# Malaria

## Vaccine investment strategy

*Background document #3*

*November 2013*

# Executive Summary

**Support for malaria vaccine has highest potential among VIS vaccines to increase impact of GAVI portfolio**

- Malaria continues to be a leading cause of U5 deaths in Sub-Saharan Africa
- Candidate vaccine (RTS,S) may be administered routinely at 6 weeks or after 5 months (pending WHO recommendation); WHO recommendation may include booster dose, timing tbc
- Vaccine does not replace other anti-malarial interventions, projected impact is incremental to on-going impact from these interventions (baseline: ~80% bednet coverage)
- Strong GAVI market shaping potential (leading buyer of vaccine)
- Uncertainty around exact vaccine efficacy and duration until new data available in 2014, but substantial health impact even at low values for both
- Future deaths averted per 100k may be comparable to Hib

**Potential implementation challenges**

- Vaccine must be viewed as part of a comprehensive approach to control malaria in order to ensure that the use of and resources allocated to other malaria interventions are not reduced
- If there are settings and age groups where efficacy is lower than other vaccines in use, communication efforts are needed to ensure continued credibility of immunization programmes
- High cost could be challenging for sustainability of country programmes, though political will is likely high

**Recommendation: based on the current assessment there is a reasonable case for GAVI support for a malaria vaccine; consider opening a window if and when the vaccine is licensed, recommended for use by the joint meeting of the WHO Strategic Advisory Group of Experts and the Malaria Programme Advisory Committee (expected in 2015) and WHO pre-qualified, taking into account updated projections of impact, cost and country demand as reviewed by the PPC.**

- Substantial impact, strong country demand, high market shaping potential
- Projected cost to GAVI: $2.2B - $3.4B over 2017-2030

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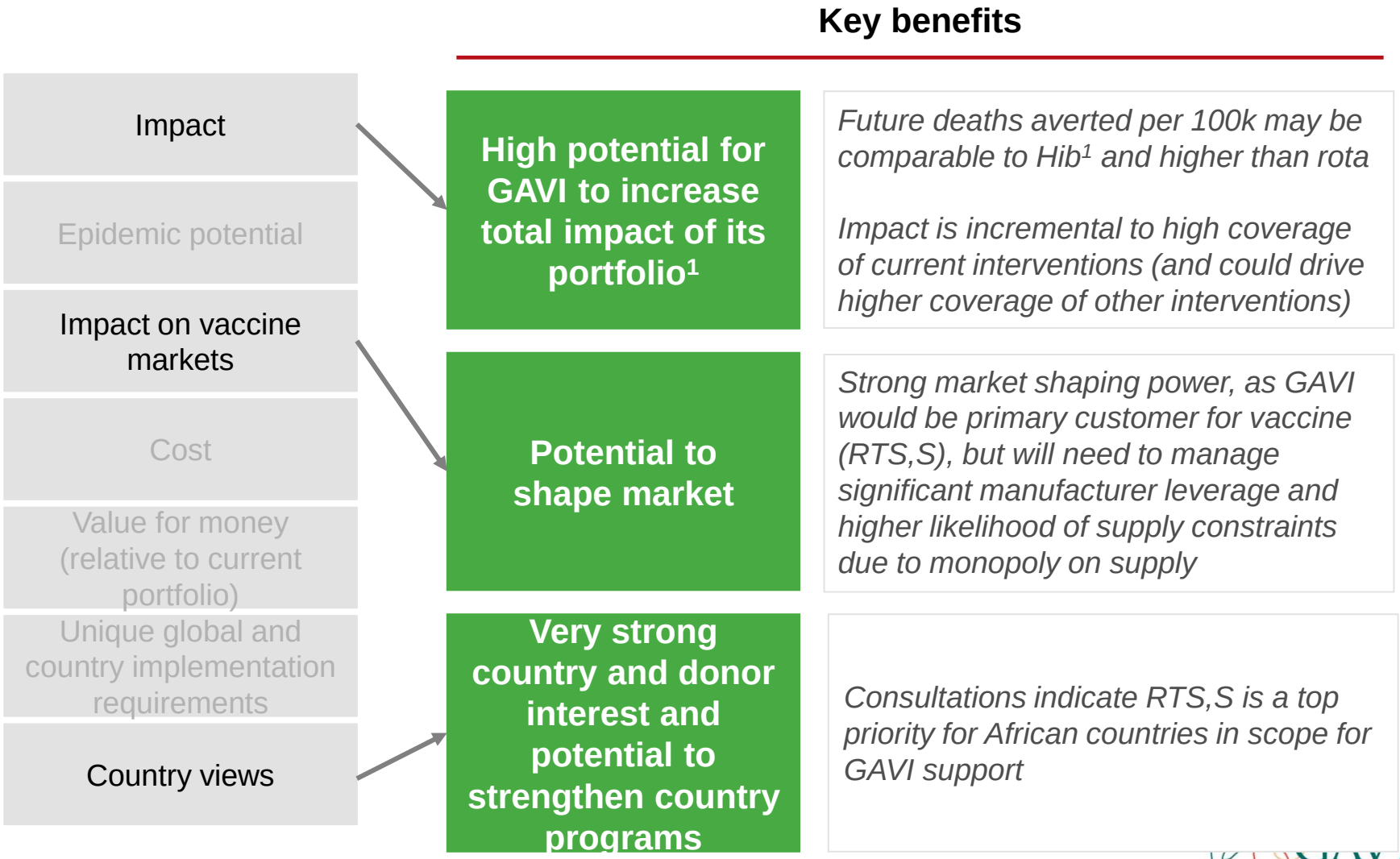
# Key malaria vaccine benefits:

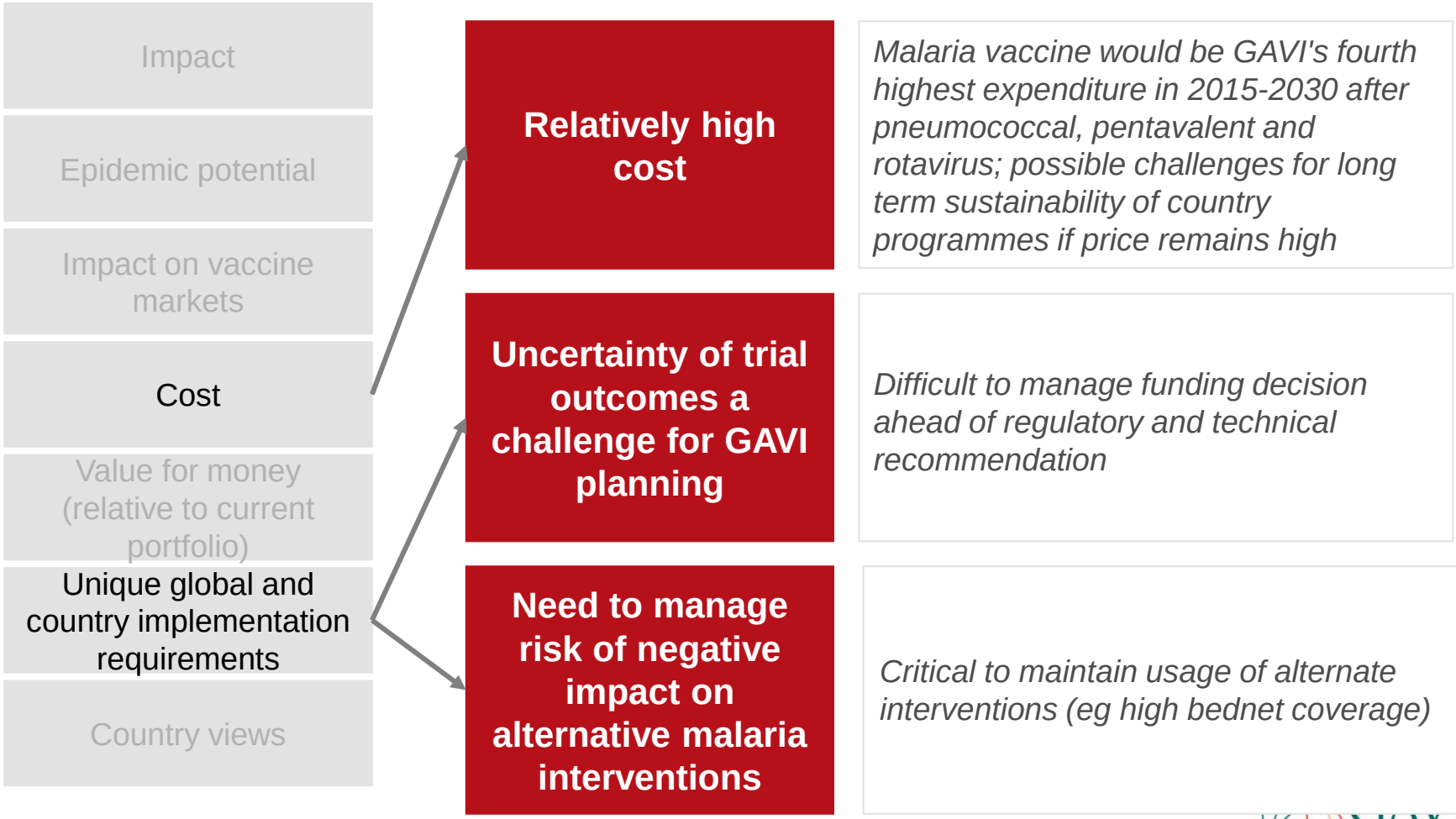
## Highest potential for public health impact, strong country and donor interest




