![MMV - Medicines for Malaria Venture]

Expert Consultation on

Seasonal Malaria Chemoprevention (SMC) and

next-generation chemoprevention medicines

· ·

13–14 January 2016
Grange Holborn Hotel, London

· ·

Contents

Background and objectives

In 2012, the World Health Organization (WHO) endorsed deployment of seasonal malaria chemoprevention (SMC) in children under 5 years of age in areas of high seasonal malaria prevalence. SMC is defined as the intermittent administration of full treatment courses of an antimalarial medicine or combination during the malaria transmission season.

This meeting was funded by UNITAID within the framework of the ACCESS-SMC project. ACCESS-SMC is a UNITAID-funded project, led by the Malaria Consortium in partnership with Catholic Relief Services (CRS), which is supporting National Malaria Control and Elimination Programs in seven countries (Burkina Faso, Chad, Guinea, Mali, Niger, Nigeria, The Gambia) to lead the first ever at-scale roll out of SMC.

Meeting objectives

The objectives of the meeting were to:

- Refine MMV's target product profiles (TPPs) for future chemoprevention treatments.
- Consider perspectives on existing medicines that may be re-purposed in the short- or medium-term to support development of chemoprevention medicines.
- Understand evidence required for normative policy change and regulatory pathways for chemoprevention medicines.

The meeting participants are listed in Appendix 1 and the agenda is included in Appendix 2. The chair (D. McGibney) and MMV would like to thank all the speakers and advisors for their contributions. This report has been reviewed and agreed by all participants.

Meeting summary

The future of SMC

SMC is a powerful tool for reducing the malaria burden in vulnerable children in areas of high seasonal malaria transmission, and is a highly cost-effective intervention. Thus, investing in efforts to look for new antimalarial drugs for use is SMC is considered worthwhile.

It is encouraging that in 2015, around 3 million children received SMC via ACCESS-SMC. However, the scalability of SMC to the 26 million children at risk is challenging. How this effort can be financed and sustained, perhaps over many years, is unclear.

SMC has been implemented in the Sahel region of Africa using monthly sulfadoxine-pyrimethamine + amodiaquine (SPAQ) during the transmission season. However, if resistance develops to either agent in this combination, there are currently no alternative options. To extend the utility of SPAQ, it is essential that the drugs provided for SMC are of high quality and have improved formulations that increase tolerability and adherence.

It is important to continue to monitor/measure the efficacy of SPAQ in the clearance of infections. Strengthening of efficacy and resistance monitoring and co-ordination across the SMC regions is necessary. However, it is uncertain how drug efficacy and resistance monitoring will be managed across the region and sustained after ACCESS-SMC has ended.

The lower level of acquired immunity following SMC and the possibility of rebound remains an important concern. Rebound can be expected to happen to some extent after 1 year of SMC, and will be more pronounced with successive years of intervention. However, the net benefits of SMC are great and the rebound can be mitigated by ensuring that other malaria control measures are reinforced post-intervention, with a long-term aim of reducing transmission to very low levels and ultimately elimination.

Strengthening health systems is of great importance. With training, health workers can collect good data and achieve high preventive efficacy rates with SMC. Delivery mechanisms for SMC are key. At present, the door-to-door method is working well, but other options may require consideration if SMC is extended to older children.

The extensive deployment of SMC with SPAQ in the Sahel and ongoing studies into other drugs for chemoprevention and for SMC provides an unprecedented opportunity to research delivery mechanisms, outcomes, the relationship between treatment and preventive efficacy, and the effects on malaria immunity. Such studies will also inform the development of future agents for SMC.

The criteria for implementation of SMC are clear, but the circumstances in which SMC would be stopped are less so. At what point should SMC be extended to children over 5 years old and at what point should SMC be replaced by targeted or focal mass drug administration (MDA) or other interventions? The programmatic and political impact of stopping SMC also needs to be considered.

Although SMC is seen as a stop-gap measure, no accurate predictions can be made for how long it will remain a useful intervention. For at least the next 5–10 years, SMC should remain a key strategy for reducing the malaria burden in children in areas of seasonal transmission. We should not assume that the incidence of malaria will decline so rapidly and extensively that we can avoid investigating alternatives to SPAQ for SMC. However, the priority for such development should focus on existing compounds as opposed to development of new molecules.

SMC drug attributes

Drugs for SMC need to be safe and well tolerated. As many children will have asymptomatic infection, the drug should be fully effective, with treatment efficacy non-inferior to SPAQ. Drugs must have a long shelf-life, be simple to administer, available in child-friendly formulations and as fixed-dose combinations, and suitable for delivery via a door-to-door campaign.

Pharmacologically, a single dose is preferable and a long half-life is required to provide post-treatment prophylaxis over the weeks following treatment. An injectable could be considered if the frequency of injection was low (once per season). Drugs for SMC should be different to those reserved for malaria treatment. Unless there is no alternative, combination therapy is always preferable to a monotherapy in order to delay resistance.

Drugs do not need to have causal efficacy, i.e. targeting both the blood stage and the initial liver stage. In fact, it may be beneficial to host immunity to have a few parasites emerging from the liver before being killed. However, if transmission can be reduced or even stopped, which is beginning to look more realistic, then the risk of reducing immunity with SMC becomes less of a concern and a drug with causal efficacy may be more desirable.

Repurposing

It is uncertain whether there will be a need for drugs directed specifically at SMC by the time that new drugs would become available and implemented, by 2025–2030. Conversely, we do not know whether SPAQ will still be efficacious within the next 5 years. Thus, it is important to re-examine currently available drugs for repurposing for SMC.

Azithromycin (AZ) is an effective chemoprotective agent in malaria, and reduces the incidence of respiratory tract infections and diarrhoea. However, the risk of bacterial resistance development with more widespread use of AZ needs to be better defined.

It is possible that chloroquine (CQ) would be effective in some parts of southern and eastern Africa for SMC, but more information is needed regarding the potential for the re-emergence of CQ resistance. An appropriate partner drug needs to be identified for use as combination therapy; SP+CQ is not well tolerated, but AZ+CQ may be a possibility.

Dihydroartemisinin/piperaquine (DHA-PQP) has good preventive efficacy in SMC. However, its widespread use would increase the potential for the development of artemisinin and piperaquine resistance. Dihydroartemisinin has a very short half-life, so in the context of SMC, it would not be the partner of choice for PQP. It would, therefore, be useful to have PQP monotherapy available for research purposes, to allow studies in combination with other drugs.

New drug development

Although an important tool today, SMC is seen as a stop-gap measure, and whether SMC will still be needed by the time a new drug could be developed is uncertain. Furthermore, the regulatory route to drug registration for SMC unprecedented. Thus, developing a drug just for SMC appears risky. A pragmatic approach is to focus drug development on identifying drugs for malaria treatment, and then reserve those which have the most favourable safety and pharmacokinetic profiles for use in SMC, should there still be a need. Should drugs appear suitable for SMC or other specific prevention and control strategies, standard methods are needed to evaluate this potential.

It may be necessary to distinguish between products that are aimed at replacing SPAQ and those which would be suitable for use in regions where there are currently no drugs suitable for use in SMC. Future drugs may have roles beyond SMC, for example in MDA and the control of epidemics. Development of TPPs for these different applications may indicate whether one drug could be developed which meets all the necessary criteria. If a drug was suitable for use in SMC, MDA and intermittent preventive treatment in pregnancy (IPTp), then this would expand its usefulness and protect against the potential decline in the population suitable for SMC. However, developing a drug for use in pregnancy in challenging.

There may be an opportunity to increase the number of compounds considered within the TPP by including those likely to have preventive efficacy in asymptomatic malaria with long post-treatment prophylaxis. Thus, thought needs to be given to the potential role for a drug that has preventive but not curative properties and whether compound screening strategies need to be amended to identify such compounds; current screening methods are focused on identifying drugs for malaria treatment. However, the relationship between therapeutic efficacy and preventive efficacy in asymptomatic disease is not clear. A curative dose is preferable in order to delay resistance development.

The impact of new tools, such as diagnostics, on the distribution and incidence of malaria is unclear. Thus, potential new drugs should not be discounted because they do not have a role to play in the current situation. For example, as malaria transmission rates decline, it may be desirable to have a drug with liver stage activity.

Regulatory issues

There is a good evidence base for SMC with which to have productive discussions with regulators regarding programmes and research studies. However, whether a drug that only has an indication for SMC is of value to the malaria community and WHO is uncertain and needs to be explored. It is unclear if new products can be developed within a timeframe relevant to the clinical need for SMC.

Actions arising

- Given the more recent experience with SMC, TCP4 (target candidate profile for chemoprotection) is under revision and input is requested from the advisors both within the meeting and through a subsequent comment and review process on the contents of this TCP.
- MMV is to investigate the costs of manufacturing PQP monotherapy tablets to good manufacturing practice (GMP) quality for research purposes and communicate this information to researchers.

Meeting report

1. WHO policy and perspectives re: seasonal malaria chemoprevention

Objective

Describe the evidence to support policy adoption of chemoprevention tools and contrast drugs for MDA versus mass chemoprevention of malaria.

Presentation: P. Olumese

A WHO policy recommendation for SMC for *Plasmodium falciparum* malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa was published in 2012,[1] and a field guide to support adoption and implementation by National Malaria Programmes in 2013.[2]

SMC is defined as the intermittent administration of full treatment courses of an antimalarial medicine or combination during the malaria transmission season. The aim is to prevent malarial illness by maintaining therapeutic drug concentrations in the blood throughout the period of greatest malaria risk. Currently, this means administering a complete treatment course of SPAQ to children aged 3–59 months at monthly intervals from the start of the malaria transmission season for a maximum of four doses during that transmission season (providing both drugs have sufficient antimalarial activity).

The Sahel region is a target area for SMC because transmission is highly seasonal, with most clinical malaria cases occurring within a 4-month period. Furthermore, within that period there is a high clinical malaria attack rate (>0.1 attack per season) in the target age group. Also, SPAQ retains >90% antimalarial treatment efficacy in this region.

The WHO policy recommendations were based on evidence from seven SMC studies conducted in areas of high seasonal malaria in children <5 years of age. These studies showed a 75% reduction in the incidence of all malarial episodes and a 75% reduction in episodes of serious malaria during the transmission season. Overall, an increase in clinical malaria in the following malaria transmission season after 1 year of SMC was not observed, though one study showed a small increase of borderline statistical significance. Serious adverse events were not reported and are probably rare.

The objective of SMC is to reduce the clinical burden of malaria in a specific population at risk; success is dependent upon the clinical treatment efficacy of the antimalarial. A background level of parasitaemia may be desirable to protect herd immunity in this context. In contrast, MDA aims to interrupt transmission by targeting all parasites in a population over a defined geographic area; success is dependent upon maximum coverage of the population and on the ability of the drug to achieve parasite clearance. However, in both SMC and MDA, drugs with a prolonged post-treatment prophylactic effect are required.

For both SMC and MDA, drug(s) will be given to non-infected individuals who will not have any immediate individual benefit from treatment. Thus, the risk:benefit profile requirements are more stringent than for malaria treatment. An important difference is that a drug for SMC must be shown to be safe in the target population, whereas any drug used in MDA must be safe across the whole population, including all age groups and pregnancy.

In conclusion, malaria control and elimination tools should always be discussed in the context of the epidemiology of the disease and the desired public health goals and objectives.

Discussion

Cost-effectiveness: Cost-effectiveness of SMC is mostly driven by the reduced need for malaria treatment and diagnostics and reduced hospitalisations. There are multiple malaria control and treatment tools available and the most appropriate combination of these will depend on the

context, so there is no global cut-off of cost-effectiveness for any particular intervention. Matthew Cairns at the London School of Tropical Medicine and Hygiene (LSTMH) is working on tools to help National Malaria Control Programmes (NMCPs) deploy malaria control interventions more cost-effectively.

SMC stopping criteria: The criteria for implementation of SMC are clear, but the circumstances in which SMC would be stopped are less so. At what point should SMC be extended to children over 5 years of age and at what point should SMC be replaced by targeted or focal MDA or other interventions? The programmatic and political impact of stopping SMC also needs to be considered. At <0.1 malaria episodes per child during the transmission season, SMC may not be cost-effective.[3] However, there is no guidance on what should be done when these levels are reached in areas where SMC is deployed.

Drug efficacy: WHO guidance is a malaria cure rate of less than 90%, should trigger a policy to implement a more efficacious replacement treatment. The last available data indicated that SPAQ treatment efficacy was >90%. However, there is currently no process in place to monitor cure rates with SPAQ.

At some point a switch to molecular markers will be necessary. There is a good link between molecular markers and failures based on clinical cases. However, molecular markers may not be so useful in predicting how successful SPAQ is at preventing infection or treating asymptomatic infection.

Anti-malarial drugs with cure rates which exceed 90% are likely to have good preventive efficacy. It is not known whether good preventive efficacy and efficacy against asymptomatic infection can be achieved with anti-malarial drugs with cure rates <90%. 'Asymptomatic' infection is also poorly defined, as though fever may be absent, anaemia and other symptoms of malaria are also important. The relationship between parasite load and the preventive efficacy of drugs is unknown. The development of drug resistance would be a concern if non-curative treatments were used.

At present, there are no clinical or molecular metrics which can be used during drug development to determine whether a drug will prevent clinical malaria, and this is an area where further research is needed. In particular, such information is necessary for the efficient and successful development of new drugs targeted at SMC.

2. The development of SMC

Objective

Describe lessons learned from development of SMC using SPAQ to inform development of next generation chemoprevention treatments.

Presentation: B. Greenwood

Chemoprevention of malaria in endemic populations is not a new idea and various approaches have been tried in different settings throughout the history of antimalarial treatment.

Chemoprevention aims to achieve protective antimalarial drug levels throughout the period at risk, whereas intermittent preventative treatment (IPT) provides a full therapeutic course at defined time points interspersed with periods without drug exposure. However, there is some overlap, as frequent IPT campaigns can have protective effects similar to chemoprophylaxis.

Although studies conducted in the late 1980s and early 1990s indicated mortality benefits of ITP in African children,[4, 5, 6] issues of feasibility and cost, and concerns regarding the impact on immunity and drug resistance dissuaded its adoption. Also, insecticide-treated bed nets (ITNs) were introduced at this time, and were seen as a better alternative.

