Session 7: Malaria Vaccine

Proposed Framework for Policy Decision on RTS,S/AS01 Malaria Vaccine

Presentation to SAGE

3 Apr 2019

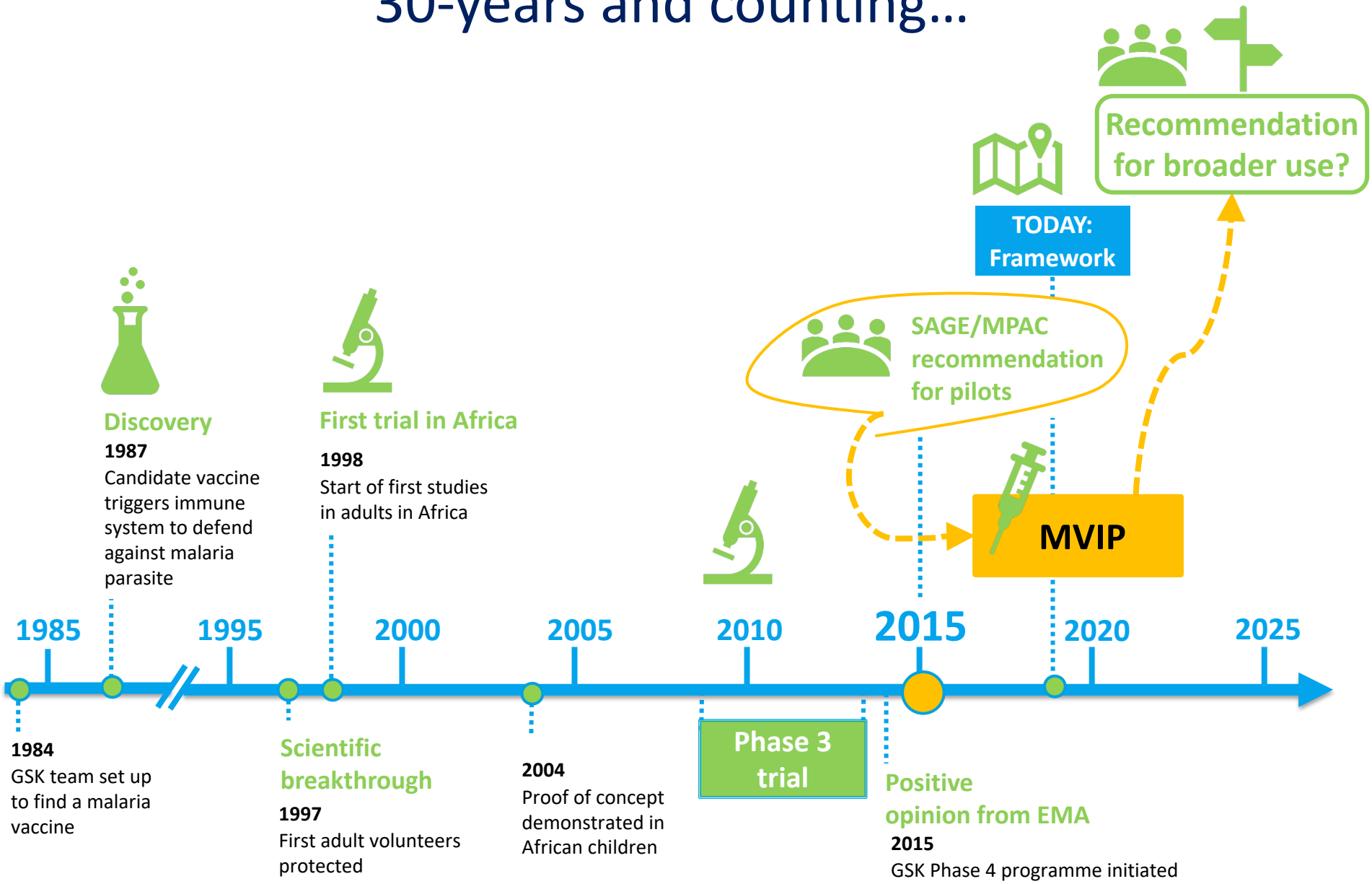
Session 7 – Malaria Vaccine

- Introduction to the session, F WERE (5 min)
- Brief update on the Malaria Vaccine Implementation Programme (MVIP) and review of data informing the Framework for Policy Decision on RTS,S/AS01, M HAMEL (20 min) - **FOR INFORMATION**
- Recommendations of the SAGE/MPAC Working Group on the Framework for Policy Decision on RTS,S/AS01, P SMITH (20 min) – **FOR DECISION**
- Discussion (75 min)

Introduction to session

Prof Fred Were

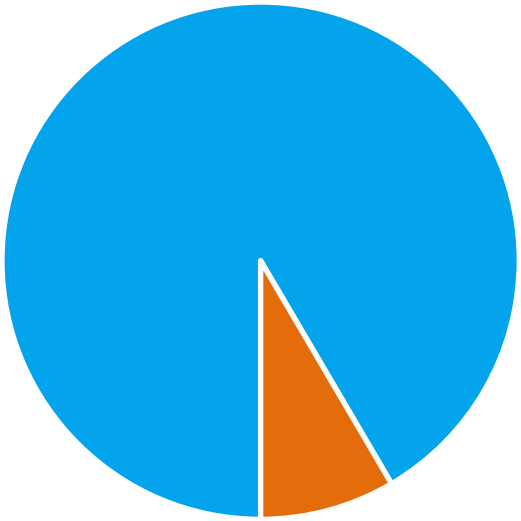
The RTS,S/AS01 malaria vaccine development: 30-years and counting…



Estimated malaria cases & deaths in the World and relative contribution of the African region, 2017

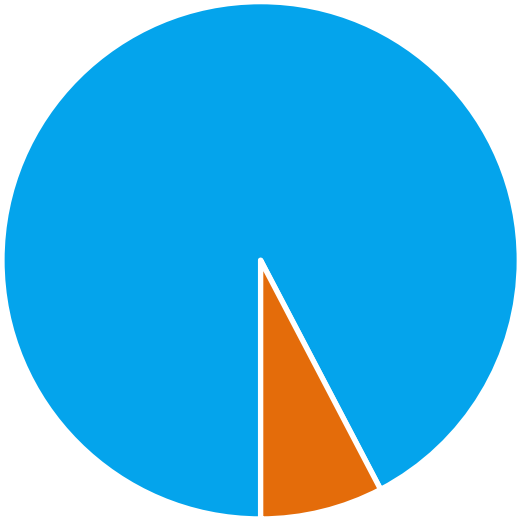
Cases 219 million | **Deaths 435 thousand**