1. Based on publicly available trial data as of September 2013

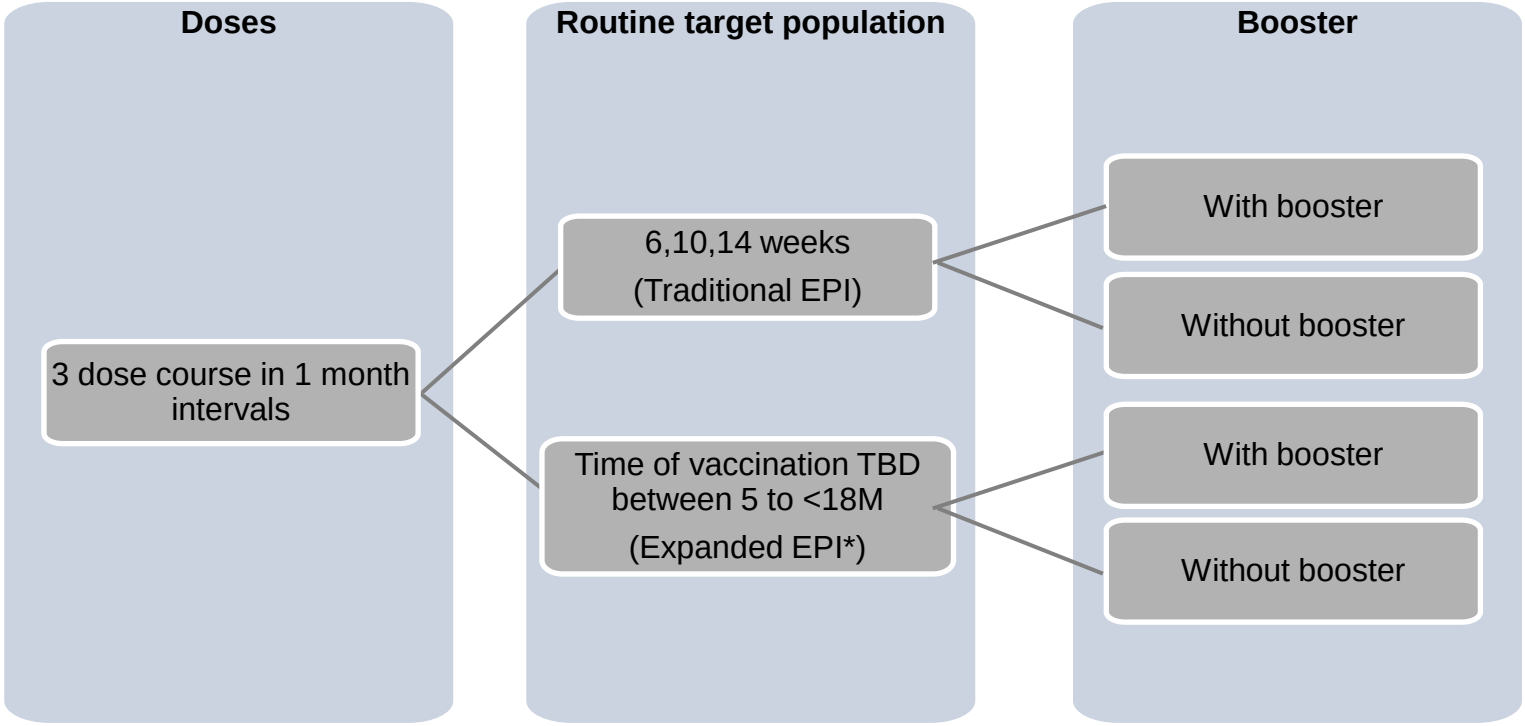
# Key malaria vaccine challenges:

## High cost and uncertainty; could negatively impact alternate interventions



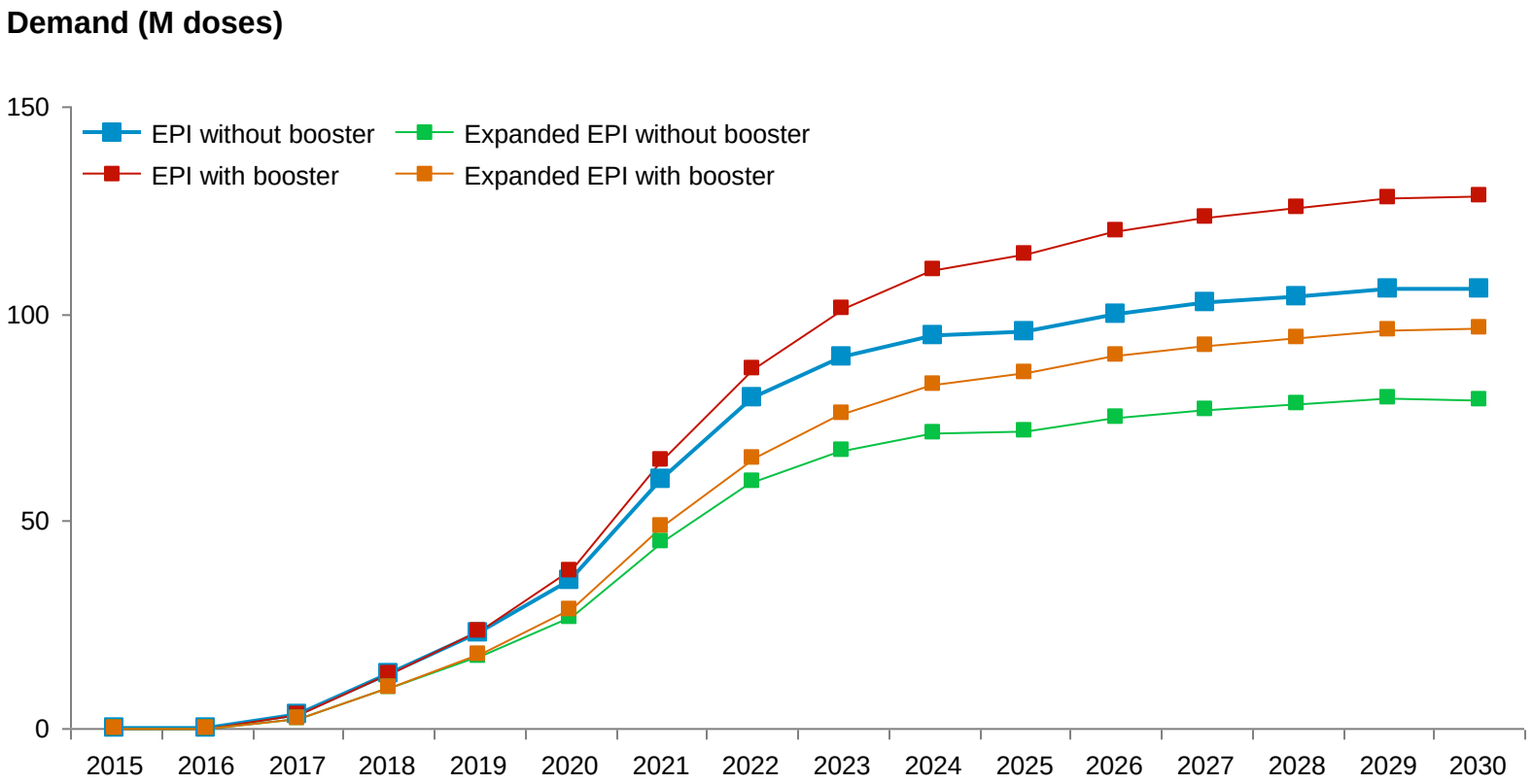
# Malaria vaccine investment scenarios: four options modelled

***Strategies and assumptions are for modeling purposes. Actual implementation strategies will be based upon guidance received from WHO's Strategic Advisory Group of Experts and other WHO expert bodies. All strategies are modelled without financial constraints.***




*SAGE has supported investigation of 'expanded EPI' vaccination scenarios SAGE meeting report from April 2013 (http://www.who.int/wer/2013/wer8820.pdf). This may include a scenario with one new visit, with other visits being combined with vitamin A administration and the existing 9 month visit for measles.

