Documentation related to Session 4 of the meeting
Click on the links below to see the pre reads and presentations

Malaria Policy Advisory Committee (MPAC) Meeting, 3–4 December 2020

Documentation for Session 4

Friday, 4 December 2020			
	Session 4	**Open**	
12:00 – 13:30	Update on the consolidated Malaria Guidelines • Vector Control – Dr Jenny Stevenson • Elimination – Dr Kim Lindblade • Chemoprevention – Dr David Schellenberg • Treatment – Dr Peter Olumese	Dr Pedro Alonso	**For guidance**
13:30 – 14:00	Update on the Malaria Vaccine Implementation Programme Background | Presentation	Dr Mary Hamel	**For decision**

World Health Organization

Malaria Guidelines Update

Malaria Policy Advisory Group

Geneva, Switzerland

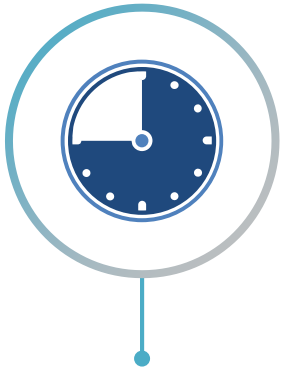
Dr Pedro Alonso, Dr Jenny Stevenson, Dr Kim Lindblade, Dr David Schellenberg and Dr Peter Olumese

4 December 2020

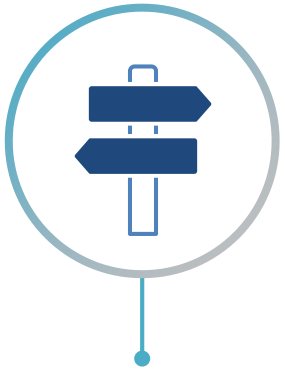
Global **Malaria** Programme

World Health Organization

3 pain points constitute case for change



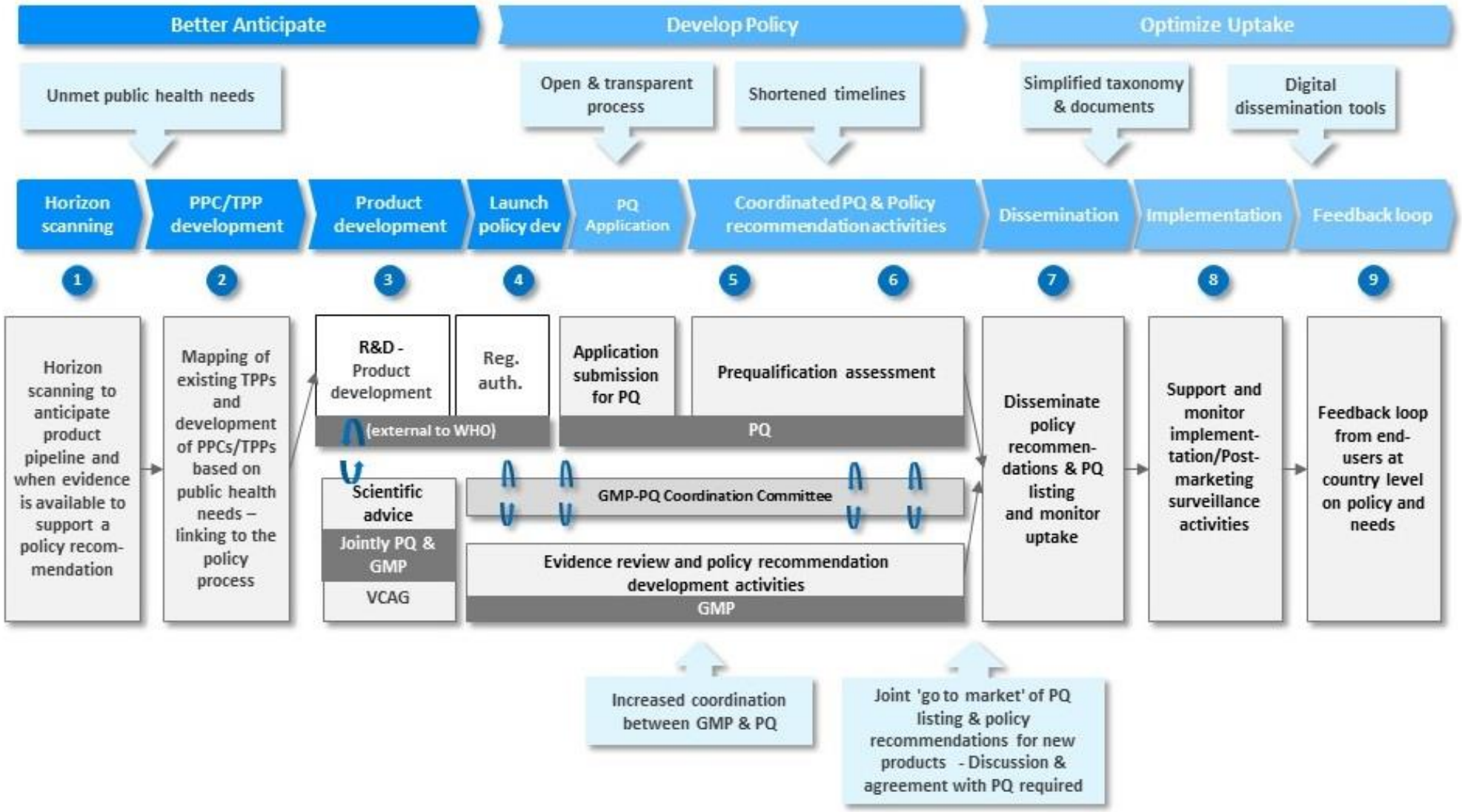
Perceived lengthy process



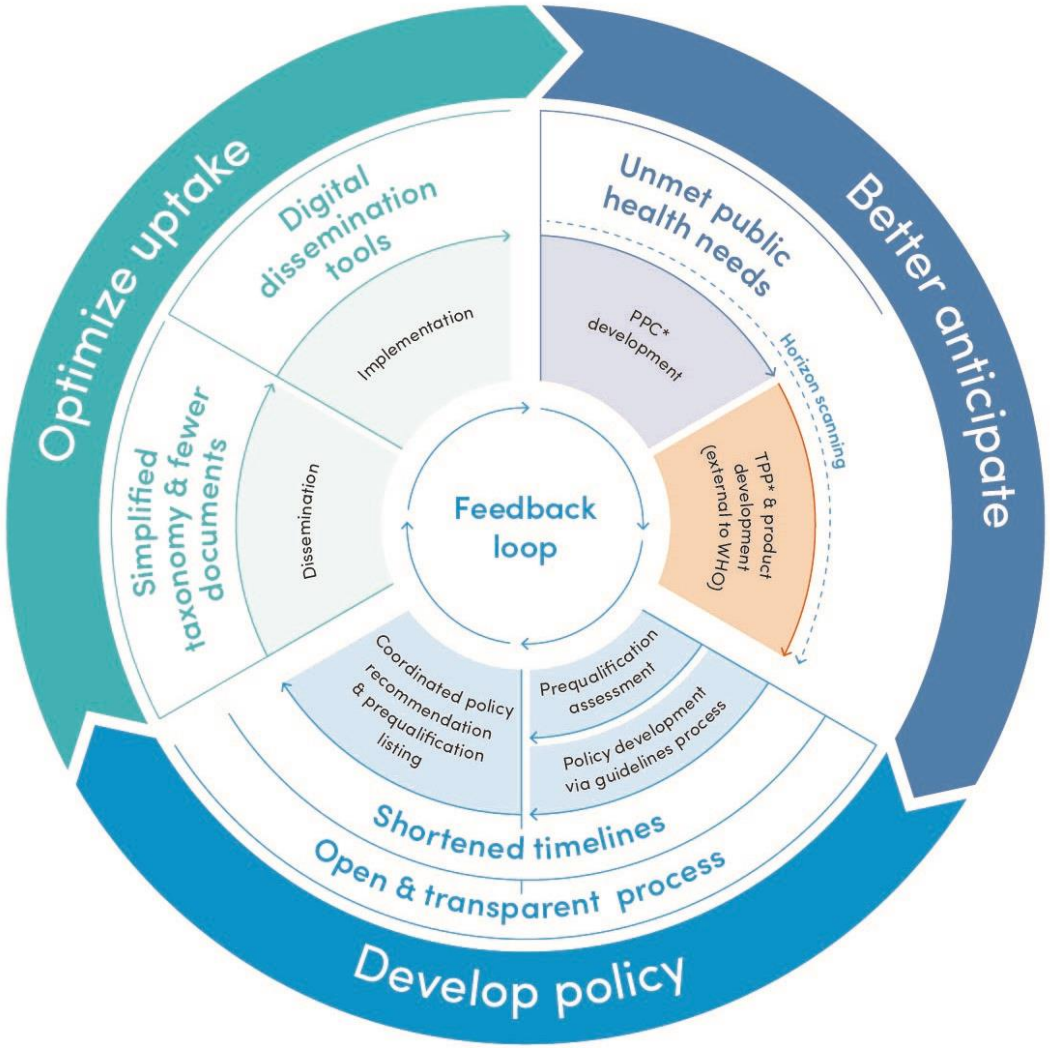
Inconsistent recommendations

Sub-optimal use of GMP output at country level

High level diagram of the GMP Policy Pathway – new products



High-level diagram of recommendation pathway



*PPC: Preferred product characteristic
*TPP: Target product profile

WHO Guidelines on malaria: improving guidance

Develop Policy

Inconsistent recommendations

- Aiming to provide timely and up-to-date guidance to countries to maximize the impact of available resources
- Using the standard WHO guideline development process overseen by the Guidelines Review Committee
- Ensuring consistency of approach to formulating recommendations across tools, strategies and technical areas
- Assembling all WHO recommendations for malaria control and elimination in one place using MAGICapp online platform – January 2021

WHO Guidelines on malaria: enhancing their use

Optimize Uptake

Sub-optimal use of GMP output at country level

- Support problem-solving approaches using local data
  - Identify recommendations that are relevant at country level
  - Define strata and mixes of interventions for each stratum
  - Optimize intervention packages by considering local contexts; prioritization to maximize impact of available resources
- Move away from overly prescriptive recommendations & reposition at a consistent level
- Clearly distinguish evidence-informed recommendations from contextual considerations
- Contextual considerations at national and subnational levels inform *how* recommendations should be applied – strategies for access

Overview of the guideline development process

What principles underlie WHO guidelines?

WHO's legitimacy and technical authority lie in its rigorous adherence to the systematic use of evidence as the basis for all policies

- Explicit and transparent process
- The process is multidisciplinary and includes all relevant expertise and perspectives
- The process and methods minimize the risk of bias
- Recommendations are based on a systematic and comprehensive assessment of the balance of a policy's or intervention's benefits and harms and explicit consideration of additional factors
- Evidence used is publicly available

Definitions and taxonomy

- **Guideline**

Any document developed by WHO that contains ***recommendations*** for clinical practice or public health policy.

