World Health Organization

Questions & answers

Day 1

Report from the Director

1. **Q:** Do we have an idea of what the *World malaria report* is likely to show in terms of deaths/case. e.g., have they gone up again?

   A: We are finalizing the analysis and will start the process of validation by countries. We plan to launch the report first week of December and will know the final results at this time.

2. **Q:** It was mentioned a few times that we are off track to meet our targets. What do you think needs to happen to change this? Do we think a new sense of urgency is needed (reflected in guidance/ funding/political will/research)? Does the WHO have any plans to address this?

   A: Targets for communicable diseases under the Sustainable Development Goals were off track before the COVID 19 pandemic, which has further exacerbated the challenge. The scale of the Africa malaria challenge remains real and underestimated. Its impact extends beyond health, impeding progress towards sustainable and equitable societies. Despite increases in health service coverage, too many people are still missing out on the malaria interventions they need and quality services. Without a greater focus on ensuring that appropriate, quality services to prevent, detect, and treat communicable diseases are accessed by all those in need, the relevant SDG targets will not be achieved.

   In response to data from the *World malaria report 2018,* the WHO Director-General, Dr Tedros Adhanom Ghebreyesus, called for an aggressive new approach to accelerate progress against malaria. The High burden to high impact (HBHI) was launched in 2019 as a country-led response – catalysed by WHO and the RBM Partnership – to reignite the pace of progress in the global malaria fight. An evaluation of the approach will help guide efforts to refine and expand the approach to other countries.

   COVID 19 presented many additional challenges for the malaria response. It also provided an opportunity to rethink our approach and learn from those at the front line. The Harvard led rethinking malaria considered the malaria challenges and opportunities in the context of COVID-19, with a focus on governance, health systems and the workforce. They concluded that malaria needs to be reframed as a societal problem, requiring strong leadership by endemic countries and a whole of society response.

   African thought leaders are also calling for strong African leadership and a broader coalition within Africa to tackle malaria, that recognizes the benefits from a primary health care (PHC) approach and a commitment to social justice and equity. This is consistent with WHO's strategic priority to accelerate progress on universal health coverage (UHC) and a radical reorientation of

health systems towards PHC. A PHC approach entails four inter-related and synergistic components, all of which are relevant for malaria:

1. Comprehensive integrated health services that embrace primary care as well as quality public health goods.
2. Multi-sectoral policies and actions to address the wider determinants of health, social and environmental
3. Engaging and empowering individuals, families and communities for increased social participation and enhanced self-care and self-reliance in health.
4. Essential public health functions for health system resilience to ensure promotion, prevention and protection for all.

Primary health care is not only critical to achieve UHC but also for health security and building health systems resilience to meet a wide range of shocks and demands. The increasing frequency of natural and human-made disasters coupled with the threat of climate change and future disease pandemics could further undermine the malaria response. There needs to be a more predictable and systematic approach to building resilience – particularly at a time when global financial resources for health and malaria are constrained. The recovery from COVID should be an opportunity to harness political and economic attention for health system resilience.

As discussed elsewhere, WHO is providing technical support for countries as they contend with specific biological threats. That will also require greater investments in research into new tools and the more effective and equitable deployment of all interventions for malaria. WHO is supporting countries use local data and knowledge to identify the appropriate mix of interventions and the optimal means of delivery.

3. **Q:** Is there an expected date for launch of the *Strategy to respond to antimalarial drug resistance in Africa*?

A: The Strategy will be launched on 18 November 2022 as part of Antimicrobial Awareness Week. The announcement will be coming soon.

4. **Q:** Thanks for the presentations. Is it possible to have access to the presentations?

   A: All of the presentations and meeting report will be available on our website in the coming weeks: https://www.who.int/news-room/events/detail/2022/10/11/default-calendar/22nd-meeting-of-the-malaria-policy-advisory-group.

