Appendix 3: Malaria

Vaccine Investment Strategy
Programme & Policy Committee Meeting
18-19 October 2018

Agenda

1. Executive summary
2. Modelled vaccination strategies
3. Demand forecast
4. Impact
5. Disease overview
6. Vaccination policy
7. Vaccine landscape
8. Resources

Glossary of Terms

Vaccination schedule	The number of doses and timing of their administration
Age group	Age at which vaccination will be administered
Country scope	Number of Gavi-supported countries included in forecast for vaccine introductions[1]
Target population	Specific population targeted to receive the vaccine
Delivery strategy	Implementation approach or programme in which vaccination will be incorporated
Introduction dates	Forecasted introduction year of vaccine in a country
Vaccine uptake	Time to ramp up to maximum coverage in target population
Coverage	Coverage assumption or analogue and yearly increase
Products	Date of WHO pre-qualification, number of doses per vial and other product-specific characteristics
Logistics	Wastage assumption[2] based on vial size and presentation, and buffer stock factored into demand
Efficacy / effectiveness	Best available information on vaccine efficacy / effectiveness
Duration of protection	Best available information of loss of protection from time of vaccination
Burden of disease	Burden of disease dataset(s) that is/are being used for modelling health impact
Currency	All monetary values are presented in US$

1. Not all countries in scope may be forecasted to introduce within the timeframe and not all countries in the forecast may benefit from Gavi financing based on the Eligibility and Transition Policy 2. Vaccine wastage assumptions from WHO

1

Executive Summary

Malaria special considerations

Consideration in VIS 2018

- No investment decision: Malaria vaccine used as a comparator to other VIS candidates and to maintain visibility to future opportunity. Future Gavi investment decision will follow potential future WHO recommendation based on data from the pilots in Kenya, Ghana and Malawi.

Modelling considerations

- For the VIS 2018 investment case phase (Nov 2018 Board): Updated demand/supply forecast and impact modelling.
- Results more consistent with analysis for the rest of the vaccines in VIS 2018.

Main changes from June 2018 analysis:

- Definition of fully vaccinated person (FVP): 4 doses
  - The change in definition of FVP (from 3 doses to 4 doses) results in a change in the denominator being used to calculate the events averted per 100,000 FVP. Due to the assumed drop-out rate between doses 3 and 4, fewer children are defined as being FVP in the VIS 2018 estimates
  - By spreading the impact of the vaccine over a smaller denominator (children receiving the fourth dose) the estimates of events averted per 100,000 FVP will be higher than if the definition had remained the same
- Updated parasite prevalence data and projections, ITN coverage, population figures, country introduction dates
  - Updated parasite prevalence shows there were more children living in low- to moderate-transmission settings (i.e., *Pf*Pr of 10% to 25%) in 2014 than in 2016, likely due to reductions in *Pf*Pr in many countries over the period
  - The proportion of children living at *Pf*Pr of 25% or greater stayed the same between 2014 and 2016, however, the greater absolute number of children living at these higher *Pf*PR thresholds in 2016 likely resulted in a greater absolute number of children at risk for age shift in disease

Malaria executive summary

Malaria causes ~445,000-720,000 deaths annually and ~210-216M cases, mostly in African children under 5 years of age

- Species of malaria parasite most prevalent in sub-Saharan Africa, and responsible for the most deaths, P. falciparum is developing resistance to Artemisinin-based combination therapy (ACTs) and mosquito vectors are developing resistance to insecticide-treated nets (ITNs)

A vaccine (RTS,S/AS01) for *P. falciparum* is available and was recommended by WHO for pilot implementation in 2015

- Goal of pilot to asses (i) programmatic feasibility of delivering RTS,S in a 4 dose schedule, (ii) Vaccine impact on mortality, (iii) Vaccine safety in the context of a routine immunization program
- Efficacy: Among children aged 5–17 months who received 4 doses of RTS,S, the vaccine prevented 39% of cases of malaria over 4 years of follow-up
- In June 2016, Gavi Board agreed to fund 50% of Phase 1 Pilot (2017-2020)

Implementation in all African Gavi-eligible countries could avert between 254-516K deaths and 49-142M cases through 2035, at ~$ 4,250-5,281 procurement cost per death

- These results account for the use of existing malaria interventions
- Estimates may change based on data from the pilot countries (or from the MVIP)

Malaria Scorecard

Modelled strategy: Routine immunization with 4 doses at 5-17 months

VIS criteria	Indicator	Results	Evaluation[1]
Health impact	Total impact averted[1]	~254-516K future deaths averted, 49-142M cases averted, 2021-2035	
	Impact averted per 100K[1]	~417 – 489 deaths, ~98-111K cases averted, 2021 – 2035, per 100k vaccinated population	
Value for money	Procurement cost per event[1]	~$ 4,250-5,281 procurement cost per death, ~$ 16-27 procurement cost per case averted	
Equity & social protection impact	Impact on vulnerable groups	Burden concentrated among low socioeconomic groups, rural poor	
	Benefits for women and girls	No special benefits of vaccination for women and girls	
Economic impact	Direct medical cost averted	n/a	
	Indirect cost averted	n/a	
Global health security impact	Epidemic potential	Not IHR notifiable; changing phenotype and population at risk; vaccine interrupts human to host transmission (however RTS,S is not a transmission blocking vaccine)	
	Impact on AMR	High impact of vaccination on AMR (6.2/10 points in expert consultation)	
Vaccine cost	Total procurement cost	~$ 2 billion total procurement cost to Gavi and countries, 2018 – 2030	
Relevant second. criteria	Vaccine market challenges / Long-term financial implications	High acceptability and market challenges, but concerns about long-term financial implications	

Additional considerations

- No investment decision: Malaria vaccine used as a comparator as any future investment decision will follow potential future WHO recommendation based on data from the pilots in Kenya, Ghana and Malawi.
- Developing resistance to Artemisinin-based combination therapy (ACTs) and to insecticide-treated nets (ITNs)
- Ongoing pilot to asses (i) programmatic feasibility of delivering RTS,S at 4 dose schedule, (ii) Vaccine impact on mortality, (iii) Vaccine safety in the context of a routine immunization program

1. Evaluation based on comparison with other VIS 2018 candidates in June 2018, except for health impact and other impact which was updated in October 2018. For Health impact and Value for money, evaluation based on deaths averted. Details on evaluation methodology can be found in Methodology appendix from June 2018

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Secondary criteria and financial implications