- **Recommendation**

Tells the intended end-user what he or she can or should do in specific situations to achieve the best health outcomes possible, individually or collectively.
Recommendations are based on systematically reviewed evidence

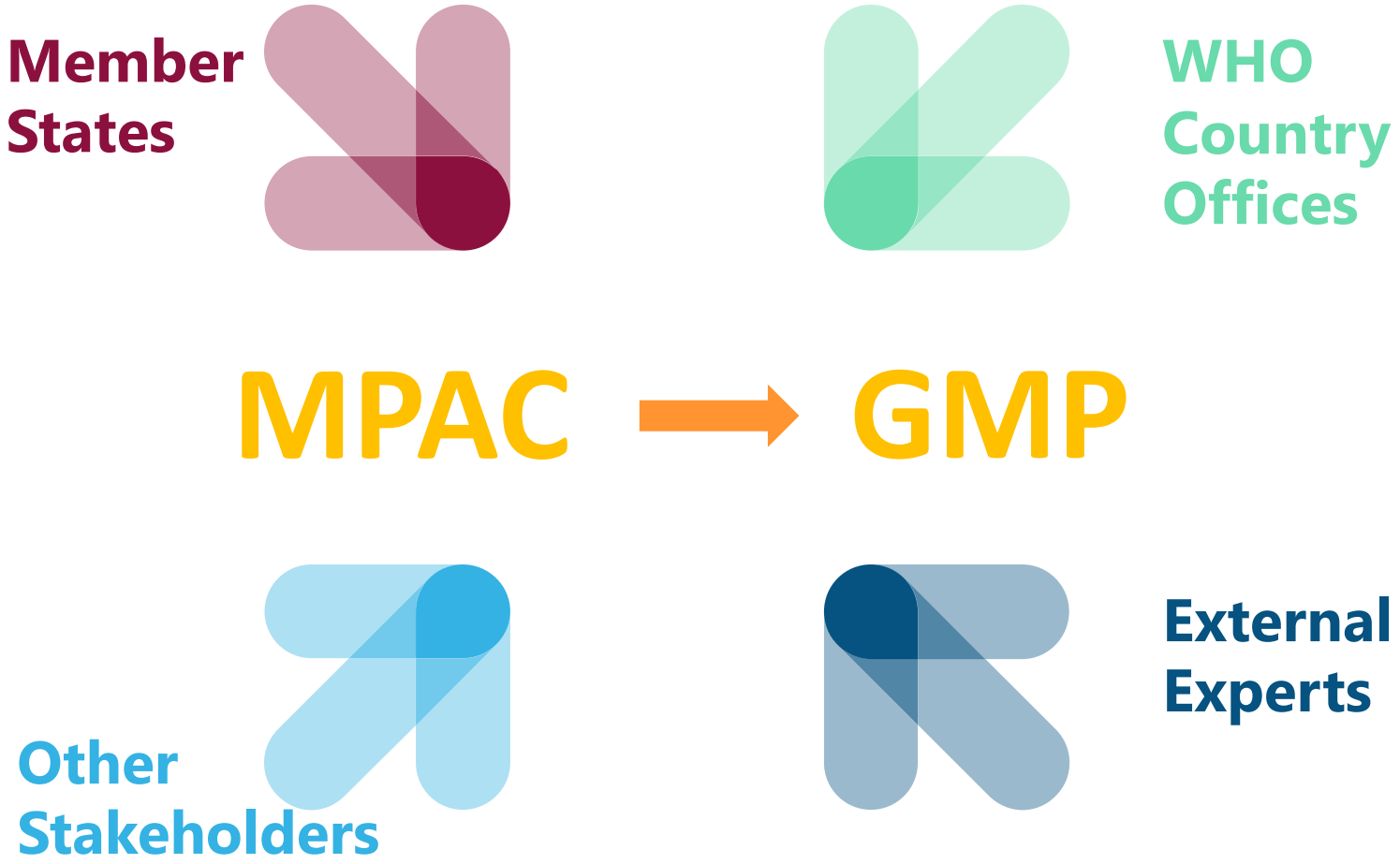
- **Policy**

Decisions, plans and actions undertaken to achieve specific health goals within a society – established and implemented by countries based on WHO recommendations contained within guidelines.

- **Guidance**

A broader term encompassing advice ranging from specific guidelines to operational considerations. Guidance is not necessarily based on a systematic review of evidence.

How are areas selected for guideline development?



Groups Involved in Developing WHO Guidelines

2. Steering group

Internal

WHO technical unit and other units or departments, regional offices. Oversees the process.

4. External review group

External

Peer review of scope and key questions and final draft guideline. Selected by the steering group.

3. Guidelines development group (GDG)

External

Formulates recommendations. Gender-balanced and broad geographic representation. Includes end-users and those affected by recommendations. Selected by the steering group.

Editorial Working Group (EWG)

External

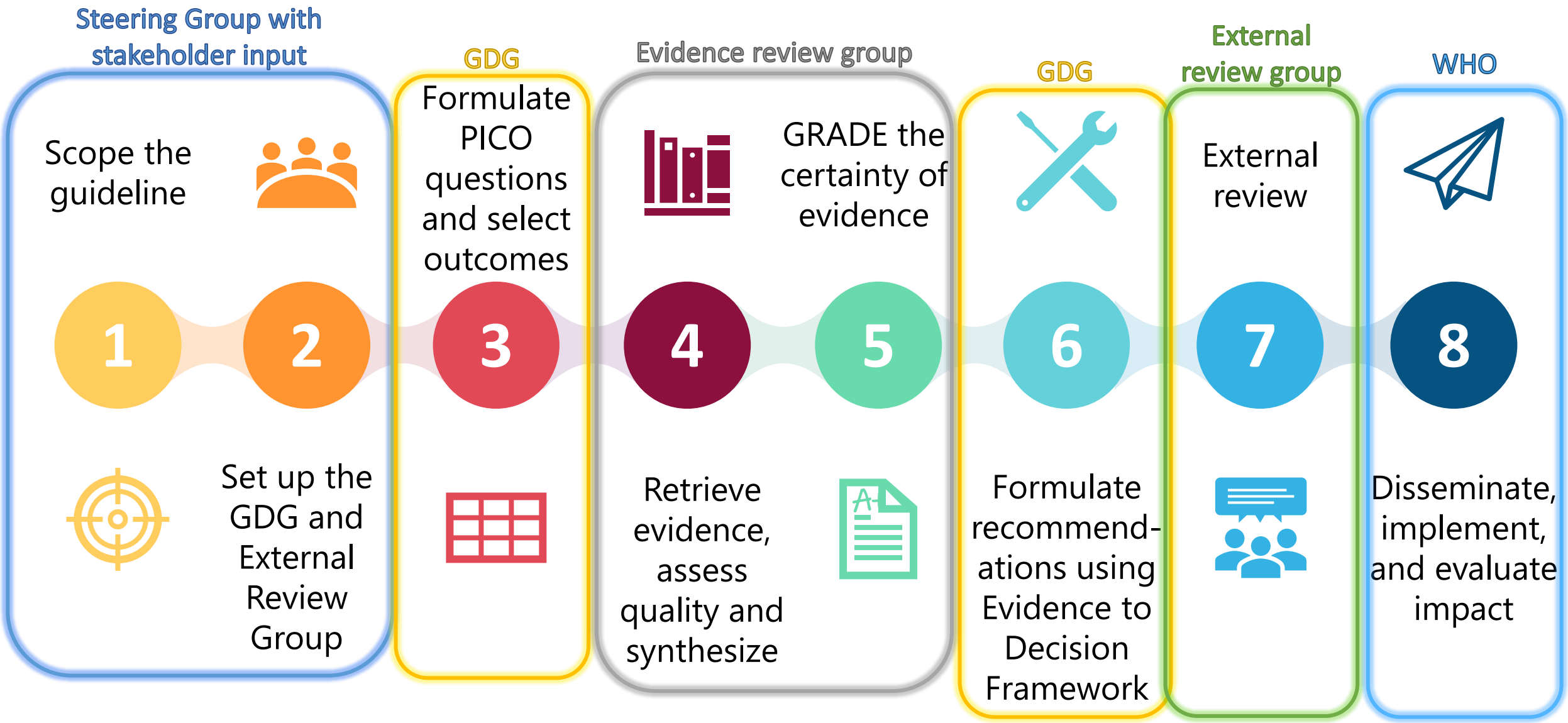
Members participate in multiple GDGs to help ensure consistency across technical areas

5. Evidence review group

External

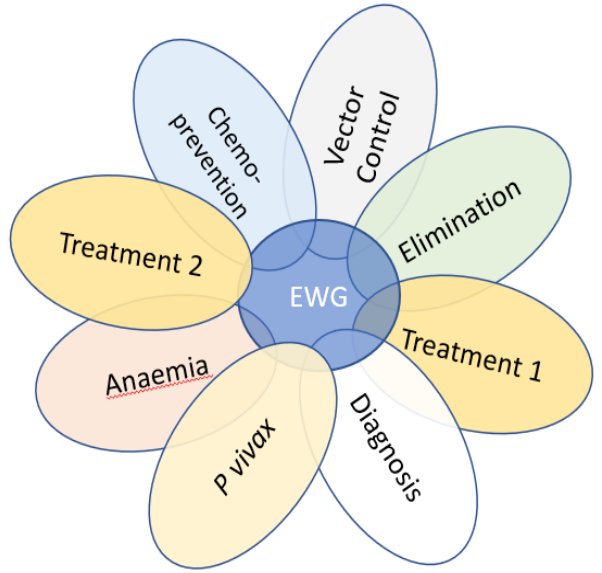
Provides a comprehensive, objective synthesis of the evidence to inform each recommendation. Selected by the steering group.

Overview of the Process of Guideline Development



GMP Guideline Development Groups

- Vector control - convened
- Elimination - convened
- Chemoprevention - convened
- Treatment – proposal submitted
- Malaria vaccine – Programme Advisory Group convened*
- Diagnosis – in discussion
- Anaemia (cross-department) in discussion
- *P. vivax* – planned



*jointly convened with IVB

Vector Control

- Steering Committee convened; GRC proposal submitted end April and approved in May
- Three evidence reviews complete: larval habitat modification/ manipulation, personal and community level protection of ITNs, housing modifications.
- Four evidence reviews ongoing: pyrethroid-PBO nets, ITN plus IRS, vector control in complex emergencies, endectocides
- First GDG meeting to discuss PICO questions held early November 2020
- Second GDG meeting to discuss completed evidence reviews and draft recommendations held mid November 2020
- Further GDG meetings planned for Q2 2021 once other reviews complete
- Publishing of first set of revisions planned for Q1 2021

Vector Control topics: discussed with GDG November 2020

- **Housing**: What are the effects of different structural house modifications on malaria disease and transmission?
  - PICO: In areas with ongoing malaria transmission or malariogenic potential, should structural house modifications versus no structural house modifications be used to prevent malaria in adults and children?
- **Larval Source Management**: What is the effectiveness of larval habitat modification or larval habitat manipulation as malaria vector control interventions?
  - PICO: In areas with ongoing malaria transmission or malariogenic potential, should larval habitat modification and/or larval habitat manipulation versus no larval habitat modification and/or larval habitat manipulation be used to prevent malaria in adults and children?
- **"How do ITNs work?:** What are the biological mechanisms by which ITNs give personal- and community-level protection against malaria?"

