii. post-discharge malaria chemoprevention (PDMC) for children admitted to the hospital with severe anaemia iv. intermittent preventive treatment in school-age children (IPTsc)	
Safety	Given that chemoprevention will be provided to asymptomatic individuals, safety and tolerability of medicines recommended for preventive treatments should provide a favourable risk benefit profile, with only mild, transient drug-related adverse events, and rare drug-related Serious Adverse Events (SAE) that can be promptly referred to and managed by the healthcare system. Any safety and efficacy risks due to food interactions should be manageable. Ideally, safety should be demonstrated in high-risk (including immunocompromised) groups, such as HIV-infected children and children with malnutrition.	Safety evaluation should consider the potential for cumulative toxicity of repeat doses. For example, up to 5 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. If the drug is to be used in low transmission settings (e.g. for transmission reduction) the risk of malaria and benefits of its prevention may be different than in higher transmission settings. In the case of MDA, there may be community benefits to transmission reduction that extend beyond individual-level protection.
Efficacy & duration	The medicine should reduce the incidence of new symptomatic malaria infections and cure existing asymptomatic infections. This will reduce clinical malaria episodes, severe disease and death. Preventive efficacy against all symptomatic malaria infections of at least 90% over a 1-month period is preferred, or 80% sustainable over at least 4 months by monthly administration.	It could be rational to set a benchmark according to existing interventions, e.g. current levels of protection afforded by SMC or PMC strategies. Preventive efficacy can be defined as an incidence rate ratio of symptomatic infections during 28 days follow-up in intervention versus control groups not receiving the chemoprevention intervention/strategy.

	A rational target level of efficacy should be justified in conjunction with targets for the duration of protection and other preferred product characteristics that influence the intervention's overall public health impact in the target population.	Where it is not acceptable to recruit a placebo group, studies should consider non-inferiority designs against the locally required standard of care.
Dose Regimen & schedule	Single dose given as directly observed therapy, ideally not more frequently than once per month	Currently used chemoprevention regimens include 3-days of SPAQ for SMC, but this is not preferred. A broad therapeutic range and similar dose ratio (i.e. mg/kg) across body weight bands will facilitate administration by age or weight.
Route of administration	Oral	
Co-administration	No adverse drug-drug or food-drug interactions, including with antiretroviral medications.	
Formulation/presentation	Dispersible fixed dose combination (or equivalent e.g. granules) with taste-masking if needed Dose per tablet/sachet designed for maximum versatility	
Product stability and storage	At least 2 years shelf life of final product at 30°C ± 2°C and relative humidity of 65% ± 5%	See guidance regarding long-term stability testing[i]
Programmatic suitability	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.
Access and affordability	Dosage, regimen, and cost of goods should enable affordable supply. Cost of delivery should	Cost-effectiveness should be evaluated.

[i] 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[1]

	be no more than current interventions. Price should not be a barrier to access in low- and middle-income countries.	
Susceptibility to loss of efficacy due to resistance	A combination of drugs should be developed with i) different modes of action, ii) a lack of reported resistance in humans to either component and iii) limited cross-resistance between partner drugs. Closely matched pharmacology should ensure periods of exposed monotherapy are minimised and coincide only with low parasitemia. Ideally, one or more of the components should have causal prophylactic activity.	Medicines for chemoprevention should ideally be different from antimalarials used as first-line treatment of malaria.

Indication for use

The primary need is for medicines which prevent and cure infection with *P. falciparum*, the parasite responsible for most severe malaria disease and death, both in and beyond Africa.

P. vivax causes substantial morbidity in South East Asia, Latin America and parts of Africa (e.g., Ethiopia and Sudan), but suitable medicines for chemoprevention of this parasite do not exist. *P. vivax* chemoprevention to prevent hypnozoite formation and reactivation and with drugs acting in the liver stage would be particularly valuable. A regulatory dossier based on protection against *P. falciparum* malaria and with *in vitro* data supporting activity against other species may be sufficient to support use in settings with mixed infections.