In 2006, a study of seasonal IPT in Senegalese children (IPTc – now termed SMC) reported an 86% reduction in the incidence of clinical malaria following three doses of SP and artesunate (AS) given monthly in the transmission season.[7] This finding prompted the establishment of an IPTc task force in 2008 and a series of studies testing various drug combinations. Across 7 trials in West Africa in children under 5 years old (12,589 participants), IPTc prevented 74% of all clinical malaria episodes.[8] Monthly administration, rather than once every two months had a greater impact on clinical malaria, though both dosing strategies improved outcome versus controls. Data on severe malaria were available from two trials (n=5964), reporting 73% efficacy for prevention of severe malaria.[8] Although there was a 34% reduction in all-cause mortality, the trials were underpowered to reach statistical significance for this outcome.[8]

Various drug combinations were tested in these studies: SP (1 dose) monthly or bimonthly; SP (1 dose) + AQ (3 doses) monthly or bimonthly; SP (1 dose) + PQP (3 doses); SP (1 dose) + AS (1 or 3 doses); AQ+AS (3 doses); and DHA-PQP (3 doses). However, it is controversial whether artemisinins should be used in chemoprevention, given their important role in malaria treatment.

The safety of SPAQ appears acceptable for use in SMC. In Senegal, over 800,000 IPTc doses have been given with one case of extrapyramidal syndrome linked to AQ. There have been no reported cases of liver damage linked to AQ or Stevens–Johnson syndrome linked to SP.

Delivery systems have also been investigated, including provision at fixed health points, delivery at outreach visits by the maternal and child health (MCH) team and via community health workers (CHWs) either at a fixed point or via a home visit. The advantage of using CHWs is that they can both deliver SMC and be responsible for malaria case management.[9]

To identify areas where seasonal malaria chemoprevention would be appropriate, spatial rainfall, malaria endemicity and population data were used to estimate highly seasonal malaria incidence, the population at risk and malaria burden.[3] In areas suitable for seasonal malaria chemoprevention, there are 39 million children under 5 years old at risk, and an estimated 33.7 million malaria episodes and 152,000 childhood deaths annually. The majority of this burden occurs in the Sahel.

Cost-effectiveness of SMC is likely to be high wherever malaria incidence exceeds 0.2 episodes per child during the peak transmission season. However, at <0.1 episodes per child during the transmission season, SMC may not be cost-effective.[3]

In conclusion, SMC is a powerful tool for reducing malaria burden in vulnerable children under 5 years old in areas of high seasonal malaria transmission. It is encouraging that in 2015 around 3 million children received SMC via ACCESS-SMC. However, there remain challenges. It is not clear whether the current high levels of SMC coverage can be sustained, and there is uncertainty regarding funding following the UNITAID grant.

In terms of drugs, resistance to SP and/or AQ may develop, and replacement regimens need to be considered. There are still questions regarding the effect of 'rebound'; an increase in malaria incidence versus background levels when children stop SMC. There are also opportunities to identify areas outside the Sahel and sub-Sahel where SMC might be useful, and scope for integrating SMC with other health interventions (nutritional supplementation, deworming, etc.).

Discussion

Drug target and immunity: Drug levels in the blood need to be sufficient to stop the development of significant parasitaemia. It is not necessary to have causal efficacy, i.e. targeting both the blood stage and the initial liver stage. In fact, it may be beneficial to host immunity to have a few parasites emerging from the liver before being killed. However, if transmission can be reduced or even stopped, which is beginning to look more realistic, then the risk of reducing immunity with SMC becomes less of a concern and a drug with causal efficacy may be more desirable.

Safety: Although the SMC studies performed so far do not have the level of safety follow up that a drug registration study would require, data are available for large numbers of children. Also, monthly home visits would have discovered any deaths and probably any severe adverse events due to SMC. In Senegal, even with enhanced pharmacovigilance, there have been only three serious adverse events detected following administrations of over 2 million doses. Thus, SPAQ appears to be safe for SMC.

Within ACCESS-SMC pharmacovigilance has been strengthened. Discussions are continuing regarding a possible cohort study to better understand the incidence of adverse events (as opposed to serious adverse events) in particular, itching/skin rash, given the potential for Stevens–Johnson syndrome.

Any safety signals for a new molecule would be more of a concern as there would be limited clinical experience.

Tolerability: The impact of itching and minor adverse events is to reduce tolerability. Consequently, a child may not receive a second dose. Thus, the impact of drug tolerability on adherence needs consideration.

Drug preventive efficacy: In the SMC studies, drug preventive efficacy was evaluated by passive detection of clinical malaria attacks presenting to health centres, confirmed by blood film. However, some cases were identified via home visits.

Drug development horizons: Originally, IPT was directed only at infants <1 year old in very high transmission areas. However, SMC has expanded to include children up to 5 years of age, and in Senegal up to 10 years old. Thus, the patient population may change over time. Seasonality of malaria is also changing with climate change. The overall trend is for a decline in malaria incidence and SMC may only be relevant for a relatively short period as a stop-gap between the situation today and pre-elimination strategies.

Drug choices: SPAQ was used because it was not being used for treatment and had a good safety profile. DHA-PQP has been used in SMC, but is only available as combination therapy. DHA-PQP in SMC is effectively monotherapy as the DHA half-life is so short. Ideally, two drugs with long half-lives should be used in combination to defer resistance development.

Dosing frequency: SPAQ provides protection for 4–6 weeks and protection declines towards the end of the 4-week dosing interval in areas with high transmission. However, at least a month between doses is required because of the risk of Stevens–Johnson syndrome. Monthly dosing provides significant benefits over bi-monthly dosing. Detection of sub-patent infection using PCR throughout the SPAQ dosing period might be informative of what dosing interval is appropriate and be useful for directing future drug development.

Resistance: It is of note that the presence of resistance effectively shortens the period of post-treatment prophylaxis, requiring more frequent dosing to maintain therapeutic blood levels.

Delivery: Integrated health campaigns are less expensive to deliver. However, drug interactions may be an issue when multiple therapeutics are given. Malnutrition is a major source of mortality and monthly contacts to administer SMC may provide an opportunity for detecting children with early malnutrition who need nutritional support.

Other areas for SMC: There are no data on SMC in southern or eastern Africa.

3. Implementation perspectives after rollout of SMC

Objective

Provide observations from rollout of SMC using SPAQ to inform development of next generation SMC drugs.

Presentation: P. Hamade

Drugs for SMC need to be safe and well tolerated. As many children will have asymptomatic infection, the drug(s) should be fully effective. Drugs must have a long shelf-life, be simple to administer and available in child-friendly formulations as fixed-dose combinations. Pharmacologically, a single dose is preferable and a long half-life is required to provide post-treatment prophylaxis over many weeks following treatment.

In terms of drug development, it should be noted that children in the Sahel are often malnourished or anaemic, and clinical trials need to include these children so that the true effects of SMC can be evaluated. Drugs used for SMC should be different from those reserved for malaria treatment. The management of breakthrough malaria should be integrated with SMC provision, if possible though integrated community case management.

The current drugs for SMC are not perfect. SP is a single dose, easy to administer and has few side effects, but resistance is high in East Africa and Stevens–Johnson syndrome is a known serious adverse event. AQ is less than ideal, requiring three daily doses per treatment course, the coated tablets are very difficult to crush and it has a bitter taste; adverse events, though common in adults appear to be low in children, and although serious adverse effects are more diverse and common than for SP, few are reported following SMC.

Field experience from a project in Nigeria, providing monthly SMC to 800,000 children under 5 years old, found very high levels of knowledge and satisfaction among local communities and the health staff involved in SMC delivery. Side effects, such as skin rashes, itching and vomiting were recorded at low levels and there were no serious adverse events. The bitter taste of AQ was well tolerated by children if accompanied by sugar, though the difficulty in crushing the tablets was a problem. CHWs were trained in how to successfully administer the drugs and how to demonstrate correct methods to mothers and care givers. Coverage levels were high; 86.9% of children received at least one SMC treatment course and 61.8% of children received at least three SMC treatment courses. Tools and approaches developed during this project were used to develop ACCESS-SMC.

ACCESS-SMC provided more than 14 million SMC treatments in 2015 to over 3.2 million children aged 3 to 59 months in Burkina Faso, Chad, Guinea, Mali, Niger, Nigeria, and The Gambia. There were only four serious adverse events reported in 2015, even with strengthened pharmacovigilance systems in all seven countries.

ACCESS-SMC has also played a catalytic role in the market, incentivising the development of a dispersible formulation and developing a demand forecast tool to inform manufacturers' production planning. SPAQ leakage into the community was low owing to strict drug reconciliation procedures. Drugs need to be ordered well in advance of need to ensure timely arrival at distribution points. In terms of delivery, door-to-door is the preferred, and possibly most cost-effective, intervention.

Some of the challenges in ACCESS-SMC have been estimating the target population, the large number of CHWs needed to deliver the drugs and the ongoing costs and sustainability of the project. Drug resistance and drug treatment efficacy surveillance also need to be considered on a regional basis, though such studies are expensive. Although children under 5 years of age are most at risk from adverse outcomes of malaria, targeting this group will have no effect on transmission. However, raising the SMC target to children aged 10 years would place further strain on human and financial resources.

There is still far to go with SMC. Across the Sahel, 26 million children under 5 years old could benefit from SMC; ACCESS-SMC will cover approximately 6.7 million in 2016 and possibly 2017, other partners cover around 8 million, leaving 12 million children without protection. It is not clear how coverage will be maintained after 2017.

4. Field experiences and expectations – recent research from SMC implementing countries

Objective

Review preliminary results of a field survey on implementation experiences with SPAQ and practitioners' expected attributes for next generation chemoprevention.

Presentation: A. Tchouatieu

A series of interviews were conducted at all levels of health provision to identify global and local preferred attributes for future SMC products in sub-Saharan Africa. Such drugs would eventually replace SPAQ once resistance emerges and potentially expand SMC into seasonal transmission areas where SPAQ is not therapeutically effective (primarily eastern and southern Africa).

At the country level, 89 interviews were conducted in the Gambia (n=41) and Burkina Faso (n=48) among caregivers, community level providers, regional and national decision makers, researchers and implementers. A further 23 interviews were conducted with the WorldWide Antimalarial Resistance Network (WWARN), NMCPs in eastern and southern Africa, and global level malaria experts.

The cost of planning and implementing SMC is high – drugs are anticipated to cost 25% of the campaign cost, while human resources account for 75%. However, SMC significantly reduces the malaria burden in the target population, i.e. children <5 years old. To ensure high participation levels, sensitisation needs to be extensive and varied, involving collaboration between stakeholders at all levels. Administration is done by teams of CHWs, with community nurses given responsibility for training, distributing drugs to CHWs and supervising them. Drugs are mainly distributed door-to-door. Community nurses monitor stock use and wastage at the local level, submitting data to the regional level on a daily basis. Campaign monitoring is extensive, with national stakeholders on the ground for each cycle of the campaign.

The choice of SPAQ was based on, in decreasing order of importance, its well-known anti-malarial efficacy and safety profile, long half-life, combination of two molecules with different mechanisms of action, the fact that the mechanisms of action is different from that of the drugs used for malaria treatment, and its low cost. In terms of alternatives to SPAQ, there was a consensus that a combination should still be sought, ideally a repurposed older drug because of the safety data available. PQP, primaquine (PQ) and AZ were mentioned as potential candidates. DHA-PQP has been investigated in several SMC studies. However, there is concern that using an artemisinin derivative in the SMC setting may accelerate resistance development to artemisinins, which are so crucial for malaria treatment. PQP has a long half-life, and if available separately, it could be used in an alternative non-ACT combination for SMC.

Three contrasting target product profiles for an SMC product were evaluated across the surveys. The overall findings were as follows.

- There was limited enthusiasm for a product that would deliver lower levels of preventive efficacy than SPAQ, in addition to fears over a lack of long-term safety data.
- In the absence of alternatives, the main value drivers remain the frequency of administration (monthly), and the child-friendly formulation.

- More frequent administration (fortnightly, weekly) is not acceptable unless preventive efficacy is approaching 100%, then there may be an incentive to remember the dosing. However, door-to-door delivery would be challenging.
- An injectable that could be given once per season emerged as an ideal candidate, as long as preventive efficacy was at least as good as SPAQ and assuming clinical experience and tolerability requirements could be met.

In conclusion, any new SMC therapy would need to be a well-known, safe product, with preventive efficacy non-inferior to SPAQ, in a child-friendly formulation and suitable for delivery via the door-to-door campaign approach, which has been shown to be effective with SPAQ. However, an injectable could be considered if the frequency of injection was low (once per season).

As SMC acceptability is reinforced, this may translate into the more rapid acceptance and adoption of new agents. However, any new drug will have to meet the current benchmark of SPAQ. It will be more acceptable and quicker to repurpose drugs for SMC, rather than develop new molecules, mainly because of safety considerations. If a new drug did not fit well into the door-to-door delivery system, a new campaign would have to be designed and implemented and shown to be as effective.

Discussion

Oral dosing limitations: For oral dosing, the maximum dosing interval is one month; it is not technically feasible to give a large enough dose to last for longer, even without safety concerns.

Injections: One injection per season might be easier to deliver than a monthly oral treatment. However, injections are not very 'child friendly', so more frequent injections are probably not acceptable. Even so, preventive efficacy would have to be high in order for a seasonal SMC injection to be considered.

If there was an injectable that could provide seasonal protection, then this would also have application outside SMC, for example, in areas of persistent transmission (given three times a year).

SMC versus RTS,s: Integration of the RTS,s malaria vaccine and SMC has not been investigated. A trial design has been proposed by B. Greenwood to compare RTS,s alone versus RTS,s plus SMC versus SMC alone. RTS,s could be given as a primer in infancy and then followed up with a single injection of RTS,s each rainy season, but the efficacy, acceptability and cost of such an approach has not yet been explored.

Target population: Should malaria incidence continue to decline, it is not clear at what point the target population becomes too small to warrant the further development of drugs for SMC.

5. Regulatory considerations for chemoprevention

Objective

To examine the key regulatory issues in developing a drug for chemoprevention.

Presentation: R. Clay

1. What is the difference between prophylaxis and seasonal chemoprevention from a regulatory perspective?

The main difference is the patient population. The population for chemoprevention is children in areas of seasonal malaria transmission.

2. What strategies may support regulatory review of chemoprevention drugs without requirements for curative efficacy?

There is specific regulatory guidance from both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) on this issue. This includes guidance for industry on neglected

tropical diseases of the developing world: developing drugs for treatment or prevention (FDA),[10] co-development of two or more new investigational drugs for use in combination (FDA),[11] and the Article 58 procedure (EMA).[12] Meetings between MMV and both regulatory agencies have been encouraging, and they are willing to provide help and guidance

There are no approved agents for chemoprevention in the US or EU and use of SPAQ in SMC is based on WHO prequalification/guidance. Thus, the regulatory pathway for a novel agent would have to be explored with the regulators, though the quality of WHO guidance and the amount of available research can form the basis of discussions for study designs and indications.