High burden to high impact (HBHI) approach

5. **Q:** What is WHO's role in engaging multi-sectorial support? Ashanti is a great example, but it has been the only one for over a decade now and can't possibly be the only company interested in this. Is there a plan on how to develop multisectoral approaches because we have been saying the same thing for a number of years now and progress isn't happening?

   A: Through the HBHI, WHO, in collaboration with the other partners, engages governments to lead a multisectoral approach and engage private sectors. The little progress is a result of weak political will and country ownership. Multisectoral cooperation can only happen if leaders enforce it.

6. **Q:** In countries with high burden of malaria, there is need to emphasize more on entomological control mechanisms such as indoor residual spraying (IRS) as part of WHO's strategy in the control of malaria.

   A: We agree. The challenge is having the resources to sustain IRS due to its high cost and governments are not investing.

Non-inferiority

7. **Q:** Is non-inferiority a requirement for WHO as it does not appear to be included in the insecticide treated net (ITN) guidelines that have been released for consultation. Will this be part of the PQ dossier requirement?

   A: It is not a requirement for prequalification (PQT), which is a separate process. For now, it is just needed for dual A.I. nets, and data to allow a non-inferiority assessment should be submitted as part of the dossier submission to PQT to help streamline the process for data submission. PQT will forward the data to GMP once the scientific validity of the studies has been assessed. Data generation to allow non-inferiority assessment is not part of the ITN guidelines, which focus on data generation for PQT assessment. GMP is in the process of updating the specific non-inferiority protocol that was originally developed to inform studies on pyrethroid-PBO nets and will make this publicly available in 2023.

8. **Q:** For the effectiveness of long-lasting insecticidal nets (LLINs), the duration of their physical integrity is as important as insecticide resistance. Could you advise on any evaluation work done to monitor and compare the ruggedness and survival time of the nets that seems ever more decreasing with increasing pressure on manufacturers to decrease price?

   A: Substantial work was done by PQT and has been fed into the revised testing guidance that is in advance draft and on which a consultation is being held from 18 to 20 October 2022.

9. **Q:** Why does non-inferiority only look at chemical aspects and not physical?

   A: As discussed during the Q&A, the PQT process will address ITN quality already in part, and the new testing guidelines have been designed to do so in more detail. If a need is identified to provide comparative data on this aspect WHO could consider building this into a non-inferiority assessment, but there may be other – more suitable methods – to do so. As you will see, the protocol used for pyrethroid-PBO nets already identified a need to assess physical durability over time, but the study that was conducted in 2020 did not go as far a re-testing pyrethroid-PBO nets after a certain time of field use due to financial and practical reasons.

10. **C:** We in industry are very concerned that the criteria for non-inferiority measured bite inhibition, but then dismissed it. This is a key action of nets so just measuring kill or knock-down misses so much.

    R: I think there is a misunderstanding here. The recommendations made in the expert group in 2021 make it clear that mortality is to be used as the primary endpoint, while data on blood feeding is to be collected with a view of considering it as a secondary endpoint. In terms of achieving epidemiological impact, killing is more important that prevention of blood-feeding. Kindly take a look at page 13 of the meeting report with regards to the endpoints to be used.

11. **C:** If studies are used from different sites, countries, etc., the variations can be huge rather than trials conducted alongside each other.

    R: This is certainly a risk and worth investigating further. The existing protocol for non-inferiority data collection already indicates that two studies from different sites are required, in an attempt to provide some generalizability of the results. We interpret this comment to expresses support for regular testing of all products on the market alongside each other, as was done for pyrethroid-PBO nets in from 2019 to early 2021. We take note of this.

12. **Q:** We understand that one of the purposes of the non-inferiority analysis is to cut down delays in products entering the market. If non-inferiority has to include entomological efficacy and durability, will the length of time required not set us back?

