World Health Organization

Questions & answers

Day 1

Report from the Director

1. **Q: Countries are endorsing the R21 Oxford vaccine. What is WHO's response to that and what will be GMP's guidance to countries?**
   R: It is not unexpected that National Regulatory Authorities (NRAs) would evaluate a vaccine for use in their own jurisdictions. These approvals do not affect the processes, already underway, by which WHO is reviewing R21/Matrix-M. WHO has a global mandate to review the quality, safety, efficacy and programmatic suitability of new vaccines to provide guidance to low and middle-income countries (LMICs). WHO policy recommendation and WHO prequalification are prerequisites for UNICEF vaccine procurement and funding support for vaccine deployment by Gavi, the Vaccine Alliance. Understanding the high demand and potential for high impact of malaria vaccines, WHO is expediting the review processes.

2. **Q: If ITNs last nearly 2 years, why does WHO not change the guidelines to reflect this reality?**
   R: The WHO guidelines are not fixed to a 3-year distribution schedule. As noted in the "Achieving and maintaining optimal coverage with ITNs for malaria prevention and control" section of the Vector Control section, it is stated: "Campaigns should also normally be planned to be repeated every 3 years, unless available empirical evidence justifies the use of a longer or shorter interval between campaigns." This guidance is based on past experience and present realities concerning the logistical challenges of organizing campaigns and available budget to purchase the required nets. It does not say that all ITNs last 3 years."

3. **Q: Can we have a home self-malaria testing kit, particularly for the malaria endemic regions, if helpful in preventing self-medication with antimalarials? Unjudicial self-medication has contributed to antimalarial resistance to drugs, a tremendous threat to the efforts in the fight against malaria.**
   R: WHO does not recommend a home self-malaria testing kit as malaria is an acute febrile illness which needs immediate diagnosis and effective treatment. Initial evidence on travellers has not provided support that malaria self-testing with RDTs is safe and effective. WHO recommends early malaria diagnosis and treatment by trained providers, as close to home as possible.

4. **Q: Interested to see that a New Strategic Information Technical Advisory Group (MSI – TAG) is being formed. What is the remit of this group?**
   R: Following the launch of the *Global technical strategy 2016-2030*, the 2018 launch of the WHO malaria surveillance reference manual, and recent changes in the WHO malaria guidelines process, WHO is establishing a standing technical advisory body, the Malaria Strategic Information Technical Advisory Group (MSI-TAG), to support the strengthening of

surveillance, monitoring and evaluation systems and the strategic use of information to accelerate the impact of national malaria programmes. In its capacity as an advisory body to WHO, the MSI-TAG shall have the following functions:

1. To provide WHO with independent evaluation of the scientific, technical and strategic aspects of malaria surveillance, monitoring and evaluation.

2. To recommend priorities to WHO and relevant technical units at all levels of the organization to strengthen national malaria surveillance, monitoring and evaluation systems and the use of data for decision making, including the installation of digital solutions and the assessment of surveillance systems.

3. To advise WHO on approaches to enhance the use of data for national and subnational decision making to support efficient, effective and equitable implementation of malaria interventions to communities.

4. To support WHO to review and improve the methods for estimation of the malaria burden, investments, interventions and impact for tracking global progress through the annual World Malaria Report.

5. **Q: Hybrid trainings in malaria - excellent idea. Any timelines/road map?**
R: As part of capacity building efforts in high burden countries, hybrid trainings (which involve a mix of in-person and virtual participation) are being considered by WHO, especially in the African region. This approach would be more cost-effective than trainings that are fully in-person.

6. **Q: In India, should we follow MSAT for malaria elimination, because we found after several rounds there is decline of malaria cases both as fever and non-fever case?**
R: Currently, mass testing and treatment (MTaT) to reduce the transmission of malaria in countries or areas that have attained very low to low levels of transmission is not recommended. The Guidelines Development Group (GDG) judged that there was moderate certainty evidence that MTaT had a trivial impact on malaria prevalence and incidence. Although there may be some benefit to health equity by reaching people who may otherwise have difficulty accessing malaria diagnostic and testing services, and the intervention was found to be acceptable to stakeholders and feasible to implement, the resources required to implement MTaT were considered to be large. The GDG felt that there may be transmission foci in very low transmission settings where an MTaT intervention could be beneficial but decided to provide a conditional recommendation against implementing MTaT to reduce the transmission of malaria. More information on interventions in the final phase of elimination and prevention of re-establishment, including evidence based on which the specific recommendation was made, can be found on the following page: https://www.who.int/publications/i/item/guidelines-for-malaria.

7. **Comment:** Insecticide-treated nets have since become a core intervention for malaria control and have contributed greatly to the dramatic decline in disease incidence and malaria-related deaths seen since the turn of the millennium. However, this time period has also seen a rise in resistance to pyrethroids (the insecticide used in ITNs), raising questions over whether the evidence from trials conducted before resistance became widespread can be applied to estimate the impact of ITNs on malaria transmission today.

8. **Comment:** Health system weaknesses in malaria-endemic countries are a function of multiple factors that greatly limit the effectiveness of health commodities, thereby compromising both quality and timeliness of care. Countries particularly need good

governance to ensure adequate resource acquisition and utilization, engage effectively with other relevant sectors, and ensure that all components of the health system function at equilibrium.

9. **Comment**: Improved diagnostics are necessary to address challenges such as the rise of HRP2/3 gene deletions or poor validity of existing diagnostics in low-transmission settings. Ultra-sensitive malaria rapid diagnostic tests have been proposed to improve detection under low transmission intensities or low parasite densities but risk biasing clinical management away from other febrile illnesses. From a health systems perspective, the introduction of new diagnostic tools must therefore be part of a broader strategy for case finding and management, instead of purely focusing on the tools.

10. **Comment**: Any minimum essential data packages should also consider relevant genomic data and address the associated challenges with computing infrastructure, genetic sequencing capabilities, and data sharing guidelines. The need for malaria molecular surveillance is increasingly evident in varying epidemiological settings to address multiple use cases. including enabling National Malaria Programs and partners to plan or deploy interventions proactively. Mathematical modelling may address some of these gaps by helping define the minimal essential data needs in space and time and focus areas, designing surveillance-response systems and making vital projections and resource allocation. However, such strategies face even greater limitations in requisite skill-sets in endemic countries.

