Documentation related to Day 1 of the meeting
Click on the links below to see the pre reads and presentations

Malaria Policy Advisory Committee (MPAC) meeting , 13–14 May 2020

Background documentation for Day 1

Wednesday, 13 May 2020			
	Session 1	**Open**	
12:00 – 12:10	Welcome by the Chair, MPAC	Dr Dyann Wirth	**For information**
12:10 – 13:15	Report from the Director, GMP Update on the RTS,S Malaria Vaccine Implementation Programme	Dr Pedro Alonso	
13:15 – 13:30	*Coffee break*		
	Session 2	**Open**	
13:30 – 14:15	Update on the classification of insecticide-treated net products and associated evaluation procedures Background| Presentation	Dr Jan Kolaczinski	**For decision**

World Health Organization

Malaria Policy Advisory Committee (MPAC) Meeting

13 – 14 May 2020

Virtual Meeting

Welcome by the MPAC Chair, Dr Dyann Wirth

Global **Malaria** Programme

World Health Organization

Report from the Global Malaria Programme

Malaria Policy Advisory Committee

Geneva, Switzerland

Pedro L. Alonso

13 May 2020

Global **Malaria** Programme

World Health Organization

The world suddenly changed (30 January 2020)

"Over the past few weeks, we have witnessed the emergence of a previously unknown pathogen, which has escalated into an unprecedented outbreak, and which has been met by an unprecedented response"- @DrTedros #2019nCoV
8:41 PM · Jan 30, 2020

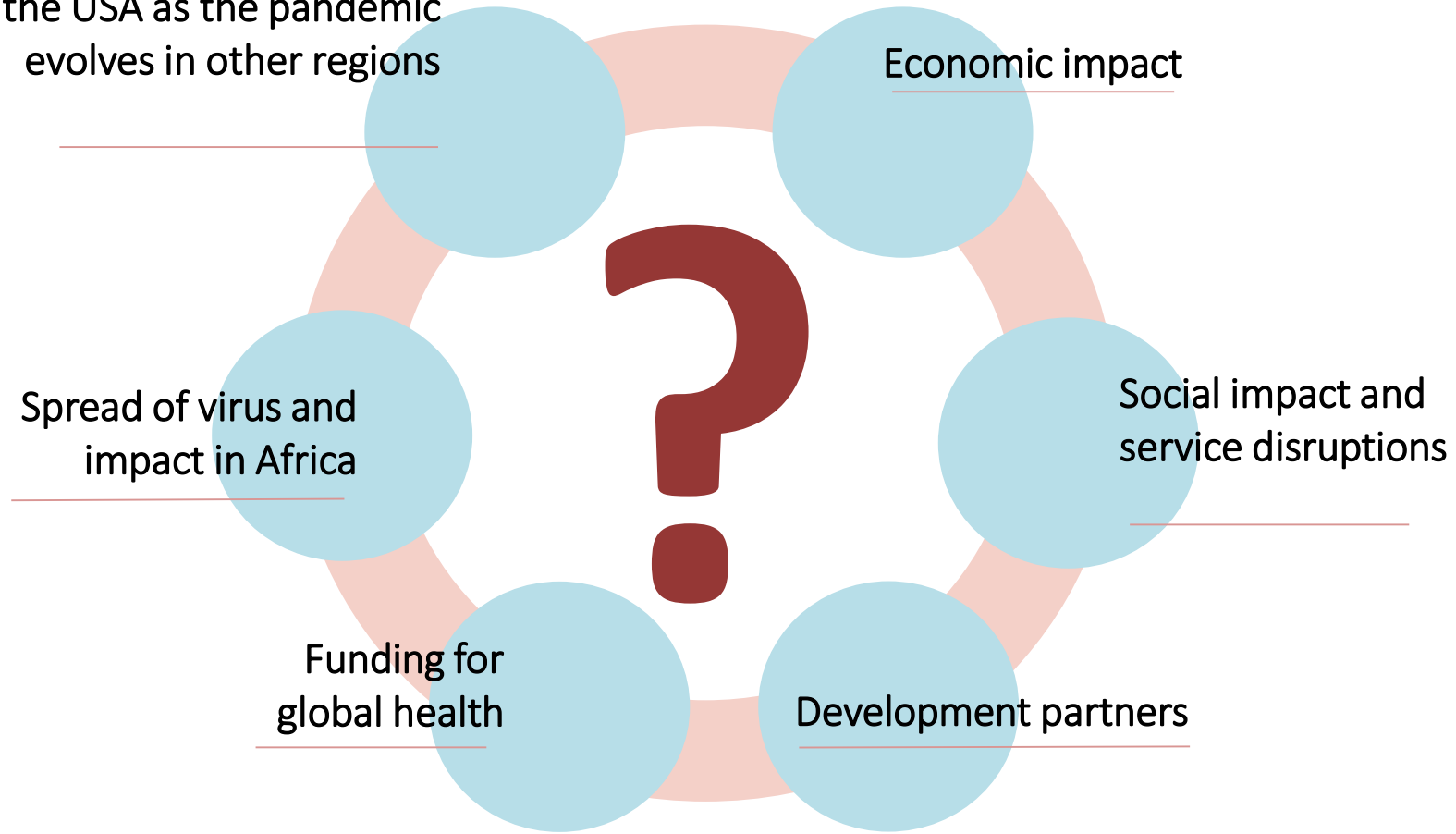
The world suddenly changed (30 January 2020)

"There are now 98 #2019nCoV cases in 18 countries outside #China, including 8 cases of human-to-human transmission in four countries: Germany, Japan, Viet Nam and the United States of America"-@DrTedros
8:43 PM · Jan 30, 2020·Twitter Web App

"We don't know what sort of damage this #2019nCoV virus could do if it were to spread in a country with a weaker health system. We must act now to help countries prepare for that possibility"-@DrTedros
8:43 PM · Jan 30, 2020·Twitter Web App

"For all of these reasons, I am declaring a public health emergency of international concern over the global outbreak of #2019nCoV."-@DrTedros
8:44 PM · Jan 30, 2020·Twitter Web App

Managing uncertainty



Malaria in the context of the COVID-19 pandemic

A time for enhanced collaboration

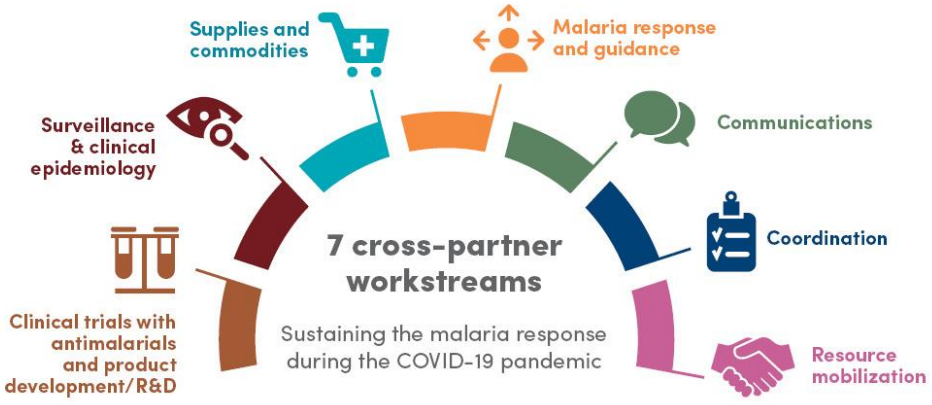
- Internal alignment and strategy:
  - GMP & Regional Advisors
  - WHE and other departments

- Key external technical partners and stakeholders

Malaria in the context of the COVID-19 pandemic

Aligning partners

In March 2020, before the pandemic had secured a strong footing in Africa, WHO established a mechanism to promote collaboration between partners and ensure a coordinated response. Malaria experts and leaders from nearly 20 organizations are lending their time and expertise across seven workstreams. Through twice weekly calls convened by WHO, they share updates on a variety of issues, from disruptions in the supply of key malaria commodities to the latest developments in clinical drug trials. This collaborative work has been welcomed by Member States as they seek to continue providing essential health services while limiting COVID-19 transmission and caring for people with symptoms of the coronavirus.

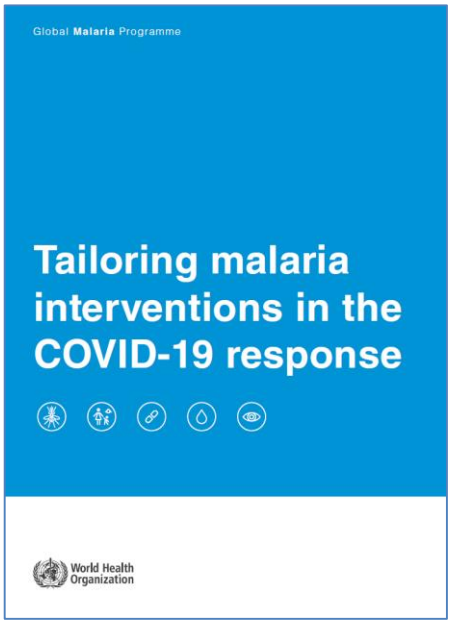


Malaria in the context of the COVID-19 pandemic

Sounding an urgent call

WHO is urgently calling on countries to maintain core malaria control services while protecting health workers and communities against COVID-19 transmission. A WHO statement, shared widely on 25 March, was issued in response to reports that some countries in sub-Saharan Africa had suspended mass insecticide-treated net (ITN) campaigns. WHO is encouraging countries to move forward with vector control activities, including ITN and indoor residual spraying campaigns. Such campaigns have been the mainstay of malaria prevention efforts in the region for nearly two decades. Countries are also strongly advised not to scale back efforts to detect and treat malaria. A Q&A provides additional background.

Malaria in the context of the COVID-19 pandemic



Delivering guidance

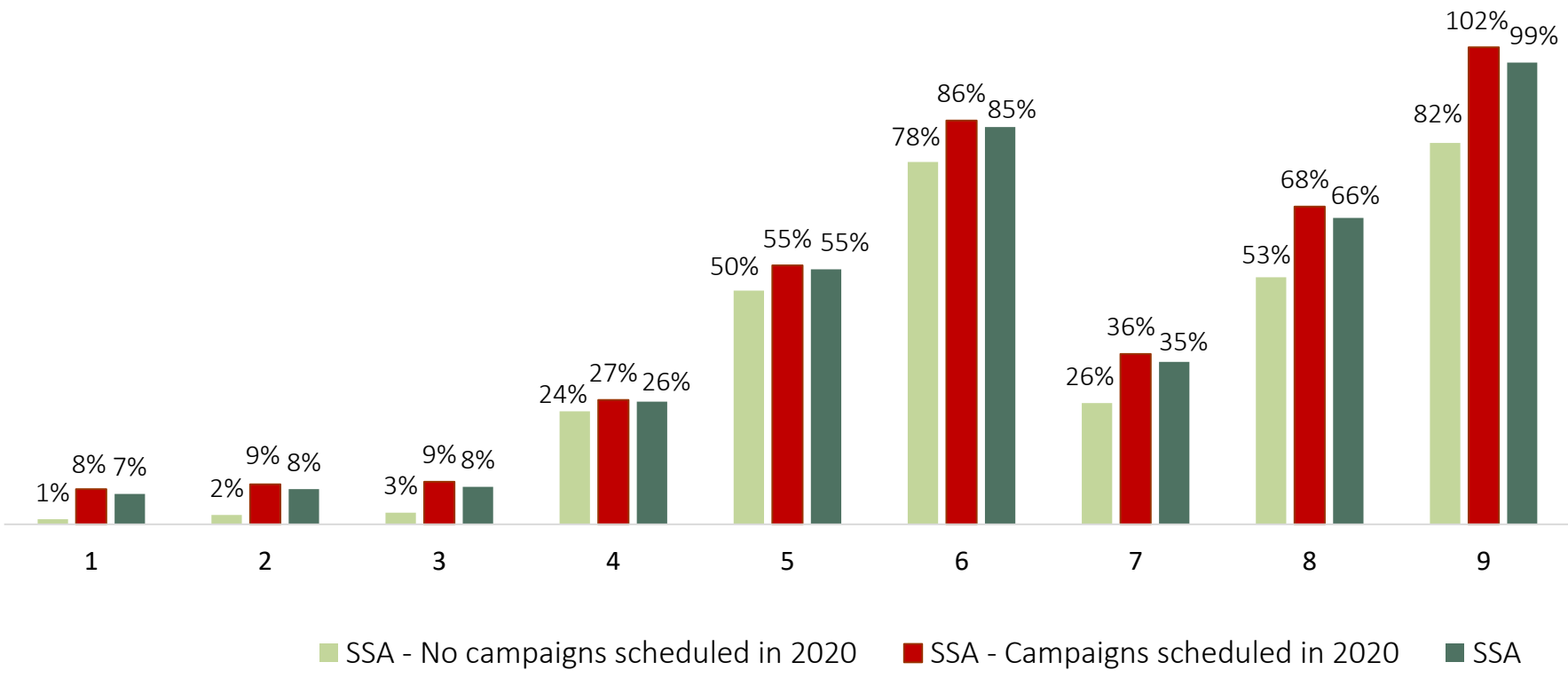
To support malaria-affected countries, WHO has issued technical guidance on how to safely maintain malaria control services in the context of the COVID-19 pandemic. *Tailoring malaria interventions in the COVID-19 response*, developed in close collaboration with partners, includes guidance on the prevention of infection through vector control and chemoprevention, testing, treatment of cases, clinical services, supply chain and laboratory activities. The document is consistent with broader WHO guidance on maintaining essential services in COVID-19 settings.

Malaria in the context of the COVID-19 pandemic

Modelling the potential impact

The findings of a new modelling analysis from WHO and partners reinforce the urgent call to maintain essential malaria control services during the pandemic. Under the worst-case scenario, in which all ITN campaigns are suspended and there is a 75% reduction in access to effective antimalarial medicines, a staggering 769 000 people in sub-Saharan Africa could die from malaria this year alone. This represents a doubling in the number of malaria deaths compared to 2018 and a return to mortality levels last seen 20 years ago.

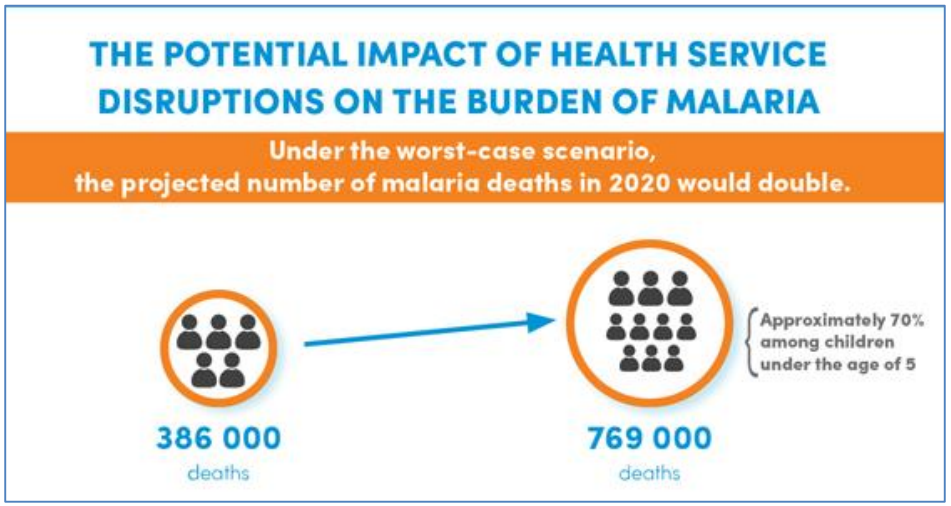
Malaria deaths in sub Saharan Africa (2020)

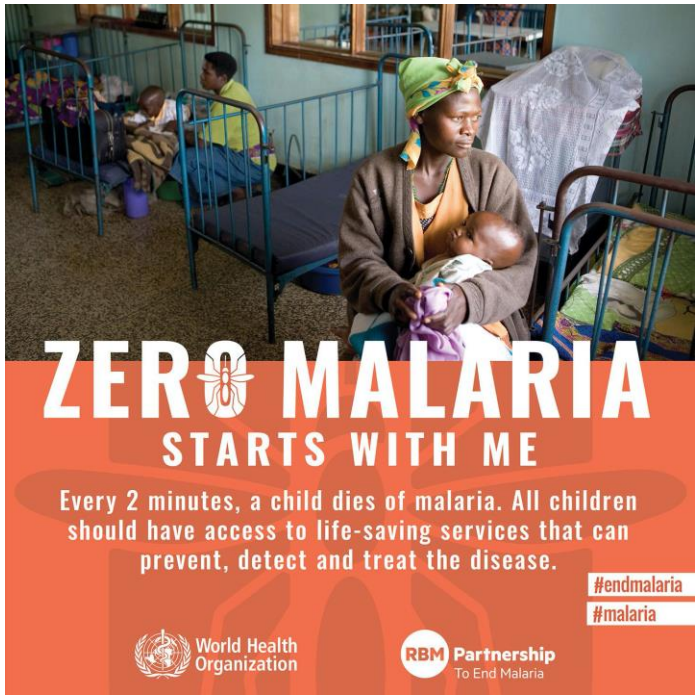


Scenarios: No LLIN campaigns in all scenarios. Change is compared with 'business as usual' scenario.
CD = Continuous Distribution, AM = Anti-Malarial.

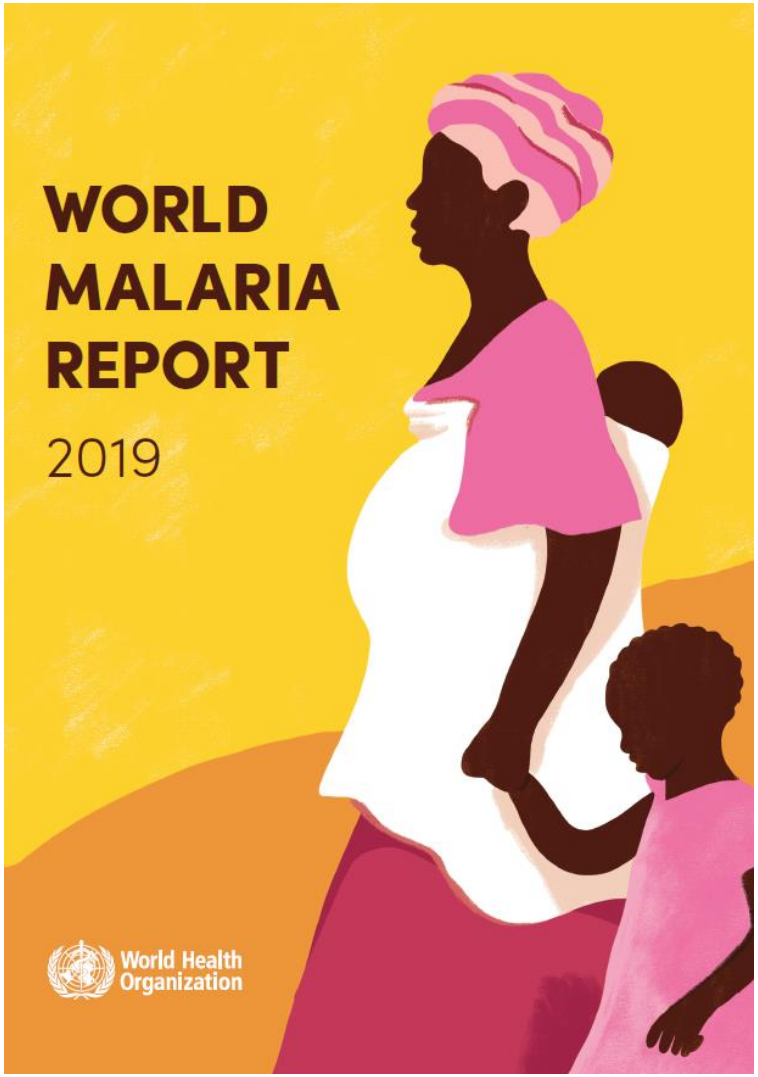
1: CD -25%, 2: CD-50%, 3: CD -75%, 4: AM -25%, 5: AM -50%, 6: AM -75%, 7: CD & AM -25%, 8: CD & AM -50%, 9: CD & AM -75%

Potential impact of health services disruptions





World Malaria Report 2019 - Highlights

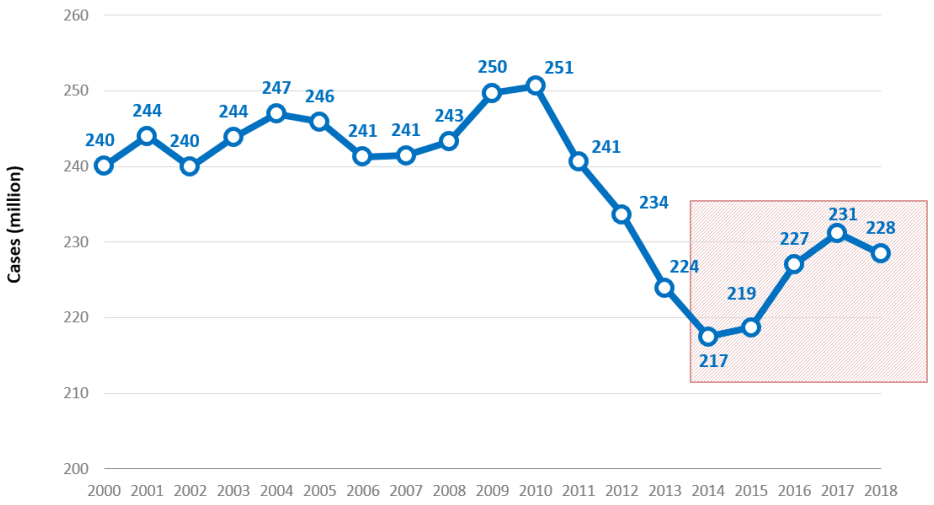


Malaria: Where were we before COVID-19?