Africa: 92%



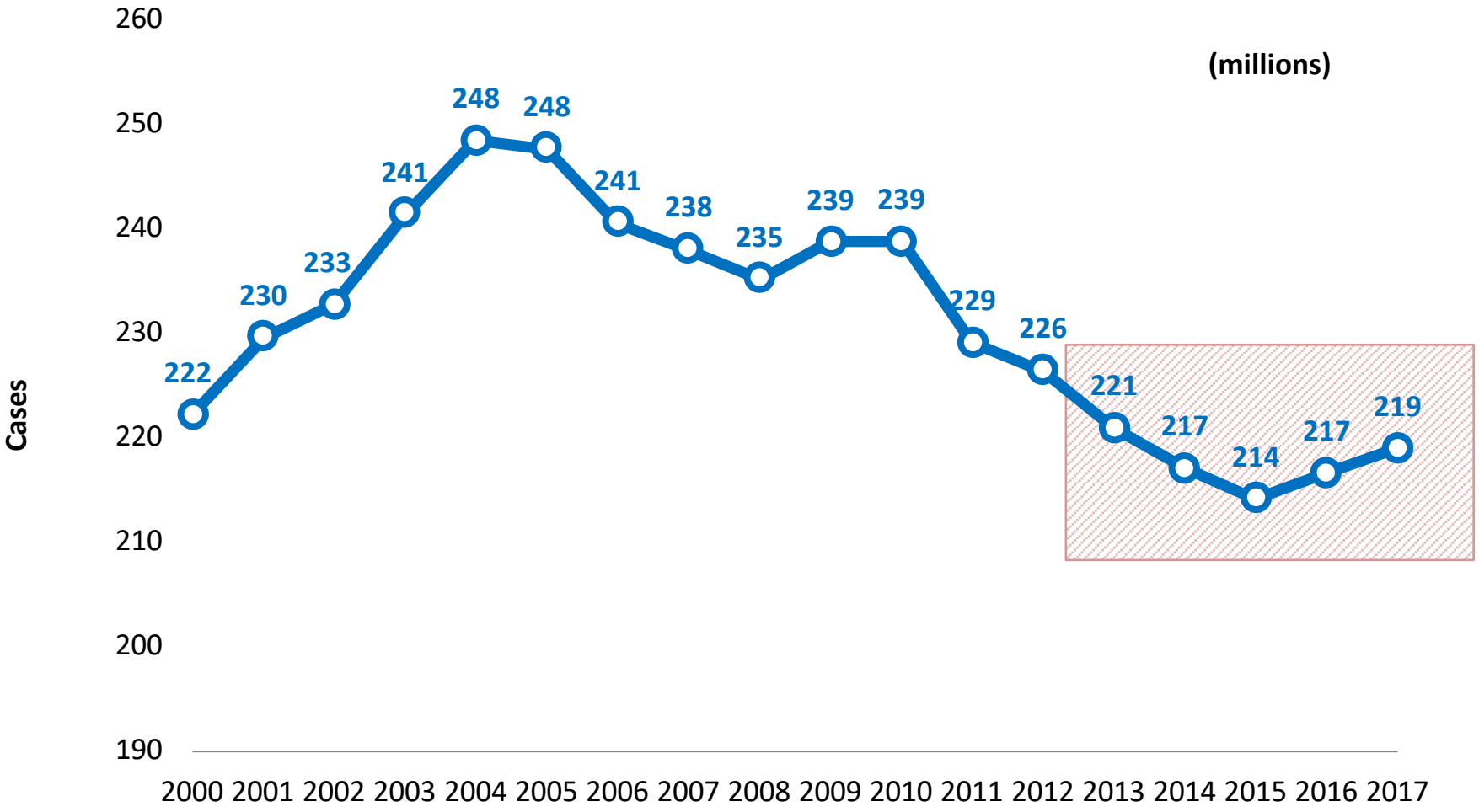
Rest of the world: 8%

Africa: 93%

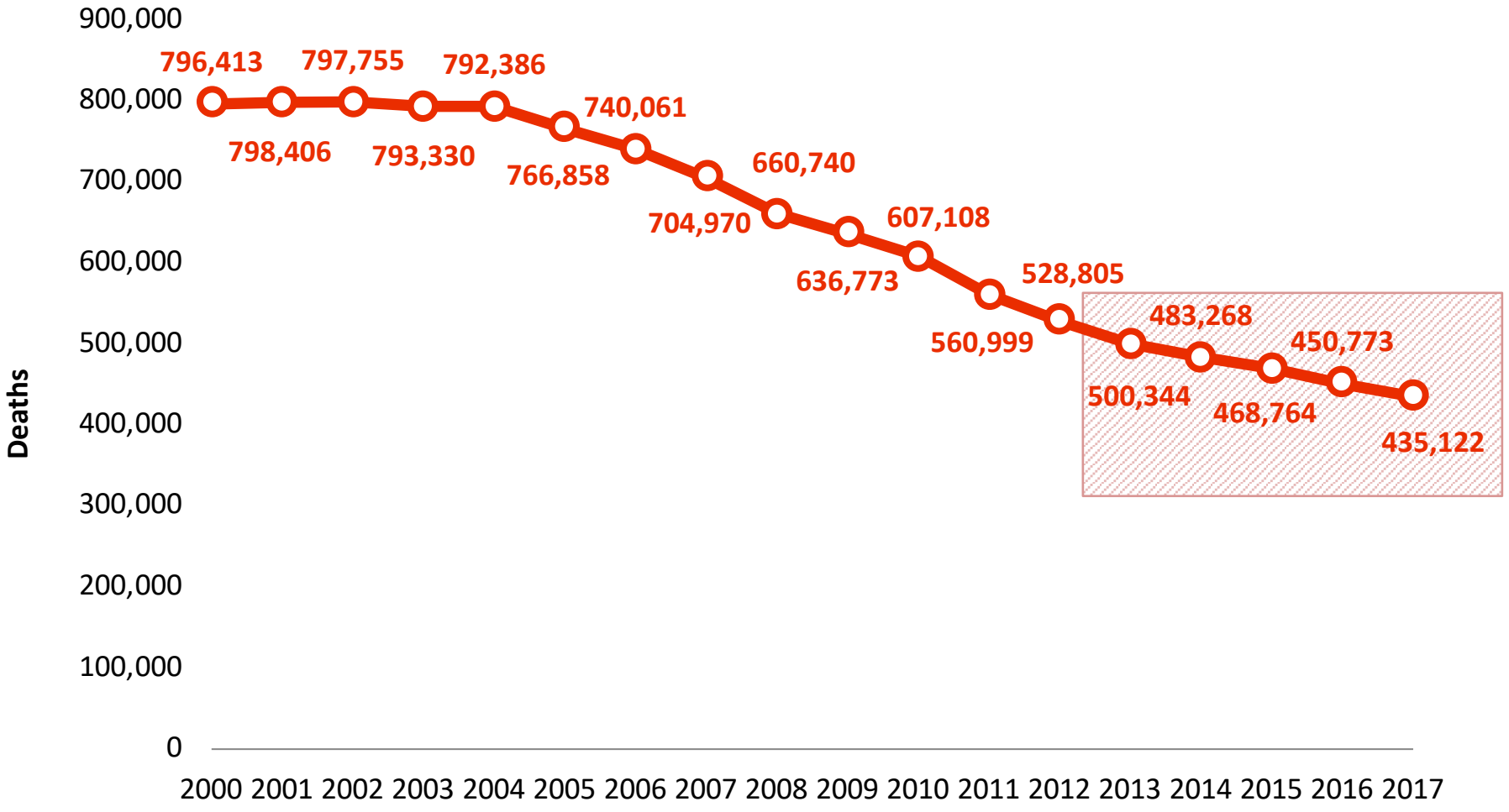


Rest of the world: 7%

Number of malaria cases worldwide, 2000–2017



Number of malaria deaths worldwide, 2000–2017

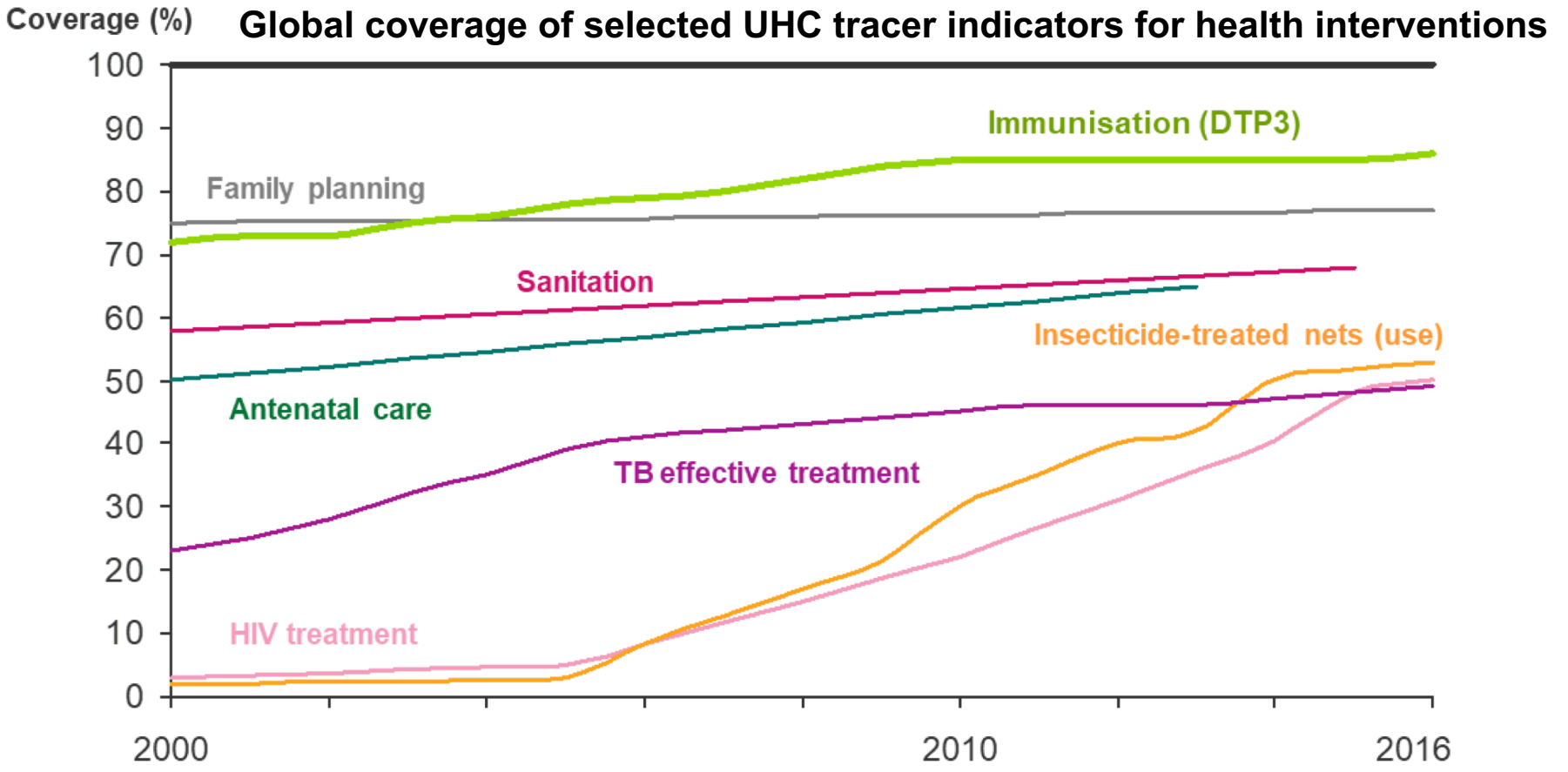


Potential value of RTS,S/AS01

- RTS,S/AS01 - while not the perfect vaccine - has potential for considerable impact when used in combination with existing tools
  - Phase 3 trial showed high impact in high transmission settings
    - Thousands of malaria episodes prevented per 1000 children vaccinated over 4 years follow-up
    - Impact provided by RTS,S/AS01 was in addition to that achieved with ITNs
    - Modeled estimates: 1 life saved for every 200 children vaccinated
  - All available malaria control tools are partially efficacious, but impact can be high
    - ITN efficacy against uncomplicated malaria is 45%[1], impact on mortality across sub-Saharan Africa has been marked
  - No other malaria vaccines ready for deployment
  - Vaccination programmes tend to have high reach (see next slide)