Other discussions:

- Resource use: Review on the cost-effectiveness of malaria interventions to provide insight on resources required for delivery of malaria vector control.
- Personal protection: Discussion on appropriate study designs and evidence-base required to assess the public health value of interventions with a primary use-pattern of personal protection which may also provide community level impact

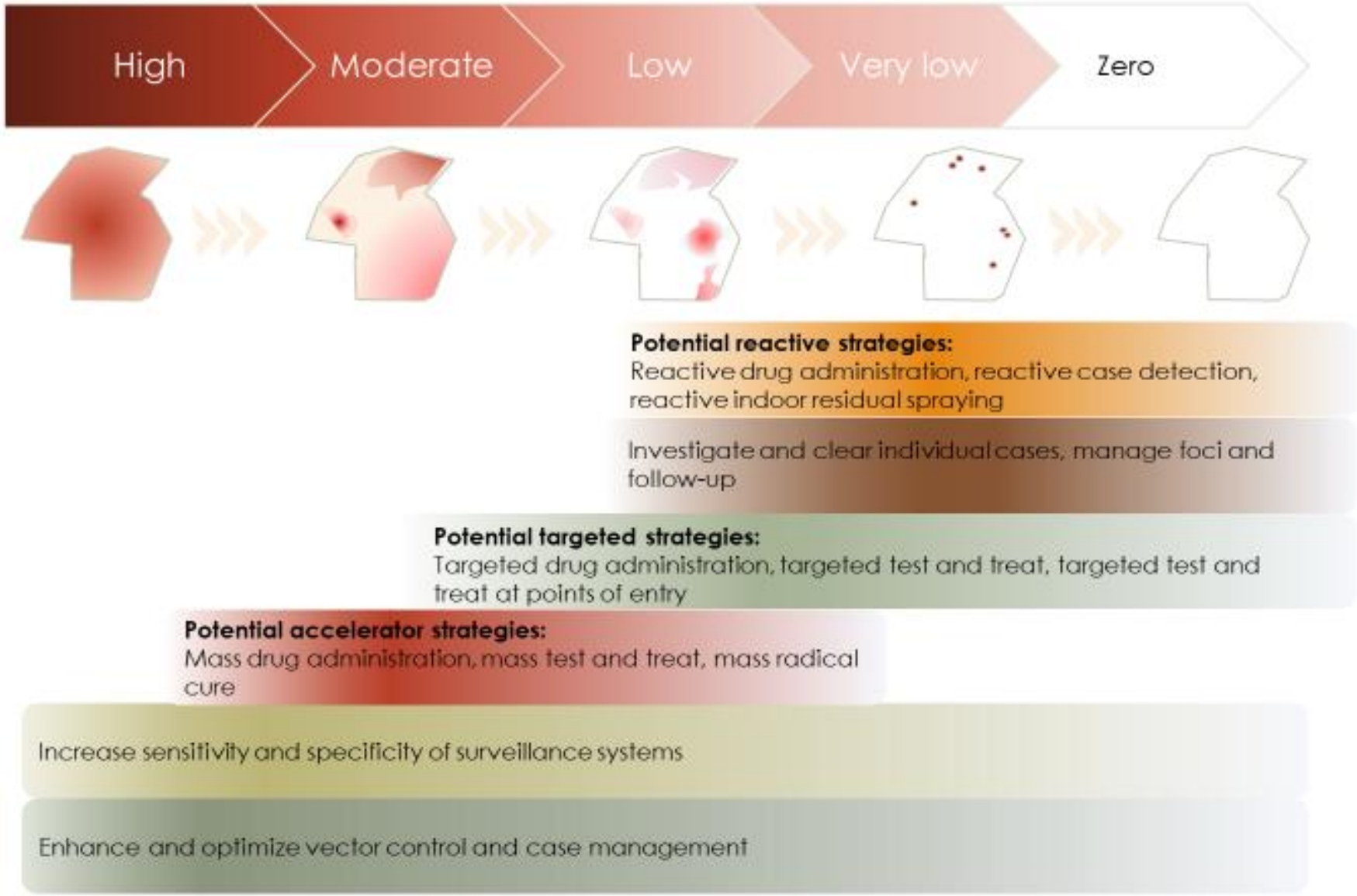
Vector Control PICO questions: ongoing reviews, meeting planned for 2021

- **Pyrethroid-PBO nets**: Does the addition of the synergist PBO to mosquito nets treated with a pyrethroid insecticide increase their epidemiological and/or entomological effectiveness?
  - PICO: In areas with ongoing malaria transmission or malariogenic potential, should LLINs treated with both PBO and pyrethroid insecticide versus LLINs treated with pyrethroid insecticide only be used to prevent malaria in adults and children?
- **ITN plus IRS**: What is the effect on malaria of additionally implementing IRS, using non-pyrethroid or pyrethroid insecticides, in communities currently using ITNs? What are the relevant deployment considerations?
  - PICO: In areas with ongoing malaria transmission or malariogenic potential where ITNs are already in use, should IRS versus no IRS be used to prevent malaria in adults and children?
- **Complex emergencies**: Which malaria vector control interventions have proven protective efficacy to reduce malaria infection and disease in humans in humanitarian emergency situations?
  - PICO: In areas affected by complex emergencies and with ongoing malaria transmission or malariogenic potential, should additional malaria-specific vector control interventions versus no additional malaria-specific vector control intervention be used to prevent malaria in refugee and IDP adults and children?

Elimination

- Steering committee convened
- GRC proposal submitted and approved
- Final list of GDG members approved after public comment period and conflict of interest assessment
- Comments by selected members of the external review group
- PICO and background questions have been finalized
- Protocols for evidence reviews are drafted by CDC and ISGlobal and soon to be reviewed by methodologist
  - To be submitted to PROSPERO
- Future GDG meetings will be convened when one or more of the systematic reviews is completed

Possible Deployment of Elimination Strategies along the Continuum



Elimination PICO questions

- **Reactive drug administration**: Should people residing with or near a confirmed malaria case be given a full therapeutic course of an antimalarial at approximately the same time to reduce human malaria transmission?
- **Reactive test and treat (reactive case detection)**: Should people residing with or near a confirmed malaria case be tested for malaria at approximately the same time and treated if positive to reduce human malaria transmission?
- **Reactive indoor residual spraying**: Should the houses of people residing with or near a confirmed case of malaria be sprayed with a residual insecticide to reduce human malaria transmission?
- **Targeted drug administration**: Should people at increased risk of malaria infection be given a full therapeutic course of an antimalarial to reduce human malaria transmission?
- **Targeted test and treat**: Should people at increased risk of malaria infection be tested for malaria and treated if positive to reduce human malaria transmission?

Elimination PICO questions (2)

- **Targeted test and treat at points of entry (border screening)**: Should people entering a country or subnational area be tested for malaria and treated if positive at the point of entry to reduce importation of human malaria parasites?
- **Mass drug administration**: Should people residing in delimited geographic areas be given a full therapeutic course of an antimalarial at approximately the same time to reduce human malaria transmission?
- **Mass test and treat**: Should people residing in delimited geographic areas be tested for malaria at approximately the same time and treated if positive to reduce human malaria transmission?
- **Mass relapse prevention**: Should people residing in delimited geographic areas with ongoing or potential *P. vivax* transmission be given an antimalarial that clears liver-stage parasites at approximately the same time to reduce transmission of *P. vivax*?

Chemoprevention

- Steering group convened. Planning proposal submitted to GRC August, approved September 2020
- Methodologist & systematic review teams identified
- GDG convened 6-10 November to review PICO questions
  - Prioritisation of outcomes & potential effect modifiers completed 23 November
  - Finalization of PICO questions ongoing
- Two-phase plan:
  - Q1.2021: Review existing recommendations on basis of updated reviews
  - Q2/Q3.2021: Consider potential modifications to existing & development of new recommendations

Chemoprevention: background papers

- Identifying groups at increased risk of malaria disease and death
  - Infants, children under 5 years, pregnant women
  - People living in endemic places with disrupted health services or in emergency situations, non-immune travelers to endemic settings, patients with underlying conditions (e.g. sickle cell), forest goers, etc.
- Ethical dimensions of chemoprevention: balancing risks and benefits
- Drug resistance: the effect of chemoprevention on drug resistance, and *vice versa*
- Drugs for chemoprevention: Preferred Product Characteristics

Chemoprevention GDG: PICO questions

1. Should women be given anti-malarial medicines as chemoprevention during pregnancy?
   - Phase 1: Should women of all gravidities be given sulphadoxine-pyrimethamine (SP) as malaria chemoprevention during pregnancy?
   - Phase 2: Should women be given antimalarial drugs other than SP as malaria chemoprevention during pregnancy?
2. Should children living in settings with perennial malaria transmission be given anti-malarial medicines as chemoprevention?
   - Phase 1: Should infants living in settings with perennial malaria transmission be given anti-malarial medicines as chemoprevention?
   - Phase 2: Should children living in settings with perennial malaria transmission be given anti-malarial medicines as chemoprevention?
3. Phase 1: Should children living in settings with seasonal malaria transmission be given anti-malarial medicines as chemoprevention?

Chemoprevention GDG: PICO questions

4. Phase 2: Is mass drug administration (MDA) a safe and effective approach to reduce the burden of malaria in moderate and high transmission settings?
   - During emergencies or periods of health service disruption, should people living in malaria-endemic settings be given anti-malarial medicines for chemoprevention?
5. Phase 2: Should children hospitalized with malaria or severe anaemia in malaria-endemic settings be given anti-malarial medicines as chemoprevention post-discharge?
6. Phase 1 or 2: In areas of moderate to high malaria transmission, should residents known to be at increased risk of clinical malaria, severe malaria, death, or other adverse effects of *P falciparum* infection, be given anti-malarial medicines as chemoprevention?