11. **Comment:** Malaria control is now mostly dependent on commodities, namely drugs, diagnostics, medicines, and insecticides, which are imperfect and often deployed and used imperfectly. The commodities also must be replenished regularly, even as resistance spreads, manufacturing costs rise, and at-risk populations increase. This “commoditization of malaria control” also has caused significant declines in practical malaria expertise in endemic countries and instead incentivized fringe and disconnected players focusing on distribution and performance of the commodities.

12. **Comment:** Major players regularly report short-term outputs, such as the number of treatment doses delivered, ITNs distributed, or houses sprayed, with only weak connections to epidemiological impact or effective delivery and use of these commodities. Indeed, there have been more than two billion ITNs and one billion doses of child ACT formulations delivered, yet key malaria trends are stagnating. These decisions raise multiple questions, including whether the products meet actual quality thresholds or if there are certain imperfections. For example, despite manufacturer claims that ITNs last more than 3 years and 20 washes, recent studies suggest these nets last far shorter periods.

13. **Comment:** Moreover, while ITNs and indoor residual spraying (IRS) effectively tackle indoor-biting and indoor-resting mosquitoes, their effectiveness is limited in areas where significant biting happens outside homes or sleeping hours. Another question is whether delivery of the commodities sufficiently covers all at-risk demographic groups, and commonly disenfranchised groups such as migrant and nomadic populations. Lastly, it demonstrates the importance of concurrent investments to build resilience in health systems and the environment and to build requisite human resource capacity to sustain gains catalysed by current commodities and minimize the decay of effectiveness.

14. **Comment:** Beyond direct investments for malaria control, there is a need to accelerate investments for R&D, especially on potentially transformative tools such as vaccines and gene drive mosquitoes. Besides the many technical challenges of developing transformative technologies, particularly vaccines, the innovation pathway for malaria remains poorly funded and takes far longer than other diseases. It is worth noting that malaria etiology was first described in 1880, yet no viable vaccine has achieved full approval. In rethinking malaria, African Governments in particular must stop the rhetoric and increase investments in control and R&D for a disease that remains a leading killer on the continent. Given the reality of significant funding gaps, the growth of indigenous funding should not be interpreted as a reason to reduce international funding.
    *https://pubmed.ncbi.nlm.nih.gov/22521906 *https://ourworldindata.org/vaccination

15. **Comment:** The issues raised above are only key examples of the many quandaries of malaria control and elimination programs in Africa. Other challenges include: i) political instability, conflicts, and displacements in some countries, which may compromise efforts to strengthen health systems, conduct relevant research or develop practical tools; ii) disconnected health care systems through ill-defined pluralism and too many partners often working without unified strategies; iii) varied cultural beliefs and unproven traditional practices about malaria and its management, which may reduce appropriate health-seeking and compromise effectiveness of case management; iv) other disease epidemics such as COVID-19 and Ebola, which may disrupt implementation of malaria control activities and reduce political commitments on malaria; v) the looming threat of climate change, which could further expand the geographic range of transmission, increase population vulnerabilities, and reverse previous gains; vi) replacement vectors or invasive vector species such as *Anopheles stephensi*, now established in the horn of Africa, and their potential to spread; and vii) inadequate communication leading to insufficient community knowledge and participation, viii) some human behaviours and practices which reduce compliance to interventions and ix) the steadily increasing populations in endemic countries leading to greater demand for malaria control.

16. **Comment:** Rethinking malaria control and elimination strategies is imperative. Holistic and systemic approaches that include communities and households to effectively stop transmission and deaths are needed. The exceptionally challenging epidemiology of malaria in Africa requires context-specific initiatives tailored to national and subnational targets. In addition, endemic countries should address the weaknesses in their health systems, improve the quality and use of data for surveillance-responses, improve technical and leadership competencies for malaria control and reduce overreliance on commodities while expanding multisectoral initiatives. The countries should also invest more in malaria control as well as on key research and development agenda, including on potentially transformative technologies such as vaccines and gene drives. Lastly, to complement these efforts, countries should build requisite resilience and capacity to broadly enhance infectious disease control.

17. **Q: There were so many good questions in the morning session and not enough time for Q&A, would it be possible to have slightly shorter presentations to allow more time for questions and discussion amongst MPAG members?**
    R: Thank you for the suggestion. This issue was discussed during the closed MPAG session and it was agreed to allow more time for Q&A in future MPAG meetings.

WHO guidelines for malaria

18. **Q: What does "pending review by GMP for expansion of recommendations for IRS" mean on a prequalified product? (this statement is on the new Vectron IRS products listing on the PQ website). This is confusing as I thought PQ was the Gold standard in terms of WHO recommendation for use of products. Does this mean that the product can be procured for IRS by donors or not?**
R: A listing by the WHO Prequalification Team (PQT) is issued when a product meets the requirements to be prequalified by WHO in terms of quality, safety and efficacy; this listing is independent from a WHO recommendation issued by a technical department. The expansion of the WHO recommendation for IRS to cover the use of new insecticide classes in malaria vector control requires comparative entomological data to allow non-inferiority analyses to be undertaken.

    As communicated under the responses regarding non-inferiority studies below, GMP launched a recent data call to conduct such assessments. A technical consultation was held in June 2023 to review these data and determine whether an extension of the recommendation is warranted. This approach is consistent with that used in 2017 when the IRS recommendation was extended to include neonicotinoid insecticides. Based on the outcome of the June 2023 review, the IRS recommendation was extended to cover broflanilide, which is reflected in the latest update of the *WHO guidelines for malaria*, published in October 2023.

19. **Q: How is cost effectiveness being determined on, what appears to be, a brand-by-brand basis? Considering the changing prices of ITNs over the years, and the fact that many are very similar in price now (even dual AI nets), how can a negative cost effectiveness be determined, and will it be reviewed as prices adjust over time? This seems to be a difficult metric to define and keep relevant.**
R: For each intervention, the guidelines provide more detail as to whether cost or cost-effectiveness evidence was considered by the Guidelines Development Group when formulating recommendations, and where such data were drawn from. For some interventions, the systematic review reported individual costs and cost effectiveness (where this is the case, the systematic report is cited and can be accessed to understand the data provided). It is recognised and articulated in the guidelines as to the limitation and caveats of these data, which are often historical and site- and/or study-specific. Countries are therefore encouraged to use current costings, for example from their ITN tenders, and local data to inform their decision-making.