The specific malaria event rate assumed in the study design will have a large impact on the design and study size. Also non-inferiority margins would have to be determined which is difficult if the assumed preventive efficacy rate is unknown. It may be possible to demonstrate superiority over SPAQ in a higher transmission rate setting. An alternative would be to conduct studies in southern/eastern Africa, where SPAQ is believed to be ineffective; in this context a placebo controlled trial could be conducted. Resistance development would be an issue for regulators and surveillance would be required.

For a novel therapy, the curative dose would need to be established in Phase II. For a combination strategy, it would be easier to add a novel agent to an existing drug or combination rather than develop a combination of two new drugs.

3. What are the minimum safety data required for the registration of a chemoprevention agent?

At present, the target population is children under 5 years old, but a development strategy may need to account for expansion of SMC into children under 10 years of age. At least some adult safety data would be needed before progressing into children. Studies would need to be large enough to provide a sufficient safety dataset for use in SMC. There would need to be a reasonable expectation that post-marketing surveillance and pharmacovigilance would be conducted in the areas where the drug was used.

In conclusion, parallel tracks can be pursued with regulators to discuss designs and key issues independently of proposed combinations. As potential combinations are identified, then discussions can become more specific.

Discussion

Drug approval: If a drug is already approved for a different indication but at the same dose, then a single add-on study in the target population with comparative dosing intervals is acceptable for the additional indication in SMC. However, the basis on which the original dose was determined may be questioned. This may lead to a requirement for further studies rather than a delay in approval.

Drug–drug interactions (DDIs): There is an expectation that DDI studies will need to be conducted with agents likely to be used in the setting. Interaction studies with vaccines may also be required. Also, the risk of haemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals may need to be evaluated. This will depend on the drug pharmacology which specific studies will need to be conducted.

Lack of comparator: In eastern and southern Africa, where there is no active comparator, then a placebo controlled study is possible. However, the FDA may require testing of two active doses of the drug to attempt to demonstrate a dose–response. Determining the test doses is problematic; the lowest dose has to be effective and the higher dose has to be safe, though the difference in outcomes between the doses needs to be large enough to differentiate. Demonstrating a dose–response is not such an issue with the EMA.

Drug efficacy: Historically, antimalarial drugs needed to demonstrate efficacy in malaria treatment before being considered for SMC. It may be possible using modelling and Phase II data to provide enough confidence in the dosing regimen to progress to SMC in Phase II, without the need for Phase III malaria treatment trials. However, the WHO and malaria community will need to decide whether a drug with an indication only for SMC is useful.

Curative or preventive dosing: The curative dose would have to be established in Phase II, as would the dosing frequency needed to maintain blood levels sufficient for effective post-treatment prophylaxis. Although symptomatic children should always receive a malaria treatment, a drug for SMC should, as a minimum, clear parasites from asymptomatic carriers.

The relationship between curative and preventive efficacy is not understood, but there is confidence that using a curative dose would have a positive effect on preventive outcomes. A curative dose is preferable in order to delay resistance development. If a lower dose is required for safety, then there will be regulatory concerns regarding the potential for resistance and probably a requirement for ongoing resistance monitoring studies. In a combination, it might be possible to have one drug given at a curative dose and the other at a preventive dose, if that drug had high preventive efficacy.

6. MMV's target candidate profiles

Objective

Outline MMV's TCP4 for categorising development candidates as chemoprevention targets.

Presentation: T. Wells

Target candidate profiles (TCPs) outline the ideal properties of a molecule for a certain application. Target product profiles (TPPs) describe how molecules should be used in a particular indication.

The MMV portfolio is available at http://www.mmv.org/interactive-rd-portfolio. All of the compounds up to and including those in Phase I are new compounds that have been discovered in the last 10 years. To develop these for SMC would probably see deployment in 2028.

The TCP is usually set to match or exceed the desirable properties of currently available 'gold standard' molecules. However, in infectious diseases, the development of resistance will eventually undermine the utility of currently available therapies in treating disease. In this case, the requirements for any new molecules being developed may become less stringent as the clinical need increases. The TCP for chemoprophylaxis (TCP4) is as follows:

Parameter	Minimum essential profile	Ideal profile
Oral dosing regimen; dose	Once per week; <1,000 mg	Once per month; <100 mg
Onset of action	Slow onset of action (48 h) against asexual blood stages or causal liver stage activity	
Clinical efficacy	>95% prevention of primary infection for all Plasmodia	>95% prevention of malaria including relapses
Transmission blocking	None	>90% prevention of oocysts at trough concentration
Resistance risk	Very low risk for blood stage	Very low; orthogonal mechanism to treatment use
Drug-drug Interactions	No unmanageable risks	No interaction with malaria, TB or HIV medicines
Oral bioavailability/food effect	>30%; <3 fold	>50%; no food effect
Safety	Low G6PD risk; acceptable therapeutic index	No G6PD risk; therapeutic index >50 fold
Cost; stability	<$0.5 adults; >2 years	<$0.25 adults; >5 years
Formulation	Acceptable clinical formulation	Acceptable clinical formulation

Available at: http://www.mmv.org/sites/default/files/uploads/docs/essential_info_for_scientists/TCPs_and_TPPs/TCP4.pdf.

Action

Given the more recent experience with SMC, TCP4 is under revision and input is requested from the advisors both within the meeting and through a subsequent comment and review process on the contents of this TCP.

Discussion

Clinical efficacy: *P. falciparum* is the current priority for chemoprophylaxis and activity against *Plasmodium vivax* is not a requirement. The relationship between treatment efficacy and preventive efficacy is not clear. For chemoprevention, it may be more relevant to look at efficacy in clearing asymptomatic infection, and this may allow more drugs to be considered. The relationship between the Phase II target of 95% prevention of infection and the impact on the reduction in malaria risk is not known.

Oral bioavailability/food effect: Drugs with long half-lives tend to be very hydrophobic, thus dispersible formulations can be difficult to achieve.

Combination versus monotherapy: The chance of successfully developing a combination is much less than for each individual drug as a monotherapy, and the development time would be extended by 3–5 years. If there is an urgent need for a new SMC, would a monotherapy be acceptable? Unless there is no alternative, combination therapy is always preferable in order to delay resistance. However, for chemoprevention, monotherapy cannot be ruled out as an option. In this case, one strategy might be to have two long-acting monotherapies which could be switched between each season. Whether in combination or sequential therapy, the two drugs would need to have different mechanisms of action.

At present there is no drug that provides 95% efficacy with a single agent for malaria treatment, so combination therapy would probably be required to reach this goal. However, we need to ask what the efficacy target is for chemo protection? Clearly the vaccine experience suggests that there is a minimum threshold, but this needs further discussion.

It is important to separate discussions for the TPP depending on whether SPAQ is still giving adequate protection. If SPAQ is still active, there may be a rationale to add a third drug to attempt to extend utility of the combination. If SPAQ fails, then the treatment/preventive efficacy target may be reduced and monotherapy might be considered. It may be possible to develop a single agent first with the option to develop a combination therapy later – this is usual in other therapy areas (HIV, TB).

From a regulatory perspective, there is a bias towards using combination therapies in order to prevent resistance. However, if a drug was to be targeted in a defined geographic area with resistance monitoring, then monotherapy might be an acceptable strategy.

Clinical need: The timeframe of 2025 for a drug registration is realistic, but the timelines for agreement within the public health sector, scaling up of the roll out, and introducing a new agent to SMC will lengthen these times significantly, unless these discussions are resolved prior to regulatory submission. Otherwise, the post approval discussions could certainly add at least five years onto the time lines. The best case scenario, in the scope of the WHO Eradication Road Map, is that by that time, the population for SMC would be very small; it might, therefore, be possible that SPAQ will last long enough. However, if SMC is scaled up to include more populous areas (e.g. Nigeria) then the drug pressure will greatly increase and resistance will emerge more quickly. As there are many unknowns, and as SMC is a stop-gap measure, then developing a drug just for SMC appears risky.

Developing a drug which could be used in SMC and pregnancy would increase the potential patient population. However, getting a new drug approved for use pregnancy is very difficult.

7. Chemoprevention 2016 – considerations for re-purposing existing medicines to expand geography of SMC impact

Objective

New chemical entities as novel chemoprevention options will not be implementable until 2025–2030. Meanwhile, ongoing research into alternative combinations of existing medicines might fill the gaps related to SPAQ use in seasonal chemoprevention. In this session, speakers will provide perspectives and research updates on medicines under consideration to expand the impact of seasonal malaria chemoprevention.

7.1   Role of antibiotics for chemoprevention of malaria and other infections

Presentation: D. Chandramohan

Doxycycline,[13, 14, 15] clindamycin,[16] and AZ[13, 14, 17] have been tested as monotherapy for malaria chemoprophylaxis, and all showed good preventive efficacy. However, doxycycline is not suitable for SMC as it cannot be given to children under 8 years of age.

AZ has also been used for MDA in trachoma control. In Ethiopia, annual, biannual or quarterly AZ dose decreased mortality in children aged 1 to 9 years from 8.3/1000 person-years (95%CI 5.3 to 13.1) to 4.1/1000 person-years (95%CI 3.0 to 5.7).[18] Even 26 months after treatment, all-cause mortality was significantly lower among 1–5 year olds who had received AZ (odds ratio 0.35; 95%CI 0.17 to 0.74).[19] Further MDA campaigns using AZ showed positive effects on the incidence of acute lower respiratory infections and diarrhoea in Tanzania,[20, 21] and on respiratory tract infections and gastrointestinal tract infections in Malawi.[22]

The findings for AZ have prompted a trial of SMC plus AZ in African children. The study includes approximately 10,000 children from Mali and Burkina Faso aged 3–59 months, who are receiving SPAQ or SPAQ+AZ monthly for the transmission season. Data are not yet available for the individual study arms, but the mortality rate with SMC±AZ was 1.5/1000 person-years versus 4.6/1000 person-years for historical controls. Hospital admissions also appeared reduced to 11.4/1000 person-years with SPAQ±AZ versus 25.0/1000 person-years for historical controls. At the end of the transmission season, malaria parasite prevalence was reduced to 4.2% (171/4042) with SPAQ±AZ compared with 61.0% (607/995) in primary school children.

Pneumococcal carriage overall and the presence of pneumococcal resistance was not affected in Burkina Faso, though carriage of macrolide-resistant pneumococci increased in Mali from 1.3% to 8.1% following one year of administration of SMA with SPAQ+AZ.

The adverse event rate at one week post SMC±AZ was 3.9% overall. The main challenges in this study were the oral administration of the drugs to young children, vomiting, and adherence to the 3-day regimen through four rounds of SMC.

It appears that AZ can be safely added to SMC; the efficacy analysis is ongoing.

Discussion

Mortality: The mechanism for the long-lasting effect of AZ (26 months) on all-cause mortality is not clear, though the studies were well conducted. However, as most deaths from pneumonia, diarrhoea, and malaria occur in the rainy season, it is possible that if deaths are prevented in this time period, then the effect could be persistent.

Antibiotic resistance: Using monthly AZ increases the potential for the development of antibiotic resistance, and this was seen in pneumococci in Mali. However, resistance may be transient, as noted in some studies of mass treatment of trachoma with AZ, and the carrier studies are being repeated at 6 months after the last SMC round to see if this effect is sustained. If AZ reduces

mortality, and if resistance is transient, then the benefit of treatment probably outweighs the resistance risk.

Adverse events: Vomiting was slightly more frequent with AZ in Burkina Faso, though data included vomiting and spitting out.

7.2   Impact of SMC in children up to 10 years from the national implementation in Senegal

Presentation: J.L. Ndiaye

In Central Senegal, in 2008, SMC was provided to children under 5 years of age, with expansion to children aged <10 years for a further two years, with 780,000 courses given over 3 years. The inclusion of older children did not greatly increase staff time/costs, as children of both age groups often lived in the same house. However, larger doses are needed for older children. Protective efficacy against clinical episodes of malaria was 60% in SMC areas for the treated children and 26% outside the age range treated. A study in south-east Senegal in 2011 found a protective efficacy of >80% for SMC in children under 5 years and 5–9 year olds. Publications from these studies are in preparation or submitted.

Mapping of malaria risk in Senegal has enabled identification of areas suitable for SMC. A pilot programme was initiated in four districts in 2013 and scaled up in 2014. To assess SMC outcomes, sentinel surveillance was conducted in a probability proportional to size sample of 32 outpatient clinics and all hospitals in or near SMC areas. In addition, a cluster sample survey was conducted in 45 villages selected by probability proportional per estimated size of populations (2012 census) at the beginning and at the end of the malaria transmission season.

Overall, SMC reduced malaria cases in children <10 years by 70% over the transmission season; and there was a 30% reduction in the annual malaria burden. Outpatient visits were reduced by around two thirds between 2012 and 2014 in children <10 years during the transmission season. SMC delivery was conducted door-to-door and coverage exceeded 90% in most districts.

SMC was safe and well tolerated. The overall adverse event rate was 0.2% (113/674,265), with abdominal pain, vomiting, fever, diarrhoea and itching being the most commonly reported adverse events. Two serious adverse events were reported from around 2 million treatments; one case of Stevens–Johnson syndrome 1 week after SMC and one Lyell syndrome 10 days after SMC – both cases recovered well. A trial of SMS messaging for adverse event reporting, with cohort event monitoring, was conducted in 2015; results are awaited.

There was no impact of SMC on molecular markers of resistance to SP and AQ (*pfdhfr* 108, 51, 59; DHPS 437, 540; *pfcrt* 72-76, *pfmdr* 86, 184, 1246), in children <10 years of age receiving SMC or in adults.

Discussion

Transmission: Malaria incidence in those >10 years of age is difficult to interpret because of the need to compare this with areas non-adjacent to the SMC zones, but the data are consistent with a modest decrease in transmission.

SMC versus MDA: SMC to MDA is not a continuum. As transmission decreases, SMC will be less effective; in this case preventive treatment can be extended to older age groups (<5 → <10 years), but it is not an elimination strategy; SMC targets only the transmission season. MDA is appropriate only in the context of 'close to elimination' or in the containment of outbreaks.

A switch from SMC to MDA requires a reconfiguration of the entire malaria control programme. The public health objectives are also very different; SMC aims to reduce malaria burden and MDA to eradicate parasites from the population.

7.3   SMC in Burkina Faso with DHA-PQP and SPAQ: a randomised inferiority trial

Presentation: I. Zongo

Currently, SMC with SPAQ is a highly effective intervention in Burkina Faso. However, because of the threat of resistance development, alternatives to SPAQ need to be investigated. DHA-PQP has high treatment efficacy and PQP has a long half-life; it was originally used in China for prophylaxis. Studies of PQP in SMC have been conducted in Senegal[23] and Gambia[24] with encouraging results. It has also been used for malaria prevention in Ugandan school children[25] and adults in Thailand.[26]

In 2009, a trial was conducted in Burkina Faso, in an area where SMC with SPAQ is highly effective, to determine whether DHA-PQP is as effective as SPAQ for SMC.[27] The primary outcome measure was the risk of clinical malaria. For three months, 742 children received monthly SPAQ and 757 received monthly DHA-PQP; an untreated control group included 250 children.