1. Pryce *et al*, Cochrane review 2018

Potential value of RTS,S/AS01: Immunization programmes tend to have higher reach than other health interventions



 Source: Graph courtesy of Gavi, based on Tracking Universal Health Coverage 2017 Global Monitoring Report

World Health Organization

Session objective

- **Present SAGE and MPAC with the recommendations by the Working Group on the Framework for Policy Decision on RTS,S/AS01 and request SAGE and MPAC's consideration of the proposed Framework**

  – For information (by M. Hamel)
    - Brief update on the Malaria Vaccine Implementation Programme (MVIP)
    - Presentation of data informing the Framework
  – For decision (by P. Smith)
    - Presentation of Working Group recommendations

Brief update on the Malaria Vaccine Implementation Programme (MVIP) and review of data informing the Framework for Policy Decision on RTS,S/AS01

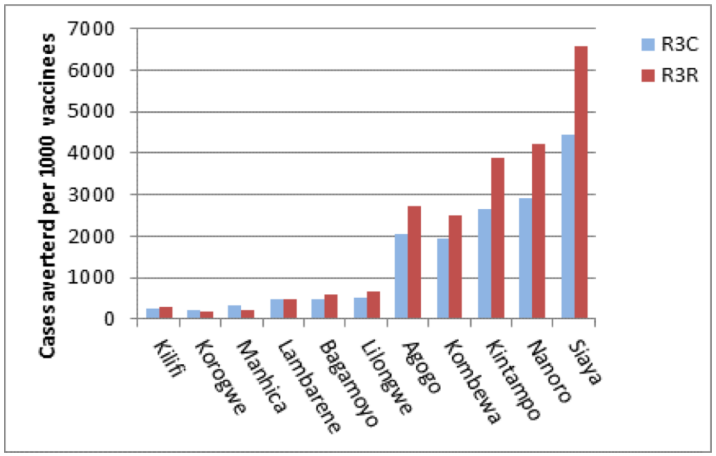
Mary Hamel

Outline

- Background on RTS,S/AS01 and MVIP update
- Framework for Policy Decision on RTS,S/AS01 and establishment of SAGE/MPAC Working Group
- Review of data informing the Working Group recommendations

Results from RTS,S Phase III Trial, 2009-2014

- RTS,S/AS01 Phase III trial
  - 15,459 children, 11 sites, 7 African countries
  - 6-12 weeks or 5-17 months at first vaccination
- Children 5-17 months, 4 doses over 4 years
  - 39% reduction in clinical malaria
  - 29% reduction in severe malaria
  - **62% reduction severe malaria anaemia**
  - 29% reduction blood transfusions
- 4 doses provided optimal benefit;
  - 3 dose group had efficacy against clinical malaria, but not against severe malaria
- High impact, especially in moderate to high transmission settings, with thousands of episodes prevented per 1000 children vaccinated over 4 years
- Modeling: 1 life saved/200 vaccinated; highly cost-effective



Clinical malaria cases averted, 3 or 4 doses, by study site and transmission, Mal 055

World Health Organization

Results from RTS,S Phase 3 Trial: Safety

- No vaccine-associated deaths
- Febrile convulsions, no sequellae
- Potential safety signals, with causality not established
  - In the 5-17 month age-category only
    - Imbalance in meningitis cases (10:1)
    - *Post hoc* analysis: numerically increased cerebral malaria cases (2:1, algorithmically derived)
  - In combined age-categories *post hoc* analysis: increased number of female deaths in those who received RTS,S vs. comparator vaccine 2:1
- Potential safety signals not observed in:
  - Pooled Phase II trials (n=2981)[1]
  - Large ongoing Phase III trial in Mali and Burkina Faso (n=4000 vaccinated children; followed for >18 months)[2]

1. Vekemans et al, Human Vaccines, 2011
2. Personal communication, Greenwood

Regulatory review

- July 2015: European Medicines Agency (EMA) issued a **positive scientific opinion** under Article 58
  - Applying the same rigorous standards as for medicines to be marketed in the EU
  - Stating that the safety profile is acceptable
  - Risk-benefit profile favourable

- May 2017: National regulatory authorities from three pilot countries authorized for use in pilot areas
  - Joint regulatory review under auspices of AVAREF

WHO position & pilot implementations

- Oct 2015: SAGE/MPAC recommended **pilot implementation** with phased, sub-national introduction through routine EPI to inform policy on public health use of vaccine
- Pilot evaluations designed to address outstanding questions:
  - **Feasibility** of reaching children with 4 doses, including 4th dose at 2 years of age
  - **Safety** in the context of routine use, emphasis on meningitis and cerebral malaria
  - **Impact** on mortality (including gender specific) and severe malaria
- Goal to inform WHO policy recommendation on the use of the RTS,S/AS01 vaccine in young children in sub-Saharan Africa
- Vaccine will be piloted in Kenya, Malawi, Ghana