20. **Q: Why is cost effectiveness being used in policy? The data used for the pyriproxyfen nets is already out of date (the price has changed) and calculations are only relevant for that particular environment (parameters will change).**
R: Please see response provided above. Please also refer to the *WHO handbook for guideline development, 2nd edition* which provides further details on the process and the consideration of resource use and cost-effectiveness within it.

21. **Comment:** Malaria control recommendations really vary according to species and this is only one size fits all. For example control needs for *An. stephensi* needs different interventions especially larviciding

22. **Q: Are there any recommendation or guidance on when to rotate between different classes of active ingredient i.e. between the new dual active nets?**
R: In the *WHO guidelines for malaria,* it is recommended that vector control programmes should avoid using a single class of insecticide everywhere and over consecutive years. Options of how this may be conducted are also provided in the guidelines, and the overarching concepts of such resistance management strategies were originally outlined in the *Global plan for insecticide resistance management in malaria vectors* (GPIRM) in 2012. How and when rotations of insecticide classes or other methods of resistance management are conducted is largely dependent on context and would likely be impacted by many aspects, not only considerations of emerging/increasing frequency or intensity of insecticide resistance in local vectors, but also considerations of feasibility and logistics, for example. Countries are therefore recommended to use local data to inform such decisions.

23. **Comment:** Much reliance seems to be being placed on dual ai nets. While these are definitely an improvement on pyrethroid only nets, where there are significant levels of pyrethroid resistance, employing dual ai nets is effectively still only a monotherapy so we need to monitor resistance to these new products very carefully and should encourage countries to maintain and expand IRS programs using other chemistries to help maintain susceptibility in mosquito populations.

24. **Q: Please clarify how cost-effectiveness is used for a policy recommendation. Without exception, the cost of new tools always changes (ACT -50%, RDTs -50%, ...) and the effectiveness of a tool varies by epidemiological setting (difference between EIR of 1 versus 300). It seems that blanket statements on cost-effectiveness are unhelpful and should not be used to define policy. Countries should define what they feel is cost effective at a given point in time for a given setting.**
R: Please see earlier response. The guidelines encourage countries to generate and use their own local data when formulating their own policies for appropriate malaria control.

25. **Q: Wouldn't it be more pragmatic to provide methodology to guide countries around how to calculate cost effectiveness for the relevant interventions in their own settings rather than include one point of data in a policy that becomes out of date the day it is published?**
R: There is already an ample amount of literature in the public domain on the generation of cost-effectiveness data, and GMP has hence not identified a need to develop or provide this to WHO member states. Within the guidelines process, information on resource use and cost-effectiveness is one of the factors that are used to determine the direction and strength of a recommendation (see chapter 10 of the WHO Handbook for Guidelines Development). Like other evidence used to inform the development of a recommendation, it is understood that the data provided to WHO will evolve over time and may, in due course, require a revisit of a recommendation. The guidelines process we have in place, including dissemination via MAGICapp, provide a ready meant to update the WHO Guidelines for malaria relatively quickly once new data are available to inform discussions by our Guidelines Development Group. With regards to the use of cost-effectiveness in informing the decision-making processes of WHO Member States, we do provide a list of the resources required to deliver each recommended intervention, so that these ingredients can be costed locally and be combined, where feasible, with local effectiveness data. For the ITNs themselves, countries should draw on the price quote to them as part of their tenders, not on data used in the WHO guidelines,

26. **Q: Why is atovaquone proguanil not included at all in the treatment guidelines? Is there a rationale for this exclusion?**
    R: The current consolidated malaria treatment guidelines do not include malaria chemoprophylaxis. All WHO recommended options for malaria chemoprophylaxis, including atovaquone-proguanil, are included in the WHO publication "International Travel and Health" (see 2020 malaria update).

27. **Q: Y a-t-il des retours sur les tests rapides de dépistage du déficit en G6PD ? Quelle est la position de l'OMS à ces sujets ? des tests approuvés par l'OMS?**
    R: WHO will convene a Guidelines Development Group in 2023 to develop recommendations on near patients G6PD test, including G6PD tests. WHO has developed a guide to conduct point-of-case testing of G6PD deficiency using currently available rapid diagnostic tests.

Comparative assessment

28. **Comment:** Numerous concerns have been raised about non-inferiority and the recent data call **and** product developers (in the I2I industry group) have raised a number of issues with this process.

29. **Comment:** 1) Data call was not clearly publicised with many developers only finding out two weeks after the call was posted. 2) The rationale for the call is unclear and unspecific in terms of data requirements. Compare this with the PQ data call which was very clear about the data required, why it was needed and what the purpose was. This has caused a lot of confusion amongst developers. 3) There is a lot of concern about the lack of coordination with PQ on this as they were clearly not informed about the call in. Product developers rely on the clarity of the evaluation process based on their pathway assessment in the PCC meeting, and there are concerns that now products in the PQ pathway can now be considered to require NI data. This erodes the clarity and trust in the WHO evaluation process. 4) Although a review of NI for IRS was indicated at the VCWG there is very little detail as to why. The fact that a recently listed IRS product that has a caveat on its listing regarding a pending policy review suggests that non-inferiority for IRS is already being implemented with no notification to developers. Overall, the uncertainty over this initiative has caused huge confusion amongst the community and developers. The clarity in terms of process and communication they have enjoyed with the PQ process has been eroded and some developers have indicated that they are considering withdrawing their products if this lack of clarity continues.

30. **Q: Overall, the gains in terms of predictability and clarity (in terms of VCAG and PQ) over the past few years are now under threat, and this is causing significant confusion. Considering that PQ is finalising its ITN guideline now, would it not make sense for that to be published and then look at whether there is a need for non-inferiority rather than appear to duplicate parts of that process? Secondly, there appears to be no clear rationale for non-inferiority for IRS. It appears that WHO is moving away from its stated product classes to assessing products on their chemical components and not their entomological effect, is this a change in policy or is WHO still focused on entomological effect as has been previously stated?**
    R. We do not share the expressed sentiment that predictability and clarity are under threat, nor is this statement representative of the comments WHO has received from many partners and regional colleagues. The vector control evaluation process has evolved since 2017 and will continue to do so to accommodate needs identified by our technical advisory groups and WHO Member States, and to stay in sync with other ongoing developments

across WHO, such as the evolution of the guidelines process. We will endeavour to clearly communicate any changes associated with this evolution once the required internal discussions have taken place.