Separate recommendations exist for the use of chemoprevention in perennial and seasonal transmission settings. Medicines requiring a wash out period may be better suited to settings with intensely seasonal transmission, where chemoprevention is given during the high transmission seasons and the period of lower transmission becomes a wash out period to mitigate potential adverse outcomes related to drug accumulation.

Target population

Malaria chemoprevention has been largely used in children aged from 2 months (PMC, formerly IPTi) up to 5 years (SMC). However, some countries are expanding the use of SMC to children up to 10 years and new WHO recommendations have 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 targeting school-aged children (IPTsc) has been shown to decrease parasite prevalence, anaemia and clinical malaria across a range of transmission settings.[4] Additionally, three months of chemoprevention targeting children recently discharged from hospital after recovery from severe anaemia has been shown to reduce post-discharge death and hospital readmissions.[5] By targeting a substantial proportion of the reservoir of malaria infection, chemoprevention may also reduce transmission, especially when given to an extended age range.[6] In the future, it would be beneficial to determine the potential benefit of chemoprevention in additional populations at increased risk of severe malaria, such as children with underlying disease (e.g. sickle cell).[7,8]

Safety

Medicines for chemoprevention will be administered repeatedly, necessitating the evaluation of potential drug accumulation and associated toxicity. In SMC and PDMC, doses are delivered during a limited period – usually 3 to 5 months – with the intention of maintaining protective blood levels for the entire risk period. Children may receive SMC for five or more consecutive years. As part of PMC, children in perennial transmission settings have received 3-6 treatments in the first year of life and 1-12 treatments in the second year of life.

Regulatory agencies have informally indicated that safety data on 3,000 exposed individuals may be sufficient when evaluating a combination of two new chemical entities (NCEs). Such sample sizes should detect uncommon adverse events (up to 1 event per 1,000 treatments) with confidence. As a reference

point, chemoprevention is currently recommended in settings with moderate or high transmission intensity, a *P. falciparum* parasite prevalence greater than 10% or an annual parasite incidence of above approximately 250 *P. falciparum* cases per 1000 people.[9] Note that these are approximate thresholds indicative of transmission and should not be regarded as absolutes for determining applicability of chemoprevention.

Efficacy and duration

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

A preventive efficacy of at least 90% over 1-month is highly desirable, or 80% efficacy sustained over at least 4 months by 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 dosing regimen) when determining 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, SMC with SPAQ has been shown to reduce the incidence of clinical malaria by 79-96% in the 28 days following each dose.[10] Similarly, IPTi in the first year of life have been shown to reduce the incidence of clinical malaria by 47-97% in the 35 days after doses at 9 months of age.[11] PDMC with monthly dihydroartemisinin-piperaquine reduced both clinical malaria and hospital readmissions by 69% and post-discharge deaths by 92%.[12] WHO has developed a standard Chemoprevention Efficacy Study (CPES) protocol which recommends follow up over a period of 28 to 42 days, depending on the medication being used.

Dose regimen and schedule

Ideally, the medicine should be administered as a single dose under directly observed therapy (DOT) at regular intervals. The current standard of care for SMC is 3-days of treatment with SP-AQ monthly, with the first day as DOT, and the second and third days unsupervised. 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 3-day monthly regimen. Ultimately, the aim is to achieve a balance between drug efficacy and simplicity of the drug regimen. While high-efficacy/single-dose regimens are ideal, moderately efficacious drugs with easy-to-follow regimens could be more 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 dosing regimen will be a major consideration when chemoprevention is deployed at scale.

Co-administration

There should be no serious drug-drug or food-drug interactions. The potential for interaction with the immunological response to vaccines should be considered. This could be a beneficial interaction, for example through reduction of the immunosuppressive effect of ongoing *Plasmodium* infection[13], 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 vaccination has been associated with reduced incidence of clinical malaria during the transmission season. Typically, an individual would not receive SMC if very recently treated with ACTs. Therefore, vaccination could result in fewer individuals receiving treatment with ACTs on days when SMC may be due. These individuals could potentially benefit from an increased period of protection if the drugs used in SMC have a longer half-life compared to the ACTs used for treatment. However, choice of drugs will vary according to national treatment guidelines, and some ACT partner drugs, such as piperaquine, may have longer half-lives.[14]

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.