The 4 components of the MVIP

Vaccination

1

RTS,S/AS01 Implementation through EPI Programme

In selected areas

Evaluation

2

Pilot evaluation commissioned by WHO

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

3

Qualitative assessment (HUS) & economic analyses

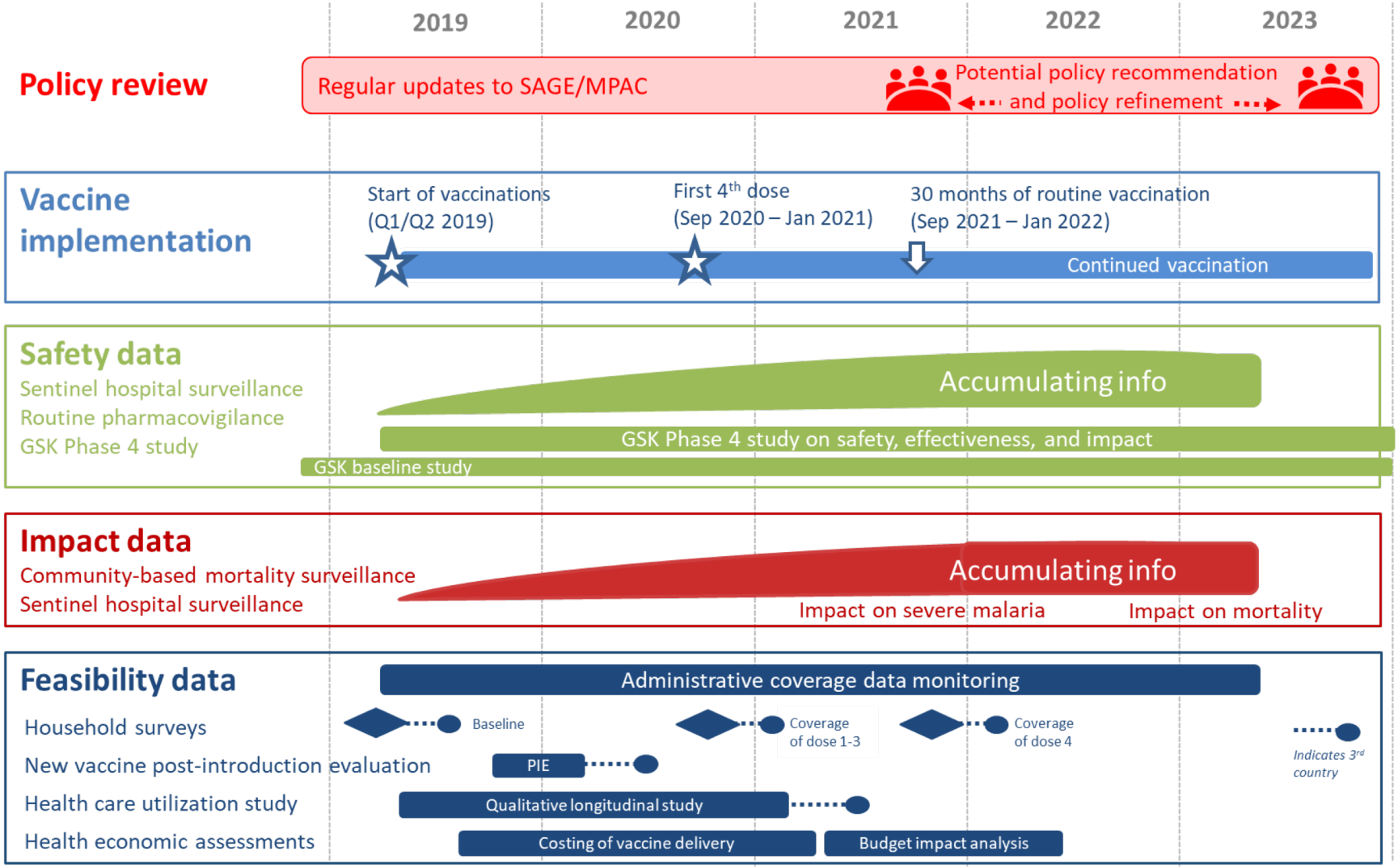
commissioned by PATH

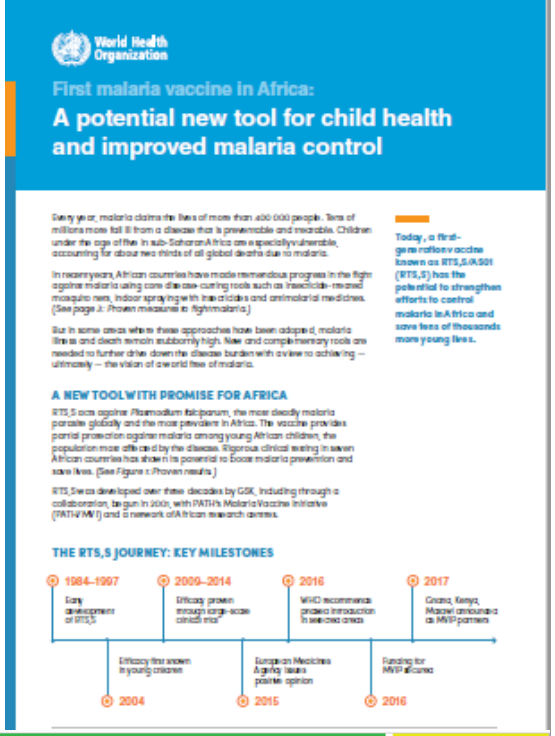
4

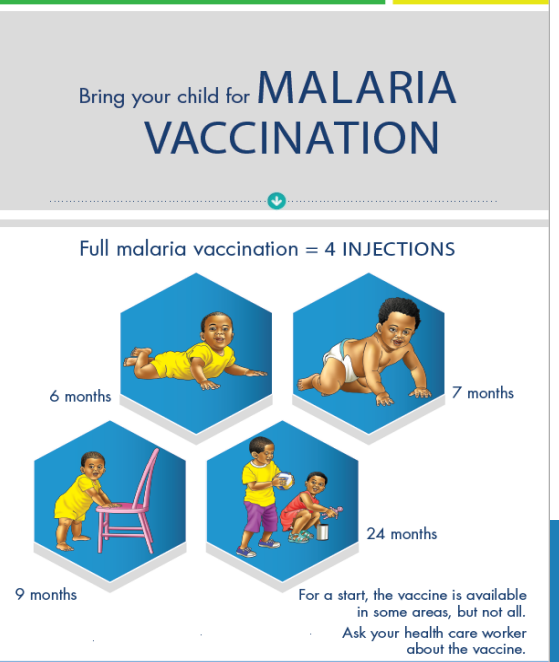
GSK Phase IV study

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

Timeline of MVIP evidence generation and review







Status: Global, regional, country communications

- General information about the MVIP on the WHO website
- Brochure on the MVIP
- FAQ about the MVIP
- FAQ about the RTS,S/AS01 Phase III trial results

Global and country level

- Crisis communication plan, table top exercise
- Launch plans, media engagement, spokesperson training
- Country level engagement with policy makers, including parliamentarian, opinion leaders, religious and community leaders, medical community
- Information, Education and Communication materials and training materials

World Health Organization

Framework for Policy Decision for RTS,S/AS01

- Framework seeks to guide how data collected through the MVIP will be used to inform a future policy recommendation on use of the RTS,S/AS01 malaria vaccine beyond the pilot
- Recommends the relative contribution to a future policy decision of data collected on feasibility, safety and impact

Working Group membership and representation

	Working group member	Representation
1	Fred Were	SAGE
2	Terry Nolan	SAGE member until Oct 2018
3	Gabriel Carrasquilla	MPAC
4	Umberto D'Alessandro	MPAC
5	Eusebio Macete	MVIP Programme Advisory Group (PAG)
6	Kim Mulholland	MVIP Programme Advisory Group
7	Peter Smith (Chair)	MVIP Programme Advisory Group
8	Quique Bassat	IVIR-AC
9	Melissa Penny	Modelers

Informing WG discussion: reviewed data and information to develop framework

- Existing data and information
  - Results from Phase 3 trial
  - JTEG report, SAGE/MPAC recommendation and WHO position paper
  - Prior vaccine policy decisions: Rotavirus, pneumococcal conjugate, and dengue vaccines case studies
  - Prior malaria intervention policy decisions: Insecticide treated nets (ITN), Intermittent preventive treatment in infants (IPTi)/pregnancy (IPTp)

Informing WG discussion: reviewed data and information to develop framework

- New data and information since the 2016 position paper recommending pilots:
  - MAL 076, long term follow up study results
  - Updated results from mathematical models by Imperial College / SwissTPH validated against MAL-076 data
  - Additional analysis of data from the Phase III trial (not shown)
  - Timeline estimating when data on RTS,S/AS01 safety, feasibility, impact will be available based on assumptions used for statistical analysis

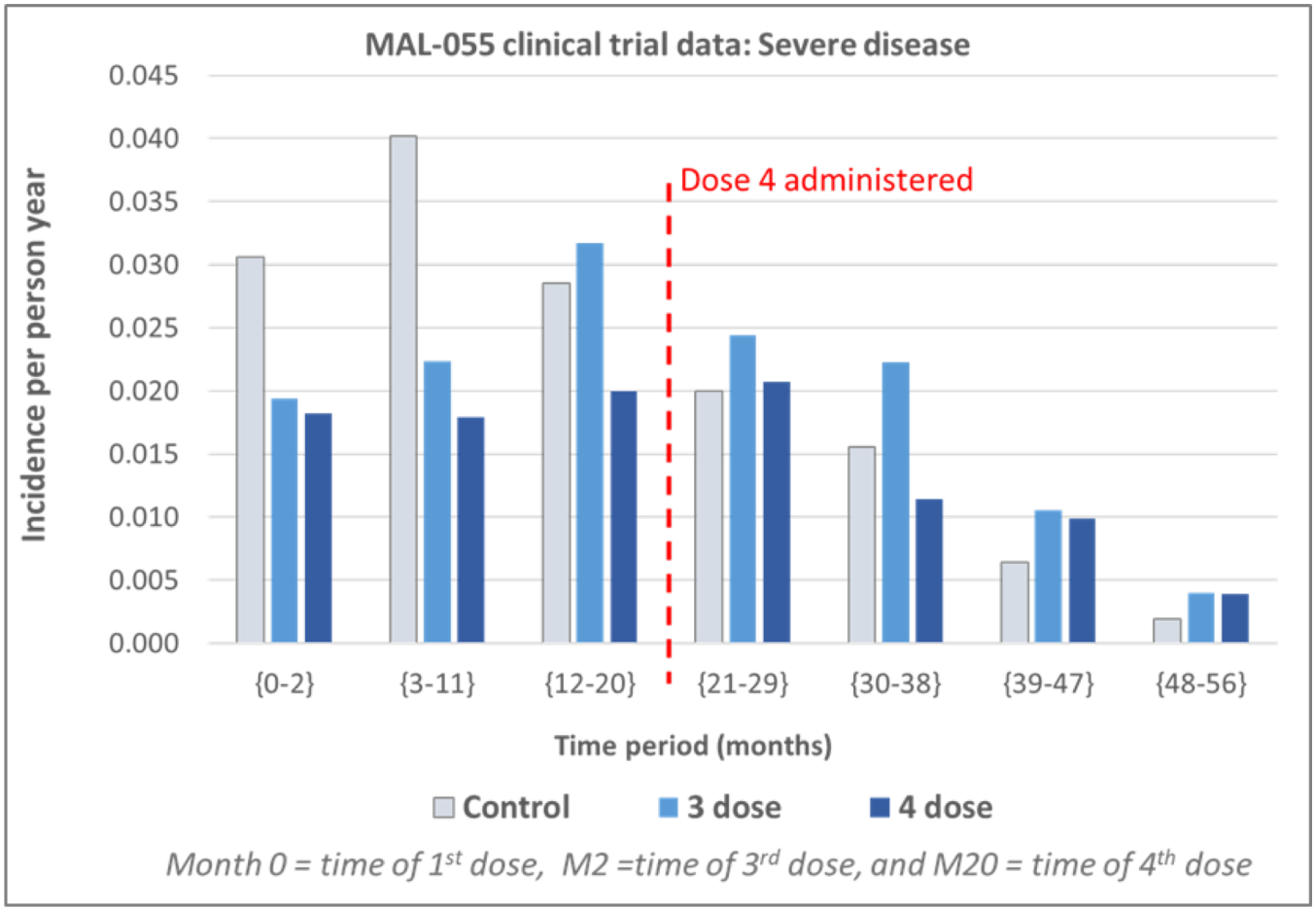
New data reviewed by the Working Group Mal 076, Long term follow-up

