World Health Organization

Questions & answers

Session 1

1. **Q:** It just took 1 year for COVID vaccine; why did it take so long for the malaria vaccine?

   A: There are several contributory reasons. The parasite which causes malaria is a much more complicated biological structure than the virus which causes COVID-19. Multiple epitopes on a variety of antigens in each part of the parasite's lifecycle can induce immune responses, but it remains unclear which responses to which epitopes are protective. The biological and immunological complexities of malaria vaccine development are no doubt compounded by the lack of a major market in high income countries.

2. **Q:** Is the IVM also considered?

   A: Yes, this approach will draw on the principles of IVM as adopted by and further enhanced by the Global Vector Control Response (GVCR). If we are to make a dramatic impact on malaria, it will require rethinking on how to affect the behavior of humans, parasites and mosquitoes and the dynamics between them, and how to affect change by collaborating across sectors. In addition to investigating opportunities to implement and scale up new interventions, rethinking malaria at country level will provide an opportunity to consider how the impact of current tools can be maximized and to learn lessons from IVM on integration and the importance of understanding and responding to the local environment.

3. **Q:** What is the strategy on surveillance and response recommended by WHO implemented in the areas close to the malaria elimination? If we have new tools to support the strategy?

   A: Please join the session on digital tools for malaria elimination surveillance scheduled for tomorrow at 14:45 CET for more information on this topic. The pre-reads and presentation materials are available for reference.

4. **Q:** Looking around the world at the remarkable progress made in COVID vaccines, why is there no real mention of a drive for vaccine innovation/new vaccines. Should we not be diversifying beyond >30 years of singular investment in 1 vaccine (based on 1 protein). Consider multiple alternative strategies, not just to get a single successful vaccine but to get myriad vaccines that work differently, can be rolled out in parallel? It appears as an onlooker that malaria vaccines beyond RTS,S are NOT being considered in the strategy or in WHO recommendations?

   A: WHO has re-convened the Malaria Vaccine Advisory Group (MALVAC) and is working on the development of a Roadmap that is expected to be launched later this year. An update was provided at our October 2019 meeting**.**

5. **Q:** L'utilisation des MILDA avec PBO se fait à partir de quel taux de résistance aux pyréthrinoïdes ? (*The use of LLINs with PBO is made after what rate of resistance to pyrethroids?*)

   A: La recommandation actuelle de l'OMS pour le déploiement de moustiquaires imprégnées de pyréthrinoïdes-PBO est la suivante : L'OMS recommande de façon conditionnelle le déploiement de moustiquaires imprégnées de pyréthrinoïdes-PBO préqualifiées par l'OMS au lieu des moustiquaires imprégnées exclusivement de pyréthrinoïdes pour la prévention et le contrôle du paludisme chez les enfants et les adultes vivant dans des zones de transmission du paludisme ainsi que dans les zones avec un potentiel paludogène lorsque le ou les principaux vecteurs du paludisme présentent une résistance aux pyréthroïdes qui est: a) confirmée, b) de niveau intermédiaire, et c) conférée (au moins en partie) par un mécanisme de résistance à base de monooxygénase, tel que déterminé par des procédures standard. Les « niveaux intermédiaires » tels qu'utilisés ci-dessus ont été définis comme une fourchette de 10% à 80% de mortalité de moustiques après exposition à un insecticide pyréthrinoïde dans des kits de test de l'OMS ou des dosages en flacon CDC. (*WHO's current recommendation for the deployment of pyrethroid-PBO nets is: WHO conditionally recommends pyrethroid-PBO nets prequalified by WHO for deployment instead of pyrethroid-only ITNs for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission or with malariogenic potential where the principal malaria vector(s) exhibit pyrethroid resistance that is: a) confirmed, b) of intermediate level, and c) conferred (at least in part) by a monooxygenase-based resistance mechanism, as determined by standard procedures. "Intermediate levels" as used above was defined as a range of 10% to 80% mosquito mortality after exposure to a pyrethroid insecticide in WHO test kits or CDC bottle assays.*)

6. **Q:** My question is about use of the existing interventions. We talk a lot about coverage – which is very good but how about increasing the use of those tools, case in point is the ITNs – going up to 80% access to at least one net but use lies way below the existing coverage rates. Your thoughts on this SBC to increase community use of those interventions.