Modelled strategy: Routine immunization with 4 doses at 5-17 months

VIS criteria	Indicator	Results	Evaluation
Other impact	U5 deaths averted, total	n/a	
	U5 deaths averted, per 100K	n/a	
	DALYs averted (cost per DALY)	~22-24 million DALYs averted, 2021 – 2035, ~$ 74-89 procurement cost per DALY	
	DALYs averted, per 100K	~25-27K DALYs averted, 2021 – 2035, per 100K vaccinated population	
Gavi comp. advantage	Vaccine market challenges	High potential to influence the market (e.g., foster competition, ensure availability of supply)	
	Catalytic investment	High potential to catalyse investments in existing interventions (e.g., ITNs)	
Implementation feasibility	Ease of supply chain integration	Packed volume of 9.9cc; 48 months shelf life at 2-8°C; VVM 14, placed on adjuvant AS01 vial	
	Need for HCW behaviour change	Some need for HCW behaviour change: Need to set up new program	
	Feasibility of vaccination time point	Existing access points, but new vaccination time-points	
	Acceptability in target population	Likely high acceptance (not included in survey), but limited efficacy might decrease demand	
	Long-term financial implications	Falls within the category of price per course >$ 5	
Alt. interventions	Alternative interventions	Prevention: IRS, ITNs, Chemoprevention; Treatment: Artemisinin-based combination therapy (ACT)	
Broader health system impact[2]	Broader health system impact	Opportunity to improve child health (nutrition interventions, deworming, treat diarrheal disease) and ANC/ PNC (opportunity to reduce maternal anaemia and low birth weight); potential reduction in ACT and ITN resistance	
Operational cost[3]	Incremental costs per vac. person	High incremental cost per vaccinated person	
Implementation costs	Additional costs for introduction	Medium: Tech. assistance, micro-planning; some demand generation and data-related costs	

1. Evaluation based on comparison with other VIS 2018 candidates, except for health impact and other impact which was updated in October 2018. 2. Broader health system impact is not evaluated for any vaccine. 3. Generic methodology based on routine campaigns. Details on evaluation methodology can be found in Methodology appendix from June 2018. 4. U5 impact not provided as age shifting skews results since not all cases and deaths are captured

Previous Gavi decisions regarding malaria

Gavi 2013 Board Decision

- Noted that based on the current assessment there is **a reasonable case** for Gavi support
- Will consider opening a window if and when vaccine is **licensed**, **recommended for use** by the joint meeting of the WHO SAGE and MPAC and WHO **pre-qualified**

Gavi 2016 Board Decision

In October 2015, due a due to outstanding questions related to the public health use of the vaccine, SAGE and MPAC **recommended pilot implementations** of RTS,S to assess:

- Programmatic feasibility of delivering RTS,S/AS01 in a 4 dose schedule
- Vaccine impact on mortality
- Vaccine safety in the context of a routine immunization programme

In June 2016, Gavi Board agreed to fund 50% of Phase 1 Pilot (2017-2020)

Malaria key assumptions

xx: included in model uncertainty range

Models

Swiss TPH

Imperial College London

Vaccination strategies

Surviving infants, 4 doses[1]

Uncertainty analysis driving ranges

Decay rate of vaccine efficacy
Differing assumptions across models on the decay rate of vaccine efficacy against infection for both the first three doses and the 4th dose will impact overall PHI as well as how much age-shift is predicted in the models

Outcome case Definitions
Different across the models

Disease burden estimates
Each model generates different disease burden estimates despite using the same parasite prevalence for a given area.

Other key assumptions

Efficacy:
Among children aged 5–17 months who received 4 doses of RTS,S, vaccine prevented approximately 4 in 10 (39%) cases of malaria over 4 years of follow-up

Duration of protection:
During the 12 months following dose 4, vaccine efficacy remained at 39% (95% CI, 32-44).

Coverage:
100-90-80 % of MCV1 (by order of the dose), 20% 4th dose drop out

1. All modelling have been done assuming a fully vaccinated child receives 4 doses

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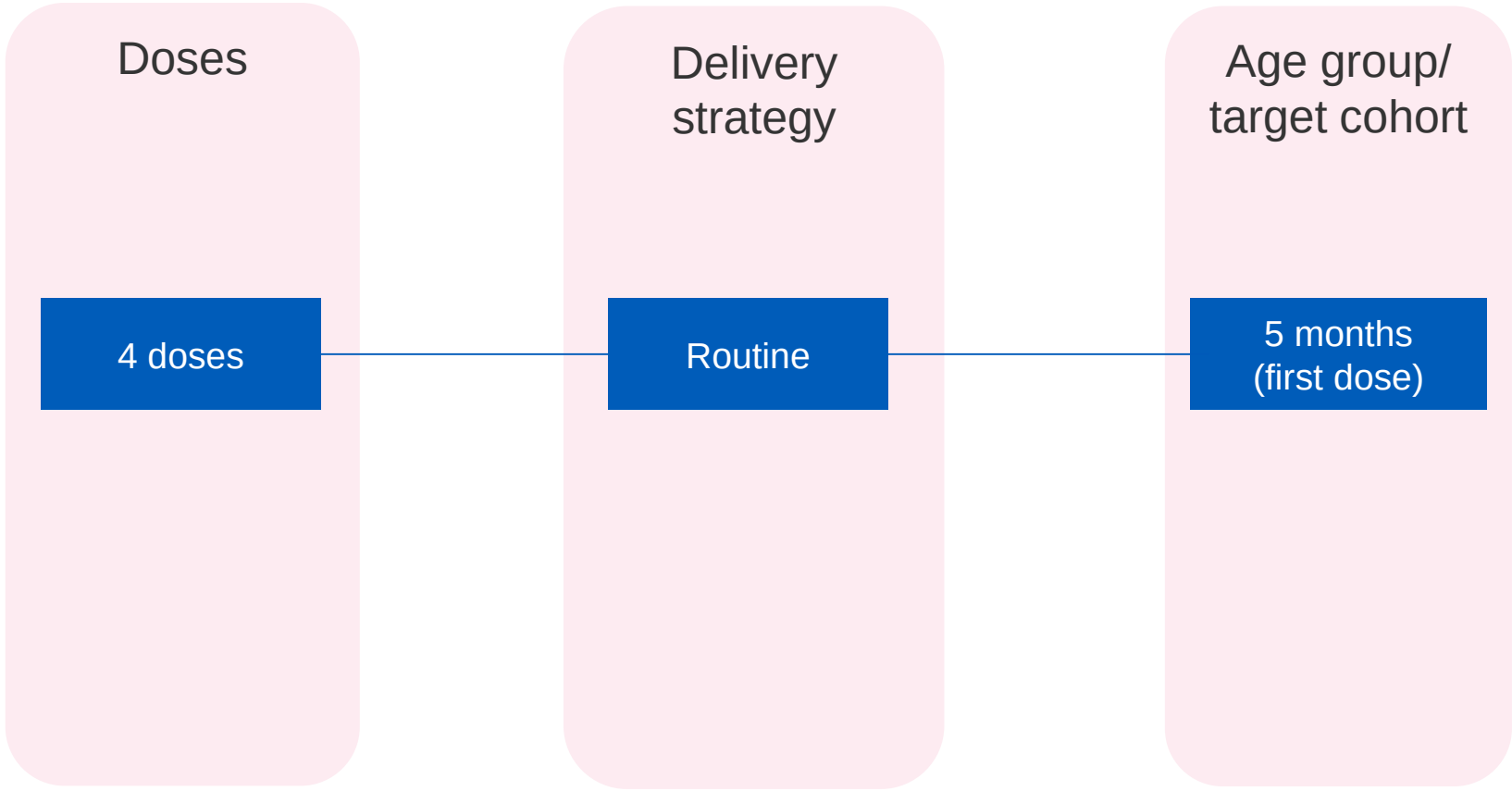
Modelled vaccination strategy