Publication of updated ITN testing guidance for data generation to support a prequalification assessment is certainly welcome. It should be noted, however, that this guidance is primarily designed to meet the need of prequalification, and not necessarily the need of technical departments to develop WHO recommendations, which are a separate WHO output. From the publicly shared draft it does not appear that these testing guidelines are aiming to address the issue of an explicit comparison with the current standard of care, which is the purpose of comparative effectiveness assessments. GMP is therefore updating its 2019 guidance on the data requirements and protocol to allow comparative efficacy assessments, which will provide an evidence base to determine which products fall under an existing WHO recommendation, where recommendations may need to be extended, and where a new WHO recommendation may need to be developed. Discussion on the role of comparative efficacy assessments as part of guidelines development were held with the WHO Guidelines Review Committee in 2023, and the outcome of these discussions will be shared at the October 2023 MPAG meeting.

We would like to clarify that there are no "product classes". There are stated "intervention classes" that are either confirmed (based on epidemiological impact having been demonstrated and a WHO recommendation being in place) or tentative (where no disease impact has been demonstrated). Products are assigned to these intervention classes upon receipt of a Determination of Pathway Request by as part of the PCC process. It should also be noted that these intervention classes are not the same as a WHO recommendation, but were established to indicate at which level epidemiological evidence needs to be generated (i.e. ≥ 2 trials per class).

WHO recommendations will initially be developed at the level of the intervention class, based on the epidemiological evidence generated by a first-in-class product, but will need to evolve to capture the proliferation and diversity of products under a class. This can, for example, be demonstrated by taking a closer look at the intervention class of "ITNs designed to kill host-seeking insecticide-resistant mosquitoes for which a first-in-class product has demonstrated public health value compared to the epidemiological impact of pyrethroid-only nets". Under this intervention class there are now three separate WHO recommendations – one for pyrethroid-PBO nets, and two for pyrethroid-chlorfenapyr nets.

Similarly, GMP has been advised by the GRC that the WHO recommendation for IRS would not be applicable to paints, as it requires a separate evidence-to-decision process to be conducted. Comparative efficacy data already play an important role in this context and will become of increasing relevance as it provides an entomological evidence base to inform GDG deliberations to allow for extension of recommendations or inform the development of new ones without products having to generate epidemiological impact data (provided that non-inferiority can be demonstrated).

31. **Q: PPCs are intended to encourage innovation and provide "Preferred Product Characteristics" for new products in order to help guide planning and development. Does WHO now suggest that PPCs should be used in policy making?**
R: PPCs serve primarily to indicate an identified public health need, and by doing so to stimulate innovation in this area. They contain information on how products will be evaluated and on the standards that should ideally be met. Vector control PPCs are consistent with this approach. Clearly the epidemiological and entomological data generated will be of relevance to the development and implementation of normative guidance.

32. **Q: Fast/slow acting is a relative measure of a mortality endpoint and so is subjective. However, following the review of Sumishield, why wasn't the policy for IRS extended to other 'slow acting compounds'?**
R: Percentage mortality is the key endpoint currently used in the WHO testing guidelines. It may be subjective, but it is the best we currently have. Any change to it would need to be informed by data indicating why a different threshold would be more appropriate and what such a threshold would consist of. Killing mosquitoes is clearly key to achieving impact of IRS against malaria. Extrapolation of data from one insecticide class to another, as proposed in the comment, would not be appropriate nor was another insecticide class being assessed at the time neonicotinoids were presented to WHO.

33. **Q: Is it likely that WHO will also adopt comparative effectiveness for other interventions, such as new antimalarial and vaccines in the future?**
R: As indicated in the presentation, GMP has initiated broader discussions on comparative assessments within WHO and will provide updates on the outcomes of these discussions in due course. With respect to vaccines, the current PPC does not require non-inferiority trials for malaria vaccines. However, recent trials have shown that different vaccine efficacy estimates can be achieved dependant on transmission intensity, vaccine schedule, length of follow up, other interventions in place (e.g. SMC) and potentially other contextual factors, including access to care. These all need to be considered when considering estimates of efficacy.

34. **Q: The process around non-inferiority is really not clear. When does non-inferiority data need to be generated? How does it change when the standard of care changes? Is it relevant to all products or only some? Why is this needed when there is a robust product evaluation system under PQ?**
R: R: WHO has noted the request for further clarification on comparative assessments and will provide such detail in due course. The document Norms, standards and processes underpinning development of WHO recommendations on vector control will be updated accordingly. With regard to the rationale and history behind this, we would kindly ask the reader to consult the relevant WHO technical consultation and MPAG reports, where the rationale has been repeatedly outlined. It should be noted that comparative efficacy assessments are used in the context of WHO recommendations, and not in the context of prequalification. A WHO recommendation and a WHO prequalification listing are two independent outcomes of a WHO evaluation process, each with its own requirements.

35. **Comment**: It is PQ's job to evaluate manufacturing changes and ensure the product still complies.

36. **Comment:** As BMGF we believe that the policy and product evaluation process was a major step forward to accelerate access to much needed new vector control tools to address resistance. HOWEVER, the process seems to have taken a step back with request for additional data which seems to go against the originally proposed process. For a WELL DEFINED class, product should only go through PQ. HOWEVER, the data call AND the repeated concerns voiced by MPAG seem to suggest that either classes are ill defined or GMP disagrees with the policy and product evaluation process.

37. **Q: It is unclear what a comparative efficacy data evaluation by GMP adds on top of PQ's product evaluation. When the epidemiological trial is used by GMP to define a new class, the typical process in recent years has been for PQ to evaluate safety/quality/efficacy for**

second in class. GMP also looking at efficacy seems to be creating a parallel pesticide evaluation scheme, and it had been decided to shift away from WHOPES model. Why is PQ approval not enough for inclusion under policy as a second-in-class?
R: The data as such are no different – they are entomological efficacy data. All that comparative assessment requires is that the studies used to generate these data include a comparator (first-in-class or appropriate other type of standard care) and are adequately powered. This is best practice in the valuation of clinical interventions and should be seen as no different for vector control products. Being able to compare entomological efficacy of a second-in-class product to a reference product for which epidemiological impact data are available provides some assurance that such disease impact may also be obtained by any product not required to generate epidemiological data, and by doing so that the broad class groupings used by WHO are appropriate and remain linked to the WHO recommendations covering classes. Comparison of products or validating any links to disease impact is not part of PQTs mandate, explaining why a WHO listing isn't sufficient with regards to normative guidance on disease control.