    A: Entomological efficacy data to allow non-inferiority assessment can easily be generated as part of the data required for the PQT dossier. If durability data were added to the non-inferiority assessment approach and if this were to require field studies after 2 to 3 years of field use, then we would envisage that these data could be added at a later stage so as to not delay market entry. As you will have noted, the area of durability assessment as part of non-inferiority evaluation is one that seemingly attracts a lot of interest but for which it is too early to provide a clear way forward until the new ITN testing guidelines have been reviewed and finalized, as these may be able to close many of the current data gaps already. Any non-inferiority assessment approach used in the area of durability would have to build on these but would need to be considered against other forms of data generation/analysis that may lend themselves to providing additional clarity on comparative product quality.

13. **C:** We concur that a non-inferiority approach (or similar) is essential to guide decision making on procurement – we need confidence that next in class products are of appropriate performance. Strongly agree with the need for these data to be publicly available.

    R: We appreciate this re-confirmation by the Global Fund of the value of undertaking comparative assessments.

14. **Q:** Clearly governments in endemic areas have been approached. Could you advise the reasons they give for not taking ownership or not investing?

    A: In general, governments in endemic areas do not have sufficient resources to conduct their own vector control evaluation process. This is why WHO originally developed WHOPES, which over the last years has been evolved into a new WHO evaluation process as outlined here.

WHO Guidelines for malaria

15. **Q:** Could uncomplicated malaria in pregnancy be defined?

    A: A pregnant women who presents with symptoms of malaria and a positive parasitological test (microscopy or RDT) but with no features of severe malaria is defined as having uncomplicated malaria.

16. **Q:** Adopting WHO malaria guidelines for developing settings may not follow a standard guideline development like GIN guideline development method. Is there any room to improve an evidence informed guideline development for developing countries?

A: The Global Malaria Programme developments recommendations following the process and standards outlined in the *WHO handbook for guideline development, 2nd ed*. The adoption of these global recommendations by countries is guided by their adaptation to the national context, and possible inclusion in national guidelines based on the advice of national and decision of the health authorities.

Day 2

Malaria vaccine

17. **Q:** Given that most of the implementation of the vaccine will be done by GAVI and EPI programmes, do you have any guidance on what roles national malaria programmes and partners will play the roll out?

    A: Although it is true that the EPI programme will deliver the vaccine, the national malaria programmes (NMPs) provide important input into where the vaccine should go initially (subnational stratification) in the context of limited supply, and the NMP are essential in the planning for social and behaviour change and information, education and communication/training materials and plans. One of the key lessons learned during the Malaria Vaccine Implementation Programme (MVIP) has been the value of the close coordination between EPI and NMP programmes in all of the 3 pilot countries. This lesson learned is being shared with countries interested in introducing the malaria vaccine.

18. **Q:** Does seasonality play a role in the Framework for allocation of limited supply given other tools are available for children under 5 in highly seasonal settings (e.g., SMC)? In other words, is this being targeted to perennial malaria settings?

    A: In a Phase 3 trial at two sites (n~6000 children), the vaccine has been shown to have high efficacy when provided just prior to the high transmission season in areas with highly seasonal malaria, with efficacy similar (non-inferior) to seasonal malaria chemoprevention (SMC), which in clinical trials has been shown to prevent 75% of malaria episodes. This important finding shows that high efficacy can be achieved with RTS,S/AS01 when the vaccine is administered strategically, before the high transmission season. And for this reason, WHO recommends that countries can implement the vaccine in this way in areas of highly seasonal transmission or areas of perennial transmission with seasonal peaks.

    Furthermore, when the vaccine was given just before the peak season, and SMC was provided during the peak season, clinically and statistically significant added benefit was shown when compared with SMC alone or when compared to the vaccine alone. Combined there was an added 68% reduction in severe malaria, and important additional reduction in mortality. [See reference: Chandramohan, D., et al., Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. N Engl J Med, 2021. 385(11): p. 1005-1017].

    The Framework considers where vaccine should be prioritized in the context of limited supply, focusing allocation initially on areas of greatest need. This does not exclude areas of highly seasonal transmission.

19. **Q:** What are the latest data on dose 4 coverage and dropout rates between doses 3 and 4?

