World Health Organization

# Questions & answers

## Day 1

### Report from the Director

1. **Q:** The African populations have been more and more urban over the 20 years 2000–2020. Since malaria is mostly rural, how much of the rate decline is due to increased urbanisation?

   **A:** We don't have a clear understanding of how much urbanization (and other developments) have contributed to the trends. We are confident they have, but most of the gains still likely due to the scale up of malaria interventions.

### Update on RTS,S and draft Framework for vaccine allocation

2. **Q:** Does RTS,S prioritization at sub-national level take into consideration SMC (and potentially IPTi implementation)?

   **A:** These will be considered in prioritization of the vaccine, during in-country analysis and planning.

3. **Q:** given the relatively high dropout rates we saw in the October 2021 MPAC Meeting (~20–30%) and the increased risk to severe malaria that missing the booster shot has for children, what efforts can be done to increase uptake? Is qualitative research being done by WHO to understand the uptake and feasibility of those in the pilot implementation?

   **A:** The EPI programmes in the three countries are using routine methods (PIRI) to increase uptake of dose 4. Fourth dose uptake continues to be monitored through the ongoing pilot implementations. It should be noted that children who received 3 doses RTS,S were not at increased risk of severe malaria, but rather the efficacy against severe malaria seen at 12 months after vaccination was not sustained. Overall in the phase 3 trial, although there was benefit against clinical malaria, there was no benefit against severe malaria when the vaccine was provided in 3 doses. However, modelling results differ, and suggest that the added benefit of the 4th dose may be minimal. We will know more about the added benefit of the 4th dose at the pilot end.

4. **Q:** Will there be any specific provision for humanitarian settings/non-MoH actors?

   **A:** Thank you for bringing this up. It was an important point raised during our consultations and will be brought back to the expert advisory group for their consideration.

5. **Q:** Why not increase the supply? There are so many vaccine companies that quickly got into the Covid vaccines, and some of these are equipped to produce the GSK vaccine.

**A:** This is a major area of focus for WHO and partners, including looking at ways to accelerate antigen product transfer, which is already underway from GSK to BBIL, and to facilitate the development pathway for malaria vaccines in the pipeline.

**Operational manual for subnational tailoring of malaria interventions**

6. **Q:** Will countries be encouraged to revise their national strategic plans (NSPs) using this framework?

   **A:** We do hope that this document is used for NSP development and implementation. We will share the draft widely for feedback from stakeholders so that it captures a wider view.

7. **Q:** On the question of intervention selection for a particular setting vis a vis resource gaps – would you also talk of when to transition?

   A: Yes, we will reflect on issues related to scaling back, rebound and resurgence.

8. **Q:** The question is not scaling back – that is easy to reflect conditions that may inform risks or lack of. What countries are experiencing is use intervention A (with good justification) and then 2–3 years down the line, they are asked to switch to another intervention because of resource gaps. It will be helpful that this is addressed in the draft document to help partners and countries take a realistic decision given that the options are few.

   **A:** Agree but in essence it is a scaling back whatever the reason for it. We think transition plans are needed in such cases and we will reach out to the community for best approaches to transition.

   However, the problems start with someone telling countries what to do, if it was a carefully done country decision, then both the choices and consequences would likely be different.

9. **Q:** How can developers of new intervention classes prepare to support practitioners of the HBHI process to include them in the range of interventions they consider in optimizing their programme.

   **A:** At this point, the document is for country use. However, the country data platforms can help with exploration of the potential impact of new products and help add up the trial and other evidence usually used for making recommendation.

10. **Q:** What role will active vector surveillance and control play? It seems to be left completely out of the equation.

    **A:** No, it's not left out. On the metrics slide we have entomological surveillance. This is core part of the tailoring.

11. **Comment:** Entomological surveillance needs to be followed with active vector control where indicated, but vector control needs to be implemented beyond LLIN & IRS, especially as *An. stephensi* continues to expand in Africa. Also, though Africa carries the bulk of the malaria burden, what works in Africa does not necessarily work in Asia or South America. In those, LLIN distribution will probably not work as expected.

### *P. knowlesi* disease burden and transmission

12. **Comment:** The name "Malaria free certification" while any kind of malaria presence looks challenging as long as it affects human and especially resulting in mortality.