38. **Comment:** The notion that non-inferiority allows you to define which product to prioritize seems flawed as it only tells you that one product is not worse that another, even if the second-in-class product is actually superior.

39. **Q: This seems to be quite a bit more than a communication issue. It seems to be confusing the process that had been clearly laid out of what is a policy question and what is a PQ question. There was a lot of clarity in VCR's May 2019 presentation, and this data call seems to add a parallel process to policy and PQ listing with unclear implications for decision making. If PQ approves multiple chlorfenapyr-based nets within GMP's chlorfenapyr net policy, why would additional comparative efficacy evaluation from GMP across those nets do anything more than undercut the value of PQ listing? While WHO needs to evaluate entomological data for second in class, that seems to be a PQ duty rather than GMP.**
R: Comparative assessment is not part of the PQT process but is required to provide some assurance that similar disease impact may be achieved by products not required to generate epidemiological data. The process for assessing these data could be conducted by PQT, the technical departments or a combination of these, but for now is led by GMP to meet its identified needs. A review of roles and responsibilities associated with vector control evaluation will be conducted and may inform changes to where the assessment of comparative data is housed within WHO.

40. **Comment:** this non-inferiority approach has always been communicated as "Exploratory" so I **don't** agree this is a communication issue.

41. **Q: It would be useful to have clarity on what is GMP's role versus PQ's role and what WHO as an organization intends to convey by a PQ listing.**
R: WHO has noted the request for further clarification on comparative assessments and will provide such detail in due course. Current roles and responsibilities are outlined in annex 2 of the WHO document 'Norms, standards and processes underpinning development of WHO recommendations on vector control' published in 2020. The document is undergoing an update to reflect the role of comparative effectiveness assessments and the respective roles and responsibilities of the WHO departments involved. In brief, WHO's PQ listings convey that a product has met the prequalification standards of quality, safety and efficacy; this is different from a WHO recommendation developed via the WHO guidelines process.

42. **Q: So GMP is building a parallel evaluation system, akin to WHOPES?**
R: WHO has, for many years, had two parallel systems: one focused on the prequalification of health products, the other on the development of WHO recommendations in the form of guidelines. There is no intention to re-create WHOPES, under which these two functions were combined and which differed from WHO-at-large functions. WHO is currently undertaking an organization-wide effort to better align the two systems to ensure that PQ listings are supported by a WHO recommendation, and vice versa, and to minimize delays from the submission of data to a listing and a recommendation being issued.

43. **Comment:** While communications have come up, and certainly need to be improved, the key issues underly this process around the definition of product classes and how non-inferiority works with the PQ evaluation. There needs to be a recognition that PQ is currently updating its guidelines for ITN evaluation so developing another process that isn't coherent with that will lead to confusion. There needs to be predictability and clarity in the evaluation process to allow developers and their partners to develop their product development investments. How this approach relates to the new PQ guidelines is totally unclear and has not been addressed.

44. **Comment:** IVCC welcomes the focus on improved communication concerning the requirements and processes for inclusion of products within a product class. There are some good examples of this for example the chlorfenapyr nets. We hope this communication will also include consultation about the appropriateness feasibility and timing of those requirements.

45. **Q: Is comparative assessment standard practice now? Because it appears to be being implemented already in the case of broflanilide**.
R: Yes it is. We refer the reader to the MPAG meeting report from the current (April 2023) meeting. WHO communication and guidance will be updated accordingly.

46. **Q: Can WHO confirm that "communication" will be discussion rather than a one-way information flow? Consultation is needed, particularly in light of the current state of confusion.**
R: WHO will not hold discussions on its data needs in the context of normative guidance, but will provide further clarification on the process in due course. Data needs for WHO prequalification are available from the PTQ VCP team, while data needs in the context of GMP's normative guidance can be summarized as: i) Data from a minimum of two epidemiological trials to inform development of new recommendations for an intervention class, ii) Comparative entomological effectiveness data for any second-in class product. These data should ideally be generated as part of studies already required by QHP PQT drawing on WHO guidance for their generation. The document Norms, standards and processes underpinning development of WHO recommendations on vector control will be updated accordingly and be accompanied by updated guidance on the generation of comparative efficacy data and its analysis

47. **Comment:** We would further request that this communication process does not become a barrier for current products that are currently ready for launch and are essential for resistance management.

48. **Q: I would like to clarify whether the comment "Pending review by GMP for expansion of existing recommendations for IRS" of VECTRON T500 in PQ list is related to the data call by GMP. If it is related, I am curious as to why there is no similar comment in the list of pyrethroid-PBO, pyrethroid-chlorfenapyr, and pyrethroid-pyriproxyfen, which are also requested to submit a data package.**
R: Yes, this was directly related to the data call. In April 2023, comparative effectiveness data on broflanilide insecticides had not been received by GMP to inform an extension of the WHO IRS recommendation, as was done for neonicotinoids in 2017. The difference here lies in Vectron T500 being from a new insecticide class that has never been used in malaria vector control, and for which evidence – be it direct or indirect – for an impact in the control of malaria needs to be assessed by WHO in the context of its guidelines.

    The other types of products mentioned in the question closely resemble products that are already listed and covered by a WHO recommendation. As such, the data would not inform an extension of the recommendations that are already in place but provide essential evidence that the recommendation that is in place for these is applicable to the product in question. With the increasing diversity in products, this needs to be validated.

49. **Comment:** Noninferiority seems to be flawed in terms of what is being advertised here. If the goal is to compare products within a single-class, noninferiority would only show that the second product is noninferior to first product, but would not inform countries if second product is superior. So it is unclear still what is gained beyond PQ confirming that the second product meets its label claims.

50. **Q: The entire vector control community was working with an extremely clear process, that starts with the Pre-Submission coordination Committee. It appears that is being revisited, even retroactively for products already in the system and very unclear where non-inferiority comes in and whether the data is actually useful. Is WHO going to re-look at the entire pathway for evaluation of vector control products that was established with the start of the PQ program?**
R: WHO is revisiting aspects to the process, including the SOPs of the Pre-Submission Coordination Committee, based on recent insights on shortcomings of the process. The overall aim will be to further improve clarity and efficiency, ultimately leading to fast and evidence-based access of innovation to the market. The process for vector control evaluation has regularly been evolved to incorporate lessons learned, and the present situation is no different. We anticipate no major changes to the pathways, but better utilization of data submitted to WHO to meet both the needs of PQT and of the technical programmes.