    A: Here are the latest observations based on data reported by MOH through the routine administrative data systems:

    - Ghana: Since programme launch up until August 2022, approximately 71% of children who received the 3rd dose have become age eligible to receive the 4th dose and received it. i.e., about ~29% of age eligible children have not (yet) received the dose 4.
    - Malawi: Since programme launch up until May 2022, approximately 70% of children who received the 3rd dose have become age eligible to receive the 4th dose and received it. i.e., about ~30% of age eligible children have not (yet) received the dose 4.
    - Kenya: Since programme launch up until July 2022, approximately 53% of children who received the 3rd dose have become age eligible to receive the 4th dose and received it. i.e., about ~47% of age eligible children have not (yet) received the dose 4.

    As you know, it's not unusual for children to show up late for vaccination. All countries continue efforts to increase uptake of the 4th dose.

20. **Q:** I did not see any updated information on relative or incremental cost effectiveness of the vaccine.

    A: Today's presentation focuses on relevant updates on progress with vaccine roll-out and the *Framework for allocation of limited supply*. In reference to the initially high vaccine price, we made reference to previous health impact and cost-effectiveness studies in which modelling has demonstrated that the vaccine is cost -effective in areas of moderate to high malaria transmission, including at a price of 10 dollars per dose. Global health partners at Gavi, WHO and UNICEF continue market shaping efforts to increase supply and reduce costs over the next few years.

21. **Q:** How are Gavi & the Global Fund planning to work together to ensure implementation of vaccines alongside existing tools & health system strengthening initiatives etc.?

    A: This is a question best directed at Gavi or Global Fund. Where WHO is also involved, there is considerable coordination, with Global Fund participating in the Gavi Malaria Vaccine Coordination Team, co-chaired by Gavi and WHO. Global Fund also provided input into the Gavi malaria vaccine application guidelines and participates in the Gavi workshops to support country application development.

22. **Q:** When will we have the final data from the MVIP for the dropout rates from dose 3 to 4? Did the phase 3 studies show any increased risk of severe malaria if children miss the 4th dose?

    A: Although highest efficacy is reached when children receive all 4 doses of the vaccine, the Phase 3 trial showed that children benefit whether they receive 3 or 4 doses of the vaccine, with a statistically significant reduction in clinical malaria through 48 months after vaccination. Statistically significant vaccine efficacy was shown against severe disease in children who were randomized to receive 4 doses, while vaccine efficacy against severe disease was not statistically significant in children randomized to receive only 3 doses of the vaccine – but there was no overall increased risk of severe disease. This finding was confirmed in a long-term follow-up study (See Tinto, H., et al., https://pubmed.ncbi.nlm.nih.gov/31300331/). During 6-7 years follow-up of a subset of Phase 3 trial study participants it was shown that during the period following RTS,S/AS01 vaccination, the incidence of severe malaria declined with age in both

vaccinated and unvaccinated groups. Although there was no evidence of continued vaccine efficacy against severe malaria during the additional three years of follow-up, neither was there evidence of increased susceptibility (i.e., there was no age-shift of severe malaria to older children). Over the entire 6-7 year period, vaccine efficacy against severe malaria was significantly positive for children receiving 4 doses in both age categories, and for those receiving 3 doses in the 6-12 week age group. Thus, children in areas with moderate to high perennial malaria transmission who received 3 or 4 doses of RTS,S/AS01 benefitted for at least 7 years after vaccination and did not have an excess risk of clinical or severe malaria. Noting these results, MPAG assessed that these data provided further reassurance on the potential impact of an age shift effect in immunized children and reinforced the safety profile of the vaccine (see October 2018 MPAG meeting report) and 2021 Full Evidence Report on the RTS,S/AS01 vaccine.