# Cumulative demand estimated to be 760M – 1.2B doses through 2030




| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *# countries introducing* | *0* | *0* | *2* | *3* | *3* | *5* | *5* | *5* | *3* | *4* | *2* | *2* | *0* | *0* | *0* | *0* |

Note: includes introductions in African countries only (both vaccine licensure and a WHO recommendation are highly likely to be restricted to Africa; vaccine indication for use in Asia is not expected in the near term); Includes demand from countries that graduate from GAVI support during 2015-2030 (following GAVI supported introduction)

# Over 2015-2030, potential to avert 590,000-1.3 million deaths at a cost of $2.2B-$3.4 billion

| | | EPI w/o booster | EPI w/ booster | Expanded EPI w/o booster | Expanded EPI w/ booster |
|---|---|---|---|---|---|
| **Impact** | **Fully vaccinated persons** | Routine: 277M | Routine: 277M<br>Boost: 155M | Routine: 208M | Routine: 208M<br>Boost: 116M |
| | **Total future deaths averted** | Imperial: 590,000<br>STPH*: 710,000 | Imperial: 730,000<br>STPH: 770,000 | Imperial: 1.1M<br>STPH: 880,000 | Imperial: 1.3M<br>STPH: 960,000 |
| | **Deaths averted per 100k vaccinated** | Imperial: 210<br>STPH: 260 | Imperial: 270<br>STPH: 280 | Imperial: 540<br>STPH: 430 | Imperial: 640<br>STPH: 470 |
| **Cost** | **GAVI procurement cost** | $2.9B | $3.4B | $2.2B | $2.5B |
| | **GAVI introduction grant** | $25M | $25M | $25M | $25M |
| | **Total GAVI cost** | $2.9B | $3.4B | $2.2B | $2.6B |
| | **Country procurement costs** | $957M | $1.1B | $718M | $853M |
| | **Country operational costs** | $98M | $130M | $98M | $122M |
| | **Total cost** | $4.0B | $4.7B | $3.0B | $3.5B |
| **Value for money** | **Total cost per death averted** | Imperial: $6,800<br>STPH: $5,600 | Imperial: $6,400<br>STPH: $6,100 | Imperial: $2,800<br>STPH: $3,400 | Imperial: $2,700<br>STPH: $3,700 |

*Swiss Tropical and Public Health Institute

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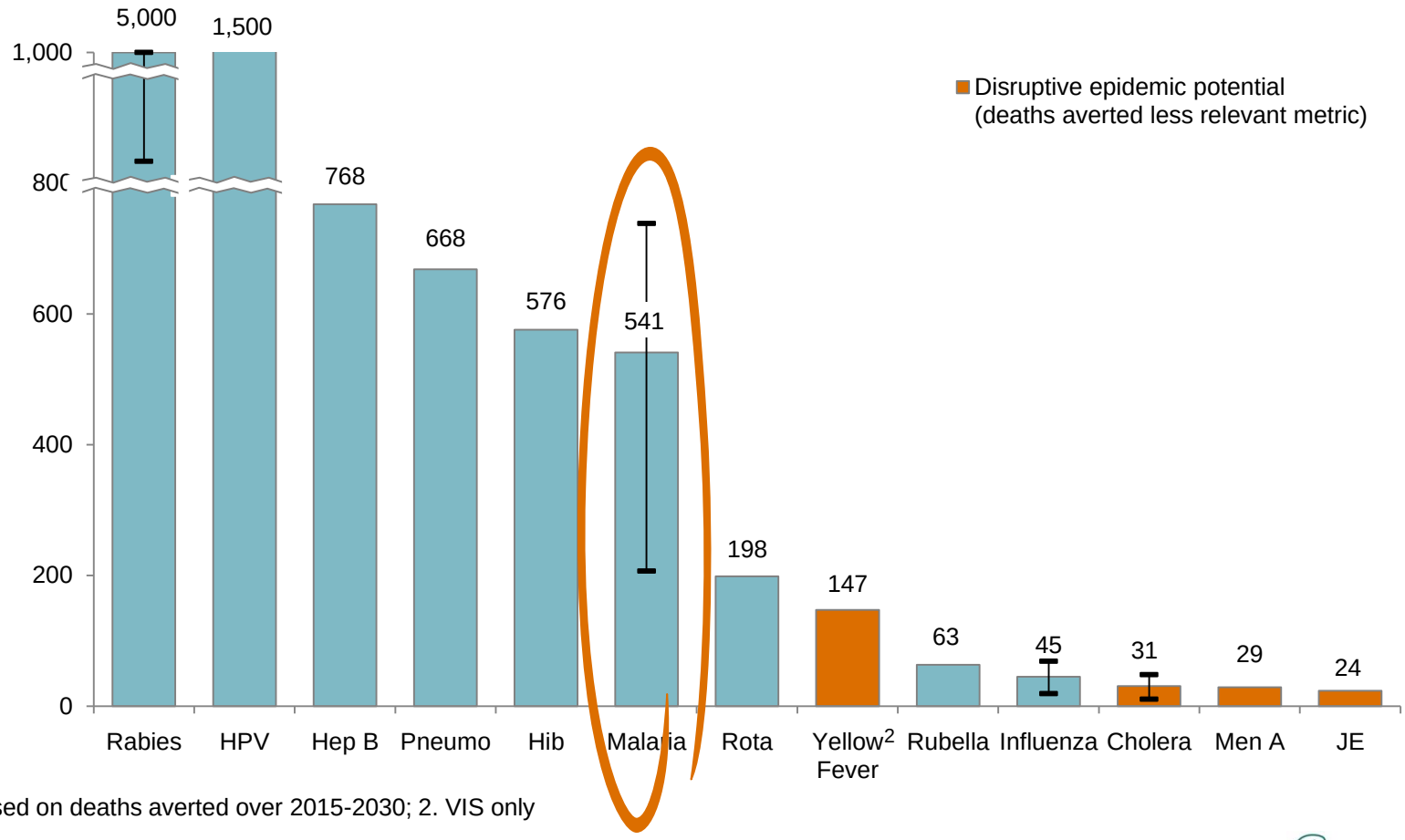
# Malaria vaccine may have impact comparable to Hib

**Future deaths averted per 100k vaccinated[1]**



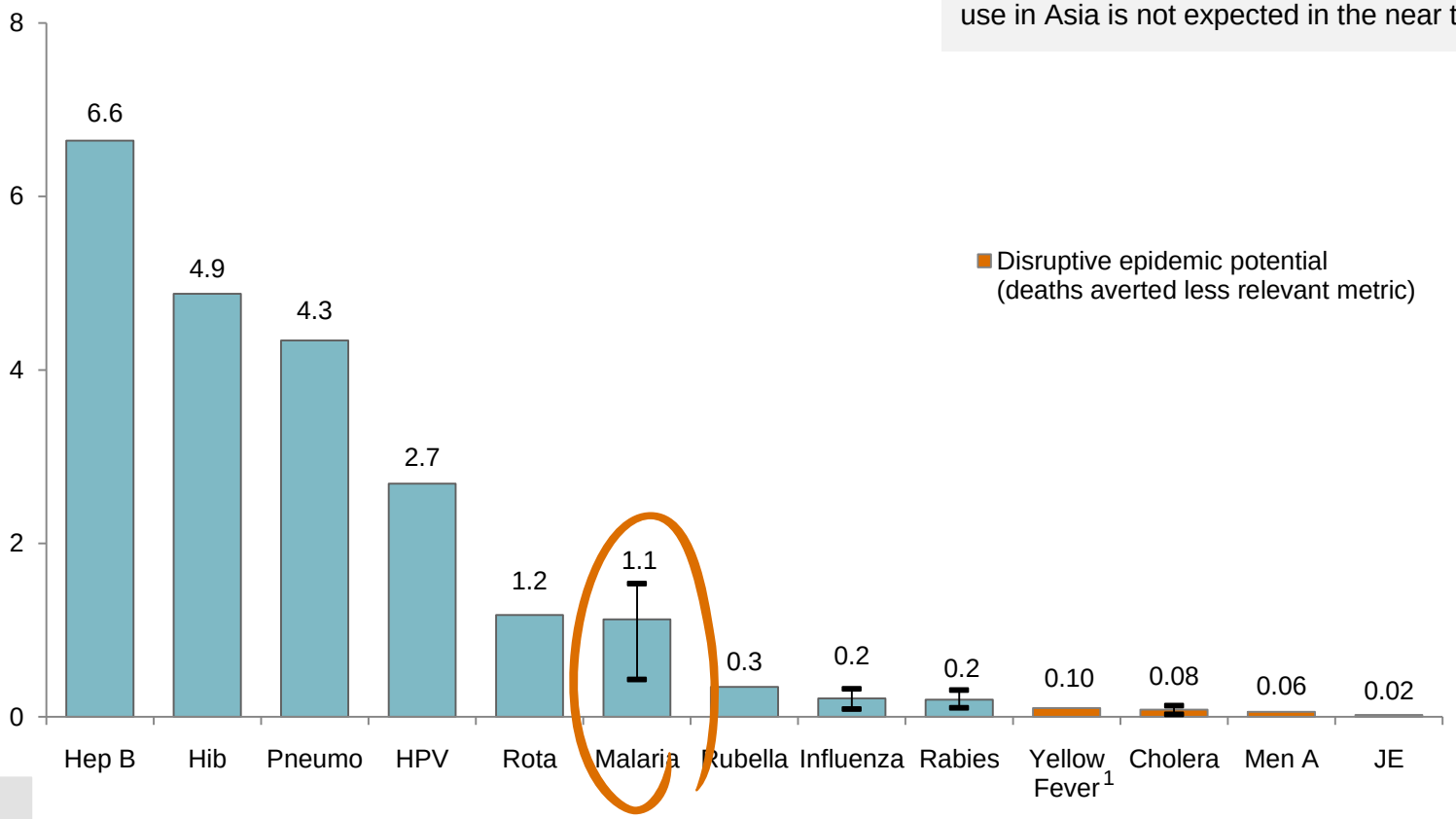

1. Based on deaths averted over 2015-2030; 2. VIS only

**Note**: Model outputs shown for Expanded EPI with booster scenario, for illustrative purposes; error bars show highest and lowest value generated by malaria sensitivity analyses and are driven by decay rate of protection; point estimate represents midpoint of Imperial and Swiss TPH models

# Potential to avert around 1 million total future deaths in Africa*

* Both vaccine licensure and a WHO recommendation are highly likely to be restricted to Africa; a vaccine indication for use in Asia is not expected in the near term.