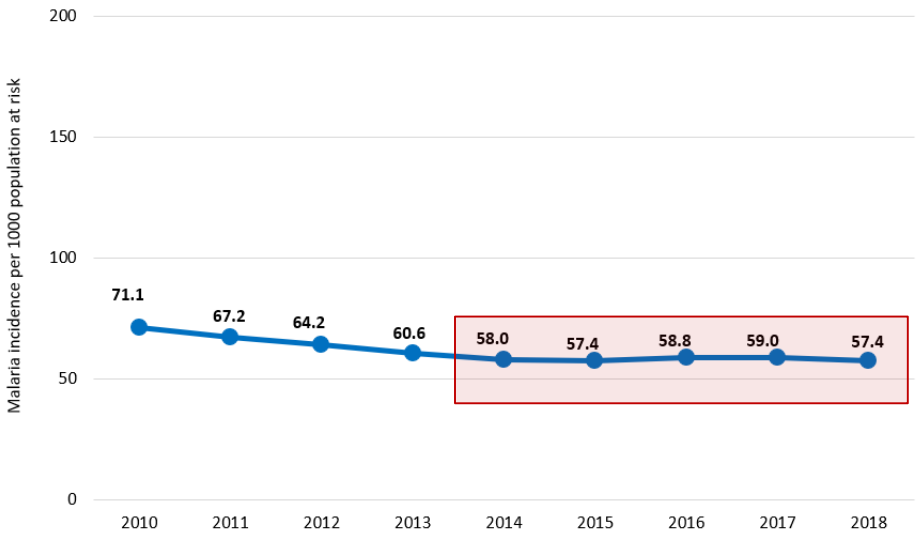
Progress has stalled in the past 4-5 years

(malaria cases, malaria case incidence rate)

Trend in malaria cases, globally, 2000–2018



Trend in malaria case incidence rate, globally, 2010–2018



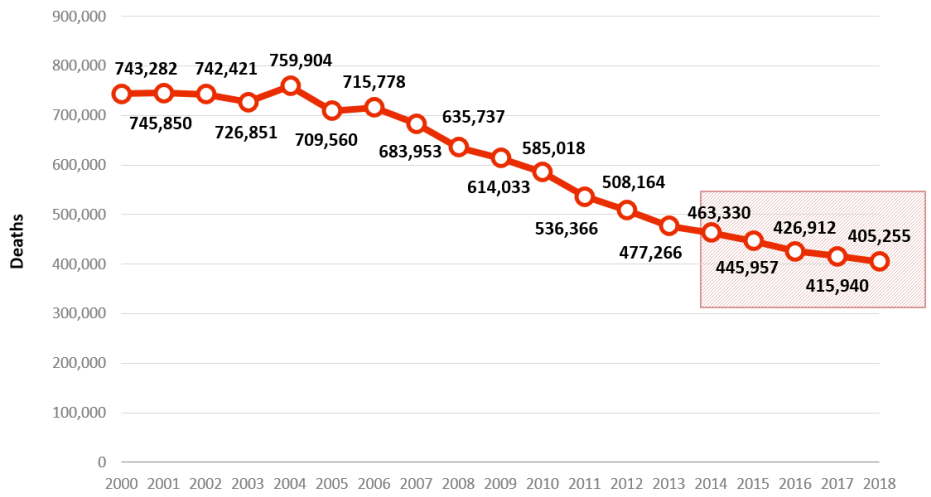
Global **Malaria** Programme

World Health Organization

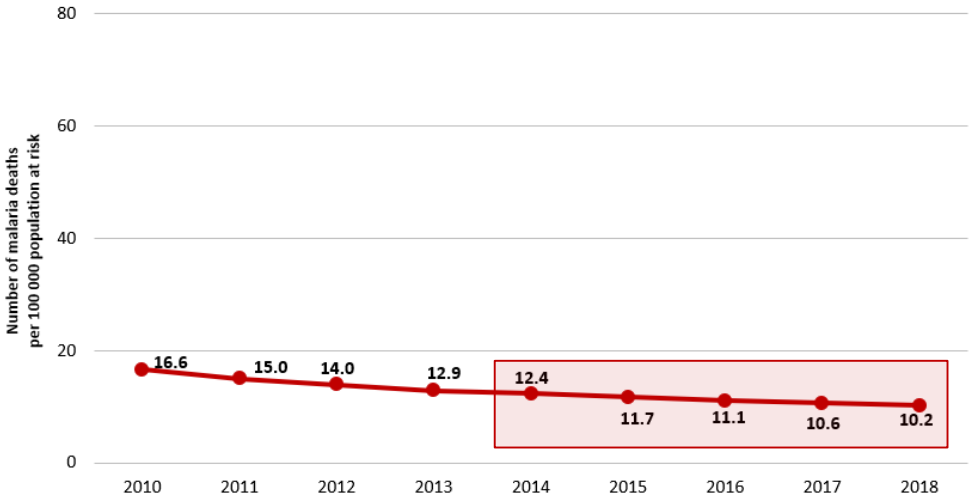
Progress has stalled in the past 4-5 years

(malaria deaths, malaria mortality rate)

Trend in malaria deaths, globally, 2000–2018

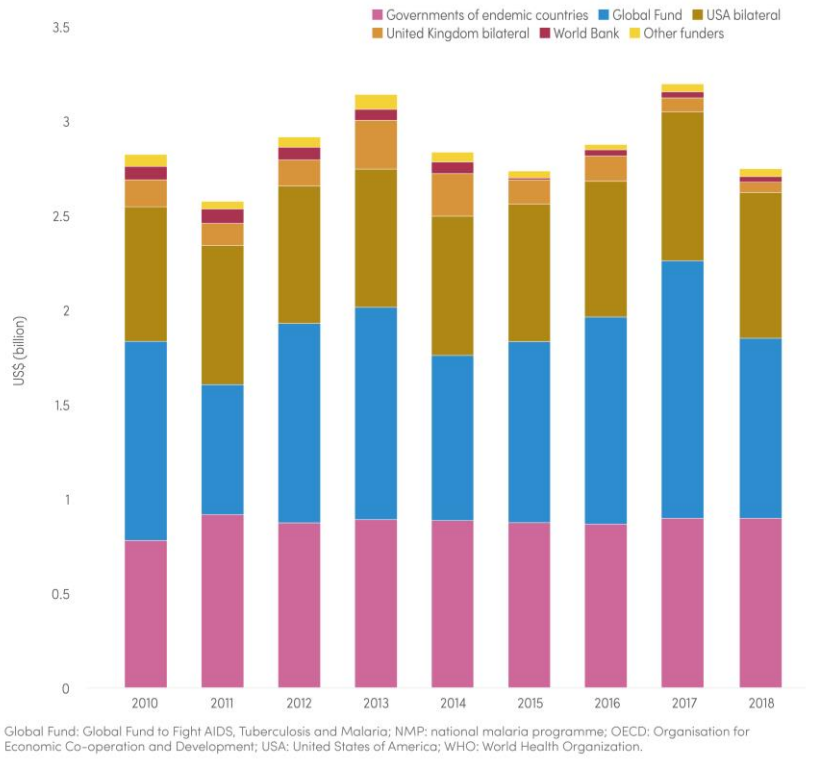


Trend in malaria mortality rate, globally, 2010–2018



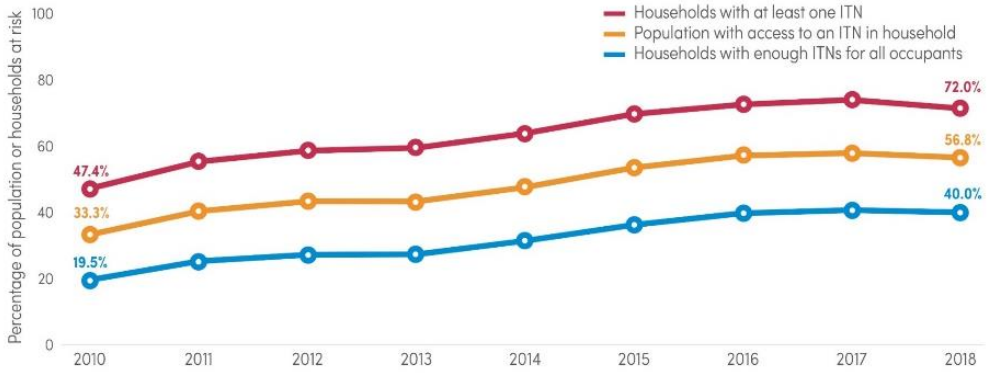
Underlying reasons: limited funding & coverage gaps

Funding for malaria control and elimination 2010–2018, by channel (constant 2018 US$)



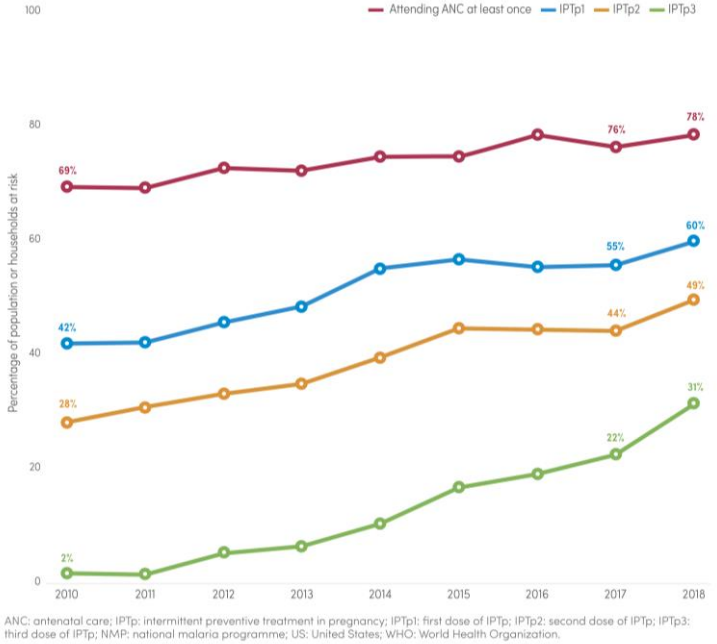
Global Fund: Global Fund to Fight AIDS, Tuberculosis and Malaria; NMP: national malaria programme; OECD: Organisation for Economic Co-operation and Development; USA: United States of America; WHO: World Health Organization.

Percentage of population at risk with access to an ITN, and percentage of households with at least one ITN and enough ITN for all occupants, sub-Saharan Africa, 2010–2018



ITN: insecticide-treated mosquito net; MAP: Malaria Atlas Project.
[a] https://map.ox.ac.uk/

Percentage of pregnant women attending ANC at least once and receiving IPTp, by dose, sub-Saharan Africa, 2010–2018

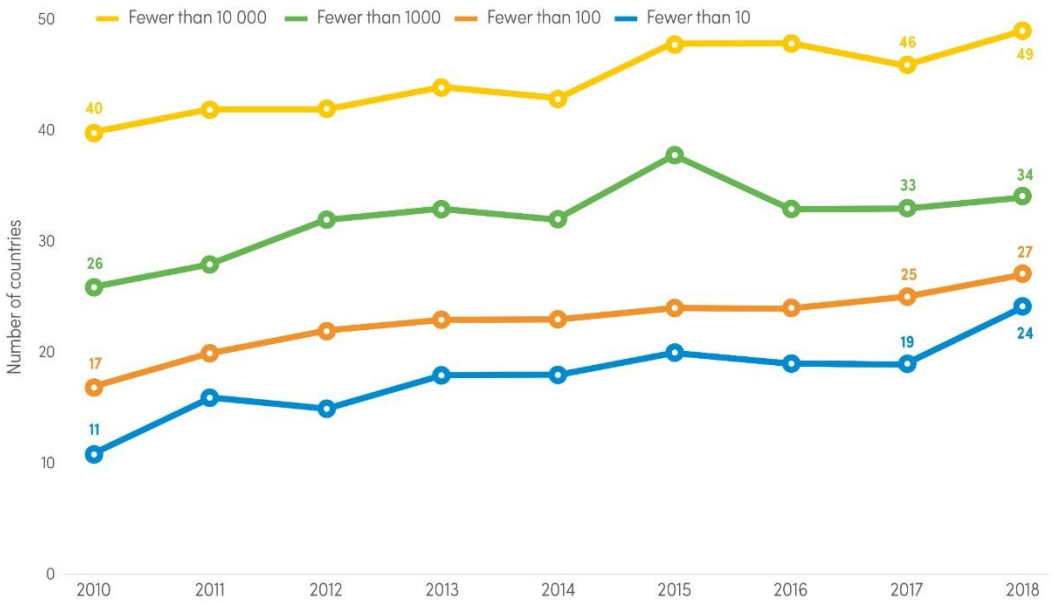


ANC: antenatal care; IPTp: intermittent preventive treatment in pregnancy; IPTp1: first dose of IPTp; IPTp2: second dose of IPTp; IPTp3: third dose of IPTp; NMP: national malaria programme; US: United States; WHO: World Health Organization.

Malaria: some good news before COVID-19

Eliminating countries

Number of countries that were malaria endemic in 2000, with fewer than 10, 100, 1000 and 10 000 indigenous malaria cases between 2010 and 2018



Source: World malaria report 2019

Certification of malaria free countries

Paraguay, June 2018

Algeria, May 2019

GTS: bold, ambitious and achievable targets

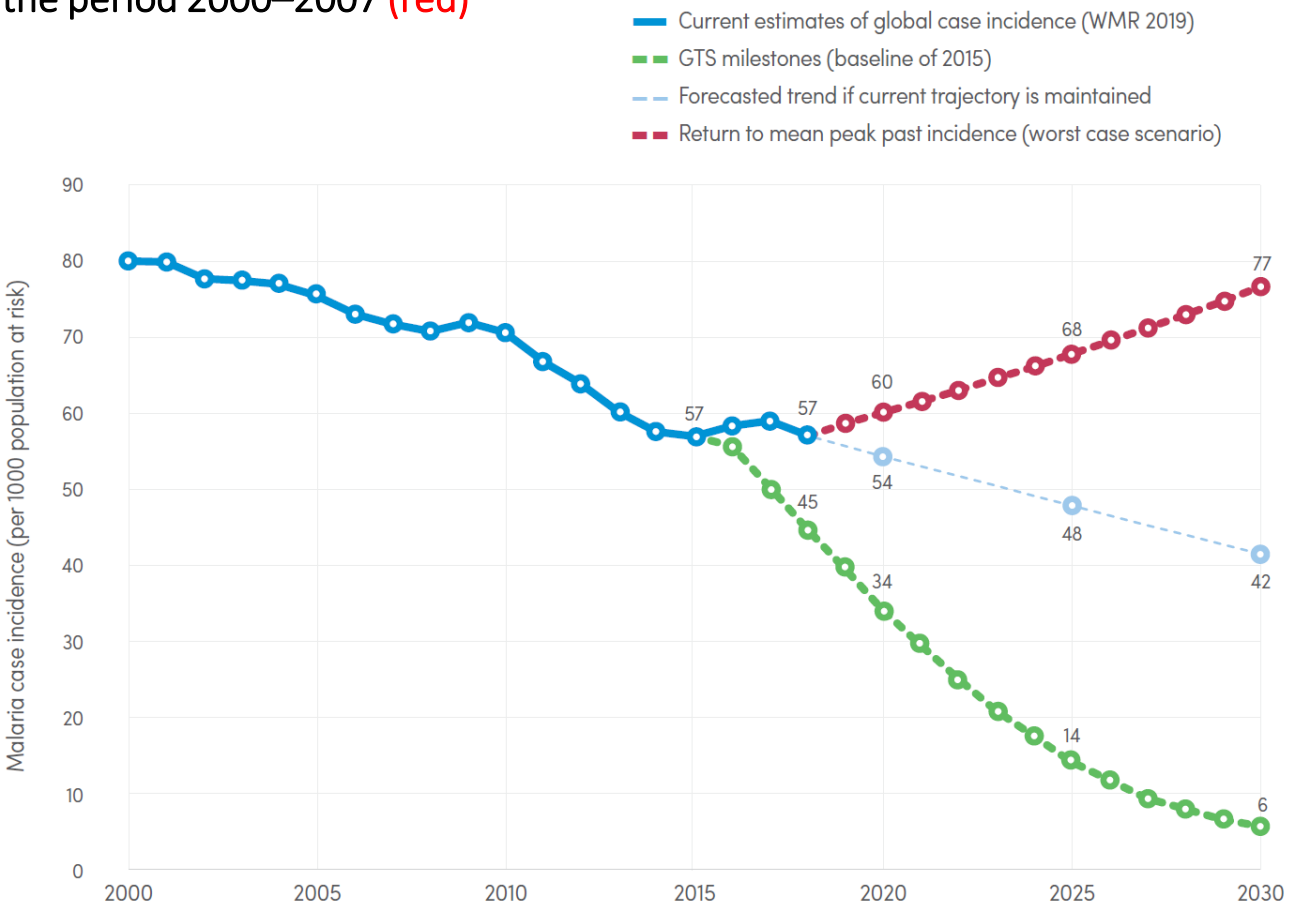
Vision – A world free of malaria

Goals	Milestones		Targets
	2020	2025	2030
1. Reduce malaria mortality rates globally compared with 2015	At least 40% ✖	At least 75%	At least 90%
2. Reduce malaria case incidence globally comparted with 2015	At least 40% ✖	At least 75%	At least 90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries ✓	At least 20 countries	At least 35 countries
4. Prevent re-establishment of malaria in all countries that are malaria free	Re-establishment prevented ✓	Re-establishment prevented	Re-establishment prevented

GTS: Global technical strategy for malaria 2016–2030

Malaria: “off track” before COVID-19

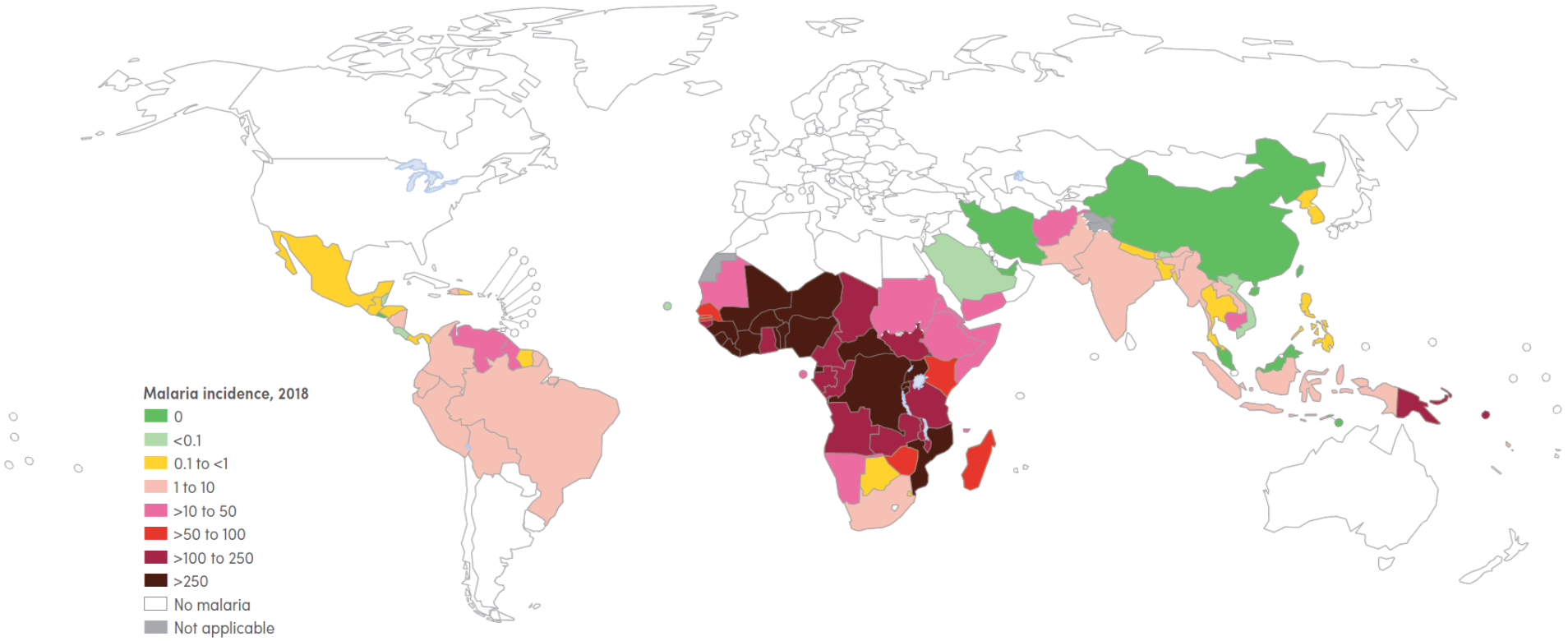
Comparison of progress in malaria case incidence considering three scenarios: current trajectory maintained (blue), GTS targets achieved (green) and worst case scenario, that is a return to mean peak past incidence in the period 2000–2007 (red)



GTS: *Global technical strategy for malaria 2016–2030*; WHO: World Health Organization; WMR: *World Malaria Report*.