Malaria vaccination strategy



1. WHO-recommended vaccination schedule is 4 doses of malaria vaccine, first 3 doses from 5 – 9 months (one month interval between doses), 4th dose 15-18 months after administration of 3rd dose

Rationale for vaccination strategy

Element	Modelled strategy	Rationale / Source
Vaccination schedule	• 4 doses, first 3 doses from 5 – 9 months (one month interval between doses) • 4th dose 15-18 months after administration of 3rd dose	• 2016 WHO position paper
Age group	• Children 5 months	• 2016 WHO position paper
Target population	• Routine administration in all surviving infants (in Africa)	• Vaccine only tested for use in Africa • For current data- used UN WPP 2017 Medium Variant at national level and then distributed to admin1 level based on Malaria Atlas Project distribution of population

Assessment of uncertainty in demand and impact analyses

	Comments
Demand	• Wider range of plausible demand compared to some other vaccines due to the nature of assumptions required, e.g. parasite prevalence, subnational targeting, coverage • Challenging to estimate timing and pace of adoption given multi-step process to reach start of programme, and absent detailed country plans or applications for Gavi support to introduce
Price	• New product, with product transfer to unknown manufacturer post-2028 • Certainty on volume is needed to define actual price
Health impact	• High quality global data set of burden available, but each model generates different disease burden estimates despite using the same parasite prevalence for a given area • Estimates of age-shift in the models are influenced by assumptions on the duration of protection, the force of infection for underlying parasite prevalence assumptions and the age-pattern of disease. Differing assumptions by each model can lead to different estimates of age-shift. • Clinical data available that assesses efficacy of doses

