WHO technical consultation on preferred product characteristics for drugs used in malaria chemoprevention

Meeting report, 15–16 December 2020

1. SUMMARY

On 15–16 December 2020, the World Health Organization (WHO) Global Malaria Programme and the Medicines for Malaria Venture (MMV) co-convened a technical consultation to consider the preferred product characteristics (PPCs) for drugs used in malaria chemoprevention. Leading scientists and experts, public health officials, regulators, those involved in the development of WHO policy recommendations on malaria, and representatives of in-country end-users (from malaria control programmes) and civil society took part. See Annex 1 for the meeting agenda and Annex 2 for the list of participants.

Previously, in October 2019, a WHO technical consultation reviewed the role of drugs for malaria prevention and recommended that research and development of new malaria drugs should place greater emphasis on their potential use for chemoprevention *(1)*. Therefore, the December 2020 meeting was convened to discuss PPCs for drugs for malaria chemoprevention. WHO has laid out a standard process for the development of PPCs, as well as a template to summarize the intended use, target population and desired attributes of products being developed. A PPC is intended to inform product developers, regulatory agencies, procurement agencies and funders about WHO's research and development priorities.

In early 2021, the WHO Global Malaria Programme launched the first stage of the consolidated *WHO Guidelines for malaria (2)*, drawing together all existing guidance on a web-based platform. This platform facilitates access to all WHO malaria recommendations and, where relevant, provides links to supporting evidence from systematic reviews. The goal is for these consolidated guidelines to provide enhanced guidance to countries to maximize the impact of the resources available to their national malaria programmes *(2)*.

Despite a concerted effort by the international community, malaria remains a major global health threat *(3)*. It has particularly significant effects in children and during pregnancy *(4, 5)*. Over the last two decades, the development of new malaria drugs has largely focused on treatment. For infectious diseases, the front line in prevention is often vaccination and, in October 2021, RTS,S/AS01

became the first malaria vaccine to be recommended by WHO for use in moderate- to high-transmission settings in sub-Saharan Africa. However, the development of new malaria vaccines remains challenging due to the complexity of the malaria parasite and the fact that, unlike many viral infections, a single infection does not result in sterilizing immunity *(6–8)*.

Over the last two centuries, drugs have played a key role in protecting against infectious diseases. In many disease areas, it can take more than a decade for a new drug to be launched following the discovery of a new molecule. The additional complexity of designing combination drugs – as is now the standard in malaria – and the need for safety data in children further lengthen this timeline. Therefore, it is particularly important that the malaria drug development and disease control communities align on the key characteristics needed in next-generation drugs to prevent malaria.

The main goal of the technical consultation was to agree on the most important PPCs for drugs to protect populations from malaria (chemoprevention), while considering relevant measures of efficacy and the safety data needed to support WHO policy recommendations. To this end, the consultation reviewed the knowledge gaps on the efficacy, safety and tolerability of existing drugs that could be used for chemoprevention, including drug combinations currently approved for malaria treatment. It also considered new combinations of molecules already approved for use that could potentially be developed to prevent malaria over the next five years. Finally, the meeting briefly discussed molecules that are in the early stages of development and could potentially be new products in the next decade.

This document lays out the use cases and PPCs for drugs for malaria chemoprevention and, bearing in mind available registered drugs and the pipeline of future opportunities, presents potential strategies for their development.

2. PPCs AND TARGET PRODUCT PROFILES (TPPs)

The meeting was co-convened by WHO and MMV to define the PPCs for drugs for use in malaria chemoprevention. PPC documents have been established by WHO to provide an overview of the key characteristics of drugs, vaccines, diagnostics and vector control products, using a common approach and template across all disease areas. PPCs typically describe the strategic health goals of the product, detailing the medical need and how the product will address it. PPCs may also reflect considerations regarding the clinical development pathway of new products that meet the PPCs. Critical to this discussion are relevant measures of efficacy and safety needed to support WHO policy recommendations. PPCs act as guides to inform product developers, regulatory agencies, procurement agencies and funders about public health priorities to stimulate the research and development of products to address the greatest health needs.

The development of PPCs provides a strong indication that products meeting the criteria will be highly beneficial for public health. PPCs are most often developed in cases where WHO has defined a priority need and development has not yet reached exploratory (Phase 2) clinical studies.

TPPs are documents that have traditionally been compiled to support the development of specific new products progressing along the development pathway. TPPs tend to focus on the regulatory context and thus product labelling. As such, they overlap to a large extent with PPCs, but are more specific.

There are three areas of difference between PPCs and TPPs. First, PPCs represent an ideal to be aimed at, while TPPs also include "minimally acceptable" standards. In doing so, TPPs can be useful tools to inform "go/no-go" decisions during the product development process. Second, TPPs tend to undergo further refinement as new data emerge, not only on new drugs, but also on the epidemiological environment in which they will be used. For example, the identification of new drug-resistant strains or changes in efficacy of existing drugs may have a profound effect on drug discovery strategies. Therefore, TPPs require more frequent updates. Accordingly, MMV typically updates its master TPP documents every three to four years (9–12). PPCs are tools developed by WHO to provide strategic guidance and high-level considerations to ensure that products meet public health needs and will also be updated approximately every 5 years to reflect scientific changes.