Geographical distribution of malaria & burden analysis

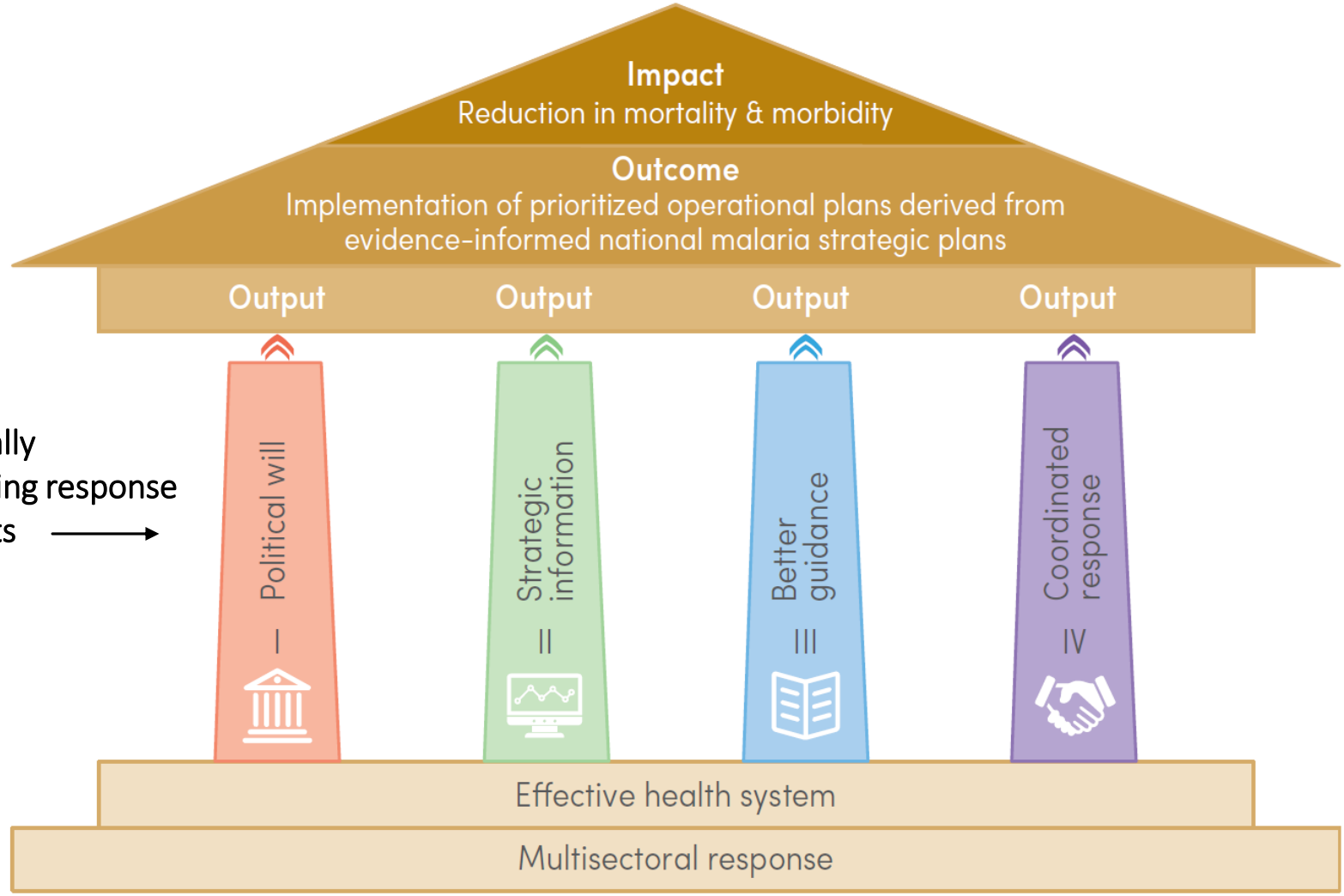
Map of malaria case incidence rate (cases per 1000 population at risk) by country, 2018



In 2017, 11 countries accounted for 70% of the global estimated case burden and 71% of global estimated deaths. These were Burkina Faso, Cameroon, the Democratic Republic of the Congo, Ghana, India, Mali, Mozambique, Niger, Nigeria, Uganda and the United Republic of Tanzania.

Source: World malaria report 2019

High Burden High Impact (HBHI) approach: a targeted response



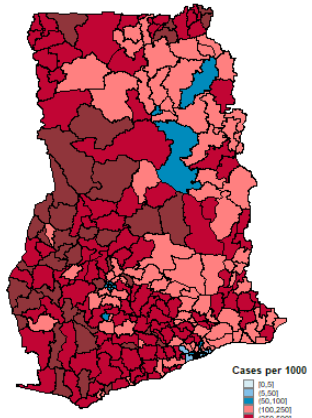
4 mutually reinforcing response elements →

Strategic use of information to drive impact (1)

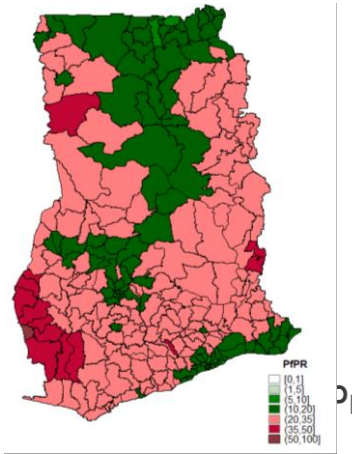
Moving from a “one-size-fits-all” approach to a tailored response, driven by data, on best mix of interventions to achieve maximum impact: **stratification**.

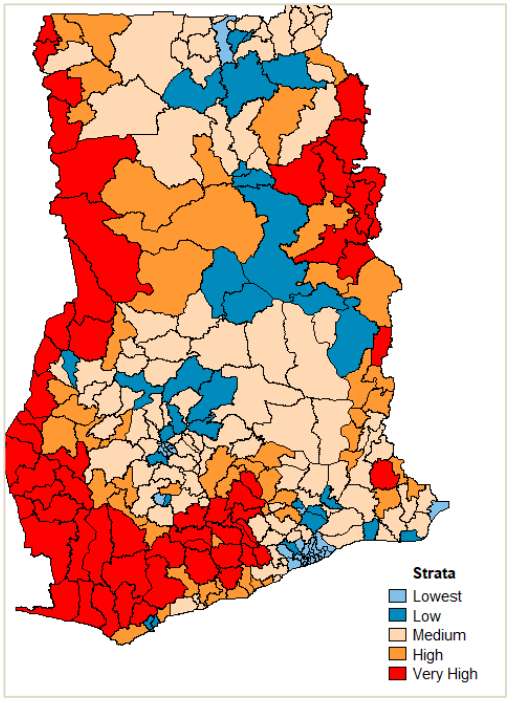
Example of the stratification process in Ghana

Adjusted incidence (2018)

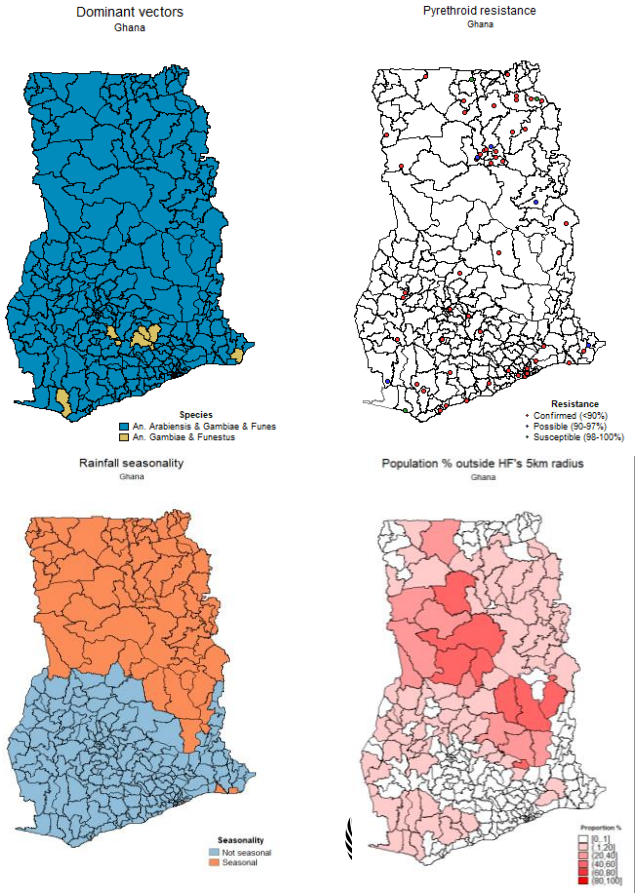


Prevalence (2018)





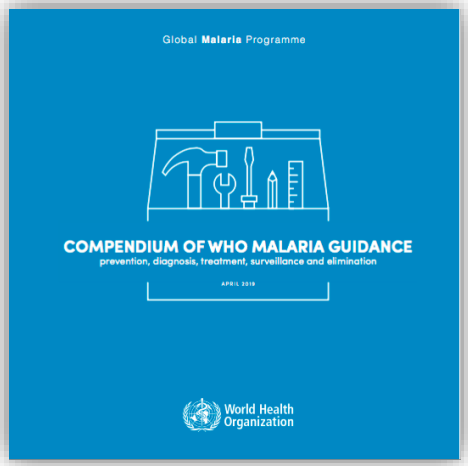
Layers of additional information



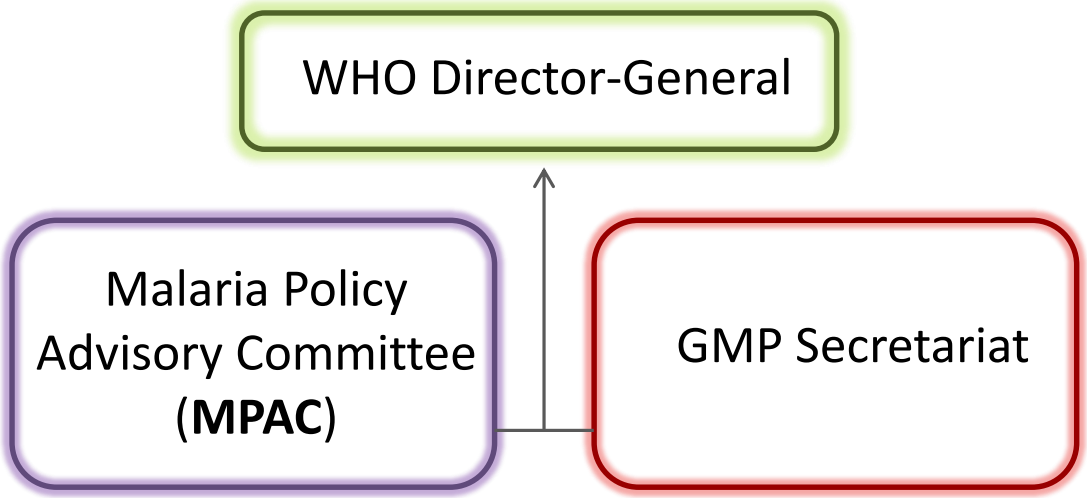
Programme

Consolidated Malaria Guidelines

- Goal: to provide enhanced guidance to countries to maximize the impact of available resources
- Assemble all WHO recommendations for malaria control and elimination in one guideline document
- Use the standard WHO guideline development process overseen by the Guidelines Review Committee
- Guide the use of local data to define mixes of interventions for specific strata, optimize considering the local context and prioritize given a resource envelope



GMP advisory bodies structure



Policy

GMP Guidelines Development Groups (GDGs)

Advisory

Vector Control Advisory Group (VCAG) w/ NTD/PQ

Malaria Elimination Oversight Committee (MEOC)

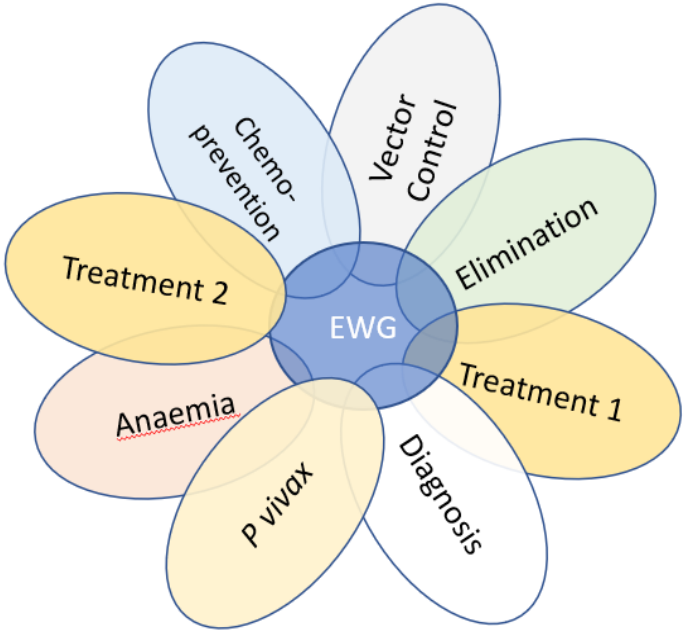
Malaria Elimination Certification Panel (MECP)

Malaria Vaccine Advisory Committee (MALVAC) w/ IVB

Other ad hoc technical consultations

Anticipated technical areas (2020-2021)

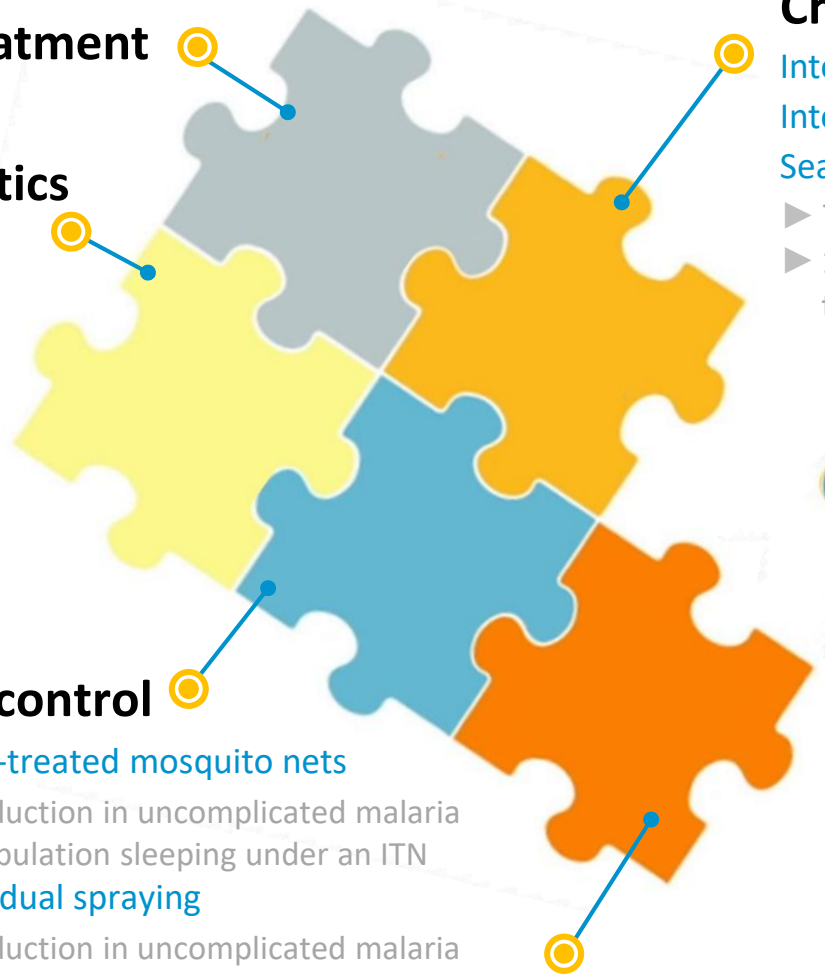
- 2020: Vector control 1, Elimination 1&2, Chemoprevention and Treatment 1
- 2021: Vector control 2, Diagnosis, *P. vivax*, Anemia and Treatment 2*



EWG: Editorial Working Group

*potentially an additional GDG on Malaria vaccines depending on the availability of data

Additional tools are needed



Treatment

Diagnostics

Vector control

Insecticide-treated mosquito nets

- 45% reduction in uncomplicated malaria
- 50% population sleeping under an ITN

Indoor residual spraying

- 14% reduction in uncomplicated malaria
- 6.6% population at risk protected

Surveillance

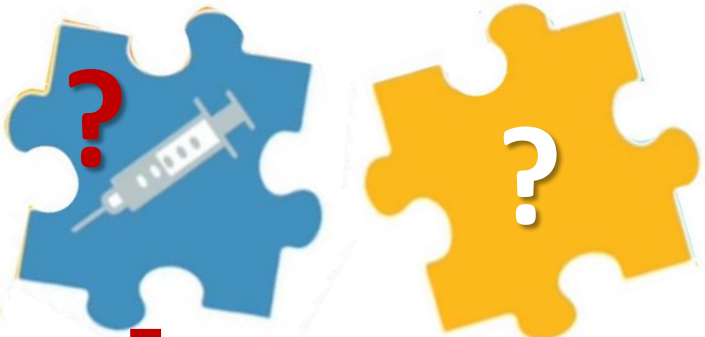
Chemoprevention

Intermittent preventive treatment in pregnancy (IPTp)

Intermittent preventive treatment in infants (IPTi)

Seasonal malaria chemoprevention (SMC)

- 74% reduction in uncomplicated malaria
- 12 countries implemented with 53% of eligible children treated



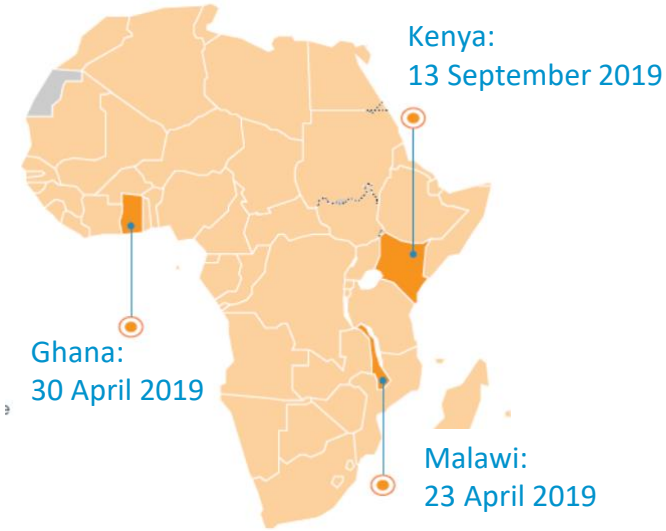
RTS,S/AS01 malaria vaccine

- 39% reduction in clinical malaria
- 29% reduction in severe malaria
- 61% reduction in severe malaria anaemia
- Potential for high coverage – e.g. DTPcv-3 in AFRO 76% in 2018

Notes: DTPcv-3 = Third dose of Diphtheria-tetanus-pertussis containing vaccine

Sources: Coverage numbers for Africa in 2017; World Health Organization. World Malaria Report, 2018; Cochrane Database Syst Rev. 2018;(11)CD000363; Cochrane Database Syst Rev. 2010;(4)CD006657; Cochrane Database Syst Rev. 2012;(2)CD003756; The Lancet 374.9700 (2009): 1533-1542; 2018 WHO/UNICEF Estimates of National Immunization Coverage

Malaria Vaccine Implementation Programme



- 1st anniversary of vaccine launch celebrated during WMD[1]
  - >270,000 children received dose 1 as part of routine childhood vaccination
- Uptake ~65% of target population
  - Considered good for new vaccine delivered at new contacts
  - Efforts continue to improve
- Covid-19: Vaccinations continue, but risk of decreased uptake
  - Fear of coronavirus infection, directives for people to stay at home, health worker fear and anticipated absenteeism, etc.
- WHO guidance to sustain safe immunization services[2]
  - Plan for catch-up vaccination of missed children when physical distancing measures are lifted

1 https://www.who.int/news-room/feature-stories/detail/lusitana-and-the-world-s-first-malaria-vaccine
2 https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/maintaining-essential-health-services-and-systems

Malaria Vaccine Pilot Evaluation

2nd annual Malaria Vaccine Pilot Evaluation investigators' meeting in Kisumu, Kenya, 29-31 October 2019