Route of administration

Oral administration is the preferred route.

Current delivery channels for paediatric chemoprevention would see diminished access and usability by some frontline workers if injectable formulations were introduced. To be considered, injectable formulations would need to provide substantial benefits, such as improved duration or higher protective effectiveness, to increase acceptability to users and affordability to the health system.

Product stability and storage

Malaria chemoprevention medicines need to be stable for prolonged periods at ambient temperatures in malaria endemic countries. In practice, this means at least 2 years at temperatures of 30ºC ± 2ºC and a relative humidity of 65% ± 5%.

Programmatic suitability

A broad therapeutic margin will allow 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 medicine.

Access and affordability

Cost and cost-effectiveness is not only impacted by the unit cost of the drug but also the operational costs of delivery. A single dose regimen of a relatively long-acting antimalarial will have a longer dosing interval and need fewer treatments than a shorter-duration drug requiring multiple days of treatment. The ability

to achieve better adherence and deliver greater impact with simpler regimens compared to longer-acting options is likely to be preferable, all other characterstics being equal.

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 reach of the intervention and cost-effectiveness, as will the use of other preventive interventions (e.g., long-lasting insecticide treated nets (LLINs), the RTS,S malaria vaccine). Local costing data are important to inform local decisions.

The minimum acceptable approach is likely to include directly observed treatment (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.

Special consideration: potential loss of efficacy due to resistance

Medicines used for chemoprevention should have, as far as it 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 other components for more than a minimum time, to reduce the risk of new infections encountering only a single drug
- Any period of monotherapy should coincide only with low parasite densities;
- A component that has causal prophylactic activity;
- Gametocytocidal effects.

These characteristics are preferred, but are not absolute requirements. For example, the relationship between resistance and chemoprevention efficacy is unclear, with evidence of the benefits of IPTp-SP despite high levels of resistance, suggesting that some level of resistance should not necessarily preclude development of the product.[9,15] It is conceivable that a third component may be needed to ensure a product with two long half-life drugs has adequate curative efficacy; although not all components would have 'closely matched pharmacology', minimising potential exposure of parasites to monotherapy would be achieved. As recommended in the WHO Malaria Guidelines as of 2022, it is encouraged that medicines used for chemoprevention are different to those used as first-line malaria treatment in a given setting,[9] which may vary according to national treatment guidelines. Gametocytocidal effects would be particularly valuable in drugs used for MDA to prevent onwards transmission.

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, unmet needs in the first trimester of pregnancy and for women co-infected with HIV. Many of the PPC considerations are the same as for

paediatric chemoprevention. In this section, attention is drawn to important additional considerations for chemoprevention in pregnancy.

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. This also provides a clear clinical development pathway. IPTp-SP in the second and third month of pregnancy has been shown to reduce maternal anaemia and low birthweight outcomes.[15]

IPTp is recommended for the prevention of malaria in pregnant women living in malaria endemic settings. This consists of SP administered at monthly intervals during the second and third trimesters; therefore, women may receive as many as 6 doses of IPTp-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, will allow women of childbearing potential with unknown pregnancy status to be protected, a particularly useful attribute where MDA is considered. Pregnant women co-infected with HIV may also benefit from new malaria chemoprevention options.

The safety of medicines for use in pregnancy is a key consideration for the mother and foetus. For the second and third trimester of pregnancy, products should have a comparable or better safety profile to WHO recommended preventive treatments with SP. There should be only mild, transient drug-related adverse events and rare, manageable drug-related serious AEs. Medicines for which preclinical studies document no embryo-foetal toxicity are preferred. Tolerability is very important and should be assessed early in development. Additionally, for use of antimalarials in the first trimester of pregnancy, the risk-benefit assessment will differ from treatment of uncomplicated malaria and will need to be taken into account.