Alignment between PPCs and TPPs has been facilitated in recent years by collaboration between WHO, disease-endemic country regulators and stringent regulatory authorities. This collaboration has resulted in closer alignment of decision-making frameworks, such as the European Medicines Agency's (EMA) Article 58 process (13) and Swissmedic's Marketing Authorisation for Global Health Products (14). It is important for global health perspectives to be acknowledged in the design of pivotal clinical studies of new products, ideally allowing for efficient regulatory review and consideration for inclusion in malaria control guidelines. Early alignment can help to prevent delays in the deployment and availability of new life-saving drugs.

The public health impact of new drugs for chemoprevention will be a function of the underlying disease burden and the preventive effectiveness of the new drugs. The latter is driven not only by the efficacy of the drug, but also by the duration of protection and the level of adherence and coverage achieved. The safety, tolerability and dosing regimen of the drug influence the adherence and, therefore, effective coverage. The number of treatments required will be determined by the duration of protection per dose and the intended period of protection. Decision-makers in ministries of health must consider which combinations of interventions will deliver the greatest health impact with the available resources, given the local costs of disease and options for its control. The cost of chemoprevention drugs and their delivery are important considerations at the national level. As such, efficacy, duration of protection, safety, tolerability, dosing regimen and the costs of delivery are inevitably linked and important considerations in PPCs.

3. BACKGROUND

Case management with highly effective antimalarial drugs has contributed to the decrease in malaria morbidity and mortality. Routine administration of antimalarial drugs as chemoprevention has also been recommended in select high-risk populations, irrespective of malaria infection status, both to treat any unrecognized *Plasmodium* infections and to prevent new ones (15). This meeting was convened to consider the characteristics and development strategies of new drugs for chemoprevention to prevent malaria disease and death, with the aims of the *Global technical strategy for malaria 2016–2030 (16)* in mind.

Several strategies can be grouped under the umbrella of chemoprevention. These strategies target different populations, use different delivery methods and are designed to achieve a variety of outcomes. WHO recommends the use of drugs to prevent malaria among people living in endemic settings who are at high risk of the adverse consequences of malaria. Intermittent preventive treatment of malaria in pregnancy (IPTp) consists of the administration of a course of a malaria drug (sulfadoxine-pyrimethamine) at antenatal care visits. Intermittent preventive treatment of malaria

in infants (IPTi) (now known as perennial malaria chemoprevention [PMC][1]) involves the administration of a course of an antimalarial drug alongside selected routine vaccinations. Children living in intensely seasonal transmission settings may be given seasonal malaria chemoprevention (SMC), which currently targets children aged 3 months to 5 years, who are given a full course of therapy at monthly intervals throughout the peak transmission season *(17, 18)*. In Senegal, SMC is provided up to 10 years of age *(19)*, and discussions are ongoing in other countries to extend the use of SMC beyond 5 years of age. Other potential use cases for malaria chemoprevention in children include post-discharge malaria chemoprevention (PDMC), which targets children at high risk of disease and death following hospital admission with anaemia. Intermittent preventive treatment of malaria in school-aged children (IPTsc) has also been shown to reduce malaria and anaemia and may improve educational outcomes *(20)*. In some use cases, mass drug administration (MDA) may be considered a form of chemoprevention to reduce disease and death from malaria. This involves the delivery of malaria treatment to every member of a defined population or geographical area at the same time and is recommended to mitigate the worst effects of malaria in epidemic situations or complex emergencies (e.g. civil unrest or Ebola outbreaks). In many malaria-endemic areas, women may not be aware of their pregnancy status or are unable to discuss it. MDA drugs must therefore also be safe for women of childbearing age who may be in the first trimester of pregnancy during the drug campaign. MDA is also recommended to help interrupt *P. falciparum* malaria transmission in areas approaching elimination and to reduce the spread of multidrug resistance, especially in the Greater Mekong subregion.

Malaria prophylaxis is another recognized approach to the prevention of malaria using drugs. Historically, the doses used for prophylaxis are somewhat lower than those used for treatment (e.g. mefloquine and atovaquone-proguanil). In the future, new prophylaxis regimens may be needed to protect non-immune migrating populations. Traditionally, prophylaxis has targeted tourists and military personnel, but increasingly this group could also include residents of urban areas at low risk of malaria in endemic countries who move to or visit higher risk rural areas, or populations migrating from low- to high-transmission areas.

Despite the number of use cases and potential public health value of malaria chemoprevention, only a small number of drugs are available for these indications. Sulfadoxine-pyrimethamine is recommended for IPTp and IPTi, and in combination with amodiaquine for SMC. Concerns about efficacy, safety and acceptability have curbed the use of other antimalarial drugs for chemoprevention. Additionally, concerns that chemoprevention may accelerate the development and spread of drug resistance has meant that some drugs have been reserved for the treatment of clinical cases. Meeting participants highlighted the need to have clear criteria to decide when a current medicine is not suitable for use as chemoprevention. Currently, such decisions are based on the prevalence of resistance mutations (e.g. for IPTi) or less well defined notions of efficacy (e.g. for SMC). Going forward, it will be important to have an operational definition of drug failure based on clinical end-points of protection.