   A: We fully agree that in addition to coverage, it is really important to improve the appropriate use of different interventions. We need to understand the barriers to access and use of interventions. By engaging those at the front line and communities, we can hear firsthand what are the challenges they face and consider how we can collectively overcome them. SBC provides an opportunity to interactively communicate, motivate and problem solve.

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7. **Q:** Comment s'y prendre pour donner réalité à ce rêve de voir le paludisme cesser d'être un problème de santé publique surtout dans ce contexte de pandémie de COVID-19, de conflits armés et désordres de tous genres (changements climatiques, problèmes financiers et économiques) ? (*How do we go about making this dream of seeing malaria cease to be a public health problem come true, especially in this context of the COVID-19 pandemic, armed conflicts and disorders of all kinds (climate change, financial and economic problems, etc.)?*)

   A: Nous vivons assurément dans un monde dynamique. Le paludisme est très sensible au contexte dans lequel il se développe, prospérant là où il y a de la pauvreté, des conflits et des bouleversements. L'inclusion du paludisme dans les ODD est une reconnaissance du fait que le succès sera tributaire de la lutte contre ces défis complexes et d'autres déterminants structurels. Les menaces offrent également des opportunités. Alors que la pandémie de COVID-19 a créé des bouleversements majeurs à travers le monde et menacé l'économie

mondiale, elle offre également une opportunité de mieux reconstruire et les leçons qui en seront tirées seront utilisées pour repenser le paludisme. Alors que les pays repensent le paludisme, il sera possible d'explorer ce qui rend les gens vulnérables à la maladie et les actions nécessaires pour s'attaquer à ces déterminants. (*It is certainly a dynamic world. Malaria is very susceptible to the broader context, thriving where there is poverty, conflict and disruption. The positioning of malaria within the SDGs is an acknowledgement that success will be determined by tackling these complex challenges and other structural determinants. The threats also provide opportunity. Whilst COVID-19 has created massive disruptions across the world and threatened the global economy, it also provides an opportunity to build back better and the lessons will be used in rethinking malaria. As countries rethink malaria, there will be opportunity to explore what makes people vulnerable to malaria and the actions needed to address these determinants.*)

8. **Q:** There is a complex political economy around the use of data for decision-making along the information chain. It is an evidence gap, which should be addressed as we make efforts to create a data-use culture for accelerated and sustained reduction in the burden of malaria. Is this something which could be added to the initiative on rethinking malaria?

   A: Reliable and timely data is valuable in supporting the decisions on malaria. A culture of using data needs to be realized by all those making decisions. This includes the communities. As countries rethink malaria, it will be important to consider how data democratization can be made to work so that communities are able to generate, analyse and use data. It will also consider the importance of open data in supporting better malaria governance.

9. **Q:** Social accountability at all levels of the health system, appears to be difficult to institutionalize. Are there any new efforts to strengthen social accountability as an aspect of resilient health systems?

   A: Tackling malaria and achieving health equity will require active participation by communities and their empowerment to shape their own health. But as many solutions lie out of their hands it also requires responsiveness of the State. The rethinking malaria at country level seeks to work with those at the frontline (communities and health providers) to identify the vulnerable and those being left behind and consider how a whole of society approach can be used to address the barriers they face. This is consistent with the work done by WHO in ensuring communities have greater control over the key decisions that affect their wellbeing and establishing a commitment for primary health care.

Session 2

Clinical malaria

10. **Q:** Do these low-level parasitemias detected by the highly sensitive RDTs infect the vector? Are they relevant for transmission?

    A: Evidence from several reports using mosquito-feeding experiments indicates that mosquitoes can be infected with low-density *P. falciparum* and *P. vivax* infections, although less efficiently than with high-density infections. For *P. vivax*, gametocyte densities closely follow those of asexual parasite stages. Transmission to mosquitoes becomes less efficient at *P. vivax* densities below the limit of detection (LOD) of expert microscopy (estimated at >10 parasites/µl),but can readily occur with infections below the LOD of field microscopy (estimated at >100 parasites/µl). For *P. falciparum*, the relation between gametocyte density transmissibility and the density of asexual parasitaemia is less predictable, and low-density infections below the detection level of expert microscopy can frequently result in mosquito

infection. The outcome of experimental mosquito feeds is influenced by a variety of host, vector and parasite factors in addition to methodological factors, but their dynamic interactions are poorly understood. Depending on the relative proportions of low- and high-density infections in a particular location, the role of each in overall transmission may vary considerably. Mosquito feeding experiments help to measure the infectiousness of low- and high-density infections for mosquitoes. However, there are limited data on the relative contributions of low- and high-density *P. falciparum* and *P. vivax* infections to the onward transmission to human populations at the community level. It is critically important to understand the contribution of low-density infections to malaria transmission in order to inform effective malaria control strategies.