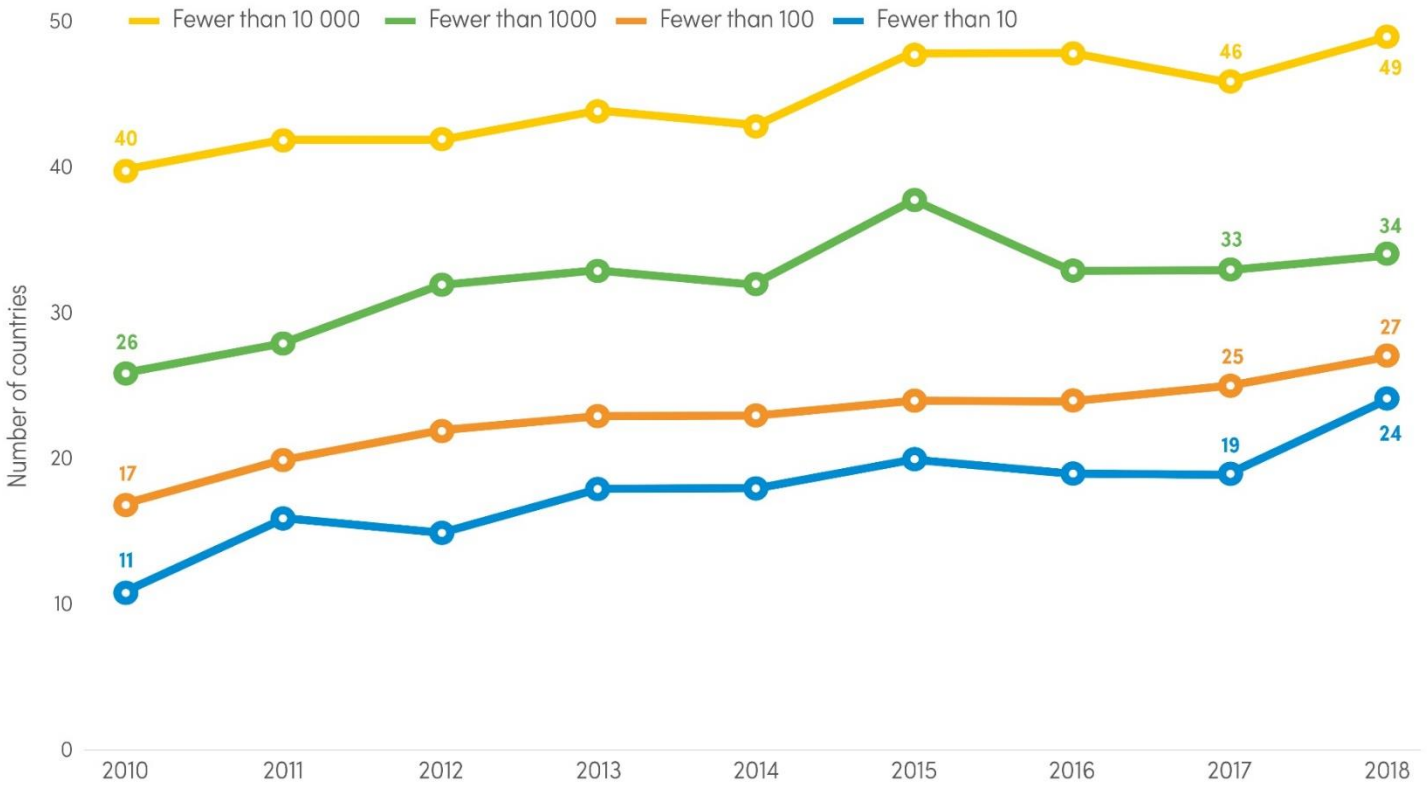
Prof Kim Mulholland (PAG member) providing training on meningitis surveillance, January 2020

- Data collection through sentinel hospital and community mortality surveillance is ongoing
  - Risk register and contingency plans developed to address potential disruptions due to COVID-19
- Monthly data quality review TCs between WHO and in-country evaluation partners
  - To identify opportunities to strengthen surveillance
- Quarterly meetings/TCs of DSMB and Programme Advisory Group (PAG)
- Data show lower meningitis rates than expected (including where lumbar puncture rates are high)
  - PAG recommends case-control study due to lower than anticipated meningitis rates and to understand added value of 4th dose
  - Fundraising ongoing
- Target timelines for policy review currently maintained: Q1 2022

Elimination – more countries moving toward elimination

FIG. 5.1.

Number of countries that were malaria endemic in 2000, with fewer than 10, 100, 1000 and 10 000 indigenous malaria cases between 2010 and 2018 *Sources: NMP reports and WHO estimates.*



NMP: national malaria programme; WHO: World Health Organization.

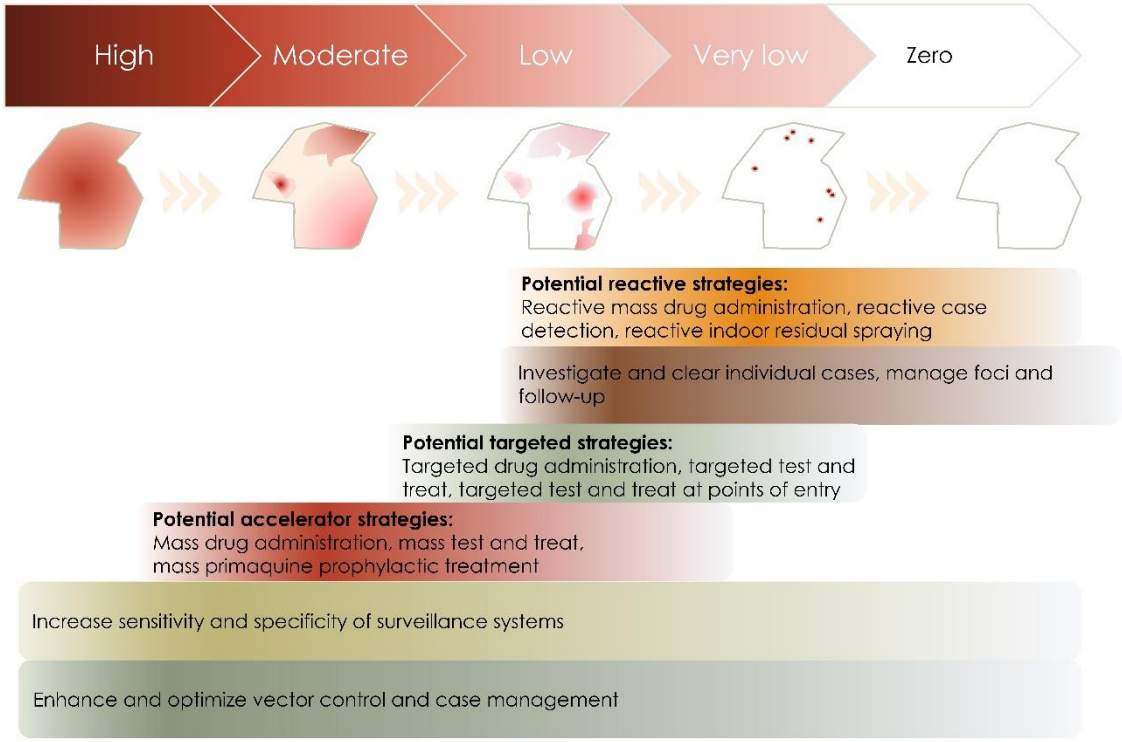
Malaria Elimination

- The world remains on target to reach GTS 2020 elimination milestone
  - Countries currently reporting 0 indigenous cases for 2019 include: Belize, Cabo Verde, China, El Salvador, Iran (Islamic Republic of), Malaysia, Timor-Leste
  - Eliminating countries facing challenges with COVID-19 and several countries with resurgences before COVID-19 but so far no COVID-19 related setbacks
- Planning for the E-2025 has begun
  - All countries not yet certified will be invited to participate
  - Clear epidemiological and health system criteria will be developed to identify additional eligible countries
  - Countries will be requested to demonstrate high-level acceptance to join the cohort and will be asked to meet several preconditions
  - The E-2025 will be launched in early 2021
- The MEOC meeting was postponed until a safe date in the future can be identified
- MEOC advocacy visits to Cabo Verde and Comoros postponed

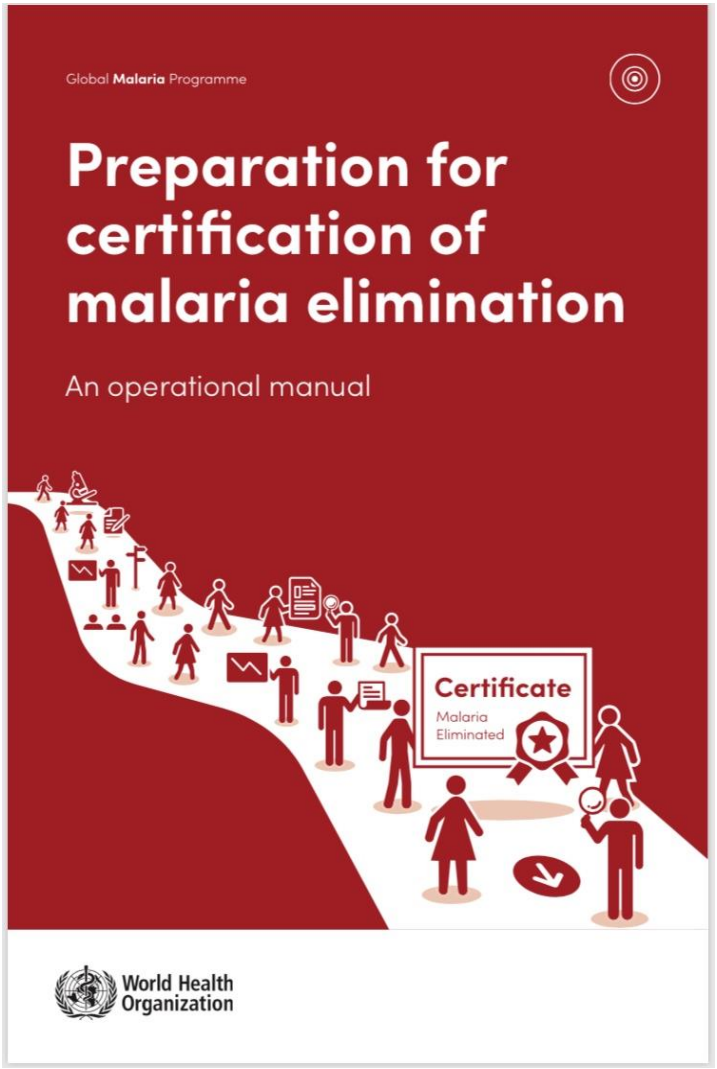
Malaria Elimination recommendation development

Planning for two guideline development groups in Q4 2020

1. Potential accelerator and targeted strategies
2. Potential reactive strategies



Malaria Elimination Certification



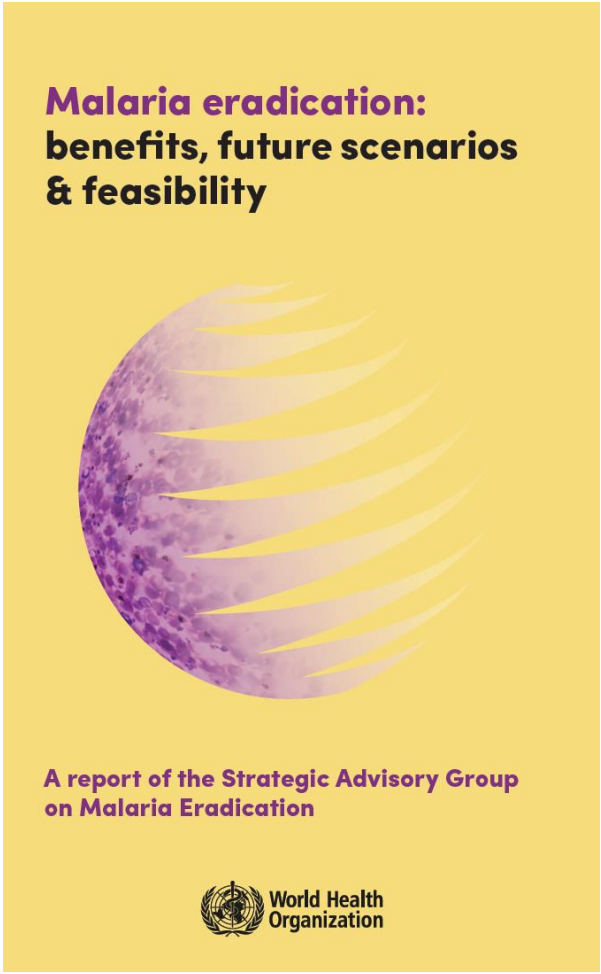
- New certification manual to be published
- Expanded guidance on certification to countries
- Provide tools to help countries organize required documentation, develop national elimination report and assess the programme to prevent re-establishment
- Expanded guidance on subnational verification

Update on certification in 2020

El Salvador	Dates of final mission to be rescheduled with the government
Azerbaijan	Delay expected but the goal remains to achieve certification in 2020
China	Preparations on track. Submission of official request expected to be in June/July.
MECP	Meeting tentatively planned for November

Strategic Advisory Group on Malaria Eradication

- Final report launched on 21 April; accompanied by MPAC statement
- Six areas identified to contribute to a successful future effort:
  1. Reinforcing the global strategy
  2. R&D for new tools
  3. Access to affordable, high quality, people-centered health care and services
  4. Adequate and sustained financing
  5. Strengthened surveillance and response
  6. Engaging communities



Global Technical Strategy for Malaria 2016 - 2030

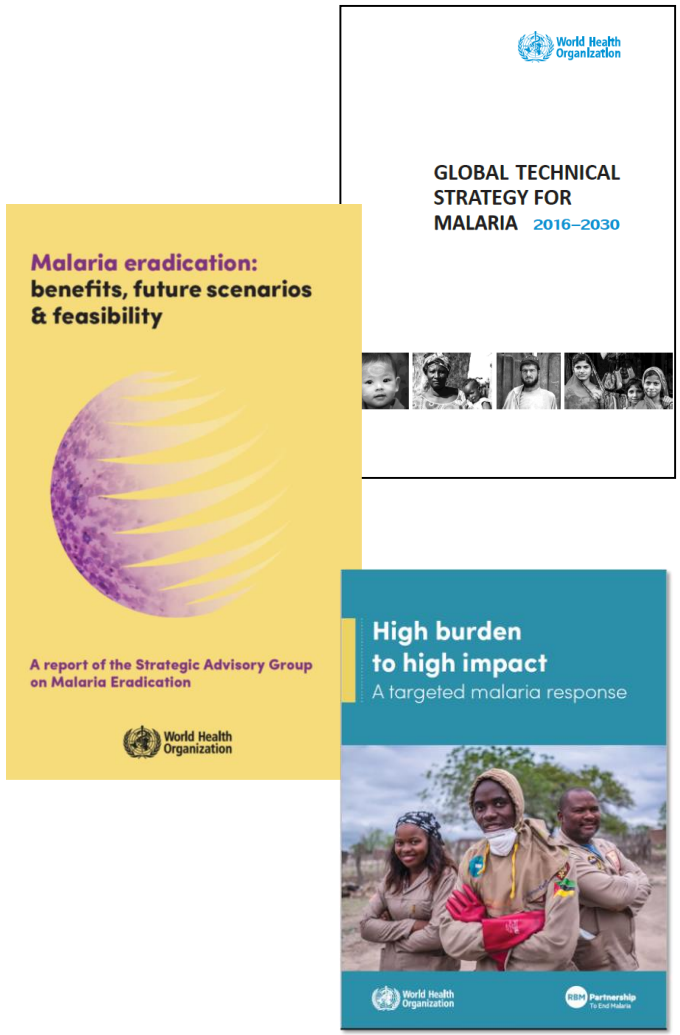
- The strategy will be updated at regular intervals in order to ensure linkage with the latest policy recommendations and complementary technical guidance
- At this stage – not intending to change the milestones and targets

Vision: A world free of malaria			
Goals	Milestones		Targets
	2020	2025	2030
1. Reduce malaria mortality rates globally compared with 2015	≥40%	≥75%	≥90%
2. Reduce malaria case incidence globally compared with 2015	≥40%	≥75%	≥90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
4. Prevent re-establishment of malaria in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

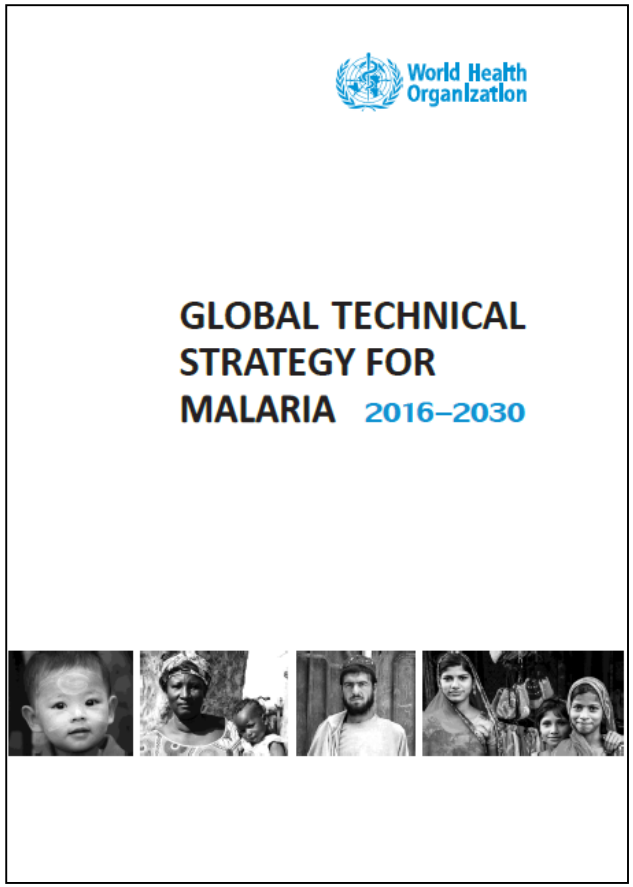
Global Technical Strategy for Malaria 2016 - 2030

Anticipated inputs to consider:

- Solicit input from countries/partners - survey
- Regional convenings
- SAGme conclusions
- HBHI experience/ prioritization of interventions
- Impact projections
- Costing



Process and timelines

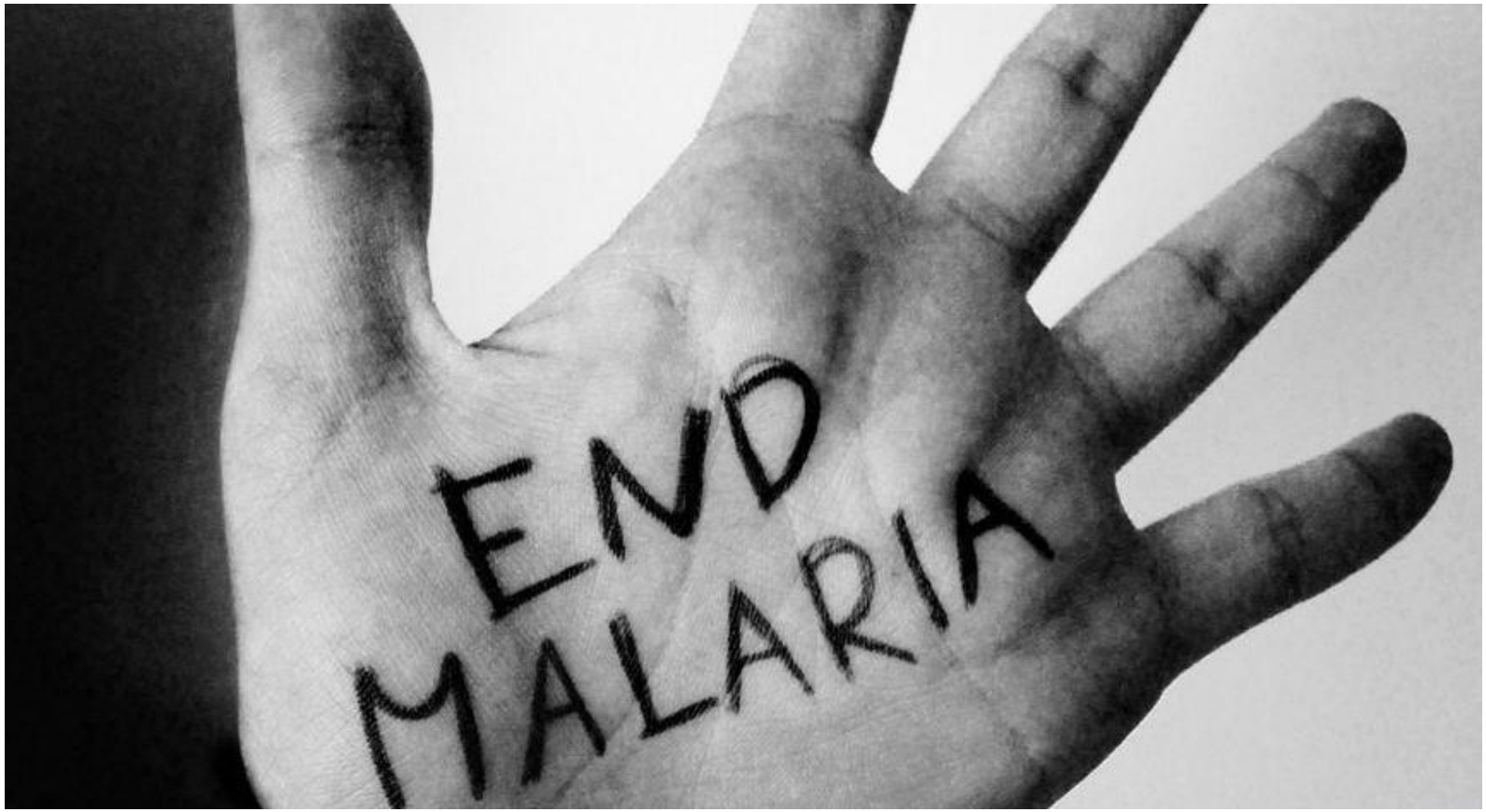


- Coordinating with RBM, GF, PMI on 5 year strategy development
- Q3 – conduct survey
- Q3 –Q4 Regional discussions combined with planned convenings
- Q4 MPAC input
- Q1 2021 Report to WHO Executive Board
- Q1 2021 submit documentation for WHA consideration & updated resolution
- Q2 2021 Update published

High level questions for group thinking

Not that we are going to solve these issues during this meeting, but for input on establishing working groups to evolve our collective thinking:

1. How does COVID-19 impact the achievement of GTS milestones and targets – informing the update?
2. What should a World Malaria Report in 2020 look like?
3. Rethinking malaria control and elimination in a COVID-19 environment?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MALARIA

Malaria Policy Advisory Committee Meeting

13—14 May 2020, Geneva, Switzerland
Background document for Session 1

Update on the RTS,S/AS01 Malaria Vaccine Implementation Programme

Background

The Malaria Vaccine Implementation Programme (MVIP) was developed to act on the 2016 WHO recommendation to pilot the RTS,S/AS01 malaria vaccine in routine immunization programmes *(1)*. The MVIP supports introduction of the malaria vaccine in selected areas of Ghana, Kenya and Malawi, and evaluation of the programmatic feasibility of delivering a four-dose schedule, the vaccine's impact on mortality, and its safety in the context of routine use. The primary aim of the Programme is to address outstanding questions related to the public health use of the vaccine in order to enable WHO policy recommendations on the broader use of RTS,S/AS01 in sub-Saharan Africa.