PPCs aim to describe the characteristics that will help to maximize a product's public health impact. For malaria chemoprevention, an ideal drug would provide protection from symptomatic malaria caused by *P. falciparum* as well as infections caused by *P. vivax* and other *Plasmodium* species. Drugs for *P. vivax* chemoprevention should ideally have liver-stage activity to prevent hypnozoite formation and/or anti-hypnozoite activity to prevent relapse *(21)*, but could also include schizonticidal activity in the blood stage.

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1   In 2022, WHO updated guidelines on the use of malaria chemoprevention in perennial transmission settings to include children aged over 12 months, and IPTi was renamed PMC.

4. CLINICAL DEVELOPMENT PATHWAYS FOR CHEMOPREVENTION DRUGS

To determine clinical development strategies for new chemoprevention drugs, it is critical to establish that the primary aim is prevention of symptomatic malaria and death, as opposed to the interruption of transmission. It is also crucial to determine the required duration of protection and target population(s). To date, all drugs used to prevent malaria have first been shown to be effective in curing malaria infections and, at some point in their history, were used to treat malaria disease. In the future, three broad drug development strategies may be considered:

1. **repurposing** of drug combinations already approved for the treatment of malaria, which will already have extensive characterization of their efficacy and safety/tolerability profile, for chemoprevention;

2. **recombination** of approved individual antimalarials, each with proven efficacy and safety when used for treatment of malaria, into new combinations for chemoprevention;

3. **development** of novel drugs or drug combinations specifically for chemoprevention.

The time required to prepare new chemoprevention drugs or drug combinations will depend on the strategy chosen 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 though strategies 1 and 2, but would need to be generated for new products (strategy 3).

Next, efficacy and pharmacodynamics data are needed to demonstrate the ability of the drug to prevent malaria. Controlled human malaria infections 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 *P. falciparum*-infected erythrocytes. Controlled human malaria infections could also be used to evaluate the protective efficacy in healthy adults inoculated intravenously with *P. falciparum* sporozoites.

The aims of subsequent Phase 2 and 3 clinical studies are to demonstrate acceptable efficacy, safety and 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 geographical regions, level of malaria seasonality, transmission intensity, drug sensitivity patterns and whether other preventive interventions are in place. In addition, study duration needs to reflect the intended use case(s) of the drug. Assessment of tolerability (e.g. vomiting) and palatability is important given the potential for these features to undermine high adherence and effective coverage 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 the opinion of public health stakeholders involved in decision-making for implementation. A placebo-controlled study design enables 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 safety to be the primary end-point in order 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 for accurate assessment of the anticipated duration of protection for the drug being evaluated.

Phase 3 chemoprevention trials are conducted in relevant target geographies and populations. Phase 3 efficacy end-points will be informed by the primary aim of the chemoprevention intervention and could include clinical episodes of malaria, anaemia, hospital admissions (all-cause and/or malaria-related), severe malaria according to WHO criteria, and mortality (all-cause and/or malaria-related). The safety and tolerability of the drug combination will also be evaluated in the Phase 3 trial(s).

Phase 3 chemoprevention studies will normally be double-blinded, randomized controlled trials designed to demonstrate superior efficacy over placebo (if sample size allows) and/or non-inferiority in terms of safety compared to the 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 the sample size. The sample size of 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 drug combination in the target population.

Individual randomization is preferred for the demonstration of a direct effect of the intervention on infection and disease end-points in recipients. 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 once a strategy is deployed at scale.

The evaluation of the extent to which the chemoprevention strategy selects drug-resistant parasites can be planned in clinical trials if markers of resistance are well established. For example, asymptomatic children receiving IPTi or SMC have been followed up to monitor markers of resistance at standard intervals. It is also feasible to conduct in vivo studies measuring efficacy of the chemoprevention drug regimen against asymptomatic infection.

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

The clinical data generated from Phase 1, 2 and 3 studies will be carefully reviewed by WHO to support a policy recommendation. Some studies could be conducted in parallel. Where a drug is being developed specifically for chemoprevention, it may not be necessary to demonstrate efficacy for disease treatment. Product development strategies should be discussed with regulators and WHO early in the development process to avoid unnecessary delays in the availability of new chemoprevention options. Assessment of acceptability, equity, cost and cost-effectiveness are key determinants of the potential public health impact of chemoprevention strategies and will be considered as part of the WHO guideline development process.

5. GENERIC PROCESSES AND TIMINGS FOR THE DEVELOPMENT OF DRUGS FOR MALARIA CHEMOPREVENTION

Each of the three strategies for the development of new drugs for chemoprevention has its own timeline.