11. **Comment:** In areas with low malaria transmission, providers are increasingly complaining about the effectiveness of RDTs currently used for malaria diagnosis. It would be very interesting to make these ultra-sensitive RDTs available in low transmission areas. In pre-elimination areas, microscopes are better than those used in other areas.

12. **Q:** I think we need to move the discussion of pyrogenic threshold from microscopic density to an antigen density at fever onset to help with RDT R&D and procurement selection for case management. As you know, HRP2 levels are not linear with parasitemia. LDH is more linearly related to microscopy. My question is **'**what additional work is planned to look at the antigen concentrations associated with fever**'**? Establishing this threshold for LDH is important, but seems outstanding.

    A: We have no specific plans in this space. Datasets that include antigen concentration and parasitemia are scarce. However, as you say, we know that the relationship between antigen concentration and parasitemia is not nicely linear, but it is better for pLDH than for HRP for good reasons. This is why for a decade of WHO product testing we assessed tests against a **'**range**'** of antigen concentrations for two thresholds – 200 p/ul and 2000 p/ul. So we have always taken this variability into consideration. As far as pyrogenic thresholds and antigen concentrations – there is little reported on this so definitely an area for additional study.

13. **Q:** Do you think a more sensitive test would allow detecting asymptomatic malaria cases in the dry season to help reduce its burden before the rainy season and potentially help with eradication?

    A: Potentially this could have an impact; seasonal chemoprophylaxis has an impact – so diagnostic testing as alternative could as well, but would need to be studied.

14. **Q:** What is the epidemiological significance of asymptomatic and submicroscopic cases in low transmission settings? What tests are considered best to detect these cases?

    A: This question has been asked for 100 years. There is no short answer and I refer you to a meeting report on this topic.

15. **Q:** Which of the positivity rate and incidence is better for assessing the impact of routine malaria control activities? The quality of population data has a strong influence on incidence.

    A: Both are important but depend on context. Incidence is susceptible to changes in population denominator but also the numerator of cases is influenced by care seeking and case reporting. While test positivity rate is less susceptible to population denominator changes, it can be influenced by changes in case definitions and diagnostic practices. Often

countries should look at both indicators as well as community parasite prevalence where available and triangulate.

16. **Q:** If the use of ultra-sensitive RDTs is not currently widely promoted in Africa, where would you recommend the use of these RDTs?

    A: So-called ultra-sensitive RDTs meet the WHO minimum performance criteria and one has been WHO prequalified on this basis. It can be procured but advantages (individual and public health benefits) of using it over other so-called "conventional" RDTs have not been well elucidated. Therefore, ultra-sensitive tests are not recommended as being preferable to conventional RDTs.

17. **Comment:** I believe that much of the confusion on the discussion around the value of hsRDTs relates to the different potential usages of these tests. I strongly agree that in a clinical use scenario, there appears to be little value and great risk to their use particularly in moderate to high prevalence settings. The open question is whether there may be a role for hsRDTs as a public health tool (i,e, outside of clinical diagnosis) . For this indication, there is evidence that mass screening and treating approaches are inferior to mass treatment/MDA. The point here, though, is that the discussion should be organized around the use case to avoid confusion.

18. **Q:** We are seeing lot of cases that are detected positives in mRDTs (WHO PQ) as faint weak bands and are often microscopy negatives upon parallel investigations. What could be the reasons for that?

    A: There are a few possibilities: 1) True false positives – although RDT specificity is very high, false positive results can occur and may potentially be related to product defect – if this problem happens often it should be reported to manufacturer; 2) Clinical false positive due to HRP2 persistence following recent treatment with antimalarials can cause a "clinical" false positive; and 3) poor sensitivity of microscopy – this can only be resolved with PCR.