**Future deaths averted, 2015–2030 (M)**




| Countries introduced with GAVI support | Hep B | Hib | Pneumo | HPV | Rota | Malaria | Rubella | Influenza | Rabies | Yellow Fever[1] | Cholera | Men A | JE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 66 | 66 | 63 | 48 | 50 | **34** | 34 | 45 | 45 | **10** | **21** | **26** | **6** |

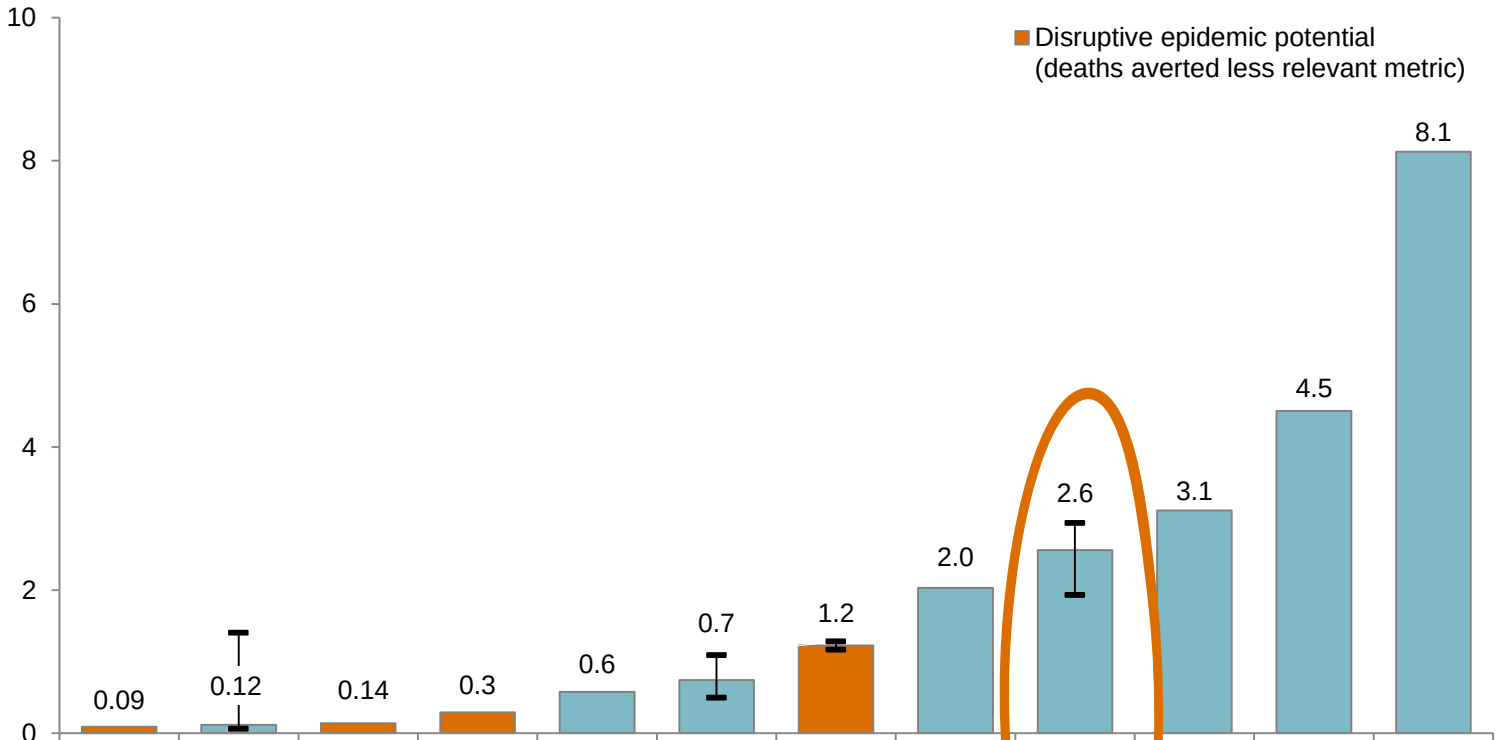
1. VIS only

*Note: **green** indicates vaccine would only be rolled out in a subset of GAVI countries*

**Note**: Model outputs shown for Expanded EPI with booster scenario, for illustrative purposes; error bars show highest and lowest value generated by malaria sensitivity analyses and are driven by decay rate of infection; point estimate represents midpoint of Imperial and Swiss TPH models

# Malaria would be GAVI's fourth-highest expenditure over 2015-2030

**Total cost to GAVI, 2015–2030 ($B)[1]**



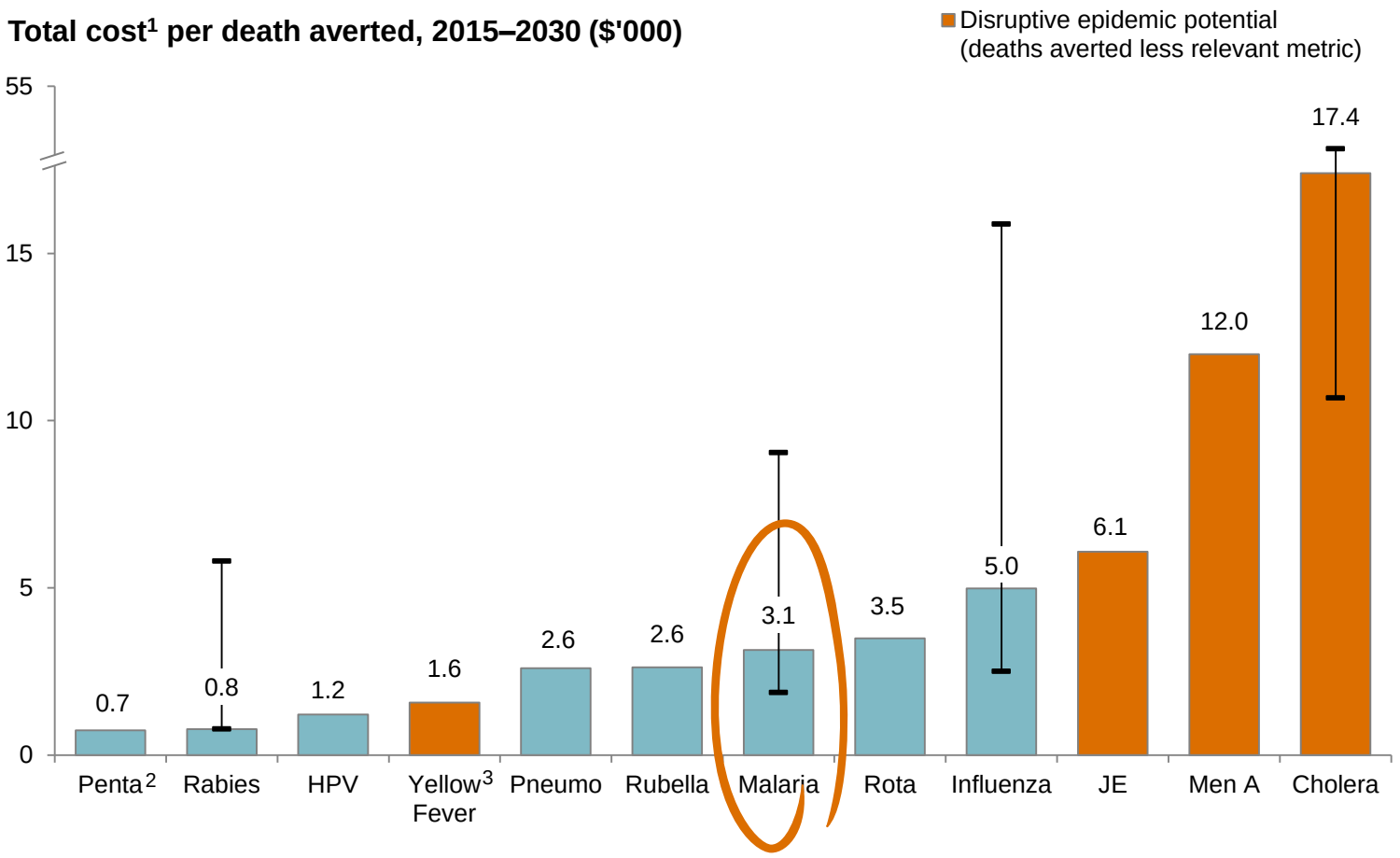

| Countries introduced with GAVI support | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 6 | 45 | 10 | 26 | 34 | 45 | 21 | 48 | 34 | 50 | 66 | 63 |

*Note: **green** indicates vaccine would only be rolled out in a subset of GAVI countries*

1. Includes GAVI procurement cost + vaccine introduction grants + GAVI operational cost grants; 2. VIS only

**Note**: Model outputs shown for Expanded EPI with booster scenario, for illustrative purposes; error bars show highest and lowest value generated by malaria sensitivity analyses and are driven by price (upper bound) and eligibility of Nigeria (lower bound) Source: GAVI Financial Forecast v7.0Fb as of July 2013, VIS analysis