13. **Q:** The evidence for human to human is very limited why the 10-case threshold?

    **A:** WHO certification of malaria elimination comes from a World Health Assembly Resolution. As stated in this WHA Resolution, after a country is certified malaria-free, it will be entered into the Official Register listing areas where malaria elimination has been achieved. The purpose of the Official Register is to provide a list of countries where it is "safe" for malaria. In other words, countries listed in the Official Register should have zero or negligible risk of malaria. It is established conclusively that *P. knowlesi* infects humans and causes disease and death. The mode of its transmission is not yet entirely clear. Most of the transmission is likely from macaques to humans although there is limited evidence suggesting transmission from human to human. However, no matter how *P. knowlesi* is transmitted, be it from human to human or from macaque to human, it is local transmission and therefore, a risk to humans. If the number of local *P. knowlesi* cases is high, the risk cannot be considered negligible and therefore, it doesn't fit the purpose of certification and the Official Register. The 10-case threshold is arbitrary but in practice, determining whether the risk of infection of *P. knowlesi* is negligible will be assessed case by case.

### Report of the technical consultation to review the classification of G6PD

14. **Q:** The gap in numbers between 45–60?? brings practical challenges. The new classification is not clear for me and I look forward reading the new recommendation to understand more. Good also to develop a standardized G6PD genotype classification for consistent reporting in future studies.

    **A:** The proposed G6PD classification of genetic variants is based on the median G6PD activity expressed as a percentage of normal activity identified in homozygous deficient females or hemizygous males in published studies. The description of the 4 classes (A, B, C and U) is provided in the report. Currently, no variants have been identified that have median G6PD enzyme activity falling between 45% and <60%. Therefore, a gap has been left between Classes B and C. If new variants are found with median G6PD enzyme activity in this range, these should be included in the "U" class and studied until solid evidence is found that they induce acute haemolytic anaemia (= Class B) or do not pose a haemolytic risk (= Class C). It should be emphasized that this system is for classifying genetic variants of G6PD according to their phenotypes and should not be used to classify individual patients with G6PD deficiency.

### Update on the WHO Guidelines for malaria

15. **Q:** Could you kindly clarify the conditions for deploying PBO LLINs? Do you mean now that as long as there is pyrethroid resistance programs can deploy PBO LLINs? we don't need to conduct PBO synergist tests?

    **A:** Yes, that is correct. MFO testing is no longer required as a pre-requisite.

16. **Q:** Will there be Portuguese versions for our many Lusophone colleagues?

    **A:** We would like to make a Portuguese version available and will consider once the Arabic and Spanish versions are launched and if the budget allows.

17. **Comment:** In elimination settings it is difficult to do studies of the size that can be taken as strong evidence. In addition, evidence cannot be generalized in low transmission settings – each setting is unique. In eliminating settings we have to be practical and take an approach that is reasonable rather than proven. Response: you're right that it's hard to do cluster-randomized controlled trials, but there are other designs that could also be used, such as controlled interrupted time series.

18. **Q:** Could there be a recommendation to evaluate combination interventions?

    **A:** WHO tried to look at the safety, quality, efficacy and public health impact of each intervention separately as this allows for a clear pathway of translating evidence from studies into recommendations. However, for operational purposes the WHO also encourages countries to look at the collective impact of different mixes of interventions in their settings when tailoring them to local context. Here, we recommend the use of stratification and modelling.

## Day 2

**Update on "Rethinking malaria"**

19. **Comment:** Besides the current impending threat of COVID-19, many more challenges are being faced in defeating malaria. Some of these are: (a) deletions of PfHPR2/3 genes in *Plasmodium falciparum* at the point-of-care diagnosis, (b) drug resistance to parasites, (c) migration of parasite strains to newer areas, (d) migration of drug-resistant parasites in low-transmission settings, (e) multi-insecticide resistance in vector mosquitoes, (f) poor disease surveillance, (g) invasion of *Anopheles stephensi* in Africa and elsewhere, (h) long-distance migration of vector mosquitoes in sub-Saharan Africa, and (i) unmet funding drift.