Strategy 1: repurpose (launch 2020–2024)

A policy change to allow *approved* treatments to be used for chemoprevention could result in the repurposing of existing drugs within the next five years. These could include three-day drug combinations (such as dihydroartemisinin-piperaquine, artesunate-pyronaridine or atovaquone-proguanil) used for monthly/three-dose chemoprevention regimens similar to those currently used for protecting children (SMC), or single-dose cures similar to those used for protecting pregnant women (IPTp) and infants (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 for this risk to be 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.

Strategy 2: recombine (launch 2024–2029)

The recombination of approved individual drugs into new combinations for malaria prevention (Fig. 1) could be achieved during the 2024–2029 time frame. For example, it is conceivable that two 4-aminoquinolines (such as pyronaridine-piperaquine or pyronaridine-chloroquine) could be combined, or that a monthly treatment dose of atovaquone-proguanil could be combined with a 4-aminoquinoline to protect against the development or spread of resistance. Table 1 provides a ranking of several possible drug combinations in this strategy. Each component could be used at the dose already approved by stringent regulatory authorities, or at a new dose, which would require regulatory review.

The development of such combinations brings a risk of unforeseen adverse events and tolerability challenges. The regulatory pathway could be through a stringent regulatory authority that assesses products intended for global health use, potentially jointly with WHO (e.g. EMA under Article 58 *(13)*, or Swissmedic under the Marketing Authorisation for Global Health Products *(14)*), or directly through WHO prequalification. It is noteworthy that none of the current chemoprevention drugs went through a regulatory label change with a stringent regulatory authority.

Fig. 1. Drug and combination selection process for strategy 2
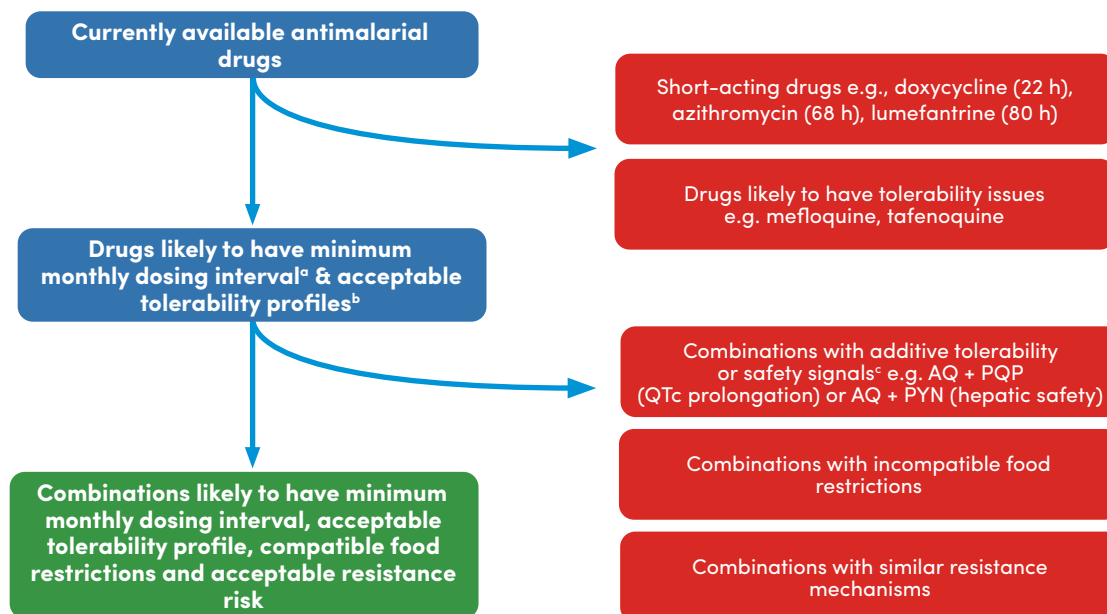
AQ: amodiaquine; ATV-PG: atovaquone-proguanil; CQ: chloroquine; PQP: piperaquine; PYN: pyronaridine

[a] Based on duration of post-dose prophylaxis following treatment

[b] For administration to healthy children

[c] Excluding rare events. AQ & CQ extrapyramidal syndrome risk (rare). Some risk of additive hepatotoxicity for ATV-PQ + PYN, can be de-risked in combination safety study

Source: Figure provided by MMV

Table 1. Ranking of potential combinations for strategy 2

	CRITERION 1: TOLERABILITY (ACCEPTABILITY / COMPLIANCE)	CRITERION 2: LOW RISK OF SAFETY CONCERN	CRITERION 3: DURATION OF PROTECTION (POTENTIAL FOR TWO-MONTH DOSING INTERVAL)	CRITERION 4: AFFORDABILITY	CRITERION 5: COMPATIBILITY REGARDING FOOD RESTRICTIONS	CRITERION 6: LOW RISK OF RAPID EMERGENCE OF RESISTANCE	CRITERION 7: SUITABLE FOR PREGNANT WOMEN (POPULATION-WIDE USE)	OVERALL SCORE	RANK
Weighting (%)	25%	15%	15%	10%	15%	15%	5%	100%	
PYN + PQP[a]	5	5	5	3	3	5	5	4.5	1
ATV-PQ[b] + PYN	4	5	3	1	4	4	5	3.75	2
ATV-PQ[b] + PQP[c]	4	5	3	2	2	4	4	3.5	3
PYN + CQ[d]	3	3	3	3	5	2	4	3.2	4
PYN + AQ[e]	2	2	3	3	4	4	3	2.9	5
ATV-PG + CQ[d]	3	3	2	2	4	2	4	2.8	6
ATV-PG + AQ[f]	2	1	1	2	4	3	3	2.2	#