# Cost per future deaths averted similar to rota

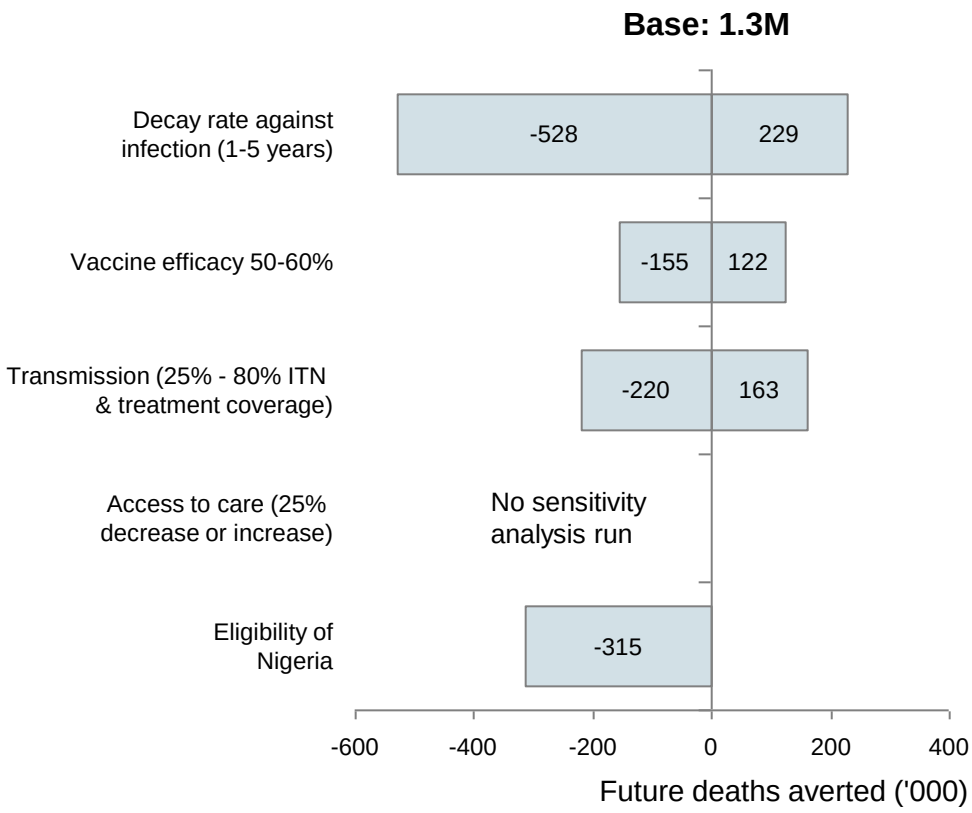



1. Includes operational + procurement cost to GAVI *and* country; 3. Includes deaths averted for Hep B and Hib; VIS only

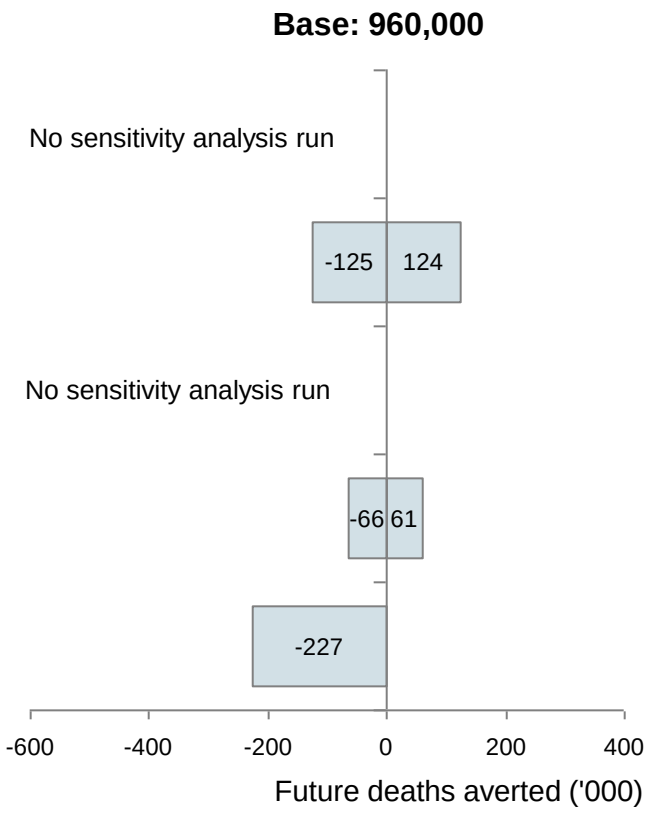
**Note**: Model outputs shown for Expanded EPI with booster scenario, for illustrative purposes; error bars based on highest cost / lowest impact and lowest cost / highest impact as generated in sensitivity analyses; point estimate represents midpoint of Imperial and STPH models Source: GAVI Financial Forecast v7.0Fb as of July 2013, VIS analysis

# Vaccine duration of protection is biggest sensitivity of high impact

## Imperial College



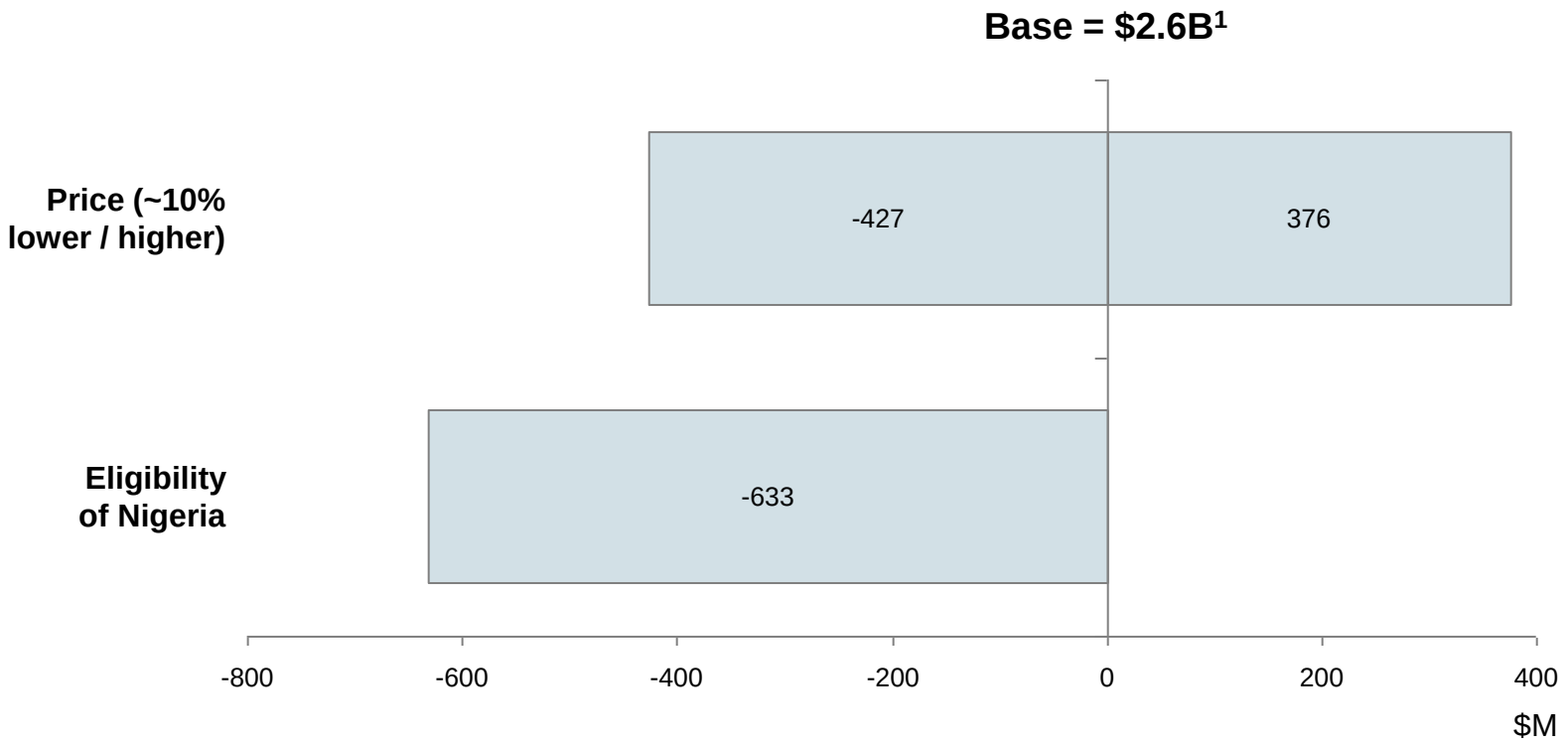

## Swiss TPH




**Note**: For illustrative purposes base case is shown as expanded EPI with booster scenario (midpoint between Imperial College and Swiss TPH model outputs)