The proportion of children who had malaria was slightly higher in the DHA-PQP group (odds ratio 1.33; 95%CI 1.02 to 1.72), but DHAPQP met the criteria for non-inferiority (an odds ratio of 1.64 was specified as the non-inferiority margin). Compared with controls, preventive efficacy at 16 weeks following the last SMC dose with SPAQ was 83% (95%CI 74 to 89) versus 77% (95%CI 67 to 84) for DHA-PQP.

The preventive efficacy of DHA-PQP was related to the circulating concentration of PQP; there was a steady reduction in the incidence of malaria with increasing PQP concentrations at day 7. Also, an increase in PQP dose was associated with a reduction in the incidence of malaria.

The incidence of mild and moderate adverse events was similar between the two treatment groups, and there were no drug-related serious adverse events. There was a decrease in adverse event incidence over successive SMC monthly rounds. There was a small decline in haemoglobin levels in children treated with DHA-PQP.

At the end of the transmission season, both drug regimens had decreased gametocyte carriage to 0.8% versus 7% in controls. Around 12% of children who received SMC had parasitaemia at the end of the transmission seasons, and in these children *pfdhfr* and *pfdhps* mutations associated with anti-folate resistance were more prevalent in parasites from those who had received SPAQ compared with those who had received DHA-PQP or controls.

In conclusion, SPAQ continues to be the treatment of choice for SMC in Burkina Faso, but DHA-PQP also has good preventive efficacy in SMC and could be used as an alternative. The study provided evidence of the high burden of malaria in the region and the potential beneficial impact of SMC.

Discussion

Role of DHA: DHA is highly effective at reducing parasite biomass, but has a very short half-life. In the context of SMC it is likely that the same results would be obtained with PQP alone.

The large scale use of DHA-PQP in SMC exposes a lot of parasites to PQP monotherapy. DHA-PQP is a valuable drug for malaria treatment and it would be unwise to use DHA-PQP for treatment and prevention.

PQP dosing interval and resistance: At the end of each dosing interval the incidence of malaria started to increase, suggesting that a 3-weekly dosing interval for DHA-PQP might be more appropriate. Modelling studies by Ian Harding indicate that resistance shortens the prophylactic duration. Although PQP has a long half-life, there is a long period at which drug concentrations are below the therapeutic level and the profile of the slope is important. Thus, the preventive efficacy of PQP appears to be more vulnerable to resistance than SPAQ.

Adverse events: The decrease in adverse events over successive SMC rounds has been seen elsewhere. It may result from mothers seeing the benefit from the decrease in malaria as SMC

continues, and hence less concerned regarding mild adverse events. The low rate of adverse events is this study may have resulted from AQ being administered as a syrup rather than crushed tablets.

7.4 Chemoprevention in non-seasonal malaria transmission settings

Presentation: P. Rosenthal and G. Dorsey (via telephone)

Data from three studies of chemoprevention in Uganda were presented; all were conducted in the Tororo District in Eastern Uganda – an area of perennial transmission with two annual peaks and an entomological inoculation rate of 310.

Study 1:[28] Conducted in 2011–2012 in 740 school children aged 6–14 years. Children were randomized to DHA-PQP given once a month, or once each school term (4 times per year), or placebo with follow up for 12 months. Monthly DHA-PQP gave excellent protection, reducing the incidence of malaria by 96% (95%CI 88 to 99), the prevalence of asymptomatic parasitaemia by 94% (95%CI, 92 to 96), and the prevalence of anaemia by 40% (95%CI 19 to 56). Termly DHA-PQP had no significant effect on the incidence of symptomatic malaria or the prevalence of anaemia, but reduced the prevalence of asymptomatic parasitaemia by 54% (95%CI 47 to 60).

Study 2:[29] Conducted in 2010–2013 in 393 infants 4–<6 months old, born to HIV uninfected mothers. Children were randomised to no chemoprevention, monthly SP, daily trimethoprim-sulfamethoxazole (TS) or monthly DHA-PQP, with treatment continued until 24 months of age and follow up for an additional year. Treatment was given unsupervised at home. Protective efficacy was 58% (95%CI 45 to 67) for DHA-PQP, 28% (95%CI 7 to 44) for TS, and 7% for SP (95%CI –19% to 28%). PQP levels were below the detection limit 52% of the time when malaria was diagnosed in the DHA-PQP arm, suggesting non-adherence. There were no differences between the study arms in the incidence of serious adverse events.

Complicated malaria or hospitalisations were uncommon and there were no differences in their incidence between treatment arms. In all four arms, the incidence of malaria increased with age and during treatment; the greatest protective efficacies of all three interventions was for children aged 6–11 months. After the intervention was stopped, the incidence of malaria was no different in the treatment groups versus controls.

Study 3:[30] *[Note that data are embargoed until publication and are not to be quoted publically].* Conducted in 2014–2015 in 300 HIV uninfected pregnant women of 12–20 weeks gestational age. Women were randomised to 3-dose SP at 20, 28 and 36 weeks gestational age (standard of care), 3-dose DHA-PQP at 20, 28 and 38 weeks gestational age or monthly DHA-PQP throughout pregnancy.

Monthly DHA-PQP completely protected women from malaria during pregnancy, whereas there were significantly more malaria episodes in the 3-dose DHA-PQP group (12 in 11 women p<0.001), which was more protective than 3-dose SP (41 episodes in 32 women p=0.001). Parasitaemia was also significantly reduced with monthly DHA-PQP (5.2% of women) versus 3-dose DHA-PQP (16.6%, p<0.001), which was more suppressive than 3-dose SP (40.5% p<0.001). The proportion of women with anaemia was reduced with monthly DHA-PQP versus 3-dose SP (p=0.04). Parasites detected in maternal blood, placental blood or placenta were significantly suppressed with either monthly or 3-dose DHA-PQP versus 3-dose SP. There was no difference in individual birth outcomes, though a composite outcome did show a benefit of monthly DHA-PQP versus 3-dose SP.

Use of DHA/PQ as therapy or in chemoprevention selected for parasites with resistance mutations in *pfcrt* and *pfmdr1*.[31, 32] Selection is in the same direction as seen with CQ or AQ, but the degree of selection appears to be modest.

In conclusion, monthly DHA-PQP offers potent preventative efficacy in children and pregnant women.

Discussion

Safety: Different DHA-PQP formulations have different product labels (there are around 30 different brands listed on Act watch). Duo-Cotecxin® (Holley-Cotec Pharmaceuticals, Beijing, China) was used in the studies in Uganda. Differences in labels reflect the differences in regulatory agencies who reviewed the files – Eurartesim was reviewed by the EMA and WHO prequalification. It would be anticipated that any generic DHA-PQP which is prequalified would be subject to the same concerns

No cardiac safety signals/Torsades de Pointes have been observed in the safety data, but these adverse events are difficult to detect in clinical trials. (F. ter Kuile has performed a meta-analysis of repeated DHA-PQP doses with a manuscript in preparation).

QT prolongation: In the studies reported above, the effect of DHA-PQP on QTc interval was evaluated in a random sub-set of 40 children and a random sub-set of 32 pregnant women. There was a trend towards longer QTc intervals, but none exceeded 450 ms.

A thorough review of the risk of QT prolongation by the WHO and EMA concluded that QT is prolonged with DHA-PQP, but there were no cardiac symptoms reported in conjunction with the ECG findings, and PQP did not induce early after depolarisations. These observations indicate that PQP has a torsadogenic potential, which is lower than that of CQ but higher than that of AM/LUM.[33]

Food effect: Fatty food increases exposure to PQP and higher doses may exacerbate QT prolongation, but most normal meals would not contain enough fat to have a major effect. Some DHA-PQP brands have label warnings to administer DHA-PQP on an empty stomach (e.g. Eurartesim®), though this requirement is not universal and so different studies have used different approaches to food. In large treatment campaigns, as in MDA or SMC, it is not feasible to restrict food and so the safety profile of DHA-PQP from clinical trials may not be wholly applicable in those settings.

Objectives: SMC is restricted to areas of seasonal malaria. In Uganda, chemoprevention cannot be delivered seasonally, anti-folates are not effective because of resistance and even giving DHA-PQP at less than monthly intervals is less effective. Such an intervention is only of benefit to the individual as long as therapy is continued, and has no effect on surrounding communities. The effect on transmission is unknown; a cluster-randomised trial of the effect of reducing malaria burden in school children on the surrounding communities has been conducted by P. Rosenthal/G. Dorsey, but has yet to report.

7.5   Is there a role for chloroquine in sub-Saharan Africa

Presentation: M. Laufer

In 1993, Malawi became the first country in Africa to switch to SP, as CQ malaria cure rates had declined to <50%. From 1992 to 2000, the prevalence of the molecular marker for CQ resistance, *pfcrt*, rapidly declined, and had disappeared by 2001.[34]

In 2002, a clinical trial was conducted in Blantyre, Malawi, including 210 children with uncomplicated *P. falciparum* malaria randomised to receive CQ or SP and followed for 28 days. The cumulative efficacy of CQ was 99% (95%CI 93 to 100), compared with 21% (95%CI 13 to 30) for SP.[35]

Systematic countrywide sampling of children aged 6–59 months across Malawi identified 685 children with *P. falciparum* parasitaemia; only one had a CQ-resistant genotype.[36] Studies of the ancestral lineage of the CQ-resistant parasites showed that they were all SE Asian types. The CQ-susceptible parasites that survived despite CQ drug pressure were diverse, and after the removal of CQ drug pressure there was a re-expansion of the CQ-susceptible strains.[37] Thus, there is a significant fitness advantage of the CQ-sensitive parasites in the absence of drug pressure.

A clinical trial to identify possible CQ combinations, was conducted in 640 children randomized to CQ alone or CQ combined with AS, AZ or atovaquone-proguanil (AVPG) for the treatment of all episodes

of uncomplicated malaria for one year.[38] Treatment efficacy for the first malaria episode was 100% for CQ monotherapy and 97.9% for subsequent episodes of malaria. Similar results were seen in each of the CQ combination groups. The incidence of *pfcrt K76* in pure form was 0%; mixed infections with both K76 and T76 were found in 2/911 infections.

In Malawi, SP use for malaria treatment was stopped in 2007, though it is still used for IPTp. There is widespread use of TS, which is the most commonly prescribed antibiotic in adults and children with fever as well as being used in all HIV-infected individuals. There is cross-resistance between SP and TS, and this may explain why even after the removal of SP drug pressure, very high rates of SP resistance have been sustained in Malawi. An alternative explanation is that there is no selective advantage of SP-susceptible strains over -resistant strains in the absence of drug pressure.

The pattern of CQ-resistant *P. falciparum* is not homogeneous across Africa. Isolates collected from 2012–2014 in Ethiopia were mostly mutant for *pfcrt*. In contrast, the majority of Tanzanian samples were wild-type for *pfcrt*.[39] In southern Kenya, samples collected in 2013 showed that the prevalence of the *pfcrt K76T* mutation had declined from 100% to 41% over the 13 years since CQ was abandoned for malaria treatment.[40] In samples collected from western Kenya, there was a significant increase in the proportion of samples with the *pfcrt* wild-type genotype, from 61.2% in 2010 to 93.0% in 2013.[41] In a study in Uganda, resistance prevalence to CQ was 80% in 2010, 85% in 2011, 73% in 2012, and 65% in 2013, but although there is a trend to increased sensitivity, most parasites are still CQ-resistant.[32] In Zambia, data obtained from two clinical trials of AZ+CQ for the treatment of uncomplicated malaria in adults indicated that CQ-resistance associated mutations had declined from in 26% 2004–2006 to 20% in 2006–2007; overall 20.8% of samples had CQ-resistance mutations.[42] More recent data (2012–2014) from northern Zambia found no evidence for CQ resistance (unpublished data).

An unpublished study in pregnant women in Malawi examined whether placental *Plasmodia* infection could be better suppressed using intermittent curative therapy, or with continuous low-dose prophylaxis. Subjects were given ITPp with SP or three curative doses of CQ during the pregnancy or weekly CQ prophylaxis. There was no difference in the incidence of malaria between treatments and very low rates of placental malaria were found in all groups. Most malaria cases were seen in women who had parasites detected at their first ante-natal visit. In women with no malaria parasites at enrolment, weekly CQ prophylaxis was protective against placental malaria, whereas IPT with CQ or SP was not. However, for women with parasites at enrolment, IPT was most protective.

Another area that requires consideration is school-age children. In Malawi, this group carries a disproportionately high burden of malaria and also has high gametocyte carriage rates. A study in Uganda, is investigating whether treatment of malaria in school-age children impacts on transmission in the community. Better measures of malaria burden are needed in this age group, as fever may not be present or is overlooked, whereas anaemia and general poor health related to malaria infection may be widespread. In the case of weekly prophylaxis, delivery via the schools might be possible, if the transmission season and school terms coincide.

If CQ was used on a large scale, the risk for the re-emergence of resistance is unknown, but concerning. Consequently, CQ should probably be used in combination with another drug. Tolerability of the combination of CQ with AZ was problematic, though a new AZ formulation may be better tolerated. With CQ, the main tolerability issue is itching, which can be severe and the tolerability of CQ versus other antimalarial agents need to be re-examined in the context of malaria prevention. In conclusion, CQ could not be used in West Africa in any setting because of sustained CQ resistance, but in the south and east of Africa, CQ may represent an alternative drug for use in applications outside of malaria treatment.

Discussion

Dosing: It may be possible to have a full dose of CQ followed by weekly low-dose preventive treatment. However, this may lead to more rapid re-emergence of resistance.

Safety/tolerability: Weekly CQ was associated with many adverse events, though some of these might have been because of the cumulative effects of CQ, owing to poor compliance with the recommended prophylactic regimens.

Acceptability: CQ is not perceived well in the community and convincing patients and NMCPs that CQ now works may be challenging.

Population: Only in areas where CQ and AQ are not used has CQ resistance declined. CQ is used for *P. vivax* in Ethiopia and ASAQ is used in Mali, for example. Thus, CQ would only be an option in the south-east of Africa.

Implications of resistance: For CQ to be adopted as a policy, more information would be needed on how rapidly CQ resistance would re-emerge should the drug be reintroduced. Also, the impact of CQ resistance on the use of ASAQ would need to be considered. There would need to be sound scientific evidence that CQ used on a large scale in SMC would be of benefit.