High uncertainty | Medium uncertainty | Low uncertainty

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3

Demand Forecast

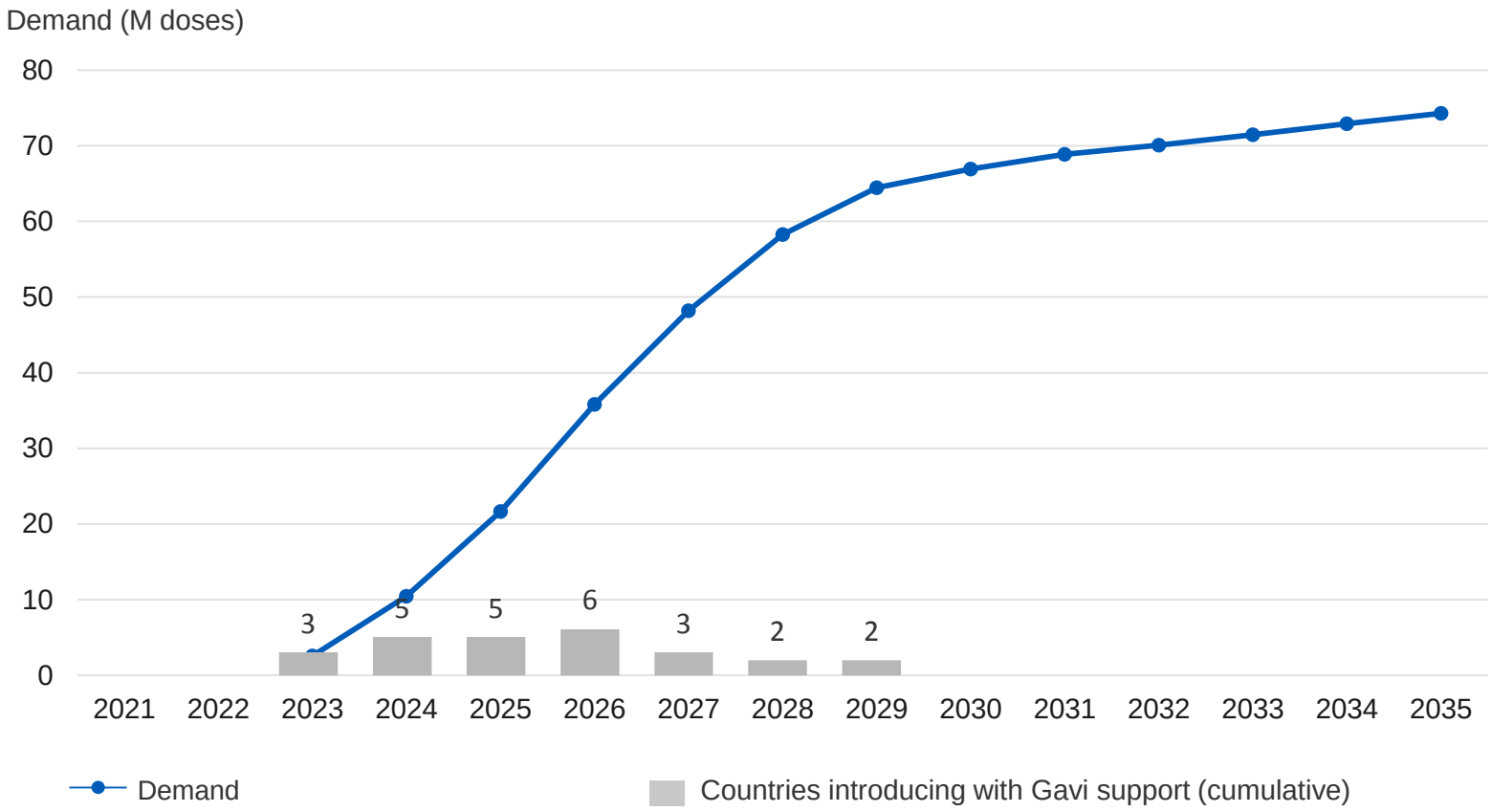
Demand forecasting assumptions

Element	Assumptions	Rationale / Source
Country scope	• 43 malaria endemic countries in Africa • 31 countries have subnational areas with parasite prevalence > 10% that are expected to introduce • 29 countries are in Gavi 73 • Generally forecasted at the admin1 (e.g., province) subnational level	• Gavi demand forecast updated in 2018 • Plasmodium falciparum malaria burden concentrated in Africa. No clinical trials outside of Africa
Target population	• Children 5-17 months	• 2016 WHO Position Paper
Delivery Strategy	• Routine	• 2016 WHO Position Paper
Introduction dates	• First introduction: 2023	• Gavi demand forecast updated in 2018
Vaccine uptake	Most countries 2 years; DRC/Nigeria up to 4 years if national programme	• Standard Gavi uptake assumptions for new vaccines
Coverage	100-90-80% of MCV1, respectively for doses 1-3, Coverage Dose 4= 20% (dropout from dose 3)	• Dose 1 anchored at MCV1 then loss at rate of 2x avg. DTP1 to DTP3 due to new visits needed; dose 4 loss > Ph3 study.
Products	PQ Date: TBD Schedule: 4 doses Presentation: 3-dose vial	
Logistics	• Wastage Factor: 1.11 • Buffer stocks = 25% of change in demand between years	• WHO wastage factor recommendations for 2-dose lyophilised presentation

Demand in countries that introduce with Gavi support ~666M through 2035[1]

Nigeria included

Scenario: 10% parasite prevalence threshold, 100-90-80% of MCV1 with 20% 4th dose dropout



Total cumulative demand from countries that introduce with Gavi support (2021-2035)

Base scenario **~666M**

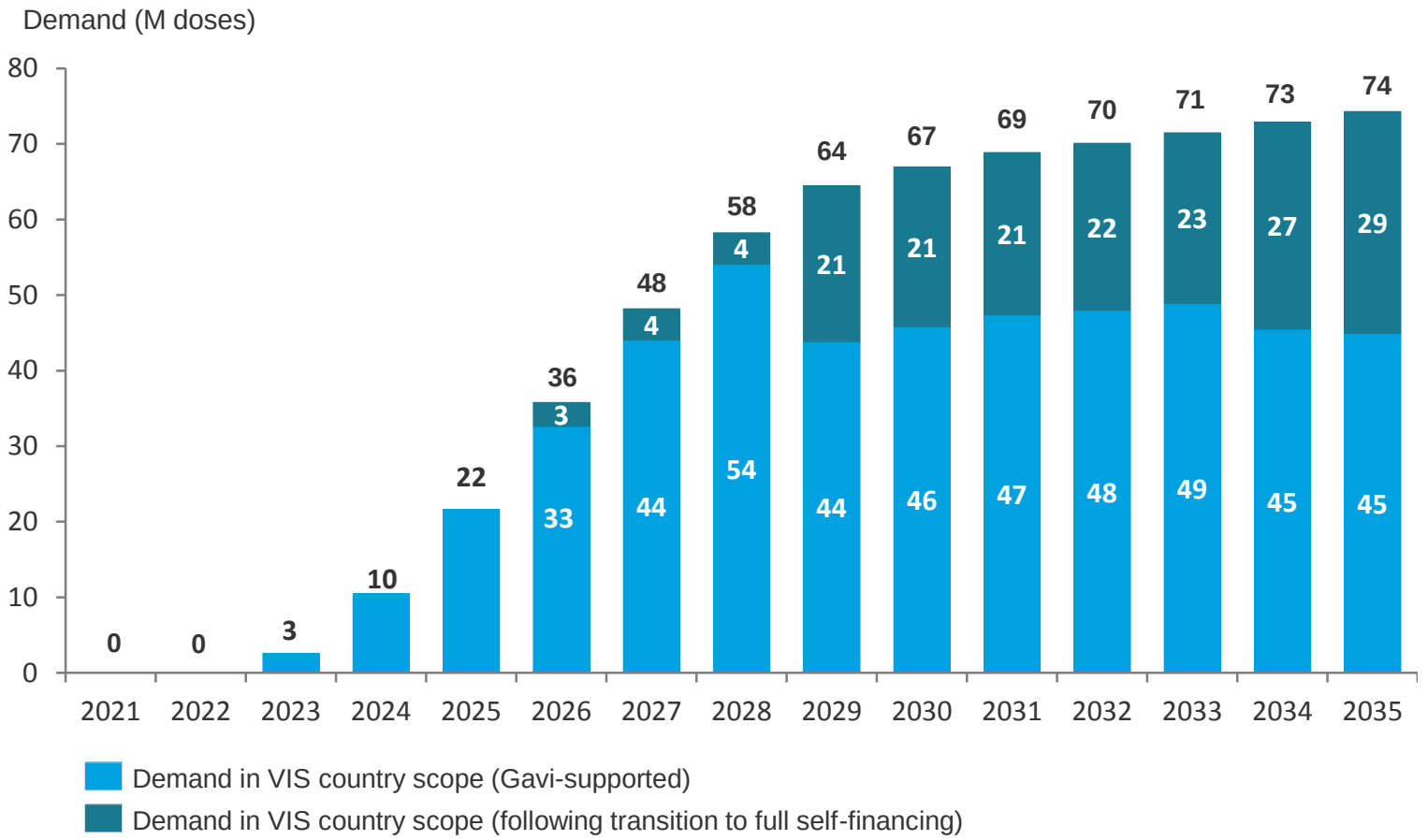
1. Based on Gavi's current eligibility and transition policy
Consideration for Gavi support to Nigeria for VIS candidates would be considered separately through the Nigeria-specific strategy which was approved by the Gavi Board in June 2018

Gavi anticipates supporting up to ~490M doses from 2021-2035

Nigeria included

Countries supported by Gavi for introduction

Scenario: 10% parasite prevalence threshold, 100-90-80% of MCV1 with 20% 4th dose dropout rate



Total cumulative demand from countries that introduce with Gavi support (2021-2035)