19. **Q:** Most of the cases reported already have taken the antibiotics. Is there a possibility of single indigenous case in the low transmission settings? We record such cases in a regular basis. What is the chance of cross-reactivity of mRDT with the other diseases?

    A: Consider the possibilities above; yes we have seen cross reactivity with some diseases and conditions with some brands of RDTs. Here is an example.

Drug efficacy and resistance in Africa

20. **Q:** Quels sont les facteurs qui favorisent la survenue des résistances aux CTA ? Quelles sont les CTA les plus concernées dans ces études ? (*What are the factors that favor the occurrence of resistance to ACTs? What are the ACTs most concerned in these studies?*)

    A: La survenue de mutation(s) liées à des résistances est un phénomène aléatoire rare favorisé par les fortes parasitémies. Une fois la résistance apparue, il faut une pression de sélection sur la mutation ou les mutations qui peuvent être due : usage inapproprié de médicaments, dose insuffisance, médicaments contrefaits ou substandards, absorption insuffisante du médicament due à des vomissements ou de la diarrhée. Dans le cas des CTA, ce phénomène peut d'appliquer sur l'un des composant ou sur les deux à la fois. Les études présentées concernent toutes les CTAs mais aucune résistance aux CTAs n'a été présentée pour l'Afrique. (*The occurrence of mutation (s) linked to resistance is a rare random phenomenon favored by*

strong parasitaemias. Once resistance has appeared, there must be selective pressure on the mutation or mutations which may be due to inappropriate use of drugs, insufficient dose, counterfeit or substandard drugs, insufficient absorption of the drug due to vomiting or diarrhea. In the case of ACTs, this phenomenon can apply to one or both components at the same time. The studies presented relate to all ACTs but no resistance to ACTs has been presented for Africa).

21. **Comment:** It's important not to overstate problems with lumefantrine. Some trials suggest decreased efficacy of AL, and this needs to be followed. But, to my knowledge, there is currently no convincing evidence of true lumefantrine resistance.

P. knowlesi

22. **Q:** For knowlesi malaria and given that Malaysia is doing PCR for diagnostics, is there capacity to sequence parasite genomes from humans and the non-human primates? Doing some phylogenetic analysis could help to shed light on whether transmission to humans is largely arising from human-human transmission following spillover (stage 4), repeated spillover (stage 2) or rare human-human transmission following spillover (stage 3).

    A: Yes, some of this information is available already (and published) and will be reviewed in the systematic review being conducted.

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23. **Q:** Based on recent studies about *P. simium* in forest areas of Atlantic Forest in southeast Brazil, should we consider making an effort to define in which the stage the pathogens of animals evolve to cause diseases confined in humans as we are concerned that this will impact our malaria elimination plan?

    A: It is possible that there will be a need to consider the implications of non-human primate malarias more broadly, but we will wait for the results of the technical consultation on *P. knowlesi* first.

24. **Q:** Is there a possibility of *P. malariae* present in few cases in forest areas of Amazonian Region is actually *P. brasilianum* and so a possible zoonosis?

    A: Not clear, but could be investigated using nucleic-acid based tests.

Session 3

HRP2 gene deletions

25. **Q:** Would MPAG consider *Pf* with HRP2 & 3 mutations an emergency of public health concern to allow an accelerated EUL process for new improved LDH PfRDT assays and prioritize surveillance efforts?

    A: MPAG is not responsible for making this designation.

26. **Q:** There are some opportunities for adding filter paper samples for HRP 2 survey work to ongoing large national surveys, such as the PHIAs for HIV. Do you think these kinds of opportunities have been maximized?

    A: These mechanisms could be useful if we have low cost, high throughput options for screening samples.

27. **Q:** For manufacturers whom are developing new RDT tests in response to these deletions, what are your recommendations? Is there any guidance for the clinical trial designs? E.g. how many deletions at minimum and how many geographical locations?

    A: Please refer to WHO technical specification series as RDTs that detect *pfhrp2/3* deletions will need to meet all the same specifications. The independent evaluation procedure led by WHO PQ includes *pfhrp2/3* deletions in the panel so tests will be assessed against these materials. We do not have information regarding the specific number of *pfhrp2* single and dual deleted parasites that must be included to make a specific claim but you could reach out to WHO prequalification regarding this question: diagnostics@who.int.