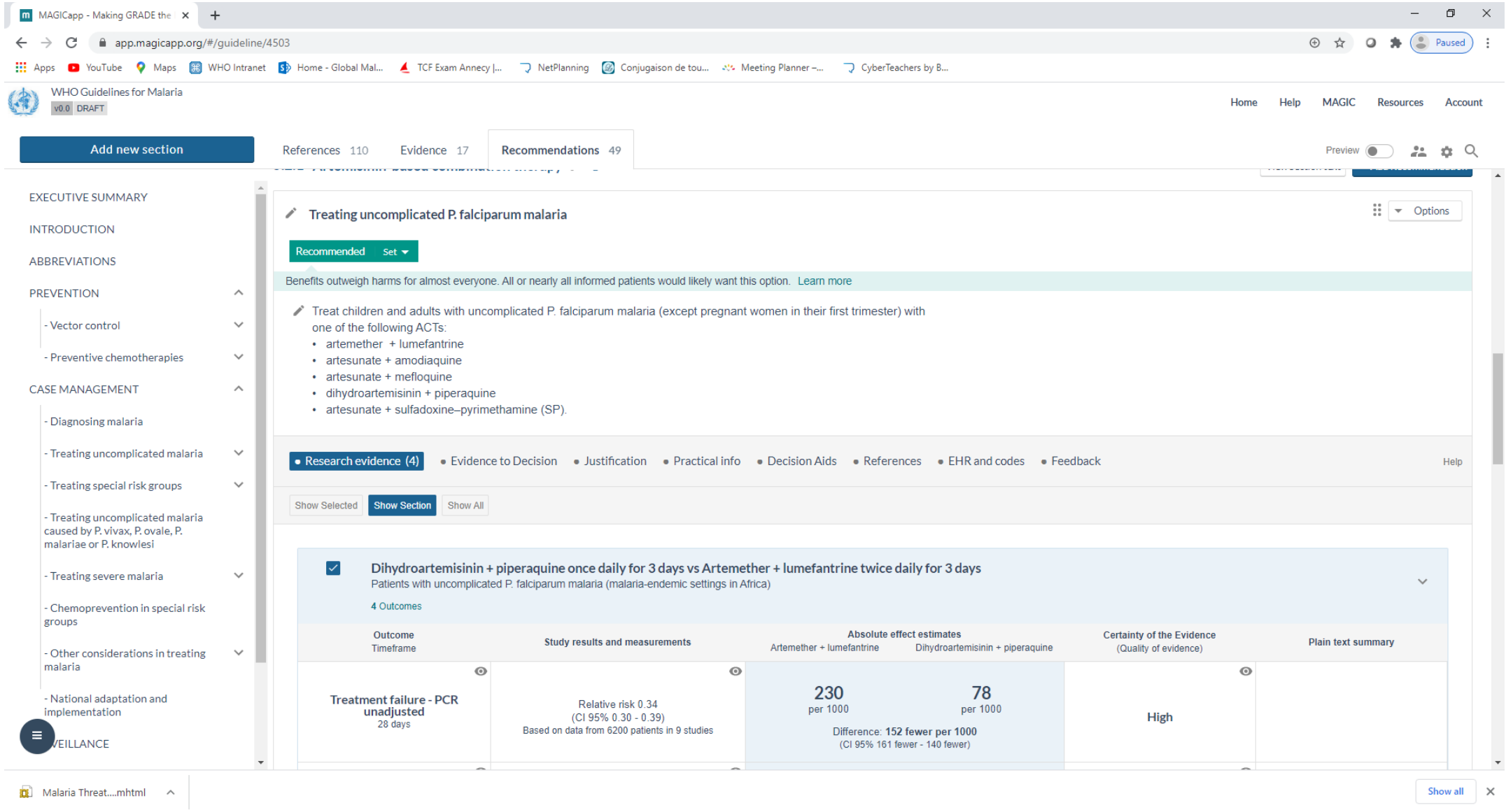
Treatment

- Steering Group convened
- Planning proposal submitted to GRC
- GDG – in the process of being selected
- Systematic reviews planned by the Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine
- PICO questions discussion in January 2021; formulation of recommendations anticipated in April 2021

Treatment – PICO questions

- **Artesunate-Pyronaridine**: In people with uncomplicated *P. falciparum* malaria, is AS-Pyr an effective and safe alternative to other recommended artemisinin combination therapies (ACTs)?
- **ACTs safety in the 1st trimester of pregnancy**: In the first trimester of pregnancy with uncomplicated *P. falciparum* malaria is any ACTs as safe and efficacious as quinine?
- **Primaquine for radical cure of non-falciparum malaria**: for radical cure, optimal dose regimen (efficacy and safety) for primaquine administration?

MAGICapp platform



Malaria Policy Advisory Committee Meeting

3—4 December 2020, Geneva, Switzerland
Background document for Session 4

World Health Organization

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

December 2020

Background

The Malaria Vaccine Implementation Programme (MVIP) was developed to act on the 2016 World Health Organization (WHO) recommendation to pilot the RTS,S/AS01 malaria vaccine in routine immunization programmes *(1)*. The MVIP supports the 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.

Information and news about the MVIP are available on the new WHO web platform *(2)*. This includes an overview of key milestones and stakeholder engagements in the development and roll-out of the programme *(3)*.

RTS,S/AS01 vaccine implementation

As of the end of November 2020, more than 1.2 million RTS,S/AS01 vaccine doses have been administered across the three MVIP countries and nearly 500 000 children have received the first dose. Despite the COVID-19 pandemic, the immunization programmes in all three countries have either maintained or improved their RTS,S/AS01 vaccine coverage compared to pre-pandemic levels. Based on administrative data, the coverage of dose 1 was 66% in Ghana (dose 3: 63%), 71% in Kenya (dose 3: 64%) and 85% in Malawi (dose 3: 69%) during the period from January to September 2020. This level of uptake meets or exceeds expectations for a new vaccine with a novel schedule, i.e., targeting children from 5 or 6 months of age for the first dose, and given the ongoing COVID-19 pandemic. Priority actions to maintain and further improve immunization performance have been identified and measures are being taken by the national immunization programmes, supported by partners, to address the issues noted.

Pilot evaluations

To date, COVID-19 has had minimal impact on the pilot evaluation, and surveillance for safety (with special focus on meningitis, cerebral malaria and sex-specific mortality) and impact has continued with

WHO/UHC/GMP/MPAC/2020.05

close monitoring of the epidemic 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 and introduced mitigation measures, including means to collect data retrospectively. 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.

The MVIP's advisory bodies continue to meet regularly to provide oversight and guidance to the Programme. Since the last update in May, the Programme Advisory Group (PAG) has met three times: on 20 May 2020, 16 June 2020 and 24–25 September 2020. The Data Safety and Monitoring Board (DSMB) has met twice: on 7–8 July 2020 and 16 September 2020. The MVIP advisory bodies have been pleased with the overall programme progress and improvements seen in both vaccine implementation and the quality of the pilot evaluations. During its most recent meeting, the PAG was reassured that a high proportion of patients admitted to sentinel hospitals and eligible for lumbar punctures (LPs) were now receiving them, and the previous concerns about LP rates have been addressed. Therefore, if there is an excess risk of meningitis similar to that suggested in the Phase 3 trial, it should be possible to detect it in the pilot evaluations. The PAG noted that the rates of meningitis detected in sentinel hospitals are lower than originally expected. As investigations into all suspected meningitis cases are now considered to be adequate, the low rates might reflect the generally lower meningitis incidence in the region as a result of high uptake of vaccines that prevent meningitis. Based on its review of the available data during its most recent meeting in September, the DSMB recommended continuation of the MVIP.

Case–control study to evaluate the added benefit of the fourth dose

In light of the data that have emerged since the original WHO position paper on RTS,S/AS01, the PAG has recommended a case–control study to evaluate the added benefit of the fourth dose and to strengthen the evaluation of safety and effectiveness endpoints. An application for funding from the European & Developing Countries Clinical Trials Partnership (EDCTP) was submitted in August 2020 by a consortium of MVIP partners. While waiting for the EDCTP's decision, the PAG recommended that data gathering for the case–control study begin, especially for meningitis and cerebral malaria. As cases are already identified through the pilot evaluations, the costs are expected to be relatively modest. WHO has been encouraged by the PAG to explore the option of using savings from existing MVIP funds to initiate this component of the case–control study as soon as possible.

Anticipated timing and process for WHO policy decision

According to the Framework for Policy Decision on RTS,S/AS01 endorsed by the Strategic Advisory Group of Experts on Immunization (SAGE) and Malaria Policy Advisory Committee (MPAC) in 2019, a WHO policy recommendation on the use of the vaccine beyond the pilot countries could be made if and when: i) concerns regarding the safety signals observed in the Phase 3 trial (i.e., related to meningitis, cerebral malaria and sex-specific mortality) have been satisfactorily resolved, and ii) severe malaria and mortality data trends have been assessed as being consistent with a beneficial impact of the vaccine *(4)*. Based on its review of the initial data, the PAG recently confirmed that, if overall event rates for meningitis, severe malaria, cerebral malaria, and mortality persist, there will be sufficient power to conduct the planned safety and impact analyses at 24 months after first vaccination (end of April 2021). This would enable a joint policy review by SAGE and MPAC in Q4 2021. In line with the Framework for Policy Decision, adjustments or refinements to the WHO policy recommendation may subsequently be made based on the MVIP final dataset expected in 2023, including data on the fourth dose.

WHO has looked at ways to ensure the efficiency of the data review and external advisory group consultation processes leading up to the SAGE/MPAC review (see Annex 1). By streamlining the

processes, the time between data availability and policy review could be reduced to approximately six months without compromising the quality of the review. In September 2020, the PAG reviewed the proposal for a streamlined policy pathway and concluded, “The PAG supports the proposed policy pathway through 2021, and agrees with the importance of streamlining processes to avoid sequential reviews among advisory bodies”.

The PAG was established in October 2017 as the MVIP’s highest level advisory body to WHO, tasked with regularly reviewing progress and providing guidance in order to ensure sound approaches to design and implementation. The PAG’s Terms of Reference have been revised to include an expanded role as a joint SAGE and MPAC working group to review the evidence on the balance of benefits and risks of RTS,S/AS01, as it becomes available *(5)*. The expanded role will call upon PAG members to review RTS,S/AS01 data from multiple sources, including MVIP data available 24 months after first vaccination (April 2021), Phase 3 trial data (MAL-055 and MAL-076 long-term follow-up), and Phase 3b trial data on RTS,S/AS01 and seasonal malaria chemoprevention (SMC) in seasonal settings. The PAG will report to SAGE/MPAC on the balance of benefits and risks, and submit recommendations on the potential wider scale use of the vaccine in sub-Saharan Africa for subsequent review by SAGE and MPAC during a joint session. Approximately two representatives from SAGE, MPAC, the Regional Immunization Technical Advisory Group (RITAG) and possibly the Global Advisory Committee on Vaccine Safety (GACVS) have been or will be appointed to serve on the PAG.