The Programme is jointly coordinated by the Global Malaria Programme (GMP), the Immunization, Vaccines & Biologicals (IVB) Department and the WHO Regional Office for Africa, in close collaboration with other WHO departments and country offices, ministries of health in pilot countries, PATH and other partners. Introduction of the malaria vaccine is country-led. Funding for the MVIP is provided by Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Unitaid.

Update since October 2019

The Ministry of Health of Kenya launched RTS,S/AS01 vaccination on 13 September 2019. This major milestone means that vaccine implementation is underway in all three MVIP countries. Data and feedback received so far suggest good acceptance of the programme by health care workers, caregivers and communities, and generally high demand in areas where adequate communication and sensitization efforts have taken place. While there has been variation in performance across geographic areas, administrative data indicate that all three countries have reached over 60% of their target population with the first dose of RTS,S/AS01. This level of uptake is considered satisfactory and within expectations for a new vaccine with a novel schedule, i.e., targeting children from 5 months of age (in Malawi) and from 6 months of age (Ghana and Kenya) for the first dose. Areas for improvement have been identified through supervisory visits, and measures are being taken by the national immunization programmes, supported by partners, to address identified issues (e.g., health workers' misunderstanding of the vaccine schedule).

The first round of data collection for the qualitative longitudinal Health Utilization Study (HUS), coordinated by PATH, began shortly after vaccination started in each country. As part of the feasibility evaluation, the HUS assesses issues related to vaccine uptake, community perceptions and acceptability of the vaccine, and service delivery challenges and successes. Early insights from the interactions with caregivers, health personnel and community members have been shared with the ministries of health and partners to help inform programmatic improvements.

The one-year anniversary of the vaccine launch on 23 April 2019 was commemorated in the context of the 2020 World Malaria Day and World Immunization Week *(2)*. An estimated 275 000 children in Ghana, Kenya and Malawi have received their first dose as part of routine childhood vaccination and should be benefiting from the added protection provided by the vaccine.

This document was prepared as a pre-read for the meeting of the Malaria Policy Advisory Committee and is not an official document of the World Health Organization.
WHO/UHC/GMP/MPAC/2020.01

Data collection through sentinel hospitals and community mortality surveillance are ongoing, with monthly data quality review by WHO and in-country evaluation partners. Opportunities to strengthen the surveillance systems have been identified through this process. Initial data show that the rates of meningitis detected in sentinel hospitals are lower than expected (including in Kenya where diagnostic capacity, i.e., lumbar puncture rate, is high). This may be a consequence of good vaccination programmes and the high uptake of the Haemophilus influenzae type B (Hib) vaccine and pneumococcal conjugate vaccine (PCV).

The MVIP's advisory bodies continue to meet regularly and provide guidance to the Programme: Since the last update, the Programme Advisory Group (PAG) met three times, on 7 November 2019, 14–15 January 2020 and 15 April 2020; and the Data Safety and Monitoring Board (DSMB) met twice, on 24–25 November 2019 and 3 March 2020.

Recommendation for case-control study and resource mobilization

In light of the data that have emerged since the original WHO position paper on RTS,S/AS01, including the extended follow-up of the phase 3 trial and modelling analyses questioning the value of the fourth dose, and the current levels of RTS,S/AS01 coverage, the PAG recommended a case-control study to evaluate the added benefit of the fourth dose of RTS,S/AS01. A case-control study would also strengthen the evaluation of existing safety and effectiveness endpoints. Efforts are underway to secure funding.

In Quarter 4 of 2019, additional funding commitments for the completion of the MVIP through 2023 were secured from the Global Fund (up to US$ 8 million) and Gavi (up to US $11.6 million). Fundraising to fill the remaining gap of approximately US$ 5.6 million is ongoing.

Gavi has agreed to work with other parties to find a financial mechanism to enable continued production of RTS,S prior to a policy recommendation in order to improve the timeliness and volume of future vaccine supply.

On 18 October 2019, WHO convened a Malaria Vaccine Stakeholder Meeting to brief stakeholders on the malaria situation, the potential role of the vaccine as a complementary control tool, and the pathway to WHO policy review.

Impact of COVID-19

Cases of COVID-19 have been reported in all three MVIP countries. At present, vaccination services (including RTS,S/AS01 vaccination) continue, although demand may decrease due to fear of coronavirus infection, directives for people to stay at home, health worker fears and anticipated absenteeism. The evaluations through sentinel hospital surveillance and community mortality surveillance continue, with close monitoring of the COVID-19 situation and respecting Ethics Review Boards (ERBs) and national guidance. Evaluation partners have instituted measures to reduce the risk of COVID-19 infection among study staff (personal protective equipment, social distancing). In anticipation of potential disruption of activities, they have also introduced measures to collect data retrospectively.

WHO has released guidance on immunization and malaria services in light of COVID-19 *(3,4)*. The guidance calls for countries to prioritize routine immunization of children in essential service delivery and for malaria control interventions to continue as long as they can be safely provided, including with modification as needed.

WHO continues to monitor the potential impact of COVID-19 on the MVIP and is in close contact with local partners to assess risks and implement mitigation measures.

Priorities for the next six months

Key priorities in the coming weeks and months include support to in-country partners to mitigate and monitor the potential impact of COVID-19 on the Programme; continued support of programmatic improvement where needed; continued support to evaluation partners to ensure the hospital- and community-based surveillance systems are fit for purpose with appropriate mitigation measures implemented; coordination and management of the data generated by the MVIP; and continuation of resource mobilization efforts to address the remaining funding shortfall for the completion of the MVIP and for implementation of a case-control study.

References

1. Malaria vaccine: WHO position paper – January 2016. Geneva: World Health Organization; 2016 (http://www.who.int/wer/2016/wer9104.pdf?).
2. Lusitana and the world's first malaria vaccine [website]. Geneva: World Health Organization; 2020 (https://www.who.int/news-room/feature-stories/detail/lusitana-and-the-world-s-first-malaria-vaccine).
3. Guiding principles for immunization activities during the COVID-19 pandemic. Geneva: World Health Organization; 2020 (https://www.who.int/immunization/news_guidance_immunization_services_during_COVID-19/en/).
4. WHO urges countries to ensure the continuity of malaria services in the context of the COVID-19 pandemic [website]. Geneva: World Health Organization; 2020 (https://www.who.int/news-room/detail/25-03-2020-who-urges-countries-to-ensure-the-continuity-of-malaria-services-in-the-context-of-the-covid-19-pandemic).

Contact

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Malaria Policy Advisory Committee Meeting

13—14 May 2020, Geneva, Switzerland
Background document for Session 2

World Health Organization

Consolidated responses to questions and comments received in response to public posting of a notice of intent to modify the classification of insecticide-treated net products and associated evaluation procedures

Questions and comments received in response to the publication of the World Health Organization's (WHO) notice of intent (NoI) to modify the classification of insecticide-treated net (ITN) products in February 2020 have been organized into broad topics as outlined below. Responses are provided to all questions and to those comments to which a response was needed; other comments are simply stated as they were provided to WHO. All responses to questions and comments are those of WHO. The identities of the individuals and organizations that responded to the NoI have been removed to maintain confidentiality.

Topic areas covered:

1. Glossary
2. General comments and questions
3. Comments and questions on proposed categorization of ITNs into classes
4. Proposals for further modification of ITN classes
5. Revised proposed ITN classification based on inputs received in response to the NoI
6. Comments and questions on the evaluation of ITNs against entomological endpoints
7. Comments and questions on product claims and labels
8. Comments and questions on prerequisites for implementation of the revised ITN classification and associated data requirements
9. Comments and questions on subsequent steps

This document was prepared as a pre-read for the meeting of the Malaria Policy Advisory Committee and is not an official document of the World Health Organization.
WHO/CDS/GMP/MPAC/2020.02

1. Glossary[1]

entomological effect Entomological effect refers to a product's effect on a disease vector in terms of killing, deterring, and reducing fertility or susceptibility to infection. Products with different biochemical modes of action may have similar entomological effects on target insects; for example, indoor residual spraying (IRS) formulations with pyrethroids and carbamates differ in their biochemical modes of action yet are considered to have a similar impact on the target insect in areas of insecticide susceptibility.

first in class First in class refers to the first product with a novel entomological effect (e.g., reducing human–vector contact, or decreasing vector survivorship, or susceptibility to infection or transmission), the public health value of which is ascertained by the Vector Control Advisory Group (VCAG) based on the demonstration of its entomological and epidemiological efficacy against vectors and human infections and/or disease, respectively. Once the public health value of a first-in-class product is ascertained, a new product class is established.

insecticide Chemical product (natural or synthetic) that kills insects: ovicides kill eggs; larvicides (larvacides) kill larvae; pupacides kill pupae; adulticides kill adult mosquitoes. Residual insecticides remain active for an extended period.

insecticide resistance Property of mosquitoes to survive exposure to a standard dose of insecticide; may be the result of physiological or behavioural adaptation.

net, insecticide-treated Mosquito net that repels, disables or kills mosquitoes that come into contact with the insecticide on the netting material. The three categories of insecticide-treated net are:

- *Conventionally treated net:* a mosquito net that has been treated by dipping it into a WHO-recommended insecticide. To ensure its continued insecticidal effect, the net should be re-treated periodically.
- *Long-lasting insecticidal net:* a factory-treated mosquito net made of netting material with insecticide incorporated within or bound around the fibres. The net must retain its effective biological activity for at least 20 WHO standard washes under laboratory conditions and three years of recommended use under field conditions.
- *Pyrethroid-PBO net:* a mosquito net that includes both a pyrethroid insecticide and the synergist piperonyl butoxide (PBO). To date, pyrethroid-PBO nets have not met the required thresholds to qualify as long-lasting insecticidal nets.

prequalification Process to ensure that health products are safe for their intended use, manufactured to quality standards and efficacious.

product class A product class in vector control is a group of products that share a common entomological effect by which it reduces pathogen transmission and thus reduces infection and/or disease in humans. For products in a class not currently recommended by WHO, efficacy trials with a first-in-class product must generate epidemiological evidence of protective

[1] The glossary provided is a subset of the glossaries in: i) *Guidelines for malaria vector control*. World Health Organization (2019), and ii) *The evaluation process for vector control products*. World Health Organization (2017).

	efficacy against infection and/or disease. The evidence is then reviewed by VCAG to validate the public health value of the product class. This validation forms the basis of a WHO policy recommendation for the new product class. A product class may contain one or more target product profiles (TPPs) depending on the intended effect of the product(s) and claim(s).
public health value	A product has public health value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans.

2. General comments and questions

Comment: It is encouraging to see the recognition to reopen testing guidelines and data requirements in order to ensure we have testing methodologies that are fit for purpose for new modes of action.

Comment: P. 1., 2nd paragraph of NoI: **"***A number of recently submitted products are similar to chlorfenapyr and pyriproxyfen containing products that were recently prequalified, raising the question as to whether prequalification assessment and potential listing of these other products should be permitted or halted until policy recommendations have been put in place."*

The prequalification assessment of these products should be halted until policy recommendations are resolved. As with any new vector control (VC) product the 'me too' products try to follow quickly but great care has to be taken that they are the same, as active ingredient (AI) levels can vary, formulation can vary and material type (nets) can vary.

Response: No new product applications have been received for ITNs containing these AIs, so there are no prequalification assessments to halt. For now, all of these nets are considered to fall under the New Intervention Pathway, which means that the next step would be the generation of epidemiological data to enable assessment of their public health value.

Comment: This document should be written in plain English so that it is clearer for the many non-English speakers who will be reviewing. Alternatively provide this document in several languages.

Response: WHO did attempt to write this document in non-technical language as possible. It was, however, assumed that readers would be familiar with other documents on the vector control evaluation process and WHO policy-making. The vcguidelines@who.int email account was available for the period of consultation to provide clarification where needed. We acknowledge that the translation of NoIs into the UN languages would be helpful, and we will endeavour to provide this in the future. An update to the document on the evaluation processes for vector control products is under development and will be translated into the UN languages once finalized.

Comment: With regards to the subsequent steps, we hope that partners including product manufacturers can continue to participate in the development of testing guidelines and evaluation standards.

Response: Yes, WHO will draw on inputs from manufacturers and researchers in the revision and further development of testing guidelines and evaluation standards. With regard to the latter, we encourage participation in the upcoming virtual MPAC meeting where the NoI and the next steps will be further discussed. For those interested in participating, we request registration via: https://www.who.int/malaria/mpac/mpacmeetings/en/

Comment: Now that we have a range of ITN classes available for use, it is possible to rotate classes, so policy development should include guidance on withdrawing the use of pyrethroid-only and also any other class of nets where they no longer achieve their expected effect, and until susceptibility is restored.

Response: The increasing availability of new vector control interventions, not only ITNs, will certainly require revision of WHO guidance on insecticide resistance management, which is planned for 2020. Guidance on withdrawing pyrethroid-only nets is, however, presently not envisaged given that: i) these nets provide increased protection to net users compared to the use of untreated nets or no nets; ii) there is insufficient supply and funding to ensure that current levels of vector control coverage can be maintained if all countries were to replace pyrethroid-only LLINs with new types of ITNs; and iii) the public health value[2] of currently available new nets has not been validated, with the exception of pyrethroid-PBO nets for which a conditional WHO recommendation is in place based on one epidemiological trial. As the evidence base and market evolve, WHO will continually review and revise its guidance on insecticide resistance management.

Comment: In parallel to the modification of the classification of ITN products, WHO Global Malaria Programme (GMP) should develop a policy recommendation to cease deployment of pyrethroid-only nets in areas of pyrethroid resistance.

Response: This comment has been addressed in the above response

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Question: This announcement is only focused on differences between AIs. Does WHO have a plan to categorize further on the basis of long-lasting insecticidal net (LLIN) structure (e.g., incorporated/coated, PES/PE/PP etc.)? Currently, the Joint Meeting on Pesticide Specifications (JMPS) specification requires the same specification and variance range in all types of LLIN products.

Response: This document is focused on the classification of ITNs based on the different entomological effects achieved by AIs currently used on nets. It is an attempt to move away from a focus on AIs to a focus on the effect that these achieve. WHO has no plans to use information on other aspects of ITN design to inform classification for policy-making. These other aspects are considered to be part of the prequalification process, which aligns with the policy-making process, and are reflected in the product listing and supporting materials.

Question: If these prerequisites are adopted in the future as a prerequisite for tools other than the immediate ones containing chlorfenapyr or pyriproxyfen, there needs to be clarity about how these multiple strains will be adjudged; e.g., PBO ITNs will not be able to prove efficacy against multiple resistance mechanisms due to their mode of action, so would a similarly specific AI in the future fall foul of this? Also, what if new AIs are more or less effective against different strains? Does that mean they are in a separate class or would require epi data due to their difference in efficacy from the first in class? These may seem speculative, but I think it is important to consider precedent for the future when determining these rules.

[2] A product has public health value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans.

Response: WHO is aware of significant differences in the performance of products covered by the current classes, and that this heterogeneity will increase when classes are collapsed. This heterogeneity in product performance creates significant challenges in product selection by WHO Member States and their implementing partners. It is not envisaged that clarity on product performance will be provided *via* the classes, which are primarily designed to validate public health value in order to then allow WHO to issue a specific policy recommendation. Instead, WHO envisages that clarity on product performance will be provided by means of an enhanced entomological evaluation process and product listings including clear product labels. In addition, WHO is considering the development of summary tables providing the list of policy-recommended and prequalified products for each intervention type (e.g., ITNs), their key performance characteristics (e.g., duration of bioavailability/residual efficacy, activity against insecticide resistant populations) and the available evidence.

Question: Mid 2nd para p. 1: *"A number of recently submitted product are similar to the chlorfenapyr and pyriproxyfen-containing products…"* – Are you able to share information on how many products this includes? This will aid our future planning.

Response: No full applications have been received to date. WHO apologizes for the inaccuracy in the above quoted section. The section refers to informal inquiries and outputs from WHO's horizon-scanning process. It is presently unclear how many products will eventually be submitted for assessment, while it is clear that a number of products are being developed. We refer the reader to the relevant page of the WHO Global Observatory on Health R&D: https://www.who.int/research-observatory/monitoring/processes/health_interventions/en/

Question: What impact will this proposed reclassification of ITNs have on the currently prequalified pyrethroid-PBO nets? How will this proposed reclassification link in terms of timing with the current PQ call out on products designed to perform against pyrethroid-resistant mosquitoes?

Response: The proposed reclassification will have no impact on the current Prequalification Team-Vector Control (PQT-VC) product review of non-pyrethroid-only ITNs, except that completion of the review and closure of the identified data gaps are prerequisites for the implementation of an ITN reclassification. The product review is part of the ongoing work to address existing data gaps for specific products that were converted from a WHOPES recommendation to a prequalification listing.

Question: The NoI mentions that "*If these data were to be provided, WHO would consider continuation of listing additional chlorfenapyr or pyriproxyfen treated nets in the absence of a specific policy recommendation. Once epidemiological data or the two products currently undergoing evaluation are available a full review of all products falling into the potential two new classes would be conducted*." Does it mean that a product that claims equivalence to Interceptor G2 can be listed without conducting the epidemiological experiment now and can be considered covered by policy recommendation now?

Response: The revision of the entomological evaluation procedures is a prerequisite for any changes to the classification system. This means that neither of the two products you ask about is currently considered to be covered by a policy recommendation. It is,

however, envisioned that once entomological evaluation procedures have evolved, and existing data gaps are closed, the modified ITN classification system will be implemented, which will allow other new net products to be assessed by PQT-VC and listed if WHO's criteria for safety, efficacy and quality are met. There would still be no specific policy recommendation in place to cover these new nets until a first-in-class product has successfully demonstrated that the class has public health value. As an interim arrangement, the prequalification of products in these classes could proceed while evidence to support WHO policy recommendations is being generated.

Question: Why is the terminology ITN used and not LLIN? Currently, all new nets with molecules other than pyrethroid need to show that they perform according to LLIN guidelines (that define performance through testing efficacy with pyrethroid susceptible mosquitoes). ITN used to be used to indicate conventionally treated nets, so use of the term ITN in this way is confusing. If next-generation LLINs will not be called LLINs but still conform to the performance criteria of an LLIN, then the definition of an LLIN may need to be reconsidered.

Response: We would like to refer readers to the *Guidelines for malaria vector control* (https://www.who.int/malaria/publications/atoz/9789241550499/en/), specifically the glossary, which outlines the terms in current use. An LLIN is a factory-treated mosquito net made of netting material with insecticide incorporated within or bound around the fibres. The net must retain its effective biological activity for at least 20 WHO standard washes under laboratory conditions and three years of recommended use under field conditions. Given that data for certain nets are not available for all insecticidal/synergist formulants and that available data clearly show that some products do not meet the wash-resistance criteria, WHO was required to re-introduce the term ITN in 2017 when the conditional policy recommendation for pyrethroid-PBO nets was developed.

Question: A flow chart laying out the process for new ITNs would be very helpful. For example, should all new ITNs containing a new AI have to go through VCAG?