28. **Q:** Do you think we could use these materials in the Americas? Because we have studies here showing deletion in an important way.

    A: Due to prevalent *Pfhrp2/3* deletions in several countries in the Americas **–** HRP2 RDTs have not been used. Instead, there is continued reliance on microscopy and in remote areas, a combination of pfLDH, HRP2, Pfv-LDH RDTs are used. I know specifically that Brazil has procured this product so they can detect HRP2 expressing parasites, as well as some % of the nonHRP2 expressing parasites using the pf-LDH. It will likely miss lower density infections about half of the time. So for the most part, HRP2 RDTs are only used if combined with a pf-LDH test line.

29. **Comment:** Great presentation on HRP2 deletion. The problem is spreading and there is a need for a Global Call for Action to address this. MPAG has spelt out clearly the implications if action is taken. We must learn lessons from how we handled insecticide & drug resistance.
30. **Q:** It is worthwhile noting that HRP-2 deletions spread throughout South America despite very infrequent use of mRDTs for malaria diagnosis (with most countries still relying heavily on microscopy). This raises a question about whether the models predicting that “pressure” will promote further spread or whether other factors are driving it.

    A: Totally agree with you, South America teaches us that there is more than *pfhrp2* RDT pressure driving this. Will investigate if WHO Emergency Use Listing Procedure (EUL) is possible but likely they will defer to the Global Fund Expert Review Panel for Diagnostics (ERPD).

31. **Comment:** There are three benchtop separate quantitative multi-antigen assays for HRP2, PfLDH and PvLDH. One is now commercially available – Quansys. These use different reagents and have not yet been fully cross correlated to assess difference in the assays to allow establishment of a threshold. Funded work for cross validation has been delayed by COVID-19.
32. **Q:** Is there an opportunity to use EUL/Emergency Use Authorization (EUA) processes to accelerate new diagnostics given this crisis?

A: GMP has not explored with WHO PQ but the GF led ERPD process is operational and there have been calls specifically for non-HRP2 based diagnosis – which is how the RapiGen test received ERPD approval. They are currently in the WHO PQ pipeline.

33. **Q:** Which countries in Africa have access to Luminex/ other antigen quantification methods? Does Ethiopia have access?

    A: GMP has not mapped the availability of Luminex or other Elisa based tests in Africa – we believe Luminex has been installed in Senegal (Cheikh Anta Diop University) but there may be others.

34. **Comment:** Just a note that the Horn of Africa is now experiencing the dual threat of HRP2/3 deletion for RDTs and *An. stephensi* emerging in these same countries. On the one hand, these are different issues affecting different parts of national malaria programmes (NMPs). However, if you consider a Horn of Africa engagement/consultation to build a joint effort, should you be doing this on both the vector control and diagnostic fronts, and perhaps others if relevant?

    A: Great suggestion.

35. **Q:** May I request that countries should be requested to pay attention to Malaria Sentinel Sites that could help track these deletions? Malaria Sentinel sites are really not effective in many countries but attempts should be made to catalyse these to track failing RDTs.

    A: Sentinel sites can be used and they may provide important signals but if they are few and far between they may miss a problem which is known to be very heterogeneous.

Urban malaria

36. **Q:** Although the epidemiology/biology of malaria is clearly different from other urban diseases (e.g. TB or dengue) can you learn any lessons from other/existing urban disease control programmes?

    A: Yes. We will be reaching to experts in other diseases programmes for lessons learned.

37. **Q:** As *Aedes* are obviously the most important urban vector, are there opportunities, especially where *An. stephensi* is involved to take a page from dengue control for a broader IVM strategy?

    A: Yes. The aim to understand how best incorporate the malaria response into IVM and entomological surveillance into broader vector borne disease surveillance.

38. **Q:** Have the private physicians in urban Africa been trained in the recognition and treatment of malaria? These guidelines disseminated through meetings and conferences of medical societies?

    A: Yes.

39. **Q:** Have there been any evaluations of the costs of addressing urban malaria especially in the context of getting out to very remote, hard to access “last mile” malaria cases where we know that children and pregnant women are dying?