51. **Q: When will the new ITN classification document be released based on the updated recommendation in the WHO guidelines for malaria?**
R: The March 2023 update to the *WHO guidelines for malaria* provides the three classes in section 4.1.1, "Interventions recommended for large-scale deployment." The section makes it clear that the classes that were provisionally endorsed by MPAG during its April 2021 meeting have now been formally established. WHO is not envisaging a separate publication on this topic.

52. **Q: What is the aim of the publication of recommendations on IRS scheduled in May/June 2023? How IRS will be evaluated?**
R: The publication of an update of recommendations on IRS is informed by an updated systematic review that was commissioned by WHO. The update will be minor and only affect some of the content under the recommendations, but not the recommendations

themselves. The protocol for the review underpinning this update was published in 2021 and is available online: https://www.medrxiv.org/content/10.1101/2021.12.13.21267747v1

The guidelines update in MAGICapp will be published on October 2023 and include broflanilide as part of one of the insecticide classes now covered by WHO's IRS recommendation.

Elimination

53. **Comment:** I have not noticed a mention of the seasonal treatment for all age groups in hilly and forest areas that was apparently useful in Odisha state of India. Like DAMaN- another state Chhattisgarh in India did a similar seasonal programme with testing and use of ITN. It was called Malaria Mukt Bastar.

54. **Q: May I know any guidance on the use of better diagnostic technique like PCR in practice regarding subclinical infection in countries planned towards elimination?**
R: Malaria infection is detected in symptomatic cases primarily in blood by RDTs or microscopy. RDTs allow detection of parasite antigens, and some tests differentiate species. Microscopy allows direct visualization of parasites, determination of species and stages and quantification of the density of parasites.

Vaccine

55. **Q: R21 has recently been approved in Ghana & Nigeria. Does this impact WHO's process? Do we know the impact of this for countries? Are there any concerns about this happening before WHO recommendation?**
R: See response above, in prior section.

56. **Comment:** The open call is published here: https://www.who.int/news-room/articles-detail/sage-malaria-policy-advisory-working-group-on-malaria-vaccines-march2023

57. **Q: Can WHO formulate guidelines that should make the inclusion of high transmission settings in vaccine trials mandatory so that the evidence to decision can be easier? It would appear that including Nigeria, DRC and Uganda that are responsible for the highest burdens is a logical step to reach conclusions.**
R: WHO guidance is available in the publication "Malaria vaccines: preferred product characteristics and clinical development considerations" (2022). The document indicates that: "Overall, study designs will need to consider the potential for the apparent vaccine efficacy to vary not only by transmission intensity, but also by the degree of seasonal variation in transmission and the vaccination strategy (e.g. seasonal administration)." Studies should be conducted in settings with the range of transmission intensities and seasonal variation in which the vaccine is intended for use. The evidence review for WHO recommendations considers the transmission settings in which a vaccine has been evaluated and WHO recommends further research, if needed, including post-authorization.

Day 2

Strategic Information for Response

58. **Q: How are countries selected for piloting the malaria surveillance tools? Can a country apply for that?**
    R: Countries can request to pilot tools through the WHO country and regional offices or directly to GMP HQ. Once the digital toolkit has been launched for surveillance assessments, WHO staff will undergo an orientation of the digital toolkit so that they are able to have direct conversations with countries on using it to carry out an assessment. For the first 6 months to one year, all countries using the tools will be asked to provide feedback to allow us to continue to improve the toolkit.

59. **Q: Are the results of the pilot tests of the Surveillance Assessment Toolkit in Burkina Faso, DRC, and other countries are publicly available? If they are, could you please provide the links?**
    R: These reports are not currently available in the public domain. WHO will seek clearance to share these reports with stakeholders and place on the website as examples.

60. **Q: Getting data from the private sector health facilities is challenging and this negatively affects completeness. Is there any experience or guidance to address this problem?**
    R: This is part of the surveillance assessment to include private facilities that are both integrated (completeness can be assessed directly) and not integrated into the NMCP malaria surveillance system or HMIS. A master facility list is required. If this is not available this is a gap and guidance is being developed by DDI in WHO on how to map out facilities in countries. Data audits and surveys are performed in private facilities during the assessment which gives countries the opportunity to assess how many cases and deaths are missing, as well as engaging with the private sector to discuss future solutions for integration through systems or routine reporting mechanisms.

61. **Q: Given than many patients seek care in the private sector, will there be a module developed to capture case-based data in the private sector (both health facilities and pharmacies)? I know that they are not included in the DHIS2 in many countries, but if we really want to meet the targets, we will need to find a way to incorporate these facilities into the surveillance system.**
    R: The module can already be used to capture data from the private sector and any other data collection points. The facility types are used to tag facilities in the system on the user permissions tree and these are then used to group the facilities so that analysis can be disaggregated by public/private sectors, for example. The issue is not technical but rather the challenge of engaging these sectors/facilities to ensure they report into the national surveillance system. Ideally the private sector should have direct access to these systems to enable reporting and access to data analysis and dashboards so that they can also monitor data quality and epidemiological indicators for their facilities. However, there are also other options to feed data from independent systems into DHIS2 to ensure all data is captured and integrated into one platform. The starting point for inclusion of the private formal and informal sectors is to implement mandatory reporting of malaria in the country for all sectors and establish reporting mechanisms and data sharing agreements as necessary.

62. **Comment:** To get the buy-in of the health staff into surveillance, a good way is to choose user-friendly mobile tools such as tablets that also allow for direct communication between the health facilities and the MoH response unit to which requests for help and supplies can

be communicated and where needed electronic payments can be made. Examples exist such as in Madagascar.

63. **Q: Does the WHO have a recommendation to the countries like Ethiopia to get real time data for malaria elimination regardless DHIS2?**
R: Countries in the elimination stage should be able to capture real time case-based data. The transition to this type of reporting from monthly or weekly aggregated data is not always easy and requires substantial technical, human and financial resources. The roll out of these case-based systems is usually done in a phased approach prioritising districts that have lowest numbers of cases and subnational elimination activities. Any country can request for the installation of DHIS2 and the case-based module in the country. However, if the country already has its own system the case-based module can be used as a template (in terms of variables collected and functionality) for the development of an in-country tailor made module. Alternatively, an existing case-based system can be adapted to ensure all elements for malaria surveillance are included.