[a] Positive resistance interaction: PYN effective against Pfcrt (PQP resistance mutation)

[b] Concerns about transmission of drug-resistant mutations

[c] Potential mutually-exclusive food restrictions

[d] Risk of resistance re-emergence limits geography. Lack of availability of appropriate paediatric doses/presentations

[e] Artesunate-amodiaquine label >4.5 kg (approximately >2 months age)

[f] Eliminated following combination safety study in healthy volunteers

Source: Table provided by MMV

Strategy 3: develop (launch 2030)

The third strategy aims at developing new drug combinations 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 would be required. The most advanced candidate molecules are currently in Phase 2 and include long-acting oral or injectable molecules, prodrugs and formulations *(12)*.

Clarity on the data package required for public health deployment would facilitate the planning of Phase 3 studies and avoid additional data requests prior to WHO recommendation and prequalification.

Since the drugs will be provided to healthy and/or asymptomatic individuals, safety and tolerability of drugs recommended for preventive treatments should provide a favourable risk–benefit profile. This may result in a higher attrition rate of drugs for chemoprevention along the product development pathway, compared to drugs for malaria treatment.

Progress with strategy 3 requires the provision of sufficient evidence for stringent regulatory authority approval, preferably through a process that includes WHO and participation of national regulatory authorities in disease-endemic countries.

6. USE CASES FOR MALARIA CHEMOPREVENTION

Existing WHO guidelines encourage the use of malaria chemoprevention to protect people at particular risk of severe disease and death. Use cases can be clustered into three related groups (Table 2).

Table 2. Use cases for protection against malaria infection

TARGET POPULATION	USE CASE	CURRENT STANDARD OF CARE	IMPORTANCE AFTER 2025
Children	Strongly seasonal transmission settings: SMC in children aged 3 months to 5 years, with potential extension up to 10 years, for prevention of severe disease and death	Three days of amodiaquine, one day of sulfadoxine-pyrimethamine, at monthly intervals, as used in SMC	High
	Perennial transmission settings: preventive treatment in infants and children in the second (and potentially subsequent) year of life (PMC)	Sulfadoxine-pyrimethamine	High
	Populations at increased risk of severe malaria: PDMC in children admitted to hospital for anaemia or children with underlying conditions (e.g. sickle cell)	None approved specifically for this indication; dihydroartemisinin-piperaquine, sulfadoxine-pyrimethamine, and artemether–lumefantrine have been evaluated.	High
	IPTsc up to 15 years of age in seasonal and perennial transmission settings	Sulfadoxine-pyrimethamine with amodiaquine or primaquine, sulfadoxine-pyrimethamine plus artesunate, artesunate–amodiaquine, and dihydroartemisinin-piperaquine have been evaluated for IPTsc.	High

TARGET POPULATION	USE CASE	CURRENT STANDARD OF CARE	IMPORTANCE AFTER 2025
Adults	Women in second and third trimesters of pregnancy (IPTp)	One-day sulfadoxine-pyrimethamine at antenatal care visits	
	Women of childbearing age and/or in first trimester of pregnancy, thereby allowing MDA in whole population	None approved; dihydroartemisinin-piperaquine has been evaluated in clinical studies.	High
Travellers	Non-immune individuals living in endemic countries, or moving between low- and high-transmission zones	Daily atovaquone-proguanil; weekly tafenoquine, mefloquine, doxycycline	
	Occupational risk groups (e.g. forest workers and miners)	As above	

6.1 Use case one: paediatric chemoprevention

The age distribution of severe *P. falciparum* malaria means that in the most highly endemic areas, children continue to be a major target population requiring protection. Despite the scale-up of control efforts across the range of malaria transmission settings in Africa, those with severe disease presenting to hospital are predominantly children under 5 years of age *(22)*.

The potential of chemoprevention has been demonstrated most recently by the success of SMC in intensely seasonal settings in the Sahel, where a three-day course of malaria treatment with sulfadoxine-pyrimethamine plus amodiaquine is given at monthly intervals to children 3–59 months old through the peak transmission season. A new regimen would be useful in seasonal areas where sulfadoxine-pyrimethamine plus amodiaquine is not currently deployed due to concerns that pre-existing resistance will make the strategy ineffective. A new combination could also be used to protect children in the Sahel should sulfadoxine-pyrimethamine plus amodiaquine start to fail or if the new regimen has more favourable characteristics (e.g. single dose, longer duration, lower cost). Although work is ongoing to develop non-artemisinin-based combinations with relatively long-acting antimalarials that could be used for SMC, there are currently no drugs in the global malaria portfolio with the potential to provide one month's protection from a single tablet in many seasonal transmission settings. SMC is generally administered to all eligible children in the community at approximately the same time during the peak transmission season.