7.6   Safety considerations and resistance monitoring in SMC implementation

Presentation: P. Milligan

The role of the LSTMH in ACCESS-SMC is to work with research groups in each country to measure SMC coverage, to measure the impact of SMC on malaria, to support pharmacovigilance and to monitor the efficacy of SMC drugs. In 2014, about 2.5 million children were treated – about 10% of the target population. In 2015, scale up was constrained by shortages of quality-assured drugs, though 7 million children were treated. SMC-ACCESS includes 7 countries, providing an opportunity to establish a baseline and standardised methods for monitoring efficacy, safety and drug resistance. Although Senegal is not one of the ACCESS-SMC countries, the same monitoring and evaluation approaches are being applied in Senegal. As SMC was started earlier in Senegal, it has been a useful model. One of the key issues is how to maintain this monitoring after ACCESS-SMC ends.

Efficacy monitoring aims to provide reassurance of efficacy after 2 years of SMC and establish a baseline for future monitoring. As well as monitoring the protective efficacy of SMC (using case–control studies), molecular markers for SPAQ resistance will be measured before and after SMC, in clinical cases and in regions adjacent to those giving SMC. Coverage and adherence will be evaluated through surveys at the end of each cycle and at the end of the transmission season. The utility of evaluating efficacy based on screening malaria cases for the date of previous SMC dose is also being investigated. Measuring parasite clearance after SPAQ is also being considered.

These data will generate estimates of coverage, estimates of efficacy of treatment from case–control studies, and estimates of impact from the sentinel surveillance. However, in later years, measurement of the continued impact of SMC will be more difficult. Although there will be case–control data, and comparison of incidence from sentinel sites in SMC and non-SMC areas, in some countries there may be no suitable comparison areas.

Safety monitoring is one of the most difficult areas to strengthen. It is dependent upon health facility staff recognising when an event may be drug related and then reporting that event. Training workshops have been conducted for national level staff at pharmacovigilance centres and NMCPs. Pharmacovigilance has also been included in cascade SMC delivery training in each country and reporting forms and guidelines made available at all health facilities. Specific known adverse events have been targeted: Stevens–Johnson syndrome, hepatotoxicity, extra-pyramidal syndrome and repeated vomiting. Follow up of serious adverse events has been organised by the research team to

make sure that there is good documentation. In addition, hospital records have been reviewed to check for any admissions that might be drug related but went unreported.

The incidence of serious adverse events has been low. Across research studies and since national introduction of SMC there have been two cases of Stevens–Johnson syndrome, three of extrapyramidal syndrome and one case of anaphylactic shock. Vomiting is the most common adverse event, though the link to SMC is not always clear.

The current research projects, conducted within the 2-year timeframe of ACCESS-SMC, will report baseline results at the end of 2016 with survey results being available by mid/end 2018. However, in terms of longer term monitoring, issues of regional co-ordination, standardization of methods and funding need to be addressed.

Discussion

Parasite clearance: This was not conduced in 2015, but might be investigated at one site in 2016. Parasite clearance is a useful measure and not difficult to determine. However, late treatment failure is usually thought of as the first sign of resistance, rather than delayed parasite clearance. The effect of immunity on parasite clearance also needs to be considered, and may be easier to look at in very young patients whose immunity is lower.

New tools; old drugs: It is not clear how long SMC will be needed and it could be a useful tool for some time. The data analyses from ACCESS-SMC are necessary to refine the tools we have, as implementation is still challenging. Even if it is not for SMC directly, the data will be valuable. Also, such information can inform the development of new strategies and drugs for the future. As new drugs won't be available for around 20 years, we have to be more imaginative in using the drugs and tools that are available.

8. Synthesis of key considerations from Day 1

The future of SMC: SMC is a highly cost-effective intervention and investing in efforts to look for new antimalarial drugs is considered worthwhile. Although SMC is a stop-gap measure, no accurate prediction can be made for how long it will remain useful. However, SMC should remain a key strategy for the reducing malaria burden in children in areas of seasonal transmission for at least 5–10 years. We should not assume that the incidence of malaria will decline so rapidly and extensively that there is no need to develop alternative drugs suitable for SMC.

Whilst looking for new drugs, we are still struggling to implement SMC now. As we learn more from the ongoing studies, this information can inform the development of new drugs.

It is important that IPT, MDA and SMC are considered separately and that the objectives of these interventions are clearly defined in the epidemiological context.

Monitoring of resistance is important and we need to better define the relationships between resistance markers and clinical efficacy in different indications.

The stopping criteria for SMC have not been considered, but SMC will continue for a long time in some regions and alternative therapies to SPAQ will be needed. The development of new drugs will take around 20 years, and this timescale may be beyond the time of greatest need for SMC. Thus, drugs targeted specifically for this indication may no longer be needed. We therefore need to be more open to investigating the drugs that are currently available and repurposing them for use in SMC.

The lower level of acquired immunity following SMC and the possibility of rebound remains an important concern. However, as malaria transmission rates fall overall, maintaining immunity may become less of an issue. Thus, the importance of maintaining immunity depends on the epidemiological context.

The scalability of SMC to the 26 million children at risk is challenging, and how this can be financed and sustained, perhaps over many years, is unclear. There are also questions regarding how the monitoring of efficacy and resistance can be co-ordinated across the region. There is currently no provision for monitoring SMC outcomes after ACCESS-SMC has ended.

Strengthening health systems is of great importance. With training, CHWs can collect good data and achieve high preventive efficacy rates. Delivery mechanisms for SMC are key. At present, the door-to-door method is working well, but other options may be better if SMC is extended to older children.

It is important that SMC is only used in areas and populations where it is appropriate. In some regions, extending SMC to children aged up to 10 years makes sense. Within SMC regions, the epidemiology of malaria is changing with the burden of disease shifting to older children. Thus, including children older than 5 years may become necessary as SMC continues.

SMC drug attributes: For new drugs or repurposing of existing drugs for SMC, the safety and efficacy profiles must be at least as good as for SPAQ. Formulations must be child-friendly and the frequency of administration compatible with door-to-door delivery, ideally monthly. However, more frequent administration could be considered for drugs with very high preventive efficacy (approaching 100%). An injectable would be acceptable from a health system perspective should preventive efficacy and safety be non-inferior to SPAQ, and if dosing could be once per transmission season.

Repurposing: It is uncertain whether there will be a need for drugs directed specifically at SMC by the time that new drugs would become available and implemented. Thus, it is important to re-examine currently available drugs for repurposing for SMC.

AZ is an effective chemo-protective agent in malaria, but also reduces the incidence of respiratory tract infections and diarrhoea. It is unclear whether AZ is acting as a third anti-malarial when added to SMC with SPAQ, or whether its effects would be more general. The risk of bacterial resistance development with more widespread use of AZ needs to be better defined.

DHA-PQP has good treatment and preventive efficacy, but the risk: benefit for SMC is unclear, because of the potential for the development of artemisinin resistance.

It is possible that CQ would be effective in southern/eastern Africa for SMC, but more information is needed regarding the potential for the re-emergence of CQ resistance. An appropriate partner drug needs to be identified for use as combination therapy.

New drug development: Drugs should not be developed only for SMC as this is a challenging pathway and there may be no need for such drugs by the time that they become available. However, if drugs appear suitable for use in SMC, or other specific prevention and control strategies, standard methods are needed to evaluate this potential. A pragmatic approach is to focus drug development on identifying drugs for malaria treatment, and then reserve those which have the most favourable safety and pharmacokinetic profiles for use in SMC.

There may be an opportunity to increase the number of compounds considered within the TCP by including those likely to have efficacy against asymptomatic malaria with long post-treatment prophylaxis. The current screening methods are focused on drugs for malaria treatment. However, the relationship between therapeutic efficacy, efficacy in asymptomatic disease and the potential for a preventive effect is not clear.

Regulatory issues: There is a good evidence base for SMC with which to have productive discussions with regulators regarding programmes and studies. However, whether a drug that only has an indication for SMC is of value to the malaria community and WHO is uncertain and needs to be explored. It is unclear if new products can be developed within a timeframe relevant to the clinical need for SMC.

9. Safety considerations and data requirements for clinical studies in SMC

Presentation: S. Duparc

Safety requirements are becoming more stringent in drug development. Safety monitoring requires all adverse events to be followed until resolved or stable and special reporting for all serious adverse events, additional adverse events of special interest (prolonged QT, hepatotoxicity, agranulocytosis, cutaneous reactions, anaphylaxis, acute renal failure and neurotoxicity/seizures), and reporting of pregnancy outcomes. Reporting is to the EMA/FDA and local regulatory agencies as well as to the WHO Uppsala Monitoring Centre.

The current development path in malaria is for full development of a fixed-dose combination for acute malaria followed post-registration by additional studies in the target population. However, if it was considered useful to develop molecules alone or in combination for SMC, then an alternative development pathway is outlined below.

For a monotherapy or for each compound in a combination therapy, the initial studies would be similar:

- Sporozoite challenge study.
- Two Phase IIa studies:
1. Assessment of efficacy in malaria asymptomatic subjects (adults and children).
2. Assessment of the ideal time interval between two treatments (children only).

For a combination therapy two additional Phase II studies would be required.

1. Phase IIb to assess the efficacy of the combination therapy in malaria asymptomatic subjects (adults then children).
2. Phase IIb to assess the ideal time interval between two treatments of the combination therapy (children only).

For a either a monotherapy or a final combination therapy, two Phase III studies would be needed:

1. Superiority study in southern Africa versus placebo to prove efficacy (target population)
2. Safety study in sub-Saharan Africa versus SPAQ (safety database in the target population)

The Medicines & Healthcare products Regulatory Agency (MHRA) accepted a programme for the development of AZCQ for IPTp including one Phase II pharmacokinetic/efficacy study measuring parasitological clearance in *P. falciparum* asymptomatic pregnant women (n=166) plus a single Phase III pivotal study in IPTp to demonstrate superiority over SP. 5044 subjects were needed to provide sufficient power (alpha 0.00125).

Discussion

1. What minimum drug safety requirements must be established <u>before</u> chemoprevention studies begin?
2. How do clinical trial data requirements re: drug safety for chemoprevention trials differ from treatment trials?

Toxicology: Preclinical toxicology requirements for an acute therapy use very short treatment durations and long-term effects are not evaluated. Thus, moving a therapy from an acute indication to a chronic indication or repeated dosing raises questions regarding long-term safety and toxicity. Animal studies are not reliable, so even if animal data are available, the clinical data have to be scrutinised carefully for safety signals.

Risk-benefit: Larger safety databases will be required for SMC because it is given to young children and because non-infected children will receive treatment. Treatment also needs to be well tolerated for a drug to be suitable for use in a public health programme.

3. Could developing new drugs specifically for SMC or IPTp be a faster route to registration and adoption?

Prophylaxis versus cure: Ten to twenty years from now there may be fewer clinical cases and more regions in pre-elimination. In that setting, it would be important for a drug to clear parasites and a curative agent is preferred.

It is unclear what level of parasites are 'asymptomatic' or 'symptomatic' and so drug therapy should aim to clear all parasites from all patients in the target group. In SMC, the treatment firstly clears parasites from the patient then protects them from further infection during the period of post-treatment prophylaxis, so for SMC this dual purpose is necessary. Failure to clear existing infections is an excellent method of selecting for resistance.

In order achieve continuous protection from monthly administration, the drug must be both potent and be given at a high dose. Thus, it is not clear how a monthly prophylactic dose could practically be achieved.

Sporozoite challenge studies: These are key in defining the period of post-treatment prophylaxis that a drug dose provides. Most studies are conducted in Europe or the US, though facilities are available in Africa. Where possible, subjects with genotypes relevant to the target population are selected. This is mainly because of differences in the adverse event profile between Caucasian and African subjects rather than differences in efficacy findings.

10. Discussion: Immunology and chemoprevention

Presentation: B Greenwood

Rebound is an increase in the incidence of malaria in the period after a period of effective malaria control has been achieved (by any means) above that which would have occurred if the intervention had not taken place.

It is important to distinguish the excess cases (rebound) from those that represent a return to the background incidence of malaria. In the graph below, if the area under the curve of the control group (purple line) is greater than that of the intervention group (green line), then the intervention resulted in a net benefit.
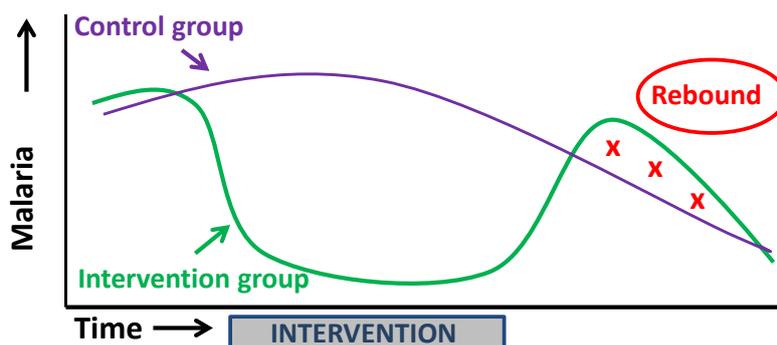
When comparing the intervention and rebound periods, the numbers of cases, and not the percentage changes in incidence, need to be considered; the incidence may have changed during the period of the intervention. For example, the incidence may decrease as the study subjects become older.

In addition, it is important to differentiate between malaria of different severities and between different types of severe malaria.

The benefits of SMC on mortality and morbidity as well as reducing the frequency of malaria episodes are substantial, and so any rebound effect would also need to be substantial in order to negate these benefits.

A study in Gambian children aged 5–6 years,[43] who had received chemoprophylaxis with Maloprim® (pyrimethamine plus dapsone) for up to 5 years showed no increase in mortality when chemoprophylaxis was stopped versus those that had received placebo. The significant mortality benefit of the intervention was sustained up to at least age 10 years. The longer the period of chemoprophylaxis, the greater was the rebound; the incidence of clinical attacks of malaria during the year after chemoprophylaxis was stopped was significantly higher than the controls only among children who had at least 5 years of chemoprophylaxis. There was no significant difference in spleen rate, parasite rate or packed cell volume between the intervention and control groups one year after chemoprophylaxis was stopped.

In Tanzanian infants aged 2–12 months,[44] who received weekly malaria prophylaxis with Deltaprim® (pyrimethamine plus dapsone) or placebo, reducing exposure to *P. falciparum* in early life with continuous malaria prophylaxis delayed the acquisition of immunity to the parasite. However, over the four years of follow up, there was no difference in the overall rate of clinical malaria, but a net benefit from prophylaxis for severe malaria and particularly severe anaemia.