64. **Q: The tools are improving and being scaled up, the data are improving. How do we shift the workload of NMCP from externally imposed processes (MPR, MPR, MOP, GFATM Applications, Retrospective Analysis, Matchbox) to continuous data for decision making?**
R: There are several activities that NMCPs can implement to ensure the continuous use of data for decision making, starting by: 1) accelerating improvements in surveillance systems and data quality; 2) establishing integrated data repositories that allow for a structured query of data and continuous improvements of quality; 3) streamlining information products for national and global stakeholders through their integration in the repository interface to ease their production; and 4) establishing long-term collaborations with local or regional analysis groups that can provide analytical support on a regular basis as well as transfer skills to ensure the continuity of data usage in the future.

65. **Comment**: We need a template to develop the narrative report of the Subnational tailoring (SNT) process upon completion.

66. **Q: Can countries do this without WHO (GMP or AFRO) support? Is there a guideline?**
R: The subnational tailoring implementation guideline will provide the information required for NMCPs and partners to follow the process recommended by WHO. The engagement of WHO colleagues in this process is highly recommended in order to ensure that the analytical products prepared to inform decision-making are adequate and aligned with WHO recommendations.

Rectal artesunate

67. **Comment:** Evidence is scarce regarding the operational feasibility of incorporating RAS into the continuum of care for severe malaria and the intervention's unanticipated consequences on the overall disease management. In addition, it is unclear how much impact the introduction of RAS will have under real-world circumstances.

68. **Comment**: The myriad of flaws detailed by the forensic statistical analysis confirms that the CARAMAL study cannot (and should not have been) be used to evaluate the effectiveness of rectal artesunate (RAS) in the prereferral treatment of severe malaria. The conclusion of the review is that "to reduce the case fatality rate for children with severe malaria, there needs to be a functional continuum of care for severely ill children, with a good referral system and referral facilities equipped to comprehensively manage a severely sick child." There is an alternative perspective with different policy implications. RAS are highly effective in saving

life in true severe malaria, and a single treatment provides the majority of this benefit. However, with deployment of ITNs and ACTs, a diminishing proportion of life-threatening illness is caused by malaria, and severe malaria is vastly over diagnosed in higher transmission settings.

69. **Comment:** In the case of children first treated with RAS by a community health worker (CHW), this may be a primary health centre (PHC) that lacks the capacity to manage a severe malaria episode. In view of improving the case management of such children, more evidence is needed to understand the pathways by which children with suspected severe malaria reach a competent and capacitated healthcare provider and whether referral completion is impacted by the administration of RAS.

70. **Q: What about the idea of CHW administering RAS until oral ACT can be safely administered?**
R: This is not recommended nor advised by WHO as antimalarial treatment is only one of the several treatments and procedures required in the management of severe malaria. Other complications and involvement of other organs cannot be managed by the community health workers nor at that level. Such complications include (but not limited to): severe anaemia, respiratory distress, renal injury, management of the unconscious child, ensuring fluid balance, among others. After the emergency treatment with RAS, all children with severe febrile illness should be referred to a facility where a full evaluation and appropriate management can be dispensed, including the management of other potential causes of the severity other than malaria.

71. **Comment**: Saying that the CARAMAL study shows that RAS was "ineffective" in the context of the study goes completely against the findings in the report from the independent committee. Key issues in the design preclude any conclusions about "effectiveness".

72. Q: Use of any drug will always select for its resistance. That's why we do studies to quantify the problem. The CARAMAL study was badly done and the analysis completely incorrect. Where is the accountability? and what really is the final recommendation? There remains much confusion in countries over this study.
R: The recommendation of WHO remains unchanged: "Where complete treatment of severe malaria is not possible, but injections are available, adults and children should be given a single intramuscular dose of artesunate and referred to an appropriate facility for further care. Where intramuscular artesunate is not available, intramuscular artemether or, if that is not available, intramuscular quinine should be used. Where intramuscular injection of artesunate is not available, children < 6 years should be treated with a single rectal dose (10mg/kg bw) of artesunate and referred immediately to an appropriate facility for further care. Rectal artesunate should not be used in older children and adults." The Global Malaria Programme is using the lessons and evidence from the CARAMAL study and other large scale deployment studies to develop a field manual to support countries in the effective deployment of RAS. Also, an updated Information Note on RAS will be published shortly to clarify any misunderstandings that persist.

73. **Comment**: Comprehensive antimalarial treatment after a dose of RAS is crucial as one dose of artesunate alone (or in combination with another only partly effective antimalarial) cannot fully clear an infection. Pre-referral treatment with RAS with or without subsequent parenteral artesunate, but without an oral ACT, constitutes artemisinin monotherapy treatment. This is a risk for both resistance development and positive selection of circulating artemisinin-resistant parasites. Curbing the remaining burden of malaria mortality remains a

top public health priority in countries with a high malaria burden. While pre-referral RAS treatment may have a beneficial health effect for an individual patient who can follow the full continuum of care, this intervention is unlikely to reduce malaria mortality in a population unless underlying health system factors are addressed. The large-scale roll-out of pre-referral RAS must be accompanied by measures to ensure definitive treatment with at least parenteral artesunate and a full course of oral ACT.

74. **Comment**: Reflecting on the RAS discussion, it seemed that there is good experience and understanding of health systems and associated process, but insufficient understanding of the biology and clinical management of severe malaria. Understanding and reducing childhood mortality is a critical objective. It is very important that therapeutic recommendations have a solid biological rationale.