20. **Comment:** There are many gaps in surveillance for which smart digital surveillance is an important strategy that need to be implemented on priority. Artificial intelligence and machine learning should find proper place to solve many ongoing problems of diagnosis and effective implementation, monitoring of the elimination programme. Routine malaria molecular surveillance of parasites and vectors at subnational and regional levels must be carried out to take correct and appropriate measures policy decision makers. As long-distance night travel and invasiveness of vector mosquitoes have been established or otherwise, LSM must find priority. Like COVID-19, other tropical diseases like malaria must be given priority with proper funding provisions.

21. **Q:** What are the efforts in determining district-specific malaria epidemiologic profiles to be used for planning of specific appropriate interventions?

    **A:** We have worked across HBHI countries on district level subnational tailoring of interventions based on their epidemiological profile, intervention, health system and other factors. WHO is also working on guidance to help countries implement subnational tailoring of interventions through the proposed SNT operational manual. WHO has also been intentional in ensuring flexibilities in the recommendations to allow countries to improve adaptation.

22. **Q:** To achieve a suitable and significant gain in the reduction of morbidity and mortality by reduction of transmission it is probably necessary to reduce parasite exposure to low levels. With the present interventions this has not been achieved in the high-transmission zones. What are your thoughts on it?

**A:** Considerable reductions in the rates of infections have been achieved with vector control, especially LLINs. However, even with the best level of efficacy and use, all our preventive interventions have modest impact. As such, we need better tools, but we also need to do more with what we have with better targeting.

23. **Q:** Sustainability of control measures by households has been difficult. Mosquito nets worn out are not replaced and re-treatments are not done in time to provide a continuous protection against mosquito bites. What are your thoughts on it?

    **A:** The constraints in this area are both financial and logistical, as more frequent ITN or IRS campaigns would require considerable addition resources but are also difficult to organize more frequently than they currently take place. Assuming that financial resources are not going to increase significantly over the coming years, one solution may be to develop more durable products and to educate ITN users to wash nets less often and/or take greater care of them to reduce wear and tear.

24. **Q:** Another major barrier to the successful malaria case management is the poor adherence to drug regimens. Underdosing is quite a common practice in many households because of poverty and the fact that clinical cure of fever is what matters to many individuals. What are your thoughts on it?

    **A:** Poor adherence is a barrier to successful case management and could contribute to the development of drug resistance. In addition to the characteristics of the medicine, there are multiple contextual factors that impede adherence, such as household poverty and quality and trust in health services. Rethinking malaria seeks to better engage communities and frontline health workers, who are well placed to address some of the local challenges.

25. **Comment:** Reduction of human exposure to infective mosquitoes is a critical element of malaria control program. However, most interventions rely on techniques that kill adult mosquitoes. Methods that target suppressing productivity or killing mosquito larvae are not given due importance because they are more labour-intensive and include source reduction. Such techniques can be sustainably used where communities are involved in malaria control.

26. **Comment:** Strengthening of surveillance should be one of the current priorities. The use of rapid diagnostic tests could be introduced for rapid epidemiologic mapping and for routine screening of suspected cases of malaria. More research is needed and should include mosquito ecological behavioural studies, systematic monitoring of drug and insecticide resistance, diagnostic techniques, and socio-cultural behaviour that hinder malaria prevention and control at household and community level.

27. **Q:** Sub-Saharan Africa needs attention for bringing down malaria morbidity and mortality. I think, strategies and WHO technical support would be required for countries which drastic reduction of malaria and moving towards elimination. Especially for SNT would indeed be very important for big countries like India.

    **A:** Agree with you. The SNT manual and urban framework, as you know, is aimed at addressing all settings.

28. **Comment:** Effective vaccines or methods for reducing mosquito vectorial capacity would add enormously to the chance of achieving this goal.

29. **Comment:** The spread of resistance also threatens progress against malaria and, unless the pace at which new tools are evaluated and implemented is accelerated, risks derailing control efforts and curtailing any ambitions of elimination.

**Update on the framework for response to malaria in urban areas**

30. **Comment**: Major challenges include:
    - poor surveillance to identify hotspots of transmission;
    - Inadequate knowledge on the distribution, behaviour and resistance profiles of local vectors;
    - weak links between research institutes and control programmes in country/government;
    - existence of multiple donors (many with their own agendas);
    - reporting requirements that put further pressure on over stretched control programmes.