Vaccine supply and access

As highlighted during the Malaria Vaccine Stakeholder Meeting convened by WHO in October 2019, timely access to affordable vaccine supply upon policy recommendation is of crucial importance. An unresolved near-term challenge is the need for financial support to ensure continuous production of RTS,S antigen prior to a policy decision. Without external financial support, manufacturing will stop in early 2021 and only resume following a policy recommendation and funding decision for procurement. According to GSK, restarting production could take up to three years, implying a delay in vaccine availability until possibly 2025. Besides the considerable loss of lives from delaying the expansion of vaccine use in MVIP countries and deployment in non-MVIP countries, not securing continued production could also jeopardize longer term supply by putting the product transfer process at risk and delaying decisions on production capacity scale-up. Acknowledging these negative implications, in December 2019, the Gavi Board approved a Gavi intervention to enable continued production of RTS,S bulk antigen, whereby Gavi identifies a third party(ies) as guarantor and devises a de-risk mechanism to minimize Gavi’s exposure to financial risk. Despite active engagement with the lead third party expressing interest in supporting continued production, a solution has not yet been found. This matter has become critically urgent and is a determining factor for future access to the vaccine.

References

1. Malaria vaccine: WHO position paper – January 2016. Geneva: World Health Organization; 2016 (http://www.who.int/wer/2016/wer9104.pdf).
2. Malaria Vaccine Implementation Programme (https://www.who.int/initiatives/malaria-vaccine-implementation-programme).
3. Key milestones in the development of the Malaria Vaccine Implementation Programme (MVIP): from pilot recommendation to vaccine introduction. Geneva: World Health Organization; 2020 (https://www.who.int/docs/default-source/immunization/mvip/mvip-milestones-to-programme-development-final.pdf).
4. Framework for Policy Decision on RTS,S/AS01 Malaria Vaccine for the Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC). Geneva: World Health Organization; 2019 (https://www.who.int/immunization/sage/meetings/2019/april/1_Session_7_Framework_for_Policy_Decision_on_RTSS-AS01_-_MALARIA_VACCINE_(for_print).pdf).
5. Terms of Reference, MVIP Programme Advisory Group (https://www.who.int/initiatives/malaria-vaccine-implementation-programme/programme-advisory-group).

Contact

For more information, please contact:

Mary Hamel, MVIP lead, WHO HQ, Immunization, Vaccines & Biologicals, hamelm@who.int
David Schellenberg, Scientific Adviser, WHO HQ, Global Malaria Programme, schellenbergd@who.int

Annex 1: Oversight, analysis and development of draft policy recommendations for joint review by SAGE and MPAC

Proposed timelines and processes (see schema next page)

- Regular updates on MVIP progress to the **PAG** (quarterly), **DSMB** (quarterly), **SAGE** (biannually), **MPAC** (biannually), **RITAG** (biannually), **IVIR-AC** (as needed), **AACVS** (at inaugural and biannual meetings) and **GACVS** (biannually).

1. **IVIR-AC** recommendations on methods feed into modelling for impact and cost-effectiveness. The outputs from the recommended models are provided to **PAG.**
2. **DSMB** considers formal analysis of MVPE safety data (based on 24 months of evaluation).
3. **DSMB** provides a formal presentation of the analysis results to **PAG, in the presence of GACVS, AACVS** and **RITAG members**. Documentation should be shared in advance of the PAG meeting so that questions and comments can be formulated among the advisory committees. Note that the DSMB report will focus on safety, potentially without considering the results on impact. During the PAG meeting, sufficient time will be allotted to considering the questions and comments from the advisory committees.
4. **PAG** reviews and summarizes the body of evidence, taking into account the DSMB analysis and inputs received from GACVS, AACVS and RITAG.
5. **PAG** sends its recommendations to **SAGE/MPAC** for policy review.
6. Joint review meeting is held by **SAGE/MPAC** (special session or VC may be required). The RITAG Chair, GACVS Chair, AACVS Chair and regional office are represented.

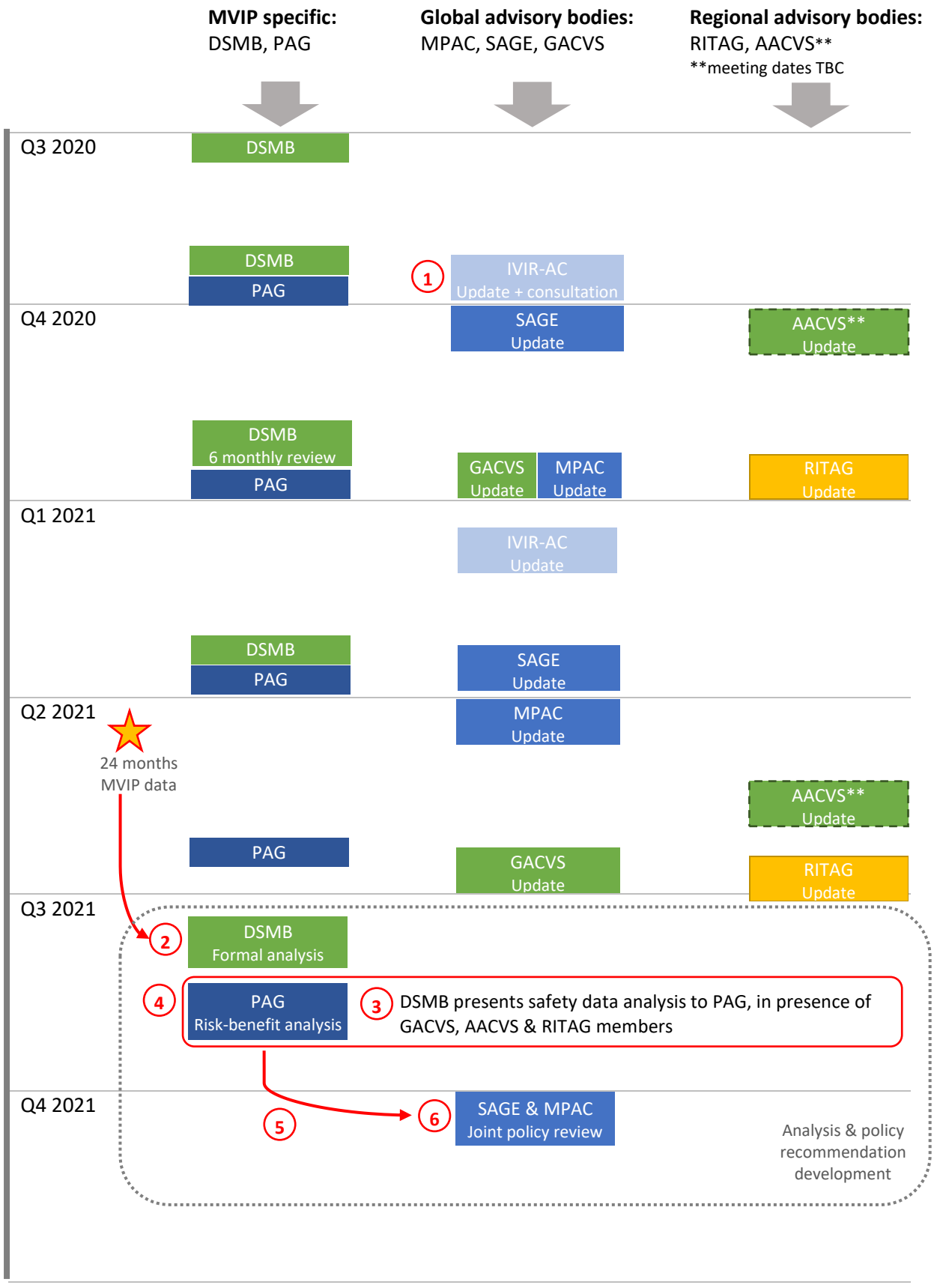
- If recommended for use by SAGE/MPAC, the vaccine will go through the WHO Prequalification expedited process.

Acronyms:

AACVS	African Advisory Committee on Vaccine Safety
GACVS	Global Advisory Committee on Vaccine Safety
IVIR-AC	Immunization and Vaccines-related Implementation Research Advisory Committee
MPAC	Malaria Policy Advisory Committee
MVIP	Malaria Vaccine Implementation Programme
MVIP DSMB	MVIP Data Safety and Monitoring Board
MVIP PAG	MVIP Programme Advisory Group
MVPE	Malaria Vaccine Pilot Evaluation
RITAG	Regional Immunization Technical Advisory Group for AFRO
SAGE	Strategic Advisory Group of Experts on Immunization

= Safety-related committee

Of note: Timings of future meetings are tentative / based on usual frequency



Malaria Vaccine Implementation Programme

World Health Organization

Malaria Policy Advisory Committee

Friday 4 December 2020

Objectives

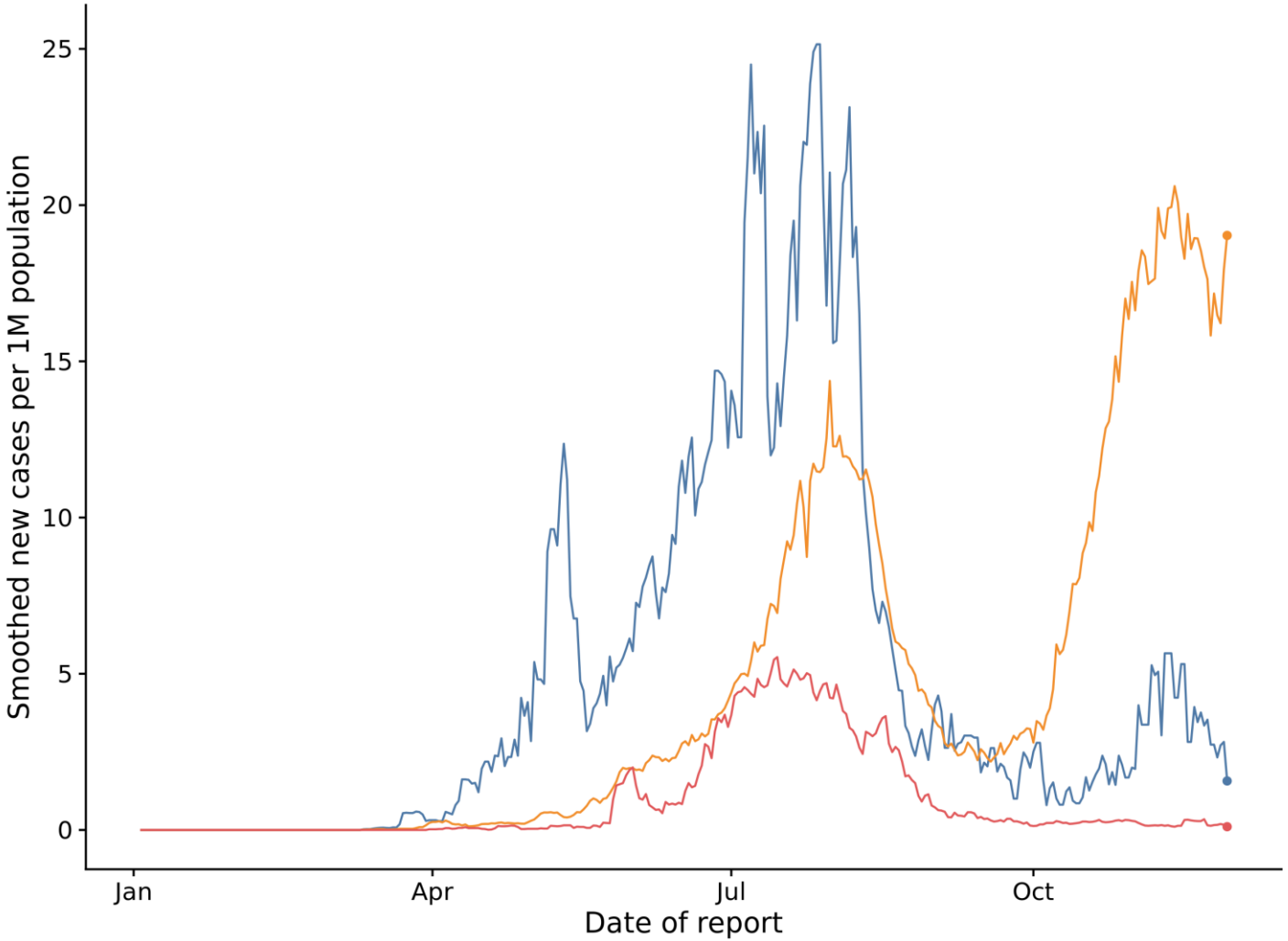
1. Programme Status
2. Timeline for data review for potential policy decision and streamlined policy pathway (seeking agreement)
3. Update on RTS,S/AS01 supply and access