In Burkina Faso,[45] three courses of SPAQ were administered to children aged 3–59 months during the 2008 malaria transmission season. There was a small increase in the rate of clinical malaria episodes in children who had previously received IPT versus placebo (IRR 1.12; 95%CI 1.04 to 1.20). There was no difference in the incidence of hospital admissions (IRR 0.94; 95%CI 0.60 to 1.47).

Data from Mali,[46] indicated that in children who had previously received three courses of SPAQ at monthly intervals, there was no increase in the incidence of clinical malaria versus controls in the year following the intervention (IRR 1.09; 95%CI 0.99 to 1.21). Incidence rates of all-cause hospital admission over the whole post-intervention period did not differ between the two groups of children either (IRR 1.55; 95%CI 0.78 to 3.11).

In conclusion, rebound is highly likely after a period of effective malaria control that has stopped, unless the transmission intensity has fallen in a sustained way during the follow up period. In nearly all circumstances, the benefit from the period of effective intervention will outweigh the deleterious impact of rebound. However, the potential for rebound to occur needs to be recognised and managed with steps to alleviate its impact, such as ensuring enhanced use of other control measures during the risk period such as long lasting insecticide-treated nets (LLIN).

Discussion

1. Risks of rebound after cessation of chemoprevention – what we know what we still need to learn

Acceptability and communication: From a parent's perspective, the gains of the intervention are not considered when the intervention stops and their children start to get malaria again, even if there is no rebound above the background incidence.

From a communication perspective, the message could be that SMC saves lives by protecting younger children, but that more attention needs to be directed to identifying and treating malaria in older children.

This is an important consideration in talking to donors, because it needs to be emphasised that SMC should cover all children up to age 5 years in order to reduce mortality, but that diagnosis and treatment services need to be maintained, as there may be an increase in malaria incidence in children over 5 years once they are no longer eligible for SMC.

Children who have received SMC appear to have lasting benefit in terms of school attendance and educational attainment. Data on longer term multi-dimensional outcomes may be of benefit in communicating SMC benefits and for increasing the acceptance of rebound.

Overall, the risk of rebound should not impair the scale up of SMC.

Risk-benefit: The period from 1–5 years carries the greatest risk of malaria mortality so even if cases are increased after the period when children have been protected with SMC, children over 5 years old are likely to have better outcomes.

Managing rebound: Rebound can be expected to happen to some extent after 1 year of SMC, and will be more pronounced with successive years of intervention. However, the net benefits are great and the rebound can be mitigated by ensuring that other malaria control measures are strengthened post-intervention, with a long-term aim of reducing transmission to very low levels and ultimately elimination. If people have become accustomed to not seeing malaria so frequently during SMC, then other control measures may seem less important, so their use needs to be reinforced.

As well as other mechanisms of malaria prevention, surveillance for severe malaria, the use of diagnostics, and active case detection need to be implemented, as well as providing sufficient drugs for treatment.

Rebound from other interventions: Rebound has not been seen with LLINs, probably because their effectiveness in preventing infection is lower than SMC. Also, LLIN potency declines with the age of the net, so the transition to the background infection rate is more gradual than with SMC. There is some indication of rebound with RTS,s, but again, the protection of the vaccine is not as high as SMC and declines gradually. Thus, the potential for rebound may depend on the effectiveness of the intervention at reducing infection and on how rapidly its protective effect declines.

Data collection: It is important to collect malaria incidence and outcomes data from older children (>5 years) in the regions where SMC is being conducted so that there is a background incidence available against which rebound effects can be compared.

2. Interactions between chemoprevention and infection–immunity: can chemoprevention offer protection while permitting development of malaria premunition?

Drug efficacy versus immunity: If drugs in the future have preventive efficacies approaching 100% and/or causal activity, will that impact immunity; will the net benefit of SMC be retained? Although we know that if people remain uninfected for 5 years immunity is lost, it is not clear what level of parasite exposure is needed to develop or sustain immunity. The interaction between age and parasite exposure on the acquisition of immunity is not well understood either. Importantly, with SMC, children are exposed to some level of infection outside the transmission season, though the transmission levels needed to induce immunity are not known.

Immunological markers: There are no validated immunological markers to indicate malaria immunity. Following SMC, antibodies appeared to be reduced versus controls, though T-cell responses were maintained, probably as a consequence of exposure to malaria outside the transmission season. Humeral or cellular immune responses could be evaluated, but the clinical incidence of malaria following SMC will be the most important outcome.

Future perspectives: Rebound is not an issue if the goal is elimination. Thus, as transmission rates decline, preserving immunity may not be so important.

11. New molecules for chemoprevention and options for repurposing

Objective

Review methods for assessing candidates in MMV's portfolio for TCP4.

Based on discussions from Day 1, the objective of this talk was focused to examine currently available agents that could be repurposed for SMC.

Presentation: T. Wells

The primary objective for MMV, as laid out in the 2013–2018 business plan, is to discover, develop and deliver medicines for the treatment of uncomplicated malaria. From the entire pre-clinical and Phase I portfolio only a handful of drugs will be registered successfully, as the attrition rates in drug development are high, with one in nine molecules entering preclinical being launched for anti-infectives. Not all of the medicines developed for the treatment of uncomplicated malaria will suitable for use in SMC. However, we need to think now about the appropriate development plan to make sure that the drugs will have the correct labelling to allow their use in SMC.

Drugs in late discovery now will start Phase I studies in 2018 and Phase IIa studies in 2019–2020. Issues with the adverse event profile might become apparent after 30–50 patients, so not until Phase II studies are completed. Registration may be possible by 2025, but acceptance and implementation in SMC could take 5–10 years after the drug becomes available. It is important that these 'post-registration' discussions with public health bodies happen as soon as possible, and certainly before the approval of new medicines. The link between the WHO and EMA via the article 58 mechanism should facilitate this process.

The most challenging target is to achieve a month of chemo protection with a single-dose oral medicine. This is an unusual requirement, requiring a half-life of >200 hours. Older drugs used for prophylaxis have often achieved long periods where plasma concentrations are above the active level, by having extremely long half-lives often by distributing into the tissues. Looking at the current portfolio, a once weekly dosing schedule is more achievable and there would be more options for drug development if this was acceptable. Moving from a once weekly to a once monthly oral dose would risk having very high initial plasma exposures (C_{max}), with the associated safety concerns.

Protection using dosing intervals greater than one month are more likely to be achieved using an injectable formulation as opposed to oral administration; though the drug would have to have a high potency to make this feasible. Formulating a combination product as an injectable would be challenging. However, there are ongoing programs in HIV to deliver molecules for PrEP (Pre-exposure prophylaxis) and lessons can be learned from those experiences. The additional complication for malaria SMC is that as the target population is children, there would be additional stringency required on the maximal size of needle used.

At present, the clinical activity against the parasite liver stages is being measured. It is not clear that this is a requirement for SMC, as it effectively adds only one additional week on to the protection. Clinical activity against the blood stages is now effectively measured in the 'Controlled Human Malaria Infection' models, and this has been useful in getting an early read out for the human pharmacokinetics and pharmacodynamics.

In terms of resistance, a value of at least 8 for Dd2 Log MIR is desirable.[47] However, drugs with long half-lives tend to have lower values, indicating a propensity to select resistant parasites.

From the current MMV portfolio, the following agents have properties relevant for TCP4.

- KAF156, DSM265 and MMV048 all show potential for chemo protection.
- DSM265 and MMV048 have potential for once per week dosing; once per month would depend on the efficacy required.

Molecule	Mechanism of action	Predicted single dose (mg)	Predicted human $T_{1/2}$ (hours, measured)	Resistance Dd2 Log MIR	Max IC_{50}-fold shift
KAF156	CarI	?	39	8	100
DSM265	DHOD	300–400	43 (100)	5.5	800
MMV048	PI4K	20–40	34 (125–237)	6	2

Discussion

There are significant barriers to developing new drugs suitable for use in SMC. Also, given the projected decline in malaria incidence, new drugs may not be available in time to be used in SMC programmes. The regulatory path for registering a drug with an indication in SMC is unprecedented. Overall, developing new agents specifically for SMC is a high risk option. Thus, at this time efforts should focus on the repurposing of existing drugs.

For repurposing of existing drugs, it is important to note that conversion to intramuscular dosing would probably still not see registration until 2025.

Lumefantrine (LUM): LUM was initially being developed as an injectable and so there are pharmacokinetic data available for intramuscular administration. Theoretically, LUM could be combined with another drug for SMC. However, as this drug is a component of the most widely used ACT for malaria treatment, artemether-lumefantrine (AL), it should not be developed for SMC.

Pyronaridine (PYN): Data on intramuscular injection have been generated for PYN during its early development by the People's Republic of China, and these data are published as abstracts in the Chinese literature. However, PYN-AS has been recently approved for malaria treatment with the cleanest safety label of all the ACTs and may be needed in Africa as an alternative ACT to ASAQ, especially if we start to see PQR-resistant strains spreading from the Greater Mekong sub-region.

Primaquine: The half-life of PQ against blood stage infections is quite short and would not be suitable for use in SMC.

Tafenoquine (TQ): With a long half-life and activity against blood infection TQ appears suited to use in chemoprevention. Also, because TQ was originally developed for prophylaxis, some of the safety studies necessary to support a chemoprevention indication have already been completed. However, the current plan is to submit TQ to the US FDA in the second half of 2017, and the project team is focused on this goal, using a 300 mg dose. Once the medicine is approved, then further studies in prophylaxis would be easier to perform (effectively being phase IV studies rather than phase III).

Importantly, both PQ and TQ cause haemolysis in individuals with G6PD deficiency. Although a point-of-care test is being developed for TQ, the extra burden and cost that this would place on an SMC campaign may make this a non-viable approach. Also, the test would have to be validated in African children with *P. falciparum* infection, which is currently not the target population for this drug. It may be possible to use lower doses of TQ, but these would need to be tested for their haemolytic potential in G6PD-deficient individuals.

Chloroquine: CQ could not be used as monotherapy in SMC as CQ resistance would probably emerge quickly under renewed drug pressure, even in areas where it has disappeared. The advantage of using CQ rather than AQ in a combination therapy for SMC is unclear. CQ was very unpopular when used for prophylaxis in pregnancy because of the incidence of itching and rash.

Piperaquine: DHA-PQP has been shown to be efficacious in preventing malaria in SMC. However, it is not clear whether the DHA is necessary for the effect, and this would certainly be a question raised if

the topic were to be discussed by a regulatory body. Although DHA will reduce the parasite load, this may not be so important in asymptomatic malaria with low levels of parasitaemia. Because of the short half-life of DHA, PQP is exposed to parasites as monotherapy during the period of post-treatment prophylaxis, increasing the potential for resistance to emerge. Concerns have been expressed that using an artemisinin as a component of SMC in millions of children would accelerate the development of artemisinin resistance. However, given that these children do not have active malaria, then the actual number of parasites exposed to the drug would be much smaller than in some of the treatment studies.

This raises the question that f the community had access to high quality formulated PQP monotherapy, would future studies would be done with PQP rather than with DHA-PQP? For use in SMC, ideally PQP should be partnered with compound with a long period where the compound is above the MIC. The cardiac safety concerns for PQP mean that, at this stage, it is difficult to see it being partnered with the related aminoquinoline compounds CQ or AQ. Studies on the safety of mefloquine/PQP combinations are currently ongoing in the Greater Mekong sub-region. SP/PQP does not add any advantage over SPAQ. AZ/PQP could be considered, and has been discussed extensively previously as a potential combination for use in pregnancy. Making monotherapy PQP available as high-quality clinical grade material would enable investigators to follow up on such avenues.

Combinations containing PQP would not be considered as a replacement for SPAQ in the areas in which SMC is currently implemented. Although DHA-PQP is not a first-line ACT in these regions, from a programmatic perspective, most of these countries have DHA-PQP as a second-line ACT for malaria treatment.

Currently PQP is not available as a monotherapy, only in the combination DHA-PQP. Thus, any studies would have to use DHA-PQP + partner. It might be valuable to have a supply of PQP monotherapy tablets produced for research purposes. For studies supported by the European & Developing Countries Clinical Trials Partnership, all drugs must be of GMP quality. Outside of a research context, as PQP monotherapy is a new product, registration studies would be required, although it is difficult to estimate the timelines for registration, as the combination is already approved. Note that it would be around four times cheaper to formulate PQP as a monotherapy than the DHA-PQP combination, so there may also be cost advantages.

Action

MMV is to investigate the costs of manufacturing PQP monotherapy tablets to GMP quality for research purposes and communicate this information to researchers.

12. Discussion: Refining criteria for chemoprevention TPP

Objective

Recap and refine expert input regarding:

- Minimum efficacy and safety requirements.
- Formulations and presentation (e.g. oral, injectable?).
- Dosing frequency – optimal versus minimally acceptable.

Discussion

Alternative dosing and delivery strategies: For antimalarial therapies, and for SMC, treatment is usually initiated by a health worker, even if it is continued at home. If a dosing strategy requires spontaneous initiation of therapy by the recipient (or carer) then adherence would probably be poor.

Ten years ago, monthly SMC appeared impossible, so it may be possible in the future to consider more frequent dosing. However, the preventive efficacy benefits would probably have to be substantial to make weekly dosing cost-effective. Weekly at-home dosing is easier to achieve than a fortnightly dosing regimen, as it is easier to remember. Also, there is now the possibility to use SMS messaging.

Any new delivery system would need to be piloted and the pilot would need to be designed so as to be scalable and implementable beyond the pilot.

SMC is not the only drug given during the rainy season and weekly dosing may be difficult to achieve among the other health campaigns.

In conclusion, if SMC is to be delivered by CHW then monthly dosing is required. If mothers were to be given a supply of drugs at the beginning of the season, then weekly dosing is acceptable, though it would be difficult to manage compliance. A single weekly dose would be preferable.

Delivery to school children: Because SMC is primarily targeted at pre-school children, extension to school aged children could still be achieved via home delivery. School delivery may also be an option, though in many areas the school terms do not coincide with the malaria transmission season.

Sequential monotherapy: Would it be possible to deliver two drugs taken 15 days apart as sequential monotherapy? The packaging would have to be very carefully adapted to the local situation. It would be difficult to calculate the 15-day interval without a reminder, such as an SMS message. It would create a lot of training needs for CHWs and add significantly to their work load for educating carers. For example, it is even difficult to have two first line ACTs being used. 3-day SMC with SPAQ is challenging, so delivering an SMC regimen with more complex dosing needs would be difficult.

Improving on SPAQ: The main issue with SPAQ is that AQ must be dosed for three days. If SP could be combined with a single-dose partner that would be a major improvement in convenience.