Response: WHO is working on an update to the 2017 information note on the evaluation process for vector control products, which is available via the following weblink: https://www.who.int/malaria/publications/atoz/evaluation-process-vector-control-products/en/. The flow chart on the process will be revised as part of the update. In any case, existing guidance already makes it clear that not all new ITNs have to generate data to validate their public health value; this is only required for one first-in-class product to establish a class and to support development of a WHO policy recommendation. The consolidation of classes, as proposed in the NoI, would lead to a reduction in the number of epidemiological trials required by WHO.

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3. Comments and questions on proposed ITN categorization into classes

Comment: When thinking about future implications of these classifications, it is unclear how new products may be evaluated that apply to more than one category. There is a risk that these guidelines could silo innovation rather than encourage innovations that develop products with differing modes of action. Again, this is where fewer, broader classes that are assessed by product claims could help provide flexibility in the future.

Response: WHO considers that this comment has, at least partially, been addressed through further modification of the classes, as proposed in section 5. As with the previous question, this one is somewhat hypothetical. The NoI indicates under step 9 of the provisional subsequent steps that WHO plans to establish a process to define similarities between existing and future ITN products, drawing on inputs from the PQ assessors' group and VCAG.

Comment: Our main critique of the proposal to modify the classification of ITN products is that it reinforces a paradigm that the solution to pyrethroid resistance lies in products containing a pyrethroid plus another AI. We would argue that the new classification system should emphasize a shift away from pyrethroid products, the distribution of which will only risk further entrenchment of resistance and establish a scheme that will better facilitate the approval of ITNs containing only novel AIs.

Response: The classification system is primarily designed to communicate which intervention classes are covered by WHO policy and which are not. It is thus informed by products currently available and/or under evaluation. WHO fully supports the notion that new AIs are needed and that, ideally, ITN products would cease to use pyrethroids. This type of information will be conveyed through the Preferred Product Characteristics that are currently under development. The classification does, however, already attempt to cater to products that do not contain pyrethroids, as it is based on entomological effects, not on product chemistry.

Comment: It would be useful for WHO to consider whether it is useful to differentiate between a) products that control pyrethroid-resistant mosquitoes but with only one AI filling this role (i.e., pyr+non-pyr treated nets or single treated net with a non-pyr) and b) products that control pyrethroid-resistant mosquitoes where more than one AI fill this role (i.e., products that include two or more non-pyrethroid insecticides). The proposed class definitions don't differentiate between these types of products, yet there are potentially important differences for insecticide resistant management. Please could WHO and its technical groups consider whether making separate classes would be important to guide planning by Member States, and if so, whether a technically feasible approach to doing so could be conceived.

Response: WHO considers that this point has been partially addressed by further modification of the classes. It should be noted that guidance on resistance management goes beyond what the classification system is designed to do. In addition, the scientific evaluation of data to support the intended use of the product is the role of PQT-VC. The use of the product in specific situations is often described through a claim on the label and, as such, data must be provided to support these specific uses, including use in resistance management. More broadly, guidance on managing resistance in specific regions is the part of the work/mandate of the technical programmes, in this case

GMP, and is communicated via guidelines. At present, resistance management guidance is captured in the *Guidelines for malaria vector control*: https://www.who.int/malaria/publications/atoz/9789241550499/en/

Comment: P. 2, Section "*Proposal*"; penultimate sentence: fecundity reduction is not mentioned here and perhaps should be.

Response: WHO acknowledges the omission of this term from the specified sentence that covers deterrence, blood-feeding inhibition, and immediate and delayed mortality. Fecundity reduction is certainly another endpoint that is equally relevant and will be considered as part of the evaluation process.

Comment: This document lacks nets containing only non-pyrethroid AI(s) (not combined with pyrethroid). Need to add.

Response: The revised classes in section 5 cover non-pyrethroid nets. Under the envisioned reclassification, it does not matter whether one, two or more AIs are used on the net, as the classification aims at distinguishing the effect that the net treatment has on the mosquito vector, not the way the net has been designed/treated.

Comment: The document states that studies are already underway that may demonstrate public health value and support policy for Classes III and IV. With this in mind, it would be useful to understand the timeframe in which the policy is expected to be published.

Response: WHO policy recommendations can be developed within weeks of data being formally submitted to WHO, provided these data allow for assessment of a product's public health value and support the issuing of a recommendation. Informing WHO of when data are likely to become available greatly facilitates planning for a timely review process. At present, it is unclear when exactly data from the two ongoing epidemiological trials on pyrethroid + chlorfenapyr and pyrethroid + pyriproxyfen nets will be submitted. A 24-month intervention period will be required for these products, which is likely to lead to the full data package (i.e., from both trials) only being available for review by mid-2020.

Comment: The document is also not clear as to whether it is a requirement for an ITN product to contain a pyrethroid insecticide for it to be included in the proposed classes (II-V) even if it demonstrates the required entomological endpoints. Subsequently, the document also needs to clarify whether an ITN containing a single novel insecticide but demonstrating the required entomological endpoints also meets the intended classes or would be viewed as first in class.

Response: There is no need for a product to contain a specific insecticide class. The proposed classification is based on the entomological effect of the AI(s) on the net. Single insecticides meeting the required (yet to be revised/defined) entomological endpoints would not be viewed as first in class if the product falls into one of the classes specified in section 5.

Comment: While it is stated in the proposal that "investigation into the value of non-inferiority are currently underway and will be reviewed… to determine whether this approach would add value to the evaluation process", we request WHO GMP further clarify this is primarily an investigation on the suitability of non-inferiority testing methodology.

Response: For Q&As on non-inferiority, WHO would like to refer the reader to a separate document that was prepared based on responses received to an NoI published in late 2018: https://www.who.int/malaria/publications/atoz/non-inferiority-protocol-QA-eng.pdf?ua=1. In sum, ongoing work on non-inferiority is exploratory. Once data from ongoing studies are available (likely in late 2020), these data will be reviewed to determine whether this method will become routine practice, and, if so, how it would be implemented and how the findings of such assessments would be made available.

Question: i) Reduction of blood-feeding only: Untreated nets. There are innovative untreated nets under development which rely on other design features (such as desiccants or a built-in trapping section rather than insecticides) to not only reduce blood-feeding but also to kill both susceptible and resistant strains. Would such nets require further approval by WHO with regard to their public health value or would they simply have to go through the PQ listing process?

Response: Untreated nets are currently not covered by a WHO policy recommendation. A first-in-class product would therefore need to generate data to allow for assessment of public health value. For specific inquiries, applicants should submit a request for determination of pathway to pqvectorcontrol@who.int.

Question: Three categories (iii, iv and v) are described. Please clarify how nets which contain elements of two categories will be handled, e.g., iv and v. Please clarify how the combination of PBO with either chlorfenapyr or pyriproxyfen will be handled (as opposed to mixtures with pyrethroids).

Response: Please review the revised proposed classification provided in section 5. Within these categories, the classification of a net employing a combination of PBO and a different AI would be driven by the other AI used, not by the PBO component. For specific inquiries, applicants should submit a request for determination of pathway to pqvectorcontrol@who.int.

Question: P. 3 Three categories (iii, iv and v) are described. If different AIs are placed on the walls and the roof, rather than in a mixture throughout, how might this impact the classification, if at all?

Response: Please review the revised proposed classification provided in section 5, which has been modified since this question was asked. In general, however, a response from WHO will depend on the specific characteristics of the product submitted for evaluation. A response would be provided by the WHO Pre-submission Coordination Committee to the applicant. WHO is unable to provide a more detailed response to this question in the absence of a concrete example. For specific inquiries, applicants should submit a request for determination of pathway to pqvectorcontrol@who.int.

Question: With these classes based purely on entomological effect, can you confirm that these are independent of chemistry? e.g., a product with no pyrethroid or other AI listed here would be considered part of an established class if it demonstrates the stated entomological effects of that class?

Response: Yes, WHO confirms that other AIs are covered by the proposed classification, provided their entomological effect is consistent with that indicated for a specific class. We would, however, like to clarify that current testing guidelines are insufficient to comprehensively assess the entomological effect(s) of products within these classes and would need to be modified to allow for comprehensive assessment of nets other than pyrethroid-only LLINs before a revised classification can be implemented.

Question: Is the sole intent that these classes guide the process of evaluation, prequalification and policy-making; or will these classes also be a tool used by Member States to help selection of tools and planning?

Response: Intervention classes guide the process for the evaluation of public health value and associated policy-making for a class. Once public health value has been demonstrated, WHO will issue a policy recommendation for a specific intervention class (and hence the products within it) for deployment. PQT assessments are conducted for each product submitted to WHO regardless of the class. Selection of tools and planning/prioritization of the deployment of vector control is a more detailed and context-dependent process that cannot be fully addressed by the policy recommendation or the PQT listing. Deployment, including the potential mix of different interventions, is context-dependent and requires further information. WHO recognizes the need to provide simplified overviews of which products are recommended under which class and how these products vary in terms of their performance, so as to inform the selection of tools and associated procurement decisions. WHO is currently assessing how best to meet this need of its Member States and their implementing partners and welcomes suggestions from partners in this regard. One potential approach under consideration is the development of overview tables akin to those formerly available under WHOPES, wherein all available products, their key performance characteristics and the associated level of evidence would be summarized based on the data provided to WHO via both the PQT process and trials assessing epidemiological impact. We invite further suggestions on this topic via: vcguidelines@who.int

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Question: If an ITN product were coated with pirimiphos methyl (slower acting than pyrethroids) + deltamethrin, would this product be included in class iii? Would this mean that this product would be covered by the policy recommendation for this class?

Response: Please refer to the revised classes shown in section 5. A product with pirimiphos methyl and deltamethrin would be considered part of class ii under the revised categorization.

Question: The first piece of evidence cited for a potential listing of any other chlorfenapyr or pyriproxyfen treated ITNs before epidemiological trials for the two potential first-in-class products have been completed is stated as the following:

i. Evidence that a new ITN product provides greater personal protection to net users than standard pyrethroid-only nets against a range of fully characterized insecticide resistant populations.

Why would evidence of personal protection be needed when classes iii. and iv. don't mention blood-feeding inhibition? Rather, they discuss killing or sterilization.

Response: Yes, this point needed modification and WHO hopes that this has been partially addressed through the revision of the classes in section 5.

Entomological evaluation procedures to assess this effect/these effects will need to be developed, as outlined elsewhere in this document and explicitly stated as a prerequisite in the NoI.

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4. Proposals for further modification of ITN classes

Comment: Proposed modification to classes, with changes proposed by the author(s) highlighted in red.

i. Reduction of blood-feeding only: Untreated nets. No specific policy recommendation in place. WHO would need to commission a systematic review on the evidence of a protective effect required to inform a potential policy recommendation or a recommendation against the use of untreated nets.

ii. ITNs designed to control pyrethroid susceptible mosquito populations that have demonstrated reduced blood-feeding and increased killing of insecticide-susceptible mosquito vectors against existing WHO evaluation standards (2): Existing prequalified pyrethroid-only nets. Policy recommendation in place.

iii. ITNs designed to control insecticide-resistant mosquito populations that have demonstrated improved efficacy compared to pyrethroid-only nets in terms of killing pyrethroid-resistant mosquito strains: This class is considered to include both insecticide treatments with active ingredients that are slower acting than pyrethroid-based formulations[3] ~~and fast-acting ones~~and through the use of synergists. It is provisionally thought to include ~~pyrethroid + chlorfenapyr nets~~pyrethroid-PBO nets that are currently covered under an interim WHO policy recommendation and pyrethroid + chlorfenapyr nets[4].

iv. ITNs designed to control insecticide-resistant mosquito populations that have demonstrated improved efficacy compared to pyrethroid-only nets in terms of sterilizing pyrethroid-resistant mosquito strains: This class is provisionally thought to include pyrethroid + pyriproxyfen nets.

[4] The new class will be established once two randomised control trials have confirmed the epidemiological impact of multiple ITNs with the same entomological effect but with different modes of action over pyrethroid-only nets.

~~**v.ITNs designed to control insecticide resistant mosquito populations that have demonstrated improved efficacy compared to pyrethroid-only nets in terms of reducing blood-feeding and of killing of pyrethroid-resistant mosquito strains:** This class includes fast-acting and excito-repellent insecticides such as the pyrethroid-PBO nets that are currently covered under an interim WHO policy recommendation.~~

Response: These inputs have been taken into account in the revision of the classes outlined in section 5.

Comment: Regarding the proposed categorization of ITNs into classes, consider less restrictive definitions of ITN classes to reduce the need to create more classes in the future. We submit the following alternative classifications for consideration:

a. Barrier-only nets: Untreated nets.

b. Single insecticide ITNs: ITNs containing a single insecticide (e.g., pyrethroid-only ITNs, but could also include other single insecticide ITNs if such a product were to be developed).

c. Multi-insecticide ITNs: ITNs containing more than one insecticide, presumably with multiple modes of action, such as a pyrethroid plus chlorfenapyr ITN, but would not exclude multiple insecticides of the same class if shown to be effective.

d. Insecticide(s) + synergist ITNs: ITNs that include one or more insecticides plus a synergist (e.g., pyrethroid + PBO ITNs).

e. Insecticide(s) + insect growth regulator (IGR) ITNs: ITNs containing one or more insecticide(s) plus an IGR that interrupts the life cycle of the mosquito (e.g., insecticide + pyriproxyfen ITNs).

Response: A similar approach is now proposed in section 5, drawing on entomological effect rather than the design of the product.

Comment: P.2, "Proposal" section of NoI: "*For each class a 'first in class' product will have to demonstrate epidemiological impact against malaria in at least two trials…*

Once a product class has been established all subsequently submitted products that demonstrate the same entomological effect so called 'second in class' would be evaluated on entomological endpoints only."

While this seems like a good idea it also makes being 'first in class' very expensive and follow on 'copy' products cheap to launch; so where is the incentive to innovate and be first in class? We have seen the mess of PBO nets following the first in class here with various insecticides, various levels of PBO but all being classed as PBO nets!

Response: WHO understands the concern over the investments required to demonstrate public health value of new vector control products. However, the need to demonstrate protective efficacy to reduce or prevent infection and/or disease in humans will remain a requirement of WHO in the absence of any validated correlation between entomological and epidemiological endpoints. Mechanisms to meet the costs associated with the required trials to demonstrate the public health value of new ITNs have been put in place through the New Nets Project funded by Unitaid and the Global Fund. WHO views the provision of incentives to be first in class as a shared responsibility with procurers and encourages the evolution of current procurement mechanisms to provide such incentives.

Comment: P.2, "Proposal" section of NoI: "*i) Reduction of blood-feeding only: Untreated nets. No specific policy recommendation in place. WHO would need to commission a systematic review on the evidence of a protective effect required to inform a potential policy recommendation or a recommendation against the use of untreated nets."*

Untreated nets should be removed from this document because they are not "ITNs" (insecticide-treated nets). There is not sufficient quality epidemiological evidence on untreated nets to justify a systematic review. Untreated nets would anyway be a new product class and require new guideline test methods, 2 epi trials, etc. WHO really should not be spending time getting distracted discussing untreated nets.

Response: Untreated nets have been removed from the revised list of classes in section 5.

Comment: P.3, "Proposal" section of NoI: "*iv) ITNs designed to control insecticide resistant mosquito populations that have demonstrated improved efficacy compared to pyrethroid only nets in terms of sterilizing pyrethroid-resistant mosquito strains. This class is provisionally thought to include pyrethroid + pyriproxyfen nets."*

How can it be improved efficacy compared to pyrethroid-only nets in terms of sterilizing mosquitoes: pyrethroid-only nets do not sterilize mosquitoes? In addition, with pyriproxyfen for example there is a lot more going on than just sterilizing the mosquito. These factors are ignored.

Response: In the revised classification in section 5, the classes have been reworded to address this and other comments.

Comment: P.3, "Proposal" section of NoI: "*v) ITNs designed to control insecticide-resistant mosquito populations that have demonstrated improved efficacy compared to pyrethroid-only nets in terms of reducing blood-feeding and of killing of pyrethroid-resistant mosquito strains: This class includes fast-acting and excito-repellent insecticides such as the pyrethroid-PBO nets that are currently covered under an interim WHO policy recommendation."*

It would be better to move the part that includes PBO nets to iii) considering that these have an interim policy recommendation. The statement "fast-acting and excito-repellent insecticides such as the pyrethroid-PBO nets" would be better stated as "pyrethroid + synergist nets" because pyrethroid-only nets are also fast-acting and excito-repellent.

Response: These inputs have been taken into consideration in the revision of the classification, as shown in section 5.

Comment: The inclusion of category 1 with untreated nets is unnecessary. Considering this guidance is for ITNs, having a category for untreated nets is confusing and as WHO does not recommend them and I would think that resources to develop evidence through a systematic review would be better used elsewhere. Considering much of these guidelines focus on 'superiority' of new tools, untreated nets are clearly inferior to treated ones, so I think this can be dropped.

Response: We agree that dropping this category will aid in simplifying the overview of ITNs. However, as is demonstrated by other questions and comments received in response to the NoI, there seems to be a need to clarify that WHO does not currently recommend the use of untreated nets for the control of malaria (and other disease) vectors, and that evidence from at least two randomized trials would be required for WHO to assess the potential public health value of untreated nets. This information has been moved to a narrative paragraph below the proposed new classes in section 5.

Comment: Similarly, I wonder whether categories 3 & 5 could be rolled into one. I wonder how effective the excito-repellency effect is considering some of the data from recent behavioural studies. Moreover, considering that this guidance states that untreated nets elicit a reduction in blood feeding, could every class not lay a claim to that entomological effect? So, having this explicitly differentiated in class 5 as opposed to 3 is confusing and I would suggest having one class for efficacy against resistant populations that is differentiated by product claims on the entomological effect.

Response: Please consult the revised classification in section 5 where this comment has been addressed.

Comment: Similarly, by using PBOs as the example in 5, I feel it needs to be caveated that this is only effective in areas where metabolic resistance is present. If other mechanisms are present, they are unlikely to exhibit this entomological effect, as per the WHO guidelines. In essence, the entomological effect this category describes is only present under certain conditions so there needs to be a clear link with product claims and the label to this effect.

Response: WHO considers that this comment has been addressed as part of the further revision to the classes, as shown in section 5. PBO nets (formerly in class iv) have now been combined with other insecticidal nets (formerly in class iii) into one class now labelled class ii. Please see the section on label claims with regard to other parts of this comment. WHO agrees that product-specific performance will need to be clearly communicated on the label.

Comment: There is also room for confusion in 5 as this category states these products are "designed to control" resistant populations, although the WHO vector control guidelines suggests PBO ITNs are not sufficient to "control" resistance. There should be alignment on terminology here.

Response: The WHO *Guidelines for malaria vector control* state that "Pyrethroid-PBO nets should not be considered a tool that can alone effectively manage insecticide resistance in malaria vectors". While there is evidence available showing that PBO nets provide improved disease control at least in some settings, the products available still deploy a pyrethroid insecticide; therefore, they are not a resistance management tool, which would be expected to act on a different target site in the mosquito. Wording of the proposed classes (see section 5) has been further revised in an attempt to address this and other comments.

Comment: Bullets iii, iv and v: these refer to "ITNs designed to control insecticide-resistant mosquitoes" that have demonstrated improved performance against "pyrethroid-resistant strains". This needs to become consistent – either by changing the first instance of "insecticide" to "pyrethroid", or, changing the wording of "pyrethroid-resistant strains" to "relevant insecticide-resistant strains". The latter approach would be more future-proof but may be too broad a technical definition for a class of products that are expected to demonstrate similar entomological performance and rely on the epidemiological impact demonstrated by the first in class. Given this, the former suggestion of sticking to "pyrethroid" may be more appropriate; but if so it may be useful to clarify in the document that WHO is also interested in products that would perform against other types of insecticide-resistant strains.

Response: The classes have been modified to replace "pyrethroid-resistant" with "insecticide-resistant". Please see section 5.

Comment: Classes ii, iii, and v are very similar. WHO should consider combining into one class: ITNs designed to control mosquito populations by reduced blood-feeding and increased killing of mosquitoes. This should not be based around pyrethroids but rather the anticipated impact of the chemical – to kill mosquitoes. Thus, there would

be three classes: Nets with no chemical, nets with a killing agent, nets with a sterilizing agent (i.e., categorize based on mode of action).

Response: These inputs have been taken into consideration in the revision of the classification, as shown in section 5.

Comment: Bullet iii: It is not clear how slow and fast acting products can be combined in the same class if next-in-class products are expected to have to show entomological similarity to first-in-class products and thereby be able to bridge epi-data linked to the first in class. Some constraints would be needed. I assume the intent is to develop these constraints as evidence is built; it may be useful to make this clear.

Response: Please note that reference to slow- and fast-acting has been removed from the classes. Yes, entomological similarity will have to be demonstrated to provide the required bridge to the epidemiological data provided by a first-in-class product, and yes, the process for this and the evidence required is still under development; the guidance development process will be informed by currently available evidence and evaluation guidance will be further modified if new evidence provides justification for such modification.