- Additional 3 years at 3/11 Phase III sites (7 years total)
- Korogwe (Tanzania), Kombewa (Kenya), Nanoro (Burkina Faso)
- Open label
- Data collection: mix of retrospective and prospective
- Overall vaccine efficacy during 7 year follow-up
  - Clinical malaria: 4 doses: 24% (95% CI:16, 31); 3 doses: 19% (95% CI: 11, 27)
  - Severe malaria: 4 doses: 37% (95% CI: 15, 53); 3 doses: 10% (95% CI: -18, 32)
- No excess cases of severe malaria (rebound) in any group
  - Any rebound in severe malaria that may have occurred in 3-dose group was time-limited
  - No rebound after 4th dose
- Very few severe malaria cases after 4 years follow-up
- No imbalance in safety signals or deaths during long term follow-up

Conclusions from the Malaria Policy Advisory Committee (MPAC) on Mal076 long term follow-up data, Oct 2018

- For children living in areas with moderate to high perennial malaria transmission who receive three or four doses of RTS,S, the benefits appear to last over at least seven years after vaccination and they do not have an excess risk of clinical or severe malaria
  - Apparent rebound after 3 doses was time limited
  - No observable rebound after 4 doses
- This important result provides further reassurance on the safety profile of the vaccine
- Other approaches to control malaria should accompany use of the vaccine

Mal055 clinical trial results: severe malaria incidence/person-year, 8-monthly intervals



Severe disease incidence per person year (MAL 055, aggregated over all clinical trial sites for 5-17 month cohort ITT population) plotted every 8 months after dose 1 is administered. A difference between the 3-dose and 4-dose groups is apparent before the fourth dose is given. Further analysis by GSK indicates this difference is likely to have arisen by chance.

Source: Modelling groups with permission from GSK

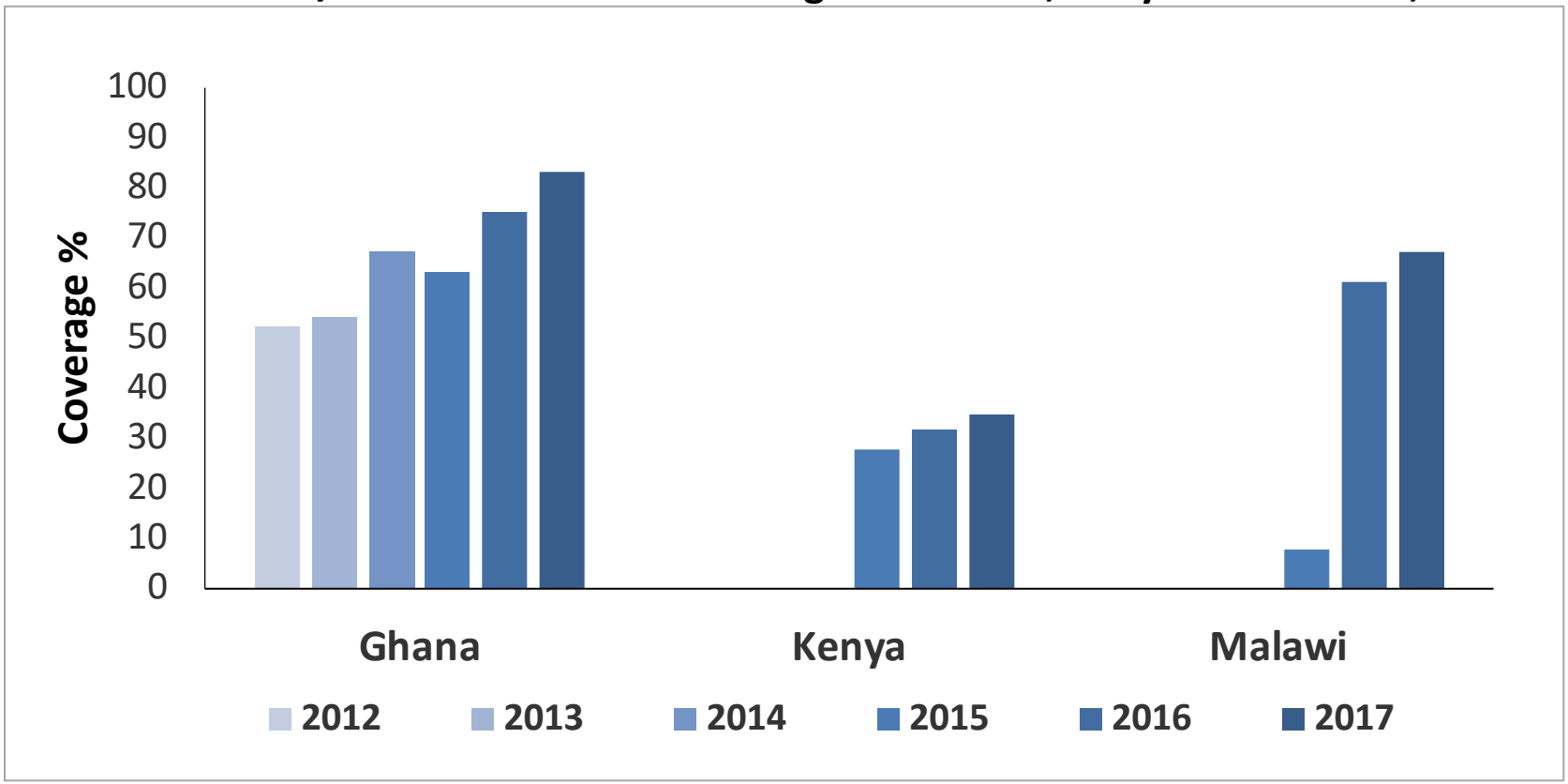
Modeling results consistent with Mal 076

- Modeling based on clinical malaria incidence from Phase 3 trial
  - Severe malaria modeled
- Validated with Mal 076 data
- Unable to reproduce extent of rebound observed in the Phase 3 trial
- Suggest fourth dose provides minimal added benefit to that provided by 3 doses
- Modeled estimates show impact dependent on
  - Parasite prevalence
  - Coverage with first 3 vaccine doses

Operational feasibility:

Expected new vaccine coverage & trajectory over time

MCV2 WHO/UNICEF estimated coverage* in Ghana, Kenya and Malawi, 2012-2017



*according to WHO/UNICEF coverage estimates, as of 15 July 2018

Working group review of estimated availability of pilot evidence

- Based on current assumptions:
  - Expected rate of accumulating events (as in protocol and Framework Policy Decision document)
  - Vaccine introduction timings (pilot introductions within 6 months)

- Updated calculations will be done when preliminary data on actual event rates are available, 4-5 months after vaccinations start
  - Estimates, case definitions, and indicators to be included in MVIP Statistical Analysis Plan, under development.

Expected **safety** data availability 24 months after first pilot country begins vaccinations

1. Meningitis (assume 0.4/1000/year):
   - 80% power to rule out a 3-fold or greater increased rate of meningitis associated with introduction of RTSS vaccine
   - Phase 3 trial results: 10-fold increase
2. Cerebral malaria (assume 2/1000/year):
   - 90% power to rule out a 2-fold or greater increase in risk of cerebral malaria
   - Phase 3 trial: 2-fold increase
3. Sex-specific mortality (assume mortality rate 8.5/1000/year):
   - 90% power to exclude female:male mortality ratio being 20% higher in the RTSS arm than in the control arm
   - Phase 3 trial: 1.9-fold increase

Expected **impact** data availability 24 months after first pilot country begins vaccinations

1. Severe malaria (assume incidence rate 2/1000/year):
   - >80% power to detect a 30% reduction in severe malaria by month 24 (data for all sentinel hospitals, all countries combined)
   - Phase 3 trial results: 29% reduction over 48 months with 4 dose schedule
2. Mortality (assume mortality rate 8.5/1000/year):
   - >80% power to detect a reduction in mortality by month 24 if the true reduction is 10%, (for all analyses, data for all countries combined)
   - Phase 3 trial results: no reduction/ not designed to measure impact on mortality

Recommendations of the SAGE/MPAC Working Group (WG) on the Framework for Policy Decision on RTS,S/AS01

Peter Smith

Working Group Chair

Working Group approach – hierarchy of data

SAFETY

Reassuring safety data are considered of primary importance and pre-condition for a positive policy recommendation

IMPACT

Data trends assessed as consistent with a beneficial impact of the vaccine for:

- **Impact on severe malaria:** an acceptable surrogate indicator for impact on mortality

or

- **Impact on all-cause mortality**

FEASIBILITY

Recommendation for broader use of RTS,S/AS01 need not be predicated on attaining high coverage including coverage of the 4th dose

Working Group approach – thought experiment

- Data on RTS,S/AS01, including Phase 3 trial results, were assessed by the EMA in 2015 and vaccine was given a "positive scientific opinion"
- Safety signals from Phase 3 trial were extensively discussed by SAGE/MPAC. It is possible that the SAGE/MPAC would have recommended the vaccine in 2016 had it not been for these signals
- WG took position that if data accumulate in MVIP to provide reassurance the safety signals observed in Phase 3 trial were likely due to chance, and impact on severe malaria or impact on mortality data trends were assessed as consistent with a beneficial impact of the vaccine-- it might be possible to make an initial recommendation for broader use before end of the MVIP
- Option would remain to refine the policy recommendation, if appropriate, when the full MVIP data set becomes available
- This strategy could accelerate the availability of a potentially life-saving vaccine