Treatment and preventive efficacy would have to be as good as SPAQ; even though the convenience improvement may result in equal effectiveness from a single-dose combination with lower efficacy than SPAQ. The main argument for maximising drug efficacy would be to decrease the potential for the development of resistance. The high uptake of SMC results from the benefits that the community can see, i.e. the reduction in malaria. Any compromise on efficacy outcomes will reduce those benefits and the acceptability of SMC will decrease.

Injectables: It is difficult to confirm that there will be a need for SMC in 10–20 years' time. However, an injectable that could provide protection for 3 months would have more widespread applications than a monthly oral formulation, such as in the management of outbreaks, for MDA and for the military.

Injectable depot formulations are technically difficult to develop. High potency is required and a mechanism for drug release from the depot to the blood is required. Thus, even for PYN and LUM, which already have data for intramuscular injection, the probability of success is low.

13. Synthesis of key considerations from Day 2

Drug development: It may be necessary to distinguish between products that are aimed at replacing SPAQ and those which would be suitable for use in other areas where there are currently no drugs suitable for use in SMC.

It will take 15–20 years before any new drugs is actively deployed in SMC: considerably later than when new medicines would be approved by regulatory agencies. Thus, repurposing of currently available drugs needs to be investigated to provide options for replacing SPAQ should the efficacy of this combination decline. To extend the utility of SPAQ, it is essential that the drugs provided for SMC are of high quality and have improved formulations that increase tolerability and adherence.

It would be useful to have PQP monotherapy to investigate in combination with other drugs. If PQP or PY are used in an SMC combination, then they cannot be used for malaria treatment as a component of ACT. There may be a role for a combination including CQ in areas where resistance to this agent has declined; SP+CQ is not well tolerated, but AZ+CQ may be a possibility.

Future drugs may have roles beyond SMC, for example in MDA and the control of epidemics. Development of TPPs for these different applications may indicate whether one drug could be developed which meets all the necessary criteria. If a drug was suitable for use in SMC, MDA and IPTp, then this would expand its usefulness in the future and protect against the potential decline in the population suitable for receiving SMC. However, developing a drug for use in pregnancy in challenging.

Thought needs to be given to the potential role for a drug that has preventive but not curative properties and whether screening strategies need to be amended to identify such compounds.

The impact of new tools, such as diagnostics, on the distribution and incidence of malaria is unclear. Thus, potential new drugs should not be discounted because they do not have a role to play in the current situation. For example, in the future, it may be desirable to have a drug with liver stage activity as malaria transmission rates decline.

Safety: DDIs cannot be managed in the field and any antimalarial drugs that are to be used across large populations need to be free of DDIs.

Dosing schedule: Weekly or fortnightly dosing of a drug at the full therapeutic dose is concerning on safety grounds; there are no currently available drugs for which weekly dosing in SMC would be accepted. However, should SPAQ fail, the use of monotherapy or more frequent dosing may have to be reconsidered.

In other indications (HIV, TB), drug combinations are given frequently and in the future malaria chemoprevention could be integrated into a healthcare package; SMC is not the only approach that may be relevant.

Implementation: Any drug for SMC needs to be implementable in the field; dosing needs to be as easy as possible, both in terms of dosing frequency and with drugs available in child-friendly formulations. Drugs need to be safe and with good tolerability and acceptability.

Delivery mechanisms are complicated and malaria will find a refuge in hard to reach populations. Thus, drugs and interventions that decrease the stress on health systems are needed.

Once SMC has been introduced and delivery systems established, these need to be maintained as re-establishing this infrastructure is challenging.

Programmatic considerations: SMC needs to be part of a malaria treatment and control policy package, with clear criteria for phasing in as well as out as the context changes. SMC is working well in the areas in which it has been implemented. However, programmatic guidance on when to use

SMC, when not to use SMC and when to stop SMC needs to be clear. There also needs to be regional co-ordination of efficacy, safety and resistance monitoring.

Transmission: SMC saves lives, but in concert with SMC, interventions that decrease transmission rates have to also be implemented.

14. Closing remarks

Without the UNITAID grant, SMC would not have been implemented. SMC is now benefitting millions of children across the Sahel; it is working well, but needs to be sustained. By the end of 2018, there will be a substantial data set on SMC, which will allow refinement of the tool going forward.

It is important to ensure that technical review panels at the Global Fund are briefed (by WHO) on the value of SMC to malaria programs (where it is an appropriate strategy), and that NMCPs include SMC operational costs in their Global Fund grant applications.

The future of these SMC programmes are uncertain, and it is possible that at the end of ACCESS-SMC the infrastructure to deliver this important intervention will collapse. Thus, we must continue to advocate for the value of SMC and for further development of delivery and monitoring systems so that SMC can be continued until it is, hopefully, no longer needed.

List of abbreviations

AQ	amodiaquine
AS	artesunate
AZ	azithromycin
AVPQ	atovaquone-proguanil
CHW	community health worker
CQ	chloroquine
DDI	drug–drug interaction
DHA	dihydroartemisinin
DHA-PQP	dihydroartemisinin + piperaquine
EMA	European Medicines Agency
FDA	US Food and Drug Administration
G6PD	glucose-6-phosphate dehydrogenase
GMP	good manufacturing practices
IPTc	intermittent preventive treatment in children
IPTp	intermittent preventive treatment in pregnancy
LSTMH	London School of Tropical Medicine and Hygiene
MCH	maternal and child health
MDA	mass drug administration
NMCP	National Malaria Control Programme
PQP	piperaquine
PQ	primaquine
SMC	seasonal malaria chemoprevention
SMS	short message service (text messaging)
SPAQ	sulfadoxine-pyrimethamine + amodiaquine
SP	sulfadoxine-pyrimethamine
TCP	target candidate profile
TPP	target product profile
TQ	tafenoquine
TS	trimethoprim-sulfamethoxazole
WHO	World Health Organization
WWARN	WorldWide Antimalarial Resistance Network

References

1. WHO, 2012. WHO policy recommendation: Seasonal malaria chemoprevention (SMC) for *Plasmodium falciparum* malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa. Available at: http://www.who.int/malaria/publications/atoz/who_smc_policy_recommendation/en/.

2. WHO, 2013. Seasonal malaria chemoprevention with sulfadoxine-pyrimethamine plus amodiaquine in children: A field guide. Available at: http://www.who.int/malaria/publications/atoz/9789241504737/en/.

3. Cairns M, Roca-Feltrer A, Garske T, Wilson AL, Diallo D, Milligan PJ, Ghani AC, Greenwood BM, 2012. Estimating the potential public health impact of seasonal malaria chemoprevention in African children. Nat Commun 3: 881. http://www.ncbi.nlm.nih.gov/pubmed/22673908

4. Greenwood BM, Greenwood AM, Bradley AK, Snow RW, Byass P, Hayes RJ, N'Jie AB, 1988. Comparison of two strategies for control of malaria within a primary health care programme in the Gambia. Lancet 1: 1121-7. http://www.ncbi.nlm.nih.gov/pubmed/2896957

5. Menon A, Snow RW, Byass P, Greenwood BM, Hayes RJ, N'Jie AB, 1990. Sustained protection against mortality and morbidity from malaria in rural Gambian children by chemoprophylaxis given by village health workers. Trans R Soc Trop Med Hyg 84: 768-72. http://www.ncbi.nlm.nih.gov/pubmed/2096501

6. Alonso PL, Lindsay SW, Armstrong JR, Conteh M, Hill AG, David PH, Fegan G, de Francisco A, Hall AJ, Shenton FC, et al., 1991. The effect of insecticide-treated bed nets on mortality of Gambian children. Lancet 337: 1499-502. http://www.ncbi.nlm.nih.gov/pubmed/1675368

7. Cisse B, Sokhna C, Boulanger D, Milet J, Ba el H, Richardson K, Hallett R, Sutherland C, Simondon K, Simondon F, Alexander N, Gaye O, Targett G, Lines J, Greenwood B, Trape JF, 2006. Seasonal intermittent preventive treatment with artesunate and sulfadoxine-pyrimethamine for prevention of malaria in Senegalese children: a randomised, placebo-controlled, double-blind trial. Lancet 367: 659-67. http://www.ncbi.nlm.nih.gov/pubmed/16503464

8. Meremikwu MM, Donegan S, Sinclair D, Esu E, Oringanje C, 2012. Intermittent preventive treatment for malaria in children living in areas with seasonal transmission. Cochrane Database Syst Rev 2: CD003756. http://www.ncbi.nlm.nih.gov/pubmed/22336792

9. Greenwood B, Bojang K, Tagbor H, Pagnoni F, 2011. Combining community case management and intermittent preventive treatment for malaria. Trends Parasitol 27: 477-80. http://www.ncbi.nlm.nih.gov/pubmed/21802363

10. US Food and Drug Administration, 2014. Guidance for industry neglected tropical diseases of the developing world: developing drugs for treatment or prevention Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm269221.pdf.

11. US Food and Drug Administration, 2013. Co-development of two or more new investigational drugs for use in combination. Available at: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm236669.pdf.

12. European Medicines Agency, 2005. Article 58 applications: Regulatory and procedural guidance. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000157.jsp&mid=WC0b01ac05800240d1.

13. Andersen SL, Oloo AJ, Gordon DM, Ragama OB, Aleman GM, Berman JD, Tang DB, Dunne MW, Shanks GD, 1998. Successful double-blinded, randomized, placebo-controlled field trial of azithromycin and doxycycline as prophylaxis for malaria in western Kenya. Clin Infect Dis 26: 146-50. http://www.ncbi.nlm.nih.gov/pubmed/9455524

14. Taylor WR, Richie TL, Fryauff DJ, Picarima H, Ohrt C, Tang D, Braitman D, Murphy GS, Widjaja H, Tjitra E, Ganjar A, Jones TR, Basri H, Berman J, 1999. Malaria prophylaxis using azithromycin: a double-blind, placebo-controlled trial in Irian Jaya, Indonesia. Clin Infect Dis 28: 74-81. http://www.ncbi.nlm.nih.gov/pubmed/10028075

15. Ohrt C, Richie TL, Widjaja H, Shanks GD, Fitriadi J, Fryauff DJ, Handschin J, Tang D, Sandjaja B, Tjitra E, Hadiarso L, Watt G, Wignall FS, 1997. Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 126: 963-72. http://www.ncbi.nlm.nih.gov/pubmed/9182474

16. Lell B, Kremsner PG, 2002. Clindamycin as an antimalarial drug: review of clinical trials. Antimicrob Agents Chemother 46: 2315-20. http://www.ncbi.nlm.nih.gov/pubmed/12121898

17. Heppner DG, Jr., Walsh DS, Uthaimongkol N, Tang DB, Tulyayon S, Permpanich B, Wimonwattrawatee T, Chuanak N, Laboonchai A, Sookto P, Brewer TG, McDaniel P, Eamsila C, Yongvanitchit K, Uhl K, Kyle DE, Keep LW, Miller RE, Wongsrichanalai C, 2005. Randomized, controlled, double-blind trial of daily oral azithromycin in adults for the prophylaxis of *Plasmodium vivax* malaria in Western Thailand. Am J Trop Med Hyg 73: 842-9. http://www.ncbi.nlm.nih.gov/pubmed/16282291

18. Porco TC, Gebre T, Ayele B, House J, Keenan J, Zhou Z, Hong KC, Stoller N, Ray KJ, Emerson P, Gaynor BD, Lietman TM, 2009. Effect of mass distribution of azithromycin for trachoma control on overall mortality in Ethiopian children: a randomized trial. JAMA 302: 962-8. http://www.ncbi.nlm.nih.gov/pubmed/19724043

19. Keenan JD, Ayele B, Gebre T, Zerihun M, Zhou Z, House JI, Gaynor BD, Porco TC, Emerson PM, Lietman TM, 2011. Childhood mortality in a cohort treated with mass azithromycin for trachoma. Clin Infect Dis 52: 883-8. http://www.ncbi.nlm.nih.gov/pubmed/21427395

20. Coles CL, Levens J, Seidman JC, Mkocha H, Munoz B, West S, 2012. Mass distribution of azithromycin for trachoma control is associated with short-term reduction in risk of acute lower respiratory infection in young children. Pediatr Infect Dis J 31: 341-6. http://www.ncbi.nlm.nih.gov/pubmed/22173140

21. Coles CL, Seidman JC, Levens J, Mkocha H, Munoz B, West S, 2011. Association of mass treatment with azithromycin in trachoma-endemic communities with short-term reduced risk of diarrhea in young children. Am J Trop Med Hyg 85: 691-6. http://www.ncbi.nlm.nih.gov/pubmed/21976574

22. Gilliams EA, Jumare J, Claassen CW, Thesing PC, Nyirenda OM, Dzinjalamala FK, Taylor T, Plowe CV, Tracy LA, Laufer MK, 2014. Chloroquine-azithromycin combination antimalarial treatment decreases risk of respiratory- and gastrointestinal-tract infections in Malawian children. J Infect Dis 210: 585-92. http://www.ncbi.nlm.nih.gov/pubmed/24652498

23. Cisse B, Cairns M, Faye E, O ND, Faye B, Cames C, Cheng Y, M ND, Lo AC, Simondon K, Trape JF, Faye O, JL ND, Gaye O, Greenwood B, Milligan P, 2009. Randomized trial of piperaquine with sulfadoxine-pyrimethamine or dihydroartemisinin for malaria intermittent preventive treatment in children. PLoS One 4: e7164. http://www.ncbi.nlm.nih.gov/pubmed/19784374

24. Bojang K, Akor F, Bittaye O, Conway D, Bottomley C, Milligan P, Greenwood B, 2010. A randomised trial to compare the safety, tolerability and efficacy of three drug combinations for intermittent preventive treatment in children. PLoS One 5: e11225. http://www.ncbi.nlm.nih.gov/pubmed/20574538

25. Nankabirwa J, Cundill B, Clarke S, Kabatereine N, Rosenthal PJ, Dorsey G, Brooker S, Staedke SG, 2010. Efficacy, safety, and tolerability of three regimens for prevention of malaria: a randomized, placebo-controlled trial in Ugandan schoolchildren. PLoS One 5: e13438. http://www.ncbi.nlm.nih.gov/pubmed/20976051

26. Lwin KM, Phyo AP, Tarning J, Hanpithakpong W, Ashley EA, Lee SJ, Cheah P, Singhasivanon P, White NJ, Lindegardh N, Nosten F, 2012. Randomized, double-blind, placebo-controlled trial

of monthly versus bimonthly dihydroartemisinin-piperaquine chemoprevention in adults at high risk of malaria. Antimicrob Agents Chemother 56: 1571-7. http://www.ncbi.nlm.nih.gov/pubmed/22252804

27. Zongo I, Milligan P, Compaore YD, Some AF, Greenwood B, Tarning J, Rosenthal PJ, Sutherland C, Nosten F, Ouedraogo JB, 2015. Randomized noninferiority trial of dihydroartemisinin-piperaquine compared with sulfadoxine-pyrimethamine plus amodiaquine for seasonal malaria chemoprevention in Burkina Faso. Antimicrob Agents Chemother 59: 4387-96. http://www.ncbi.nlm.nih.gov/pubmed/25918149

28. Nankabirwa JI, Wandera B, Amuge P, Kiwanuka N, Dorsey G, Rosenthal PJ, Brooker SJ, Staedke SG, Kamya MR, 2014. Impact of intermittent preventive treatment with dihydroartemisinin-piperaquine on malaria in Ugandan schoolchildren: a randomized, placebo-controlled trial. Clin Infect Dis 58: 1404-12. http://www.ncbi.nlm.nih.gov/pubmed/24621953

29. Bigira V, Kapisi J, Clark TD, Kinara S, Mwangwa F, Muhindo MK, Osterbauer B, Aweeka FT, Huang L, Achan J, Havlir DV, Rosenthal PJ, Kamya MR, Dorsey G, 2014. Protective efficacy and safety of three antimalarial regimens for the prevention of malaria in young Ugandan children: a randomized controlled trial. PLoS Med 11: e1001689. http://www.ncbi.nlm.nih.gov/pubmed/25093754

30. Kakuru A, Jagannathan P, Muhindo M, Natureeba P, Awori P, Nakalembe M, Opira B, Olwoch P, Ategeka J, Nayebare P, Clark TD, Feeney ME, Charlebois ED, Rizzuto G, Muehlenbachs A, Havlir DH, Kamya MR, Dorsey G, 2016. Dihydroartemisinin-piperaquine for the prevention of malaria in pregnancy. NEJM In press.