A: Not much in recent times that we are aware of. There are research studies that look at the cost of specific interventions. What we hope to implement is the cost-effectiveness analysis of current malaria interventions in urban areas

40. **Q:** A lot of urban malaria is related to travel to malaria endemic areas mostly in rural areas. Chemoprophylaxis is not something that is widely practiced especially in sub-Saharan Africa. Is this something you would consider including in the framework?

    A: Not much in recent times that we are aware of. There are research studies that look at the cost of specific interventions. What we hope to implement is the cost-effectiveness analysis of current malaria interventions in urban areas.

Received by email

41. **Q:** Will South America (Amazonian Region) be part of the strategy proposed by WHO for urban areas?

    A: Yes, the strategy will be global and will draw on lessons learned from all regions.

Severe malaria

42. **Q:** Although there is more that could be done to better train hospital staff on the management of severe malaria, there have been great efforts over recent years to roll out such training in many countries. One of the gaps that seems always to be overlooked is in the detection of danger signs at first point of care. There is ample evidence that the weak links both at facility and community level is that health workers either fail to assess or fail to identify signs of severe febrile illness. Quality Assurance programs do focus on improving these skills in health workers, but have been less than fully successful. Will there be further focus on this aspect of the continuum of care?

    A: Yes, we will certainly give this an additional focus.

43. **Q:** Is there evidence (or clear lack of evidence) that Kelch-13 mediated delayed clearance after intravenous or IM artesunate confers any increased mortality risk?

    A: There is no evidence as to K-13 mediated delayed clearance after parenteral artesunate affecting mortality. It is important to remember that parenteral treatment is just the initial step in the treatment of severe malaria. This is followed with a full treatment course of an effective ACT. However, since rapid clearance of parasites is considered essential in the management of severe malaria, the current recommendation based on expert opinion is to combine parenteral artesunate and quinine for the initial treatment of severe malaria in areas of known artemisinin resistance, this is then followed with a complete course of an effective ACT once the patient can tolerate oral medications.

44. **Q:** Severe malaria is a somewhat neglected. There could be deaths occurring from severe malaria from low transmission areas where health workers may not readily recognize malaria which then rapidly progresses to severe malaria and deaths. Maybe this is an area to add to the “rethinking malaria” to give it the emphasis it requires.

    A: Yes, it is certainly part of it.

45. **Comment:** It is up to NMPs to ensure that curriculums of pre-service trainings are updated. User-friendly, brief technical notes in consulting rooms; large flow charts in outpatient departments (OPDs) and consulting rooms; and on-site supportive supervision (OTSS) go a long way to improve uptake of new guidelines.

46. **Q:** An operational learning from the CARAMAL project where UNICEF was the implementer: in some settings, upwards of 60% of patients were still positive for malaria at day 28 of follow up post discharge. Are there any socio-economics elements that are being considered in how we address severe malaria? Changes need to be made to the iCCM algorithm: severe disease symptoms recommend an immediate referral without an RDT making it difficult to track how closely the severe malaria symptoms differentiate from other severe disease. Also there is a need to stress that rectal artesunate (RAS) is just pre-referral and the need to ensure care-takers completed care-seeking at tertiary care. Thus the need for significant investments into social and behavior change communication (SBCC) around 1) early care-seeking and 2) how to truly manage severe malaria from diagnosis to complete cure.

    A: This is a valid comment. WHO will continue to support countries in their efforts to strengthen all aspect of quality of care.

Classification of ITN products

47. **Q:** What would be the difference in classification from pyrethroid/pyriproxiphen and pyrethroid/chlophenaphyr?

    A: These two types of products are considered to be in different classes, as outlined in the May 2020 MPAC report.

48. **Q:** Will this classification be reflected in the WHO PQT VCP/ JMPS process evaluation?

    A: The new system is in place to classify ITNs into different categories for the purposes of determination of public health value and establishing the first in class product. This classification system does not impact the prequalification assessment of the safety, entomological efficacy and quality of the ITN. The JMPS evaluation is specifically for the purpose of establishing product manufacturing specifications and applies to all ITNs regardless of their classification.

49. **Q:** is there a plan for incorporating larviciding as a supplementary recommended mosquito control method alongside ITNs and IRS?