Efficacy should primarily be demonstrated in terms of the prevention of any malaria infection, regardless of symptoms, in the mother. Key outcomes of interest to policy makers are maternal anaemia and low birthweight. Other outcomes of interest include maternal placental infection, severe malaria, safety (adverse events) in the mother, hospitalization, and death; and foetal/infant adverse pregnancy outcomes (spontaneous abortion, stillbirth or pre-term delivery), malaria infection, anaemia, severe malaria, hospital admissions and death. Documentation of foetal outcomes (foetal loss, birth weight) will facilitate evaluation of the full effects of the medicine. When IPTp-SP has been given in settings with high levels of SP resistance, the effects on low birth weight were found 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.[16] 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 providing protection for one month or longer. Although fixed dose formulations are preferred, co-packaged tablets may be more acceptable in pregnancy than in paediatrics. As with chemoprevention in children, monthly administration is likely to be more feasible and acceptable than weekly dosing.

Pharmacokinetics should be evaluated in the second and third trimesters 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 food intake prior to arrival in 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 in pregnancy and conditions including HIV co-infection.

Safety and tolerability data from exposure in pregnant subjects will be required, in addition to data following exposure in non-pregnant subjects to support WHO recommendations and regulatory

submissions. The evaluation of the safety of new medicines in pregnancy requires data from over 1,000 exposures[17] and, in the absence of spontaneous reporting, these data need to be generated in specific clinical trials or pregnancy registries. A commitment to gather relevant safety data in Phase 3 or 4 studies (e.g. through interventional clinical trials for non-teratogenic combinations and/or a registry of first trimester exposures) may also be needed.

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

Characteristic	***Description***	***Comments***
Indication for use	Prevention of *P. falciparum* malaria infection in pregnant women living in malaria endemic settings	
Target population	Pregnant women living in malaria endemic areas.	Drugs that are safe and efficacious in all trimesters, i.e. including early in the first trimester, will allow women of childbearing potential with unknown pregnancy status to receive the medicines without pregnancy testing, which will particularly useful for MDA.
Safety	Comparable or better safety profile compared with WHO recommended preventive treatments for pregnant women in endemic countries, providing a favourable risk benefit profile. Only mild, transient drug-related adverse events and rare, manageable drug-related serious AEs. Compounds for which preclinical studies document no embryo-foetal toxicity are preferred. Tolerability is very important and should be assessed early in development.	Safety and tolerability data from exposure in pregnant subjects will be required in addition to data following exposure in non-pregnant subjects to support WHO recommendations and regulatory submissions. Evaluation of the safety of new medicines in pregnancy requires data from over 1,000 exposures[17] and, in the absence of spontaneous reporting, these data need to be generated in specific clinical trials or pregnancy registries. Commitment to gather relevant safety data in Phase 3 or 4 studies (e.g. through interventional clinical trials for non-teratogenic combinations and/or a registry of first trimester exposures) may also be needed.

Efficacy & duration	Preventive efficacy against malaria infections in the mother, including placental malaria, of at least 75% over a 6-month period preferred. 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 dosing regimen and adherence when delivered through routine healthcare systems.	Efficacy should primarily be demonstrated in terms of the prevention of any malaria infection, regardless of symptoms, in the mother. Main outcomes of interest are maternal anaemia and low birthweight. Other outcomes of interest include maternal placental infection, severe malaria, safety (adverse events) in the mother, hospitalization, and death; and foetal/infant adverse pregnancy outcomes (spontaneous abortion, stillbirth or pre-term delivery), malaria infection, anaemia, severe malaria, hospital admissions and death. Documentation of foetal outcomes (foetal loss, birth weight) will facilitate evaluation of the full effects of the medicine.
Dose Regimen & schedule	Single dose administration, ideally in one tablet, with duration of protection of at least one month	Monthly administration is likely to be more feasible and acceptable than weekly dosing. 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.
Route of administration	Oral	
Co-administration	Drug-drug and food-drug interactions should be evaluated in pregnant women and manageable in practice. Potential interactions should be evaluated with vaccinations (e.g. tetanus), other drugs (e.g. folate, iron) given routinely in pregnancy and conditions including HIV co-infection.	A regimen that does not allow food intake prior to arrival in antenatal clinic is unlikely to be realistic, but some brief food restrictions after treatment may be acceptable.