# Key uncertainties underlying cost to GAVI are price and eligibility of Nigeria

**Expanded EPI with booster**

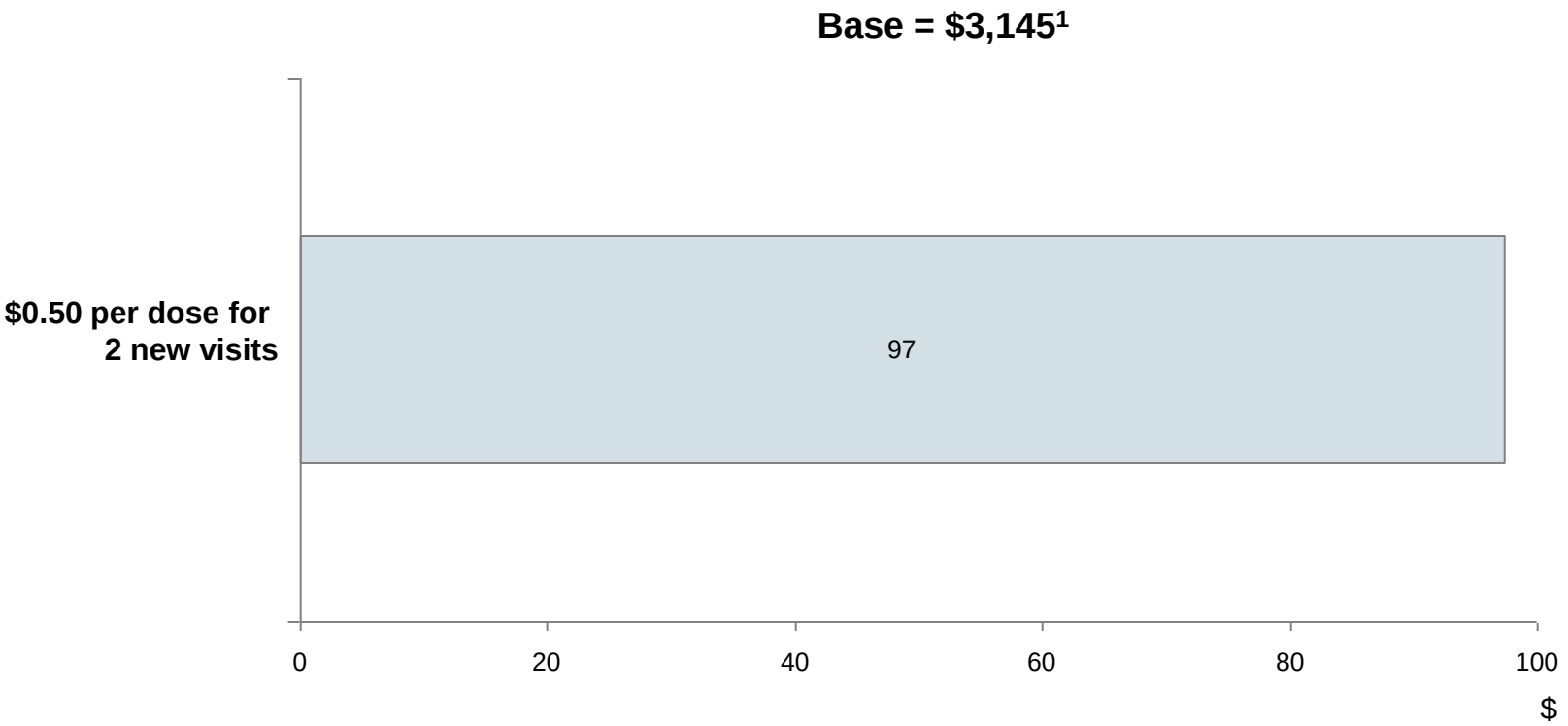



1. Total cost to GAVI

**Note**: for illustrative purposes base case is shown as expanded EPI with booster scenario (midpoint between Imperial College and Swiss TPH model outputs)

# Increased operational cost of new immunisation visit has minimal effect on value for money

**Expanded EPI with booster**

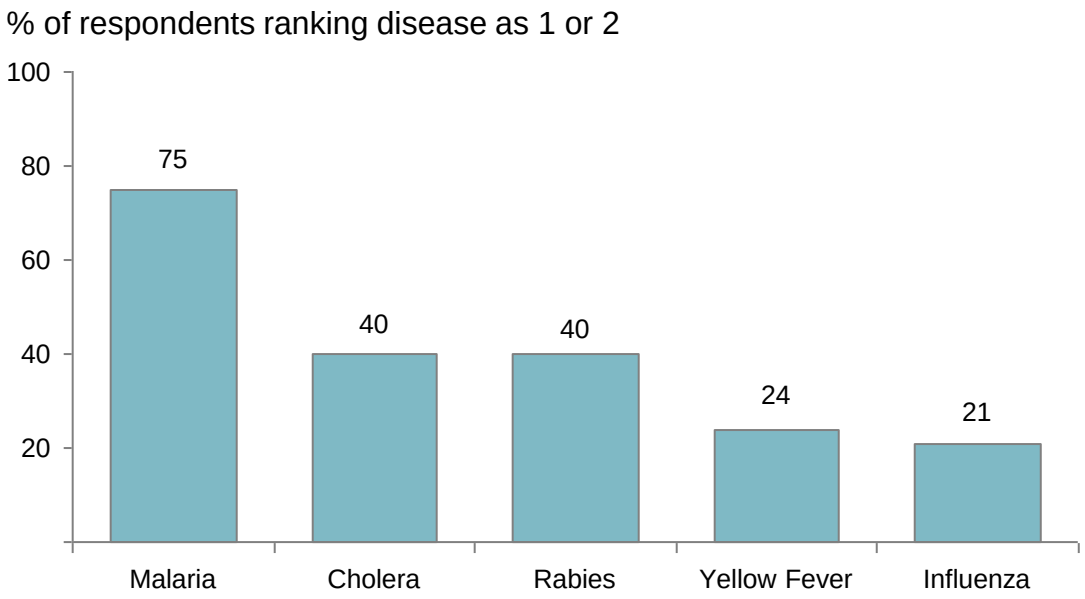



1. Total cost per future death averted

**Note**: For illustrative purposes base case is shown as expanded EPI with booster scenario (midpoint between Imperial College and Swiss TPH model outputs); sensitivity assumes 5x increase in operational cost per dose for 2 new visits to clinic (including booster) to finish a full course of malaria vaccination

# A malaria vaccine is highest priority according to country respondents

**Survey respondents:**
**malaria ranked as highest priority for country introductions**




| Average priority | 1.9 | 2.8 | 3.1 | 3.8 | 3.4 |
|---|---|---|---|---|---|

## Quotes from in-depth country interviews

**"If there is *anything* available to combat malaria, my country would want it"**

**"We have high coverage of ITN, IRS, RDT, coartem, environmental work in swamps, but malaria is still a high burden. The arsenal of interventions is not enough."**

**"Partial vaccine efficacy is no issue; the same applies to other vaccines. This vaccine is the highest priority – even if efficacy is low."**

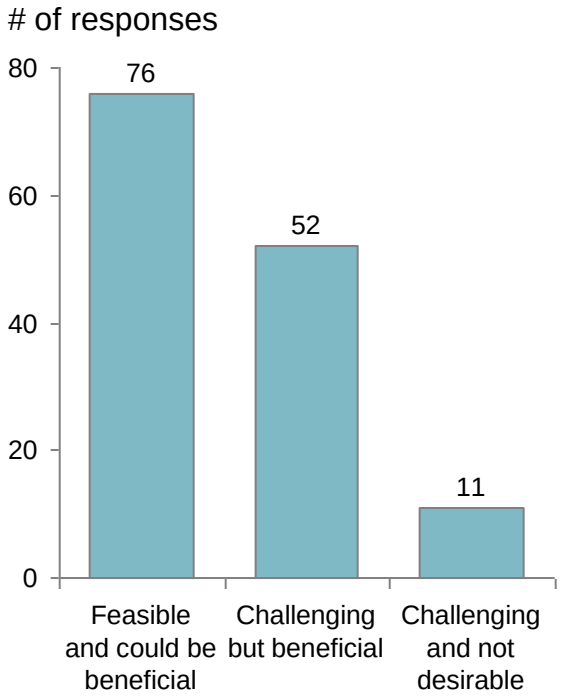
**"Large rural population, many illiterate. But everybody knows malaria. Malaria vaccine could boost the confidence of the community in the health system overall"**

Source: 2013 GAVI country consultation survey, total responses = 182, 93 from countries in scope for GAVI support of malaria
Question: Please rank all of the following vaccines in terms of prioritisation for future introduction in your country