Programme status

WHO/F.Combrink

COVID-19 cases in MVIP countries: incidence per 1M population

As of 30 Nov 2020



Data taken from COVID Intel database on 2020-11-30.
The lines and associated text show the trend in incidence of COVID-19 cases.

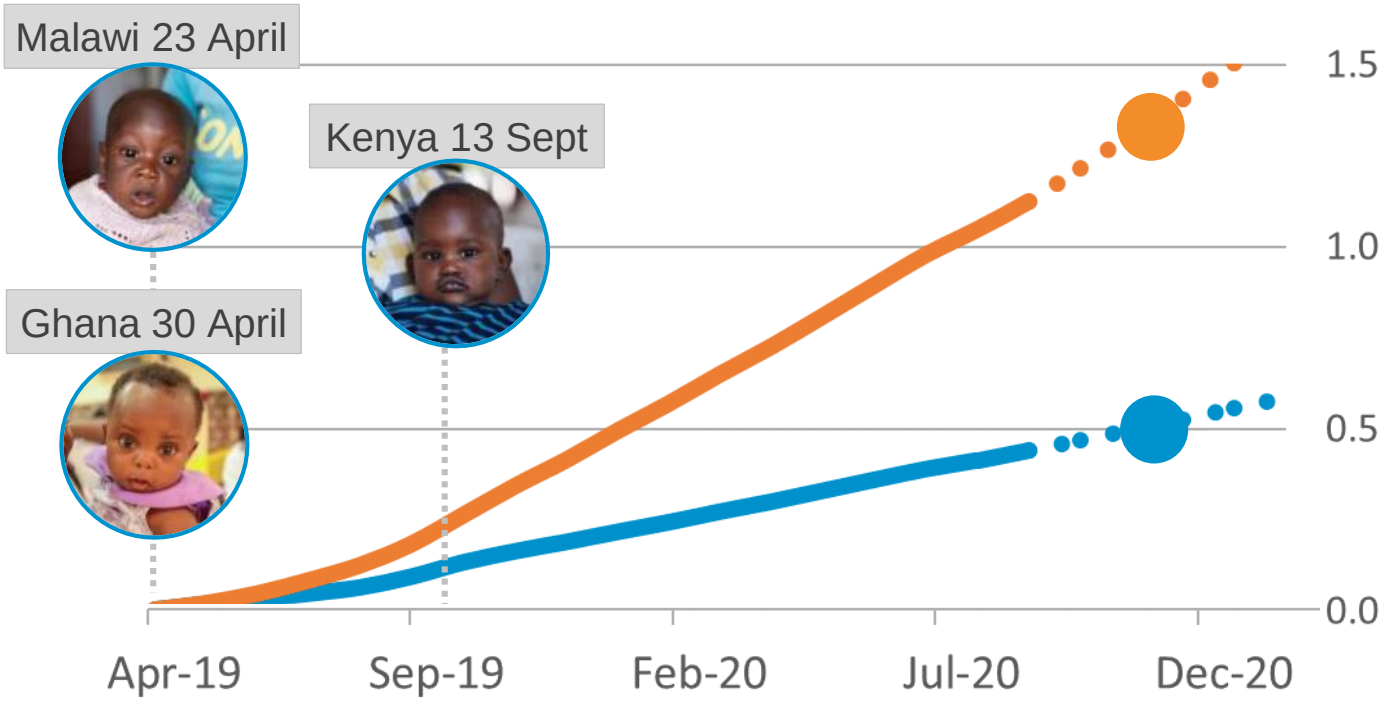
Kenya
82,605 cases
1,445 deaths

Ghana
51,379 cases
323 deaths

Malawi
6,025 cases
185 deaths

Source:
https://covid19.who.int/

Current situation and trends



>1.3 million
doses
administered

~500,000
children
received dose 1

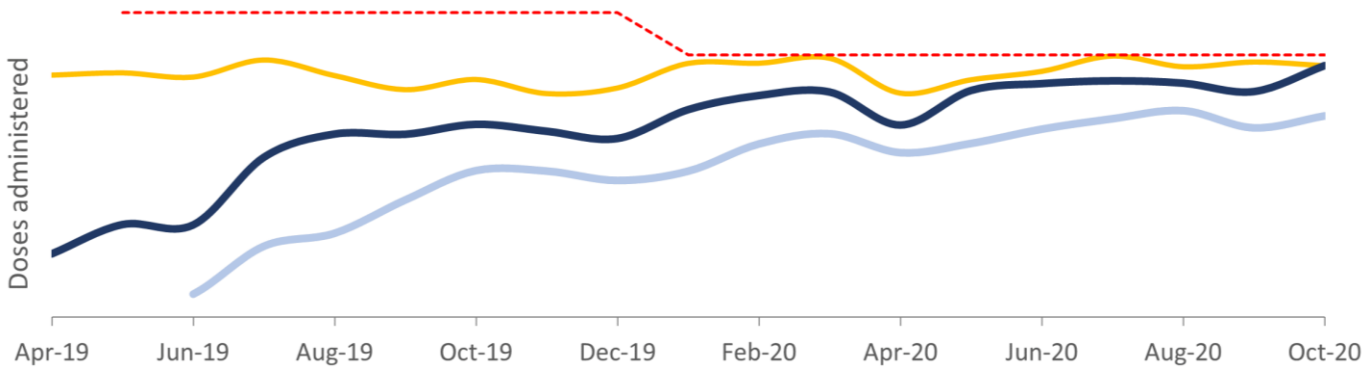
- **Vaccine uptake ~ 70%, dose 4 administration beginning**
- **Evaluation components** functioning in all countries with data accumulation ongoing

Estimates as of 26 November 2020. Based on monthly administrative data reports until September 2020. Projections thereafter.

Immunization coverage in MVIP areas[1]

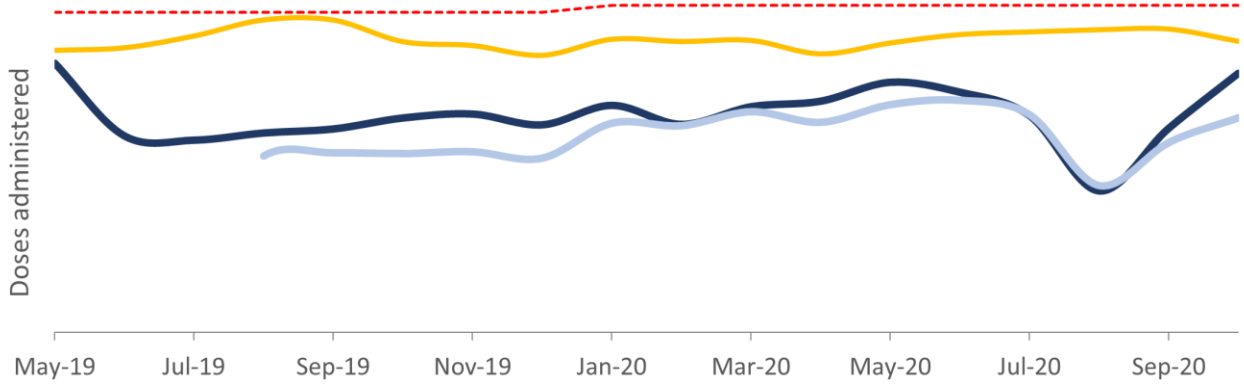
Coverage Jan. – Oct. 2020

Malawi



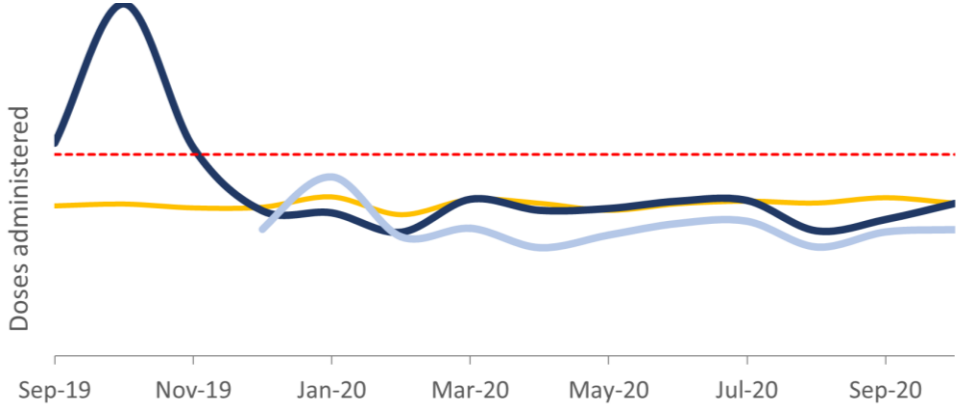
Penta-3	95%
RTS,S-1	86%
RTS,S-3	70%

Ghana



Penta-3	90%
RTS,S-1	68%
RTS,S-3	64%

Kenya



Penta-3	76%
RTS,S-1	71%
RTS,S-3	64%

1 Administrative data

MVIP Governance:
Quarterly meetings of DSMB and PAG

Data Safety & Monitoring Board (DSMB), 1,2 December 2020

- Safety data reassuring; DSMB recommend continuation of pilots
- Noted that GSK biannual report to EMA was received, and EMA maintains the positive scientific opinion; no change in favourable risk-benefit profile
- **DSMB stated that the safety data event rates support analysis for WHO consideration of a policy recommendation in 2021**