    **A:** Great list of challenges, many of which were discussed by the thematic groups.

31. **Q:** In the spirit of the Global Vector Control Response and the Global Arbovirus Initiative, will this urban strategy include response to Aedes-borne diseases as well as malaria?

    **A:** We do reflect on other VBDs and I am familiar with the GAI. We try to align a lot with a very strong intention for integration. However, we don't go into the details of the control of other VBDs.

32. **Q:** Will a particular focus be made on the threat of *An. stephensi* in Africa?

    **A:** Yes, we will launch a regional initiative for a response against *An. stephensi* in the Horn of Africa by middle of 2022 and are hoping to hold a meeting of countries and their partners in the region before the end of the year. We would also like to draw your attention to the WHO Vector Alert which was issued in 2019 and the theme documenting existing and new reports of this vector in Malaria Threats Map. WHO will continue to build on these efforts and explore opportunities to integrate them with other responses to emerging malaria threats in Africa.

33. **Q:** How will all the proposed activities/changes align with country planning and budgeting? Without this I do not see how this will succeed. In fact, not only aligned with planning and budgeting but also with current structures/governance.

    **A:** I think we need to think of this as a decision that is centred on city planning and budgeting to which the national malaria programmes contribute. Where activities are to be built into the specific malaria budgets and funding request, this will likely be only a part of a broader urban malaria response.

34. **Q:** How can we control Malaria in urban cities with no drainage system and low environmental sanitation?

    **A:** This is where urban development plans intersect with the malaria response. As this infrastructure is developed, other interim interventions can play a role. This will be context specific, and it may that the interventions we use in rural areas will be applicable here.

**Update on the development of a strategy to respond to antimalarial drug resistance in Africa**

35. **Q:** Since 2012, MPAG has stated that Artemisia use could lead to resistance. Beyond referencing Elfawal et al 2015, which found that artemisia whole plant use "can overcome parasite resistance and is actually more resilient to evolution of parasite resistance," is there any published scientific evidence that shows that using Artemisia tea increases resistance that you can provide, or will Artemisia whole plant use be reviewed in the phase 1b technical review? I know there is plenty of evidence for Artemisinin monotherapies and resistance but the

categorization of Artemisia as being a monotherapy is widely contested and regarding studies on the whole plant use and resistance the only reference cited in WHO documents is Elfawal et al 2015.

**A:** There are now in vitro data showing that tea selects for artemisinin partially resistant parasites. I hope this will be published soon.

36. **Comment:** I ask this because in my discussions with Artemisia users and promoters in Sub-Saharan Africa, including government officials, doctors and medical professionals, they cite a lack of evidence showing that the plant will lead to resistance and reference Elfawal 2015; Yarell 2014; Maranga, 2018, etc. who have argued that it doesn't lead to resistance, so having some scientific studies or publications that supports MPAG's position might help in convincing governments and medical personnel to stop using Artemisia and may also counter some of the negative media coverage that has come since 2017 that portrays MPAG's opposition as financial and political rather than based in science.

37. **Q:** The question as to the role of vector control is interesting, as they have parallel issues with generation of resistance and the same strategies may be helpful and needed, particularly where insecticide and drug resistance occur together.

    **A:** GMP has developed a Global Plan for Insecticide Resistance management and is current developing a strategy to address antimalarial drug resistance in Africa.

38. **Q:** Why is Artemether-lumefantrine so dominating, it is a price question?

    **A:** Artemether-lumefantrine was the first marketed fixed dose ACT. The price is similar to artesunate-amodiaquine but lower to the other ACTs.

39. **Comment:** Another angle that should be seriously integrated in dealing with malaria resistance in Africa in particular is the implementation. There are lots of implementation challenges which I am optimistic that with the rethinking malaria and enabling community participation in all stages will help at least to mitigate the resistance from the community. Different areas need different strategies that suit their peculiarities. These should be well considered before implementing any strategy.

40. **Q:** Is there any plan to check the antimalarial medicine – are the drugs effective for mixed infections when *P. falciparum* is always with another species?

    **A:** Yes. All ACTs are efficacious against falciparum and vivax malaria. Except maybe AS+SP for vivax. Of course, for radical cure of vivax additional primaquine should be give respecting contraindications