Recommendation 1: **SAGE and MPAC should consider recommending a step-wise approach for review and policy decision on broader use of RTS,S/AS01 based on emerging data from pilot studies**

Step 1: Recommendation on use of RTS,S/AS01 beyond pilot countries could be made if:

i. concerns regarding **safety signals** observed in Phase 3 trial (meningitis, cerebral malaria and sex-specific mortality) are satisfactorily resolved, by demonstrating either the absence of a risk of an important size, or an assessment of a positive risk-benefit profile despite adverse event(s); and

ii. severe malaria trends are assessed as consistent with a beneficial impact; or

iii. mortality data trends are assessed as consistent with beneficial impact

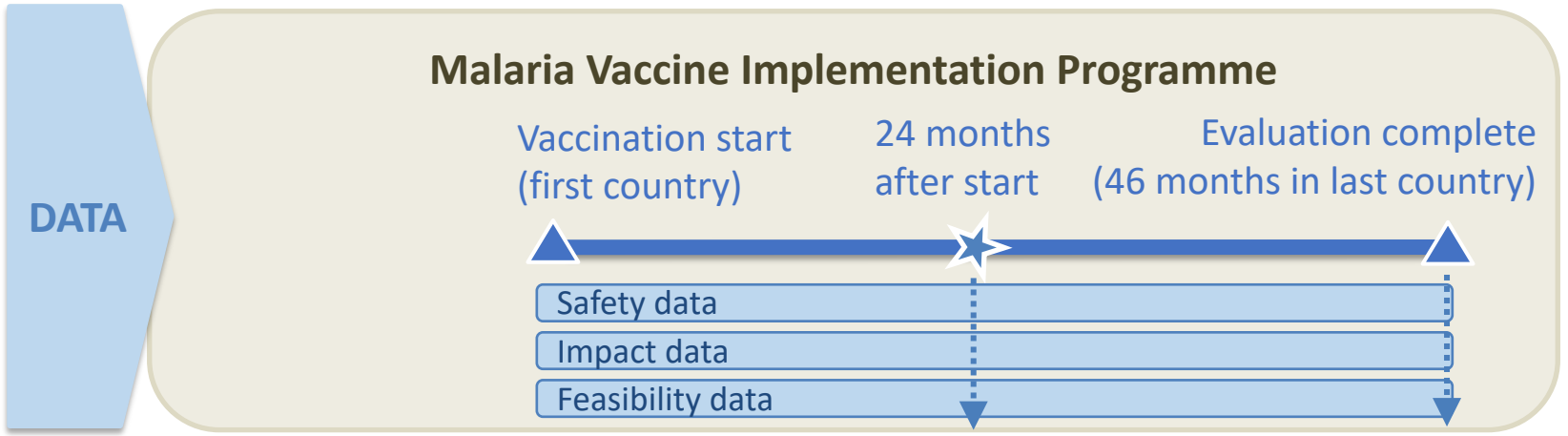
Based on current assumptions related to vaccine introduction timings and expected rate of accumulating events, such data on safety and impact would be available approximately 24 months after RTS,S/AS01 introduction

Recommendation 1: **SAGE and MPAC should consider recommending a step-wise approach for review and policy decision on broader use of RTS,S/AS01 based on emerging data from pilot studies**

Step 2: Adjustments or refinements to policy recommendation for broader use of RTS,S/AS01 based on final MVIP data set, with particular focus on the value of fourth dose

Available approximately 50 months after start of vaccination in 3rd country

Proposed step-wise approach to policy recommendation



2017	2018	2019	2020	2021	2022	2023

POLICY

1

Policy recommendation for broader use if and when:

i. Concerns regarding safety signals satisfactorily resolved; and
ii. Severe malaria data trends assessed as *consistent with a beneficial impact* of the vaccine; or
iii. Mortality data trends assessed as *consistent with beneficial impact* of the vaccine

2

Adjustments or refinements to policy recommendation if needed based on the final MVIP data set

Rationale for step-wise approach

- A decision on the broader use of a potentially life-saving vaccine beyond the pilot countries should be made at earliest possible timepoint when robust evidence is available to ascertain a positive risk-benefit profile of the vaccine
- Framework for Policy Decision seeks to reduce some uncertainty around the timing of a policy recommendation, which will facilitate advanced planning for potential outcomes, including:
  - An advanced signal to the manufacturer, that may be needed to maintain vaccine production and increase the likelihood of uninterrupted supply
  - A trigger for financing mechanisms to be in place should there be a recommendation for broader use of RTS,S/AS01

Recommendation 2: **There is a need to resolve safety concerns on meningitis, cerebral malaria, and sex-specific mortality to establish the risk-benefit profile of the vaccine, as reassuring safety data are required for a policy recommendation.**

- **Mechanism to resolve safety concerns:**
  - Data from sentinel hospitals in MVIP
  - GSK Phase 4 study (set up following EMA favourable assessment)
  - Routine pharmacovigilance reporting of AEFI and pre-specified AESI
  - All subject to ongoing review by DSMB
- **Estimated data availability:**
  - Assuming no true excess risk of meningitis, cerebral malaria or female mortality, relative risks of specified magnitude could be ruled out approximately 24 months after vaccine introduction
  - Updated timing if estimated event rates modified
- **Other considerations:**
  - If any excess risks observed, risk-benefit assessments necessary
  - Benchmarking against other vaccines with known risks (e.g. rotavirus vaccine risk of intussusception) would be useful

Recommendation 3: **The policy recommendation for broader use could be made in the absence of data showing vaccine impact on mortality.** Impact on severe malaria is an acceptable surrogate indicator for impact on mortality, and could support a policy recommendation if assessed as consistent with a beneficial impact.

- WG recommendations on impact on severe malaria and mortality align with MPAC recommendations made in Oct 2018, based on MAL 076
  - Concern regarding a potential excess risk of severe malaria in long-term follow-up of children who miss 4th dose has been reduced
- **Estimated data availability:** Data on the impact on severe malaria may be available approximately 24 months after vaccine introduction
  - Unlikely that a 10% country-specific impact on mortality demonstrable before pilot evaluations end
- **Policy precedence:** SAGE has not required demonstration of mortality impact for other vaccines prior to making initial recommendation for vaccine use. Data on mortality impact have resulted in modifications of recommendations.
- **Other considerations:** Impact of vaccine on severe malaria would not necessarily be the same in programmatic implementation as in the Phase 3 trial

Recommendation 4: **A policy recommendation for broader use of RTS,S/AS01 need not be predicated on attaining high coverage (including coverage of the fourth dose).**

- MAL-076 long-term follow up data indicate
  - rebound in severe malaria among children who received only 3 doses of RTS,S/AS01 was time limited
  - absence of rebound after 4th dose
- **Policy precedence:**
  - Implementation data are rarely available at time of initial vaccine policy recommendation, rather findings from post-marketing studies are incorporated later
- Target threshold for vaccine coverage (incl. 4th dose) should not be defined to inform a policy decision.
  - Vaccine coverage attained, and methods used to increase coverage, can be used to guide future strategies for improved vaccine implementation

Recommendation 5: **Barring substantial adverse impact on coverage of other vaccines or malaria control interventions, effect of RTS,S/AS01 introduction on coverage of these interventions should not influence policy recommendation.** Rather these indicators should inform strategies for implementation, including areas to call attention or provide opportunities for improvement.

- RTS,S/AS01 is proposed as complementary to other malaria interventions
- RTS,S/AS01 immunization regimen provides new contacts for children in 2YOL, providing opportunities to increase coverage of other childhood vaccines and enhance delivery of other malaria interventions
- MVIP includes interviews of parents and health workers to understand the obstacles and opportunities for vaccine delivery
- Reduction in health intervention uptake, coverage or use associated with vaccine introduction could be addressed with targeted interventions and/or messaging

Recommendation 6: **Cost-effectiveness estimates should be regularly refined, as data become available for increasingly precise calculations, and presented at appropriate time points.**

- Cost-effectiveness of RTS,S/AS01 was assessed as favourable compared to that of several other vaccines
  - RTS,S/AS01 is expected to be highly cost-effective in moderate to high malaria transmission settings alongside other malaria interventions
- **Policy precedence:** Cost-effectiveness is rarely incorporated into an initial vaccine policy recommendation for broader use
- Need to validate and/or update existing modelled estimates on public health impact and cost-effectiveness
- Cost-effectiveness estimates for SAGE/MPAC should be refined as more data become available from MVIP

Recommendation 7: **Expansion within MVIP countries should be synchronized with recommendation for broader use across sub-Saharan Africa.**

- In MVIP, vaccine deployment for 30 months (minimum):
  - MVIP countries could decide to continue vaccinations, as any pause is detrimental to programme operations and community mobilization
  - Vaccination in comparison areas advised by the WHO Ethics Committee
- There should be regular SAGE/MPAC briefings on plans for vaccine expansion
- Provided there is sufficient vaccine supply, NRAs are in agreement, and a positive risk/benefit profile is maintained, vaccine should not be withheld from comparison areas until after MVIP end
- Important to address risk of vaccination interruption in advance, due to time required for decision making, financing, vaccine availability, and implementation planning
  - Creative mechanisms should be considered to ensure supply and funding are available

Recommendation 8: **In the context of step-wise approach to policy recommendations, the pilots should continue through to completion of data collection to establish the public health value of the fourth dose, including assessment of the vaccine's impact on mortality.**

- The MVIP should continue to generate data through end of evaluation (expected to be 46 months in each country)
  - Regardless of whether an earlier policy recommendation is provided (barring a safety concern resulting in stopping MVIP)
- If it is found upon completion of the Programme that the 4th dose provides little incremental benefit, the initial recommendation could be modified (e.g. to a 3-dose regimen)

Recommendation 9: **Conflicting data among MVIP countries would require careful investigation into the reasons for differences.** Continue forward with plans for analysis even if data are delayed or not available in all countries.