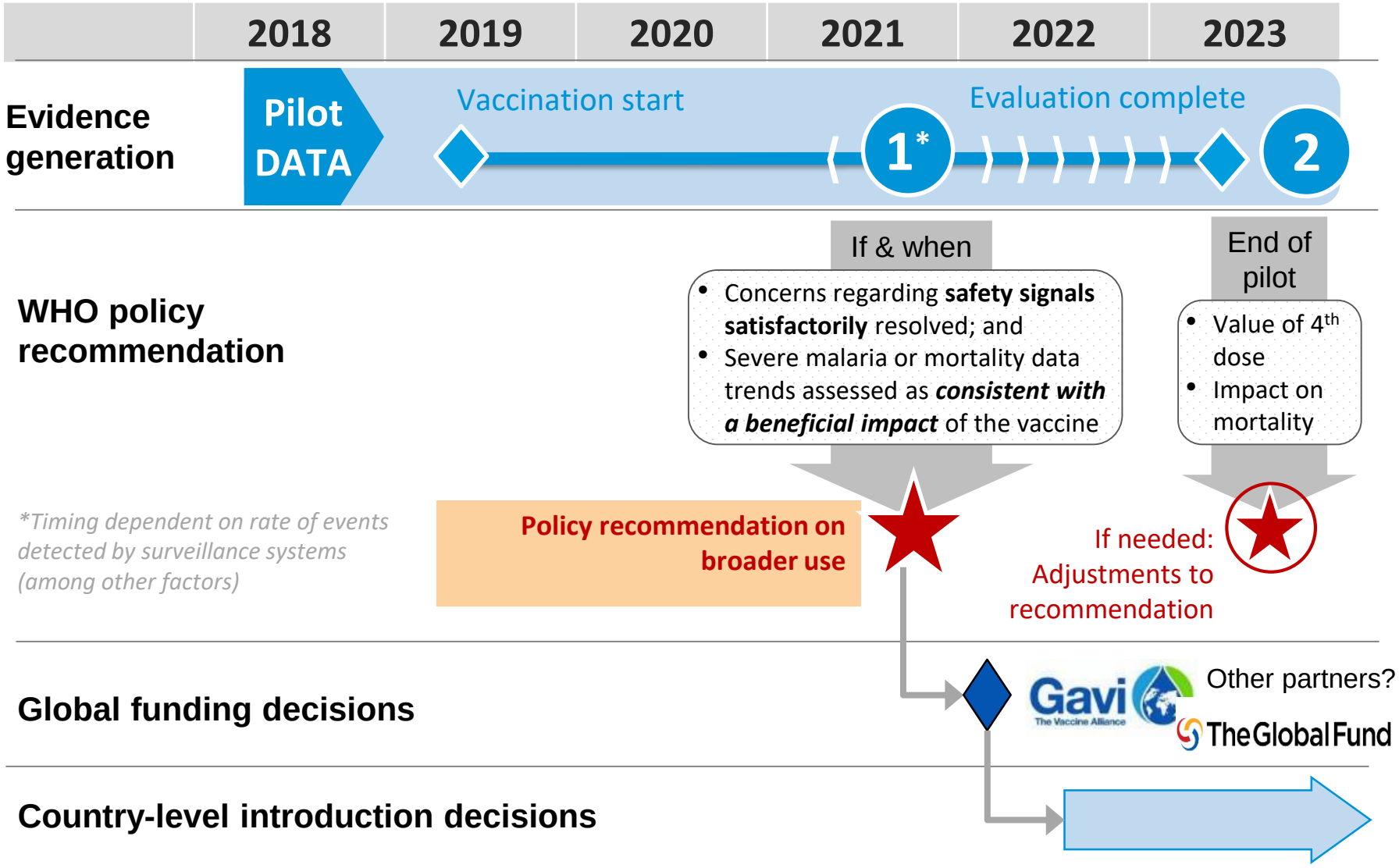
Programme Advisory Group (PAG), 3,4 December 2020

- PAG recommends overall event rates for meningitis, severe malaria, cerebral malaria, and mortality at current levels indicate there will be sufficient power to conduct planned safety and impact analyses at 24 months after first vaccination
    - Target timelines for policy review : **Q4 2021**

Timeline for data review and potential policy decision

Credit: WHO/Neil Thomas.

Next steps: Framework for WHO Policy Recommendation on RTS,S/AS01



Policy and financing pathway

Inputs

Data & info available for analysis (target: Q2 2021)

- MVPE hospital surveillance
- MVPE mortality surveillance
- MVPE midline household survey (G + M)
- Phase IV progress reports + data request
- EMA positive opinion
- HUS initial findings
- Economic evaluations/ updates
- AEFI/AESI (routine system)
- Immunization coverage – administrative data
- New vaccine post introduction evaluation
- Phase 3 (MAL055) & long-term follow-up (MAL076)
- Phase 3b: RTS,S & SMC

Outputs

Evidence package (target: July/August 2021)

- MVIP statistical analysis on safety and impact
- RTS,S/AS01 full benefit-risk report

Evidence review (target: Q3 2021)

- MVIP DSMB formal review of safety analysis
- MVIP PAG review of RTS,S/AS01 benefit-risk
- SAGE/MPAC joint review of PAG recommendations

Outcomes

WHO policy recommendation on broader use (target: October 2021)

Financing decision (target: December 2021)

Gavi Board investment decision on support for vaccine roll-out

Regulatory (target: TBC)

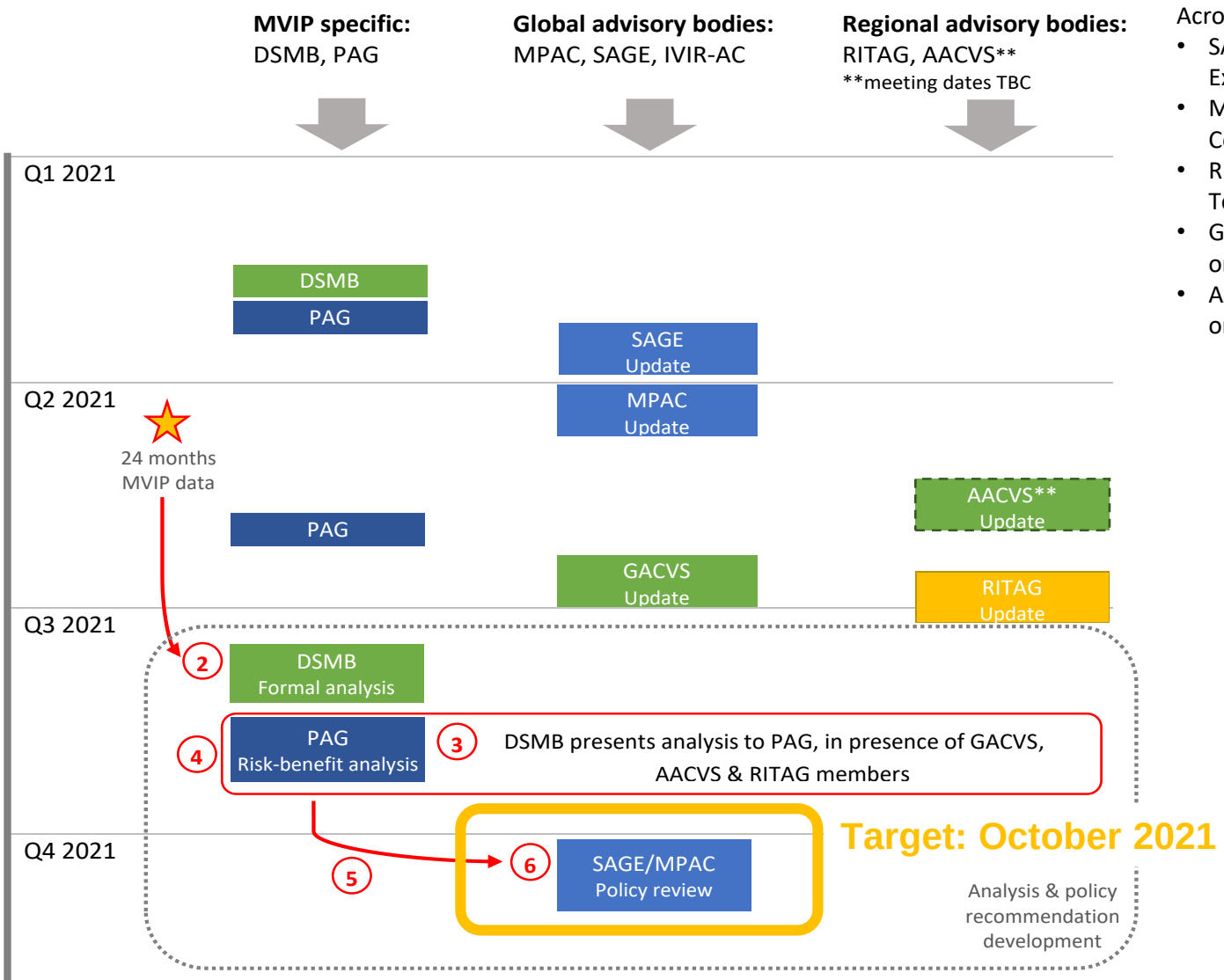
Prequalification & in-country authorizations

Country-level decisions (target: begin in 2022)

MVIP countries may wish to expand + non-MVIP countries

Stakeholder alignment and engagement

Proposed WHO policy pathway for MPAC endorsement



Acronyms:

- SAGE: Strategic Advisory Group of Experts on Immunization
- MPAC: Malaria Policy Advisory Committee
- RITAG: Regional Immunization Technical Advisory Group for AFRO
- GACVS: Global Advisory Committee on Vaccine Safety
- AACVS: African Advisory Committee on Vaccine Safety

World Health Organization

Thank you

www.who.int

The four components of the Malaria Vaccine Implementation Programme

World Health Organization

Vaccination

1

RTS,S/AS01 Implementation through EPI Programme

In selected areas of Ghana, Kenya & Malawi with community engagement

Evaluation

2

Pilot evaluation commissioned by WHO

Incl. sentinel hospitals surveillance; community-based mortality surveillance; 3 household surveys