31. Conrad MD, LeClair N, Arinaitwe E, Wanzira H, Kakuru A, Bigira V, Muhindo M, Kamya MR, Tappero JW, Greenhouse B, Dorsey G, Rosenthal PJ, 2014. Comparative impacts over 5 years of artemisinin-based combination therapies on *Plasmodium falciparum* polymorphisms that modulate drug sensitivity in Ugandan children. J Infect Dis 210: 344-53. http://www.ncbi.nlm.nih.gov/pubmed/24610872

32. Tumwebaze P, Conrad MD, Walakira A, LeClair N, Byaruhanga O, Nakazibwe C, Kozak B, Bloome J, Okiring J, Kakuru A, Bigira V, Kapisi J, Legac J, Gut J, Cooper RA, Kamya MR, Havlir DV, Dorsey G, Greenhouse B, Nsobya SL, Rosenthal PJ, 2015. Impact of antimalarial treatment and chemoprevention on the drug sensitivity of malaria parasites isolated from ugandan children. Antimicrob Agents Chemother 59: 3018-30. http://www.ncbi.nlm.nih.gov/pubmed/25753626

33. European Medicines Agency, 2011. Assessment report: Eurartesim (dihydroartemisinin / piperaquine phosphate) Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001199/WC500118116.pdf.

34. Kublin JG, Cortese JF, Njunju EM, Mukadam RA, Wirima JJ, Kazembe PN, Djimde AA, Kouriba B, Taylor TE, Plowe CV, 2003. Reemergence of chloroquine-sensitive *Plasmodium falciparum* malaria after cessation of chloroquine use in Malawi. J Infect Dis 187: 1870-5. http://www.ncbi.nlm.nih.gov/pubmed/12792863

35. Laufer MK, Thesing PC, Eddington ND, Masonga R, Dzinjalamala FK, Takala SL, Taylor TE, Plowe CV, 2006. Return of chloroquine antimalarial efficacy in Malawi. N Engl J Med 355: 1959-66. http://www.ncbi.nlm.nih.gov/pubmed/17093247

36. Frosch AE, Laufer MK, Mathanga DP, Takala-Harrison S, Skarbinski J, Claassen CW, Dzinjalamala FK, Plowe CV, 2014. Return of widespread chloroquine-sensitive *Plasmodium falciparum* to Malawi. J Infect Dis 210: 1110-4. http://www.ncbi.nlm.nih.gov/pubmed/24723474

37. Laufer MK, Takala-Harrison S, Dzinjalamala FK, Stine OC, Taylor TE, Plowe CV, 2010. Return of chloroquine-susceptible falciparum malaria in Malawi was a reexpansion of diverse

susceptible parasites. J Infect Dis 202: 801-8.
http://www.ncbi.nlm.nih.gov/pubmed/20662717

38. Laufer MK, Thesing PC, Dzinjalamala FK, Nyirenda OM, Masonga R, Laurens MB, Stokes-Riner A, Taylor TE, Plowe CV, 2012. A longitudinal trial comparing chloroquine as monotherapy or in combination with artesunate, azithromycin or atovaquone-proguanil to treat malaria. PLoS One 7: e42284. http://www.ncbi.nlm.nih.gov/pubmed/22912697

39. Golassa L, Kamugisha E, Ishengoma DS, Baraka V, Shayo A, Baliraine FN, Enweji N, Erko B, Aseffa A, Choy A, Swedberg G, 2015. Identification of large variation in *pfcrt, pfmdr-1* and *pfubp-1* markers in *Plasmodium falciparum* isolates from Ethiopia and Tanzania. Malar J 14: 264. http://www.ncbi.nlm.nih.gov/pubmed/26152336

40. Kiarie WC, Wangai L, Agola E, Kimani FT, Hungu C, 2015. Chloroquine sensitivity: diminished prevalence of chloroquine-resistant gene marker pfcrt-76 13 years after cessation of chloroquine use in Msambweni, Kenya. Malar J 14: 328. http://www.ncbi.nlm.nih.gov/pubmed/26296743

41. Lucchi NW, Komino F, Okoth SA, Goldman I, Onyona P, Wiegand RE, Juma E, Shi YP, Barnwell JW, Udhayakumar V, Kariuki S, 2015. In vitro and molecular surveillance for antimalarial drug resistance in *Plasmodium falciparum* parasites in western Kenya reveals sustained artemisinin sensitivity and increased chloroquine sensitivity. Antimicrob Agents Chemother 59: 7540-7. http://www.ncbi.nlm.nih.gov/pubmed/26392510

42. Sagara I, Oduro AR, Mulenga M, Dieng Y, Ogutu B, Tiono AB, Mugyenyi P, Sie A, Wasunna M, Kain KC, Djimde AA, Sarkar S, Chandra R, Robbins J, Dunne MW, 2014. Efficacy and safety of a combination of azithromycin and chloroquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in two multi-country randomised clinical trials in African adults. Malar J 13: 458. http://www.ncbi.nlm.nih.gov/pubmed/25425434

43. Greenwood BM, David PH, Otoo-Forbes LN, Allen SJ, Alonso PL, Armstrong Schellenberg JR, Byass P, Hurwitz M, Menon A, Snow RW, 1995. Mortality and morbidity from malaria after stopping malaria chemoprophylaxis. Trans R Soc Trop Med Hyg 89: 629-33. http://www.ncbi.nlm.nih.gov/pubmed/8594677

44. Aponte JJ, Menendez C, Schellenberg D, Kahigwa E, Mshinda H, Vountasou P, Tanner M, Alonso PL, 2007. Age interactions in the development of naturally acquired immunity to *Plasmodium falciparum* and its clinical presentation. PLoS Med 4: e242. http://www.ncbi.nlm.nih.gov/pubmed/17676985

45. Konate AT, Yaro JB, Ouedraogo AZ, Diarra A, Gansane A, Soulama I, Kangoye DT, Kabore Y, Ouedraogo E, Ouedraogo A, Tiono AB, Ouedraogo IN, Chandramohan D, Cousens S, Milligan PJ, Sirima SB, Greenwood BM, Diallo DA, 2011. Morbidity from malaria in children in the year after they had received intermittent preventive treatment of malaria: a randomised trial. PLoS One 6: e23391. http://www.ncbi.nlm.nih.gov/pubmed/21858097

46. Dicko A, Barry A, Dicko M, Diallo AI, Tembine I, Dicko Y, Dara N, Sidibe Y, Santara G, Conare T, Chandramohan D, Cousens S, Milligan PJ, Diallo DA, Doumbo OK, Greenwood B, 2011. Malaria morbidity in children in the year after they had received intermittent preventive treatment of malaria in Mali: a randomized control trial. PLoS One 6: e23390. http://www.ncbi.nlm.nih.gov/pubmed/21858096

47. Ding XC, Ubben D, Wells TN, 2012. A framework for assessing the risk of resistance for anti-malarials in development. Malar J 11: 292. http://www.ncbi.nlm.nih.gov/pubmed/22913649

Appendix 1: Meeting participants

Chair

Dr David McGibney, McGibney & Company Limited

Speakers and advisers

Prof. Umberto d'Alessandro, MRC, The Gambia

Dr Valentina Buj, UNICEF

Prof. Daniel Chandramohan, LSTMH, UK

Dr Robert Clay, Highbury Regulatory Science, UK

Prof. Abdoulaye Djimdé, MRTC, University of Bamako, Mali

Prof. Grant Dorsey, UCSF School of Medicine, USA

Prof. Brian Greenwood, LSHTM, UK

Dr Prudence Hamade, Malaria Consortium

Prof. Feiko ter Kuile, LSTM, UK

Prof. Miriam Laufer, University of Maryland, USA

Dr Paul Milligan, LSHTM, UK

Prof. Jean Louis Ndiaye, Cheick Anta Diop University, Senegal

Dr Peter Olumese, WHO-GMP, Switzerland

Prof. Philip Rosenthal, UCSF School of Medicine, USA

Prof. David Schellenberg, LSTMH, UK

Dr Laurence Slutsker, CDC Center for Global Health (CGH), USA

Dr Issaka Zongo, IRSS, Burkina Faso

MMV

Stephan Duparc, Chief Medical Officer, Research & Development

George Jagoe, Executive Vice President, Access & Product Management

Fiona Macintyre, Director, Clinical Development, Research & Development

Thomas Rueckle, Director, Translational Medicine, Research and Development

André-Marie Tchouatieu, Associate Director, Access & Product Management

Kim van der Weijde, Intern, Access & Product Management

Tim Wells, Chief Scientific Officer, Research & Development

Rapporteur

Naomi Richardson, Magenta Communications Ltd

Appendix 2: Meeting agenda

Day 1	Topic, objectives and key questions	Presenter/ facilitator
09.15 – 09.30	**Introductions, agenda review and objectives of the meeting**	**D. McGibney (Chair) / G. Jagoe**
09.30 – 10.00	**WHO Policy and Perspectives re: Seasonal Malaria Chemoprevention** • *Evidence to support policy adoption of chemoprevention tools* • *Contrasting drugs for mass-drug administration supporting elimination versus mass chemoprevention of malaria*	**P. Olumese**
10.00 – 10.30	**The development of SMC** *Objective:* Describe lessons learned from development of SMC using SPAQ to inform development of next generation chemoprevention treatments.	**B. Greenwood**
10.30 – 10.45	**Implementation perspectives after roll out of SMC** *Objective:* Provide observations from rollout of SMC using SPAQ to inform development of next generation SMC drugs	**P. Hamade**
10.45 – 11.15	**Field experiences and expectations – recent research from SMC implementing countries** *Objective:* Review preliminary results of field survey on implementation experiences with SPAQ and practitioners' expected attributes for next generation chemoprevention	**A. Tchouatieu**
11.30 – 12.15	**Regulatory considerations for chemoprevention** *Key issues:* • *What is the difference between prophylaxis and chemoprevention from a regulatory perspective?* • *What strategies may support regulatory review of chemoprevention drugs without requirements for demonstration of curative efficacy?* • *What are the minimum safety data required for registration of chemoprevention drugs?*	**R. Clay**
12.15 – 13.00	**MMV's target candidates profiles** *MMV's TCP4 for categorizing development candidates as chemoprevention targets*	**T. Wells**
14.00 – 17.00 **(15 to 20 min per speaker)**	**Chemoprevention 2016 – considerations for re-purposing existing medicines to expand SMC impact** *Objective:* NCEs as novel chemoprevention options will require an estimated 4-5 years before approval. Meanwhile, alternative combinations of existing medicines might help fill gaps related to SPAQ's use in chemoprevention. *In this session, speakers will provide perspectives and research updates on medicines under consideration to expand the impact of seasonal malaria chemoprevention*	
	The role of antibiotics in malaria chemoprevention	**D. Chandramohan**
	Impact of SMC in children up to 10 years from the national implementation in Senegal	**J.L. Ndiaye**
	SMC in Burkina Faso with Dihydroartemisinin - piperaquine and SP+AQ: A Randomized Non inferiority trial	**I. Zongo**

14.00 – 17.00 (15 to 20 min per speaker)	Chemoprevention in non-seasonal malaria transmission settings	P. Rosenthal/ G. Dorsey *(by dial-in)*
	Is there a role for chloroquine in sub-Saharan Africa?	M. Laufer
	Safety considerations and resistance monitoring in SMC implementation	P. Milligan
17.00 – 17.30	**Synthesis of key considerations from Day 1 proceedings**	D. McGibney N. Richardson, rapporteur
Day 2	**Topic**	**Presenter**
09.00 – 09.15	**Opening reflections on Day 1 and review of Day 2**	D. McGibney
09.15 – 10.00	**Safety considerations and data requirements for clinical studies in SMC** • *What minimum drug safety requirements must be established <u>before</u> chemoprotection studies begin?* • *How do clinical data requirements differ for chemoprevention trials vs treatment trials?*	S. Duparc (facilitator)
10.00 – 10.45	**Discussion: Immunology and chemoprevention** • *Risks of rebound after cessation of chemoprevention – what we know, what we still need to learn?* • *Interactions between chemoprevention and infection-immunity: can chemoprevention offer protection while permitting development of malaria premunition?*	Facilitator: B. Greenwood
10.45 – 11.15	**New molecules for chemoprevention** *Objective:* Review methods for assessing candidates in MMV's portfolio for TCP4 • *Compounds in development with tissue schizonticide activity for causal prophylaxis;* • *Screening cascade: cell models, animal models, and human challenge models, phase IIa assessments.* • *Blood schizonticides: human challenge models and phase IIa assessments*	T. Wells
11.30 – 12.15	**Discussion: Refining criteria for chemoprevention TPP** *Objective:* Recap and refine expert input re: • *Minimum efficacy and safety requirements* • *Formulations and presentation (e.g. oral, injectable?)* • *Dosing frequency– optimal vs minimally acceptable*	**MMV Facilitation T. Wells / G. Jagoe / S. Duparc**
12.15 – 12.45	**Summary of Day 2 discussions and meeting conclusion**	D. McGibney and N. Richardson
12:45 – 13.00	**Acknowledgements and meeting closure**	G. Jagoe