Recommendation 10: **Criteria are suggested that could result in WHO not making a recommendation for use of vaccine in routine immunization programmes or deferring a policy decision to a later time point.**

- To *not make a recommendation* if:
  - there is a clear safety risk (e.g. an excess of meningitis among those vaccinated) assessed to be unfavourable in context of risk-benefit profile, or
  - there is something in the risk-benefit profile that could critically undermine the confidence and trust in national immunization programmes
- To *defer a decision* to the end of the pilot evaluations if:
  - there is significant uncertainty about safety issues (meningitis, cerebral malaria, sex-specific mortality), or
  - much less than expected impact on hospitalized malaria

Conclusion

- Value of Framework as future reference depends on joint support from SAGE/MPAC
  - MPAC members invited to join today's discussion
  - MPAC requested to provide formal endorsement of Framework in its meeting next week
- SAGE/MPAC endorsement of the proposed Framework would imply
  - Once data described for step 1 is available, SAGE/MPAC would be requested to consider a policy recommendation for broader use of RTS,S/AS01 in sub-Saharan Africa
  - Regular update on MVIP progress will continue to be provided

Thanks & Acknowledgements

Working Group members

- Quique Bassat
- Gabriel Carrasquilla
- Umberto D'Alessandro
- Eusebio Macete
- Kim Mulholland
- Terry Nolan
- Melissa Penny
- Peter Smith (Chair)
- Fred Were

Partners

- Cynthia Bergstrom
- Rebecca Casey
- Azra Ghani
- Scott Gordon
- Alexandra Hogan
- Farzana Muhib
- Laurence Slutsker
- Ryan Thompson
- Jenny Waldorf

Back-up

Expert review: Treatment assignment *per* study period for all "Confirmed" cases of cerebral malaria (n=23)

Study period (Month)	R3R+R3C	R3R	R3C	C3C
M0-20	--	2	6	4
M21-SE	--	3	6	2

23/340 (6.8%) cases where at least one expert felt that it was a case of cerebral malaria (*i.e.* the **18** cases where both experts agreed/assessed as "Confirmed" plus **5** cases where there was disagreement but at least one assessor felt that it was a case of cerebral malaria).

Expert Review: Treatment assignment *per* study period for all "Possible" cases of cerebral malaria (*i.e.* n=37)

Study period (Month)	R3R+R3C	R3R	R3C	C3C
M0-20	--	3	10	7
M21-SE	--	7	8	2

37/340 (10.9%) cases where either both experts agreed that they were cases of cerebral malaria (*n=18*) **or** both experts were uncertain/could not rule-out whether it was a case of cerebral malaria or not (*n=13*) **or** both experts disagreed but at least one expert felt that it was a case of cerebral malaria or was uncertain/could not rule it out (*n=6*).

Imbalance in 3 and 4 dose group prior to 4th dose provided

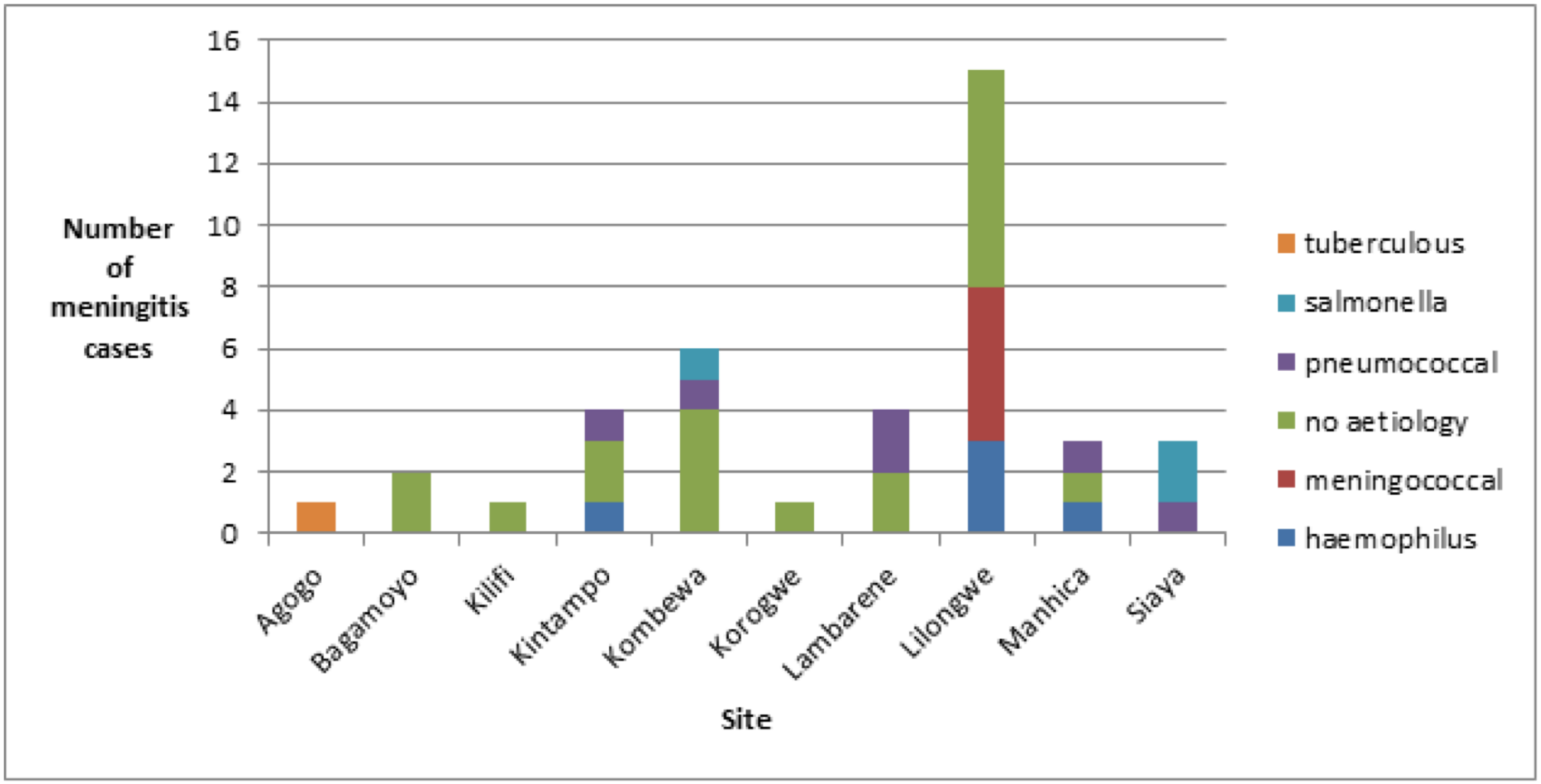
Source: JTEG Background paper (Sept 2015)

Serious Adverse Events: Meningitis 5-17 Months Group

5-17 month age group	4 dose schedule N=2976		3-dose schedule N=2972		Controls N=2974	
	n	%	n	%	n	%
At least one SAE	**720**	24.2	**752**	25.3	**846**	28.4
At lease one SAE excluding malaria	**673**	22.6	**704**	23.7	**784**	26.4
Fatal SAE	**61**	2.0	**51**	1.7	**46**	1.5
At least one related SAE	**8**	0.3	**4**	0.1	**1**	0.0
Meningitis (any pathogen)	**11**	0.4	**10**	0.3	**1**	0.0