A large burden of disease also exists in settings with year-round transmission, and WHO recommends chemoprevention to protect young children in perennial transmission settings. IPTi involves a full course (single tablet) of sulfadoxine-pyrimethamine administered alongside certain vaccinations in the first year of life. This strategy builds on existing contacts with the Expanded Programme on Immunization (EPI) to target young children living in areas with year-round transmission. As a result of the linkage with EPI, IPTi is currently a directly observed therapy (single tablet). In 2022, IPTi was updated to PMC in light of new data documenting the value of chemoprevention in children aged 12 to 14 months.

Intensely seasonal and truly perennial transmission patterns may be considered opposite ends of a spectrum. However, many malaria-endemic settings do not lie at either extreme, but have year-round transmission with seasonal variation in intensity. In some settings, it may be useful to explore the potential of a two-pronged strategy in which very young children are protected from perennial transmission at specific ages, and older children receive chemoprevention during seasons with increased transmission.

Target population(s). Malaria chemoprevention has been largely used in children aged from 2 months (IPTi, now PMC) up to 5 years (SMC), but some countries are expanding the use of SMC to children aged 6–10 years. Although these children may have a lower risk of severe disease and death than younger children, they carry a substantial burden of uncomplicated malaria, which may impact educational and health outcomes. A clear vision is needed on the evidence needs for endorsing the use of new types or combinations of drugs to provide protection in this age group.

In 2022, updated WHO Guidelines for malaria *(2)* also extended the use of chemoprevention to school-aged children (IPTsc) up to 15 years of age. IPTsc has been shown to decrease parasite prevalence, anaemia and clinical malaria across a range of transmission settings *(20)*.

Malaria infection carries an increased risk of unfavourable outcomes in certain patient populations, such as children admitted to hospital with severe anaemia who can benefit from receiving PDMC *(23, 24)*. It will also be important to determine the potential benefit of long-term protection in other at-risk groups with underlying conditions, such as children with sickle cell disease *(25, 26)*. As of 2022, several studies are investigating the efficacy of dihydroartemisinin–piperaquine, sulfadoxine–pyrimethamine and proguanil as chemoprevention for children with sickle cell anaemia in Kenya (NCT03178643) *(27)*, Malawi and Uganda (NCT04844099) *(28)*.

Access and affordability. Cost and cost-effectiveness are important considerations. The cost should include not only the cost of goods, but also operational costs such as delivery. Costs vary over time and between locations; consequently, local data are needed to inform national and subnational decisions. For IPTi, the costs of the drug and its delivery are as low as US$ 0.40. For SMC, although the cost of the product is the same across all countries, the implementation costs vary *(29)*. SMC has been considered cost-effective at around US$ 1 per child per year for the drug, and US$ 5 per child per year including the operational costs. An important dimension of access is the availability of sufficient supply to meet demand. It took two years for the sulfadoxine–pyrimethamine plus amodiaquine supply to meet demand.

Safety and tolerability. For all chemoprevention indications, safety and tolerability must account for the likelihood of repeat administrations and the duration of treatment. Typically, the amount of preclinical and clinical safety data for new drugs intended for chronic use is greater than the amount in the current regulatory dossiers for historical antimalarials. It will be important to have well documented repeat use studies in the target population. For perennial transmission, chronic year-round administration would present an additional safety challenge if this approach were ever recommended.

Efficacy. Efficacy expectations are informed by existing estimates of SMC's preventive efficacy with sulfadoxine–pyrimethamine plus amodiaquine, where reductions in the number of clinical malaria cases of over 80% were seen in field trials *(30)*.[2] Although drugs with lower efficacy could deliver important public health impact in settings where disease burden is particularly high, it makes sense to aim for similarly high efficacy in

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2   Systematic reviews of randomized controlled trials document a 30% reduction in clinical malaria with PMC and an 83% reduction in clinical malaria with SMC. However, the most important driver of the difference in efficacy estimates is likely to be the proportion of total time at risk during which the strategies offer protection, rather than the intrinsic properties of the drug. SMC is intended to cover the entirety of a relatively brief transmission season. Four doses over four months should provide a high level of protection when evaluated in places where most transmission occurs over only four months of the year. In perennial transmission settings, three doses have generally been evaluated and can be expected to protect children for about 25% of their first year of life. In studies of IPTi, the duration of protection of sulfadoxine–pyrimethamine has been shown to be 42 days in settings without parasite resistance mutations; this was reduced to 21 days in a setting where 89% of parasites carried the quintuple mutation *(31)*. Therefore, in addition to protective efficacy, duration of protection is important when evaluating a product for chemoprevention.

new drugs for chemoprevention. New regimens do not necessarily need to demonstrate non-inferiority in regions where sulfadoxine-pyrimethamine (for IPTi) or sulfadoxine-pyrimethamine plus amodiaquine (for SMC) are deployed, especially in areas where these drugs are not standard of care and placebo-controlled studies may still be acceptable.