75. **Comment:** Zambia study had 3x times more rectal artesunate beneficiaries (11,486) than the three CARAMAL countries combined (3,402)! Cf. publication in WHO Bulletin: https://cdn.who.int/media/docs/default-source/bulletin/online-first/blt.22.289181.pdf?sfvrsn=63869308_7

Community-based IPTp

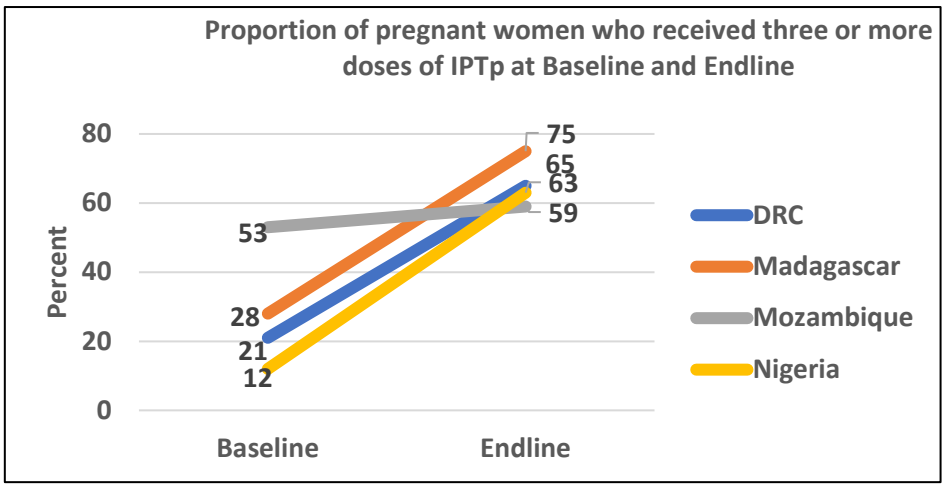
76. **Comment:** While IPTp uptake has never been optimal, I think there's need to review the **denominator** for the IPT3 especially.

77. **Comment**: Physiological changes such as increased intravascular volume, delayed gastric emptying time, elevated oestrogen and cortisol levels and increased body fat content alter the absorption, distribution and elimination of many antimalarials during pregnancy. If the effect of IPTp is mainly prophylactic, then short-acting drugs would be expected to provide little **direct** benefit in asymptomatic pregnant women living in high-transmission areas since rapid parasite elimination is unnecessary. Drugs with long half-lives would, therefore, appear better choices, but monotherapy with any of these agents would be inappropriate given global patterns of drug resistance and the consensus on the need for combination therapies.

78. **Q: c-IPTp should be an opportunity to sensitize pregnant women and encourage them to go to the health facility for antenatal care (ANC). How is the SP supply mechanism at community level?**
R: Uninterrupted availability of quality-assured SP is key to success of c-IPTp and should be ensured through the existing national medicine supply management systems in proposed sites for c-IPTp, rather than creating parallel systems. The TIPTOP approach included monthly data review and commodity re-supply meetings between CHWs and their health facility focal points. Re-supply with SP was undertaken considering past consumption. CHWs were provided with lockable boxes to store SP back at the community level, out of reach of children, and protected from unauthorized access.

79. **Comment:** The need to have enough frontline community health workers (CHWs) and to pay them regularly has been reemphasized as well as to recognize them as full-fledged staff.

80. **Q: Assuming that the approach has more impact when initial coverage is very low, are you considering an approach to maintain gains in places with acceptable coverage? Is there any documentation focused on this given the experiences gained where teams in the field have actually faced this scenario of high initial coverage?**
R: The c-IPTp approach focused on increasing IPTp-3 coverage. The TIPTOP Project Evidence Report documented that TIPTOP quantitative household surveys revealed IPTp3+ coverage increased significantly in the project districts in all project countries (see below graph).



Furthermore, the study concluded that the lower the IPTp3+ coverage at baseline, the higher the percentage increase at endline. There were, however, several contextual factors that influenced the observed modest increase of IPTp3+ coverage in Mozambique, such as the low ratio of CHWs to pregnant women served, compared to other countries as well as disruptive incidents like cyclones, flooding and insecurity that occurred in specific intervention districts during the project implementation.

Results of a c-IPTp study conducted in Malawi were presented during the June 2022 WHO technical consultation on c-IPTp (full report accessible via Technical consultation to assess evidence on community-based delivery of intermittent preventive treatment in pregnancy for malaria (who.int)). In summary, the IPTp3+ coverage in these districts was quite high to start, and the interventions did not have the intended effect on IPTp3+. For further details see Rubenstein BL, Chinkhumba J, Chilima E, Kwizombe C, Malpass A, Cash S, et al. A cluster randomized trial of delivery of intermittent preventive treatment of malaria in pregnancy at the community level in Malawi. Malar J. 2022 Jun 21;21, 195. doi: 10.1186/ s12936-022-04216-4.

Seasonal malaria chemoprevention (SMC)

81. **Q: SMC relies on two drugs which are compromised by resistance. It needs continuous evaluation to assess chemoprophylactic efficacy. Is MPAG confident that assessing SMC with the same "TES" methodology recommended for treatment evaluation is appropriate?**
R: Drugs to which resistance has developed to a degree that compromise treatment efficacy can still have a role in chemoprevention. Therefore, there is a need to assess the efficacy of these drugs when used for preventive chemotherapy. To support countries and partners in this, a first malaria chemoprevention efficacy study protocol was released in July 2022 (available at: https://www.who.int/publications/i/item/9789240054769). This protocol adapts some of the principles and practices underlying treatment efficacy monitoring to provide standardized approaches for monitoring and evaluating the efficacy of medicines

used for malaria chemoprevention. An update of this document will be done when additional experience is gained from studies of chemoprevention efficacy

Anopheles stephensi

82. **Comment:** Invasion of *An stephensi* is really a challenge but there is need to plan for **integrated** approach for urban malaria and dengue control as vectors are sharing same breeding containers - source reduction and intensified IEC to involve community is important.

HRP2 gene deletions

83. **Q: Does the model predicting HRP2 risk in Africa take into account current malaria transmission? For example, Cabo Verde has had no indigenous transmission for several years. Should it really be considered 100% at risk for HRP2 deletions?**
R: The current model is based on the 2020 Malaria Atlas Project estimates for a country. These included, at the time, very low transmission for Cabo Verde, even if in 2019 zero local cases were reported. Consequently, if HRP2/3 deletions did arrive in this setting and transmission is re-established, the model would predict it to increase very quickly. However, the chance that imported deletions would fade out as a result of the very low transmission is also very high. Consequently, regions such as Cabo Verde are susceptible but the predicted trajectories are very stochastic because of the low transmission. Certainly areas with very low transmission regions are less of a risk to malaria control/diagnostics because the very low number of cases means that alternative diagnostics/microscopy could be used instead.