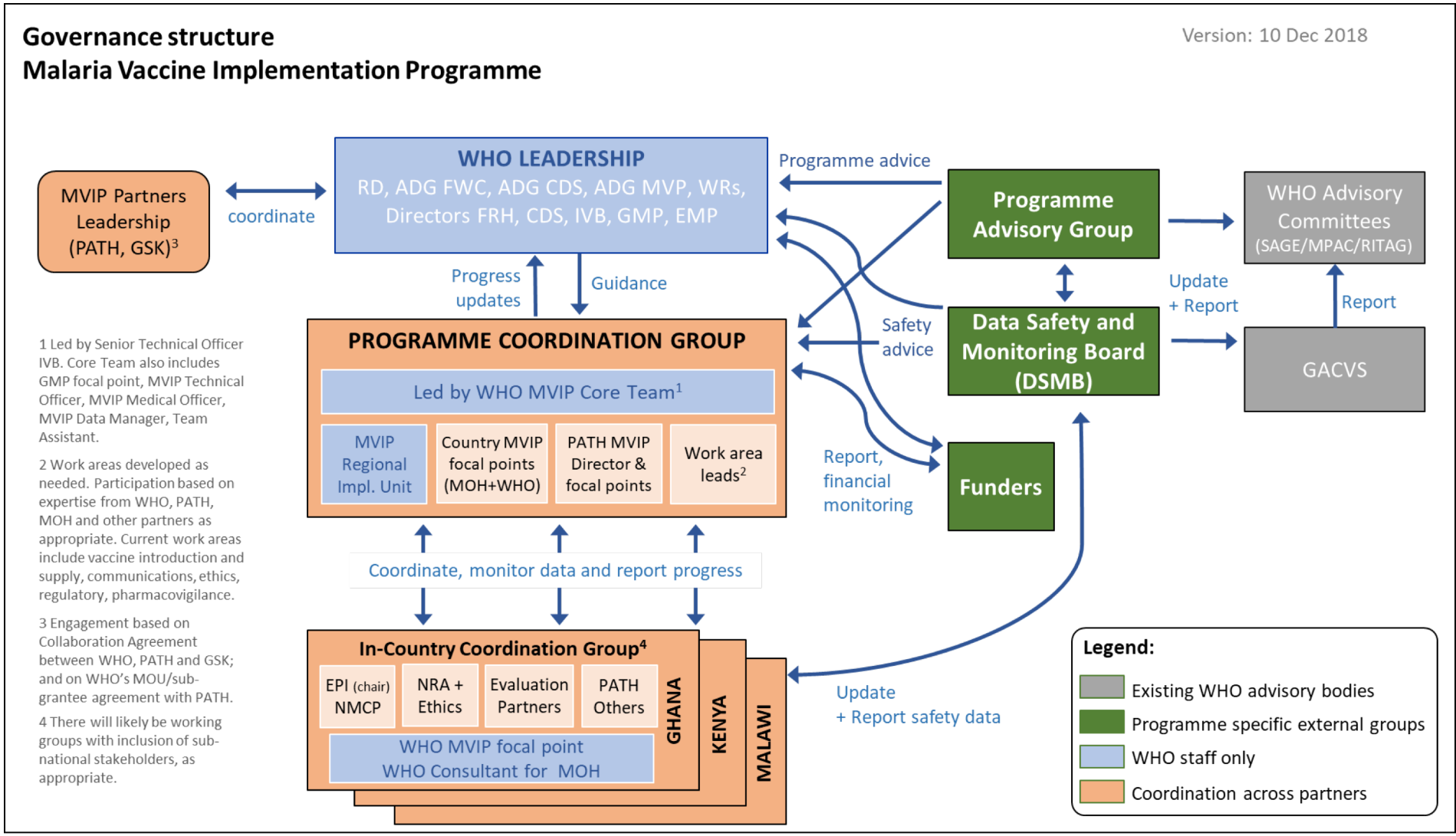
Low number of meningitis cases in control arm of 5-17 month olds age-category

Meningitis cases by site and etiology



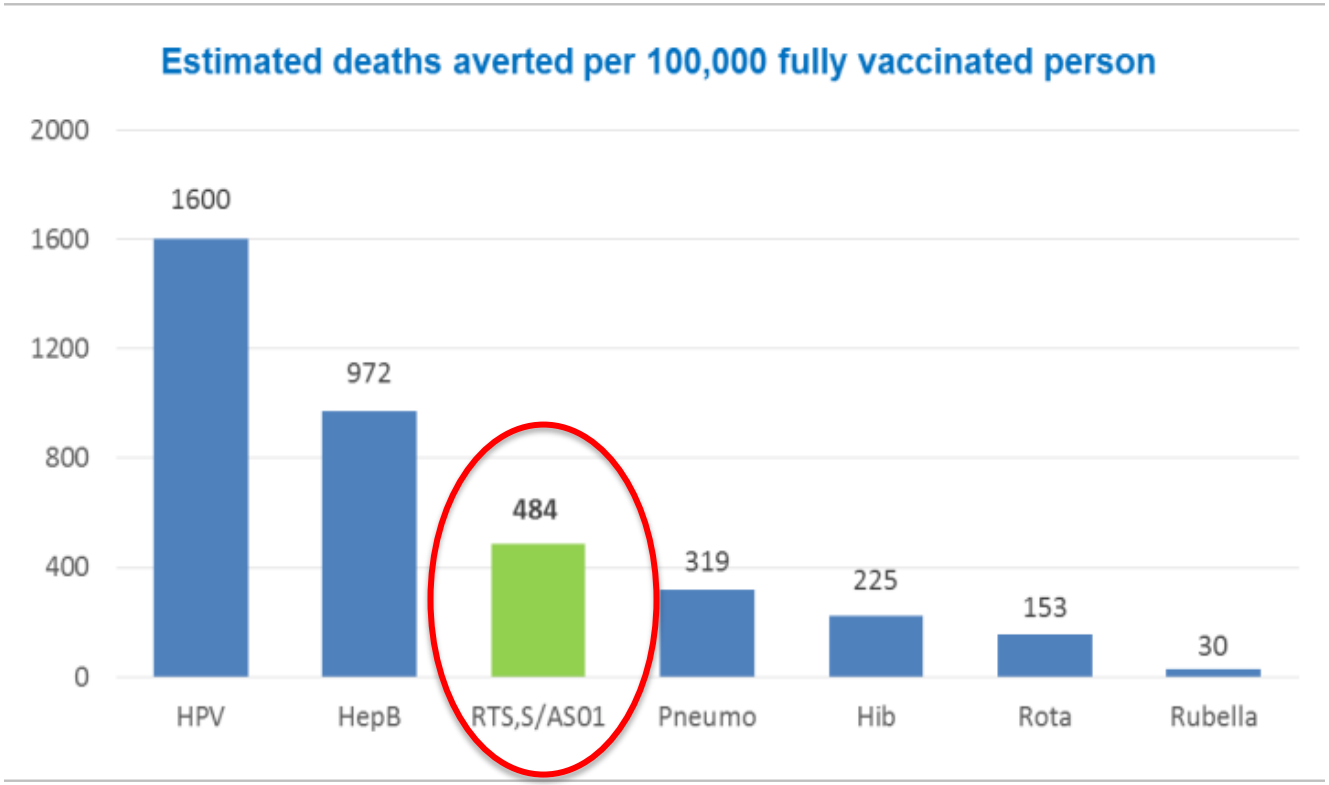
World Health Organization

MVIP Governance and Coordination



World Health Organization

Potential number of deaths averted per 100,000 fully vaccinated persons compares favorably with other Gavi-supported vaccines



Source: For RTS,S/AS01: Penny MA, Verity M, Bever CA, et al. Public health impact and cost-effectiveness of RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. Lancet 2016.
All other vaccines: Estimated deaths averted per FVP over 2015-2030 based on Gavi Strategic Demand Forecast v.11, 2014 impact analysis

Models indicate RTS,S is cost-effectiveness

- At **a hypothetical** vaccine price of $5 a dose median incremental vaccine cost effectiveness ratio is
  - **$87 (range $48-$244) per DALY averted**
  - $25 ($16-$222) per clinical case averted.
- **RTS,S compares favourably relative to global cost effectiveness estimates of several other vaccines.**

Penny MA et al. Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. 2015, Lancet, Vol. 15, pp. 0140-6736

MVIP evaluation partners

Ghana	Kenya	Malawi
Kintampo Health Research Centre (KHRC)	**National Foundation for the Centers for Disease Control and Prevention, Inc. (CDC Foundation)**	**The College of Medicine**
Navrongo Health Research Centre (NHRC)	**The U.S. Centers for Disease Control and Prevention (CDC)**	Malawi-Liverpool-Wellcome Trust Clinical Research Programme (MLW)
Research and Development Division (RDD) of Ghana Health Service	The KEMRI-Wellcome Trust Research Programme (KWTRP)	The University of North Carolina Project Malawi (UNCPM)
University of Ghana School of Public Health Malaria Research Centre, Agogo Presbyterian Hospital	The Walter Reed Project (WRP)	
University of Health and Allied Services (UHAS)	The Kenya Medical Research Institute (KEMRI)	
Noguchi Memorial Institute for Medical Research		

Integration of RTS,S/AS01 into the childhood vaccination schedule

The upper part of the table reflects Ghana's vaccination and Vitamin A schedule

WHO position : A 4-dose schedule is required, with the first dose given as soon as possible after 5 months of age, doses 2 and 3 given at monthly intervals, and the fourth dose given 15–18 months after the third dose .

Child Age / Vaccine/1	Birth	6 wks	10 wks	14 wks	5 mo	6 mo	7 mo	9 mo	12 mo	18 mo	22 mo	24 mo
BCG	1											
Oral polio	0	1	2	3								
DTP-HepB-Hib (penta)		1	2	3								
Pneumococcal conj.		1	2	3								
Rotavirus		1	2									
Inactivated Polio				1								
Meningococcal A conj.										1		
Measles-Rubella								1		2		
Yellow Fever								1				
Vitamin A						1			2	3		4
RTS,S in Ghana						1	2	3				4
RTS,S in Kenya						1	2	3				4
RTS,S in Malawi					1	2	3				4	

Programme Advisory Group members

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Fredrick Were	Vaccine and immunization research, child health, SAGE

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