Dosing regimen. Any new drugs or drug combinations should not increase the complexity compared to current regimens, so it should be a single dose for IPTi and three doses or less for SMC. The discussion recognized the advantage of simpler, ideally single-dose regimens. A broad therapeutic margin is important to enable dosing by weight or by age, but with relatively few dosing groups. Any new drugs for chemoprevention would need pharmacokinetics that produce very long periods of drug exposure. Currently, in some settings, monthly dosing with sulfadoxine-pyrimethamine plus amodiaquine results in malaria cases appearing a week before the next SMC cycle. Finally, operational feasibility will also depend on the frequency of dosing when deployed at scale; if home administration is safe and tolerable, then weekly administration may be feasible. In the future, if chemoprevention is potentially used in high-risk groups such as children with sickle cell disease, daily chemoprevention could be considered. However, the number of such cases is much smaller than for SMC.

Formulation and presentation. In all use cases, the optimal formulation and presentation would be as a dispersible drug, and sublingual formulations may be an advantage in areas where access to clean water is limited. Ideally, there should be no impact of food on drug absorption.

The impact of chemoprevention regimens on the immunological response to routine vaccinations should also be considered. Some current antimalarials have been shown to affect the host response to vaccination (e.g. chloroquine) in the case of yellow fever *(32)* and rabies *(33)*. Ideally, any new chemoprevention should be compatible with all routine immunizations. The co-delivery of the malaria vaccine RTS,S/AS01 and SMC has been shown to deliver greater benefits than either intervention alone *(34)*.

6.2 Use case two: chemoprevention in pregnant women

The criteria for new drugs are similar to those defined above for children, with additional considerations for chemoprevention in pregnant women highlighted below.

Target population

Women with known pregnancy. This is the use case for drugs replacing IPTp in the second and third trimesters of pregnancy. In classical drug development, once safety and efficacy have been established in adults, it is permissible to start studying the safety of drugs in the third, then second trimesters of pregnancy. Therefore, for new drugs or drug combinations being developed, it is possible to explore the pharmacokinetics, safety and efficacy of dosing regimens soon after launch, or in parallel to Phase 3 if available data are supportive.

In this use case, the standard of care is currently sulfadoxine-pyrimethamine, given as three 500 mg tablets no more frequently than monthly during the second and third trimesters of pregnancy. The ideal case for a next-generation therapy would be one tablet per month that could also be given in the first trimester and is safe in HIV-positive women on cotrimoxazole prophylaxis. Single doses of drugs currently used in three-day regimens (such as artemisinin-based combination therapies) could be considered for this use case, but dose optimization would be required.

Women of childbearing age or first trimester pregnancy. Widespread use of drugs to protect the entire population (MDA) will include women who might be in the first trimester of pregnancy or who may become pregnant during the MDA. Since widespread access to contraception and pregnancy testing cannot be assumed in many malaria-endemic countries, drugs should ideally be known to be non-teratogenic and safe in the first trimester before being deployed to the entire population. Given the complexity of obtaining such data, studies of inadvertent exposures in the first trimester of pregnancy can be conducted as exposure in the second and third trimesters is evaluated and before interventional clinical trials in the first trimester. Clear guidance on the type of data needed to support such a recommendation is a critical part of a PPC. It is also assumed that such drugs would be potentially used on asymptomatic carriers of parasites. Ideally, a new drug would be able to protect without the need for an initial clearance of parasites from the asymptomatic hosts.

Efficacy targets could be defined primarily based on the efficacy of existing treatments to reduce low birthweight in babies and anaemia in the mother. However, the effects of IPTp with sulfadoxine-pyrimethamine on birthweight have been documented in settings with high levels of the sextuple mutation and in settings with low malaria transmission. These studies found that malaria-specific effects were minimal, suggesting that the benefits of sulfadoxine-pyrimethamine for low birthweight may be mediated through non-malarial mechanisms; further research investigating this is ongoing. In the meantime, other outcomes of interest include clinical malaria, placental infection, parasite prevalence, severe malaria, hospitalization, death and safety (adverse events) in the mother, and adverse pregnancy outcomes (miscarriage, stillbirth or pre-term delivery), parasite prevalence, anaemia, severe malaria, hospital admission and death in the child. Focusing on the malaria-specific effects of drugs used in pregnancy will enable the use of safe and efficacious drugs in women of childbearing age, for instance in MDA campaigns.

Dosing regimen. The regimen for pregnant women should ideally be a fixed dose, regardless of body weight. There should be no food restrictions prior to arrival at the antenatal clinic or after the woman has taken the dose. Potential interactions with vaccinations (e.g. tetanus) should be considered, as should interactions with other treatments women receive during pregnancy, such as iron and folate supplementation or cotrimoxazole prophylaxis in HIV-positive women. Tolerability is very important and should be assessed early in drug development. Experience with azithromycin-chloroquine suggested that a large pill burden and low tolerability were key factors leading to the failure of that regimen *(35)*.