Gavi supported[2] **~490M**

Post transition demand **~176M**

1. Based on Gavi's current eligibility and transition policy
2. This demand is used to calculate 'procurement cost to Gavi and countries', which itself is used in the calculation of 'value for money'

Consideration for Gavi support to Nigeria for VIS candidates would be considered separately through the Nigeria-specific strategy which was approved by the Gavi Board in June 2018

4

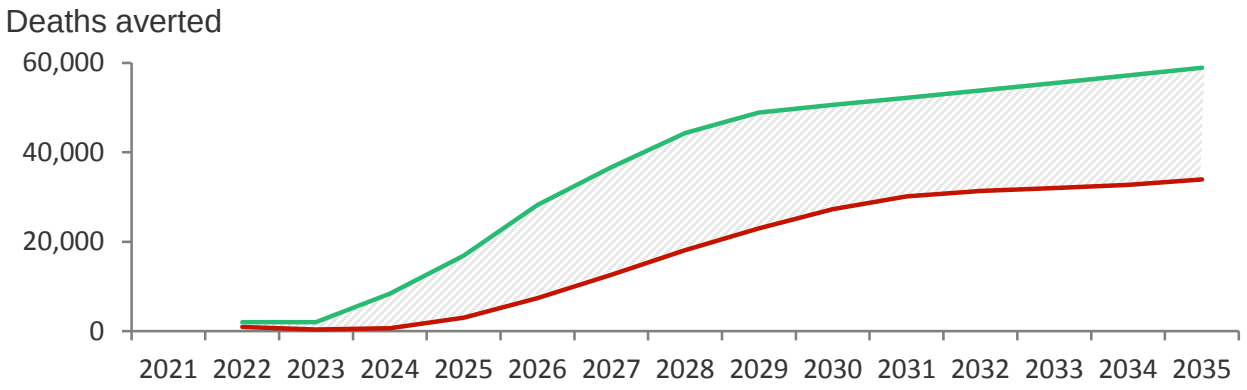
Impact

Malaria vaccine could avert between ~254-516K future deaths and ~49-142M future cases through 2035

Nigeria included

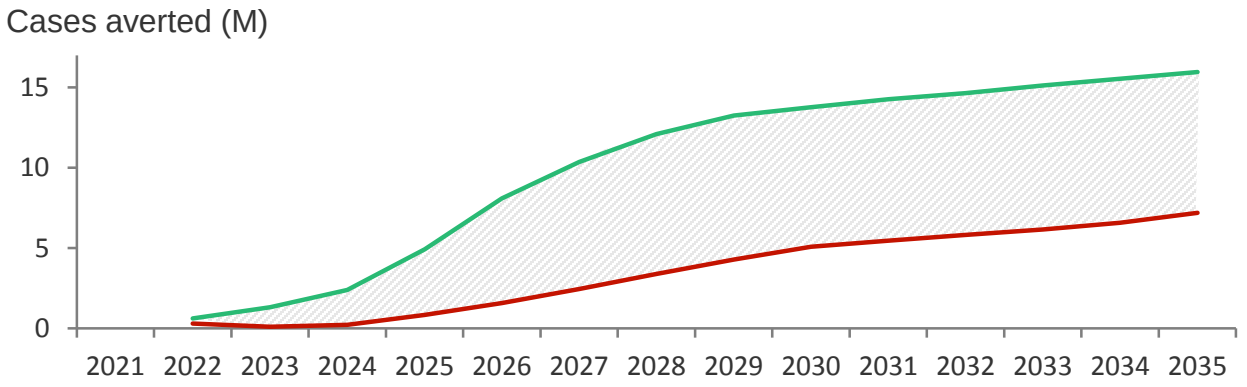
Scenarios: 5-20% parasite prevalence threshold, 100-95-90% or 100-90-80% or 90-80-70% of MCV1 with 15-25% 4th dose dropout

Deaths



	Total deaths averted (2021-2035)	Deaths averted per 100K vaccinated
Max	~516K	~489
Min	~254K	~417

Cases



	Total cases averted (2021-2035)	Cases averted per 100K vaccinated
Max	~142M	~111K
Min	~49M	~98K

Range of impact driven by different disease burden estimates and assumptions on duration of immunity used in Swiss TPH and Imperial models
Consideration for Gavi support to Nigeria for VIS candidates would be considered separately through the Nigeria-specific strategy which was approved by the Gavi Board in June 2018

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Impact modelling assumptions

Element	Assumptions	Rationale / Source
Efficacy	• 39% over 4 years in children who receive 4 doses with the first dose of the vaccine at 5 months of age	• Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial (Lancet, Volume 386, No. 9988, p31–45, 4 July 2015)
Duration of protection	• Waning efficacy over time: Efficacy: During the 12 months following dose 4, vaccine efficacy remained at 39% (95% CI, 32-44)	• Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial (Lancet, Volume 386, No. 9988, p31–45, 4 July 2015)
Source of disease burden data	• 2016 Malaria Atlas Project (MAP)/Oxford state/province level prevalence estimates	• Expert input