3

Qualitative assessment (HUS) & economic analyses

commissioned by PATH

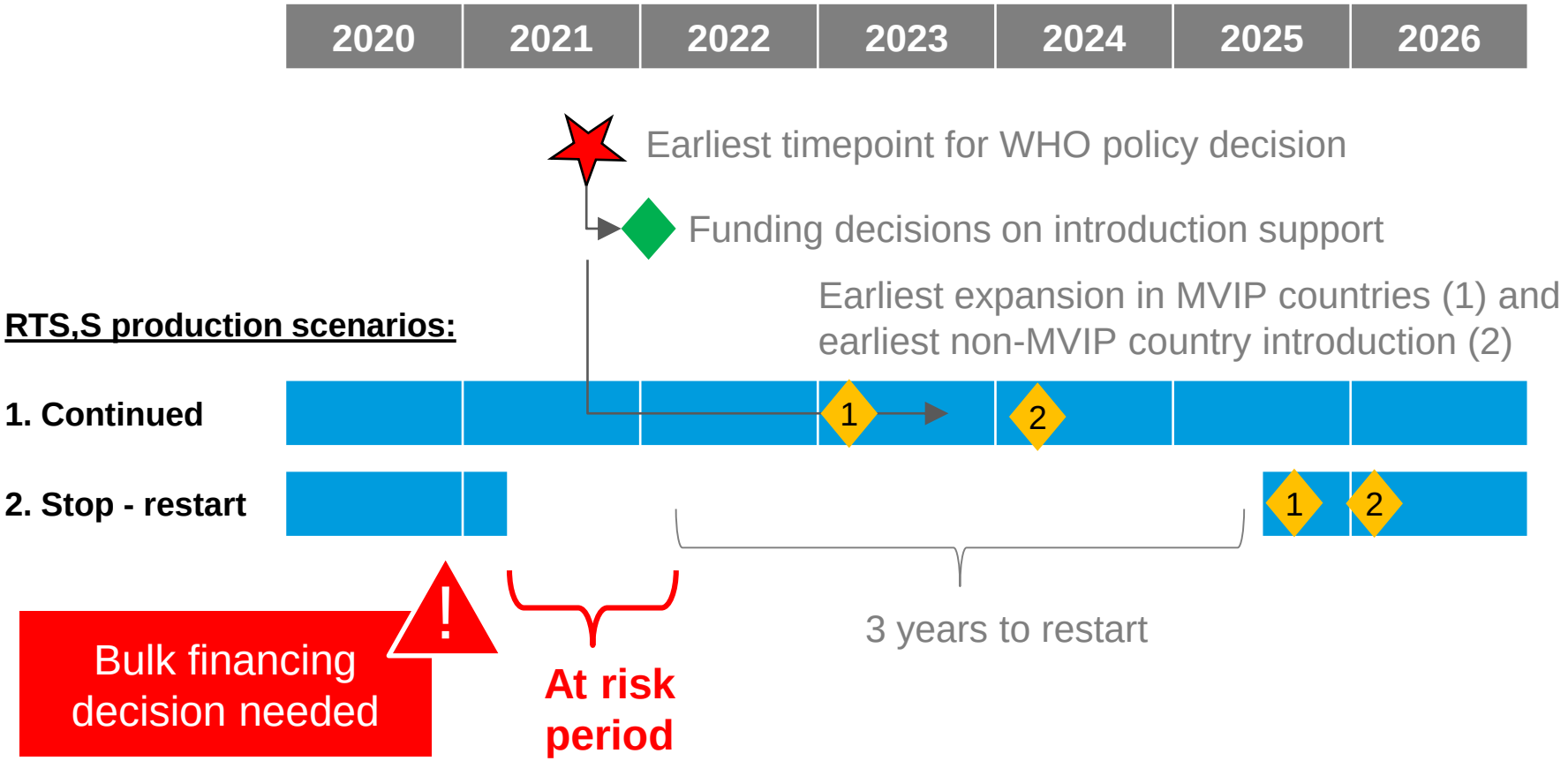
4

GSK Phase IV study

Safety, effectiveness and impact
Part of GSK's EMA Risk Management Plan

Future access: Importance of continued RTS,S bulk production

- **Sufficient donation doses to complete the MVIP. However:**



Future access: funding needs

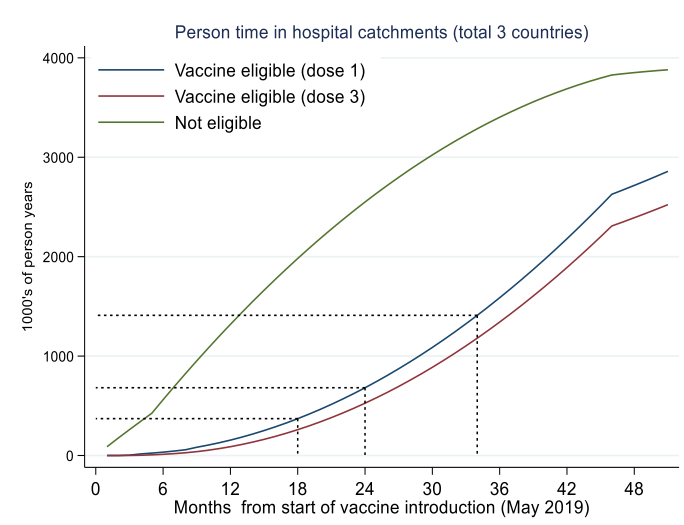
Type of investment	Risks (if no investment)
1) Immediately needed: Guarantee to cover costs of continuation of RTS,S bulk production (~$20 M per year)	• Expansion beyond vaccinating areas in MVIP countries likely not possible until 2025. • Introduction in non-MVIP countries at least 2 years delayed. • Risk to RTS,S product transfer & risk of a second RTS,S supply gap in 2029/2030. • Inherent risks and delays caused by stop-and-restart. • Higher average vaccine price.
2) Soon needed: Funding to enable expansion of vaccine production capacity	• Supply is limited to 15 million doses per year (estimated 5-7 years needed for expansion)

Timing of analyses: number of events required for analyses of safety and impact

Outcome	Effect in the phase 3 trial	Population effect if average coverage is: 60%	70%	Number of cases required for 90% power	Observed event rate/1000	Events up to July 2020	Projected events by Q2 2021
Safety:							
Meningitis	10-fold increase	6.4	7.3	70-100 cases under 5 yrs	0.01-0.06	48	77
Cerebral malaria	2-fold increase	1.6	1.7	300-350 cases under 5 yrs	0.1-0.2	191	355
Mortality ratio girls:boys	2-fold increase in mortality in girls	1.6	1.7	2000-2500 deaths (among vaccine-eligible)	0.8-2.7	1632	3200
Impact:							
Severe malaria	34% efficacy*	20%	24%	about 4000 cases under 5 yrs	0.9-3.9	2913	5476

*Efficacy against severe malaria, months 0-20

Predicted power at month 24

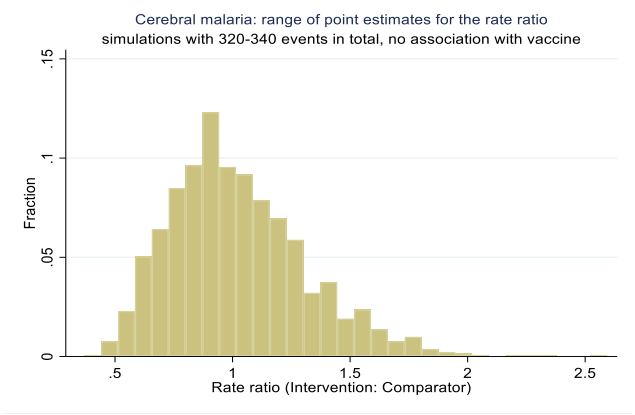


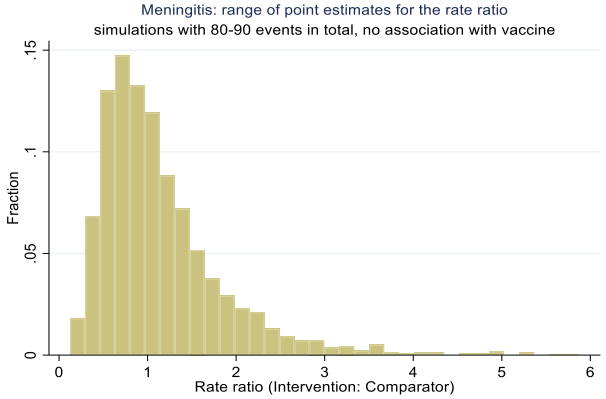
	Cerebral malaria	Meningitis	
	2.6	10.5	(Rate ratio in phase3)
Coverage:	Population level effect:		
60%	1.9	6.7	
70%	2.1	7.7	
80%	2.3	8.6	
90%	2.4	9.6	
100%	2.6	10.5	

Power to exclude rate ratio of:				
No. of events	2	2.1	2.2	2.3
340-350	76%	81%	85%	89%
330-340	76%	80%	83%	86%
320-330	71%	77%	82%	84%
310-320	71%	76%	81%	84%
300-310	69%	75%	79%	83%

Power to exclude rate ratio of:			
No. of events	5	6	7
80-90	83%	89%	92%
70-80	78%	85%	89%
60-70	73%	80%	85%

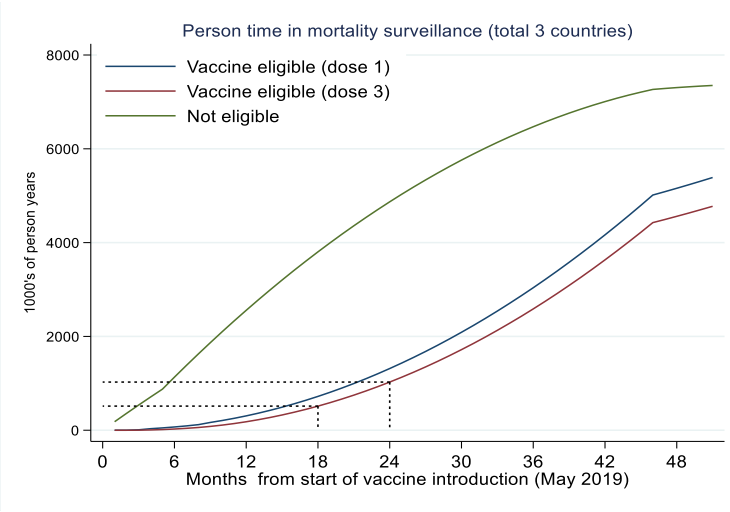
Predicted range of point estimates (rate ratios for cerebral malaria, meningitis), assuming no effect





Mortality

month	Effect % reduction	Events (Total)	Events (Eligible)	power
24	15%	9014	4308	95%
24	10%	9100	4396	64%
46	10%	17671	8443	92%
46	9%	17727	8499	87%
46	8%	17784	8554	78%



Coverage	70%	70%	70%
Efficacy	40%	40%	30%
% deaths due to malaria	20%	30%	30%
% impact	5.6%	8.4%	6.3%