Formulation/presentation	Fixed dose formulations preferred, but co-packaged tablets may be more acceptable in pregnancy than in paediatrics.	
Product stability and storage	Same as for use cases listed above.	Same as for use cases listed above.
Programmatic suitability	Same as for use cases listed above.	Same as for use cases listed above.
Access and affordability	Same as for use cases listed above.	Same as for use cases listed above.
Susceptibility to loss of efficacy due to resistance	Same as for use cases listed above.	Same as for use cases listed above.

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. Individuals growing up in localised 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). Thus, it will become increasingly important to protect travelers within and between endemic countries. Adult travellers may also include 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. Inconsistent use of chemoprevention may result in incomplete protection, delayed treatment seeking, suboptimal parasite detection and potentially enhance the risk of resistance selection. Long-acting formulations requiring minimal engagement with health care services may therefore be advantageous. As in other use cases, the aim is to prevent infection with *P. falciparum* and, by extension, all other plasmodial 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.

Travelers within endemic countries are less likely than tourists from non-endemic countries to support high costs of many chemoprophylaxis regimens.

Characteristic	***Description***	***Comments***
Indication for use	Prevention of malaria infection in 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
Target population	Non-immune individuals travelling to endemic areas	Adult travellers may also include high-risk occupational groups such as miners and agricultural workers who may be regular or irregular workers, highly exposed to mosquitoes and not formally employed.
Safety	Safety and tolerability comparable to or better than other WHO recommended preventive treatments in use in endemic countries, providing a favourable risk benefit profile. Only mild, transient drug-related adverse events, and rare drug-related Serious Adverse Events (SAE) that can be promptly referred to and managed by the healthcare system. Any safety and efficacy risks due to food effects should be manageable.	Medicines with low risk of cumulative toxicity would be beneficial if repeated dosing over prlonged periods is needed. Ideally, safety should be demonstrated in high-risk (including immunocompromised) groups, such as HIV-infected individuals.
Efficacy & duration	Preventive efficacy of at least 90% over a 1-month period against all symptomatic malaria infections, or 80% sustainable over at least 4 months by monthly administration.	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 dosing regimen and adherence.
Dose Regimen & schedule	Single dose administration, ideally in one tablet, with duration of protection of at least one month	Monthly administration is likely to be more feasible and acceptable than weekly dosing.

Route of administration	Oral	
Co-administration	No adverse drug-drug or food-drug interactions, including with antiretroviral medications.	
Formulation/presentation	Fixed dose formulations preferred, but co-packaged tablets may be more acceptable in adults than in paediatrics.	
Product stability and storage	Same as for use cases listed above.	Same as for use cases listed above.
Programmatic suitability	Same as for use cases listed above.	Same as for use cases listed above.
Access and affordability	Same as for use cases listed above.	Same as for use cases listed above.
Susceptibility to loss of efficacy due to resistance	Same as for use cases listed above.	Same as for use cases listed above.

Annex 1: Generic approaches and indicative timelines for the development of medicines for malaria chemoprevention

Three broad approaches may be considered for the development of new medicines for malaria chemoprevention: (i) re-purpose, (ii) re-combine and (iii) develop.

Approach I: Re-purpose

This approach sees the re-purposing of approved malaria treatments for use as chemoprevention and could result in deployment by 2025. These could include three-day drug combinations (such as dihydroartemisinin (DHA)-piperaquine, pyronaridine-artesunate or atovaquone-proguanil) used for monthly, 3-dose chemoprevention regimens similar to those currently used for protecting children (SMC), or single-dose cures similar to those used for IPTp and IPTi.

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. Decision-making for implementation will need to balance short-term gains (in terms of cases averted and lives saved) and longer-term risks, should deployment lead to an increase in resistance and the loss of a drug class.

Approach II: Re-combine

The re-combination of approved individual drugs into new combinations for malaria prevention could be achieved during 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, or if used at a new dose, would require further study.