    A: A recommendation for larviciding as a supplementary vector control intervention is already in place. We kindly ask you to reference the *WHO Guidelines for malaria*.

50. **Q:** ITNs represent important financial needs to fight malaria, beside quality of the product, do we have strong evidences of their efficacy to reduce malaria transmission in all the settings, including South America? Is a clear benefit/risk ratio defined for each setting including environmental impacts? Beside this, their correct uses are very difficult in the field and community worker approaches are keys to improve them.

    A: ITNs are probably the vector control intervention that comes with the strongest evidence base out of all available options. The evidence-base has been comprehensively assessed in a systematic review by the Cochrane Infectious Diseases group (Pryce et al. 2018). Overall, the reviews showed that ITNs are very effective at reducing malaria-related death and illness. We

kindly refer you to the review, which included six studies from Latin America, for further details. Information for each setting varies, with there being more evidence from Sub-Saharan Africa than from other parts of the world.

51. **Q:** One of the most important qualities of an ITN is the durability of its physical integrity. Should we not mandate systematic standardized monitoring of longevity of ITNs to get data and create incentives for industry to develop more rugged ITN?

    A: As part of the review of the current data requirements to support the quality aspects of ITNs, it has been identified that there clearly is a gap in data requirements which can indicate the physical durability of ITNs when used in the real world. Currently, the main data point assessed that provides some information on physical durability is bursting strength. As part of the plan to strengthen the data required, PQT/VCP are considering introducing additional data requirements which could include material snag strength, abrasion and resistance to hole formation. This proposal will be prepared for consultation with stakeholders. These data requirements would also assist with post prequalification monitoring and quality assurance activities.

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52. Q: Further clarity is requested with respect to ITN Class number two, which reads "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" in respect to:

    - Our understanding is that this class may contain multiple first-in-class products, as ITN's with different chemistries and/or different modes of actions, may fit into this class, for example, a pyrethroid-PBO ITN and a pyrethroid-chlofenapyr ITN. Each of these "sub-categories" will have its own policy recommendation based on the data generated by the first-in-class.

      A: The evolution of the ITN classification into three classes happened after trials for PBO nets and for a pyrethroid-chlorfenapyr product were initiated. WHO is now awaiting data from these trials to confirm this class. In any case, the vision for the future is that the class, not each type of product/chemistry/mode of action, would be provided with a WHO recommendation.

    - If so, the second-in-class products to each of these "sub-categories" need to be compared in semi-field studies (entomological endpoints) to the first-in-class in order to be covered by the policy recommendation linked to that "sub-category".

      A: No decision with regards to comparative evaluation of products within a class has been taken by WHO. As communicated earlier, WHO is looking into the potential use of non-inferiority studies using experimental huts to determine comparative performance of ITNs and, potentially, other products within the same class. A technical consultation on this topic is scheduled for September 2021, based on the outcome of which next steps in this area will be decided.

Digital solutions for malaria elimination surveillance

53. **Q:** What are the approximate costs of in-country implementation of piloting and scale-up of these tools?

    A: It is still too early to determine the cost of piloting and scale up of the tools as each of the 4 countries were at different levels of implementation. Countries that piloted these tools were selected based on interest from malaria programs, long term in-country presence by core partners, in-country capacity and existing adoption of surveillance processes and use of digital solutions. Cost implications will vary from country to country depending on the level of programme capacity, infrastructure in place and readiness. We will be working with countries to collect some of this information.

54. **Q:** Some countries have (apparently) good digital tools for malaria which are not DHIS2-based. Is there provision for strengthening these and integrating them?

    A: Where such request is made, we will support countries to strengthen their systems. The DSME tools are generally interoperable with other digital platforms and can be used in elimination surveillance as add-ons.

55. **Q:** When will those tools be fully available for countries and what is the difference of those tools with tracker module in the DHIS-2 platform? As some countries are deployed tracker module for malaria elimination surveillance.

    A: Tools will be available in two to three months. In the DSME tracker module of DHIS2 has also been updated to address the gaps highlighted that the tools. To take up these enhanced features a DHIS2 version upgrade will be required.

56. **Q:** Adequate consideration of entomological component for the digital systems being proposed.
57. **A:** A separate entomology module in DHIS2 is available for use for all settings to which DSME tools are interoperable.