# Country openness to new immunisation visits and awareness that vaccine cannot replace other interventions

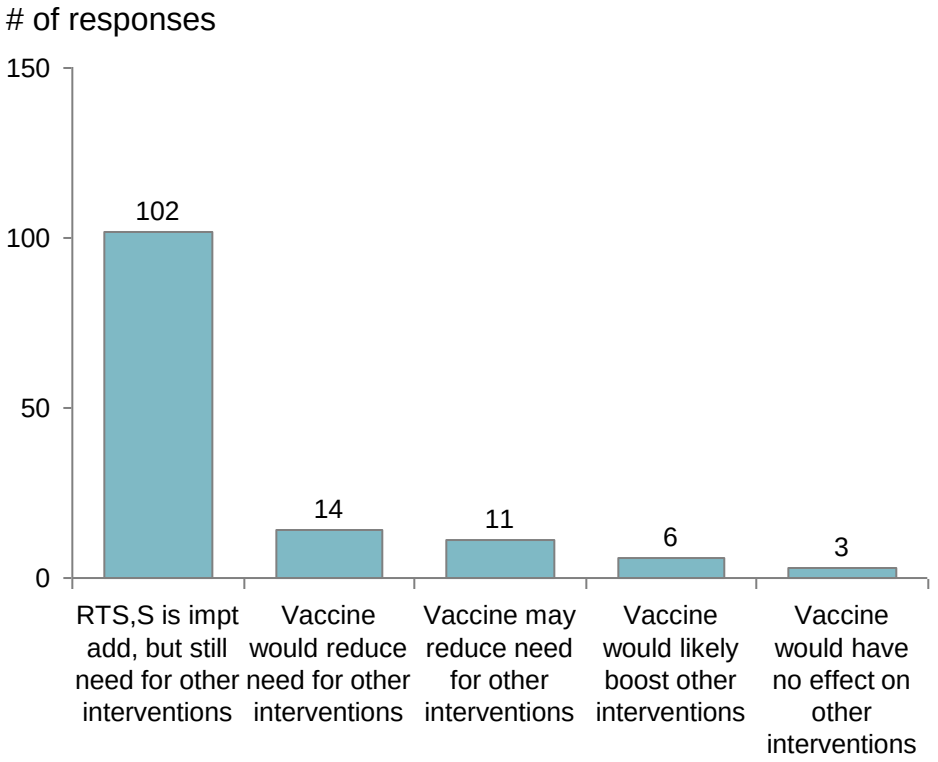
**Respondents positive on ability to add new visits for 5-17M age group**

***Question: Please indicate the statement(s) that most closely apply in your country***




**Respondents emphasized that vaccine could not displace other malaria interventions**

***Question: Please indicate the statement(s) that most closely apply in your country***




Source: 2013 GAVI Phase II country consultation survey
Note: question only posed to 136 respondents ranking malaria as first or second priority for introduction

# Implementation would require managing possible global supply shortage and communication needs

| | Area of focus | Unique implementation requirements | Unique costs |
|---|---|---|---|
| Global level | Policies and processes | ▪ WHO position TBD; few required GAVI policy changes currently foreseen; coordination with the GFATM required | ▪ N/A |
| | Supply | ▪ Account for supply constraints through 2020 (impact likely small) | ▪ No direct costs |
| Country level | Health workforce | ▪ HR/training requirements for RTS,S similar to those for vaccines already in health system | ▪ N/A |
| | Social mobilisation, education, communication | ▪ Manage risk to program credibility if efficacy lower than other vaccines in use (eg. rota)<br>▪ Additional training/social mobilisation/programmatic investments for initiating new routine visits for immunisation (expanded EPI scenario only) | ▪ Cost accounted for in operational costs[1] |
| | Supply chain infrastructure and logistics | ▪ Requirements for RTS,S similar to those for vaccines already in health system | ▪ N/A |
| | Surveillance | ▪ No unique surveillance requirements | ▪ N/A |
| | Planning, coordination, integration | ▪ Expanded EPI scenario would require infrastructure to support at least one additional touch point<br>▪ Manage potential for older (not eligible) age groups to present for vaccination (implications for forecasting in intro year)<br>▪ Coordinate with malaria control program to ensure vaccine does not undermine the use of other malaria interventions | ▪ Focused organizational effort |

1. Expected to be covered by GAVI Vaccine Introduction Grant, MoH, partners

Unique but manageable

May not be manageable in short term / within current GAVI model

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# Options for a malaria vaccine investment

**Defer consideration** of support for malaria vaccine until further clinical trial data available

**Decide to open country support window** if/when vaccine is licensed, recommended for use by SAGE and WHO pre-qualified

**Defer decision: note strong case based on current assessment and expect to open a window** if/when vaccine is licensed, recommended for use by SAGE and WHO pre-qualified, taking into account updated projections of impact, cost and country demand as reviewed by the PPC

***Recommended option***

**Decide GAVI will not support malaria vaccines**

# Implications of no GAVI support

**Potentially limited uptake in absence of GAVI support**

- Procurement cost likely too high for most governments to support independently
- Other funders such as the Global Fund to Fight AIDS, TB and Malaria may consider supporting the vaccine

**Lack of clear signal from GAVI might cause manufacturer to limit supply past 2020**

**Missed opportunity to build on and expand the impact of current malaria control programmes**

# Malaria: experts and sources consulted

## Sources

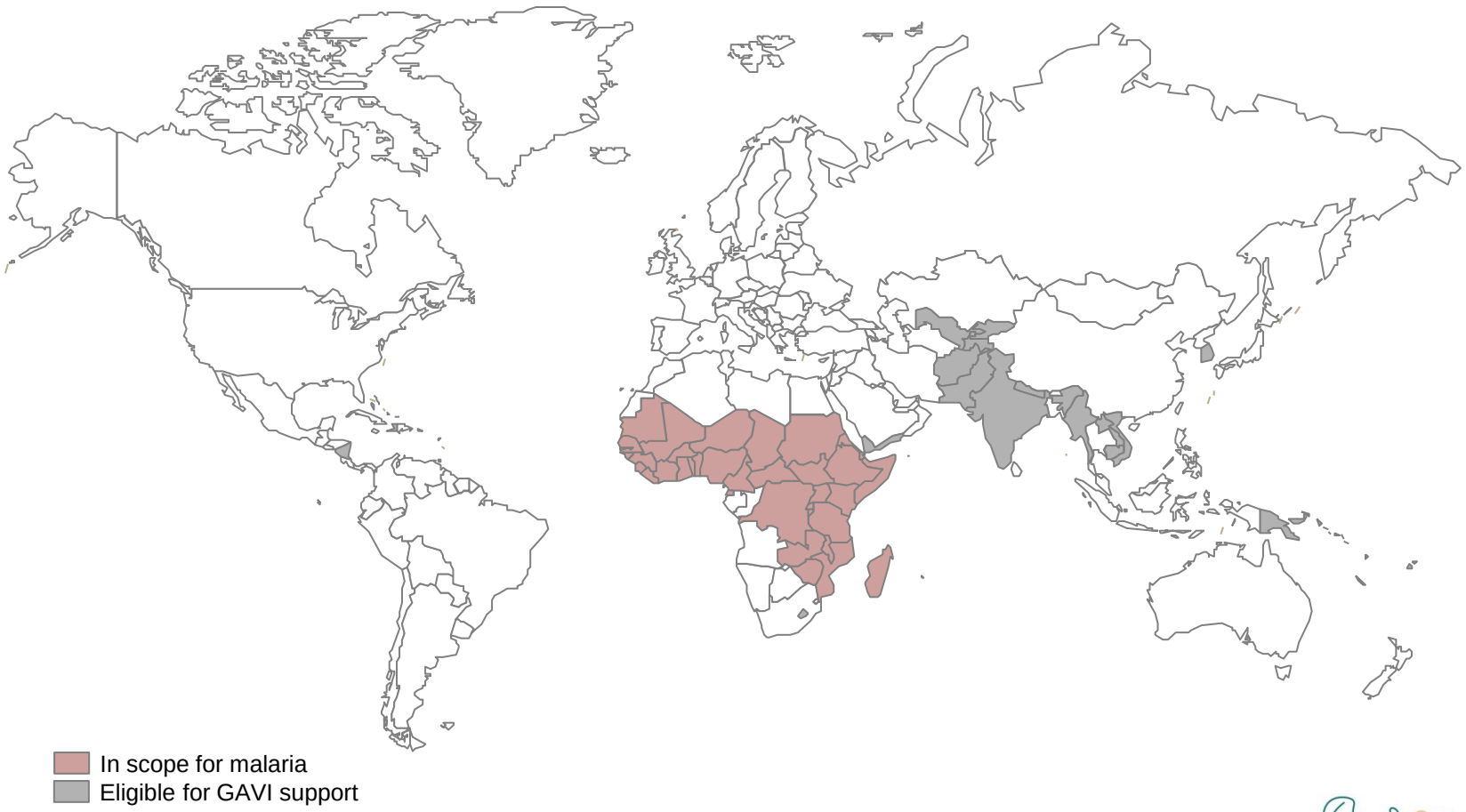
- WHO Malaria Fact Sheet
- WHO World Malaria Report (2012)
- IHME GBD 2010
- Malaria Atlas Project
- Model published in: Smith T, Ross A, Maire N, Chitnis N, Studer A, *et al.* Ensemble modeling of the likely public health impact of a pre-erythrocytic malaria vaccine. PLoS Med 2012, 9(1): e1001157.
- Griffin JT, Hollingsworth TD, Okell LC, Churcher TS, White M, et al. (2010) Reducing Plasmodium falciparum Malaria Transmission in Africa: A Model-Based Evaluation of Intervention Strategies. PLoS Med 7(8): e1000324. doi:10.1371/journal.pmed.1000324