5

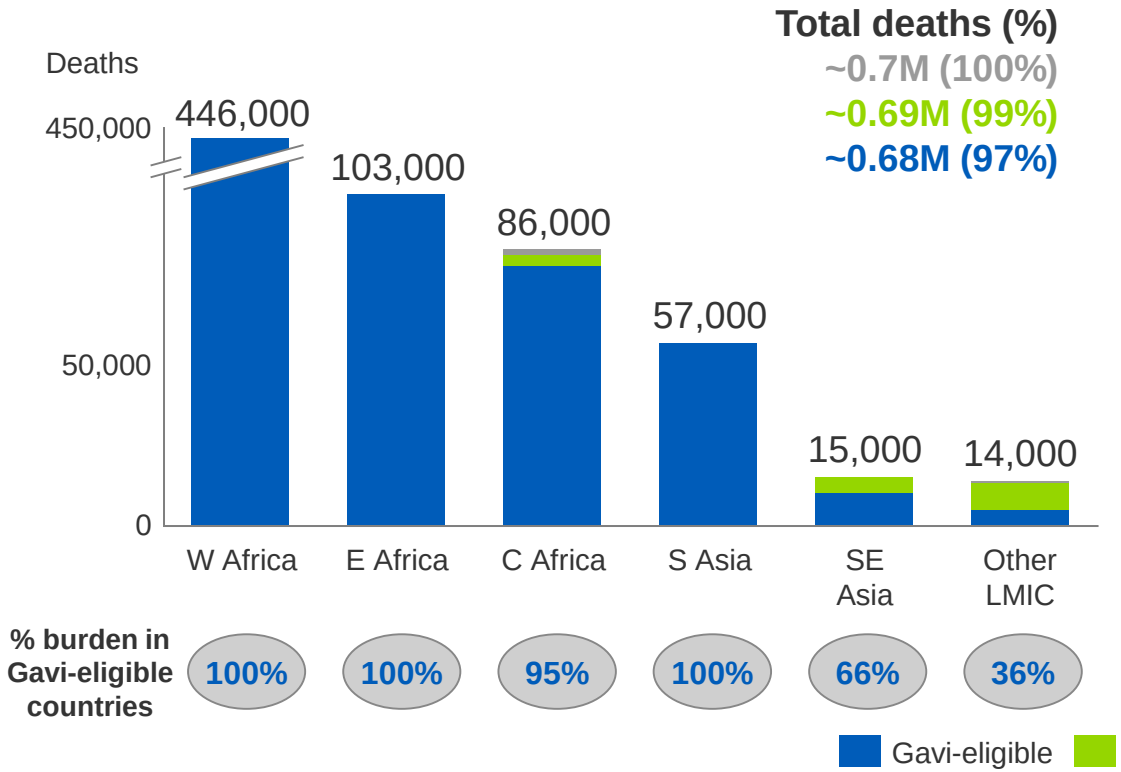
Disease Overview

Malaria Disease Context

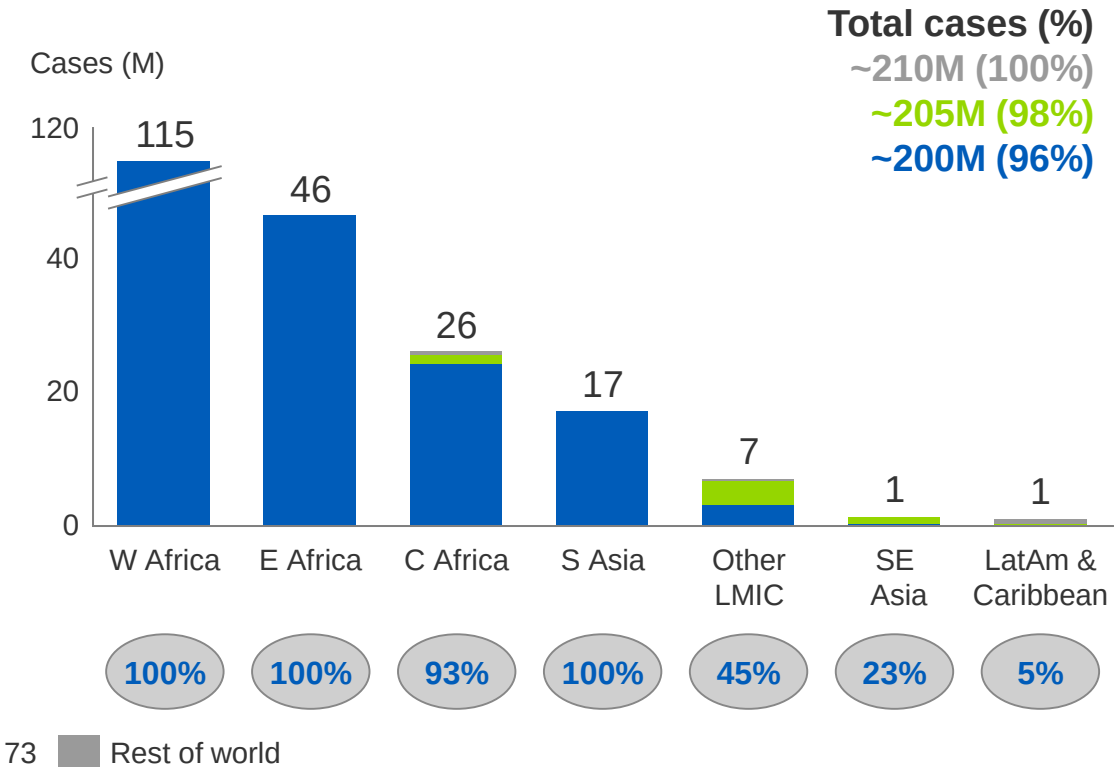
What is Malaria?	Mosquito-borne disease caused by a parasite. Of the 5 parasite species, Plasmodium falciparum (prevalent in African continent) is responsible for 99% of the malaria cases globally in 2016. It is an acute febrile illness that can be life-threatening. It is preventable and curable.
How is Malaria transmitted?	Caused by Plasmodium parasites that are transmitted to people through the bites of infected female Anopheles mosquitoes.
How widespread is Malaria?	In 2016, the WHO African Region accounts for 91% of malaria cases and deaths worldwide, followed by the WHO South-East Asia Region (6%) and the WHO Eastern Mediterranean Region (2%). Of the 91 countries reporting indigenous malaria cases in 2016, 15 countries – all in sub-Saharan Africa, except India – carried 80% of the global malaria burden. Most vulnerable are children under 5 and pregnant women. In 2016, an estimated 216 million cases of malaria occurred worldwide (95% confidence interval [CI]: 196–263 million) and an estimated 445,000-720,000 deaths from malaria globally. Incidence rate of malaria is 63 cases per 1000 population (2017 World Malaria report and GBD)
What are the symptoms and outcomes of Malaria?	i) Time to symptoms: >7 days after the infective mosquito bite. ii) Initial symptoms: May be mild and difficult to recognise as being due to malaria. Include fever, chills, headache, muscular aching and weakness, vomiting, cough, diarrhoea and abdominal pain iii) Severe symptoms related to organ failure may supervene, such as acute renal failure, pulmonary oedema, generalized convulsions, circulatory collapse, followed by coma and death. In high transmission areas the most common cause of death is severe malaria anaemia – a result of the parasite invading and destroying red blood cells, increasing uptake of parasitized red cells by the spleen, and bone marrow suppression, reducing the production of red cells.
What are the current and potential future interventions for Malaria?	Prevention through IRS, ITNs, Chemoprevention (Intermittent preventive therapy, Seasonal malaria chemoprevention); Case management using Rapid diagnostic tests, microscopy confirmed diagnosis and treatment with artemisinin-based combination therapy (ACT). Next malaria vaccine more than 10 years away
What are the outbreak/epidemic GHS implications of Malaria?	Factors that increase the mosquito population/ increase vector capacity to transmit malaria parasites include changes to the environment (increased rainfall, climate change), weakened malaria control interventions or resistance to parasite or antimalarial drugs (AMR), emergencies (violent conflict, natural disasters- displaced people), population movement and seasonal labours.
What are the AMR challenges of Malaria?	Plasmodium falciparum has developed resistance to artemisinin in 5 countries of the Greater Mekong sub region and resistance of malaria vectors to the 4 insecticide classes commonly used in ITNs or IRS. Of the 76 malaria endemic countries that reported standard monitoring data for 2010 to 2016, resistance detected in 61 countries to at least one insecticide in one malaria vector from one collection site. In 50 countries there was resistance to two or more insecticide classes, which weakens existing interventions. insecticide resistance highly prevalent in sub Saharan Africa