Comment: Bullets ii – v. Do you envisage products being in more than one class? The current wording implies all products in class v) would also fall into class iii) and it could be that some products in class iv) also fall into class iii). This may not matter but again it links to the question around how Member States may or may not use these classes for operational/strategy purposes.

Response: Please consult the revised classes in section 5. It is envisaged that products will only fall into one class.

Comment: The classes iii–v are worded as "*ITNs designed to control insecticide-resistant mosquitoes"*, yet it is also mentioned that products that are "designed to" control resistant mosquitoes may be prequalified under class ii whilst evidence is built (mentioned in *Provisional subsequent steps* no. 8). We welcome this potential opportunity; however, to make this proposed way forward align with the wording, WHO may want to consider changing the wording of classes iii–v (potentially the words "*designed to control insecticide-resistant mosquito populations"* could be deleted in each case, with the focus left on what the products have demonstrated they can actually do), or making a clearer statement about the fact that products "designed to" control insecticide-resistant mosquitoes can also be considered to fall into class ii if the performance criteria are met.

Response: Please see section 5 for the reworded classification based on the inputs received in response to the NoI. WHO considers that all "new nets" have been designed to improve the protective efficacy to reduce or prevent infection and/or disease in humans compared to the current standard of care, namely pyrethroid-only nets, the efficacy of which is threatened by the emergence and spread of pyrethroid resistance. While assessing activity against pyrethroid-susceptible mosquito populations is a good starting point for any evaluation, WHO will require supporting information on all criteria against which a product has been evaluated. This will need to include data on the product's effectiveness against a range of characterized insecticide-resistant

mosquito strains. This information should be included in the PQ product dossier and, if supported, will be stated in the product labelling and use information. The suggestion to remove "designed to" was therefore not implemented in the revised classification in section 5. We fully agree that all nets should come with appropriate information that communicates to the procurer and user how the product it works.

Comment: Bullet ii: *"reduced"* and *"increased"* are comparative terms; it should be clarified what these refer to. Here, we assume the comparison is to untreated nets.

Response: The definition of class ii (now class i) has been further modified to address this comment.

Comment: A compound that is not fast-acting may, nevertheless, offer good levels of blood-feeding inhibition and, therefore, personal protection, if exposure to it affects the host-seeking behaviour of mosquitoes. So, a combination of two slow-acting insecticides, of which one inhibits host-seeking, could fall into class v.

Response: Please see revised classes in section 5. Reference to slow- and fast-acting has been removed.

Comment: The document acknowledges that the 20-wash resistance threshold is possibly too high a bar for evaluation of duration of effectiveness. This idea could be developed further by stating that 20 washes was chosen not because of an objective requirement from field use, but from the ability of one class of insecticides, incorporated into or coated onto an ITN, to reliably resist this number of washes. If other kinds of chemicals are going to be used, then the criteria for duration should be fit for purpose, ideally based on real field requirements.

Response: WHO agrees that the assessment of wash resistance, and the bioavailability of insecticides in the absence of washing and under field conditions, needs to be reviewed, including the minimum standards associated with it. This will be addressed through the development of revised WHO testing guidelines.

Comment: Policy development should include withdrawal of recommendation of pyrethroid-only nets where they no longer achieve their expected effect.

Response: As indicated in the response to a similar comment, WHO currently has no intention of withdrawing its recommendation for pyrethroid-only nets, given that these nets continue to provide protection from malaria.

Comment: Ideally, even with the development of a new ITN classification system, WHO will remain flexible in support of large-scale trial deployment, etc., as has been done with the Interceptor G2 and Royal Guard. Responding to insecticide resistance and removing barriers to ITN innovation are urgent issues, which WHO did a good job addressing by being flexible in support of the New Nets Project.

Response: WHO considers that the ongoing consultation around ITN classification clearly indicates the intent to be as flexible as possible, while finding the right balance between addressing the public health need for tools to manage insecticide resistance

and upholding WHO's responsibility to provide evidence-based guidance to its Member States. In the absence of the demonstration of public health value, the large-scale deployment of products will not be explicitly recommended. Well-designed trials to demonstrate public health value do not need to be "large-scale". Large-scale deployment in the absence of a well-designed evaluation approach does in fact run the risk of compromising quality, while it is the quality of the data generated that will determine the strength of a WHO policy recommendation and associated guidance.

Comment: It would be helpful to understand what areas WHO may wish to focus on in this regard in light of the known products and AIs that are in the pipeline. One example could be relooking at the fact these classifications are focused on pyrethroid resistance, where there are other types of resistance that present and have the potential to develop. Such an approach could help guide research to inform these decisions.

Response: WHO is concerned about all types of insecticide resistance and aims to evolve the evaluation process and associated classification of products to provide a comprehensive insecticide resistance management/mitigation response. The classification proposed here attempts to capture existing products and those currently under development.

Question: P.3, "Proposal" section of NoI: "*iii) ITNs designed to control insecticide-resistant mosquito populations that have demonstrated improved efficacy compared to pyrethroid-only nets in terms of killing pyrethroid-resistant mosquito strains: This class is considered to include both insecticide treatments with active ingredients that are slower acting than pyrethroid-based formulations, and fast-acting ones. It is provisionally thought to include pyrethroid + chlorfenapyr nets.*"

This mentions "in terms of killing pyrethroid-resistant mosquito strains," but there is a possibility that new AIs will have repellent/blood-feeding inhibition effects. So, this should not be limited to "killing". We suggest expanding this or adding one more category.

We cannot see why this mentions "slower acting/fast acting". Replace with "active ingredients other than pyrethroids".

Why is there a Category iii and v as they appear to be the same?

Response: WHO considers that these points have been addressed in the revision of the classes, as provided in section 5. The explicit mention of a repellent/blood-feeding inhibition effect has not been included, as in the absence of a killing effect, it is unlikely that such effect would be sufficient to significantly impact disease transmission. For now, no product with only a repellent/blood-feeding inhibition effect has been submitted to WHO for evaluation. If such product were to be submitted, epidemiological data from two trials would be required to assess its public health value.

Question: We have one observation about the class v: ITNs designed to control insecticide-resistant mosquito populations that have demonstrated improved efficacy compared to pyrethroid-only nets in terms of reducing blood-feeding and of killing of pyrethroid-resistant mosquito strains. According to your document, PBO nets belong in this group. Speaking hypothetically, an ITN containing a single new AI with a new mode of action (MoA) but showing repellency would belong in this group. According to your

statement, the PBO nets would be the first in class and the hypothetical nets as second in class would be covered by the interim WHO policy recommendation for PBO nets. Wouldn't it make more sense to have a separate class for pyrethroids with synergists like PBO considering their MoA is also the same as pyrethroid-only nets?

Response: Kindly review the revised classification in section 5. We have not merged PBO nets with pyrethroid-only nets, as they do provide improved performance against (some) pyrethroid-resistant mosquito populations.

Question: For class iii, does the net need a slow and a fast-acting insecticide or does the class encompass any insecticide that kills slowly or quickly? Our interpretation was the latter, so for example if a net just had chlorfenapyr on it and nothing else, it would fall into class 3 as well. Is this interpretation correct? Likewise, if an ITN with another insecticide can be shown to deliver the same level of mosquito mortality, we assume it would fit into this class.

Response: Both modes of action are covered by class ii in the revised classification outlined in section 5.

Question: Is a pyrethroid-PBO ITN really the best example of an ITN that demonstrates improved efficacy against pyrethroid-resistant mosquito strains in terms of both mortality and reduced blood-feeding (class v)? PBO can only synergize pyrethroids where resistance is largely due to P450-based mechanisms, and there is increasing evidence from West Africa that PBO ITNs can't be assumed to be effective against all pyrethroid-resistant strain/populations. Or is it recommended for geographies where the pyrethroid resistance is known to be predominantly due to P450-based mechanisms? In addition, pyrethroid-PBO ITNs aren't examples of ITNs with two insecticidal compounds: it is a pyrethroid plus a synergist.

Response: Pyrethroid-PBO nets may not be the best example, but they are certainly one example of a net that has been designed to provide improved performance over pyrethroid-only nets in areas of pyrethroid resistance, although we acknowledge that this impact varies depending on geography and associated vector resistance profiles, among other variables. As outlined in section 5, pyrethroid-PBO nets have new been moved into the previous class iii (now class ii), and the former class v has been removed.

Question: If there is a new bi-treated, non-pyrethroid ITN that incorporates a fast-acting alternative to a pyrethroid that inhibits blood-feeding plus chlorfenapyr, would it fall under class iii or class v? How will the process be handled if a product appears to straddle two of the proposed classes (a combination of fast- and slow-acting non-pyrethroid insecticides)?

Response: Please see revised classes in section 5. Reference to slow- and fast-acting has been removed.

Question: Why frame the classes around pyrethroid resistance only? Moving forward there will ideally be multiple classes of insecticides available for ITNs. IRS as an intervention consists of only one class of product where programs can choose the right product for the right location based on resistance profiles (whether the insecticide is slow- or fast-

acting). Epidemiological-based testing in two locations for a product class tells us very little about the ability of a product to overcome resistance to different compounds in different settings where different resistance mechanisms may be at work.

Response: WHO's overall focus goes well beyond pyrethroid resistance. Where applicable, "pyrethroid resistance" has been replaced by "insecticide resistance" in the revised classification shown in section 5.

Question: We recognize that some ITNs have a different chemical composition on the walls versus the roof of the net. We would like to confirm that, regardless of the net design, the measure of performance will be based on the entomological endpoints, regardless of ITN structure.

Response: This is correct. The design of an ITN product does not affect its classification.

Question: Where multiple manufacturers are developing products that fit into a single category, could it be assumed that a class can be established based on two epi studies on separate products with the same entomological effects?

Response: Under the further revised classes (section 5), there are only three classes foreseen for now. For these, data on epidemiological endpoints aimed at demonstrating public health value are either available or are being generated. This includes two ongoing trials for both the pyrethroid + chlorfenapyr and pyrethroid + pyriproxyfen nets; both trials are using the same products. WHO does not presently foresee the need to draw on data from two different products to assess the public health value of these classes. As a general response, we would like to clarify that bridging between products or between prototypes/versions of a product is feasible under the WHO evaluation process, but it does create additional challenges and should be avoided where feasible.

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5. Revised proposed ITN classification based on inputs received in response to the NoI

i. **ITNs designed to kill host-seeking insecticide-susceptible mosquito populations that have demonstrated public health value compared to untreated nets and whose entomological effects consist of killing and reducing the blood-feeding of insecticide-susceptible mosquito vectors**: Existing prequalified pyrethroid-only nets. Policy recommendation in place.

ii. **ITNs designed to kill host-seeking insecticide-resistant mosquitoes and for which a first-in-class product has demonstrated public health value compared to the epidemiological impact of pyrethroid-only nets:** This class is provisionally thought to include both insecticide treatments with active ingredients other than pyrethroid-based formulations and nets with synergists. It includes pyrethroid-PBO nets that are currently covered under an interim WHO policy recommendation. The class would be expanded to include pyrethroid + chlorfenapyr nets once their public health value has been demonstrated by means of at least two geographically separate epidemiological trials. The class would then be expanded to also include other products with the same entomological effect but with different chemical modes of action to pyrethroid-only nets without the need for further epidemiological trials.

iii. **ITNs designed to sterilize and/or reduce the fecundity of 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:** This class is provisionally thought to include pyrethroid + pyriproxyfen nets and will be created once the public health value of a first-in-class ITN product containing an insect growth regulator has been demonstrated by means of at least two geographically separate epidemiological trials.

It is anticipated that the above framework for ITN classes may need to evolve depending on what other products are submitted for evaluation by WHO and based on the data generated by products under evaluation. WHO will initiate a process to define the similarities between existing and future ITN products, drawing on the PQT-VC assessors' group and VCAG. This process will enable the evolution of the classification system for ITNs and other vector control products. Untreated nets are not included in the above classification, as they are not treated with an insecticide and are not recommended by WHO.

6. Comments and questions on the evaluation of ITNs against entomological endpoints

Comment: As a manufacturer we urgently need clear guidelines to guide our experiments, and we have reflected on this problem many times.

Response: PQT-VC is aware of the need for clear and concise guidelines. Work on revised guidelines has been initiated with the objective to align these guidelines with the requirements of the prequalification programme. The document will be designed to separate the information on process, data requirements, methodology, operational policy, and so on to ensure that the guidelines meet the needs of all stakeholders. In the meantime, PQT-VC encourages manufacturers to continue to use the pre-submission process and protocol review service to assist them in guiding their data generation.

Comment: Guidance on prerequisites and next steps is welcome and helpful as a show of intent and transparency of process. In terms of clarifications, it would help to better understand the precise definition of "greater personal protection" and "multiple resistant strains". On the latter point, I feel this is extremely important to define whether you are talking about lab/wild strains, resistance mechanisms, species, etc.

Response: It is acknowledged that both these terms will require clear definition as part of the revision of WHO testing guidance. The NoI indicates that WHO has taken note of this need and will work with its technical advisory groups to ensure that these definitions are developed as part of the revisions to the testing guidelines.

Comment: The word "resistance" needs to be clarified. First, the minimum level of resistance should be set as a range, say 10–100 at LC50 relative to a susceptible strain. Lower levels hardly play any role in mosquito control, and higher levels may not lead to full control by the new net. The resistance mechanism should also be known. You cannot expect PBO nets to overcome other R mechanisms than P450 based oxidases. Pyriproxyfen is metabolized by some P450 oxidases in whiteflies, so maybe the combination pyrethroid+pyriproxyfen will only help where kdr and GSH are problems, but that could be interesting enough, if specified. So, the meaning of resistance should be qualified. That will also encourage ministries of health (MoHs) to get national mosquito sensitivity data right before deciding on what to ask for.

Response: As indicated in the previous responses, WHO has taken note of the need to provide definitions of this and other terms.

Comment: Quote (page 3), "the evaluation standards should be designed to provide confirmation that new ITN products are entomologically superior to pyrethroid-only nets". While this seems logical, it may be meaningless. This is clearly illustrated by the two first PBO nets that WHO first evaluated in lab tests and then a malaria impact study was made on one of these that led to a WHO recommendation of PBO nets. The problem is simply that WHO and independent authors were comparing products with the same pyrethroid but with very different surface concentrations. Due to polymer composition, Olyset made out of HDPE releases next to no permethrin, whereas Olyset Plus made out of low and high density polyethylene releases a lot, so Olyset

Plus is surely a lot more effective but it is not related to PBO. PBO migrates faster than permethrin in polyethylene, so when they are in the same yarn, PBO is gone after two years, which is exactly what the field study showed.

Deltamethrin in Permanent 3 was dosed higher than in Permanet 2 so of course it worked better. Therefore, even if it seems logical from an entomological point of view to compare a new product with an existing one, it cannot ascribe an eventual superior effect to the second insecticide or synergist unless the pyrethroid are dosed the same and released at the same rate, basically unless the surface concentration is the same, because this is all the mosquito meets.

Surface concentrations can be measured (as shown in my poster at the recent RBM meeting). Or, the producer can be asked to make test nets that are identical to the new net except for absence of the second insecticide or synergist. This was suggested by WHO some years ago but turned down by some industry representatives that said it would need a new, extra product development. Even if this is somewhat right, such a product would be a lot closer to the combined product than any other products and the comparison therefore be more fair. We should not "let the best be the enemy of the better". I suggest that WHO therefore stand by the proposal raised some years ago.

Response: WHO takes note of these inputs and will take them into consideration as part of the revision of the testing guidance.

Comment: The requirement for companies to show "Evidence that any additional ingredient added to the net (e.g., insect growth regulator, second insecticide) is biologically active" is great, but should it be specified that any test procedure for this should be possible to use in field settings where conditions are different from controlled laboratory settings (temperature, etc.)? As I understand it, there is currently no standard procedure to evaluate the ability of chlorfenapyr to kill mosquitoes in field environments unless a set of experimental huts is built (and even then it is still not clear whether the tests conducted in the huts are capturing the full impact of this insecticide). Ongoing research work may provide assays for chlorfenapyr and pyriproxyfen. However, if this work is unsuccessful yet randomized controlled trials show epi impact beyond what would be expected based on entomological data generated in experimental hut trials, there will be no assay that can directly link entomological impact as measured in the field with epi outcomes. For pyrethroid-only and pyrethroid-PBO nets, we had discriminating dose/intensity bioassays to link to hut trials, but these don't seem to work for novel modes of action. The lack of reliable and easily implementable entomological test procedures would greatly impede our ability to guide field deployment in future or see whether resistance was developing to these new chemistries. For me, getting good field entomological assays for new chemistries is essential for inferring epi from ento and getting them before the product goes to the field.

Response: WHO is aware of the limitations of current test procedures for the entomological evaluation of new types of nets, and the challenges faced in assessing the entomological effects of some repurposed AIs, including reliable and replicable susceptibility testing for these compounds in field settings. The revision of ITN testing guidelines will draw on current best practice and evidence, as will the revision of WHO's *Test procedures for insecticide resistance monitoring in malaria vector mosquitoes*. Consultation to find solutions to the challenges identified in the above

comment will form part of this process. An iterative process requiring active engagement of stakeholders, including manufacturers and researchers, will be needed to inform any revisions to the guidance documents in order to reflect current science, and to further explore whether epidemiological outcomes can be inferred from entomological endpoints.

Comment: The bar of 20 washes is not meaningful. The 20 washes are repeated laboratory washes with intervals fixed by a mortality test. WHO published data on Permanent 2 (that is the most tested net in WHOPES evaluations since often used as reference net) shows that Permanent 2 on mortality criterion resist five washes with five days wash interval, 10 with three days and only one day interval makes the net resist 20, since so little has re-emerged to be washed off. But the official regeneration time is one day since the three washes made at start does not remove enough of the deltamethrin from the surface to bring mortality below 100%. This has nothing to do with regeneration. Field tests made with wash marked nets show that nets are washed three–six times in three years but lose most insecticide anyhow, as has been known since Kilian's study of Permanent 2 in 2005, therefore probably to evaporation and handling.

Response: We have noted the need to review the use of 20 washes as a proxy for wash-fastness/bioavailability under field conditions, and WHO PQT-VC will be reviewing this procedure as part of the revision of the ITN testing guidelines.

Comment: The testing (which should drive the label) should then differentiate whether the chemical does this for all kinds of resistant mosquitoes, some kinds only, or susceptible ones only. WHO shouldn't need a class or a policy for every type of net but rather support countries to make decisions about which net is best for their ento situation based on the label of a product, which should be very clear about what kind of bug it kills. "Insecticide-resistant" is implicitly defined as just "pyrethroid-resistant", ignoring the fact that resistance could arise to any insecticide. What happens when you get resistance to chlorfenapyr or pyriproxyfen? It seems like it's a precedent that would lead to a multiplicity of classes based on (resistance status of a population) x (various insecticides). And then each of those needs an RCT, but those RCTs can only be in a location with the right resistance status…this is likely to be impractical and lead to significant delays in future product introductions.

Resistance management is a claim, not the basis of a product class, and the two should not be mixed up.

Response: WHO considers that these points have been addressed in other parts of this Q&A document and in the revised classification.

Comment: In consideration of how net deployment decisions will be made, the proposed classes and corresponding policies must be accompanied by clear product labelling. Net manufacturers have been informed of WHO PQT-VC labelling improvement efforts that include ensuring product claims are substantiated by supporting data. Coordination between WHO GMP and PQT-VC will be appreciated, so that a product dossier submission can fulfil clear entry into an ITN class.

Response: Following this consultation and a decision regarding this proposal, an implementation plan will need to be developed and new/additional data requirements and/or labelling information that may need to be incorporated into the PQT-VC dossier will be considered as part of that plan.

Comment: Substantial efforts by manufacturers are being made to bring to market ITN products that address insecticide-resistant malaria vectors. The ongoing efforts to develop and test products will benefit from the WHO revised testing guidance/evaluation standards (Proposed provisional step 5) being made available as soon as possible.

Response: PQT-VC is aware of the need for clear and concise guidelines. Work on revised guidelines has been initiated with the objective to align the guidelines with the requirements of the prequalification programme. The document will be designed to separate the information on the process, data requirements, methodology, operational policy, and so on to ensure that these guidelines meet the needs of all stakeholders. In the meantime, PQT-VC encourages manufacturers to continue to use the pre-submission process and protocol review service to assist them in guiding their data generation.

Comment: The currently established criteria for a pyrethroid net to be considered 'long-lasting' is if bioefficacy against susceptible *Anopheles* mosquitoes is retained for at least 20 standard WHO washes (as a proxy for three years of field use). Thus, it is our understanding that pyrethroid (and pyrethroid containing) products that meet the established current criteria should be considered long-lasting insecticidal nets (LLINs).

As these criteria are investigated for AIs other than pyrethroids, WHO may consider aspects such as the documented differences between protocols of WHO standard washing in the lab (Phase I) and washing for semi-field, experimental hut studies (Phase II). Furthermore, in the former WHOPES system, an LLIN that fulfilled the 20 standard WHO washes criteria would still be required to meet WHOPES Phase III criteria in order to achieve a full recommendation. Under WHO PQT-VC assessment, data could be generated through WHOPES Phase III studies, other longitudinal study designs, or as part of post market surveillance activities within a defined time period. Criteria based on real field use of LLINs are essential. A situation where nets, which do not meet their expected lifespan (i.e., three years), are listed together with LLINs in the same class gives a false sense of protection and must be avoided.