## Experts

- Joachim Hombach, WHO
- Vasee Moorthy, WHO
- Marcel Tanner, Swiss TPH
- Brian Greenwood, LSHTM
- Farzana Muhib, PATH Malaria Vaccine Initiatve
- Carla Botting, PATH Malaria Vaccine Initiative
- Katya Galactionova, Swiss TPH
- Fabrizio Tediosi, Swiss TPH
- Peter Smith, LSTMH
- Christian Lengeler, Swiss TPH
- Rob Newman, WHO
- Brad Gessner, AMP
- Azra Ghani, Imperial College
- Jamie Griffin, Imperial College
- Michael White, Imperial College
- Thomas Smith, Swiss TPH
- Caitlin Bever, Swiss TPH
- Melissa Penny, Swiss TPH

# Appendix

# 37 countries in scope for malaria (Africa)



# Demand forecasting assumptions (1 of 2)

## Modelled scenario: routine immunisation at 6,10,14 weeks in EPI schedule with / without booster

| Element | Assumptions | Rationale / source |
|---|---|---|
| Country scope | ▪ 37 GAVI-eligible countries in Africa in scope<br>▪ 34 countries forecasted to introduce with GAVI support in 2015-2030 | Burden concentrated in Africa<br>Vaccine indication likely for Africa only |
| Target population | ▪ Routine: Surviving infants | Per clinical trials and partner inputs |
| Introduction dates | ▪ First introduction: 2017<br>▪ Timing of subsequent introductions based on countries with clinical trials, percentage of risk population, and mortality | Assumes PQ of GSK candidate by 2016 |
| Uptake | ▪ Routine: 2 to 4 years to max uptake, depending on country size | Standard GAVI uptake assumptions (new vaccine following EPI schedule) |
| Coverage | ▪ Demand: routine: DTP2;<br>▪ Fully vaccinated population: routine: DTP3 | Standard analogue used for routine 3 dose course |
| Products | ▪ Schedule: 3 doses; 4 week interval between dosing<br>▪ Presentation: 2 dose lyophilised vial | Per GSK candidate and clinical trials |
| Logistics | ▪ Wastage Factor: 1.11 | WHO recommendation for 2 dose lyophilised vial |
| Booster | ▪ 18 months after 3rd dose<br>  ▪ 20-30% drop-off (depending on country-specific U5 MR) due to mortality and booster compliance | Partner inputs |

# Demand forecasting assumptions (2 of 2)

## Modelled scenario: Expanded EPI strategy targeting 5-<18M (routine) with / without booster

| Element | Assumptions | Rationale / source |
|---|---|---|
| Country scope | ▪ idem | idem |
| Target population | ▪ Routine: Surviving infants | Per clinical trials and partner inputs Given the anticipated vaccination strategy for Malaria, Surviving Infant cohort was used as a proxy for the routine target population |
| Introduction dates | ▪ idem | idem |
| Uptake | ▪ Routine: idem | idem |
| Coverage | ▪ Demand: DTP2 with 25% discount<br>▪ Fully vaccinated population: DTP3 with 25% discount | 25% standard discount applied because at least 1 vaccination will require a new visit |
| Products | ▪ idem | idem |
| Logistics | ▪ idem | idem |
| Booster | ▪ idem | idem |

# Malaria vaccine impact modelling assumptions

Note: detailed impact modeling methods available on request, please contact vis@gavialliance.org

| | Swiss TPH[1] | Imperial College[2] |
|---|---|---|
| **Model structure** | ▪ Ensemble model (combines 6 input models)<br>▪ Individual model; simulates population 100,000 in 5-day time-steps<br>▪ Seasonal but not spatial<br>▪ Includes direct and indirect [3] deaths | ▪ Single model<br>▪ Intervention simulation model; individual based with simulated population<br>▪ Spatial and seasonal<br>▪ Includes direct deaths only |
| **Key assumptions** | ▪ **Efficacy[4] :** 31.3% (EPI), 55.8% (expanded EPI)<br>▪ **Treatment-seeking[5] :** 15%-52% (country-specific)<br>▪ **Transmission:** MAP-Oxford country-level prevalence and access to care estimates<br>▪ **Decay rate:** 3 years to half initial efficacy (exponential decay) | ▪ **Efficacy[4] :** 31.3% (EPI), 55.8% (expanded EPI)<br>▪ **Treatment-seeking[5] :** 8% - 54% (country-specific)<br>▪ **Transmission:** MAP/Oxford state/province level prevalence estimates, 2011 ITN coverage rates<br>▪ **Decay rate:** 3 years to half initial efficacy (exponential decay) |

[1] Smith T, Ross A, Maire N, Chitnis N, Studer A, et al. (2012) Ensemble Modeling of the Likely Public Health Impact of a Pre-Erythrocytic Malaria Vaccine. PLoS Med 9(1): e1001157. doi:10.1371/journal.pmed.1001157 [2] Griffin JT, Hollingsworth TD, Okell LC, Churcher TS, White M, et al. (2010) Reducing *Plasmodium falciparum* Malaria Transmission in Africa: A Model-Based Evaluation of Intervention Strategies. PLoS Med 7(8): e1000324. doi:10.1371/journal.pmed.1000324 3. Indirect refers to malaria-associated deaths not directly attributed to malaria, both Swiss TPH and Imperial models include transmission effects 4. Vaccine efficacy against clinical disease 5. Probability of seeking effective care

# Detailed impact modelling assumptions (1 of 2)

## Swiss TPH

**An ensemble model[1] that uses 6 separate models to provide an average estimate of vaccine impact**

**Individual stochastic model simulating a population of 100,000 people in 5-day time steps**

- Dynamic model
- Not a spatial model
- Includes seasonality of malaria transmission

**Includes:**

- New infections, parasite densities, naturally acquired immunity, uncomplicated and severe malaria episodes, deaths, hospitalized malaria episodes, infectiousness to mosquitoes, case management (uncomplicated and severe) and vaccination with a pre-erythrocytic vaccine

## Imperial College

**One model[2] used with 100 parameter sets used to estimate uncertainty**

**Individual-based stochastic simulation model**

- Dynamic model
- Spatial model
- Includes seasonality of malaria transmission

**Includes:**

- New infections, parasite densities, naturally acquired immunity, uncomplicated and hospitalized malaria episodes, deaths, infectiousness to mosquitoes, ITN, IRS, treatment rates (ACT coverage) and vaccination with a pre-erythrocytic vaccine

[1] Smith T, Ross A, Maire N, Chitnis N, Studer A, et al. (2012) Ensemble Modeling of the Likely Public Health Impact of a Pre-Erythrocytic Malaria Vaccine. PLoS Med 9(1): e1001157. doi:10.1371/journal.pmed.1001157

[2] Griffin JT, Hollingsworth TD, Okell LC, Churcher TS, White M, et al. (2010) Reducing *Plasmodium falciparum* Malaria Transmission in Africa: A Model-Based Evaluation of Intervention Strategies. PLoS Med 7(8): e1000324. doi:10.1371/journal.pmed.1000324

# Detailed impact modelling assumptions (2 of 2)

| Key Assumptions | Swiss TPH | Imperial College |
|---|---|---|
| **Vaccine efficacy against clinical disease** | Vaccine efficacy based on Phase 3 trials against clinical disease: 31.3% in 6-12 week olds, 55.8% in 5-17M olds<br>Assumes that vaccine efficacy decay rate against clinical disease is shorter than the decay rate of vaccine protection against infection | |
| **Vaccine protection decay rate against infection** | The decay rate[1] of vaccine efficacy against infection in the model was 3 years, consistent with analysis of Phase 2 long-term follow-up data<br>Assumes an exponential decay of protection against infection | |
| **Access to care** | Probability of seeking effective treatment for each episode is country-specific (15% to 52%) adjusted to DHS data and contains a scaling factor to reach effective treatment level | Treatment rates are country-specific (8% to 54%) from DHS and Multiple Indicator Cluster Survey data |
| **Transmission*** | Uses the MAP-Oxford[2] country level prevalence estimates, access to care assumptions and model relationships between prevalence and EIR to calculate country specific entomological inoculation rate or EIR (model input) | Uses the MAP-Oxford[2] state/province level prevalence estimates and applied the 2011 ITN coverage rates to adjust prevalence rates (model input) to current levels. Rainfall data allows malaria seasonality to be incorporated into prevalence estimates |

[1] The decay rate of vaccine protection against infection is defined as the time after vaccination at which the vaccine protection against infection is 50% of initial value, assuming exponential decay of protection

[2] Gething et al 2011. A new world malaria map: Plasmodium falciparum endemicity in 2010 Malaria Journal 10:378 doi:10.1186/1475-2875-10-378

* P. falciparum prevalence estimates are the most widely collected data on disease burden

# Potential future role of RTS,S as contributor to *P. falciparum* elimination in low transmission settings

- Malaria elimination is feasible in certain low burden countries
- Requires deliberate efforts to block transmission in foci with comprehensive, tailored anti-malarial intervention packages as part of a surveillance-response strategy
- Mathematical modeling predicts substantial transmission/herd effects in low transmission settings if RTS,S were given in mass campaigns achieving high coverage in all ages. RTS,S acts on *P. falciparum* only, no effect on *P. vivax*.
- Initial vaccine licensure highly likely to be for 6 weeks – 17 months for morbidity reduction
- Unclear at this stage what additional clinical trial data would be required for a potential future recommendation on use of RTS,S for contribution to elimination of *P. falciparum* (timeframe for potential recommendation here beyond 2015)
- Initial supply planning by manufacturer does not include use for elimination in specific settings