Malaria estimated to cause ~0.7M deaths, ~210M cases, >96% in Gavi-eligible countries (GBD 2016)

Deaths by region



Cases by region



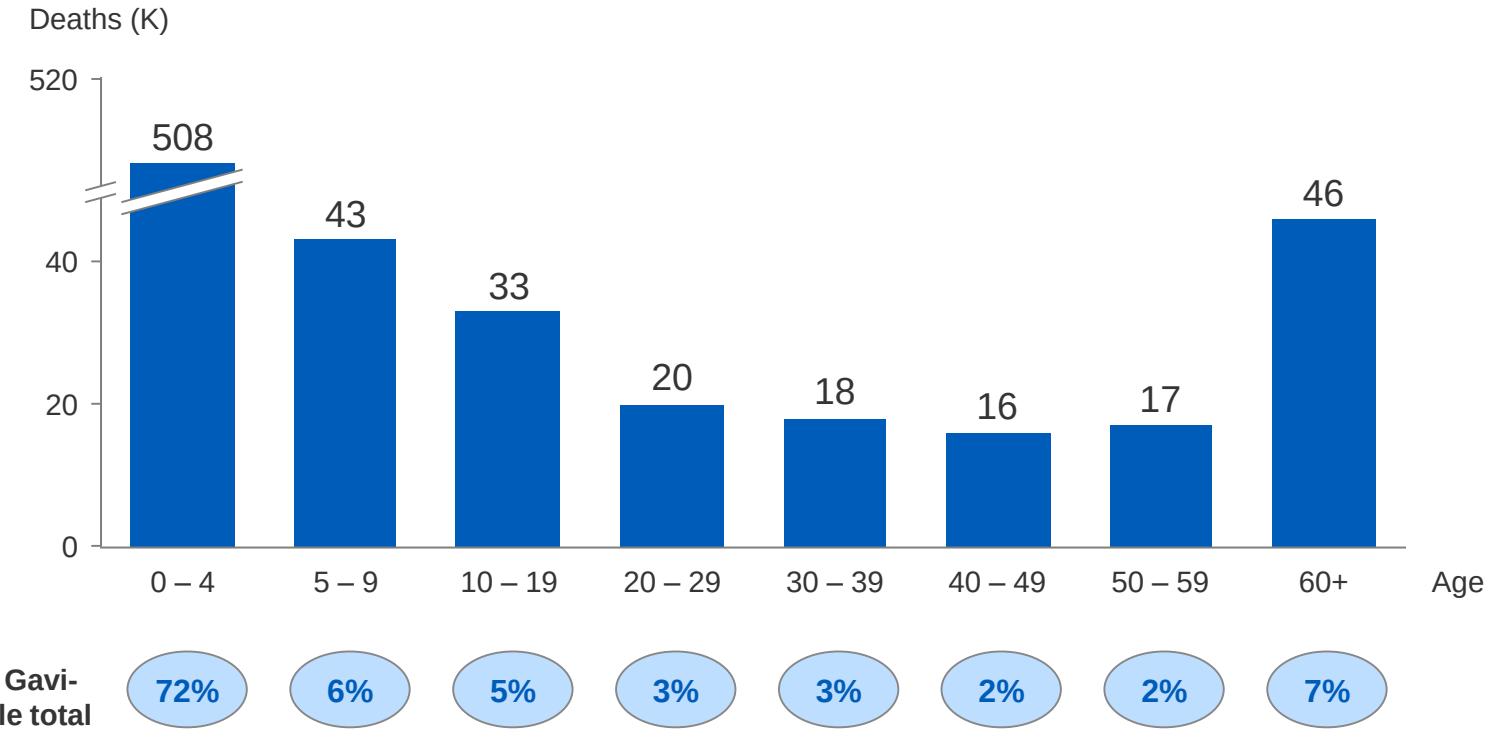
Gavi-eligible | Gavi 73 | Rest of world

Source: IHME Global Burden of Disease Study, 2016

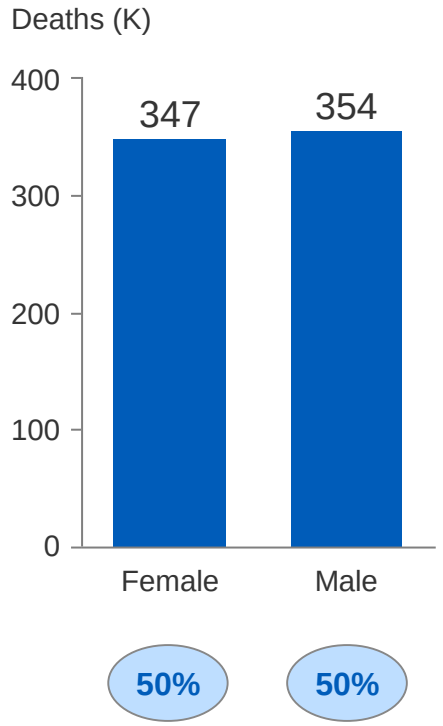
Note: Impact modelling uses Malaria Atlas Project data. IHME GBD data used as comparator across VIS 2018 vaccine decks

Deaths in Gavi countries due to malaria are highest among under 5s (GBD 2016)

Deaths by age group



Deaths by gender



Note: Data represents Gavi-eligible countries only. Impact modelling uses Malaria Atlas Project data
Source: IHME Global Burden of Disease Study, 2016