The potential value of chloroquine, administered weekly, may warrant consideration in settings where its efficacy has been restored and where sulfadoxine-pyrimethamine has failed as IPTp prophylaxis.

Safety. The United States Food and Drug Administration has made recommendations on how and when to include pregnant women in drug development clinical trials *(36)*. Extensive clinical experience in the second and third trimesters is available for drugs that are being repurposed or recombined for IPTp. However, available data on the safety and tolerability of drugs in the first trimester are scarce. The evaluation of the safety of new drugs in pregnancy requires data from over 1000 exposures *(37)*, and, in the absence of spontaneous reporting, these data need to be obtained from specific clinical trials or pregnancy registries.

The responsibility for managing long-term safety requires careful attention, since most antimalarials are produced by a range of manufacturers, including generic manufacturers. In some cases, the original marketing authorization holder no longer sells the drug.

6.3 Use case three: non-immune travellers

WHO encourages the use of antimalarial drugs at subtherapeutic doses to prevent the development of malaria among travellers or non-immune individuals. Traditionally, this intervention has been used by tourists, health workers and military personnel. This use remains important in cases where there are significant deployments of health personnel to areas of endemic viral infections (e.g. in Ebola management), where it is important to exclude malaria from other causes of fever.

Increasingly, this use case extends to workers and other residents within low- and middle-income countries, travelling from malaria-free zones to endemic areas. 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 living or growing up in localized areas without malaria (e.g. urban settings) are less exposed to malaria and can be expected to have less naturally acquired immunity; therefore, they are at high risk of adverse malaria outcomes should they visit rural areas. A similar situation occurs among children at boarding schools or university students moving between low- and high-transmission zones. The current drugs used for prophylaxis of Western travellers could be used by such populations, and more work on defining the use case and affordability is needed.

During the meeting, the importance of including chemoprevention for high-risk occupational groups was emphasized. This includes, for example, miners and agricultural workers who may be regular or irregular workers at high risk of malaria infection and not formally employed. The programmatic complexity should not be underestimated. Inconsistent use of chemoprevention may result in incomplete protection, delayed treatment seeking, suboptimal parasite detection and potentially the risk of resistance selection. Long-acting formulations requiring minimal engagement with health care services may therefore be advantageous. Given that irregular workers tend to avoid interactions with health care workers, a long-acting depot injection or monoclonal antibody with minimal engagement with health care may be a good solution for this group.

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ANNEX 1. MEETING AGENDA

Session 1: Tuesday, 15 December 2020		
13:00–13:05 CET	**Welcome and opening remarks**	Pedro Alonso
13:05–13:20	**Introduction, use cases, the role of PPCs and meeting objectives**	David Schellenberg
13:20–13:50	**Safety, efficacy, and other evidence needs to inform decisions: how much of what sort of data?**	Brian Greenwood
13:50–14:05 **14:05–14:20**	• Technical considerations • Operational considerations	Phil Rosenthal James Tibenderana
14:20–15:50	**Chemoprevention in children 1–5 years, perennial transmission** • Pharmacokinetic and pharmacodynamic considerations • Critical safety considerations • Efficacy – what evidence is needed • Formulation / presentation preferences • Dosing regimens – how many doses, at what frequency, duration of protection • Co-administration considerations – vaccines, other drugs • Route of administration • Product stability and storage • Access and affordability, scale of demand, cost • Drug resistance	Lead discussants: Corine Karema Caterina Guinovart
15:50–16:00	**Wrap-up session 1**	Umberto d'Alessandro (Chair)
Session 2: Wednesday, 16 December 2020		
13:00–13:10	**Recap Session 1**	Umberto d'Alessandro (Chair) Chair
13:10–14:10	**Chemoprevention: special considerations** • Infants, children aged > 5 years, school-aged children • All-age MDA • Underlying health conditions • Seasonal transmission settings • Post-discharge chemoprevention • Occupational risk group (forest goers, miners, etc.)	Lead discussants: Olugbenga Mokuolu Marcus Lacerda Sarah Staedke

14:10–14:55	**Additional considerations in pregnancy** • Critical safety considerations • Efficacy – what evidence is needed • Dosing regimens – how many doses, at what frequency, duration of protection • Pharmacokinetic and pharmacodynamic considerations • Formulation / presentation preferences • Co-administration considerations – vaccines, other drugs • Route of administration • Product stability and storage • Access and affordability, scale of demand, cost	Lead discussants: Feiko ter Kuile Regina Rabinovich Abdoulaye Djimde Mimi Darko
14:55–15:15	**Opportunities to meet the PPC with existing approved malaria drugs and combinations of existing approved malaria drugs?**	Tim Wells
15:15–15:25	**Next steps**	Umberto d'Alessandro (Chair)
15:25-15:30	**Closing remarks**	Pedro Alonso

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