Response: Your understanding of the current situation is correct, i.e., if a pyrethroid-only net were to meet the current criteria, it would be considered an LLIN. For pyrethroid-PBO nets, however, the wash fastness of the PBO component would also need to be demonstrated for the net to be called long-lasting. In order to ensure that vector control tools would continue to be available to procurers and thus to populations in need of these products, the PQ programme established a staged approach to implementation. First, the process and dossier formats and evaluation approach were put in place; now the attention has turned to reviewing the current data requirements, methods and policy supporting these requirements, and the consideration of establishing post-market activities. While implementation is moving forward, current requirements remain in place and need to be followed.

Comment: Please include estimated timelines for provisional subsequent steps such as writing new guidelines (page 4).

Response: The proposal is to develop a number of guidelines that will apply to ITNs and split the guidance into process and procedures, data requirements, methods and labelling, and supporting policy. PQT-VC hopes to complete the first guideline by the end of the year.

Comment: Furthermore, whilst it is clear, that a first-in-class product would require epidemiology studies to support policy, it is not clear as to whether a second-in-class product would require a long-term field study assessing entomological endpoints to enable a PQ listing. We hope that this could also be clarified.

Response: This issue is under discussion as part of the initiative looking at data requirements.

Question: P. 3 "It is essential that terms such as 'significantly better' and 'pyrethroid-resistant' are clearly defined". We agree. At what stage will WHO define these phrases or is the onus on the prospective supplier?

Response: As indicated under the previous response, WHO has taken note of the need to develop the required definitions.

Question: P. 2, Para. 2 "*This in turn may require formal comparative testing against the 'first-in-class' product or a suitable alternative to demonstrate such similarity in entomological performance*."

1. *May* require or *will* require? Under what circumstances would formal comparative testing not be required?
2. Please clarify what is meant by "a suitable alternative" together with one or more illustrative examples.
3. In order to facilitate the conduct of non-inferiority trials, can WHO make it a requirement that manufacturers of first-in-class products make their product(s) available for non-inferiority testing to potential second-in-class suppliers?

Response: This section of the NoI refers to ongoing work on non-inferiority testing, which was covered under an NoI in late 2018. Please refer to

https://www.who.int/malaria/publications/atoz/non-inferiority-protocol/en/, including the detailed Q&A section at the bottom of the webpage. It should be noted that this work is ongoing and will not be completed before the end of 2020 at the earliest. Whether or not non-inferiority testing will become a routine component of the evaluation process will be determined once data to advance the discussion are available. For now, this means that the answer to question 1 is "may". The answer to question 2 is covered in section 4.1 "Active comparator of the study protocol" posted on the above website. The answer to question 3 is "no", WHO cannot make this a requirement, but would explore ways in which to facilitate this process if it were to become a routine procedure.

Question: The notice of intent mentions that "*If these data were to be provided, WHO would consider continuation of listing additional chlorfenapyr or pyriproxyfen treated nets in the absence of a specific policy recommendation. Once epidemiological data or the*

two products currently undergoing evaluation are available a full review of all products falling into the potential two new classes would be conducted." Does it mean that a product that claims equivalence to Interceptor G2 can be listed without conducting the epidemiological experiment now? and can be considered covered by policy recommendation now?

Response: The revision of the entomological evaluation procedures is a prerequisite for any changes to the classification system to be implemented. This means that an equivalent product to Interceptor G2 will not be listed until the prerequisites outlined in the NoI and in this Q&A document have been met. Neither chlorfenapyr- nor pyriproxyfen-treated nets will be covered by a policy recommendation until the data demonstrating their public health value have been made available. But yes, the concept proposed here is that if entomological evaluation procedures are evolved and existing data gaps are closed, a modified classification system will be implemented that will allow other new net products to be assessed by PQT-VC; if the WHO criteria for safety, efficacy and quality are met, these products will then be listed even while data generation to assess their public health value is ongoing. There would, however, be no policy in place to recommend these new nets until a first-in-class net has successfully demonstrated that the intervention has public health value.

Question: P.4 "… but it may be that 20 washes is an unrealistically high bar." We agree. It is difficult to maintain the same wash resistance or physical durability when PBO is incorporated into the fibre/yarn. When combined with pyrethroids, PBO tends to bleed faster than pyrethroids by virtue of its oily nature. How does WHO propose to address this?

Response: WHO agrees that the assessment of wash resistance, as well as the bioavailability of insecticides in the absence of washing and under field conditions, needs to be reviewed, including the minimum standards associated with it. This will be addressed as part of developing revised WHO testing guidelines.

Question: P. 4 "Assessing chemical and physical durability is, however, considered as very important to ensure that in the process of re-formulating a net to contain more than one active ingredient the performance of the active ingredients, and of the net itself, is not diminished." We already know that the incorporation of PBO may negatively impact the physical durability of HDPE nets. Thus, a balance needs to be struck between improved performance against multiple resistant strains on the one hand and the potential reduced wash resistance or physical durability on the other. How does WHO propose to address this balance?

Response: WHO agrees with the comment that assessing chemical and physical durability is an important aspect of the quality and efficacy assessment. While aspects of this are already incorporated into the PQT-VC assessment, this needs to be augmented. Two initiatives are currently underway, including the data call-in associated with the product review and activities to review the quality specifications of ITNs; these will help to inform any additional new data requirements to address this issue.

Question: It merits discussion as to whether we continue to determine chemical durability based on wash testing at all or should we just use the epi and/or community-based (formerly Phase 3) trials to determine if the impact still remains?

Response: WHO agrees that the issue of determining chemical durability based on washing needs to be considered within the context of the PQT-VC review and will be included as part of the initiative to review the current data requirements.

Question: How relevant is the washing method for artificially ageing nets? This may be relevant for pyrethroids but does it overestimate effects for different molecules (or underestimate)? How well does this link to real-life behaviour?

Response: Issues such as these are important and will be considered, along with other related issues, as part of the initiative that is currently underway to review data requirements and appropriate methods.

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7. Comments and questions on product claims and labels

Comment: There needs to be a clearer link to product label claims being assessed by PQT so that developers can be clear about how those claims will help them navigate product classes in the future. This is particularly pertinent when making claims against resistant strains, which need to be defined and the performance standards developed.

Response: We agree that clearer links between WHO policy recommendations for intervention types and classes and corresponding products will be beneficial to guide decision-making by WHO Member States, as will be summary overviews of the available products and their underpinning evidence base. WHO has identified this area as a need and will be addressing it as part of the ongoing evolution of the vector control evaluation process.

Comment: P. 1, paragraph 1 of NoI: "*For lack of a better alternative, both products are currently considered as covered by the WHO policy recommendation for pyrethroid-only nets, given that they contain a pyrethroid + chlorfenapyr or a pyrethroid + pyriproxyfen and are as such assumed to provide an epidemiological impact that is at least as good as that of a pyrethroid-only net.*"

This is NOT consistent with the label claims being made for the Royal Guard net. The DOL on the PQ website (https://www.who.int/pq-vector-control/prequalified-lists/RoyalGuardLabelling.PDF) states:

"7. Product Claims a. Royal Guard® is a first in class next generation dual active ingredient LLIN combining a pyrethroid (Alphacypermethrin) and an insect growth regulator (Pyriproxyfen) b. The combination of pyrethroid and insect growth regulator active ingredients in DCT's Royal Guard® LN is intended to result in the knockdown, mortality and/or reduced fecundity of mosquitoes that survive exposure to the pyrethroid. c. Royal Guard® LN has been shown to reduce mosquito fecundity. The intended benefit of reducing fecundity in female mosquitoes is an overall reduction in the vector population."

This needs to be urgently addressed.

Also, any new nets combining pyrethroids with novel AIs should NOT be accepted until the impact of the new AI is assessed. This will avoid pyrethroid + novel AI nets being submitted and being given PQ listing based on their containing just a pyrethroid with soft claims being made about the value of the additional AI, with no intention of evaluating the additional AI.

Response: A number of PQT-VC decisions were made before GMP developed the proposal for this new classification. As this proposal moves forward to the implementation stage, naturally, decisions made with respect to products already prequalified will be considered in light of any new classification. It will be necessary to give careful consideration to how this will be managed in a transparent and equitable manner.

Comment: In addition, we support the view that newer products that do not contain pyrethroid insecticides may not meet the current established 20 wash criteria but still add public health value. With this in mind, we strongly suggest that products are evaluated against their individual label claims. The claims, if met, should be published as part of the PQ listing, enabling procurers to make informed decisions.

Response: Yes, WHO supports this approach. However, as yet to be defined minimum standards will have to be met. This may not be 20 washes, or a different procedure from net washing may be required; however, information on bioavailability will be required to inform procurers as to how long a net will remain insecticidal.

Comment: In consideration of how net deployment decisions will be made, the proposed classes and corresponding policies must be accompanied by clear product labelling. Net manufacturers have been informed of WHO PQT-VC labelling improvement efforts that include ensuring product claims are substantiated by supporting data. Coordination between WHO GMP and PQT-VC will be appreciated, so that a product dossier submission can fulfil clear entry into an ITN class.

Response: Currently, the declaration of product labelling that PQT-VC provides to the manufacturer includes directions for the safe use of the product, precautions and warnings, product guarantee, and claims for the product that are supported by appropriate data. Any further labelling information that may be required as a result of the implementation of the proposed new ITN classes will be determined through discussion with the relevant areas in WHO.

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8. Comments and questions on prerequisites for implementation of revised ITN classification and associated data requirements

Comment: P. 4 of NoI, "Pre-requisites" section: "*Assessing chemical and physical durability is however considered as very important."*

Chemical durability can be high over life of net but this can mean it is not being evolved and therefore available to the mosquito. Physical durability is a minefield and, as has been shown at VCWG by Albert Kilian, varies enormously between countries for the same product. So comparisons between products must be treated with extreme caution.

Response: WHO is aware of the challenges associated with assessing physical and chemical durability and the heterogeneity in performance both within and between products. Attempts to improve on assessments will be made as part of revising WHO's testing guidance.

Comment: P. 4 of NoI, "Pre-requisites" section: "*8) Products containing pyriproxyfen or chlorfenapyr will be assessed by PQT-VC with a view of listing them under the current policy recommendation for pyrethroid-only nets until specific policy recommendations for these potential new classes have been developed."*

This is OK, however their label claims must be very clear that these products are ONLY equivalent to pyrethroid only LLINs.

Response: The information that PQT-VC provides to manufacturers regarding label content is based on the findings of the science assessment of the product data and the specific product claims supported by the data. The label does not include any information concerning the policy in place to support public health use.

Question: Section "*Pre-requisites…"* Bullet i, p.3: Is the stress on a range of "multiple" populations implying that products may need to demonstrate performance in more than the traditional two entomological field sites?

Response: This question will be addressed as part of the initiative currently underway in PQT-VC to review the current data requirements for ITNs.

Question: Bullet ii. P.3-4: Why does GMP and its advisory groups not consider it necessary to be prescriptive about the generation of evidence of biological activity of the two actives? Wouldn't guidance on types of strains to be used, for example, help consistency in reviewing evidence of submitted products? Would this not be part of the testing guidelines? Or is the implication that requirements for these "(old) phase 1" type of data would be more flexible with the specific efficacy criteria and testing approaches focusing on semi-field/experimental hut (old phase 2) type of data?

Response: PQT-VC is responsible and accountable for the development of guidance for entomological evaluation, while the technical departments – GMP and NTD – are consulted in the process. Guidance on this type of data collection will certainly be provided as part of the revised test procedures that are currently under development. However, any such guidance needs to be informed by our present understanding of how best to evaluate vector control products and the availability of well characterized

resistant strains. WHO will be as clear as presently possible when it comes to the type of evidence required, but it is also planning to evolve the guidance further based on the new evidence on test procedures and endpoints that is being generated by manufacturers and researchers.

Question: Evaluation of personal protection is counter to the stated mission of VCAG to assess interventions with community benefit. Is it WHO's position that replicating personal protection sufficiently achieves community protection? Such a position would obviously affect other interventions, like topical repellents.

Response: Please refer to the actual role of VCAG, as outlined on the website: https://www.who.int/vector-control/vcag/en/. VCAG's functions are stated as follows:

1. To provide guidance to product developers, innovators and researchers, through WHO, on the generation of epidemiological data and study designs to enable assessment of the public health value of new vector control interventions;
2. To assess the public health value of new vector interventions submitted to WHO;
3. To provide advice to WHO, for submission to the Malaria Policy Advisory Committee (MPAC) and the Strategic and Technical Advisory Group for neglected tropical diseases (STAG), on the public health value of new interventions.

Public health value is defined as follows: *A product has public health value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans.* Such protection may be provided via community or personal protection, or both.

To answer the question posed above, it is not WHO's position that replicating personal protection sufficiently achieves community protection. Tools designed to provide only personal protection will need to be assessed for this effect using other study designs. Discussions on how best to generate the required evidence base are ongoing.

Question: P. 3 of NoI, "Pre-requisites" section: *i. "Evidence that a new ITN product provides greater personal protection to net users than standard pyrethroid-only nets against a range of fully characterized insecticide resistant populations. It is essential that terms such as 'significantly better' and 'pyrethroid resistant' are clearly defined and that the new ITNs – both first- and second-in-class – show superior performance against multiple resistant populations."*

Insecticides, except for pyrethroids, which give personal protection to ITNs seem to be rather limited. Does "provide greater personal protection" include a structural or mechanical barrier?

There should be evidence that a new ITN product provides greater kill of mosquitoes whether through chemical or sterilizing or other mechanism.

Also, what does characterized insecticide-resistant population mean?

A certain level of pyrethroid resistance? Levels vary widely in the field so how can comparison be totally fair?

Does "multiple resistant population" mean resistance to at least two chemical classes, such as pyrethroid and carbamate? Or three, or four, etc.? This needs clarifying.

Response: The revision of the ITN testing guidelines will address these issues and include standards to be met for ITNs. It should be noted that the current PQT-VC process requires manufacturers to compile a dossier that includes data to support the use of the product and any claims made for that product. The claim is only permitted if it is considered an appropriate and reasonable claim to make for a vector control product and if the data support the claim.

Question: P. 4 of NoI, "Pre-requisites" section: *iii. Evidence that the product is "at least as good as a pyrethroid only net for the full duration of its expected lifespan."*

Does "full duration of its expected lifespan" mean three years?

Response: Yes, based on current guidance this would mean three years, given that in most settings this is the intended replacement interval through mass campaigns. However, it is recognized that the bioavailability of insecticides other than pyrethroids and of synergists poses challenges, and a three-year duration of improved efficacy over pyrethroid-only nets has yet to be achieved. At a minimum, however, new types of nets should demonstrate that they do not start to perform worse than pyrethroid-only nets after their initial period of improved performance comes to an end.

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9. Comments and questions on subsequent steps

Comment: Our company supports the proposed action to close existing data gaps for currently prequalified products (Provisional subsequent step 6 in the notice of intent). Assuring completeness of product dossiers including a robust evidence base to support efficacy claims is required irrespective of the currently underway non-inferiority trials. Since the transition from WHOPES to WHO PQT-VC, some prequalified pyrethroid-PBO nets that do not have adequate datasets to support claims against pyrethroid resistant mosquitoes are currently listed with the supporting WHO policy recommendation for pyrethroid-PBO nets. In our interactions with procurement agencies, we find this gives the impression that the WHO policy is applicable to any net containing PBO. The proposed classification of ITN products by entomological effect necessitates that, at minimum, a robust evidence base is available to justify a product claim and inclusion to the relevant class.

Response: PQT-VC has initiated the product review for non-pyrethroid ITNs. The correspondence outlines the data gaps that have been identified for these products and the timeline for submission of the data.

Comment: It is stated that one of the provisional subsequent steps, following the modification of the classification of ITN products, will be for WHO to develop and publish WHO testing guidance/evaluation standards for the entomological evaluation of ITNs other than pyrethroid-only LLINs. We hope that WHO will invite IVCC and companies manufacturing mosquito vector control products to participate in the revision of the WHO LLIN guidelines. Further, having participated in the revision of these guidelines in 2017, but with the revised guidelines still not being published three years later, we hope that the revised guidelines would be made available quickly to help guide manufacturers in the testing of ITN products for WHO PQT evaluation and test facilities in the modification of their test method SOPs.

Response: The review of the existing WHO guideline on data requirements and PQ testing methodologies for vector control products is the responsibility of PQT-VC. This group has publicly committed to adhering to a number of principles, which include openness, transparency and engagement of stakeholders. These principles will also be adhered to for this initiative. The guideline that was revised in 2017 will be further revised to reflect guidance arising from the current review of data requirements and methods. In addition, the guideline will be further revised to clearly separate the information that pertains to process, operational policy, data requirements and methods.

Question: Section "*Provisional next steps"*, No. 5: When will this guidance be available? We welcome the proposed approach and are conscious that absence of these guidance pieces will now be the bottleneck to products designed to control pyrethroid-insecticide being considered for prequalification. The guidance will be needed before manufacturers can start developing the appropriate dataset.

Response: This question will be addressed through the development of a systematic implementation plan, which will be initiated when and if this proposed approach is adopted.

Question: Section "*Provisional next steps"* No. 6: How will this be undertaken and who will be responsible? Is there a timeline envisaged?

Response: As above, this will be addressed through the implementation plan that will be put into place once the proposal for the classification of ITNs is finalized.

Question: Section "*Provisional next steps"* No. 8: Why are CFP and Pyriproxyfen specifically mentioned here? Would it not be the case that other products could also follow this pathway in future?

Response: The proposed revision of the ITN classification was triggered by the recent submission of products similar to the chlorfenapyr- and pyriproxyfen-containing products that were recently prequalified. Changes in the classification would, however, also impact other new ITN products when these are submitted to WHO for evaluation.

Questions: P. 3 of NoI, "Pre-requisites" section. "*It is envisaged that prior to proceeding with WHO PQT-VC assessment and potential listing of any other chlorfenapyr or pyriproxyfen treated ITNs before epidemiological trials for the two potential 'first-in-class' products have been completed, companies will need to provide three types of evidence:"*

Please clarify this statement: Are all three types necessary for each assessment, or does this mean that three types of evidence are permitted?

Response: GMP presently envisages that all three are required, not a selection of these data, to support implementation of the revised process, as proposed in the NoI. For PQT-VC, the process for all products seeking a prequalification listing consists of the submission of data to support safe use, quality and assessment of entomological effectiveness; data to support any specific claims also need to be submitted.

Changes to the classification of ITN products: for decision

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Malaria Policy Advisory Committee Meeting , Geneva

13 May 2020

Global **Malaria** Programme

World Health Organization

Background

- Identified inconsistencies in the classification and public health evaluation of ITNs when compared to other vector control products
- Arrival of new vector control products, including ITNs, with complex chemical formulations requires a revisit of ITN classification and evaluation processes / standards
- Consulted broadly with MPAC, VCAG and externally with partners through a notice of intent (NoI) published February 2020
- Q&A published in response to feedback to the NoI
- Today's session presents the revised ITN classification developed based on the proposed policy, public comments and the next steps
- Overall aim is to balance the public health need for deployment of new vector control tools with WHO's responsibility of providing evidence-based guidance to WHO Member States.

Proposed New ITN Classes: for decision

1. **ITNs designed to kill host-seeking insecticide-susceptible mosquito populations that have demonstrated public health value compared to untreated nets and whose entomological effects consist of killing and reducing the blood-feeding of insecticide-susceptible mosquito vectors**: Existing prequalified pyrethroid-only nets. Policy recommendation in place.

2. **ITNs designed to kill host-seeking insecticide-resistant mosquitoes and for which a first-in-class product has demonstrated public health value compared to the epidemiological impact of pyrethroid-only nets:** This class is provisionally thought to include both insecticide treatments with active ingredients other than pyrethroid-based formulations and nets with synergists. It includes pyrethroid-PBO nets that are currently covered under an interim WHO policy recommendation. The class would be expanded to include pyrethroid + chlorfenapyr nets once their public health value has been demonstrated by means of at least two geographically separate epidemiological trials. The class would then be expanded to also include other products with the same entomological effect but with different chemical modes of action to pyrethroid-only nets without the need for further epidemiological trials.

3. **ITNs designed to sterilize and/or reduce the fecundity of 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:** This class is provisionally thought to include pyrethroid + pyriproxyfen nets and will be created once the public health value of a first-in-class ITN product containing an insect growth regulator has been demonstrated by means of at least two geographically separate epidemiological trials.

Next Steps

Implementation of the revised classification requires:

- Revision of ITN testing guidelines to allow comprehensive evaluation of nets other than pyrethroid-PBO products.
- Identification and closure of existing data gaps on new types of nets currently prequalified (incl. pyrethroid+PBO nets). This has been initiated by PQT-VC
- Update WHO documentation on the evaluation process to reflect changes made to ITN classification and evaluation
- Establishment of a process within WHO to define similarities for existing and future ITN products
- Review of the ITN classification within a period of 3 years to establish whether the revised classification continues to capture the available products and those under development, and whether there may be opportunities to further simplify classification