All countries provide messages through their Social and Behaviour Change (SBC) and Information, Education and Communications (IEC) materials emphasizing the 4-dose schedule, and that completing the 4-dose schedule is important for optimal benefit. All countries continue efforts to increase uptake of the 4th dose and monitoring of 4th dose uptake. As part of the Malaria Vaccine Implementation Programme, each of the 3 countries have conducted or plan to conduct coverage surveys at around 30 months after vaccination began. Monitoring of the 4th dose uptake will continue through the routine systems.

Elimination

23. **Q:** what is the current stance on *P. knowlesi* with respect to certification in countries where this may be present?

    A: Please see the MPAG meeting report from March 2022, agenda item 3.

Framework for the response to malaria in urban areas

24. **Q:** Could ITN acceptability in urban areas be improved through more consideration of the preferences of urban residents, for example through greater availability of conical nets?

25. **Q:** While you did not speak to it today, have you addressed an expected *An. stephensi* expansion into new urban areas?

    A: Yes, we do reflect on *An. stephensi* in the framework.

Rectal artesunate

26. **Q:** The primary goal of CARAMAL was to "understand whether the introduction of RAS can indeed reduce severe malaria case fatality". But this goal cannot be obtained because it is an observational study and thus suffers from various confounding/selection biases. So why use an observational study to assess whether a lifesaving intervention is useful?

    A: Indeed, this observational study is informative on some of the determinants of effectiveness and was not appropriately designed to assess impact. The results will help to develop implementation guidance for the safe and effective delivery of this intervention.

27. **C:** This observational study does not provide reliable evidence of treatment effects. CARAMAL has obvious potential sources of bias and contradicts evidence from an earlier RCT.

    R: This is an important focus of the WHO Technical Consultation that will be held on 18-19 October.

28. **C:** Just an observation that in MAGICapp malaria guidelines, the information note is accessed as a link at the end of section 5.5.3. It would be easy to miss, ignore, or skip this - perhaps it would be better to move the link up in the body of the rectal artesunate paragraph to draw attention to it.

    R: The information note does not include guideline recommendations but is included for information as are other relevant references listed in the Guidelines.

Pfhrp2/3 gene deletions

29. **Q:** Do we have any data emerging on how many deaths due to delayed or absent diagnosis may be attributed to a false negative diagnosis?

    A: We have not attempted to estimate morbidity or mortality associated with delayed or misdiagnosis. We are not sure that there is hard data, but certainly anecdotal.

    R: That is what I thought, but it will be great to gather such information on the clinical outcomes as mentioned in the discussion. Your leadership is much appreciated.

30. **Q:** Regarding the MTM and Dashboard or planned and ongoing studies, is this available to the general public. If so, how can we access it?

    A: The dashboard with planned and ongoing studies will be available for download every month in excel format. As we just launched the questionnaire last week, we don't yet have a download to share but expect we will have data to share in early December – here is the link to the survey and here is the link to the page (scroll down to the blue box) to see where you will be able to download the info monthly.

An. stephensi

31. **Q:** It was mentioned that that *An. stephensi* has displaced *An. arabiensis* in many places. How come this happens if the breeding sites are mostly different?

    A: We are not aware of any displacement that is taking place.

32. **C:** The inclusion of the areas where *An. stephensi* has not been recorded is vital and this should include the sampling type, effort and any temporal/seasonal elements.

    R: We fully agree. This feature is being added to Malaria Threats Map.

33. **Q:** Who are the partners to be convened in the meeting Q1 2023?

    A: The partners will be a combination of national malaria control programme staff, researchers, funders, WHO staff, and others.

34. **C:** Regarding integrated control, remember that by larviciding you will also control *Aedes aegypti* so a double benefit.

    R: Yes, good example of integrated control as envisaged under the Global Vector Control Response.

35. **Q:** What funding is available for surveillance? Where can programmes look to for support with this?

    A: There is no specific *An. stephensi*-specific funding available that we are aware of. However, programs can work to integrate their ongoing surveillance for *Aedes* or *Anopheles* mosquitoes to better understand the spread of *An. stephensi*. They may also be able to work with research groups who can apply for outside funding to conduct surveillance for *An. stephensi*.