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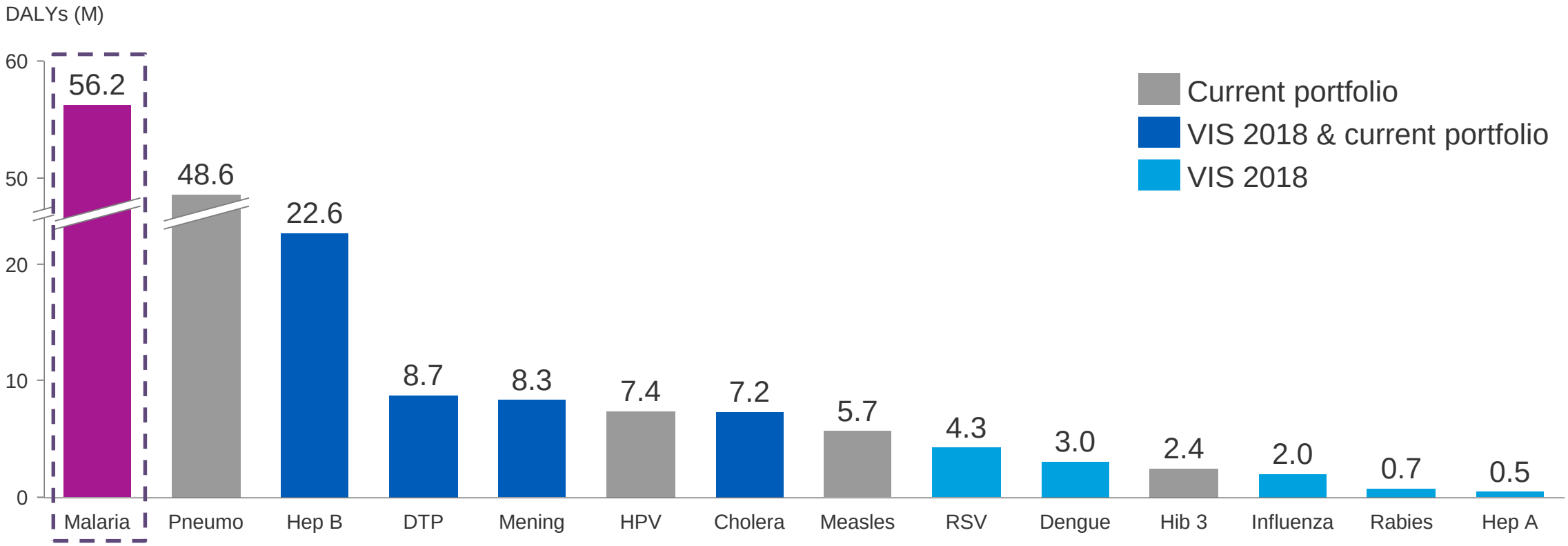
Global malaria burden estimated at ~56M DALYs (GBD 2016)



Note: Hepatitis B incl. liver cancer due to Hepatitis B & Cirrhosis and other chronic liver diseases due to Hepatitis B. HPV incl. cervical cancer. Meningitis incl. Meningococcal meningitis only
Source: IHME Global Burden of Disease Study 2016

6

Vaccination Policy

Policy overview

Source	Policy summary and considerations
WHO position paper (2016)	• WHO recommends further pilots addressing gaps in knowledge, before considering wider country level introduction. evaluation of RTS,S/AS01 through • Recommends pilot implementations use 4-dose schedule of the RTS,S/AS01 in 3–5 distinct epidemiological settings in sub-Saharan Africa, at subnational level, covering moderate-to-high transmission settings. • Malaria vaccine given as 3-dose initial series with a minimum interval between doses of 4 weeks, followed by a 4th dose 15–18 months after the 3rd dose. The 1st dose should be administered as close as possible to age 5 months and the 3rd dose should be completed by 9 months of age.
WHO GTS for Malaria/ Action and Investment to defeat Malaria AIM) (2016-2030)	By 2030, the strategy aims to including: • Reducing malaria case incidence by at least 90% • Reducing malaria mortality rates by at least 90% • Eliminating malaria in at least 35 countries • Preventing a resurgence of malaria in all countries that are malaria-free • Near-term milestones for 2020 include reductions in malaria case incidence and death rates of at least 40% and the elimination of malaria in at least 10 countries. • Harnessing innovation and expanding research (including for malaria vaccines and implementation research)
SDG (Target 3.3) 2015-2030	Goal 3.3: By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases

Gavi's investment in Malaria

2016 Malaria Vaccine Implementation Programme (MVIP)

- Approved US$ 24.6 million (equivalent to half of the funding request) for Phase 1 of the WHO-led Malaria Vaccine pilots to be implemented during 2017-2020.
- Co-investments by Global Fund ($15m) and Unitaid ($9.6m) for Phase 1
- The MVIP will support introduction of the malaria vaccine in selected areas of 3 pilot countries (Ghana, Kenya and Malawi) and assess:
  - Programmatic feasibility of delivering RTS,S at 4 dose schedule
  - Vaccine impact on mortality
  - Vaccine safety in the context of a routine immunization programme

7

Vaccine landscape

Vaccine characteristics

	RTS,S/AS01
Manufacturers	GSK
Technology	Pre-erythrocytic stage hybrid recombinant protein vaccine
Indication	Children 5 months (1st dose), 3rd dose should be completed by 9 months of age. 4th dose should be administered at 15–18 months
Dosing schedule	4 doses
Formulation	Lyophilized
Doses per vial	2
Temperature	2-8C
Packed volume	9.9cm3/dose
Efficacy	39% after receiving 4 doses, over an average 46 months (~4 years) of follow-up
Duration	During the 12 months following dose 4, vaccine efficacy remained at 39% (95% CI, 32-44)
Interactions	TBD
Licensure year	TBD
Est. WHO PQ year	TBD- No PQ process at this stage as SAGE/MPAC recommendation only for pilot introduction
Administration	Injection, intramuscular
Gavi country feasibility?	Yes

8

Resources

Malaria: key sources

Sources

- Malaria vaccine: WHO position paper January 2016, Weekly epidemiological record- No 4, 2016, 91, 33–52
- World Malaria report 2017
- WHO Global technical strategy for malaria 2016–2030 (GTS)
- Penny MA, Verity R, Bever CA, Sauboin C, Galactionova K, Flasche S, et al. Public health impact and cost-effectiveness of the RTS, S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. Lancet. 2015;387:367–75
- Lu, F. et al. Emergence of indigenous artemisinin-resistant Plasmodium falciparum in Africa. N. Engl. J. Med. 376, 991–993 (2017).
- Artemisinin and artemisinin-based combination therapy resistance: status report, WHO (2016)
- Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial (Lancet, Volume 386, No. 9988, p31–45, 4 July 2015)
- Gavi PPC/Board background slides for decision on RTS,S Pilot support, April/June 2016
- Global Burden of Disease, Institute for Health Metrics and Evaluation (IHME), 2016