Approach III: Develop

This approach aims to develop new drug combinations specially 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 EMA article 58 or Swissmedic's MAGHP) would be valuable. In the early 2020s, the most advanced candidate molecules were in Phase 2 clinical development and included long-acting oral or injectable molecules, prodrugs and formulations.[18]

Annex 2: Clinical development pathways of medicines for chemoprevention

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 medicines 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:

(i) the low proportion of individuals likely to be infected at the time of treatment in most situations;

(ii) the availability of alternative treatments, should they be needed;

(iii) 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. Additionally, prevented infections will reduce the pressure on any blood schizonticides;

(iv) the simplification of evaluation studies if using infection endpoints in a controlled human malaria infection (CHMI) 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 and/or well. Therefore, in comparison to the development of medicines for case management, chemoprevention drugs must have a very good safety profile if a favourable benefit - risk outcome is to be achieved. This may result in a higher attrition rate along the product development path of drugs for malaria chemoprevention compared to 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 medicine to prevent malaria. CHMI could be used to demonstrate the ability of the drug or drug combination to clear *P. falciparum* asexual blood stage parasites in healthy adults inoculated intravenously with Pf-infected erythrocytes. CHMI could also be used to evaluate the protective efficacy in healthy adults inoculated intravenously with Pf sporozoites (PfSPZ). Clinical trials of naturally-exposed individuals with an infection endpoint, rather than clinical disease, may allow smaller sample sizes. Product developers should become familiar with the generic WHO Chemoprevention Efficacy Study protocol, which is being finalized.[2]

Phase 2 and 3 clinical studies aim to demonstrate efficacy, safety, tolerability and to evaluate pharmacokinetics in the identified target population(s). When designing these clinical trials, careful consideration is needed of the number of trial sites, their geographic regions, level of malaria seasonality, intensity of transmission, drug sensitivity patterns and other preventive interventions are in place. The duration of the studies should reflect the duration for the intended use of the drug. The assessment of

[2] https://www.who.int/teams/global-malaria-programme/case-management/drug-efficacy-and-resistance/tools-for-monitoring-antimalarial-drug-efficacy

tolerability and palatability (e.g. minor adverse events, taste) is important given its potential 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 an intervention is intended for use, the view of local ethical committees, the needs of regulators to support licensure, and opinion of public health stakeholders involved in decision-making for implementation. A placebo-controlled study design allows the measurement of the baseline infection rate and establishes the level of protection against new infections, calculated from the incidence rate ratio (IRR) of positive parasitaemia/symptomatic malaria in the active treatment compared with the placebo arms. However, where placebo-controlled trials are not possible, a Phase 3 program might consider safety as the primary endpoint to demonstrate an adequate threshold of safety 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 allow 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 endpoints will be informed by the primary aim of the chemopreventive intervention. Where high efficacy against infection has been demonstrated in phase 2, a primary endpoint 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) being secondary outcomes. For example, assessment of efficacy against new infections, using a combination of active and passive surveillance, could potentially be measured alongside clinical disease endpoints using parallel cohorts or in a randomly selected sub-population.[19,20] 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 endpoint. 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 sample size allows) and/or non-inferiority in terms of safety when compared to recommended chemopreventive interventions in the region. The primary endpoint (and its attack rate), design, comparator, and expected level of efficacy are key drivers of sample size. The sample of size of the Phase 2 and 3 programs 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.

The incidence rate ratio (IRR) of all symptomatic *P. falciparum* episodes is a reasonable primary endpoint 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 endpoints 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 randomised trials and/or operational monitoring of malaria incidence reduction once a strategy is deployed at scale.

The amount of human data required for determination of 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. Developers are directed to existing guidance.[21]

The selection of drug resistant parasites can be monitored in clinical trials if markers of resistance are well established.[22] 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.[23]

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 pre-qualification (PQ) should be sought for medicines intended for malaria chemoprevention. The clinical data generated from Phase 1, 2 and 3 studies will be carefully reviewed by the WHO to support inclusion in guidelines and prequalification. Some studies could be conducted in parallel. Where a drug is developed specifically for chemoprevention, it may not be necessary to demonstrate efficacy when used for the treatment of disease. Product development strategies should be discussed with regulators and the 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 avoid unnecessary delays. Assessments of acceptability, equity, costs and cost-effectiveness are key determinants of the potential public health impact and will be considered as part of the WHO guideline development process. Developers are encouraged to refer to the WHO Coordinated Scientific Advice (CSA) Procedure[24] to ensure that their planned data packages, especially regarding the extent of the safety data, are likely to meet the needs of the technical and PQ reviews.

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